Medicinrådet

Bilag til Medicinrådets vurdering af larotrectinib (Vitrakvi) til behandling af NTRK-fusion-positiv kræft

Vers. 2.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. larotrectinib
2. Ansøgers endelige ansøgning vedr. larotrectinib

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20.05.2025

KLE/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.06.2025
Leverandør	Bayer
Lægemiddel	Vitrakvi (larotrectinib)
Ansøgt indikation	Behandling af NTRK-fusion-positiv kræft
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (revurdering, blev vurderet første gang i 2021)

Prisinformation

Amgros har forhandlet følgende pris på Vitrakvi (larotrectinib).

[redacted]

Flad rabat:

Amgros har forhandlet følgende pris.

Tabel 1: Forhandlet pris baseret på en "flad rabat":

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Vitrakvi	25 mg, 56 stk. Kapsler, hårde	10.669,55	[redacted]	[redacted]
Vitrakvi	100 mg, 56 stk. Kapsler, hårde	42.678,19	[redacted]	[redacted]
Vitrakvi	20 mg/ml, 2x50 ml. Oral opløsning	15.242,21	[redacted]	[redacted]

Priserne er betinget af Medicinrådets anbefaling, og vil træde kraft torsdag den 19.06.2025, hvis Medicinrådet anbefaler Vitrakvi baseret på denne "flade" rabatpris.

Hvis Medicinrådet *ikke* anbefaler Vitrakvi, indkøbes det til AIP.

Patientinitieringsmodel

[redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Vitrakvi	25 mg, 56 stk. Kapsler, hårde	10.669,55	[redacted]	[redacted]
Vitrakvi	100 mg, 56 stk. Kapsler, hårde	42.678,19	[redacted]	[redacted]
Vitrakvi	20 mg/ml, 2x50 ml. Oral opløsning	15.242,21	[redacted]	[redacted]

[redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
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Vitrakvi	100 mg, 56 stk. Kapsler, hårde	42.678,19	[redacted]	[redacted]
Vitrakvi	20 mg/ml, 2x50 ml. Oral opløsning	15.242,21	[redacted]	[redacted]

Priserne er betinget af Medicinrådets anbefaling, [redacted]

Konkurrencesituationen

Nuværende behandling er "best supportive care" og omfatter ikke medicinsk behandling. Rozlytrek (entrectinib) har EMA godkendelse til indikationen, men blev ikke anbefalet af Medicinrådet i 2021, og Roche har valgt ikke at ansøge Medicinrådet om en revurdering.

I tabel 4 er vist lægemiddeludgifter pr. patient ved behandling med Vitrakvi, såvel ved flad rabat som ved aftale om [redacted]

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering*	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift (SAIP, DKK)
[redacted]				
[redacted]	100 mg, 56 stk. Kapsler, hårde	100 mg oralt 2 gange dagligt	[redacted]	[redacted]
[redacted]	100 mg, 56 stk. Kapsler, hårde	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	100 mg, 56 stk. Kapsler, hårde	100 mg oralt 2 gange dagligt	[redacted]	[redacted]
[redacted]**	100 mg, 56 stk. Kapsler, hårde	[redacted]	[redacted]	[redacted]

*jf. EMA produkt resume og vurderingsrapporten pkt. 2.3.2. For voksne og børn med et kropsareal ≥ 1,0 m^2

** [redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Ikke anbefalet		Link til beslutning
England	Anbefalet		Link til vurdering
Sverige	Anbefalet		Link til beslutning

Opsummering

[redacted].

Application for the assessment of Vitrakvi® for the treatment of NTRK fusion positive solid tumours

Colour scheme for text highlighting	
Colour of highlighted text	Definition of highlighted text
	Confidential information

Contact information

Contact information	
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Name (External representation)	**Not applicable**
Title	
Phone number	Not applicable
E-mail	

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Tables and Figures

Abbreviations

Abbreviation	Definition
2L	Second line
AACR	American Association for Cancer Research
AE	Adverse event
AHRQ	Agency for Healthcare Research and Quality
AIC	Akaike information criterion

ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BMJ	British Medical Journal
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CEA	Cost-effectiveness analyses
CEM	Cost-effectiveness model
CGDBs	Clinic-genomic databases
CI	Confidence interval
CMN	Congenital mesoblastic nephroma
CNS	Central nervous system
CR	Complete response
CRC	Colorectal cancer
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DMC	Danish Medicines Council
DoR	Duration of response
DRG	Diagnosis-related group
EC	European Commission
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group performance status
EMA	European Medicines Agency
Embase	Excerpta Medica Database
EORTC QLQ-C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
ePAS	Extended primary analysis set
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
ERG	Evidence review group
ETV6	Erythroblast transformation specific variant transcription factor 6 gene
FISH	Fluorescence in situ hybridisation
FMI	Foundation Medicine Inc.
FOLFIRI	Folinic acid, fluorouracil and irinotecan hydrochloride
FOLFOX	Folinic acid, fluorouracil and oxaliplatin
GIST	Gastrointestinal stromal tumour
GP	General practitioner
Gr	Grade
HAS	Haute Autorite de Sante
HCRU	Healthcare resource utilization
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health state utility values
HTA	Health Technology Assessment
ICC	Intra-cohort comparator
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
IHC	Immunohistochemistry
IPD	Individual patient data
IQWIG	Institute for Quality and Efficiency in Health Care
IRC	Independent Review Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ISRCTN	International Standard Randomised Controlled Trial Number Register

ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
LOT	Line of therapy
MA	Meta-analysis
MAIC	Matching-adjusted indirect comparison
MASC	Mammary analogue secretory carcinoma
MedDRA	Medical Dictionary for Regulatory Activities
MEDLINE	Medical Literature Analysis and Retrieval System Online
MRI	Magnetic resonance imaging
N/A	Not available / Not applicable
NCPE	National Centre for Pharmacoeconomics
NCT	National Clinical Trial
NGS	Next-generation sequencing
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
NTRK	Neurotrophic tyrosine receptor kinase
OR	Overall response
ORR	Overall response rate
OS	Overall survival
pCR	Pathological complete response
PD	Progressive disease
PD-L1	Programmed death-ligand 1
PedsQL	Paediatric Quality of Life Inventory
PFS	Progression-free survival
PH	proportional hazards
PICOS	Population, interventions/comparators, outcomes and study design
PR	Partial response
PSA	Probabilistic sensitivity analysis
PT	Preferred term
PTC	Papillary thyroid carcinoma
QALY	Quality adjusted life-years
QLQ-C30	Quality of Life Questionnaire-Core 30
QoL	Quality of life
RANO	Response Assessment in Neuro-Oncology
RCT	Randomized controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RT-PCR	Reverse-transcription polymerase chain reaction
RWD	Real-world data
RWE	Real-world-evidence
SAEs	Serious adverse events
SD	Stable disease
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SoC	Standard of care
STS	Soft tissue sarcoma
TA	Technology appraisal
TEAEs	Treatment-emergent adverse events
ToT	Time on treatment
TPC	Treatment of physician's choice
TRK	Tropomyosin receptor kinase

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Vitrakvi®
Generic name	Larotrectinib
Therapeutic indication as defined by EMA	Larotrectinib as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion (1), • who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • who have no satisfactory treatment options
Marketing authorization holder in Denmark	Bayer
ATC code	L01XE53
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	19/09/2019
Has the pharmaceutical received a conditional marketing authorization?	This medicine received a conditional marketing authorisation. This was granted in the interest of public health because the medicine addresses an unmet medical need and the benefit of immediate availability outweighs the risk from less comprehensive data than normally required.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	N/A
Other therapeutic indications approved by EMA	No
Other indications that have been evaluated by the DMC (yes/no)	No
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Capsules (two pack sizes: 56 capsules a 25mg and 56 capsules a 100mg) and oral solution (2x50 ml at 20 mg/ml)

Abbreviations: NTRK, Neurotrophic tyrosine receptor kinase; EMA, European Medicines Agency; EC, European Commission; DMC, Danish Medicines Council; ATC, Anatomical Therapeutic Chemical; N/A, not available or not applicable

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Larotrectinib (Vitrakvi®) as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion (1).
Dosage regimen and administration:	The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs (2). Dosing in paediatric patients is based on body surface area (BSA). The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib

Summary	
	twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs (2).
Choice of comparator	There are no treatment options available for patients that specifically target NTRK gene fusion cancers. Danish clinical practice recommends standard of care (SoC) for solid tumours varied on the bases of tumour type. The approach taken to identifying the comparator is to consider SoC after patients have exhausted all satisfactory treatment options. SoC is consisting of chemotherapy, radiotherapy, surgery, targeted therapies, and/or immuno-oncology agents in this submission.
Prognosis with current treatment (comparator)	The prognosis for this group of patients is extremely variable, as there are widely different types of cancer involved. However, overall, the group must be regarded as incurably ill with a relatively short average remaining lifespan. TRK inhibitors like larotrectinib has shown high overall response rates (ORR) (ORR 65% ePAS8 (n=302) (assessed by IRC) and durable responses) in both adults and children with NTRK fusion-positive solid tumours, in stark contrast to poor outcomes with SoC therapies.
Type of evidence for the clinical evaluation	Indirect treatment comparison, matching-adjusted indirect comparison (MAIC). Comparing larotrectinib against real-world-evidence (RWE) data.
Most important efficacy endpoints (Difference/gain compared to comparator)	Response rate: ORR is an accepted efficacy endpoint in oncology studies. • Larotrectinib: 193 (ORR 65%) (IRC assessed) and 193 (ORR 64%) [58;69 CI] (investigator assessment) • SoC (Bokemeyer et al): Not reported Other more direct measures of clinical benefit such as overall survival (OS) and progression-free survival (PFS) were included as secondary endpoints. OS: • Larotrectinib: median OS after weighting was 30.8 months • SoC: median OS after weighting was 10.3 months PFS: • Larotrectinib: median PFS after weighting was 19.22 months • SoC: median PFS was not reported Refer to Section 6 and 7.
Most important serious adverse events for the intervention and comparator	In the overall safety analysis set (larotrectinib trials), pneumonia and pyrexia were the most common serious adverse events (SAEs), occurring in 19 (4%) and 15 (3%) patients, respectively. Other SAEs reported in ≥1% of patients were dyspnoea (in 10 [2%] patients), diarrhoea (in 8 [2%] patients), vomiting (in 7 [2%] patients), hypoxia, seizure, and sepsis (each in 6 [1%] patients), and abdominal pain, muscular weakness, pneumonia aspiration, pulmonary embolism, and respiratory failure (each in 5 [1%] patients) (3). In absence of safety data from the SoC/comparator source informing the clinical efficacy, adverse event (AE) rates were derived from available appraisal documents (tumour sites sourced from previous NICE TAs)
Impact on health-related quality of life	Clinical documentation: Utility values were informed by EQ-5D-5L (adult) and PedsQL (paediatric) estimates taken directly from the patients enrolled in the larotrectinib clinical trial program. Health economic model: The health economic model demonstrates an improvement in health-related quality of life.

Summary	
Type of economic analysis that is submitted	Cost-utility analysis Partitioned survival model (PartSA)
Data sources used to model the clinical effects	The larotrectinib trials (extended primary analysis set (ePAS)8, data cut-off (DCO) 20 July 2023) (4, 5) and Bokemeyer et al. (6) were used to inform the PartSA model.
Data sources used to model the health-related quality of life	Health-related quality of life measured with EQ-5D-5L in the larotrectinib trials, using the DCO from 2021 (ePAS6) (7). UK population weights were used in the base case.
Life years gained	5.4 years
QALYs gained	4.9 QALY
Incremental costs	2,269,131 DKK
ICER (DKK/QALY)	463,332 DKK/QALY
Uncertainty associated with the ICER estimate	Deterministic: The parameter with largest impact on the ICER is the PFS extrapolation of the larotrectinib arm. Scenario: The parameters with largest impact on the ICER are the PFS and OS extrapolation of the larotrectinib arm.
Number of eligible patients in Denmark	Annually: 5 eligible patients
Budget impact (in year 5)	DKK 816,165

Abbreviations: AE, adverse event; DCO, data cut-off; ePAS, extended primary analysis set. QALYs, quality-adjusted life year; NTRK, Neurotrophic Tyrosine Receptor Kinase; ICER, incremental cost-effectiveness ratio; ORR, overall response rate; SAEs, Serious Adverse Events; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; PedsQL, Pediatric Quality of Life Inventory.

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

3.1.1 Pathophysiology

TRK fusion cancer is cancer characterized by the presence of NTRK gene fusions (NTRK fusion cancer has a complex molecular pathology characterized by the presence of NTRK gene fusions e.g. NTRK1, NTRK2, and NTRK3), leading to the formation of oncogenic TRK fusion proteins (driver of tumourigenesis). NTRK gene fusions have been reported across a wide range of solid tumour histologies as the primary oncogenic driver in both adult and paediatric patient populations (8-11).

3.1.1.1 NTRK signalling pathway

Under normal physiologic conditions, the NTRK gene family (NTRK1, NTRK2, and NTRK3) encodes the tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC, regulating the proliferation, growth, and survival of neurons, through activation by neurotrophins (12-14) (15-17). Activation of the TRK signalling pathway triggers downstream signalling cascades that regulate various cellular processes such as cell growth, differentiation, survival, and apoptosis (refer to Figure 1).

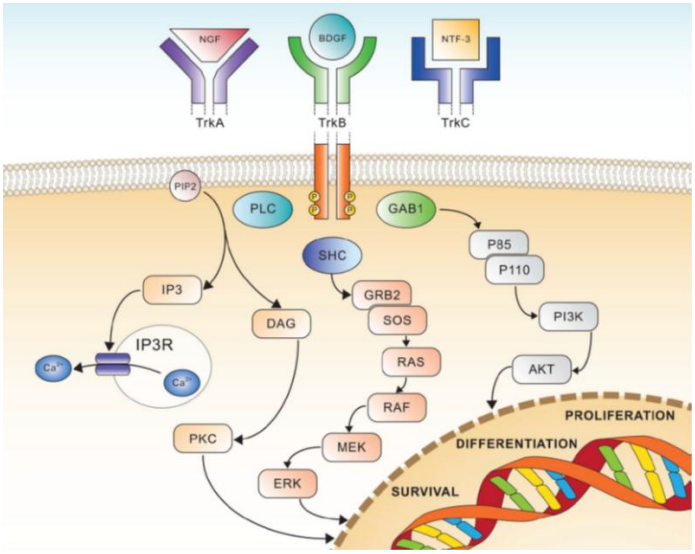


Figure 1 TRK signalling pathways

Adapted from Amatu A, Sartore-Bianchi A, Siena S (2016) (12)

AKT =v-AKT murine thymoma viral oncogene homologue; BDGF = brain-derived growth factor; DAG = diacyl glycerol; ERK = extracellular signal-regulated kinase; GAB1 = GRB2-associated binding protein 1; GRB2 = growth factor receptor-bound protein 2; IP3 = inositol trisphosphate; MEK = mitogen-activated protein kinase; NGF = nerve growth factor; NTF-3 = neurotrophin 3; PI3K = phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2 = phosphatidylinositol 4,5-bisphosphate; PKC = protein kinase C; PLC = phospholipase C; RAF = rapidly accelerated fibrosarcoma kinase; RAS = rat sarcoma kinase; SHC = Src homology 2 domain containing

3.1.1.2 NTRK gene fusions

In all reported NTRK gene fusions, the 3' region of the NTRK gene (encoding the kinase domain) is joined with a 5' sequence of a fusion partner gene by an intrachromosomal or intrachromosomal rearrangement, and the resultant oncoprotein is typically a constitutively activated or overexpressed kinase, leading to activation of downstream oncogenic pathways (12). This constitutively active downstream signalling leads to unchecked cellular proliferation and growth through the TRK pathway (12, 18, 19). This structural alteration leads to constitutive activation of the TRK kinase, driving downstream signalling pathways involved in cell growth and survival. The resultant uncontrolled TRK signalling promotes tumour initiation and progression in affected tissues. The identification of NTRK fusions has significant implications in oncology, as they represent actionable targets for precision medicine approaches such as targeted therapies with TRK inhibitors.

All patients with TRK fusion cancers, no matter the afflicted solid organ, share the same disease mechanism. The fusion partners vary based on histologic cancer type, with more common cancers typically having a higher number of known and unknown fusion partners (8, 12, 19-21), whereas more rare histologic cancer types commonly have 1 known fusion partner.

3.1.2 Detection of TRK fusion cancer

Multiple testing methods are available to identify patients with tumours harbouring NTRK gene fusions/TRK fusion cancer, including immunohistochemistry (IHC), fluorescence in situ hybridisation (FISH), reverse-transcriptase PCR (RT-PCR) and both DNA-based and RNA-based next-generation sequencing (NGS).

More than 80 different fusions have been identified with 3 NTRK genes and multiple 5' NTRK gene fusion partners have been identified (8, 22). IHC is highly sensitive for detecting

TRK protein expression , offering advantages like low cost and fast turnaround time. However, for the vast majority of patients in the larotrectinib clinical development program, their NTRK fusion was detected using either DNA or RNA based NGS (EPAR pp. 14-15 and p. 105).

In Denmark, FISH, IHC, and NGS are often used for testing genetic alterations in cancer patients. Currently, routine testing for NTRK fusions is not conducted for all tumour site locations (23). According to a understood clinical practice, patients with the following tissue locations such as pancreatic, glioma and biliary cancer would have been tested for NTRK fusions within clinical routine. Although DNA based NGS is already being performed for a range of cancer types, these analyses will not necessarily be able to detect NTRK fusions. For most cancers (e.g., non-small cell lung cancer (NSCLC), colorectal cancer, ovarian cancer, and brain tumours), where NGS testing is already conducted, the analysis is performed on DNA based NGS. In previous DMC assessment of larotrectinib, the expert committee assessed that patients would be tested through IHC. If TRK protein expression is detected/confirmed a NGS test would be performed as a follow-up test (23). NGS will typically be available regardless of treatment location but is most commonly conducted at university hospitals (23).

3.1.3 Clinical presentation and prognosis

The clinical presentation and prognosis of NTRK fusion-positive tumours can vary depending on several factors including the tumour type, location, and specific NTRK gene involved. NTRK gene fusions have been reported the following histologies: colorectal cancer (CRC), NSCLC, thyroid carcinoma, spitzoid melanoma, glioblastoma multiforme, infantile fibrosarcoma (IFS), mammary analogue secretory carcinoma (MASC) of the salivary gland, invasive breast carcinoma, secretory breast carcinoma, Congenital mesoblastic nephroma (CMN), gastrointestinal stromal tumour (GIST), soft tissue sarcoma (STS), head and neck carcinomas, acute myeloid leukaemia, intrahepatic cholangiocarcinoma, and many other tumours (24).

A systematic review identified limited published data on the prognosis of patients with the NTRK gene fusion; only six publications in three tumour sites included a comparison with patients without the NTRK gene fusion. The presence of an NTRK gene fusion has been shown to be associated with a worse prognosis or more aggressive tumour in patients with metastatic colorectal cancer, and papillary thyroid carcinoma. Patients with cellular CMN featuring an NTRK gene appeared to have a better prognosis than cellular CMN without an NTRK fusion (16, 17, 25).

Furthermore, a systematic literature review (SLR) was conducted in Medline, Embase, Cochrane, and PubMed to identify studies comparing the OS of patients with NTRK gene fusion-positive vs NTRK gene fusion-negative tumours. Five retrospective matched case-control studies published before 11 August 2022, were assessed for inclusion. The median OS was not estimable in the studies by Bridgewater et al and Zhu et al because of a lack of events, but in the three other studies, it ranged from 10 to 16.5 months (Lassen 2023 (26)). Additionally, real-world analyses show that the presence of *NTRK* fusions does not confer any survival, and there is actually a trend toward a shorter survival in the absence of TRK inhibitor treatment (Bazhenova 2021; Hibar 2022; Santi 2021; Bridgewater 2022; Zhu 2022) (27-31). An ad-hoc analysis of pooled data from the 3 clinical trials for

larotrectinib to determine patient disease course prior to larotrectinib initiation reported that there was a short time from first diagnosis to the development of advanced or metastatic disease, supporting the premise that NTRK gene fusions do not generally have a positive prognostic value (32).

NTRK gene fusions are reported to be mutually exclusive of other oncogenic drivers when found in any given cancer; therefore, the appropriate therapy for patients with TRK fusion cancer should be specifically targeted to this oncogenic driver. Prior to the regulatory approvals of larotrectinib and entrectinib, TRK fusion cancer had no effective therapy that targeted NTRK gene fusions, and as such, patients with tumours harbouring NTRK gene fusions historically received SoC treatment defined by tumour histology guideline recommendations.

The unmet need in NTRK fusion-positive cancer lies in the limitations of traditional cancer treatments, which focus on the tumour's location rather than its genetic drivers. NTRK gene fusions can occur in various cancer types, and conventional site-specific therapies may not be effective for all patients. A 'tumour-agnostic' approach that targets NTRK gene fusions addresses this gap by providing a treatment based on the cancer's genetic cause, leading to more personalized and potentially more effective therapies for patients with NTRK fusion-positive cancers.

3.1.4 Patients' functioning and health-related quality of life

Evidence has shown that use of targeted therapy paired with a specific oncogenic driver leads to better outcomes for patients than using a "one-size-fits-all" treatment approach with SoC therapies. Use of targeted therapies has been shown to provide maximum benefit and have the potential to improve patient quality of life (QoL) (33).

3.2 Patient population

The annual number of patients eligible for larotrectinib treatment in Denmark is uncertain due to limited data on the prevalence of NTRK fusions among Danish cancer patients. Larotrectinib is only indicated when all other treatment options are exhausted. Estimates must account for dropout between treatment lines across various cancers. From the previous assessment report on larotrectinib by DMC, the expert committee estimated that there are ~10,000 Danish patients annually with incurable cancer. Of these, about one-third (3,300) may exhaust all treatment options while still being fit for additional therapy. Within this group, potential candidates for larotrectinib include patients with rare cancers where NTRK fusions are common (e.g., infantile fibrosarcoma) and more frequent cancers like colorectal, lung, and melanoma, where NTRK fusions occur in ~0.3%. Among the ~1,400 annual brain tumour cases, approximately 10 patients may benefit. In total, the committee estimated 10–40 patients annually might qualify for larotrectinib in Denmark. However, this estimate is highly uncertain and depends on the implementation of NTRK testing. (23).

Less than 1% of all cancer cases occur in children, with approximately 380 children diagnosed with cancer annually. The 5-year survival rate for children with cancer is above 80% (23). However, the incidence and prevalence data for the full cancer population was informed by the previous DMC assessment report as mentioned above, refer to Table 4 below.

Table 1 Incidence and prevalence in the past 5 years

Year	2019	2020	2021	2022	2023
Cancer overall incidence in Denmark	45,179	45,056	47,127	47,514	N/A**
Prevalence in Denmark	10,000	10,000	10,000	10,000	10,000
Larotrectinib candidate prevalence	10-40	10-40	10-40	10-40	10-40
Global prevalence*	<1%	<1%	<1%	<1%	<1%

Abbreviations: N/A, not available / not applicable.

Notes: In 2022, 47,514 new cases of cancer were registered by the Danish Cancer Registry (2022 as latest report)

* For small patient groups, also describe the worldwide prevalence.

** assuming 47,514

In previous DMC assessment, the expert committee estimated approximately 10-40 patients (adults and children) yearly would be eligible for treatment with larotrectinib in Denmark (23). However, the patient count is uncertain. Firstly, there is insufficient data on the frequency of NTRK fusion among Danish cancer patients, and secondly, larotrectinib is indicated only after other treatment options have been exhausted. In DMC's base case from previous assessment, it is assumed that 20 patients (10 children, 10 adults) will be eligible for larotrectinib treatment in the first year, with 30 patients (10 children, 20 adults) in subsequent years. However, this estimate is considered unrealistic knowing that the inclusion criteria of the NAVIGATE (NCT02576431) and SCOUT (NCT02637687) studies were lenient enough to never reject a patient in Denmark since the enrolment in 2017. This is comparable to clinical practice as NTRK patients can receive treatment with a wide ECOG performance status from 0-3. In addition, larotrectinib is reimbursed in Sweden and Finland, where less than 8 and 3 patients are treated with larotrectinib per year, respectively. Hence, it is expected that 5 patients annually would be eligible for treatment with larotrectinib.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	5	5	5	5	5

Source: DMC expert committee, Assessment report larotrectinib

NTRK fusions are rare and detected with highly variable frequency across tumour types in both children and adults (below 1% of solid tumours) (15, 34, 35). Based on a meta-analysis of literature available, the overall incidence of NTRK gene fusion in solid tumours is estimated to be 0.52 per 100,000 persons globally in 2018 and the calculated overall NTRK gene fusion 5-year prevalence was and 1.52 per 100,000 persons (36). NTRK fusions are found at low frequencies (commonly <1%) in a range of common tumour types and at high frequencies (up to or greater than 90%) in rare cancer types (secretory breast carcinoma, mammary analogue secretory carcinoma and infantile fibrosarcoma) (refer to Figure 2). Furthermore, it is unclear whether there are geographical and epidemiological differences in the occurrence of NTRK fusions. Table 4 below.

An SLR was conducted to determine the incidence, prevalence, and abundance of NTRK gene fusions in patients with select solid tumours, including CRC, NSCLC, IFS, thyroid cancer, salivary gland cancer, sarcomas, and melanoma (37). The SLR was conducted in Embase, Medline, and Cochrane databases on 15 March 2023. It is important to acknowledge that thyroid cancer, salivary gland cancer, and sarcomas, are associated with a variable

frequency of NTRK gene fusion expression, likely due to the heterogeneity of the patient populations included.

Table 3 SLR on the epidemiology of solid tumours (NTRK+ gene fusions)

Tumour types	N (included publications)	Frequency of NTRK-fusion (%)
CRC	44	0.02% - 50%
NSCLC	16	0.07% - 11.76%
IFS	7	25% - 100%
Thyroid cancer	64	0.25% - 33.33%
Salivary gland cancer	28	0.87% - 96.3%
Sarcoma	28	0.34% - 75%
Melanoma	14	0.21% - 56.25%

Abbreviations: NTRK, neurotrophic tyrosine receptor kinase; CRC, colorectal cancer; NSCLC, non-small cell lung cancer; IFS, infantile fibrosarcoma,

Another publication, Forsythe et al., reported that frequency of NTRK gene fusions varies considerably according to tumour histology, occurring rarely (<0.1% to 3%) in common histologies, such as NSCLC and CRC, and more often (>90%) in several uncommon tumours, such as secretory breast carcinoma IFS.

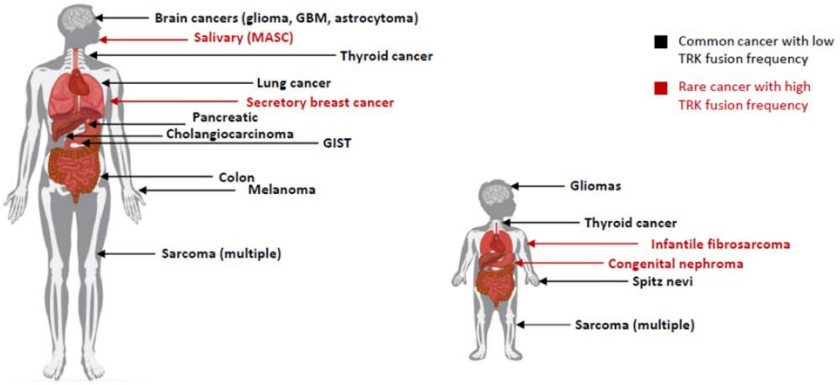


Figure 2 Distribution of NTRK gene fusions across tumour histologies
Source: BAYER 2023 GVD

Based on the previous DMC assessment of larotrectinib (23), the DMC provided an overview of the frequency of NTRK-fusion in various cancer/tumour types (refer to Table 4).

Table 4 NTRK-fusion frequency

Tumour types	Frequency of NTRK-fusion (%)
Infantile fibrosarcoma	Approx. 100
Secretory carcinoma in both salivary gland and breast	Approx. 100
Cancer types in the respiratory tract, digestive system, breast, and brain	< 5
Lung cancer, colorectal cancer, melanoma, and breast cancer	0.1 – 1

Abbreviations: NTRK, neurotrophic tyrosine receptor kinase
Source: DMC (23)

3.3 Current treatment options

Currently, there are no approved treatment options in Denmark specifically for patients with NTRK fusion-positive solid tumours, however treatment recommendations regarding NTRK fusion-positive cancer have been included within Danish guidelines (e.g. as neoadjuvant treatment in GIST) (38). However, several cancer treatment guidelines do not

mention NTRK fusion positive specific treatment, and patients are most likely to receive treatment for the specific tumour site, irrespective of NTRK status.

In Danish clinical practice, the majority of cancer patients receive standard treatment primarily based on the tissue of origin and the extent of the cancer. For many cancer types, surgery aimed at cure is often the first choice. When surgical treatment is not possible or insufficient, patients are offered either radiation therapy and/or medical treatment (chemotherapy, targeted therapy, or immunotherapy) considered as SoC. In paediatric cancers, chemotherapy is common, but for rare cancers or cases where standard treatments fail, patients may join trials for experimental therapies or receive palliative care (considered as SoC) (23).

Unlike traditional approaches tied to tissue type, larotrectinib targets NTRK gene fusions across solid tumours, regardless of origin. It is used when other treatments are exhausted, so there is no standard regimen for eligible patients.

3.4 The intervention

Table 5 Description of larotrectinib

Overview of larotrectinib	
Therapeutic indication relevant for the assessment	Larotrectinib as monotherapy is indicated for the treatment of adult and paediatric patients with solid tumours that display a NTRK gene fusion.
Method of administration	Oral capsules or oral solution
Dosing	The recommended dose in adults is 100 mg larotrectinib twice daily, until disease progression or until unacceptable toxicity occurs. Dosing in paediatric patients is based on BSA. The recommended dose in paediatric patients is 100 mg/m^2 larotrectinib twice daily with a maximum of 100 mg per dose until disease progression or until unacceptable toxicity occurs (2).
Dosing in the health economic model (including relative dose intensity)	Adults: average dose of 191.72 mg (N/A) Paediatrics: average dose of 134.48 mg (N/A)
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Until disease progression or until unacceptable toxicity occurs. In the model: until progression
Necessary monitoring, both during administration and during the treatment period	Both treatment and intervention are associated with inclusion of oncology visits, CT scans, liver tests and blood test. Disease management costs were sourced from DRG-tariffs and laeger.dk. Only costs associated with the PF health state were considered relevant. See Section 11.4 and Table 46.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	The presence of an NTRK gene fusion in a tumour specimen should be confirmed by a validated test prior to initiation of treatment with larotrectinib, refer to 3.1.2.
Package size(s)	Larotrectinib is available as hard capsules (25mg, 100mg) to be taken orally, or as an oral solution (20mg/mL).

Abbreviations: NTRK, neurotrophic tyrosine receptor kinase; BSA, body surface area; N/A, not available / not. applicable

3.4.1 Description of ATMP

Larotrectinib specifically targets the TRK proteins, irrespective of the location or histology of the tumour, turning off signalling pathways that usually allow NTRK fusion-positive cancers to grow (tumour-agnostic).

Larotrectinib has demonstrated efficacy in diverse tumour types with NTRK gene fusions, showing rapid and substantial antitumour activity in patients with locally advanced or metastatic cancers that were not controllable with other therapies. Patients in clinical studies had often undergone multiple prior treatments. The treatment was effective regardless of NTRK isoform, tumour type, or patient age, but had no effect in patients without an NTRK fusion (39). Larotrectinib is effective across a wide range of tumours, including rare types and subsets of common tumours, in both paediatric and adult patients. The safety profile is predictable and manageable, supporting treatment based on the presence of the NTRK gene fusion.

3.4.1.1 Mechanism of action

Larotrectinib is an orally bioavailable, adenosine triphosphate (ATP)-competitive and highly selective TRK inhibitor (selective TRK inhibitor) that specifically targets the TRK family of proteins, which includes TRKA, TRKB, and TRKC. These proteins are encoded by the NTRK1, NTRK2, and NTRK3 genes, respectively.

In tumours with NTRK gene fusions, the 3' region of the NTRK gene (encoding the kinase domain) is joined with a 5' sequence of a fusion partner gene by an intrachromosomal or intrachromosomal rearrangement and if in-frame, leading to the production of constitutively active TRK fusion proteins that drive cancer cell proliferation. Larotrectinib inhibits the kinase activity of these TRK fusion proteins, thereby halting tumour growth and inducing cancer cell death (see also Figure 1).

3.4.2 The intervention in relation to Danish clinical practice

As per the EMA label, larotrectinib is expected to be used in patients whose tumours are advanced, have spread to other parts of the body or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments.

In contrast to the traditional approach to cancer treatment, which is largely dependent on histology (tissue type), larotrectinib is not indicated for a specific type of cancer but for all cases of solid tumours with NTRK fusion and regardless of age (tumour-agnostic). For this reason, and because larotrectinib is indicated when other treatment options are exhausted, there is no standard treatment for patients eligible for larotrectinib in Danish clinical practice. It is approved for all solid tumours with NTRK fusion, making it a tissue-agnostic treatment option. This approach marks a significant shift in cancer treatment, moving from traditional site-specific therapies to 'tumour-agnostic' or 'pan-tumour' therapies (See Table 6).

Published in Danish medical news, a Danish clinical expert from Rigshospitalet, presented data at the European Lung Cancer Congress in 2023 (40), showing that larotrectinib is highly effective in treating NSCLC with NTRK fusion. The study, which includes Danish participants, demonstrated that larotrectinib provides long-lasting responses, even in patients with brain metastases. This indicates that larotrectinib can significantly benefit

patients with this specific genetic alteration, offering a targeted treatment option where traditional therapies may fail (40, 41).

3.4.2.1 Larotrectinib criteria - testing

Patients can be treated with larotrectinib if they have an NTRK fusion in a tumour sample. Currently, routine testing for NTRK fusions in tumour samples is not conducted in Danish clinical practice. NGS, IHC, and FISH can all be used to detect fusions (refer to 3.1.2). From previous DMC assessment, the expert committee estimated that between 1,500 and 2,000 patients need to be tested to identify the 20 adult patients eligible for larotrectinib (23).

3.5 Choice of comparator(s)

Due to the very specific mutational status, there are currently no effective treatments approved in Denmark for NTRK-fusion positive solid tumours. However, as mentioned in Section 3.3, most patients receive SoC therapy. The clinical data (data on OS) is informed by Bokemeyer et al. using RWE data from the Flatiron database (6). Matching-adjusted indirect comparison was used to match population characteristics from patients with advanced/metastatic TRK fusion-positive cancer from three larotrectinib trials to aggregate data from patients in the Flatiron Health/Foundation Medicine database who received SoC. It has been assumed that included patients received SoC in respective tumour types. No further details regarding the SoC drugs were provided in the paper by Bokemeyer et al. It is acknowledged that this is a limitation, however, to date the paper by Bokemeyer et al. is the only paper which provides the most robust data on NTRK fusion positive patients on SoC.

Meaning that there are several relevant and potential comparators that need to be considered in this appraisal. The approach taken to identifying the comparator is to consider SoC after patients have exhausted all satisfactory treatment options. This means later lines / last line of chemotherapy represented by the tumour specific treatment regimens presented in Appendix O.3.1.

Table 6 Overview of comparator

Overview of comparator	
Generic name	Tumour-site specific, refer to Appendix O.3.1.
ATC code	Tumour-site specific, refer to Appendix O.3.1.
Mechanism of action	Tumour-site specific, refer to Appendix O.3.1.
Method of administration	Tumour-site specific, refer to Appendix O.3.1.
Dosing	Tumour-site specific, refer to Appendix O.3.1.
Dosing in the health economic model (including relative dose intensity)	Tumour-site specific, refer to Appendix O.3.1.
Should the pharmaceutical be administered with other medicines?	Tumour-site specific, refer to Appendix O.3.1.
Treatment duration/ criteria for end of treatment	Tumour-site specific, refer to Appendix O.3.1.
Need for diagnostics or other tests (i.e. companion diagnostics)	Tumour-site specific, refer to Appendix O.3.1.
Package size(s)	Tumour-site specific, refer to Appendix O.3.1.

In addition, some patients may receive radiotherapy or surgery (resection). However, it should be noted that patients enrolled in the larotrectinib clinical trial programme were heavily pre-treated, with 74% of patients received at least one and 26% patients received

>3 prior systemic therapies. The majority of patients had also previously surgical (71%) and radiotherapy treatment options (37%) (42) (Table 3-10 in clinical report (data on file), ePAS8).

In summary the population enrolled in the larotrectinib arm of the economic model reflects patients that have exhausted satisfactory treatment options, where remaining treatment options would not be of clinical benefit.

3.6 Cost-effectiveness of the comparator(s)

The comparator, SoC, has not been evaluated by the DMC in the treatment of NTRK fusion positive solid tumours. However, SoC can reasonably be assumed to be cost-effective and the most relevant comparator, as SoC is and has been used in standard clinical practice for many years.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The primary endpoint for efficacy analyses from the larotrectinib trials is ORR. Tumour responses were assessed using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria according to IRC assessment and investigator assessment. Duration of response (DoR), safety, OS and PFS are included as secondary endpoints. QoL is included as an explorative endpoint.

Response rate (measured as ORR), OS and PFS are relevant efficacy outcomes included in this application. These outcomes have been previously deemed relevant by the DMC within the area of oncology, as well as previous assessment of larotrectinib (in NTRK fusion positive solid tumours) (23, 43). The efficacy outcomes sourced from the larotrectinib trials are defined in Table 7 below.

Table 7 Efficacy outcome measures relevant for the application – larotrectinib

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
ORR	20 July 2023	ORR is defined as the proportion of patients with best OR of confirmed CR, pCR, or PR. Responses were confirmed by a repeat assessment no less than 28 days.	Investigators assessment and independent review committee (IRC)-assessed according to RECIST, version 1.1.
CR	20 July 2023		Investigator assessment and IRC-assessed
pCR	20 July 2023	pCR is defined as a CR achieved by patients who are treated with larotrectinib and subsequently undergo surgical resection with no viable tumour cells and negative margins on their postsurgical pathology evaluation.	Investigator assessment and IRC-assessed
PR	20 July 2023		Investigator assessment and IRC-assessed
SD	20 July 2023		Investigator assessment and IRC-assessed

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OS	20 July 2023	OS is defined as the time to death from any cause.	Investigator assessment and IRC-assessed. KM estimates were used for analyses.
PFS	20 July 2023	PFS is defined as the number of months elapsed between the date of the first dose of treatment and the earliest date of documented PD or death (whatever the cause).	Investigator assessment and IRC-assessed. KM estimates were used for analyses. IRC disease assessments were performed by using RECIST version 1.1.
DoR	20 July 2023	Duration of response is defined as the time from the start date of CR, pCR, or PR (whichever response was recorded first) to the earlier of documented PD or death due to any cause.	Investigator assessment and IRC-assessed. KM estimates were used for analyses. IRC disease assessments were performed by using RECIST version 1.1.
Time to response	20 July 2023	Time to response is defined as the number of months elapsed between the date of the first dose of larotrectinib and the first documentation of objective response (CR, pCR, or PR, whichever occurred earlier) that was subsequently confirmed.	Investigator assessment and IRC-assessed

Abbreviations: OR, overall response; ORR, overall response rate; pCR, pathological complete response; CR, complete response; SD, stable disease; OS, overall survival; KM, Kaplan-Meier; PFS, progression-free survival; PR, partial response; PD, progressive disease; DoR, duration of response; IRC, Independent Review Committee, RECIST, Response Evaluation Criteria in Solid Tumours

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Source: Bayer, 2024 (4) Global Value Dossier (data on file) and Larotrectinib pooled analysis set clinical report (data on file, section 1.4.3)

For the comparative analysis of larotrectinib vs SoC informed by the Bokemeyer et al. (2023), the only reported and available efficacy endpoint is OS. The comparator dataset does not provide information on other key endpoints such as ORR, PFS, DoR, safety outcomes, or health-related quality of life (HRQoL). Refer to section 6 for a detailed explanation of how this is handled.

Validity of outcomes

OS is considered an important clinical endpoint in clinical trials within oncology and is highly regarded as the gold-standard endpoint for establishing clinical benefit. PFS is a commonly used endpoint within oncology trials and is essential to assess how long a treatment can delay disease progression, particularly in cancers with a high likelihood of progression. ORR is an immediate measure of the antineoplastic activity of a treatment. In patients with limited treatment options, demonstrating a significant tumour shrinkage (through ORR) can indicate a meaningful clinical benefit. Efficacy endpoints were accepted in the first submission from 2021 (23).

4. Health economic analysis

A cost-effectiveness analysis was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model (CEM) [404 Bayer larotrectinib DK CEM v0.27 - 29 Nov

2024 final]. The objective of the CEM is to assess the cost-effectiveness of larotrectinib vs. SoC in NTRK-fusion positive solid tumours. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained

4.1 Model structure

The economic model is a cohort state transition model with a survival partition approach. In the prior DMC assessment of larotrectinib, a mixture-cure model was submitted, however, the DMC had issues fully accepting this approach (23). Hence, a standard parametric survival model was used. The model allows to test potential curative effects of larotrectinib, using alternative curves for OS such as Gompertz and Generalised Gamma, refer to Section 8 and Section 12.2.1 The partitioned survival model is a well-established approach widely used for cost-effectiveness analysis in oncology therapies and is frequently employed in submissions to the DMC. The model features three distinct mutually exclusive health states: progression-free survival, progressed-disease, and death. Patients in the PFS were treated with either larotrectinib or the SoC, and their status was determined as either stable or responsive to treatment. As time progressed, patients could either move directly to the death state or first advance to the progressed-disease, where they could receive best supportive care (BSC) before ultimately reaching the death (refer to Figure 5).

The proportion of patients in the 'progression-free' health state is equal to the survival function value for PFS, while the proportion of patients in the "dead" health state is equal to 1 less the survival function value for OS. Lastly, the proportion of patients in the 'progressed' health state is equal to the survival function of OS – PFS. To ensure that the fitted PFS and OS matched the published trial data, additional assumptions were made only to estimate the extrapolated portions of the curve (44).

- The OS curve represents the proportion of patients at any timepoint that are still alive (split between 'progression free' and 'progressed' health states)
- The PFS curve represents the proportion of patients at any timepoint that are progression-free, making up the 'progression-free' health state
- The difference between the OS and PFS curve at any timepoint represents the proportion of patients that are still alive, but not progression-free, thus making up the 'progressed' health state

Both larotrectinib and the chosen comparator arm(s) of the model follow the same health states (44).

Larotrectinib

As mentioned, the model structure includes the following health states: progression-free, progressive disease (PD), and death (44) (

Figure 3).

Figure 3 Illustration of partitioned survival model structure

Comparator arm

The comparator arm was also represented by the same 3 health states assigned to larotrectinib patients (

Figure 3). However, in the model, it is possible to choose different comparators. In the base case used for this analysis, the comparator selected is SoC (FLATIRON as provided by Bokemeyer et al.) (6).

Alternatively, the comparator can also be chosen to present a comparator arm stratified by tumour site reflecting clinical practice (using the tumour site location distribution presented in Table 8). Using this option, the comparator arm of the economic model is stratified into 12 model engines reflecting the tumour sites enrolled in the larotrectinib clinical trial programme (providing a weighting of the site distribution). Each considers the health outcomes, quality-of-life and costs of patients currently treated in the absence of larotrectinib. It is from these populations and comparators that the eligible larotrectinib population will be drawn. In this sense each tumour site enrolled in the clinical trial programme has its own control reflecting conventional practice (44). Each of the comparator engines independently generates its own results (health outcomes, utilities and costs) for a given tumour-site. These results are weighted based on the number of patients enrolled into the larotrectinib trial to form a balanced control (contributions of each comparator engine are presented in Table 8). Once weighted, the pooled results of the comparator arm can be assessed versus the outcomes derived from the larotrectinib arm of the model and an incremental analysis can be performed

It is noteworthy to mention, that the chosen comparator, SoC (Bokemeyer et al.) only informs OS. Therefore, for modelling purposes regarding HRQoL and cost input (and response data), the tumour site specific inputs has been used to inform the SoC arm (due to data limitations). Again, by using the tumour site location distribution presented in Table 8, a weighted average for e.g. HRQoL in PF and PD health state has been undertaken. A detailed extrapolation approach will be outlined later in the submission. The model structure for this optional comparator arm stratified by 12 tumour locations can be found in Appendix N. Please, also refer to Appendix O for further information regarding tumour-site specific inputs (clinical and health economic).

Table 8 presents the larotrectinib patient population by patient per tumour site enrolled into the clinical trial programme.

Table 8 Tumour site weightings in the economic model

Tumour-site groupings in CEM	Patients per tumour site	Calculated contribution of each comparator engine (rebased to 100%)
STS*	N/A	N/A
GIST	5	2%
Non-GIST	48	17%
Paediatrics *Incl. 2 CMN and 1 lip fibromatosis*	27	9%
IFS	49	17%
NSCLC**	32	11%
Salivary	27	9%

Melanoma	11	4%
Colorectal	25	9%
Colon	24	N/A
Rectal	1	N/A
Thyroid[a]	31	11%
Breast[b]	15	5%
Appendix	1	N/A
Bone sarcoma	3	1%
Cholangiocarcinoma	4	1%
Pancreatic	7	2%
Prostate	2	N/A
Cervix	2	N/A
Cancer of unknown primary	2	N/A
Gastric	3	N/A
Hepatic	1	N/A
External auditory canal	1	N/A
Uterus	1	N/A
Oesophageal	2	N/A
Oesophageal	1	N/A
Thymus	1	N/A
Duodenal	1	N/A
Testes	1	N/A
Thymus	1	N/A
Urothelial	1	N/A
Total	**302**	**100%**

Abbreviations: CEM, cost-effectiveness model; STS, soft tissue sarcoma; IFS, infantile fibrosarcoma; GIST, gastrointestinal stromal tumour; NSCLC, non-small cell lung cancer; CNS, central nervous system; N/A, not available / not applicable.

[a] For the inclusion of thyroid cancer, follicular and papillary thyroid cancer was considered

[b] For breast cancer, 9 patients (3%) has non-secretory breast cancer and 6 patients (2%) had secretory breast cancer.

*from the ePAS8, 72 in total with STS. Calculated using the proportion of paediatric and adults to get the numbers for non-GIST and paediatric STS (plus 2 CNM and one lipofibromastosis)

**assumed lung cancer

Sources: Bayer 2024, table 9-2.

4.2 Model features

The features of the economic model are presented in Table 9.

Table 9 Features of the economic model

Model features	Description	Justification
Patient population	Patients with NTRK cancers	According to EMA indication
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	A lifetime horizon is used in the economic model. For model engines considering adult patients only this was determined to be 40 years, for paediatric populations and pooled populations (adult and paediatric patients) this was determined to be 80 years	To capture all health benefits and costs in line with DMC guidelines. Based on mean age at diagnosis in the Danish adult population (37 years).

Model features	Description	Justification
Cycle length	7 days	Selected to accommodate the evidence sources used in the model where treatment and assessment of outcomes regularly occur over a set number of weeks.
Half-cycle correction	Yes	To account for costs and benefits which can occur any time during the cycle.
Discount rate	3.5 %	According to DMC guidelines
Intervention	Larotrectinib	Weighted OS and PFS data (ePAS8, DCO 20 July 2023) (using the MAIC weights from Bokemeyer et al, refer to Section 7 and Section 8) Other relevant data from ePAS8 than OS and PFS will be presented as unweighted in the model. Drug dose per day: 191.72 mg (adults); 134.48 mg (paediatric)
Comparator(s)	Licensed and recommended treatments for the indications (Denmark)	According to national treatment guideline. However, in absence of NTRK fusion positive specific guidelines, the comparator has been considered to follow the tumour-site specific clinical practice.
Outcomes	Health-related: LYs, QALYs, Costs: Total and incremental costs ICER	Key trial data outcomes (OS (weighted), PFS (weighted), ToT (PFS as a proxy)) are used to populate the partitioned-survival model.

Abbreviations: NTRK, neurotrophic tyrosine receptor kinase; EMA, European Medicines Agency; DMC, Danish Medicines Council; OS, overall survival; PFS, progression-free survival; ePAS, extended primary analysis set; DCO, data cut-off; MAIC, matching-adjusted indirect comparison; LYs: life years; QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; ToT: time on treatment

5. Overview of literature

5.1 Literature used for the clinical assessment

The latest available clinical SLR was conducted on 06 August 2020, the full details of which are provided in Appendix H. While our SLR encompasses studies up to 2020, we believe it remains highly relevant and valuable for this resubmission. Although the 12-month limit is acknowledged, significant gaps or shifts in the field have not been identified that would undermine the review's findings. However, the submission will be supplemented with later published data to inform both the larotrectinib and SoC arm. The aim of the clinical SLR (2020) was to gather comprehensive clinical information (clinical efficacy, real-world effectiveness, and safety outcomes) for patients with NTRK fusion-positive solid tumours who are treated with NTRK-fusion-targeted therapies. However, because of a later DCO including the ePAS8 (20 July 2023), the clinical efficacy of larotrectinib will be informed by latest available data from the larotrectinib trials. For the comparator, SoC, the clinical efficacy is informed by the publication by Bokemeyer et al. (2023) (6). To date, this publication is considered the only paper which provides the most robust data on NTRK fusion patients on SoC (with the exception of Santi et al. (2024) (45) which was captured in an updated SLR conducted, however, only reported in an unpublished MAIC analysis

conducted by Bayer). Santi et al (2024) does not demonstrate a significant difference to Bokemeyer et al (2023) (46).

However, in a SLR reported by Lassen et al (2023) (26) that follows the search strategy outlined in Appendix L, 3 studies were identified as a source to validate and represent the efficacy of SoC in terms of chemotherapy.

Additionally, a real-world evidence study (VICTORIA study) (47) was conducted to describe and compare OS in adult patients with solid tumours harbouring TRK fusion who received SoC in the real-world setting with patients who received larotrectinib in clinical trials, focusing on NSCLC, CRC, thyroid cancer, STS, and salivary gland carcinoma for the full cohort and by tumour type if sample sizes allowed. This study is considered highly relevant for validation of the efficacy outcomes validation as well as the data collection period covered 01 January 2011, and ended in June 2023, supporting the lack of an updated SLR. Please refer to Appendix M for a more detailed description of the VICTORIA study.

Table 10 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, DCO and expected DCO)	Used in comparison of*
Data on file. Unpublished data (2023): Larotrectinib Extended Pooled Analysis Set Study Summary: ePAS8 (Data Cutoff: 20 July 2023) (4)	LOXO-TRK-14001 SCOUT; LOXO-TRK-15003 NAVIGATE; LOXO-TRK-15002	NCT02122913 NCT02637687 NCT02576431	Start: 04 May 2014 (LOXO-TRK-14001); 16 December 2015 (LOXO-TRK-15003); 30 September 2015 (LOXO-TRK-15002) / ePAS8 comprises n=302 patients: PAS (n=55) plus 247 patients who subsequently started study treatment by 19 January 2023. Completion: 09 April 2021 (LOXO-TRK-14001); 30 September 2026 (LOXO-TRK-15003); 31 October 2025 (LOXO-TRK-15002) DCO: 20 July 2023 Future DCO N/A	Larotrectinib vs. SoC for patients (adults and paediatrics) with NTRK+ fusion positive solid tumours.
Full paper; Bokemeyer C, Paracha N, Lassen U, Italiano A, Sullivan SD, Marian M, Brega N, Garcia-Foncillas J. Survival Outcomes of Patients With Tropomyosin Receptor Kinase Fusion-Positive Cancer Receiving Larotrectinib Versus SoC: A Matching-Adjusted Indirect Comparison Using Real-World Data. JCO Precis Oncol. 2023 Jan 7. (6)	N/A	N/A	Flatiron/FMI patient data (January 2011 to December 2019)	Larotrectinib vs. SoC for patients (adults and paediatrics) with NTRK+ fusion positive solid tumours. To inform OS for SoC, informed by the FLATIRON registry, reported by Bokemeyer et al. 2023.

Abbreviations: NTC, National Clinical Trial; N/A, not available / not applicable; NTRK, Neurotrophic tyrosine receptor kinase; OS, overall survival; SoC, standard of care; FMI, Foundation Medicine Inc.

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

The HRQoL SLR was conducted together with the clinical SLR. The latest available clinical SLR was conducted on 06 August 2020, the full details of which are provided in Appendix I. The aim of the HRQoL SLR (2020) was to gather comprehensive utility information (HRQoL and health state utility data) for patients with NTRK fusion-positive solid tumours. HRQoL data from the larotrectinib clinical trials (LOXO-TRK-15002 and LOXO-TRK-15003) were available (DCO = July 2021, ePAS6). These data were used in a mapping exercise to generate utilities for larotrectinib in the base case cost-effectiveness analysis. For this submission, the chosen comparator has no information regarding HRQoL. Therefore, the comparator-specific utility values were taken

from the following sources shown in Table 11 below (utilizing the SLR[i] conducted in 2020 and in previous SLR submitted to National Institute for Health and Care Excellence (NICE)).

Table 11 Relevant literature included for (documentation of) health-related quality of life

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
NSCLC: National Institute for Health and Care Excellence (NICE). Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy [TA502]. NICE; 2018., Committee papers from 03 August 2017 (p. 257) (48)	Weighted average of tumour-specific health utilities for progression-free and PD.	Weighted average of tumour-specific health utilities Refer to Section 10 and Appendix O.2.
Salivary: Liberato N, Rognoni C, Rubrichi S, Quaglini S, Marchetti M, Gorlia T, et al. Adding docetaxel to cisplatin and fluorouracil in patients with unresectable head and neck cancer: a cost–utility analysis. Annals of oncology. 2012;23(7):1825-32. (49)		
Melanoma: NICE. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab TA357 (50)		
Colorectal: NICE. Trifluridine–tipiracil for previously treated metastatic colorectal cancer [TAK405]. NICE; 2016. Committee papers from 22 July 2016 (p. 398) (51) / Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013;381(9863):303-12.(52)		
GIST: NICE. Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [TA488]. 2017., committee papers from 22 July 2016 (p. 237) (53) / Poole CD, Connolly MP, Chang J, Currie CJ. Health utility of patients with advanced gastrointestinal stromal tumors (GIST)		

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
after failure of imatinib and sunitinib: findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer. 2015;18(3):627-34.(54)		
Non-GIST: NICE. Trabectedin for the treatment of advanced soft tissue sarcoma [TA185]. NICE; 2010. Manufacturer's submission from 29 June 2009 (p. 75) (55) / Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health and quality of life outcomes. 2008;6:1-15.(56)		
STS (paediatrics): Zuluaga-Sanchez S, Hess LM, Wolowacz SE, D'Yachkova Y, Hawe E, Vickers AD, et al. Cost-Effectiveness of Olaratumab in Combination with Doxorubicin for Patients with Soft Tissue Sarcoma in the United States. Sarcoma. 2018;2018:6703963 (57) / Delea T, Amdahl J, Nakhaipour H, Manson S, Wang A, Fedor N, et al. Cost-effectiveness of pazopanib in advanced soft-tissue sarcoma in Canada. Current Oncology. 2014;21(6):e748. (58)		
Breast: NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens [TA423]. 2016. Committee papers from from 03 November 2016 (p. 456 / 33) (59) /Kaufman PA, Awada A, Twelves C, Yelle L, Perez EA, Velikova G, et al. Phase III open-label randomized study of eribulin mesylate versus capecitabine in patients with locally advanced or metastatic breast cancer previously treated with an anthracycline and a taxane. J Clin Oncol. 2015;33(6):594-601. (60) / Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state		

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
utilities for metastatic breast cancer. Br J Cancer. 2006; 95:683-90 (61)		
Glioma: NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) [TA23]. NICE; 2001. HTA report from 27 April 2001 (p. 33) (59).		
Pancreas: NICE. Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine [TA440]. NICE; 2017. Committee papers from 12 April 2017 (p. 390). (62)		
Thyroid follicular and papillary: NICE. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Committee papers, Table 39 (63)		
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health and quality of life outcomes. 2008;6:1-15 (56)	Adverse reaction disutilities	Utility decrements reported for the same tumour site were preferred over use of utility decrements from other tumour site or making assumption for event proxies. Refer to Section 10
ICER. Ovarian Cancer. An assessment of poly ADP-ribose polymerase (PARP) inhibitors. 2017.(64)		
Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010;8:50.(65)		
Tabberer M, Stamuli E, Walker M, Summerhayes M, Lees M. PCN74 UTILITIES ASSOCIATED WITH NON-SMALL CELL LUNG CANCER (NSCLC): A COMMUNITY STUDY. Value in Health. 2006;9(6):A298.(66)		
Doyle N. Cancer survivorship: evolutionary concept analysis. Journal of advanced nursing. 2008;62(4):499-509. (67);		
Lane S, Levy AR, Mukherjee J, Sambrook J, Tildesley H. The impact on utilities of differences in body		

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
weight among Canadian patients with type 2 diabetes. Curr Med Res Opin. 2014;30(7):1267-73. (68)		

Abbreviations: NSCLC= non-small cell lung cancer; NICE= National Institute for Health and Care Excellence; TA= technology appraisal; GIST= gastrointestinal stromal tumour; ICER= incremental cost-effectiveness ratio; PD, progressive disease

5.3 Literature used for inputs for the health economic model

The economic SLR was conducted together with the clinical SLR. The latest available clinical SLR was conducted on 06 August 2020, the full details of which are provided in Appendix J. There are no published estimates of healthcare resource use for the patients with TRK Fusion cancer. Given the lack of UK clinical experience outside of a clinical trial setting for treatments for TRK-Fusion cancer (and histology independent treatments in general), primary research would have not been able to adequately inform health care resource use for the population enrolled in the trial. Health state costs for larotrectinib were assumed equal to the weighted average of the comparator's costs, using the tumour site distribution in the larotrectinib clinical trial. This approach was validated by UK clinicians interviewed as part of the clinical validation. All clinicians interviewed considered this an appropriate assumption given the data available, and expected this would likely be conservative, and overestimate health care resource use for larotrectinib. For the comparator arm, as per the other model inputs, healthcare resource use was modelled independently for each tumour site. Where a NICE TA was available, the approach selected was to use the healthcare resource utilization (HCRU) inputs used to inform the Committee's preferred assumptions. Data collection for HCRU inputs for the tumour locations without a NICE TA was based on the SLR output where possible and otherwise broader targeted searches were conducted for published articles, where no evidence was found in the SLR.

Table 12 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
NSCLC: NICE. Erlotinib and gefitinib for treating non-small-cell lung cancer that has progressed after prior chemotherapy TA374 (69)	HCRU	NICE TA (committee recommendation)	Refer to Section 11.4
Salivary: National Institute for Health and Care Excellence (NICE). Nivolumab for treating squamous cell carcinoma of the head and neck after platinum-based chemotherapy [TA430]. NICE; 2017.Committee papers from 20 July 2023 (p. 201).(70)			

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Melanoma: NICE. Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma (TA268). Submission document, Table 37 (71)			
Colorectal: NICE. Trifluridine–tipiracil for previously treated metastatic colorectal cancer [TAK405]. NICE; 2016. Committee papers from 22 July 2016. (p. 194) (51)			
STS adults (GIST): GIST NICE model; NICE. Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [TA488]. 2017. Committee papers from 12 October 2017 (p. 286)/Physician survey			
STS adults (non-GIST): NICE. Trabectedin for the treatment of advanced soft tissue sarcoma [TA185]. NICE; 2010. (55) Manufactures submission from 29 June 2009 (p. 82) / Jönsson L, Justo N, Musayev A, Krishna A, Burke T, Pellissier J, et al. Cost of treatment in patients with metastatic soft tissue sarcoma who respond favourably to chemotherpy. The SArcoma treatment and Burden of Illness in North America and Europe (SABINE) study. Eur J Cancer Care (Engl). 2016;25(3):466-77. (72)			
STS paediatrics: Amdahl J, Manson SC, Isbell R, Chit A, Diaz J, Lewis L, et al. Cost-effectiveness of pazopanib in advanced soft tissue sarcoma in the United kingdom. Sarcoma. 2014;2014:481071.(73)			
Breast: NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens [TA423]. 2016. Committee papers from 03 November 20216 (p. 223) (59)			

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
CNS/glioma: NICE. Guidance on the use of temozolomide for the treatment of recurrent malignant glioma (brain cancer) 26 April 2001 HTA report from (section "3. Economic analysis of temozolomide for malignant glioma") NICE TA23{National Institute for Health and Care Excellence., 2001 #84			
Pancreas: NICE. Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine [TA440]. NICE; 2017. Committee papers from 12 April 2017 (p. 176)(62)			
Thyroid: NICE. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine [TA535]. NICE; 2018.Assessment report from 15 August 2017 (p. 138) (63)			
DMC. Bilag til Medicinrådets anbefaling vedrørende larotrectinib til behandling af NTRK-fusion-positiv kræft. DMC; 2021. (23)	HCRU for larotrectinib	Suggested/preferred by the DMC	Refer to Section 11.4
N/A	HCRU: Cholangiocarcinoma	Weighted average of comparators with available data	Refer to Section 11.4
Sundhedsdatastyrrelsen. DRG-takster 2024 2024 [Available from: https://sundhedsdatastyrelsen.dk/da/afregning-og-finansiering/takster-drg/takster-2024.(74)	Adverse event costs and HCRU costs	The cost of treating an adverse event was assumed not to vary based on the patient's tumour site. This approach has been applied in previous NICE TAs, where the cost of treating AEs was based on reported costs for other tumour locations	Refer to Section 11.4 and 11.5
Sundhedsdatastyrelsen. InteraktivDRG 2024 [Available from: https://casemix360.solutions.iqvia.com/InteractiveProd.(75)			
DMC. Catalogue for unit cost v.1.7. 2023.(76)	HCRU costs	As per guidelines	Refer to Section 11.4
Laetsch TW, DuBois SG, Mascarenhas L, Turpin B, Federman N, Albert CM, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. The Lancet Oncology. 2018;19(5):705-14. (9)	Adverse event incidence rates	NICE TA (committee recommendation) and SLR/TLR	Refer to Section 9.1

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017;389(10066):255-65.(77)			
NICE. Pembrolizumab for treating advanced melanoma after disease progression with ipilimumab TA357 (50)			
Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. New England Journal of Medicine. 2015;372(20):1909-19.(78)			
Demetri GD, Reichardt P, Kang Y-K, Blay JY, Joensuu H, Schaefer KB, et al. An updated overall survival analysis with correction for protocol-planned crossover of the international, phase III, randomized, placebo-controlled trial of regorafenib in advanced gastrointestinal stromal tumors after failure of imatinib and sunitinib (GRID). Journal of Clinical Oncology. 2015;33:110. (79)			
Mascarenhas L, Lyden ER, Breitfeld PP, Walterhouse DO, Donaldson SS, Paidas CN, et al. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group. Journal of clinical oncology. 2010;28(30):4658-63.(80)			
NICE. Eribulin for treating locally advanced or metastatic breast cancer after 2 or more			

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
chemotherapy regimens (TA423). 21 December 2016; Committee papers Table 65 Page 174 of 212 (59)			
Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. New England Journal of Medicine. 2010;362(14):1273-81.(81)			
Batchelor TT, Mulholland P, Neyns B, Nabors LB, Campone M, Wick A, et al. Phase III randomized trial comparing the efficacy of cediranib as monotherapy, and in combination with lomustine, versus lomustine alone in patients with recurrent glioblastoma. J Clin Oncol. 2013;31(26):3212-8.(82)			
NICE. Pegylated liposomal irinotecan for treating pancreatic cancer after gemcitabine (TA440). 26 April 2017. Committee papers page 32, Issue 19 (62)			
BAYER. Individual Patient Data. Efficacy analysis set, ePAS8 [data on file]. 2024.(5)			

Abbreviations: NSCLC= non-small cell lung cancer; STS= soft tissue sarcoma; CNS= central nervous system; NICE= National Institute for Health and Care Excellence; TA= technology appraisal; GIST= gastrointestinal stromal tumour; ICER= incremental cost-effectiveness ratio; DMC= danish medicines council; N/A= not applicable; DRG= diagnosis-related group; HCRU= health care resource use; SLR= systematic literature review; TLR= targeted literature review;.

6. Efficacy

6.1 Efficacy of larotrectinib compared to SoC for patients with NTRK+ solid tumours

6.1.1 Relevant studies

Individual patient data (IPD) for adult and paediatric patients harbouring TRK fusion-positive tumours from larotrectinib trials (LOXO-TRK-1400, SCOUT, and NAVIGATE; data cutoff: July 2023) (pooled Analysis Set Study Summary: ePAS8 (DCO: July 2023) describes the efficacy of larotrectinib in patients with NTRK fusion solid tumours at a median follow-up time of 40 months (IRC assessed). The pooled analysis dataset ePAS8 was based on 302 patients (patients eligible for extended primary analysis set who were enrolled 6 months before the July 2023 data cutoff) who were enrolled across the 3 larotrectinib studies and met the following criteria: had a documented *NTRK* gene fusion as determined by local testing, had a non-CNS primary tumour that could be assessed according to RECIST, version 1.1, and had received 1 or more doses of larotrectinib. Analyses were conducted using the intention-to-treat (ITT) approach.

A MAIC was used to facilitate a cross-trial comparison of the OS of larotrectinib vs non-TRK inhibitor-based SoC reported by Bokemeyer et al. (2023). In the MAIC performed by Bokemeyer et al. (2023), IPD for adult and paediatric patients harbouring TRK fusion-positive tumours from larotrectinib trials (LOXO-TRK-1400, SCOUT, and NAVIGATE; data cutoff: July 2020) and aggregate real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron/Foundation Medicine database were used. The key inclusion criteria for patients in the aggregate real-world data SoC comparator cohort included locally advanced or metastatic diagnosis from January 2011 to December 2019, no prior treatment with a TRK inhibitor, ≥1 test by NGS on tumour tissue and ≥1 NTRK fusion-positive test result, no visit gap of >90 days after diagnosis, and no prior unlabelled study drug as part of a clinical trial (6). Since a later DCO is now available (July 2023), the weights derived from the MAIC has been applied to the ePAS8 data. The larotrectinib trials and Bokemeyer et al. are presented below in Table 13.

As mentioned, only a comparison of OS of larotrectinib vs SoC reported by Bokemeyer could be conducted. To inform PFS for the comparator arm, please refer to Section 8. In the absence of disease response rate for the comparator arm, response data for tumour-site specific locations can be found in Appendix O.1. This has been used to inform the response data for SoC using the weight of tumour-site specific cancers observed in the larotrectinib trials (presented in Table 8).

Table 13 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
LOXO-TRK-14001, NCT02122913 Data on File. ISE 275-7556. Bayer Healthcare Pharmaceuticals, Inc. July 2023 (83)	Phase 1, dose escalation, multicentre, open-label and single-arm	Start in May 2014 & DCO 20 July 2024	Adult patients with advanced solid tumours (including both TRK fusion-positive and fusion-negative	Larotrectinib, a dose of 50 mg once daily to 200 mg twice daily.	N/A	The primary endpoint for efficacy analyses was ORR (DCO 20 July 2023). Duration of response (DCO 20 July 2023), safety (DCO 20 July 2023), OS (DCO 20 July 2023) and PFS (DCO 20 July 2023) were included as secondary endpoints. QoL was included as an exploratory endpoint (DCO: ePAS6 2021). Tumour responses were assessed by using RANO or RECIST v1.1 criteria.
SCOUT, NCT02637687 Data on File. ISE 275-7556. Bayer Healthcare Pharmaceuticals, Inc. July 2023 (83)	Phase 1 / 2, multicentre, open-label and single-arm	Start in December 2015 & Study Completion Date in August 2027. DCO 20 July 2024	Paediatric patients with advanced solid tumours*	Larotrectinib, a dose up to 100 mg/m^2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution), the maximum dose is 100 mg per dose	N/A	The primary endpoint for efficacy analyses was ORR. Duration of response, safety, OS and PFS were included as secondary endpoints. QoL was included as an exploratory endpoint (PRO data from ePAS6, DCO July 2021). Tumour responses were assessed by using RANO or RECIST v1.1 criteria. ePAS8 (DCO 20 July 2023).
NAVIGATE, NCT02576431 Data on File. ISE 275-7556. Bayer Healthcare Pharmaceuticals, Inc. July 2023 (83)	Phase 2, multicentre, open-label	Start in September 2015 & Study Completion Date in September	Only adolescent and adult patients with tumours	Larotrectinib, a dose of 100 mg twice daily (25 mg, 100 mg capsules	N/A	The primary endpoint for efficacy analyses was ORR. Duration of response, safety, OS and PFS were included as

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	and single-arm	2025. DCO 20 July 2024	harbouring a documented NTRK gene fusion	or 20 mg/mL oral solution).		secondary endpoints. QoL was included as an exploratory endpoint (PRO data from ePAS6, DCO July 2021). Tumour responses were assessed by using RANO or RECIST v1.1 criteria. ePAS8 (DCO 20 July 2023).
Bokemeyer et al. (2023) (6) Bokemeyer C, Paracha N, Lassen U, Italiano A, Sullivan SD, Marian M, Brega N, Garcia-Foncillas J. Survival Outcomes of Patients With Tropomyosin Receptor Kinase Fusion-Positive Cancer Receiving Larotrectinib Versus SoC: A Matching-Adjusted Indirect Comparison Using Real-World Data. JCO Precis Oncol. 2023 Jan;7:e2200436. doi: 10.1200/PO.22.00436. PMID: 36689698; PMCID: PMC9928633.	MAIC using aggregate real-world data identified in the Flatiron/Foundation Medicine databased.	Published in 2023. The key inclusion criteria for patients in the aggregate real-world data SoC comparator cohort included locally advanced or metastatic diagnosis from January 2011 to December 2019	Patients with locally advanced/metastatic TRK fusion-positive cancer	N/A	N/A	The outcome of interest was OS (DCO: July 2020).

Abbreviations: MAIC, matching-adjusted indirect comparison; NTC, National Clinical Trial; SoC, standard of care; OS, overall survival; TRK, tropomyosin receptor kinase; NTRK, neurotrophic tyrosine receptor kinase; PFS, progression-free survival; QoL, quality of life; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria in Solid Tumours; ORR, overall response rate; N/A, not available / not applicable; ePAS, extended primary analysis set, DCO, data cut-off

*It should be noted that the phase 2 enrollment of the pediatric study (SCOUT) also included only patients with tumours harboring a documented NTRK gene fusion; however, these patients were assigned to a cohort based on tumour location (intracranial vs extracranial)

Notes: All patients recruited after the initial 55 fulfilling the definition of PAS were included in one of the extended primary analysis sets (ePASx) that are defined per data cut-off (for further definition of analysis sets and timing of data cut-offs. For this submission, ePAS8 = 20 July 2023

6.1.2 Comparability of studies

Reported by Bokemeyer et al., selecting a comparator to represent the SoC population, the Flatiron/FMI analysis by Hibar et al/Demetri et al was chosen because, as a US-wide longitudinal database of health care practice data, it provided a vast amount of information on baseline characteristics, as well as aligned on the index date with that used in the larotrectinib studies.

Reported in the original MAIC, by Bokemeyer et al., matching was performed on the following variables: NTRK1, age, Eastern Cooperative Oncology Group performance status (ECOG PS), prior lines of systemic therapy, disease stage, brain metastases, and tumour type (uterine, biliary, stomach, endometrial, cancer of unknown primary, breast, salivary gland, NSCLC, STS, and CRC) (6). Reported by Bokemeyer et al. Two analyses were conducted after matching. The first was conducted to validate the performance of matching, that is, if matching were performed adequately, then the two groups will be similar in the pretreatment survival period, defined as the time from locally advanced/metastatic disease diagnosis (index date) to larotrectinib initiation (refer to Figure 4). The second was to estimate the treatment effect of larotrectinib versus SoC on OS (defined as the time from index date to death).

Figure 4 Pretreatment survival for the log-rank test

To accommodate the difference in TRK inhibitor use between cohorts (i.e., SoC excluding TRK inhibitors in Flatiron/FMI v larotrectinib studies), the effect of larotrectinib was nullified by readjusting the survival time such that it would reflect the time period between the index date and the date of larotrectinib initiation. Using a log-rank test to validate the performance of matching this pretreatment survival suggested no difference between the two groups (P = .31) (6).

6.1.2.1 Comparability of patients across studies

Table 14 presents baseline characteristics of patients included in ePAS8 (pooled analysis), and patients included in the publication by Bokemeyer et al. 2023 (representing SoC). Overall, the baseline characteristics across different studies are similar. However, some differences appear. For instance, 21% are ≥65 years old in ePAS8, while 39.3% are ≥65 years old in the flatiron/FMI as reported group and 29.4% in the larotrectinib before matching group. Patients in ePAS8 and in the larotrectinib before matching group have a similar ECOG PS, e.g., 88% and in 87.1% with a ECOG PS of 0-1, respectively, while 50% of patients in the flatiron/FMI as reported group has a ECOG PS of 0-1. Although for 42.9% in the flatiron/FMI as reported group, the ECOG PS is unknown. Further, a similar share of patients in ePAS8 and in the larotrectinib before matching group are NTRK1 positive (45% and 42.4%, respectively), while 82.0% are NTRK1 positive in the flatiron/FMI as reported group. Internally, in Bokemeyer et al. 2023, differences were accounted for by matching (creating the flatiron/FMI adjusted group and the larotrectinib after matching group) (6). In this submission, the differences that were adjusted for in the MAIC by Bokemeyer et al were assumed to transferable to be used in a MAIC re-weighting analysis (please see section 7 and Appendix C).

Table 14 Baseline characteristics of patients in ePAS8 (pooled analysis, DCO 20 July 2023) and before and after matching of larotrectinib efficacy population and Hibar et al./Demetri et al./Flatiron/ FMI database (reported by Bokemeyer et al. 2023 (larotrectinib DCO: ePAS5 2020))

	ePAS8 (pooled analysis)	Hibar et al./Demetri et al./Flatiron/FMI database (reported by Bokemeyer et al. 2023)			
	Larotrectinib (n= 302)	Flatiron/FMI, As Reported (N = 28)	Larotrectinib, Before Matching (N = 85)	Flatiron/FMI, Adjusted (N = 28)	Larotrectinib, After Matching (N = 85[‡])
Age, median (range), years	44.0 (0-90)	N/A	N/A	N/A	N/A
Age, ≥65 years, %	N/A	39.3	29.4	39.3	39.3
Age, distribution, n (%)					
<1 month	2 (<1)	N/A	N/A	N/A	N/A
1 month to <1 year	33 (11)	N/A	N/A	N/A	N/A
1 to <2 years	8 (3)	N/A	N/A	N/A	N/A
2 to <6 years	20 (7)	N/A	N/A	N/A	N/A
6 to <12 years	19 (6)	N/A	N/A	N/A	N/A
12 to <16 years	12 (4)	N/A	N/A	N/A	N/A
16 to <18 years	5 (2)	N/A	N/A	N/A	N/A
18 to <45 years	53 (18)	N/A	N/A	N/A	N/A
45 to <65 years	87 (29)	N/A	N/A	N/A	N/A
65 to <75 years	43 (14)	N/A	N/A	N/A	N/A
≥75 years	20 (7)	N/A	N/A	N/A	N/A
Male, n (%)	143 (47)	N/A	N/A	N/A	N/A
No history of smoking, %	N/A	57.1	N/A	57.1	Not matched
ECOG PS score, n (%)					
0	149 (49)[a]	N/A	N/A	N/A	N/A
1	117 (39)[a]	N/A	N/A	N/A	N/A
2	29 (10)[a]	N/A	N/A	N/A	N/A
3	7 (2)[a]	N/A	N/A	N/A	N/A
Grouped ECOG PS score, %					
0-1	N/A	50.0	87.1	50.0	50.0
2-4	N/A	7.1	12.9	50.0[Ω]	50.0
Unknown	N/A	42.9	—	—	—
Prior cancer treatments, n (%)					
Surgery	213 (71)	N/A	N/A	N/A	N/A

	ePAS8 (pooled analysis)	Hibar et al./Demetri et al./Flatiron/FMI database (reported by Bokemeyer et al. 2023)			
	Larotrectinib (n= 302)	Flatiron/FMI, As Reported (N = 28)	Larotrectinib, Before Matching (N = 85)	Flatiron/FMI, Adjusted (N = 28)	Larotrectinib, After Matching (N = 85‡)
Radiotherapy	113 (37)	N/A	N/A	N/A	N/A
Systemic therapy	213 (71)	N/A	N/A	N/A	N/A
No. of previous systemic regimens, n (%)					
0	80 (26)	N/A	N/A	N/A	N/A
1	83 (27)	N/A	N/A	N/A	N/A
2	63 (21)	N/A	N/A	N/A	N/A
≥3	76 (25)	N/A	N/A	N/A	N/A
No. of lines of therapy since diagnosis, %					
0-2	N/A	71.4	77.7	71.4	71.4
≥3	N/A	10.7	22.4	28.6Ω	28.6
Unknown	N/A	17.9	-	-	-
Tumour type, n (%)					
STS	72 (24)	(21.0)	(22.4)	(21.0)	(21.0)
Infantile fibrosarcoma	49 (16)	N/A	N/A	N/A	N/A
Lung	32 (11)	N/A	N/A	N/A	N/A
NSCLC	N/A	(18.0)	(12.9)	(18.0)	(18.0)
Thyroid	31 (10)[b]	N/A	N/A	N/A	N/A
Salivary gland	27 (9)	(7.0)	(21.2)	(7.0)	(7.0)
Colon	24 (8)	N/A	N/A	N/A	N/A
Colorectal	N/A	(32.0)	(5.9)	(32.0)	(32.0)
Breast	15 (5)[c]	(4.0)	(1.2)	(4.0)	(4.0)
Melanoma	11 (4)	N/A	N/A	N/A	N/A
Pancreatic	7 (2)	N/A	N/A	N/A	N/A
Gastrointestinal stromal tumour	5 (2)	N/A	N/A	N/A	N/A
Cholangiocarcinoma	4 (1)	N/A	N/A	N/A	N/A
Bone sarcoma	3 (<1)	N/A	N/A	N/A	N/A
Gastric/stomach	3 (<1)	(4.0)	N/A	(4.0)	—

	ePAS8 (pooled analysis)	Hibar et al./Demetri et al./Flatiron/FMI database (reported by Bokemeyer et al. 2023)			
	Larotrectinib (n= 302)	Flatiron/FMI, As Reported (N = 28)	Larotrectinib, Before Matching (N = 85)	Flatiron/FMI, Adjusted (N = 28)	Larotrectinib, After Matching (N = 85‡)
Congenital mesoblastic nephroma	2 (<1)	N/A	N/A	N/A	N/A
Cancer/carcinoma of unknown primary	2 (<1)	(4.0)	(1.2)	(4.0)	(4.0)
Prostate	2 (<1)	N/A	N/A	N/A	N/A
Cervix	2 (<1)	N/A	N/A	N/A	N/A
Appendix tumour	1 (<1)	N/A	N/A	N/A	N/A
Hepatic	1 (<1)	N/A	N/A	N/A	N/A
Rectal	1 (<1)	N/A	N/A	N/A	N/A
External auditory canal	1 (<1)	N/A	N/A	N/A	N/A
Uterus	1 (<1)	(4.0)	N/A	(4.0)	—
Endometrial	N/A	(4.0)	N/A	(4.0)	—
Oesophageal	1 (<1)	N/A	N/A	N/A	N/A
Duodenal	1 (<1)	N/A	N/A	N/A	N/A
Thymus	1 (<1)	N/A	N/A	N/A	N/A
Lipofibromatosis	1 (<1)	N/A	N/A	N/A	N/A
Testes	1 (<1)	N/A	N/A	N/A	N/A
Urothelial	1 (<1)	N/A	N/A	N/A	N/A
Biliary	N/A	(4.0)	N/A	(4.0)	—
Metastatic disease at enrolment, n (%)					
No	81 (27)	N/A	N/A	N/A	N/A
Yes	221 (73)	N/A	N/A	N/A	N/A
Stage at initial diagnosis, %					
0-II	N/A	17.9	20.0	17.9	17.9
III-IV	N/A	64.3	61.2	64.3	64.3
Unknown	N/A	17.9	—	17.9	—
Brain metastases, %					
Yes	N/A	17.9	9.4	17.9	17.9
No or unknown	N/A	82.1	90.6	82.1	82.1

	ePAS8 (pooled analysis)	Hibar et al./Demetri et al./Flatiron/FMI database (reported by Bokemeyer et al. 2023)			
	Larotrectinib (n= 302)	Flatiron/FMI, As Reported (N = 28)	Larotrectinib, Before Matching (N = 85)	Flatiron/FMI, Adjusted (N = 28)	Larotrectinib, After Matching (N = 85‡)
NTRK gene, n (%)					
NTRK1	136 (45)	(82.0)	(42.4)	(82.0)	(82.0)
NTRK2	11 (4)	N/A	N/A	N/A	N/A
NTRK3	144 (48)	N/A	N/A	N/A	N/A
Inferred NTRK3[d]	11 (4)	N/A	N/A	N/A	N/A

Abbreviations: DCO, data cut-off; ECOG PS, Eastern Cooperative Oncology Group performance status; ePAS, extended primary analysis set; FMI, Foundation Medicine Inc.; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; N/A, not available / not applicable; —, not explicitly matched

[a] This ECOG PS score included all patients in the ePAS8 (N=302), including both pediatric and adult patients. For pediatric patients, Karnofsky or Lansky scores for pediatric patients were mapped to ECOG PS score for this integrated analysis. b For thyroid cancer, 24 patients (8%) had differentiated thyroid cancer and 7 patients (2%) had non-differentiated thyroid cancer. c For breast cancer, 9 patients (3%) has non-secretory breast cancer and 6 patients (2%) had secretory breast cancer.

d For infantile fibrosarcoma, congenital mesoblastic nephroma, and secretory breast cancer, patients with either an erythroblast transformation specific variant transcription factor 6 gene (ETV6) rearrangement or NTRK3 rearrangement are considered as inferred ETV6-NTRK3 fusion/inferred NTRK3 fusion based on the known incidence of the alteration in this patient population (Bourgeois 2000; Rubin 1998). ǂ Effective sample size = 13.14.

[Ω] Imputed missing value.

Sources: Bayer 2024, table 3-8, table 3-9, and table 3-10 (4); Bokemeyer et al. 2023, table 2 (6).

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

It is expected that the study population from larotrectinib trials will be very similar to patients seen in Danish clinical practice for NTRK fusion positive solid tumour patients. According to the available DMC guidelines, no precise patient characteristics has been provided for the specific mutation. However, from the previous larotrectinib submission, the DMC stated that 2/3 of all cancer cases are seen in patients over 60 years.

Table 15 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population ((23))	Value used in health economic model (ePAS8 data)
Age	60	39**
Gender	N/A*	50%

Abbreviations: N/A, not available / not applicable
*from latest DMC larotrectinib assessment "slightly more men than females", however, no estimates/proportion available.
** mixed adults and children population age, from trial.

6.1.4 Efficacy – results per ePAS8 (pooled analysis)

ITT population

The number and proportion of patients that discontinued the study in the different treatment arms and the primary reason for discontinuation are presented in Table 16.

Table 16 Discontinuation in ePAS8 (pooled analysis, DCO: 20 July 2023)

	ePAS8 N=302
Discontinuation of study treatment, n (%) [a]	207 (69)
Death	11 (4)
Protocol violation	2 (<1)
PD	118 (39)
Physician decision	14 (5)
AE	14 (5)
Patient decision	14 (5)
Withdrew consent	3 (<1)
Non-compliance	1 (<1)
Other	30 (10)

Abbreviations: AE, adverse event; DCO, data cut-off: ePAS, extended primary analysis set; PD, progressive disease
Notes: [a] Patients in Study 20290 who were in wait-and-see are considered ongoing.
Source: Bayer, 2024, table 3-6 (4).

6.1.4.1 Overall response

OR results are presented in Table 17. The ORR for the ePAS8 by IRC assessment was 65% (95% CI: 59, 70). The ORR by IRC assessment and Investigator assessment was consistent with those by IRC assessment.

Table 17 Overall response in ePAS8 (pooled analysis set, DCO: 20 July 2023)

	ePAS8 N=302
IRC assessment: Best OR, n (%)	
Any CR	82 (27)
CR	65 (22)
pCR Ω	17 (6)
PR	113 (37)
SD	55 (18)
less than 16 weeks	17 (6)
16 weeks or more	38 (13)
less than 24 weeks	27 (9)

24 weeks or more	28 (9)
IRC assessment: OR ǂ	
Number of patients with OR (confirmed CR/pCR/PR)	195
ORR, % (95% CI)	65 (59, 70)
Investigator assessment: Best OR, n (%)	
Any CR	58 (19)
CR, confirmed	48 (16)
pCR Ω	10 (3)
PR, confirmed	135 (45)
PR, pending confirmation	2 (1)
SD	69 (23)
less than 16 weeks	21 (7)
16 weeks or more	48 (16)
less than 24 weeks	38 (13)
24 weeks or more	31 (10)
Investigator assessment: OR ǂ	
Number of patients with OR (confirmed CR/pCR/PR)	193
ORR, % (95% CI)	64 (58, 69)

Abbreviations: CI, confidence interval; CR, complete response; DCO, data cut-off; ePAS, extended primary analysis set; IRC, Independent Review Committee; OR, overall response; ORR, overall response rate; pCR, pathological complete response; PR, partial response; SD, stable disease.
Notes: Ω Patients on larotrectinib therapy who underwent surgical resection with no viable tumour cells and negative margins on postsurgical pathology report were considered a CR by surgery/pathology, and their pre-surgical best response was reclassified pCR after surgery. ǂ ORR is the proportion of patients with a best overall response of confirmed CR, pCR, or confirmed PR. Responses were confirmed by a repeat assessment performed no less than 28 days after the criteria for response were first met. Patients with unconfirmed CR following PR are considered confirmed responders.
Notes: *Patients 20290-102-051 and 20290-852-133 did not have repeat assessment to confirm the PR since the patients had surgery soon after the initial PR; therefore, the BOR by Investigator assessment for these patients is PR pending confirmation. The patients did not achieve a pCR*
Source: Bayer, 2024, table 3-13 (4).

6.1.4.2 Time to response

Time to response results is presented in Table 18. Median time to first response for the 195 responding patients in according to IRC assessment was 1.84 months (range: 0.89 to 22.90). Summary statistics of the time to best response were similar to those for the time to first response. Results were consistent by IRC assessment and Investigator assessment.

Table 18 Time to response in ePAS8 (pooled analysis set, DCO: 20 July 2023)

	ePAS8 N=302
IRC assessment	
Time to first response, months	
Responding patients (confirmed CR/pCR/PR)	195
Median (range)	1.84 (0.89, 22.90)
Time to best response, months	
Responding patients (confirmed CR/pCR/PR)	195
Median, range	2.33 (0.89, 35.84)
Investigator assessment	
Time to first response, months	
Responding patients (confirmed CR/pCR/PR)	193
Median, range	1.84 (0.89, 9.07)
Time to best response, months	
Responding patients (confirmed CR/pCR/PR)	193
Median, range	1.87 (0.89, 47.11)

Abbreviations: CR, complete response; DCO, data cut-off; ePAS, extended primary analysis set; IRC, Independent Review Committee; pCR, pathological complete response; PR, partial response.
Source: Bayer, 2024, table 3-15 (4).

6.1.4.3 Duration of response

Duration of response results are presented in Table 19. At the time of the DCO, 195 patients had achieved a response by IRC assessment. At a median follow-up time of 36.9 months, median DoR was 43.3 months. By IRC assessment and Investigator assessment the summary statistics for DoR were similar.

Table 19 Duration of response in ePAS8 (pooled analysis set, DCO: 20 July 2023)

	ePAS8 N=302
IRC assessment	
Responding patients (confirmed CR/pCR/PR)	195
Progressed, n (%)	77 (39)
Censored, n (%)	118 (61)
Median duration of follow-up, months [a]	36.9
Median DoR, months (95% CI) [a]	43.3 (32.9, not estimable)
Investigator assessment	
Responding patients (confirmed CR/pCR/PR)	193
Progressed, n (%)	85 (44)
Censored, n (%)	108 (56)
Median duration of follow-up, months [a]	40.0
Median DoR, months (95% CI) [a]	43.3 (29.7, 58.6)

Abbreviations: CI, confidence interval; CR, complete response; DCO, data cut-off; DoR, duration of response; ePAS, extended primary analysis set; IRC, Independent Review Committee; pCR, pathological compete response; PR, partial response.
Notes: [a] Using Kaplan-Meier method.
Source: Bayer, 2024, table 3-17 (4).

The KM plot of DoR for the ePAS8 (IRC assessment) is shown in Figure 5.

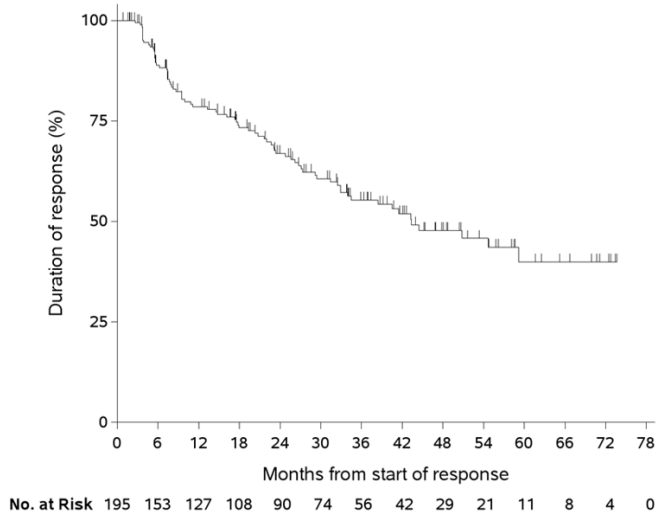


Figure 5 Kaplan-Meier Plot of Duration of Response – IRC Assessment (ePAS8)
Abbreviations: ePAS8, extended primary analysis set 8; IRC, Independent Review Committee
Note: Vertical tick marks represent the DoR for the 118 censored patients at DCO.
Source: : Bayer, 2024, figure 3-3 (4).

6.1.4.4 Progression-free survival

Progression-free survival results are presented in Table 20. At the time of the DCO, 150 patients (50%) in the ePAS8 had progressed or died and 152 (50%) were censored. At a median follow-up time of 35.9 months, median PFS was 28.1 months. Statistics for PFS based on Investigator assessment were similar to those by IRC assessment.

Table 20 Progression-free survival in ePAS8 (pooled analysis set, DCO: 20 July 2023)

	ePAS8 N=302
IRC assessment	
Progressed or died, n (%)	150 (50)
Censored, n (%)	152 (50)
Median duration of follow-up, months [a]	35.9
Median duration of PFS, months (95% CI) [a]	28.1 (19.6, 35.8)
Rate of PFS, % (95% CI) [a]	
≥6 months	75 (70, 80)
≥12 months	62 (56, 68)
≥18 months	58 (52, 64)
≥24 months	54 (48, 60)
≥36 months	43 (37, 50)
≥48 months	39 (32, 46)
≥60 months	33 (25, 40)
≥72 months	30 (22, 39)
Investigator assessment	
Progressed or died, n (%)	163 (54)
Censored, n (%)	139 (46)
Median duration of follow-up, months [a]	38.9
Median duration of PFS, months (95% CI) [a]	23.7 (16.6, 31.5)
Rate of PFS, % (95% CI) [a]	
≥6 months	73 (68 ,78)
≥12 months	61 (55, 67)
≥18 months	55 (48, 61)
≥24 months	50 (43 ,56)
≥36 months	42 (35, 48)
≥48 months	37 (30, 44)
≥60 months	31 (23, 38)
≥72 months	29 (21, 37)

Abbreviations: CI, confidence interval; DCO, data cut-off; ePAS, extended primary analysis set; IRC, Independent Review Committee; PFS, progression-free survival.
Notes: [a] Using Kaplan-Meier method.
Source: Bayer, 2024, table 3-18 (4).

The KM plot of PFS for the ePAS8 (IRC assessment) is shown in Figure 6.

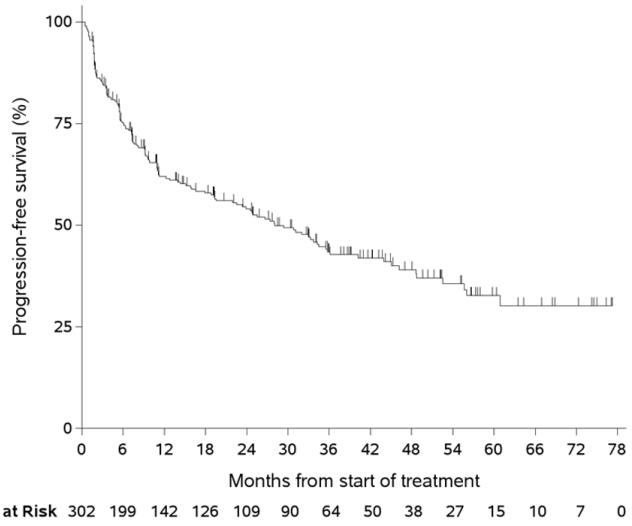


Figure 6 Kaplan-Meier plot of progression-free Survival – IRC assessment (ePAS8, DCO: 20 July 2023)

Abbreviations: DCO, data cut-off; ePAS, extended primary analysis set; IRC, Independent Review Committee.
Notes: Vertical tick marks represent the PFS times for the 152 censored patients.
Source: Bayer, 2024, figure 3-4 (4).

6.1.4.5 Overall survival

OS results are presented in Table 21. With median follow-up periods of 47.0 months in ePAS8, median OS was not yet estimable.

Table 21 Overall survival in ePAS8 (pooled analysis set, DCO: 20 July 2023)

	ePAS8 N=302
Alive/censored, n (%)	203 (67)
Dead, n (%)	99 (33)
Median duration of follow-up, months [a]	47.0
Median duration of OS, months (95% CI) [a]	Not yet estimable (63.4, not yet estimable)
Rate of OS, % (95% CI) [a]	
≥6 months	91 (88, 94)
≥12 months	83 (79, 87)
≥18 months	76 (71, 81)
≥24 months	74 (68, 79)
≥36 months	70 (64, 75)
≥48 months	64 (58, 70)
≥60 months	61 (55, 68)
≥72 months	57 (50, 65)

Abbreviations: CI, confidence interval; DCO, data cut-off; ePAS, extended primary analysis set; OS, overall survival.
Notes: [a] Using Kaplan-Meier method.
Source: Bayer, 2024, table 3-19 (4).

The KM plot of OS for the ePAS8 is shown in Figure 7.

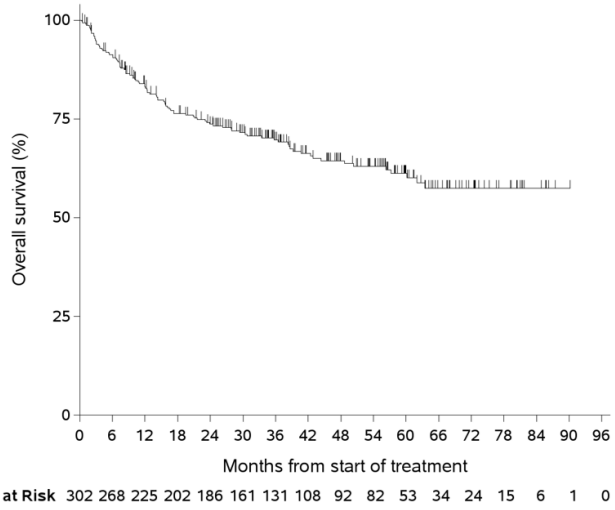


Figure 7 Kaplan-Meier plot of overall survival (ePAS8, DCO: 20 July 2023)

Abbreviations: DCO, data cut-off; ePAS, extended primary analysis set; OS, overall survival.
Notes: OS is defined as the number of months elapsed between the date of the first dose of larotrectinib and the date of death (whatever the cause). Patients who were alive or lost to follow-up as of the DCO date were right-censored. The censoring date was determined from the date the patient was last known to be alive.
Source: Bayer, 2024, figure 3-5 (4).

Upon request from the DMC, Appendix P includes tables/figures on the ePAS8 data, separately for the paediatric and adult population (DCO 20 July 2023).

6.1.5 Efficacy – results per Hibar et al./Demetri et al.

Data on discontinuation, OR results, time to response, DoR, and PFS are not available from Hibar et al./Demetri et al. (reported by Bokemeyer et al. 2023) (6). Therefore, only OS results are presented below.

6.1.5.1 Overall survival

OS results reported by Bokemeyer et al are presented in Table 22. Larotrectinib (after matching) was associated with a 78% lower risk of death (HR, 0.22; 95% CI, 0.09 to 0.52; P = .001), which corresponds to a 29.5-month median survival advantage, compared with non–TRK-inhibitor SoC.

Table 22 Overall survival in Hibar et al./Demetri et al. (reported by Bokemeyer et al. 2023) (larotrectinib DCO: ePAS5 2020)

	Flatiron/FMI (N = 28)	Larotrectinib, before matching (N = 85)	Larotrectinib, after matching (N = 85‡)
Median OS, months (95% CI)	10.2 (7.2, 14.1)	Not reached	39.7 (16.4, not estimable)
HR for larotrectinib vs. SoC (95% CI), p-value	Reference	0.09 (0.05, 0.19), P = .00	0.22 (0.09, 0.52), P = .001

Abbreviations: CI, confidence interval; DCO, data cut-off; ePAS, extended primary analysis set; FMI, Foundation Medicine Inc.; HR, hazard ratio; OS, overall survival; SoC, standard of care.
Note: HR from Cox model was used to compare the groups. ‡ Effective sample size = 13.14.
Source: Bokemeyer et al. 2023 (6).

The KM plot of OS is shown in Figure 8. In the after-weighting KM plot, the dip in larotrectinib survival at 16 months is explained by a single patient whose severe disease profile (≥ 3 lines of prior therapy, stage 3/4 disease, ECOG PS 2/4, and comorbid lung cancer with CNS metastasis) resulted in a higher assigned weight, thus amplifying the death event at 16 months.

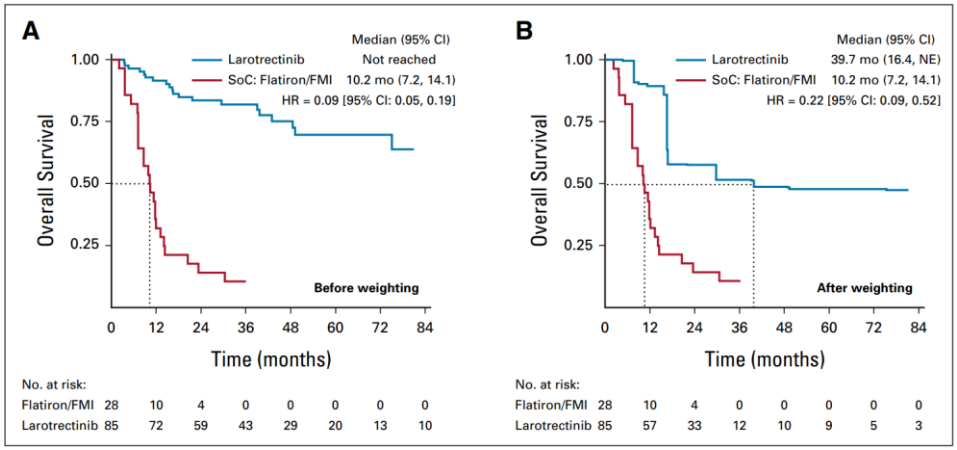


Figure 8 Kaplan-Meier curve of overall survival from time of metastatic/locally advanced diagnosis (A) before and (B) after weighting

Abbreviations: CI, confidence interval; FMI, Foundation Medicine Inc.; HR, hazard ratio; mo, months; NE, not estimable; SoC, standard of care.
Notes: Bokemeyer et al. 2023, figure 2 (6).

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

As described in Section 6.1.2, the key difference was in the baseline patient characteristics. While every effort was made to adjust for variables and the MAIC assumes that all effect modifiers are considered, the analysis was limited by small sample sizes and baseline characteristics reported in the Flatiron/Foundation Medicine database.

7.1.2 Method of synthesis

As the larotrectinib trials are single-arm trials, there is no direct head-to-head evidence to compare the clinical efficacy of larotrectinib and SoC for NTRK fusion positive solid tumours. To inform the comparative analyses between larotrectinib and SoC, a MAIC was conducted in 2023 (Bokemeyer et al. 2023) (6).

IPD from the larotrectinib trials (ePAS5 data set, DCO: July 2020) were matched to the average baseline characteristics from real-world data in the Flatiron/Foundation Medicine database based on data availability (NTRK gene, age, smoking history, ECOG PS, select tumour types, practice type, number of lines of therapy since diagnosis, stage at diagnosis, and presence of brain metastases). The outcome of interest was OS. For SoC patients with missing data, the number of lines of therapy since diagnosis and ECOG PS variables were imputed such that patients with missing values were assumed to be in the more severe categories (i.e., ≥3 lines of therapy; ECOG PS 2-4) (Bokemeyer 2023) (6).

With the availability of a more recent data cut from 2024, ePAS8 (DCO: July 2023), the ePAS8 data was matched with the MAIC weights (derived from Bokemeyer et al., where IPD data from 2020 were matched to the average baseline characteristics from Hibar et al/Demetri et al.). Hence, for this submission, a later data cut, July 2023, has been re-weighted with the MAIC derived weights informed by Bokemeyer et al (6).

The re-weighted analysis maintains the same sample size as in the original MAIC; 85 patients for larotrectinib and 28 patients for SoC (Hibar et al/Demetri et al) (effective sample size for larotrectinib after adjustment is 13.14). Although the new data cut includes additional patients, the re-weighting process constrains the analysis to the same populations previously used to preserve the comparability of the results (n=85) (6).

As mentioned, the outcomes described are OS and PFS (for SoC, only OS), both of which are based on the latest and matched ePAS8 data set. With that said, other relevant clinical inputs used for health economic modelling purposes that cannot be matched includes e.g. ORR and DoR.

7.1.2.1 Estimating weights for larotrectinib trials

Patient characteristics

A total of 192 patients from the larotrectinib trials (ePAS 5 data cutoff: July 2020) were assessed for inclusion, 85 of which met all inclusion criteria. Reported baseline characteristics for 28 patients were available for inclusion from aggregate real-world data in the Flatiron/Foundation Medicine database (Hibar et al/Demetri et al). Matching was performed on the following variables: *NTRK1*, age, ECOG PS, prior lines of systemic therapy,

disease stage, brain metastases, and tumour type (uterine, biliary, stomach, endometrial, cancer of unknown primary, breast, salivary gland, NSCLC, STS, and CRC).

Reported by Bokemeyer et al, baseline characteristics before and after matching in the primary analysis are summarized in Table 14. The weight distribution can be found in Figure 9.

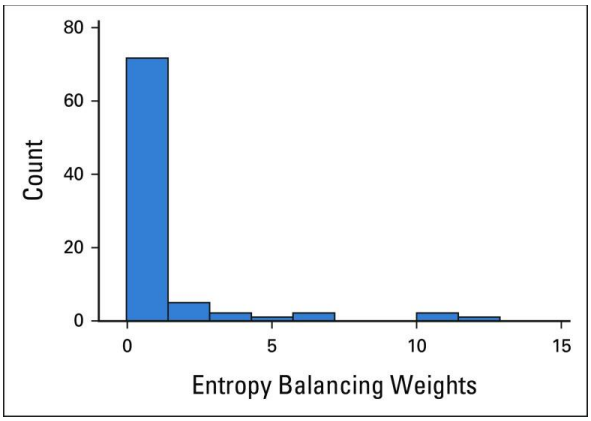


Figure 9 Weight distribution, Bokemeyer et al 2023
Histogram of patient weights. Upon diagnosing the weight distribution, most weights were ≤ 1, with some outliers with higher weights. Weight > 1 means that an individual carries more weight in the reweighted population than in the larotrectinib trial population. Weight < 1 means that an individual carries less weight than in the larotrectinib trial population.

7.1.2.2 Estimating relative treatment effect

As previously mentioned, after matching an analysis was conducted to estimate the treatment effect of larotrectinib versus SoC on OS (defined as the time from index date to death). HRs with corresponding 95% CIs were used to assess OS between larotrectinib and non–TRK-inhibitor SoC before and after matching. Refer to Figure 10.

7.1.3 Results from the comparative analysis

Original MAIC analysis

HRs with corresponding 95% CIs were used to assess OS between larotrectinib and non–TRK-inhibitor SoC/FLATIRON before and after matching (refer to Figure 10). The median OS for TRK fusion-positive patients in the Flatiron/Foundation Medicine database was 10.2 months (95% CI: 7.2, 14.1). Prior to matching, the median OS for larotrectinib was not reached and after matching, median OS was 39.7 months. Larotrectinib was associated with a 78% lower risk of death (HR=0.22; 95% CI: 0.09, 0.52; P=0.001), which corresponds to a 29.5-month median survival advantage for larotrectinib compared with non-TRK inhibitor SoC/FLATIRON (Bokemeyer 2023). Refer also to Appendix C.

Larotrectinib *v* SoC	HR	Robust Standard Error	*P*	95% CI
Before weighting	0.09	0.03	.00	0.05 to 0.19
After weighting	0.22	0.10	.00	0.09 to 0.52

Figure 10 Larotrectinib vs SoC: Overall survival from time of metastatic/locally advanced diagnosis, index date. As reported by Bokemeyer et al 2023

In the after-weighting KM plot (refer to Figure 8), the dip in larotrectinib survival at 16 months is explained by a single patient whose severe disease profile (≥ 3 lines of prior

therapy, stage 3/4 disease, ECOG PS 2/4, and comorbid lung cancer with CNS metastasis) resulted in a higher assigned weight, thus amplifying the death event at 16 months.

Re-weighted analysis

The Schoenfeld test of the proportional hazard assumption produced a p -value of 0.05293. This result suggests that we do not have sufficient evidence to reject the null hypothesis, implying that the proportional hazards (PH) assumption likely holds (and the Cox regression captures the ratio of hazards between larotrectinib and SoC over time).

Important considerations

Schoenfeld p-values can be sensitive to the sample size: A small p-value (like < 0.05) could be due to a large sample size, even if the effect is not practically meaningful. Hence, the p-value should be considered with a graphical assessment, such as inspecting Schoenfeld residuals plots over time.

Therefore, given that the p-value is very close to 0.05 (as well as being underpowered), this result could be considered borderline, warranting cautious interpretation. Refer to the Schoenfeld residuals presented in Appendix D.

Table 23 presents the unweighted and the weighted survival estimates for OS of larotrectinib vs SoC, based on the ePAS8 data and the FLATIRON registry data reported in Bokemeyer et al (6).

Table 23 Results from the comparative analysis of larotrectinib vs SoC (FLATIRON), ePAS8

Population	Sample size		Median OS (95% CI)		Hazard ratio (95% CI)
	Laro ePAS8	SoC	Laro ePAS8	SoC	Larotrectinib vs. SoC
Before weighting	85	28	Not yet estimable (63.4, not yet estimable)	10.2 (7.2; 14.1)	0.39 (0.15; 1.02)
After weighting	13.14	28	30.8 (8.5; N/A)	10.2 (7.2; 14.1)	0.16 (0.09; 0.29)

Abbreviations: N/A, not available / not applicable; OS, overall survival; CI, confidence interval; SoC, standard of care; ePAS, extended primary analysis set.
Source: Larotrectinib pooled analysis, ePAS8 DCO 2023 and FLATIRON registry data, Bokemeyer et al.

7.1.4 Efficacy – results per overall survival

The OS was shorter in the FLATIRON population compared to the ePAS8 population. This trend is observed in the unweighted analyses, as well as in the adjusted analyses. Figure 11 below presents the larotrectinib unweighted and weighted, and the SoC (FLATIRON) KM curves for OS.

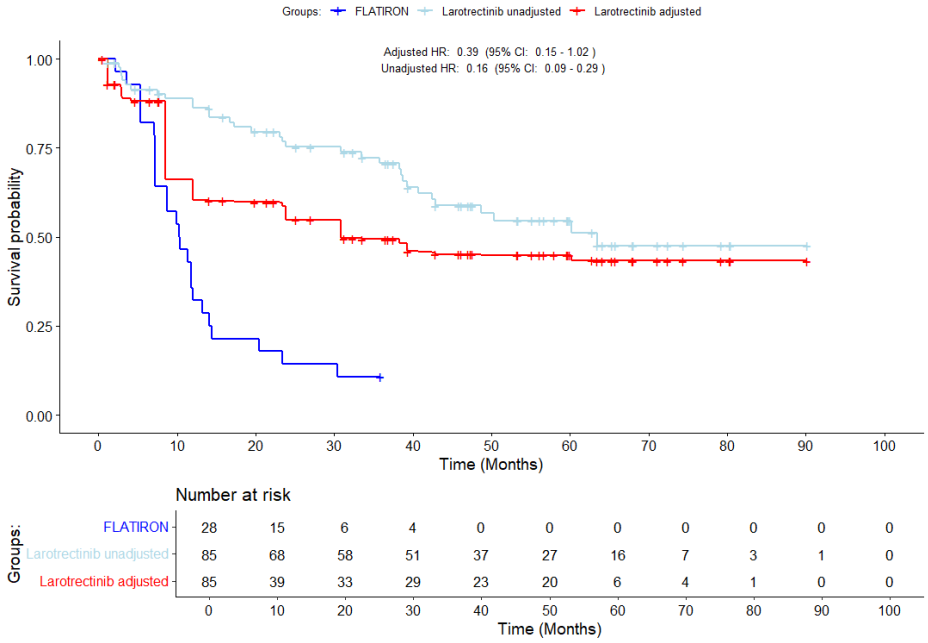


Figure 11 Kaplan-Meier, larotrectinib (ePAS8) vs FLATIRON (SoC), before re-weighting and after re-weighting

Abbreviations: HR, hazard ratio; CI, confidence interval; SoC, standard of care; ePAS, extended primary analysis set.

7.1.5 Efficacy – results per progression-free survival

In the absence of comparator data on PFS, a comparative analysis cannot be provided. However, to the match the larotrectinib population for both OS and PFS, the MAIC weights have been applied to the larotrectinib ePAS8 PFS data set.

Table 24 Results from the comparative analysis of larotrectinib vs SoC (FLATIRON), ePAS8

Population	Sample size		Median PFS (95% CI)		Hazard ratio (95% CI)
	Laro ePAS8	SoC	Laro ePAS8	SoC	Larotrectinib vs. SoC
Before weighting	85	N/A	23.7 (16.6, 31.5) (investigator assessed) 28.1 (19.6, 35.8) (IRC)	N/A	N/A
After weighting	13.14	N/A	19.22 (7.23; N/A)	N/A	N/A

Abbreviations: ePAS, extended primary analysis; PFS, progression-free survival; SoC, standard of care; N/A, not available / not applicable.

Source: Larotrectinib trials, DCO 20 July 2023, ePAS8, Bokemeyer et al 2023 (6).

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

As mentioned previously in Section 7, a MAIC conducted by Bokemeyer et al. 2023 (6) conducted a MAIC analysis, comparing Larotrectinib IPD from the ePAS5 data set (DCO 20 July 2020) vs published aggregate real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron Health/Foundation

Medicine database. The MAIC weights derived from this study have been used to conduct a re-weighting analysis for the ePAS8 (DCO 20 July 2023) data set.

A limitation of the Bokemeyer et al MAIC data is that it does not contain PFS nor ToT data for the SoC/FLATIRON arm (hence, no PFS nor ToT comparison was made). As a result, the PFS of the SoC/FLATIRON arm was generated using the ratio of OS to PFS from the intervention arm as a conservative assumption (the re-weighted ePAS8 data, refer to Section 7).

Regarding the ToT, PFS has been used as a proxy for ToT due to the lack of this data for the SoC/FLATIRON arm. As a result, patients are assumed to receive treatment until progression. Furthermore, from the ePAS8 clinical study report (CSR), the ToT (unweighted) reported a mean and median of 22.24 and 14.44 months, respectively. Refer to Table 24 for overview of the PFS for larotrectinib before and after weighting. The similar medians for PFS (Table 24) and ToT imply that patients stay on treatment until disease progression, supporting the rather conservative assumption (PFS as a proxy for ToT) in the base case.

The efficacy inputs in the model are PFS and OS. A comparison of the ePAS7 data vs tumour-site specific comparators (basket) is also available in the model.

8.1.1 Extrapolation of efficacy data

The extrapolations of OS and PFS were generated using a standard parametric model. Standard parametric modelling estimates patient progression over a specified timeframe through a variety of different distributions, including exponential, Weibull, lognormal, log-logistic, Gompertz, and generalized gamma. In this application, parametric modelling can be selected for use for both treatment arms; that is, OS and PFS for the Larotrectinib arm and OS for the SoC/FLATIRON arm.

Base case parametric functions for OS and PFS for larotrectinib and SoC/FLATIRON were chosen based on goodness-of-fit metrics, including the Akaike information criterion (AIC) and Bayesian information criterion (BIC), in addition to visual evaluations of the correspondence between predicted and actual PFS and OS curves. Lasty, clinical plausibility of long-term extrapolations was assessed using smoothed hazard plots. Survival estimates were adjusted for background mortality observed in the Danish general population.

Appropriate curve selection was determined according to statistical (AIC and BIC), visual goodness of fit and the clinical plausibility of extrapolations. Appendix D provides a detailed description of the extrapolation method used in this analysis.

8.1.1.1 Extrapolation of overall survival

Table 25 summarises assumptions and extrapolation methods of OS. In the base case analysis, a log-normal distributions were chosen for larotrectinib and SoC/FLATIRON, respectively. For scenario analysis, the use of the Exponential distribution was selected for both arms (most pessimistic fits).

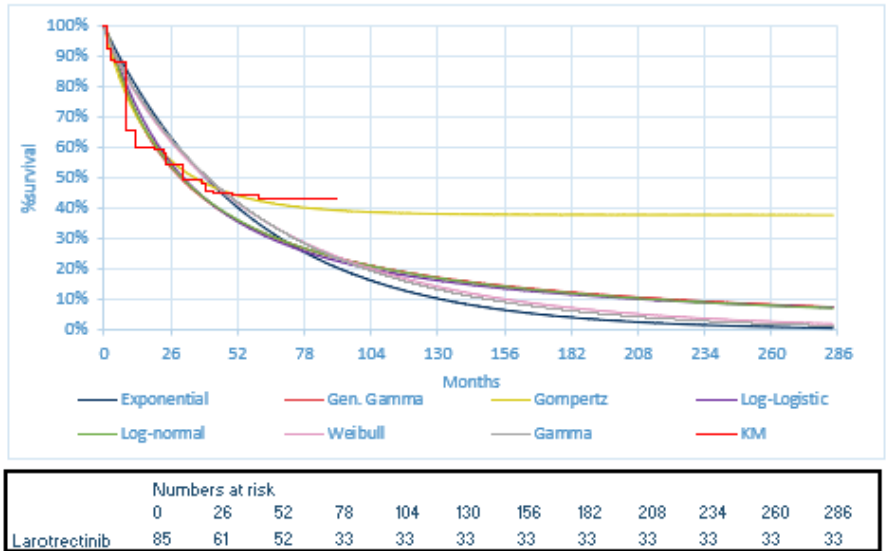
Table 25 Summary of assumptions associated with extrapolation of overall survival

Method/approach	Description/assumption
Data input	Larotrectinib: IPD from the ePAS8 (5) dataset re-weighted with the MAIC weights provided by the MAIC conducted by Bokemeyer et al (6). SoC: Bokemeyer et al. using aggregate real-world data from patients with locally advanced/metastatic TRK

Method/approach	Description/assumption
	fusion-positive cancer identified in the Flatiron Health/ Foundation Medicine database (6).
Model	The extrapolation of OS can be generated using single parametric curves models. The considered parametric distributions include Exponential, Weibull, Lognormal, Loglogistic, Gompertz, and Generalized Gamma.
Assumption of PH between intervention and comparator	PH assumption is not clearly violated. Single fitting (see Appendix D.1.3).
Function with best AIC fit	Larotrectinib: Gompertz SoC/FLATIRON: Log-Logistic
Function with best BIC fit	Larotrectinib: Gompertz SoC/FLATIRON: Log-Logistic
Function with best visual fit	Larotrectinib: Gompertz demonstrated clearly the most optimistic fit. Exponential demonstrated the most pessimistic fit. The remaining distributions demonstrated a more similar fit to the data. SoC/FLATIRON: all curves demonstrated similar fit
Function with best fit according to evaluation of smoothed hazard assumptions	Larotrectinib: None of the smoothed hazard curves demonstrated a good fit. However, Gompertz illustrated the best fit SoC/FLATIRON: Generalised-gamma and log-logistic showcased similar fit
Validation of selected extrapolated curves (external evidence)	NA
Function with the best fit according to external evidence	Larotrectinib: Log-normal SoC/FLATIRON: all curves demonstrated similar fit
Selected parametric function in base case analysis	Larotrectinib: Log-normal SoC/FLATIRON: Log-normal
Adjustment of background mortality with data from Statistics Denmark	Yes.
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.

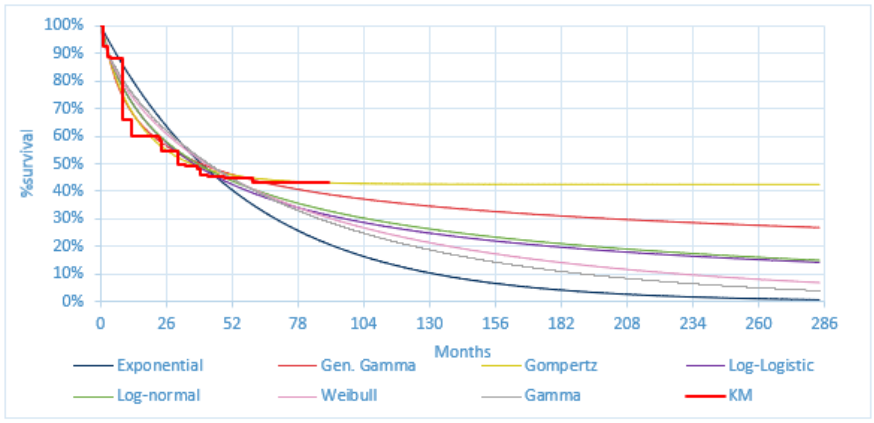
Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; ePAS, extended primary analysis; MAIC, matching-adjusted indirect comparison; SoC, standard of care; OS, overall survival; N/A, not available / not applicable; PH, proportional hazards

Refer to Figure 11 in Section 7 that presents the larotrectinib unweighted and weighted, and the SoC/FLATIRON KM-curves for OS. Figure 12 and Figure 13 below demonstrate the joint and single fit of OS for (weighted) larotrectinib, including the numbers a risk, respectively.



	Numbers at risk											
	0	26	52	78	104	130	156	182	208	234	260	286
Larotrectinib	85	61	52	33	33	33	33	33	33	33	33	33

Figure 12 Larotrectinib, OS, joint fit (including numbers at risk)
Abbreviations: OS, overall survival; KM, Kaplan-Meier.



	Numbers at risk											
	0	26	52	78	104	130	156	182	208	234	260	286
Larotrectinib	85	61	52	33	33	33	33	33	33	33	33	33

Figure 13 Larotrectinib, OS, single fit (including numbers at risk)
Abbreviations: OS, overall survival; KM, Kaplan-Meier.

Figure 14 and Figure 15 present the extrapolation models for OS in the Larotrectinib arm and the SoC/FLATIRON arm, respectively. The figures show the extrapolation over 80 years (i.e., 960 months) (lifetime horizon). Refer to Appendix D.1.5 for further details.

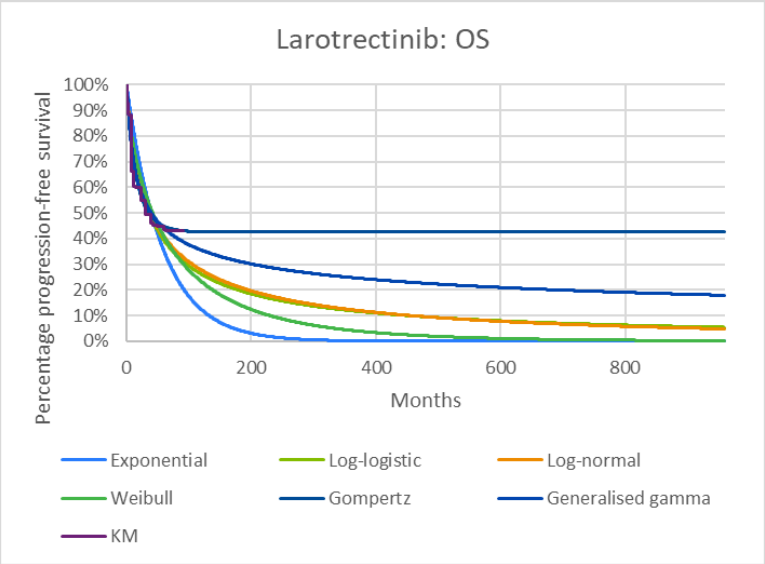


Figure 14 Extrapolation model for overall survival (OS), larotrectinib, reweighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al.
Abbreviations: OS, overall survival; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison; IPD, individual patient-level data

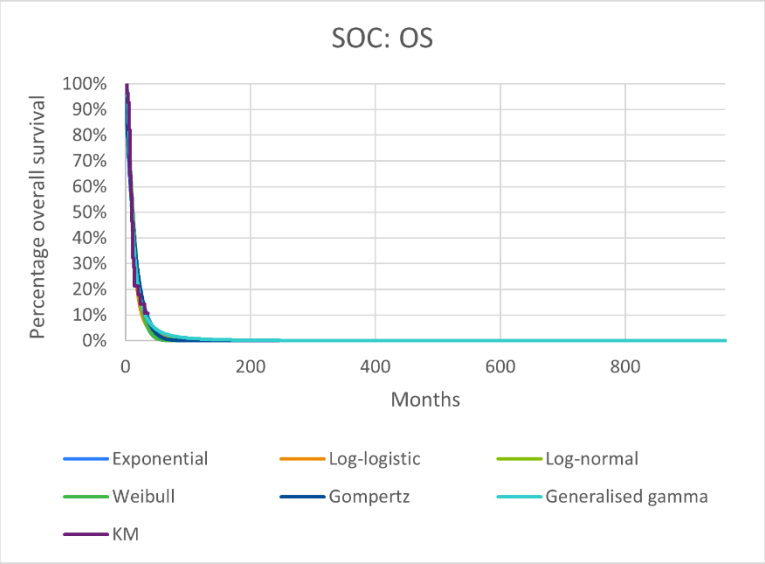


Figure 15 Extrapolation model for overall survival (OS), SoC, Bokemeyer et al., aggregated RWD
Abbreviations: KM, Kaplan-Meier; SoC, standard of care; OS, overall survival; RWD, real-world data

8.1.1.2 Extrapolation of progression-free survival

Table 26 summaries assumptions and extrapolation methods of PFS. In the base case analysis, log-normal distribution was chosen for larotrectinib. For scenario analysis, the use of the Exponential distribution was selected (most pessimistic fit).

Table 26 Summary of assumptions associated with extrapolation of progression-free survival

Method/approach	Description/assumption
Data input	Larotrectinib: IPD from ePAS8 data set (5) re-weighted with the MAIC derived weights informed by Bokemeyer et al (6). SoC/FLATIRON: Since no PFS data was obtained from Bokemeyer et al. to inform the SoC/FLATIRON arm, the

Method/approach	Description/assumption
	PFS curves were inferred by using the ratio of OS to PFS from the weighted ePAS8 data (6) (5).
Model	The extrapolation of PFS (larotrectinib only) can be generated using single parametric curves models. The considered parametric distributions include Exponential, Weibull, Lognormal, Loglogistic, Gompertz, and Generalized Gamma.
Assumption of PH between intervention and comparator	PH not tested for PFS as the efficacy outcome due to lack of PFS data for SoC/FLATIRON.
Function with best AIC fit	Larotrectinib: Weibull SoC/FLATIRON: N/A
Function with best BIC fit	Larotrectinib: Weibull SoC/FLATIRON: N/A
Function with best visual fit	Larotrectinib: Gompertz and Generalised Gamma demonstrated clearly the most optimistic fits. Exponential demonstrated the most pessimistic fit. The remaining distributions demonstrated a more similar fit to the data. SoC/FLATIRON: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Larotrectinib: None of the smoothed hazard curves demonstrated a good fit. However, log-normal and log-logistic showcased the best fit. SoC/FLATIRON: N/A
Validation of selected extrapolated curves (external evidence)	Not available
Function with the best fit according to external evidence	Larotrectinib: N/A SoC/FLATIRON: N/A
Selected parametric function in base case analysis	Larotrectinib: Log-normal SoC/FLATIRON: N/A
Adjustment of background mortality with data from Statistics Denmark	All models are adjusted for background mortality with data from statistics Denmark.
Adjustment for treatment switching/cross-over	No.
Assumptions of waning effect	No.
Assumptions of cure point	No.

Abbreviations: IPD, individual patient-level data; AIC, akaike information criterion; BIC, bayesian information criterion; ePAS, extended primary analysis set; MAIC, matching-adjusted indirect comparison; SoC, standard of care; OS, overall survival; PFS, progression-free survival; N/A, not available / not applicable; PH, proportional hazards

Figure 16 below demonstrates the single fit of PFS for (weighted) larotrectinib, including the numbers a risk.

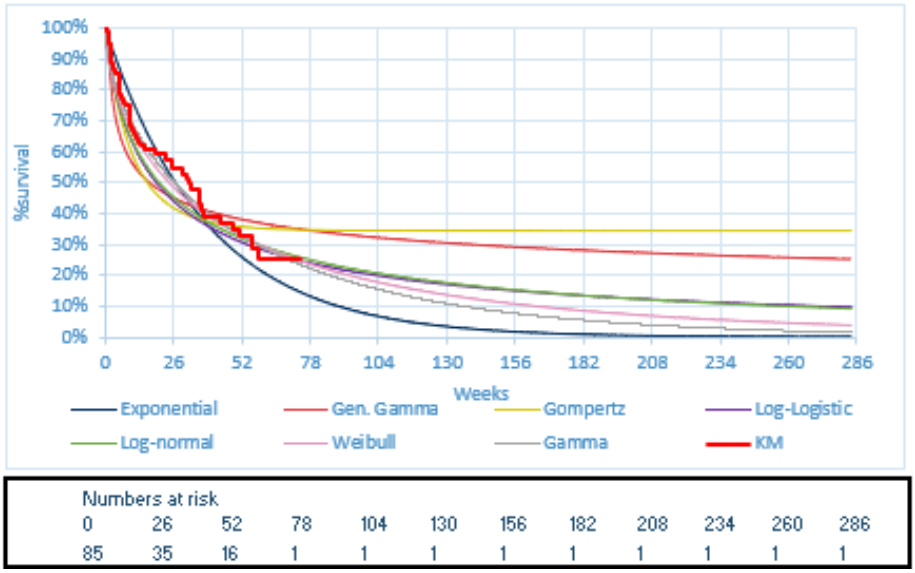


Figure 16 Larotrectinib, PFS, single fit (including numbers at risk)
Abbreviations: KM, Kaplan-Meier; PFS, progression-free survival

Figure 17 presents the extrapolation models for PFS in the Larotrectinib arm. The figures show the extrapolation over 80 years (lifetime horizon). Refer to Appendix D for further details.

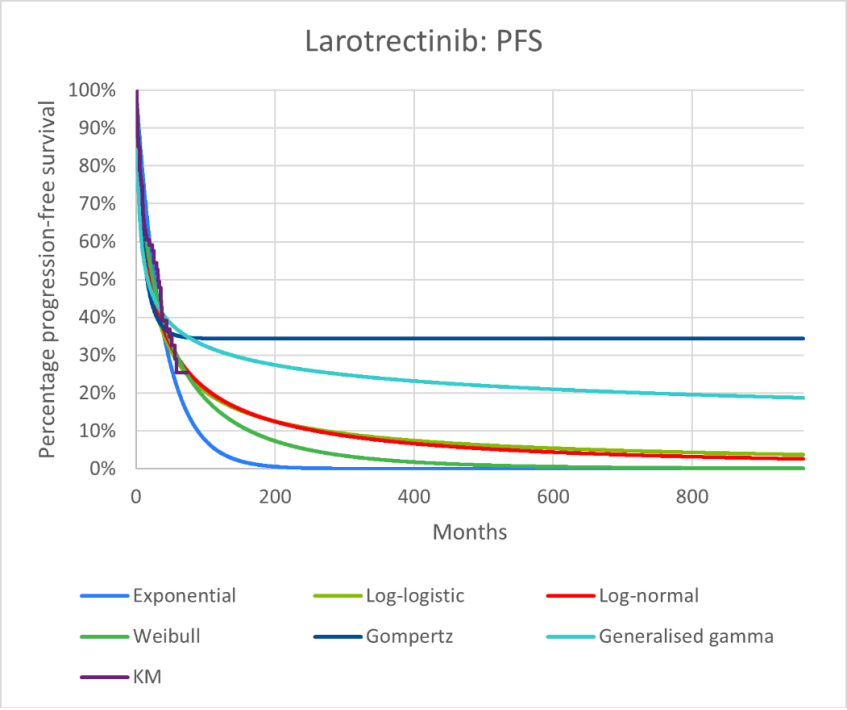


Figure 17 Extrapolation model for progression-free survival larotrectinib, reweighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al.
Abbreviations: IPD, individual patient-level data; ePAS, extended primary analysis set; PFS, progression-free survival; KM, Kaplan-Meier; MAIC, matching-adjusted indirect comparison

8.1.2 Calculation of transition probabilities

Not applicable.

Table 27 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	N/A
	Death	N/A	N/A
Recurrence	Death	N/A	N/A

8.2 Presentation of efficacy data from

Not applicable.

8.3 Modelling effects of subsequent treatments

Not applicable. No subsequent treatments were included in the model.

8.4 Other assumptions regarding efficacy in the model

Table 28 below summarises the key model assumptions.

Table 28 Key model assumptions

	Assumption	Justification
ToT	PFS is used as proxy for ToT in the base case (using larotrectinib ePAS8 data)	Due to lack of ToT data from the SoC/FLATIRON arm. Refer to Table 20 Progression-free survival in ePAS8 (pooled analysis set, DCO: 20 July 2023). Table 20 for overview of the PFS for larotrectinib before and after weighting. The similar medians for PFS (Table 20) and ToT imply that patients stay on treatment until disease progression, supporting the rather conservative assumption (PFS as a proxy for ToT) in the base case. For this reason, PFS curves were utilised as a proxy to model ToT. To facilitate a fair comparison between the two treatment arms, the very same assumption was applied to the larotrectinib arm.
PFS	The ratio of OS to PFS from the larotrectinib base case data was used to generate the PFS of the SoC/FLATIRON arm.	A limitation of the Bokemeyer et al MAIC data is that it does not contain PFS nor ToT data for the SoC/FLATIRON arm (hence, no PFS nor ToT comparison was made). As a result, the PFS of the SoC/FLATIRON arm was generated using the ratio of OS to PFS from the intervention arm as a conservative assumption (the re-weighted ePAS8 data, refer to Section 7).
HCRU	Multiple sources for health state resource use and cost were identified for the comparator treatments. Health state costs for larotrectinib were assumed equal to the weighted average of the comparator's costs, using the tumour site distribution in the larotrectinib clinical trial. Refer to Section 10.	All clinicians interviewed considered this an appropriate assumption given the data available, and expected this would likely be conservative, and overestimate health care resource use for larotrectinib.
AE	Data is unavailable to understand the timing and duration of AEs for larotrectinib and comparators. One-time upfront cost / disutility.	This removes the need for complicated and/or impossible to justify assumptions for temporality of AE impact by tumour site, and this approach has been used in past NICE submissions in oncology.

Abbreviations: ToT, time-on-treatment; PFS, progression-free survival; ePAS, extended primary analysis set; HCRU, health care resource use; DOC, data-cut-off; AE, adverse event; SoC, standard of care; OS, overall survival; MAIC, matching-adjusted indirect comparison; NICE, National Institute for Health and Clinical Excellence.

8.5 Overview of modelled average treatment length and time in model health state

Table 29 and Table 30 presents the estimates in the model for the modelled average OS and PFS, respectively. The estimates are undiscounted, without half-cycle correction and adjusted for background mortality of the Danish population, as requested by the DMC (84).

Table 29 Estimates in the model - OS

	Modelled average OS (Partitioned survival model")	Modelled median OS ("Partitioned survival model")	Observed median OS from relevant study (5, 6)
Larotrectinib	124.1 months	38.3 months	Before matching, the median OS for larotrectinib was not reached; after matching, OS was 30.8 months Refer to Table 23
SoC/FLATIRON	14.9 months	10.9 months	10.2 months (95% CI, 7.2 to 14.1)

* Before matching, the median OS for larotrectinib was not reached; hence, the provided median is estimated after the matching took place

Abbreviations: N/A, not applicable, OS, overall survival; SoC, standard of care

Table 30 Estimates in the model - PFS

	Modelled average PFS (Partitioned survival model")	Modelled median PFS (Partitioned survival model")	Observed median PFS from relevant study (5, 6)
Larotrectinib	84.7 months	20.5 months	Before weighting: median PFS of 23.7 months After weighting: 19.22 months
SoC/FLATIRON	12.8 months	9.2 months	Bokemeyer et al: N/A

Abbreviations: PFS, progression-free survival; SoC, standard of care

Table 31 presents the modelled average treatment length and time in the model health states.

Table 31 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	PF [years]	PD [years]
Larotrectinib	7.05*	7.06	3.28
SoC/FLATIRON	1.06*	1.07	0.17

*Due to the lack of ToT for the SoC arm, a conservative approach was taken, using PF as a proxy for ToT in both arms.

Abbreviations: SoC, standard of care; PF, progression-free; PD, progressive disease

9. Safety

The safety profile of larotrectinib for the treatment of adult and paediatric patients who had locally advanced or metastatic NTRK fusion-positive solid tumours is based on the analysis of AEs that occurred in 3 clinical studies (Studies LOXO TRK-14001, LOXO TRK 15002 [NAVIGATE], and LOXO-TRK-15003 [SCOUT]). Refer to Section 9.1. Adverse events for the comparators were assumed to be zero (considered rather conservative approach).

9.1 Safety data from the clinical documentation

The population for safety analysis within this submission is a pooled analysis, comprising 'all patients with NTRK fusion-positive cancer from LOXO-TRK-14001, NAVIGATE and SCOUT studies, who have received ≥ 1 dose of larotrectinib, as 20 July 2023 (ePAS8). This

population aligns with the decision problem and the safety inputs within the economic model.

Safety Analysis Set: ePAS8 (n=302)

The safety analysis set includes the 302 patients of the ePAS8 who provide the primary analysis set for efficacy evaluation. This analysis set excludes patients with primary CNS tumours. There were 13 (4%) patients from Study 20288, 189 (63%) patients from Study 20289, and 100 (33%) patients from Study 20290 contributing to this analysis set.

The patients in ePAS8 analysis set meet the following criteria:

- Documented NTRK fusion as determined by local testing
- Non-primary CNS tumour with 1 or more measurable lesions at baseline as assessed by the IRC, Investigator and RECIST v1.1
- Received 1 or more doses of larotrectinib

Adverse events were classified using MedDRA (Medical Dictionary for Regulatory Activities) Version 18.1. Treatment-emergent AEs (TEAEs) were defined as those events that started on or after the date of the first dose of larotrectinib study drug. The severity of each AE was graded, when applicable, using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Table 32 Overview of safety events. Safety analysis set, ePAS8 (DCO 20 July 2023)

	Larotrectinib, ePAS8 (N=302) All / drug-related (3)	Comparator (N=x) (source)	Difference, % (95 % CI)
Number of adverse events, n	N/A	N/A	N/A
Any TEAE, n	297 (98) / 259 (86)	N/A	N/A
Number and proportion of patients with ≥1 adverse events, n (%)	N/A	N/A	N/A
Number of serious adverse events*, n	136 (45) / 25 (8)	N/A	N/A
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	N/A	N/A	N/A
Number of CTCAE grade ≥ 3 events, n	187 (62) /68 (23)	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade 3 events§, n (%)	N/A	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	N/A	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	28 (9)	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	5 (2)	N/A	N/A

Abbreviations: ePAS, extended primary analysis set; DCO, data-cut-off; TEAE, treatment emergent adverse events; CTCAE, Common Terminology Criteria for Adverse Events; N/A, not available / not applicable
Source: Bayer data on file, safety analysis report, July 2023 DCO, table 2-3 (3)

Most SAEs were not considered by the Investigator to be related to the study drug, with 34 (8%) patients who had at least 1 drug-related SAE. The same proportion of patients had at least 1 treatment emergent SAE in the NTRK gene fusion analysis set and the Efficacy-evaluable NTRK gene fusion analysis set (45% in each). In Table 33 the frequency of

treatment-emergent serious adverse events occurring in >2 patients from the overall safety analysis set (n= 444) are reported (SAE overview from ePAS8 is not provided).

Table 33 Serious adverse events (time point). Overall safety analysis set (DCO 20 July 2023)

Adverse events	Larotrectinib (N=302) All / study drug-related		Comparator (N=x)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)	201 (45) / 34 (8)	N/A	N/A	N/A
Pneumonia	19 (4) / 1 (<1)	N/A	N/A	N/A
Pyrexia	15 (3) / 1 (<1)	N/A	N/A	N/A
Dyspnoea	10 (2) / 0	N/A	N/A	N/A
Diarrhoea	8 (2) / 1 (<1)	N/A	N/A	N/A
Vomiting	7 (2) / 2 (<1)	N/A	N/A	N/A
Hypoxia	6 (1) / 0	N/A	N/A	N/A
Seizure	6 (1) / 0	N/A	N/A	N/A
Sepsis	6 (1) / 0	N/A	N/A	N/A
Abdominal pain	5 (1) / 1 (<1)	N/A	N/A	N/A
Muscular weakness	5 (1) / 1 (<1)	N/A	N/A	N/A
Pneumonia aspiration	5 (1) / 0	N/A	N/A	N/A
Pulmonary embolism	5 (1) / 0	N/A	N/A	N/A
Respiratory failure	5 (1) / 0	N/A	N/A	N/A
Acute kidney injury	4 (<1) / 0	N/A	N/A	N/A
ALT increased	4 (<1) / 4 (<1)	N/A	N/A	N/A
Cellulitis	4 (<1) / 0	N/A	N/A	N/A
Dizziness	4 (<1) / 1 (<1)	N/A	N/A	N/A
Gait disturbance	4 (<1) / 1 (<1)	N/A	N/A	N/A
Gastroenteritis	4 (<1) / 0	N/A	N/A	N/A
Influenza	4 (<1) / 0	N/A	N/A	N/A
Pericardial effusion	4 (<1) / 0	N/A	N/A	N/A
Skin infection	4 (<1) / 0	N/A	N/A	N/A
Viral infection	4 (<1) / 0	N/A	N/A	N/A
Ascites	3 (<1) / 0	N/A	N/A	N/A
AST increased	3 (<1) / 3 (<1)	N/A	N/A	N/A
Constipation	3 (<1) / 0	N/A	N/A	N/A
Dehydration	3 (<1) / 0	N/A	N/A	N/A
Fall	3 (<1) / 0	N/A	N/A	N/A
Fatigue	3 (<1) / 0	N/A	N/A	N/A
Headache	3 (<1) / 1 (<1)	N/A	N/A	N/A
Hydrocephalus	3 (<1) / 0	N/A	N/A	N/A
Hyponatraemia	3 (<1) / 1 (<1)	N/A	N/A	N/A
Joint dislocation	3 (<1) / 0	N/A	N/A	N/A
Malaise	3 (<1) / 1 (<1)	N/A	N/A	N/A
Malignant neoplasm progression	3 (<1) / 0	N/A	N/A	N/A
Osteomyelitis	3 (<1) / 0	N/A	N/A	N/A
Pleural effusion	3 (<1) / 0	N/A	N/A	N/A
Pyelonephritis	3 (<1) / 0	N/A	N/A	N/A
Urinary tract infection	3 (<1) / 0	N/A	N/A	N/A
Wound infection	3 (<1) / 0	N/A	N/A	N/A

Abbreviations: DCO, data-cut-off; N/A, not available / not applicable
source: (3)

Health economic model

The incidences of AEs associated with larotrectinib in the model were based on the data from the ePAS8 population (safety analysis set, n=302) (DCO 20 July 2023). In the model, only TEAEs grade 3-4 adverse events that occurred in ≥5% of patients in the relevant treatment arm were included within the economic assessment.

Table 34 Adverse events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)		N/A	N/A	N/A
Abnormal liver function[a]	31 (10)	N/A	Bayer ePAS8 CSR	Grade 3-4 adverse events that occurred in ≥5% of patients
Anaemia	22 (7)	N/A	Same as above	Same as above
Neutropenia	31 (10)	N/A	Same as above	Same as above
Weight increased	16 (5)	N/A	Same as above	Same as above

Abbreviations: N/A= not available or applicable; CSR= clinical study report

[a] includes ALT and AST

source: Bayer CSR for safety analysis set, ePAS8 (DCO 2023) (3)

9.2 Safety data from external literature applied in the health economic model

Adverse events for the comparators were assumed to be zero in the absence of robust data regarding the composition of the FLATIRON SoC basket.

Table 35 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Abbreviations: N/A, not available / not applicable

10. Documentation of health-related quality of life (HRQoL)

Table 36 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	LOXO-TRK-15002 trial [NAVIGATE] NCT02576431)	HRQoL data was collected to estimate HSUVs for PF and PD states. These estimates have been applied to all patients.
PedsQL	LOXO-TRK-15003 [SCOUT] NCT02637687	HRQoL data was collected in the trial; however, these estimates have not been applied in the application.

Abbreviations: HRQoL, health-related quality of life; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; PedsQL, Pediatric Quality of Life Inventory; HSUVs, health states utility values; PF, progression-free; PD, progressive disease.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

HRQoL of larotrectinib was assessed in LOXO-TRK-15002 (patients aged 18 and older) and LOXO-TRK-15003 (patients aged 1 month to 21 years) in the ePAS6 patient population (DCO July 2021) (PROs were not recorded in any data cut after ePAS6) using the instruments European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), EQ-5D-5L and PedsQL. In this application only the two latter instruments (i.e., EQ-5D-5L and PedsQL) were considered relevant. However, only EQ-5D-5L was applied in the base case. The EQ-5D utility index were used to collect HRQoL. Visual analogue scale scores were not available.

For the SoC/FLATIRON arm, HRQoL were identified from the SLR and prior NICE TAs (Bayer Data on File ePAS7 CEM 2023). Refer to Appendix O.2.

10.1.2 Data collection

10.1.2.1 EQ-5D-5L

The EQ-5D-5L questionnaire was administrated every 8 weeks during the first year of follow-up, and every 12 weeks after one year of follow-up. Of the 140 ePAS6 patients who were under treatment in the trial, 128 had a baseline assessment. No further information can be provided. The pattern of missing data and completion are reported in Table 37 below.

Table 37 Pattern of missing data and completion

Time point	HRQoL population N=140	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients	Number of patients for whom data is missing (% of patients)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	140	12 (8.6)	140	128 (91.4)
Cycle 3 Day 1	140	14 (11.3)	124	110 (88.7)
Cycle 5 Day 1	140	10 (9.2)	109	99 (90.8)

Time point	HRQoL population N=140	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 7 Day 1	140	16 (15.1)	106	90 (84.9)
Cycle 9 Day 1	140	12 (12.6)	95	83 (87.4)
Cycle 11 Day 1	140	14 (16.9)	83	69 (83.1)
Cycle 13 Day 1	140	10 (13.0)	77	67 (87.0)
Cycle 16 Day 1	140	11 (17.2)	64	53 (82.8)
Cycle 19 Day 1	140	12 (21.4)	56	44 (78.6)
Cycle 22 Day 1	140	39 (76.5)	51	39 (76.5)
Cycle 25 Day 1	140	9 (20.9)	43	34 (79.1)
Cycle 28 Day 1	140	10 (24.4)	41	31 (75.6)
Cycle 31 Day 1	140	15 (41.7)	36	21 (58.3)
Cycle 34 Day 1	140	10 (31.3)	32	22 (68.8)
Cycle 37 Day 1	140	8 (29.6)	27	19 (70.4)
Cycle 40 Day 1	140	8 (36.4)	22	14 (63.6)
Cycle 43 Day 1	140	3 (21.4)	14	11 (78.6)
Cycle 46 Day 1	140	4 (36.4)	11	7 (63.6)
Cycle 49 Day 1	140	3 (37.5)	8	5 (62.5)
Cycle 52 Day 1	140	3 (37.5)	8	5 (62.5)
Cycle 55 Day 1	140	(60.0)	5	2 (40.0)
Cycle 58 Day 1	140	3 (60.0)	5	2 (40.0)
Cycle 61 Day 1	140	1 (100.0)	1	-

Abbreviations: HRQoL, health-related quality of life.
Notes: The median time on treatment for ePAS6 is 14.1 months

10.1.3 HRQoL results

The mean change from baseline for the EQ-5D-5L index score for non-progressed and progressed patients are presented in Figure 18 and Figure 19, respectively. The analysis set includes all participants (ITT) who initiated the study treatment and completed at least one patient-reported outcome assessment at baseline. The summary statistics are for non-progressed and progressed patients are presented in Table 38 and Table 39, respectively.

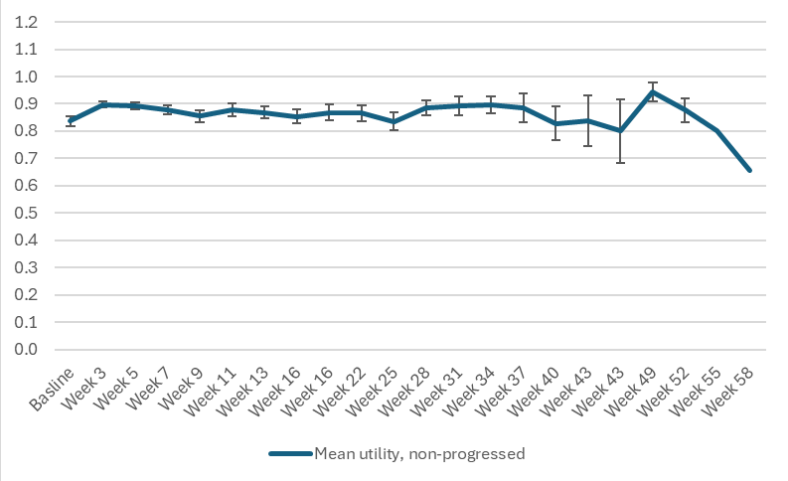


Figure 18 EQ-5D-5L (DK weighted) mean change from baseline utility value for larotrectinib, non-progressed
Abbreviations: CI, confidence interval

Table 38 HRQoL EQ-5D summary statistics, non-progressed

	Intervention, Larotrectinib		Comparator, SoC/FLARITON		Intervention vs. comparator
	N=140	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	113*	0.836 (0.020)*	N/A	N/A	N/A
Cycle 3 Day 1	103	0.898 (0.011)	N/A	N/A	N/A
Cycle 5 Day 1	89	0.893 (0.012)	N/A	N/A	N/A
Cycle 7 Day 1	75	0.879 (0.016)	N/A	N/A	N/A
Cycle 9 Day 1	72	0.855 (0.021)	N/A	N/A	N/A
Cycle 11 Day 1	60	0.879 (0.024)	N/A	N/A	N/A
Cycle 13 Day 1	58	0.869 (0.021)	N/A	N/A	N/A
Cycle 16 Day 1	43	0.854 (0.027)	N/A	N/A	N/A
Cycle 19 Day 1	35	0.868 (0.029)	N/A	N/A	N/A
Cycle 22 Day 1	32	0.865 (0.031)	N/A	N/A	N/A
Cycle 25 Day 1	31	0.835 (0.033)	N/A	N/A	N/A
Cycle 28 Day 1	28	0.885 (0.027)	N/A	N/A	N/A
Cycle 31 Day 1	20	0.894 (0.034)	N/A	N/A	N/A
Cycle 34 Day 1	17	0.895 (0.032)	N/A	N/A	N/A
Cycle 37 Day 1	14	0.885 (0.052)	N/A	N/A	N/A
Cycle 40 Day 1	12	0.828 (0.062)	N/A	N/A	N/A
Cycle 43 Day 1	8	0.837 (0.094)	N/A	N/A	N/A
Cycle 46 Day 1	7	0.800 (0.116)	N/A	N/A	N/A
Cycle 49 Day 1	4	0.943 (0.034)	N/A	N/A	N/A
Cycle 52 Day 1	4	0.877 (0.043)	N/A	N/A	N/A
Cycle 55 Day 1	1	0.801 (N/A)	N/A	N/A	N/A
Cycle 58 Day 1	1	0.654 (N/A)	N/A	N/A	N/A

Abbreviations: HRQoL, health-related quality of life; EQ-5D, EuroQol 5-Dimensions 5-Levels
*Full PRO analysis set

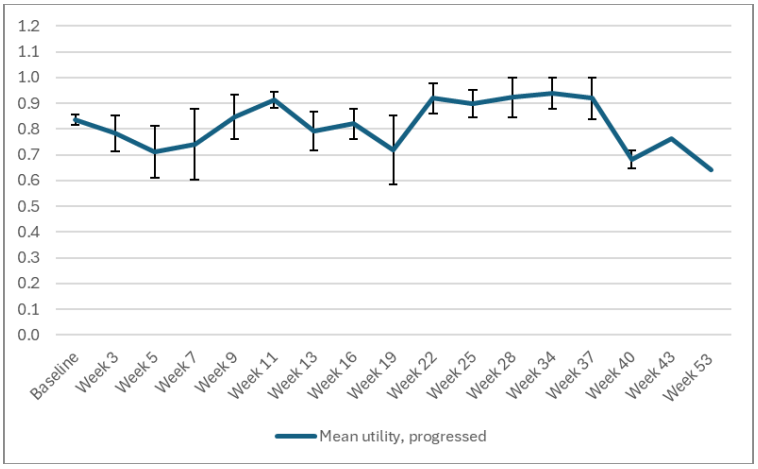


Figure 19 EQ-5D-5L (DK weighted) mean change from baseline utility value for larotrectinib, progressed
Abbreviations: CI, confidence interval

Table 39 HRQoL EQ-5D summary statistics, progressed

	Intervention, Larotrectinib		Comparator, SoC/FLARITON		Intervention vs. comparator
	N=140	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value

Baseline	NA	NA	N/A	N/A	N/A
Cycle 3 Day 1	5	0.784 (0.070)	N/A	N/A	N/A
Cycle 5 Day 1	5	0.711 (0.102)	N/A	N/A	N/A
Cycle 7 Day 1	10	0.740 (0.137)	N/A	N/A	N/A
Cycle 9 Day 1	9	0.847 (0.086)	N/A	N/A	N/A
Cycle 11 Day 1	7	0.914 (0.032)	N/A	N/A	N/A
Cycle 13 Day 1	7	0.792 (0.076)	N/A	N/A	N/A
Cycle 16 Day 1	7	0.821 (0.058)	N/A	N/A	N/A
Cycle 19 Day 1	4	0.719 (0.135)	N/A	N/A	N/A
Cycle 22 Day 1	3	0.919 (0.058)	N/A	N/A	N/A
Cycle 25 Day 1	3	0.899 (0.053)	N/A	N/A	N/A
Cycle 28 Day 1	2	0.924 (0.077)	N/A	N/A	N/A
Cycle 34 Day 1	2	0.940 (0.060)	N/A	N/A	N/A
Cycle 37 Day 1	2	0.920 (0.081)	N/A	N/A	N/A
Cycle 40 Day 1	2	0.682 (0.034)	N/A	N/A	N/A
Cycle 43 Day 1	1	0.761 (N/A)	N/A	N/A	N/A
Cycle 53 Day 1	1	0.641 (N/A)	N/A	N/A	N/A

Abbreviations: HRQoL, health-related quality of life; EQ-5D, EuroQol 5-Dimensions 5-Levels
*Full PRO analysis set

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV calculation

As described in section 10.1.1, the HSUVs for the PF and PD health state was derived from the EQ-5D-5L collected in clinical trials for larotrectinib (LOXO-TRK studies: LOXO-TRK-15002 and LOXO-TRK-15003). The base case analysis of the economic model uses the HSUV using Danish tariffs, using the methodology provided by Jensen et al (85).

Heath impact of AEs was incorporated as utility decrements (disutilities) per event. Age adjustment to the utility values has been applied in accordance with DMC's guidance and source: "*Appendiks: Aldersjustering for sundhedsrelateret livskvalitet*" (86).

The active comparator CEM allows the health state utility across tumour types to be stratified by PF and PD. Proportions of patients within each response category in the early CEM were informed by the key clinical trials, identified via the review of relevant NICE TAs, the SLR and targeted literature searches if not available from the previous two sources. A summary of the health state utility values used to generate a weighted average for SoC/FLATIRON (Refer to Appendix F). As no IPD was available for the SoC/FLATRIONC arm, UK weights were applied to the base case analysis (for comparators IPD is not available, hence only reported utility values (i.e. UK) can be used).

10.2.1.1 Mapping

Not applied.

10.2.2 Disutility calculation

Not applicable. Disutility calculations were derived from external literature.

10.2.3 HSUV results

Table 40 presents an overview of HSUVs used in the model in the base case. For tumour specific utilities refer to Appendix F

For the scenario analysis, UK weights for the larotrectinib arm was applied (Table 41). This was done to enable a comparison of the two arms using the same country specific tariff. Estimates were crosswalk developed by Van Hout et al., 2012 to derive mapped utility values, as recommended by NICE for data gathered using the EQ-5D-5L (24, 25). Table 41 Overview of health state utility values (scenario analysis)

Table 40 Overview of health state utility values (base case analysis)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs for progression-free (PF)				
PF HSUV – DK weighted (base case), larotrectinib	0.868 (0.857; 0878)	EQ-5D-5L	DK	Collected in clinical trials for larotrectinib (LOXO-TRK studies: LOXO-TRK-15002 and LOXO-TRK-15003).
PF HSUV – UK weighted (base case), SoC/FLARITON	0.562 (N/A)	EQ-5D-3L	UK	Health state utility values from available literature were used to generate a weighted average. Refer to Appendix F.
HSUVs for progressed (PD)				
PD HSUV – DK weighted (base case), larotrectinib	0.806 (0.756; 0.855)	EQ-5D-5L	DK	Collected in clinical trials for larotrectinib (LOXO-TRK studies: LOXO-TRK-15002 and LOXO-TRK-15003).
PD HSUV – UK weighted (base case), SoC/FLARITON	0.449 (N/A)	EQ-5D-3L	UK	Health state utility values from available literature were used to generate a weighted average. Refer to Appendix F.

Abbreviations: HRQoL, health-related quality of life; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; HSUV, health state utility values

Table 41 Overview of health state utility values (scenario analysis)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs for progression-free (PF)				
PF HSUV – UK weighted (base case), larotrectinib	0.790 (0.75; 0.82)	EQ-5D-3L	UK	Collected in clinical trials for larotrectinib (LOXO-TRK studies: LOXO-TRK-15002 and LOXO-TRK-15003).
PF HSUV – DK weighted, applied for SoC arm	0.868 (0.857; 0878)	EQ-5D-5L	DK	Suggested scenario analysis based on correspondence with the DMC, refer to Section 12.2.1
HSUVs for progressed (PD)				
PD HSUV – UK weighted (base case)	0.730 (0.75;0.82)	EQ-5D-3L	UK	Collected in clinical trials for larotrectinib (LOXO-TRK studies: LOXO-TRK-15002 and LOXO-TRK-15003).
PD HSUV – DK weighted,	0.868 (0.857; 0878)	EQ-5D-5L	DK	Suggested scenario analysis based on correspondence

applied for SoC arm	with the DMC, refer to Section 12.2.1

Abbreviations: PF, progression-free; PD, progressed disease; SoC, standard of care; DMC, Danish Medicines Council; HSUV, health state utility value

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

In the absence of QoL data from the SoC/FLATIRON data (reported by Bokemeyer et al) used as the comparator in this analysis, utility values for SoC/FLATIRON arm were informed by several sources (tumour-specific utility values).

A summary of the health state utility values used to generate a weighted average for SoC/FLATIRON is presented in Appendix O.2.

10.3.1 Study design

Not applicable. Only used for disutilities.

10.3.2 Data collection

Not applicable. Only used for disutilities.

10.3.3 HRQoL Results

Not applicable. Only used for disutilities.

10.3.4 HSUV and disutility results

The active comparator CEM also considers the HRQoL impact of AEs by means of applying disutilities relating to the included grade 3/4 AEs. The disutilities for each grade 3/4 AE sourced from the previous NICE submissions are provided in Table 42 which have been updated, where possible, based on the results of the suite of SLRs. To capture the full impact of the AEs, disutilities are applied to the full modelled cohort within the first cycle for each arm based on the event rates from the relevant clinical trials. The HRQoL impact of AEs are applied in the first cycle of the model, which is a simplistic approach applied as a result of missing or inconsistent evidence available for the comparators regarding the time to resolution or reversal of AEs.

Table 42. Overview of literature-based health state utility values

Disutility	Decrement	Source	Assumption
Alopecia	-0.045	Nafees 2008 (87)	NSCLC - hair loss
Anaemia	-0.090	Nafees 2008 (87)	NSCLC - neutropenia
Cardiac dysfunction	-0.024	ICER ovarian 2016 (64)	Ovarian cancer - hypertension
Colitis	-0.047	Nafees 2008 (87)	Nafees - diarrhoea
Diarrhoea	-0.047	Nafees 2008 (87)	Nafees - diarrhoea
Dyspnoea	-0.050	Doyle 2008 (67)	Doyle - dyspnoea
Fatigue	-0.073	Nafees 2008 (87)	NSCLC - fatigue
Febrile neutropenia	-0.090	Nafees 2008 (87)	NSCLC - febrile neutropenia
Hypertension	-0.024	ICER ovarian 2016 (64)	Ovarian cancer - hypertension
Increase alkaline phosphatase level	-0.090	ICER ovarian 2016 (64)	NSCLC - neutropenia

Increase in total bilirubin	-0.090	ICER ovarian 2016 (64)	Ovarian cancer - hypertension
Infection	-0.200	Beusterien 2010 (65)	CLL - pneumonia
Leukopenia	-0.090	Nafees 2008 (87)	NSCLC - neutropenia
Nausea	-0.048	Nafees 2008 (87)	NSCLC - nausea and vomiting
Nausea/vomiting	-0.048	Nafees 2008 (87)	NSCLC - nausea and vomiting
Neurosensory	-0.150	Tabberer 2006 (66)	NSCLC - neuropathy
Neutropenia	-0.090	Nafees 2008 (87)	NSCLC - neutropenia
Peripheral neurotoxicity	-0.150	Tabberer 2006 (66)	NSCLC - neuropathy
Pulmonary	-0.050	Doyle 2008 (67)	NSCLC - dyspnoea
Reversible veno-occlusive disease	-0.200	Beusterien 2010 (65)	CLL - pneumonia
Septic deaths	-0.200	Beusterien 2010 (65)	CLL - pneumonia
Thrombocytopenia	-0.090	Nafees 2008 (87)	NSCLC - neutropenia
Vomiting	-0.048	Nafees 2008 (87)	NSCLC - nausea and vomiting
Increased weight	-0.051667	Lane 2014	Assumptions
Pneumonia - fatal	-1	Assumption	Fatal event brings utility to 0
Sepsis - fatal	-1	Assumption	Fatal event brings utility to 0
Suicide	-1	Assumption	Fatal event brings utility to 0
Large intestine perforation - fatal	-1	Assumption	Fatal event brings utility to 0
Tumour lysis syndrome - fatal	-1	Assumption	Fatal event brings utility to 0
Dyspnea - fatal	-1	Assumption	Fatal event brings utility to 0

Abbreviations: NSCLC, non-small cell lung cancer; ICER, incremental cost-effectiveness ratio

11. Resource use and associated costs

The model considers the following two cost categories: direct medical costs (i.e., pharmaceutical costs, administration costs, disease management cost and AE-related costs), and direct nonmedical costs (i.e., patient time and transport costs), consistent with the restricted societal perspective as described in the DMC guidelines (84). In the absence of ToT data from the SoC/FLARITON arm, all direct medical costs were modelled based on the pre-progression health state. While this approach is likely to overestimate costs, it was applied uniformly to both arms.

Given the heterogeneity in the resource use/management cost data from individual tumour locations, the components of HCRU and their frequency of resource use per health state was based on the methodology applied in the NICE submission for regorafenib in the treatment of adults with STS GIST (Bayer Data on File ePAS7 CEM 2023).

All costs were valued in 2024 DKK.

11.1 Medicines - intervention and comparator

To allow for use across the adult and paediatric populations, larotrectinib is available in different formulations (25mg capsules, 100mg capsules and oral solution (20 mg/ml)), with an expected equivalent price across formulations.

All pharmaceutical costs were sourced from the medicinpriser.dk (2024) and applied as pharmacy purchasing prices. The least expensive cost per mg of drug was used to represent unit cost, and drug wastage was not considered for comparators in the base case. A summary of the intervention and comparator costs for each tumour site are presented in Table 43. Drug dosage and accusation costs are presented in Table 44.

For the SoC/FLATIRON arm, a weighted average of tumour-specific costs was included to balance the cost inputs (Refer to Table 44). Refer to Table 206 in Appendix O.3 for the overview of the tumour-specific drug costs.

Table 43 Medicines used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK])(88)
Larotrectinib (oral)	100 mg	56 pcs	42,678
	25 mg	56 pcs	10,670
	20 mg/ml	2 x 50 ml bottles	15,242
SoC/FLATIRON	Refer to Table 206 in Appendix O.3		

Abbreviations: IV, intravenous

Table 44 Drug dosing and total acquisition costs

Regimen	Administra-tion	Popula-tion	Dose	Rela-tive dose inten-sity	Frequency	Vial shar-ing	No	Mod-elled cost per day [DKK]
Intervention								
Larotrectinib	Oral	Adult	Average dose: 191.61 mg	N/A	Once daily	No	1,461	1,461
	Oral	Paediatric	Average dose: 132.06 mg	N/A	Once daily	No	1,025	1,025
Pooled comparator, SoC/FLARITON arm								
SoC/FLATIRON	The drug cost was based on a weighted average of all acquisition costs derived from all specific tumour sites. Weighted average of tumour-specific regimens, refer to Appendix O.3							
Basket of treatment	Weighted average cost of 693 DKK*							

Abbreviations: NSCLC, non-small cell lung cancer; IV, Intravenous; GIST, gastrointestinal stromal tumour; TPC, treatment of physician's choice; CNS, central nervous system.
*Sum of pharmaceutical- and administration costs

11.2 Medicines– co-administration

Not applicable.

11.3 Administration costs

Administration costs for comparators were calculated based on the administration procedure(s) required in each treatment cycle and the number of administrations. Drugs administered orally were assumed to incur no administration cost. Administration costs (Table **45**) were obtained from DRG tariffs 2024.

The larotrectinib modelled pooled cohort is formed of 33% paediatric and 67% adult patients, based on the larotrectinib clinical trial programme. The paediatric patient's treatment formulation is split across 25mg capsules, 100mg capsules and oral solution (20 mg/ml). Presentations of larotrectinib used in the economic model reflect those received in the larotrectinib clinical trial programme and are presented within Figure 16.

Individual patient data from the clinical trial programme for the paediatric proportion of patients are included within the modelled engine, tracking the age of each patient in order to determine switching to adult formulation and dosing and update the proportional split of the overall cohort across all formulations.

For the pooled comparator arm, a weighted average of tumour-specific costs was included to balance the administration cost inputs (refer to Appendix O).

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion, Bokemeyer et al.	N/A*	1,550.00	11MA98	DRG-tariffs 2024 (74)
SoC/FLATIRON	All cost items were based on a weighted average of administration costs derived from all specific tumour sites. Weighted average cost of 693 DKK* Refer to Appendix O.			

Abbreviations: IV, intravenous; DRG, diagnosis-related group.
*Sum of pharmacetucical- and administration cost

11.4 Disease management costs

Disease management costs were sourced from DRG-tariffs and laeger.dk. Only costs associated with the PF health state were considered relevant.

The frequencies for larotrectinib were informed by a previously assessment by DMC. For larotrectinib the costs were assumed to identical for adults and paediatric patients. As for the administration costs, a weighted average of tumour-specific costs was included to balance the administration cost inputs for the SoC/FLATRION arm (refer to Appendix O).

Table 46 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Oncologist visit	Every 4th week	1,989	1st consultation, specialist	The Danish Health Data Authority (2024) (74)
CT scan	Every 4th week	2,021	30PR07	The Danish Health Data Authority (2024) (74)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Blood test	Every 4th week	23	Micro-based approach	Rigshopsitalets Labportal (2024) (89)
Liver function test	Every 4th week	23	Micro-based approach	Rigshopsitalets Labportal (2024) (89)
SoC/FLATIRON	All cost items were based on a weighted average of disease management costs derived from all specific tumour sites. Weighted average start-up (one-off cost) of 974 kr. Weighted average costs of 687 kr. Refer to Appendix O - Table 208 and Table 209.			

Abbreviations: DRG, diagnosis-related group; DMC, Danish Medicines Council; CT, computed tomography

11.5 Costs associated with management of adverse events

The costing codes and unit costs associated with the management of AEs were sourced from the latest version of DRG tariffs, DMC catalogue for unit cost and other relevant websites, as outlined in Table 47. Costs associated with AEs were applied once during the initial model cycle, consistent with the assumption that AEs are primarily associated with treatment initiation rather than ongoing management throughout the entire treatment course. Cost of each AE for larotrectinib was multiple by the frequency presented in Table 34. The cost of treating an adverse event was assumed not to vary based on the patient's tumour site (larotrectinib).

In absence of AE incidence rates for the comparator, SoC/FLATIRON, a weighted average of the tumour-specific safety inputs was applied to the comparator arm. Please refer to Appendix O, Table 210.

The costs of treating AEs are shown in Table 47.

Table 47 Cost associated with management of adverse events

Adverse event	DRG code	Unit cost/DRG tariff [DKK]	Reference
Abnormal liver function	Based on two GP consultations and a blood test	335	DMC catalogue for unit cost 2024 (76); Laeger.dk, Takstkort 2024 (90)
Anaemia	16MA98 Action diagnosis: Anaemia UNS (DD649)*	2,111	Interaktiv.drg (75)
Neutropenia	16MA98 Action diagnosis: Neutropenia UNS (DD709)	2,111	Interaktiv.drg (75)
Thrombocytopenia	16MA98 Action diagnosis: Thrombocytopenia UNS (DD696)*	2,111	Interaktiv.drg (75)
Increased weight	Consultation, GP	156	DMC catalogue for unit cost 2024 (76)

Abbreviations: GP, general practitioner; UNS, Unspecified; DRG, Diagnosis-related group; DMC, Danish Medicines Council; B-ALP, bone-specific alkaline phosphatase
* Secondary diagnosis: Unspecified tumour with other localisation (DD487)
¶ Priority = Urgent; Duration = >12 hours

11.6 Subsequent treatment costs

Not applicable.

Table 48 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	N/A	N/A	N/A	N/A

11.7 Patient costs

Patient costs for transportation and time spent have been included as per the requirements from the DMC. Based on DMC's unit cost catalogue (2024), a unit cost of 140 DKK was applied to all visits and healthcare activities in the model to account for travel expenses, and a unit cost of 188 DDK was used for all patient and informal care hours on treatment-related activities. Patient costs were only considered applicable for patients in the progression-free health state; however, as no data on ToT were available for the comparator arm, all patient costs were modelled using progression-free survival curves.

The frequency of hospital visits was based on the patient resource use (i.e., administration or disease management). No extended validation on the grouping of the items related to the frequency associated with disease management were available. To avoid double counting, the highest frequency of each item in progression-free health state was used to capture the frequency of hospital visits associated to disease management. Lastly, patient costs associated with AEs were not included.

Patient hours associated with administration and disease management activities were only considered for adult patients and informal care hours were only considered relevant for paediatric patients. Informal care hours were calculated based on the total hours of patient care, plus one additional hour for transportation per round trip per hospital visit. Patient hours associated with NRKT testing was applied as a one-off cost in the first treatment cycle. These were only evident for the larotrectinib arm. Patient hours used in the model are reported in Table 49.

Patient hours used per hospital visit are reported in Table 49. The patient costs associated with the comparator arm were estimated by calculating the weighted average of societal costs from each specific tumour site (reported in Appendix 0).

Table 49 Patient costs used in the model

Activity	Time spent [hours]
Hospital visit, Larotrectinib - adults	Total patient hours: 2 NRKT testing hours: 2
Hospital visit, Larotrectinib - paediatrics	Informal care hours: 2 NRKT testing hours: 3
Hospital visit, SoC/FLATIRON; Bookemeyer et al.	All cost items were based on a weighted average of societal costs derived from specific tumour sites. Refer to Appendix O.

Abbreviations: N/A, not available / not applicable.

Notes: Patients hours associated with administration and disease manamgenet activities were only considered for adult patients to avoid double counting. Informal care hours were calculated based on the total hours of patient care, plus one additional hour for transportation to and from the hospital for treatment per hospital visit. Informal care hours were only considered for paediatric patients.

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

Palliative care costs were omitted in the analysis, as they are generally not considered in DMC assessment.

Testing cost

As mentioned in the clinical section, Section 3.1.2, patients can be treated with larotrectinib if they have an NTRK gene fusion in a tumour sample. Routine testing for NTRK gene fusion is not performed on tumour samples, and there are no clinically validated tests or companion diagnostics available to conduct the test. NGS and IHC can be used to detect fusions. This cost item was also discussed in the previous DMC assessment of larotrectinib.

Therefore, testing costs are included in the cost-effectiveness model as a one-off cost in the first cycle for all patients treated with larotrectinib. The model assumes that NTRK fusion testing is necessary for identifying patients eligible for treatment with larotrectinib.

The testing process involves two steps:

- IHC is performed first
- NGS is used to confirm the results for those who test positive by IHC

The DRG tariff 31PR02 has been applied in the model, with a cost of 4,718 DKK (assumed to cover all testing costs)

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 50.

Table 50 Base case overview

Feature	Description
Comparator	SoC/FLATIRON published by Bokemeyer et al. Using tumour-specific treatment regimens in the absence of SoC definition in the FLATIRON data.
Type of model	Partitioned survival model
Time horizon	80 years (lifetime)
Treatment line	Last line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in the larotrectinib trials. Danish population weights were used to estimate health-state utility values for the larotrectinib arm. For the SoC/FLATIRON arm, a weighted average based on tumour-specific utility inputs, was applied.
Costs included	Pharmaceutical costs Disease management costs Costs of adverse events Testing costs (larotrectinib only) Patient costs
Dosage of pharmaceutical	Based on weight. However patient body surface area based on the larotrectinib trials was used when no tumour-specific BSA is available from the TA.
Average time on treatment	Intervention: 4.762* Comparator: 1.049 years*

Feature	Description
Parametric function for PFS	Intervention: Log-normal Comparator: Since no PFS data was obtained from Bokemeyer et al. to inform the SoC/FLATIRON arm, the PFS curves were inferred by using the ratio of OS to PFS from the weighted ePAS8 data (6) (5).
Parametric function for OS	Intervention: Log-normal Comparator: Log-normal
Inclusion of waste	No
Average time in model health state Health state 1 Health state 2 Health state 3 Death	Progression-free: Larotrectinib = 4.76 / SoC=1.05 PD: Larotrectinib = 1.88 years / SoC= 0.164 years

Abbreviations: PFS, progression-free survival; OS, overall survival; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels
*PFS used as a proxy to model ToT: Estimates discounted; PD, progressive disease

12.1.1 Base case results

In the model base case where larotrectinib is compared against SoC presented by the FLATIRON data reported by Bokemeyer et al, discounted results are presented in Table 51.

The discounted incremental costs of 2,269,131 DKK and incremental QALYs of 4.9 resulted in an ICER of 463,332 DKK / QALY versus SoC/FLATIRON.

Table 51 Base case results, discounted estimates

	Larotrectinib	SoC/FLATIRON	Difference
Pharmaceutical costs	2,284,532	263,869	2,020,662
Pharmaceutical costs – co-administration*	N/A	N/A	N/A
Administration*	N/A	N/A	N/A
Testing costs	4,718	0	4,718
Disease management costs, PF	250,674	37,761	212,913
Disease management costs, PD	N/A	N/A	N/A
Costs associated with management of adverse events	9,694	214	9,480
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	46,710	24,812	21,358
Total costs	**2,595,788**	**326,657**	**2,269,131**
Life years gained - PF	4.76	1.05	3.71
Life years gained – PD	1.88	0.16	1.72
Total life years	**6.6**	**1.2**	**5.4**
QALYs – PF	4.06	0.59	3.47
QALYs - PD	1.52	0.07	1.44
QALYs (adverse reactions)	-0.02	-0.01	-0.02
Total QALYs	**5.6**	**0.7**	**4.9**

Incremental costs per life year gained	**417,978 DKK**
Incremental cost per QALY gained (ICER)	**463,332 DKK**

Abbreviations: QALY= quality-adjusted life-years; SoC= standard of care
*Included in pharmaceutical costs

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications (for the PSA), including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by ±20% or by a specific standard errors or predefined upper and lower limits (hence lower value and upper value are provided in the table below). The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 52 and as a tornado diagram in Figure 20.

Table 52 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			2,269,131	4.90	463,332
Lower bounds					
PFS log-normal shape (sigma) - Larotrectinib Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
PFS log-normal scale (mu) - Larotrectinib Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Progression free health state cost - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Progressed disease utility - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Total patient cost per cycle, progression-free (larotrectinib)	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
OS log-normal shape (sigma) - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
OS log-normal scale (mu) - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.85	[redacted]
Adverse event disutility (weighted average) - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.80	[redacted]
Adverse event cost (weighted average) - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Model paediatric start age (years)	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Upper bounds					

PFS log-normal shape (sigma) - Larotrectinib Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
PFS log-normal scale (mu) - Larotrectinib Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.83	[redacted]
Progression free health state cost - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.89	[redacted]
Progressed disease utility - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.82	[redacted]
Total patient cost per cycle, progression-free (larotrectinib)	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
OS log-normal shape (sigma) - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.89	[redacted]
OS log-normal scale (mu) - Bokemeyer	[redacted]	Parameter uncertainty	[redacted]	4.95	[redacted]
Adverse event disutility (weighted average) - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.99	[redacted]
Adverse event cost (weighted average) - Larotrectinib adults	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]
Model paediatric start age (years)	[redacted]	Parameter uncertainty	[redacted]	4.90	[redacted]

Abbreviations: OS, overall survival; PFS, progression-free survival

Figure 20 One way sensitivity analysis – tornado graph

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings, refer to Table 53. Important factors for estimating the ICER of treatment with larotrectinib include: extrapolations of OS and PFS, PFS assumption for the SoC/FLARITON arm, utilities weighted with UK tariffs, and time horizon.

Table 53 Scenario analysis

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case				**4.9**	
OS larotrectinib					
Gompertz		Structural uncertainty and potential curative effect.		8.0	
Generalised Gamma		Same as above		6.4	
Exponential		Structural uncertainty		2.9	
OS SoC/FLARITON					
Gompertz		Structural uncertainty		4.9	
Exponential		Structural uncertainty		4.9	
PFS larotrectinib					
Gompertz		Structural uncertainty		5.0	
Exponential		Structural uncertainty		4.8	
PFS assumption					
100 % progressed in SoC/FLARITON arm		Structural uncertainty		5.0	
Utility analysis					
UK weights applied to the larotrectinib arm		To test the impact of treatment-specific utilities.		4.3	
Time horizon					
10-years		Alternative time horizon		2.8	

Abbreviations: OS, overall survival; QALY, Quality-adjusted life years

12.2.2 Probabilistic sensitivity analyses

A scatter plot of 1,000 simulations, including a 95% confidence cloud, is presented in Figure 21, with a cost-effectiveness acceptability curve presented in Figure 22. The full set of parameters included in the model (including details of distributional forms) and the PSA analysis are presented in Appendix G.

Figure 21 Cost-effectiveness scatterplot

Figure 22 Cost-effectiveness acceptability curves for larotrectinib

Convergence plots for costs and QALYs can be found in Figure 23 and Figure 24, respectively.

Figure 23 Convergence for costs

Figure 24 Convergence for QALYs

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending larotrectinib in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model will affect the results of the budget impact model.

The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient time and transportation cost have not been included as per the DMC guidelines (84).

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where larotrectinib is recommended as a standard treatment and the scenario where larotrectinib is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

In the previous DMC assessment of larotrectinib, the expert committee estimated approximately 5 patients (adults and children) yearly would be eligible for treatment with larotrectinib in Denmark (23), refer to Section 3.2 for further information. The share is assumed to grow up to approximately 100% in years 0 to 1.

Table 54 Number of new patients expected to be treated over the next five-year period if the pharmaceutical is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Larotrectinib	5	5	5	5	5
SoC/FLATIRON	0	0	0	0	0
			Non-recommendation		
Larotrectinib	0	0	0	0	0
SoC/FLATIRON	5	5	5	5	5

Budget impact

Table 55 Expected budget impact of recommending the pharmaceutical for the indication, DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Larotrectinib is recommended	[redacted]	[redacted]	[redacted]	[redacted]	835,007
Larotrectinib is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	18,842
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	816,165

14. List of experts

NA

15. References

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Appendix A. Main characteristics of studies included

Table 56 Main characteristic of ePAS8

Trial name: ePAS8	**NCT number:** NCT02122913, NCT02637687, NCT02576431
Objective	IPD for adult and paediatric patients harbouring TRK fusion-positive tumours from larotrectinib trials (LOXO-TRK-14001, SCOUT, and NAVIGATE; (pooled Analysis Set Study Summary: ePAS8 (DCO: 20 July 2023) describes the efficacy of larotrectinib in patients with NTRK+ solid tumours. The clinical development program includes 3 clinical trials in adult and paediatric patients, which are open to all solid tumour histologist due to the limited numbers of patients with *NTRK* fusion-positive solid tumours. The 3 trials are: **LOXO-TRK-14001 (NCT02122913)** • Adult patients with advanced solid tumours (including both TRK fusion-positive and fusion-negative) **SCOUT (NCT02637687)** • Paediatric patients with advanced solid tumours[a] **NAVIGATE (NCT02576431)** • Only adolescent and adult patients with tumours harbouring a documented NTRK gene fusion
Publications – title, author, journal, year	N/A
Study type and design	**LOXO-TRK-14001 (NCT02122913)** • Phase 1, dose escalation, multicentre, open-label and single-arm **SCOUT (NCT02637687)** • Phase 1/2, multicentre, open-label and single-arm **NAVIGATE (NCT02576431)** • Phase 2, multicentre, open-label and single-arm
Sample size (n)	The ePAS8 dataset consists of 302 patients in a series of pooled analysis sets derived from the original primary analysis set (PAS) of 55 patients, first established with a DCO in July 2017. Over time, subsequent datasets (ePAS, ePAS2, ePAS4, ePAS5, ePAS6, and ePAS7) have been created, each extending the follow-up period and including additional patients. The ePAS8 dataset, with a July 2023 DCO, includes patients from ePAS7 (N=272) and an additional 30 patients who were enrolled after the ePAS7 DCO. This initial evaluation of the ePAS8 analysis set is performed using data from the 20 JUL 2023 cut-off date.
Main inclusion criteria	All patients in ePAS8 had been enrolled at least 6 months before the DCO and met the following inclusion criteria: documented NTRK gene fusion based on local testing, a non-CNS primary tumour that could be assessed according to RECIST version 1.1, and receipt of at least one dose of

larotrectinib. Additional inclusion criteria for each trial are as follows:

LOXO-TRK-14001 (NCT02122913)

- Adult patients with a locally advanced or metastatic solid tumour that has progressed or was nonresponsive to available therapies, are unfit for standard chemotherapy or for which no standard or available curative therapy exists
- Proof of a malignancy harbouring a NTRK fusion
- ECOG score of 0, 1 or 2 and a life expectancy of at least 3 months
- Adequate hematologic, hepatic, and renal function

SCOUT (NCT02637687)

Phase 1:

- Dose escalation: Birth through 21 years of age at C1D1 with a locally advanced or metastatic solid tumour or primary CNS tumour that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy exists; OR Infants from birth and older with a diagnosis of malignancy and with a documented NTRK fusion that has progressed or was nonresponsive to available therapies, and for which no standard or available curative therapy exists; OR Patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection. Phase I dose escalation cohorts are closed to enrolment.
- Dose expansion: In addition to the above stated inclusion criteria, patients must have a malignancy with a documented NTRK gene fusion with the exception of patients with infantile fibrosarcoma, congenital mesoblastic nephroma or secretory breast cancer. Patients with infantile fibrosarcoma, congenital mesoblastic nephroma or secretory breast cancer may enrol into this cohort with documentation of an ETV6 rearrangement by FISH or RT-PCR or a documented NTRK fusion by next generation sequencing.

Phase 2:

- Infants from birth and older at C1D1 with a locally advanced or metastatic infantile fibrosarcoma, patients with locally advanced infantile fibrosarcoma who would require, in the opinion of the investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection; OR Birth through 21 years of age at C1D1 with a locally advanced or metastatic solid tumour or primary CNS tumour that has relapsed, progressed or was nonresponsive to available therapies and for which no standard or available systemic curative therapy exists with a documented NTRK gene

fusion (or in the case of infantile fibrosarcoma, congenital mesoblastic nephroma or secretory breast cancer with documented ETV6 rearrangement (or NTRK3 rearrangement after discussion with the sponsor) by FISH or RT-PCR. Patients with NTRK-fusion positive benign tumours are also eligible; OR Potential patients older than 21 years of age with a tumour diagnosis with histology typical of a paediatric patient and an NTRK fusion may be considered for enrolment following discussion between the local site Investigator and the Sponsor.

- Patients with primary CNS tumours or cerebral metastasis
- Karnofsky (those 16 years and older) or Lansky (those younger than 16 years) performance score of at least 50.
- Adequate hematologic function
- Adequate hepatic and renal function

NAVIGATE (NCT02576431)

- Locally-advanced or metastatic malignancy with an NTRK1, NTRK2, or NTRK3 gene fusion, identified through molecular assays as routinely performed at CLIA or other similarly-certified laboratories. Subjects who have an NTRK gene fusion identified in a lab where CLIA or equivalent certification cannot be confirmed by the Sponsor at the time of consent may have been enrolled in Cohort 9 as per protocol versions 1.0 - 8.0. From protocol version 9.0: CLIA or similar certification of the lab performing the fusion assay is required. However, patients may be included after discussion with the sponsor if the lab performing the fusion assay is not CLIA or similar certified.
- Subjects who have received prior standard therapy appropriate for their tumour type and stage of disease, or who have no satisfactory alternative treatments and in the opinion of the Investigator, would be unlikely to tolerate or derive clinically meaningful benefit from appropriate SoC therapy.
- Subjects must have at least one measurable lesion as defined by RECIST v1.1 (91). Subjects with solid tumours without RECIST v1.1 measurable disease (e.g., evaluable disease only) had been eligible for enrolment to Cohort 8 as per protocol versions 1.0 - 8.0, regardless of tumour type. Subjects with primary CNS tumours should meet the following criteria:
    1. Have received prior treatment including radiation and/or chemotherapy, with radiation completed > 12 weeks prior to C1D1 of therapy, as recommended or appropriate for that CNS tumour type.
    2. Have ≥ 1 site of bi-dimensionally measurable disease (confirmed by MRI and evaluable by

RANO criteria), with the size of at least one of the measurable lesions ≥ 1 cm in each dimension and noted on more than one imaging slice.

3. Imaging study performed within 28 days before enrolment. If on steroid therapy, the dose must be stable for at least 7 days immediately before and during the imaging study.
4. Must be neurologically stable based on stable neurologic exam for 7 days prior to enrolment.

For subjects eligible for enrolment to bone health cohort, inclusion criterion 3 is modified as the following:

5. Subjects must have at least one lesion at baseline (measurable or non-measurable as defined by RECIST v1.1 or RANO criteria, as appropriate to tumour type).
6. Subjects with primary CNS tumours must be neurologically stable based on stable neurologic exam for 7 days prior to enrolment.

- At least 18 years of age
- Performance Status: ECOG score ≤ 3. If enrolled with primary CNS tumour to be assessed by RANO, KPS ≥ 50%.
- Tumour tissue before treatment (mandatory). If neither fresh tissue can be obtained nor archival tissue is available patients might be enrolled after consultation with the sponsor.
- Adequate organ function as defined by the following criteria:
    1. Serum AST and serum ALT < 2.5 x ULN, or AST and ALT < 5 x ULN if liver function abnormalities are due to underlying malignancy
    2. Total bilirubin < 2.5 x ULN, except in the setting of biliary obstruction. Subjects with a known history of Gilberts Disease and an isolated elevation of indirect bilirubin are eligible
    3. Serum creatinine < 2.0 x ULN OR an estimated glomerular filtration rate ≥ 30 mL/minute using the Cockcroft-Gault formula: (140- age) x body weight (kg) x 0.85 (if female)/serum creatinine (mg/dL) x 72 with either result acceptable for enrolment.
- Ability to comply (or for guardian to ensure compliance) with outpatient treatment, laboratory monitoring, and required clinic visits for the duration of study participation.
- Willingness of men and women of reproductive potential to use double effective birth control methods, defined as one used by the subject and another by his/her partner, for the duration of treatment and for 1 month following study completion.

Trial name: ePAS8	NCT number: NCT02122913, NCT02637687, NCT02576431
	• For subjects eligible for enrolment to bone health cohort only: life expectancy of at least 6 months, based on investigator assessment.
Main exclusion criteria	**LOXO-TRK-14001 (NCT02122913)** • Patients with unstable primary central-nervous-system tumours or metastasis, exceptions possible • Clinically significant active cardiovascular disease or history of myocardial infarction • Active uncontrolled systemic bacterial, viral, or fungal infection • Current treatment with a strong CYP3A4 inhibitor or inducer • Pregnancy or lactation **SCOUT (NCT02637687)** • Major surgery within 14 days (2 weeks) prior to C1D1 • Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to C1D1, ongoing cardiomyopathy; current prolonged QTc interval > 480 milliseconds • Active uncontrolled systemic bacterial, viral, or fungal infection • Current treatment with a strong CYP3A4 inhibitor or inducer. EIAEDs and dexamethasone for CNS tumours or metastases, on a stable dose, are allowed. Phase 2 only: • Prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK, including Entrectinib, Crizotinib and Lestaurtinib. Patients who received a TRK inhibitor for less than 28 days of treatment and discontinued because of intolerance remain eligible. **NAVIGATE (NCT02576431)** 1. Investigational agent or anticancer therapy within 2 weeks prior to the planned start of larotrectinib or 5 half-lives, whichever is shorter, and without recovery of acute and/or clinically significant toxicities from that therapy. 2. Prior progression while receiving approved or investigational tyrosine kinase inhibitors targeting TRK. Subjects who received less than 28 days of treatment and discontinued because of intolerance or toxicity are eligible. 3. Symptomatic or unstable brain metastases. (Note: Subjects with asymptomatic brain metastases are eligible to participate in the study.) Subjects with primary CNS tumours are eligible. 4. Uncontrolled concurrent malignancy that would limit assessment of efficacy of larotrectinib. Allowed conditions may include but are not limited to in situ cancers of cervix, breast, or skin, superficial bladder cancer,

Trial name: ePAS8	NCT number: NCT02122913, NCT02637687, NCT02576431
	limited-stage prostate cancer, and basal or squamous cancers of the skin. 5. Active uncontrolled systemic bacterial, viral, or fungal infection CTCAE grade ≥ 2; unstable cardiovascular disease, or other systemic disease that would limit compliance with study procedures. Unstable cardiovascular disease is defined as: 1. In adults, persistently uncontrolled hypertension defined as systolic BP > 150 mmHg and/or diastolic BP > 100 mmHg despite antihypertensive therapy. 2. Myocardial infarction within 3 months of screening. 3. Stroke within 3 months of screening. 6. Inability to discontinue treatment with a strong CYP3A4 inhibitor or inducer 7. Currently recovering from AEs/ ADRs due to previous treatments (excluding alopecia). Inclusion is only advised once the AE/ADR resolves or recovers to baseline or at least to CTCAE grade 1. 8. Known or suspected hypersensitivity against the active substance or any of the ingredients of the IMP. 9. Known history of HIV infection. All patients must be screened for HIV up to 28 days prior to study drug start using a blood test for HIV according to local regulations. 10. HBV or HCV infection. All patients must be screened for HBV and HCV up to 28 days prior to study drug start using the routine hepatitis virus laboratorial panel. Patients positive for HBsAg or HBcAb will be eligible if they are negative for HBVDNA. Patients positive for anti-HCV antibody will be eligible if they are negative for HCV-RNA.
Intervention	**Enrolled and treated, by study (in ePAS8)(4):** • Study number 20288: 13 patients • Study number 20289: 189 patients • Study number 20290: 100 patients **LOXO-TRK-14001 (NCT02122913) Study 20288** Larotrectinib, a dose of 50 mg once daily to 200 mg twice daily. **SCOUT (NCT02637687) Study 20290** Larotrectinib, a dose up to 100 mg/m2 twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution), the maximum dose is 100 mg per dose. **NAVIGATE (NCT02576431) Study 20289** Larotrectinib, a dose of 100 mg twice daily (25 mg, 100 mg capsules or 20 mg/mL oral solution).
Comparator(s)	N/A
Follow-up time	After a median follow-up of 36.9 months, the median DoR was 43.3 months.

Trial name: ePAS8	NCT number: NCT02122913, NCT02637687, NCT02576431
	After a median follow-up of 35.9 months, the median PFS was 28.1 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary endpoint for efficacy analyses was ORR. Duration of response, safety, OS and PFS were included as secondary endpoints. QoL was included as an exploratory endpoint. Tumour responses were assessed by using RANO or RECIST v1.1 criteria. **Other endpoints:** In adolescents and adults (NAVIGATE trial), evaluate changes from baseline in HRQoL and health utility measures as measured by the EORTC QLQ-C30 and EQ-5D-5L for patients aged 18 years and older and the PedsQL-Core for patients aged 12 to 17 to evaluate changes from baseline in HRQoL. In paediatrics (phase 2 SCOUT trial), evaluate changes from baseline in QoL and health utility measures as measured by the Wong-Baker FACES Scale and PedsQL-Core. The PedsQL-Core scale was completed by the patient or their parent/caregiver.
Method of analysis	Analyses were conducted using the ITT approach
Subgroup analyses	Subgroup analyses were conducted in the ePAS8 dataset by age, comparing the paediatric and adult populations. The analysis focused on efficacy and treatment outcomes for patients with confirmed CR, PR, or pCR. The following key analyses were performed: 1. **ORR according to IRC Assessment** A subgroup analyses were conducted of 195 patients. These analyses provided a median time to response[b], expressed in months along with the IQR. 2. **Efficacy Outcomes for the ePAS8 Population** An analysis of 182 patients, on the following efficacy outcomes were analysed: • **Median Time to Response**: The number of months (IQR) from the first dose to confirmed response. • **Median DoR**: Reported in months with a 95% CI, indicating the duration for which the patients maintained their response to larotrectinib. • **Median Follow-up for DoR**: Measured in months with IQR, providing insight into the length of follow-up for these patients' responses. 3. **Efficacy Endpoints in the Paediatric Population** Another analysis was conducted on the paediatric subset (n=85). The efficacy endpoints included: • **Median DoR**: Expressed in months with a 95% CI, this reflects the duration that paediatric patients maintained their response to the treatment. • **Median Follow-up for DoR**: Measured in months with IQR, this provides the length of

Trial name: ePAS8	NCT number: NCT02122913, NCT02637687, NCT02576431
	time the paediatric patients were followed to assess their duration of response.

Other relevant information

Abbreviations: ePAS, extended primary analysis set; IPD, individual patient level data; TRK, tyrosine receptor kinase; DCO, data cut-off; NTRK, Neurotrophic tyrosine receptor kinase; RECIST, Response Evaluation Criteria in Solid Tumours; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; C1D1, Class 1 Division 1; OR, Overall response; FISH, fluorescence in situ hybridization; RT-PCR, reverse-transcription polymerase chain reaction; CLIA, Clinical Laboratory Improvement Amendments; MRI, magnetic resonance imaging; RANO, Response Assessment in Neuro-Oncology; KPS, Karnofsky Performance Score; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal; EIAEDs, Enzyme-inducing anti-epileptic drugs; CTCAE, Common Terminology Criteria for Adverse Events, BP, blood pressure; AEs, adverse events; ADRs, adverse drug reactions; IMP, Investigational Medicinal Product; HIV, human immunodeficiency virus; HBV, hepatitis B; HCV, hepatitis C; HBsAg, hepatitis B surface antigen; HBcAb, Hepatitis B core antibody; HBVDNA, hepatitis B virus DNA; HCV-RNA, hepatitis C virus ribonucleic acid; N/A, not available / not applicable; ORR, Overall response rate; OS, overall survival, PFS, progeression free survival; QoL, quality of life; HRQoL, health related quality of life; EORTC QLQ-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L, EuroQol 5-Dimensions 5-Levels; PedsQL-Core, Paediatrics Quality of Life – Core Module; ITT, intention-to-treat; CR, complete response; PR, partial response; pCR, pathological com-plete response; IRC, independent review committee; IQR, interquartile range; DoR, duration of response, CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging.

[a] It should be noted that the phase 2 enrollment of the pediatric study (SCOUT) also included only patients with tumours harboring a documented NTRK gene fusion; however, these patients were assigned to a cohort based on tumour location (intracranial vs extracranial)

[b] The time to response was defined as the period from the first dose of larotrectinib to the first documented objective response (CR, pCR, or PR), whichever occurred earliest and was subsequently confirmed.

Table 57 Main characteristic of studies included

Trial name: Bokemeyer	NCT number: NCT02122913, NCT02637687, NCT02576431
Objective	Larotrectinib, a highly specific TRK inhibitor, previously demonstrated high response rates in single-arm trials of patients with TRK fusion-positive cancer, but there are limited data on comparative effectiveness against SoC regimens used in routine health care practice, before widespread adoption of TRK inhibitors as SoC for TRK fusion-positive cancers. MAIC, a validated methodology that balances population characteristics to facilitate cross-trial comparisons, was used to compare the OS of larotrectinib versus non-TRK-inhibitor SoC.
Publications – title, author, journal, year	Zhang W, Schmitz AA, Kallionpää RE, Perälä M, Pitkänen N, Tukiainen M, Alanne E, Jöhrens K, Schulze-Rath R, Farahmand B, Zong J. Neurotrophic tyrosine receptor kinase gene fusions in adult and paediatric patients with solid tumours: a clinicogenomic biobank and record linkage study of expression frequency and patient characteristics from Finland. Acta Oncol. 2024 Jul 5;63:542-551. doi: 10.2340/1651-226X.2024.26452. PMID: 38967220; PMCID: PMC11332464. Willis C, Au T, Hejazi A, Griswold C, Schabath MB, Thompson J, Malhotra J, Federman N, Ko G, Appukkuttan S, Warnock N, Kong SX, Hocum B, Brixner D, Stenehjem D. Clinical characteristics and treatment patterns of patients with *NTRK* fusion-positive solid tumours: A multisite cohort study at US academic cancer centers. J Manag Care Spec Pharm. 2024 Jul;30(7):672-683. doi: 10.18553/jmcp.2024.30.7.672. PMID: 38950155; PMCID: PMC11217863. Santi I, Vellekoop H, M Versteegh M, A Huygens S, Dinjens WNM, Mölken MR. Estimating the Prognostic Value of the NTRK Fusion Biomarker for Comparative Effectiveness Research in The Netherlands. Mol Diagn Ther. 2024 May;28(3):319-328. doi: 10.1007/s40291-024-00704-2. Epub 2024 Apr 14. PMID: 38616205; PMCID: PMC11068666.

Trial name: Bokemeyer	NCT number: NCT02122913, NCT02637687, NCT02576431
Study type and design	MAIC using aggregate real-world data identified in the Flatiron/Foundation Medicine database.
Sample size (n)	85 larotrectinib patients and 28 non-TRK-inhibitor SoC patients
Main inclusion criteria	**Intervention** • July 2020 DCO for the integrated patient population • Known dates of initial metastatic diagnosis • Age ≥ 18 years • TRK inhibitor-naive • Prior lines of systemic therapies ≤ 4 **Comparator** • ≥ 1 test by next-generation sequencing on tumour tissue • ≥ 1 NTRK fusion-positive test result • Locally advanced or metastatic diagnosis between January 2011 and December 2019 • No prior treatment with a TRK inhibitor • No visit gap of > 90 days after diagnosis • No prior unlabelled study drug as part of a clinical trial
Main exclusion criteria	**Intervention** N/A **Comparator:** The study excluded other potential comparators (Voyager 1, Voyager 2, Santi, and Zhu) because they lacked essential data such as ECOG performance status, CNS metastasis, baseline characteristics, and OS analysis, or had mismatches in the index date definitions. These limitations made them unsuitable for accurate comparison. Hibar et al./Demetri et al. was chosen as the comparator because it provided the necessary baseline characteristics and aligned index dates.
Intervention	The intervention was larotrectinib, administered orally in doses ranging from 50 mg once daily to 200 mg twice daily.
Comparator(s)	The comparator was SoC treatments, which included chemotherapy, radiotherapy, surgery, targeted therapies, and/or immuno-oncology agents, depending on the type of cancer. The SoC data were drawn from real-world data in the Flatiron Health/Foundation Medicine database.
Follow-up time	N/A
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	The primary endpoint was OS, defined as the time from diagnosis of advanced/metastatic disease to death.
Method of analysis	Individual patient data from three larotrectinib trials (NCT02122913, NCT02637687, and NCT02576431) were compared with published aggregate real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron Health/Foundation Medicine database. OS was defined as the time from advanced/metastatic disease diagnosis to death. After matching population characteristics, the following analyses were conducted: • A log-rank test of equality to test whether the two groups were similar before larotrectinib initiation

Trial name: Bokemeyer	NCT number: NCT02122913, NCT02637687, NCT02576431
	• Estimation of treatment effect of larotrectinib versus non–TRK-inhibitor SoC. These analyses are limited to prognostic variables available in real-world data.
Subgroup analyses	N/A
Other relevant information	N/A

TRK, tropomyosin receptor kinase; SoC, standard-of-care; MAIC, matching-adjusted indirect comparison; OS, overall survival; DCO, data cut-off; N/A, not available / not applicable; ECOG, Eastern Cooperative Oncology Group, CNS, central nervous system

Appendix B. Efficacy results per study

Results per study

Table 58 Results per ePAS8 (pooled analysis, DCO: Jule 2023)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CR (IRC assessment)	Larotrectinib	302	n: 65 (22%)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
pCR (IRC assessment)	Larotrectinib	302	n: 17 (6%)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
PR (IRC assessment)	Larotrectinib	302	n: 113 (37%)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
SD (IRC assessment)	Larotrectinib	302	n: 55 (18%)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Response rates were summarised	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										descriptively by number and percentage.	
ORR (IRC assessment)	Larotrectinib	302	65 (59, 70)	N/A	N/A	N/A	N/A	N/A	N/A	ORR by IRC assessment and RECIST v1.1 or Response Assessment in Neuro-Oncology Criteria, defined as the proportion of patients with best OR of confirmed CR (or pCR) or confirmed PR. Responses (CR or PR) were to be confirmed by a repeat assessment performed no less than 28 days after the criteria for response were first met. Response rates were summarised descriptively by number and percentage. Point estimates are accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
CR confirmed (investigator assessment)	Larotrectinib	302	n: 48 (16%)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
pCR (investigator assessment)	Larotrectinib	302	n: 10 (3%)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
PR confirmed (investigator assessment)	Larotrectinib	302	n: 135 (45%)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
PR pending confirmation (investigator assessment)	Larotrectinib	302	n: 2 (1%)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
SD (investigator assessment)	Larotrectinib	302	n: 69 (23%)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage.	Bayer 2024 (4)
ORR (investigator assessment)	Larotrectinib	302	64 (58, 69)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Response rates were summarised descriptively by number and percentage. Point estimates are accompanied by a 2-sided 95% exact binomial CI using the Clopper-Pearson method.	Bayer 2024 (4)
Median time to first response (IRC assessment)	Larotrectinib	302	1.84 (range: 0.89, 22.90) months	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Time to response and time to best response (calculated for responders only) were summarised descriptively by calculating the median and interquartile range.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median time to best response (IRC assessment)	Larotrectinib	302	2.33 (range: 0.89, 35.84) months	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. Time to response and time to best response (calculated for responders only) were summarised descriptively by calculating the median and interquartile range.	Bayer 2024 (4)
Median time to first response (investigator assessment)	Larotrectinib	302	1.84 (range: 0.89, 9.07) months	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Time to response and time to best response (calculated for responders only) were summarised descriptively by calculating the median and interquartile range.	Bayer 2024 (4)
Median time to best response (investigator assessment)	Larotrectinib	302	1.87 (range: 0.89, 47.11) months	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. Time to response and time to best response (calculated for responders only) were summarised descriptively by calculating the median and interquartile range.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median DoR (IRC assessment)	Larotrectinib	302	43.3 (32.9, not estimable) months	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. DoR (calculated for responders only) was summarised descriptively using the KM method with the 95% CI about the median calculated using Greenwood's formula. Median follow-up for DoR (only presented in Table 19) was estimated according to the KM estimate of potential follow-up.	Bayer 2024 (4)
Median DoR (investigator assessment)	Larotrectinib	302	43.3 (29.7, 58.6) months	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. DoR (calculated for responders only) was summarised descriptively using the KM method with the 95% CI about the median calculated using Greenwood's formula. Median follow-up for DoR (only presented in Table 19) was estimated according to	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										the KM estimate of potential follow-up.	
Median duration of PFS (IRC assessment)	Larotrectinib	302	28.1 (19.6, 35.8) months	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The median PFS is based on the KM estimator. Analytical methods used for DoR were also used for PFS.	Bayer 2024 (4)
≥6 months rate of PFS (IRC assessment)	Larotrectinib	302	75% (70, 80)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the KM estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
≥12 months rate of PFS (IRC assessment)	Larotrectinib	302	62% (56, 68)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥18 months rate of PFS (IRC assessment)	Larotrectinib	302	58% (52, 64)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										sided 95% CIs using Greenwood's formula.	
≥24 months rate of PFS (IRC assessment)	Larotrectinib	302	54% (48, 60)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥36 months rate of PFS (IRC assessment)	Larotrectinib	302	43% (37, 50)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	
≥48 months rate of PFS (IRC assessment)	Larotrectinib	302	39% (32, 46)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥60 months rate of PFS (IRC assessment)	Larotrectinib	302	33% (25, 40)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the KM estimator. The proportion of patients alive and without documented PD at 6-monthly	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	
≥72 months rate of PFS (IRC assessment)	Larotrectinib	302	30% (22, 39)	N/A	N/A	N/A	N/A	N/A	N/A	IRC assessed. The survival rates are based on the Kaplan–Meier estimator. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
Median duration of PFS	Larotrectinib	302	23.7 (16.6, 31.5) months	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The median PFS is based on the KM estimator. Analytical	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Differ-ence	95% CI	*P* value	Differ-ence	95% CI	*P* value		
(investiga-tor assess-ment)										methods used for DoR were also used for PFS.	
≥6 months rate of PFS (investiga-tor assess-ment)	Larotrectinib	302	73% (68 ,78)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Green-wood's formula.	Bayer 2024 (4)
≥12 months rate of PFS (investiga-tor assess-ment)	Larotrectinib	302	61% (55, 67)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										sided 95% CIs using Greenwood's formula.	
≥18 months rate of PFS (investigator assessment)	Larotrectinib	302	55% (48, 61)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥24 months rate of PFS (investigator assessment)	Larotrectinib	302	50% (43 ,56)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										sided 95% CIs using Greenwood's formula.	
≥36 months rate of PFS (investigator assessment)	Larotrectinib	302	42% (35, 48)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥48 months rate of PFS (investigator assessment)	Larotrectinib	302	37% (30, 44)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										sided 95% CIs using Greenwood's formula.	
≥60 months rate of PFS (investigator assessment)	Larotrectinib	302	31% (23, 38)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-sided 95% CIs using Greenwood's formula.	Bayer 2024 (4)
≥72 months rate of PFS (investigator assessment)	Larotrectinib	302	29% (21, 37)	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessed. The proportion of patients alive and without documented PD at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib were calculated according to the KM method, along with 2-	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										sided 95% CIs using Greenwood's formula.	
Median duration of OS	Larotrectinib	302	Not yet estimable (63.4, not yet estimable) months	N/A	N/A	N/A	N/A	N/A	N/A	Patients who were alive or lost to follow-up as of the DCO date were right-censored. Overall survival was summarised descriptively using the KM method with the 2 sided 95% CI about the median calculated using Greenwood's formula. Median follow-up for OS (only presented in Table 21) was estimated according to the KM estimate of potential follow-up.	Bayer 2024 (4)
≥6 months rate of OS	Larotrectinib	302	91% (88, 94)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										a manner similarly to that described above for PFS.	
≥12 months rate of OS	Larotrectinib	302	83% (79, 87)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)
≥18 months rate of OS	Larotrectinib	302	76% (71, 81)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)
≥24 months rate of OS	Larotrectinib	302	74% (68, 79)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	
≥36 months rate of OS	Larotrectinib	302	70% (64, 75)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)
≥48 months rate of OS	Larotrectinib	302	64% (58, 70)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)

Results of pooled analysis of LOXO-TRK-14001 (NCT02122913), SCOUT (NCT02637687), and NAVIGATE (NCT02576431)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
≥60 months rate of OS	Larotrectinib	302	61% (55, 68)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)
≥72 months rate of OS	Larotrectinib	302	57% (50, 65)	N/A	N/A	N/A	N/A	N/A	N/A	The proportion of patients alive at 6-monthly intervals until 24 months and 12-monthly intervals thereafter following the initiation of larotrectinib was evaluated in a manner similarly to that described above for PFS.	Bayer 2024 (4)

Abbreviations: CR, complete response; DCO, data cut-off; DoR, duration of response; ePAS, extended primary analysis set; IRC, Independent review committee; N/A, not available / not applicable; OR, overall response; ORR, overall response rate; OS, overall survival; pCR, pathological compete response; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

Note: In the result column (the 4th column), 95% CIs are provided in parentheses unless otherwise stated. For instance, in some cases percentages or ranges are provided instead.

Source: Bayer 2024 (4).

Table 59 Results per Hibar et al./Demetri et al. (reported by Bokemeyer et al. 2023) (Larotrectinib DCO: ePAS5 2020)

Results of Hibar et al./Demetri et al. (reported by Bokemeyer et al. 2023; DCO: ePAS5 2020)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Out-come	Study arm	N	Result (95% CI)	Differ-ence	95% CI	*P* value	Differ-ence	95% CI	*P* value		
Median OS	SoC/Flatiron or Flatiron FMI as reported	28	10.2 (7.2, 14.1) months	Reference			Reference			The median survival is based on the KM estimator. HR from Cox model was used to compare the groups.	Bokemeyer et al. 2023 (6)
	Larotrectinib, before match-ing	85	Not reached	N/A	N/A	N/A	0.09	0.05, 0.19	0.00		
	Larotrectinib, after matching	85‡	39.7 (16.4, not estima-ble) months	29.5 months	N/A	N/A	0.22	0.09, 0.52	0.001		

Abbreviations: DCO, data cut-off; ePAS, extended primary analysis set; FMI, Foundation Medicine Inc.; HR, hazard ratio; N/A, not available / not applicable; OS, overall survival.
Notes: ‡ Effective sample size = 13.14.
Source: Bokemeyer et al. 2023 (4).

Appendix C. Comparative analysis of efficacy

C.1 Methodology

As the larotrectinib trials are single-arm trials, there is no direct head-to-head evidence to compare the clinical efficacy of larotrectinib and SoC for NTRK fusion positive solid tumours. To inform the comparative analyses between larotrectinib and SoC, a MAIC was conducted in 2023 (Bokemeyer et al. 2023) (6).

With the availability of a more recent data cut from 2024, ePAS8 (DCO: July 2023), the ePAS8 data was matched with the MAIC weights (derived from Bokemeyer et al., where IPD data from 2020 were matched to the average baseline characteristics from Hibar et al/Demetri et al.). Hence, for this submission, a later data cut, July 2023, has been re-weighted with the MAIC derived weights informed by Bokemeyer et al (6). The re-weighted analysis maintains the same sample size as in the original MAIC; 85 patients for larotrectinib and 28 patients for SoC (Hibar et al/De metri et al) (effective sample size for larotrectinib is 13.14). Although the new data cut includes additional patients, the re-weighting process constrains the analysis to the same populations previously used to preserve the comparability of the results (n=85) (6).

C.1.1 The original MAIC conducted by Bokemeyer et al

Individual patient data from three larotrectinib trials (ClinicalTrials.gov identifiers: NCT02122913, NCT02637687, and NCT025 76431) were compared with published aggregate real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron Health/Foundation Medicine database. OS was defined as the time from advanced/metastatic disease diagnosis to death. After matching population characteristics, the analyses included (1) a log-rank test of equality to test whether the two groups were similar before larotrectinib initiation; and (2) estimation of treatment effect of larotrectinib versus non–TRK-inhibitor SoC. These analyses are limited to prognostic variables available in real-world data.

Bokemeyer et al. selected following published sources for comparative effectiveness studies: Voyager 1/Bazhenova et al (27), Voyager 2/Bridgewater et al (28), Santi et al (30), Zhu et al (31), and Hibar et al (29) (previously presented by Demetri et al (92)). Studies that did not provide sufficient patient data were omitted, and the study by Hibar et al/Demetri et al was selected as the non–TRK-inhibitor SoC comparator.

C.1.1.1 Data sources in original MAIC

Data were collected from three clinical trials involving TRK fusion-positive tumours: a phase I trial (20288/LOXO-TRK-1400), SCOUT, and NAVIGATE. The phase I trial evaluated larotrectinib (50–200 mg daily) in adults with advanced solid tumours (both TRK fusion-positive and negative). SCOUT (phase I/II) assessed larotrectinib (9.6–100 mg/m² twice daily) in paediatric patients with advanced solid or CNS tumours. NAVIGATE (phase II) examined larotrectinib (100 mg twice daily) in paediatric and adult patients with advanced TRK fusion-positive tumours. Eligibility criteria were previously reported.

For the non–TRK-inhibitor SoC comparator, Flatiron/FMI data identified NTRK fusion-positive adults not treated with TRK inhibitors. Patients met criteria such as confirmed NTRK fusion, advanced/metastatic diagnosis (2011–2019), no TRK inhibitor or investigational drug use, and continuous follow-up within 90 days of diagnosis.

C.1.1.2 Sample selection

To increase population, overlap between the two populations before matching on the selected baseline characteristics, the following inclusion criteria were applied:

- July 2020 data cutoff for the integrated patient population
- Known dates of initial metastatic diagnosis
- Age ≥ 18 years
- TRK inhibitor-naive
- Prior lines of systemic therapies ≤ 4

C.1.1.3 Statistical methods

MAIC methodology was used to compare larotrectinib versus non–TRK-inhibitor SoC.21,22 Individual patient data from the larotrectinib trials were matched to the average baseline characteristics from Hibar et al/Demetri et al (presented in Section 6 and Section 7). Baseline characteristics selected were based on data availability. HR from Cox model was used to compare the two groups.

For SoC patients with missing data in the number of lines of therapy since diagnosis (17.9%) and ECOG PS (42.9%), variables were imputed such that patients with missing values were assumed to be in the more severe categories (i.e., ≥ 3 lines of therapy; ECOG PS 2-4). These assumptions were made to estimate a conservative HR, which were subsequently tested in a sensitivity analysis that used fewer conservative assumptions.

Two analyses were conducted after matching. The first was conducted to validate the performance of matching, that is, if matching were performed adequately, then the two groups will be similar in the pretreatment survival period, defined as the time from locally advanced/metastatic disease diagnosis (index date) to larotrectinib initiation. The second was to estimate the treatment effect of larotrectinib versus SoC on OS (defined as the time from index date to death). Statistical analyses were conducted in Stata 15, and statistical significance was set a priori at $P < .05$.

C.1.1.4 Results

Bokemeyer et al. identified five studies that enrolled TRK-fusion-positive cancer patients who received non–TRK-inhibitor SoC regimens: Voyager 1/Bazhenova et al (27), Voyager 2/Bridgewater et al (28), Santi et al (30), Zhu et al (31), and Hibar et al (29)/Demetri et al (92). Because of limitations of statistical methods used, it was important that the studies identified report KM estimates of OS and comprehensive baseline characteristics. Three studies were omitted for further analysis because of the following limitations: Voyager 1/Bazhenova et al was missing data on ECOG PS, CNS metastasis,

and line of therapy, and had differences/misalignment in index date. Voyager 2/ Bridgewater et al only reported baseline characteristics for the full cohort, and not for the matched cohort used in the analysis. Santi et al lacked sufficient baseline characteristics, and the index date definition could not be aligned with that of larotrectinib. Zhu et al did not include OS analysis. The Hibar et al/Demetri et al study provided sufficient data both on baseline characteristics and index date that aligned with the larotrectinib studies and was selected for further analysis.

C.1.1.5 Patient characteristics

A total of 192 patients from the larotrectinib trials were assessed for inclusion in the MAIC. After applying the sample selection criteria, 160 patients had complete information on date of initial metastatic diagnosis: 94 were adult patients, 93 were TRK inhibitor-naïve, and 85 had four or more prior lines of systematic therapy. The 85 patients who met all criteria were included in the larotrectinib population. Hibar et al/Demetri et al reported baseline characteristics for 28 patients with TRK-fusion-positive tumours.

Baseline characteristics before and after matching in the primary analysis are summarized in Figure 25 below. The weight distribution can be found in Figure 9.

Characteristic (%)	Flatiron/FMI, As Reported (N = 28)	Larotrectinib, Before Matching (N = 85)	Flatiron/FMI, Adjusted (N = 28)	Larotrectinib, After Matching (N = 85[a])
NTRK1	82.0	42.4	82.0	82.0
Age ≥ 65 years	39.3	29.4	39.3	39.3
No history of smoking	57.1	NA	57.1	NM
ECOG PS				
0-1	50.0	87.1	50.0	50.0
2-4	7.1	12.9	50.0[b]	50.0
Unknown	42.9	—	—	—
Tumor types				
Uterine	4.0	NA	4.0	—
Biliary	4.0	NA	4.0	—
Stomach	4.0	NA	4.0	—
Endometrial	4.0	NA	4.0	—
CUP	4.0	1.2	4.0	4.0
Breast	4.0	1.2	4.0	4.0
Salivary gland	7.0	21.2	7.0	7.0
NSCLC	18.0	12.9	18.0	18.0
Soft tissue sarcoma	21.0	22.4	21.0	21.0
Colorectal	32.0	5.9	32.0	32.0
Practice type				
Academic	14.3	NA	14.3	NM
Community	85.7	NA	85.7	NM
No. of lines of therapy since diagnosis				
0-2	71.4	77.7	71.4	71.4
≥ 3	10.7	22.4	28.6[b]	28.6
Unknown	17.9	—	—	—
Stage at initial diagnosis				
0-II	17.9	20.0	17.9	17.9
III-IV	64.3	61.2	64.3	64.3
Unknown	17.9	—	17.9	—
Brain metastases				
Yes	17.9	9.4	17.9	17.9
No or unknown	82.1	90.6	82.1	82.1

Figure 25 Baseline characteristics before and after matching of larotrectinib efficacy population (ePAS5) and Hibar et al/Demtri et al/ FLATIRON/FMI database

C.1.1.6 Overall survival

Refer to Section 7.1.3.

C.2 Data sources

With the availability of a more recent data cut from 2024, ePAS8 (DCO: July 2023), the ePAS8 data was matched with the MAIC weights (derived from Bokemeyer et al., where IPD data from 2020 were matched to the average baseline characteristics from Hibar et al/Demetri et al.). Hence, for this submission, a later data cut, July 2023, has been re-weighted with the MAIC derived weights informed by Bokemeyer et al (6). The re-weighted analysis maintains the same sample size as in the original MAIC; 85 patients for larotrectinib and 28 patients for SoC (Hibar et al/De metri et al) (effective sample size is 13.14). Although the new data cut includes additional patients, the re-weighting process constrains the analysis to the same populations previously used to preserve the comparability of the results (n=85) (6).

C.2.1 Re-weighting

In this analysis, weights derived from the Bokemeyer et al. MAIC using the ePAS5 data vs SoC/FLATIRON data were applied to the larotrectinib ePAS8 data. These weights, originally calculated to balance baseline characteristics with the SoC (Hibar et al/Demetri et al/ FLATIRON/FMI database) arm from Bokemeyer et al. were reused to ensure alignment of the updated ePAS8 data with the comparator population. A weighted Cox PH model was used to analyse the reweighted ePAS8 dataset, maintaining consistency with the methodology and comparator population from the original MAIC.

C.3 Endpoint

The MAIC resulted in one outcome: OS. OS was defined as the time from advanced/metastatic disease diagnosis to death. Table 60 below shows the comparative analysis result between larotrectinib (ePAS8) and SoC/FLATIRON.

Table 60 Comparative analysis of studies comparing larotrectinib (ePAS8) to SoC/FLATIRON for patients with NTRK fusion positive solid tumours

Outcome	Studies included in the analysis	N	Result (95% CI)	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
				Difference	CI	P value	Difference	CI	P value		
Median overall survival (weighted)	SoC/FLATIRON	28	10.2 (7.2; 14.1)	20.5	N/A	N/A	HR: 0.16	(0.09; 0.29)	0.0542	Weighted cox-model using weights from the Bokemeyer et al. MAIC	Yes
	Larotrectinib, ePAS8	85	30.8 (9.5; N/A)								Yes

Appendix D. Extrapolation

This appendix specifies the extrapolation of the included endpoints: OS and PFS for both the larotrectinib and SoC arm.

Table 61 Extrapolation of OS and PFS

Model	Larotrectinib		SoC/FLATIRON	
	OS	PFS	OS	PFS
Data availability	Yes	Yes	Yes	No
Extrapolation method	Weighted cox-model using weights from the Bokemeyer et al. MAIC. Followed by standard parametric fitting	Using the MAIC weights (OS) to adjust PFS data. Followed by standard parametric fitting	Bokemeyer et al 2023 MAIC. Followed by standard parametric fitting	No. Larotrectinib PFS/OS ratio was applied to the SoC/FLATIRON OS.

Abbreviations: OS= overall survival; PFS= progression-free survival; MAIC= matched-adjusted indirect comparison; SoC= standard of care.

For larotrectinib, OS and PFS are derived from the ePAS8 dataset re-weighted with MAIC weights informed by Bokemeyer at al. (6). OS in the SoC/FLATIRON arm is based on aggregated RWD MAIC estimates obtained from Bokemeyer et al. The PFS of the SoC/FLATIRON arm was generated using the ratio of PFS/OS from the intervention arm as a conservative assumption (the re-weighted ePAS8 data, refer to Section 7).

Due to the absence of comparative analysis of ToT, PFS is used as proxy for ToT in the base case (using larotrectinib ePAS8 data).

Survival statistics were conducted in R, and the results were exported to Excel.

D.1 Extrapolation of overall survival

D.1.1 Data input

Larotrectinib

Overall survival in the larotrectinib arm was assessed and extrapolated using MAIC weights derived from Bokemeyer et al., which were applied to re-weight the ePAS8 dataset (DCO: 20 July 2023) obtained from the larotrectinib trials.

As the larotrectinib trials are single-arm trials, there is no direct head-to-head evidence to compare the clinical efficacy of larotrectinib and SoC for NTRK fusion positive solid tumours. To inform the comparative analyses between larotrectinib and SoC, a MAIC was conducted in 2023 (Bokemeyer et al. 2023) (4).

In the MAIC performed by Bokemeyer et al. (2023), IPD for adult and paediatric patients harbouring TRK fusion-positive tumours from larotrectinib trials (LOXO-TRK-1400, SCOUT, and NAVIGATE; data cutoff: July 2020) and aggregate real-world data from patients with

locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron/Foundation Medicine database were used. Since a later DCO is now available (July 2023), the weights derived from the MAIC has been applied to the ePAS8 data. Refer to Appendix C for further information.

SoC/FLATIRON

As mentioned above, OS for SoC was obtained from the Bokemeyer et al. using aggregated real-world data from patients with locally advanced/metastatic TRK fusion-positive cancer identified in the Flatiron/Foundation Medicine database were used.

D.1.2 Model

As described previously, extrapolation of OS was generated using a standard parametric model.

For both arms the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

Based on the OS data derived from the MAIC analysis (refer to Appendix C) provided by Bokemeyer al. (6)., separate individual parametric models were investigated for the larotrectinib arm and SoC/FLATIRON arm. Appropriate curve selection was determined according to statistical (AIC and BIC), visual goodness of fit and the clinical plausibility of extrapolations. The log-normal parametric model was selected to model OS for both arms (this will be justified in the following subsections).

D.1.3 Proportional hazards

The result of the Schoenfeld Residuals test (p-value = 0.053) signifies a non-significant relationship between time and hazard, suggesting that the PH assumption holds. However, p-values are sensitive to the power of the dataset and should not be analysed alone without considering the relationship of hazards over time. The visual inspection of the Schoenfeld residuals plot for the treatment effect model clearly shows that the PH-assumption is violated (i.e., the treatment lines fall outside the confidence bounds) (Figure 26). This conclusion is supported by the log-cumulative hazard plot, where the lines initially overlap at early time points and then progressively diverge at later time points (Figure 27). Therefore, independent models were used for all analyses.

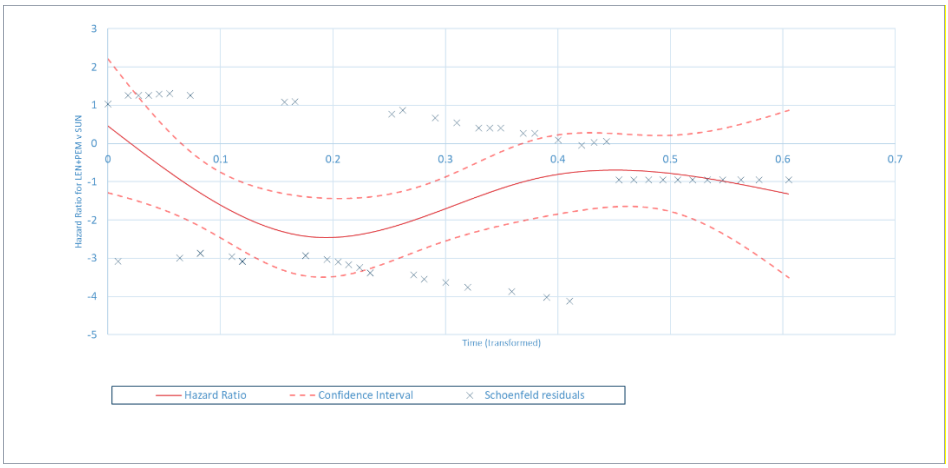


Figure 26 Schoenfeld residuals plot, larotrectinib vs SoC

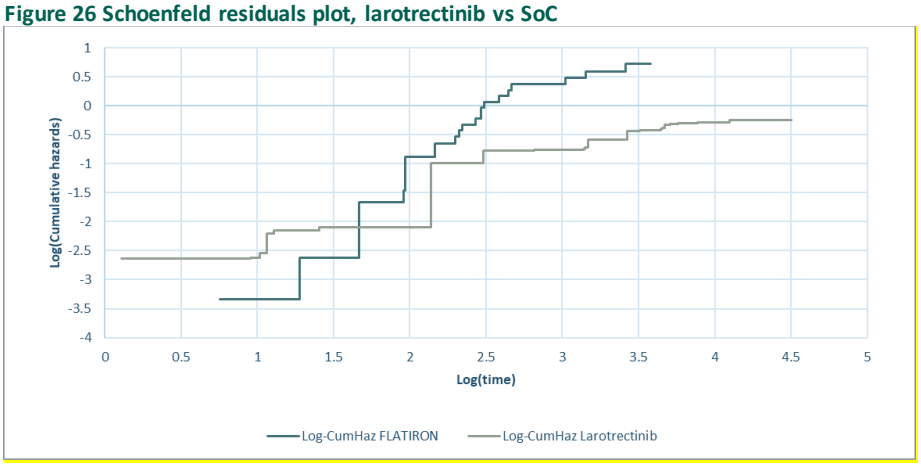


Figure 27 log-cumulative hazard for OS

D.1.4 Evaluation of statistical fit (AIC and BIC)

Table 62 presents the statistical fit of each OS parametric model for both larotrectinib and SoC/FLATRIRON

Table 62 OS statistical fit, AIC and BIC for parametric survival models

Model	Larotrectinib (reweighted ePAS8)		SoC/FLATRION	
	AIC	BIC	AIC	BIC
Exponential	347.36	349.80	187.56	188.89
Gompertz	**332.95**	**337.84**	189.49	192.15
Log-logistic	335.48	340.36	179.35	182.01
Log-normal	338.02	342.90	**178.37**	**181.04**
Weibull	334.14	341.47	180.03	184.02
Generalised gamma	341.96	346.84	186.43	189.10

Abbreviations: AIC = Akaike information criterion, BIC = Bayesian information criterion, OS = overall survival

Larotrectinib

The Gompertz model has the best statistical fit according to both the AIC and BIC statistics.

SoC/FLATIRON

The log-normal model has the best statistical fit according to both the AIC and BIC statistics.

D.1.5 Evaluation of visual fit

Larotrectinib

The visual fits for all fitted standard parametric models for OS for larotrectinib covering the entire time horizon are shown in Figure 28. The figure shows that the Gompertz model produces the best visual fit and is the only model that captures the plateau in OS observed in the end of the KM curve; however, the visual inspection is poor.

It is expected that it is clinically implausible for survival to plateau beyond 50 months. The Exponential model demonstrates the most pessimistic fit, with survival rapidly decreasing around 50 months, thereby underestimating survival. The Generalized Gamma model provides a more optimistic fit, showing only a slight decrease in survival after 100 months. The log-normal model was selected for the base case, as it was believed to produce the most reliable estimate.

The selected log-normal model for the base case extrapolation of larotrectinib OS adjusted for the general mortality rate is shown in Figure 31.

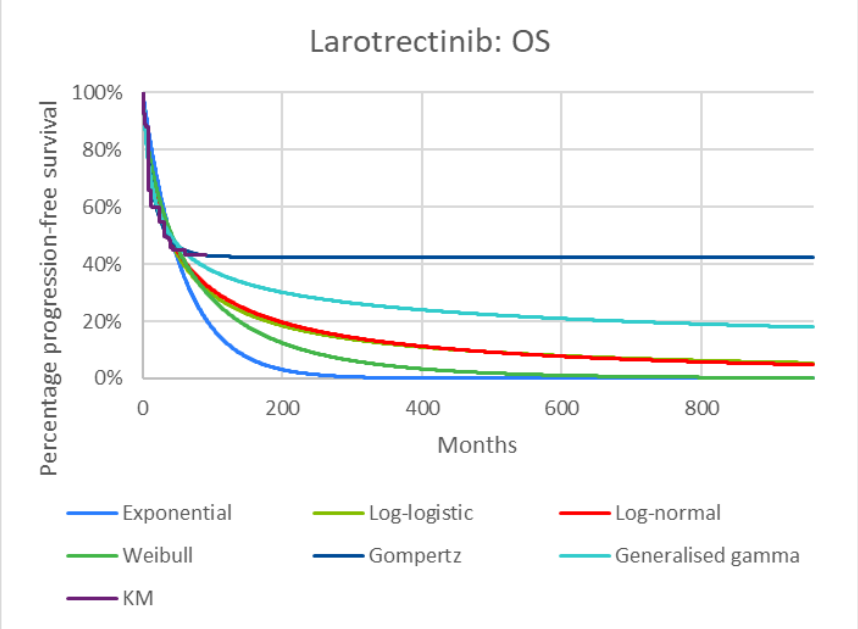


Figure 28 Extrapolation model for overall survival (OS) for larotrectinib, reweighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al (80 years)

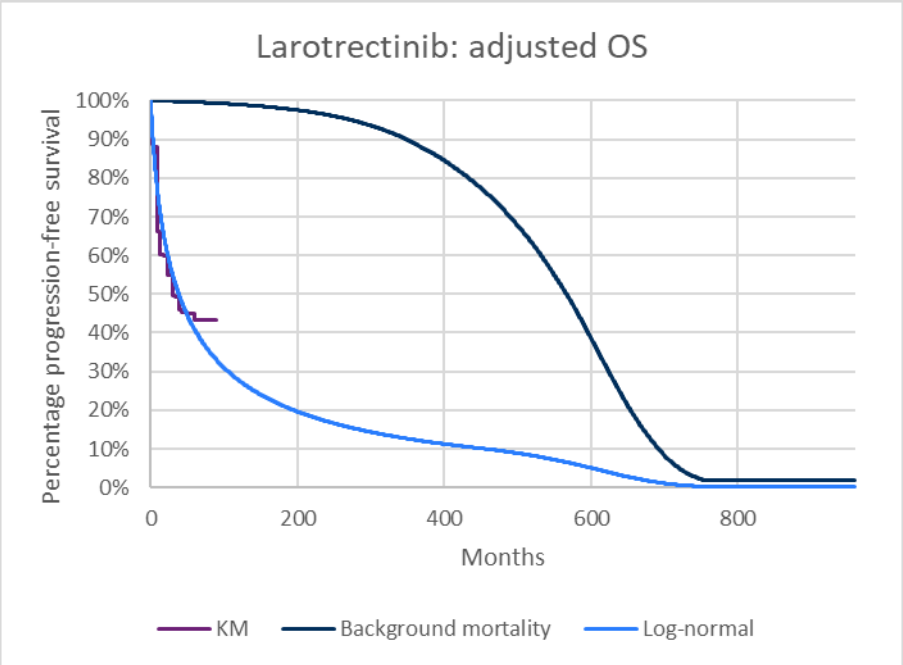


Figure 29 Extrapolation model for adjusted overall survival (OS) for larotrectinib, reweighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al (80 years)

SoC/FLATIRON

The visual fits for all fitted standard parametric models for OS for SoC/FLATIRON, displaying the entire model horizon, are illustrated in Figure 21.

All models generally follow the KM-curve closely. The log-normal model was used in the base case as the visual fit of all extrapolations is quite similar.

The selected log-normal model for the base case extrapolation of SoC OS adjusted for the general mortality rate is shown in Figure 31.

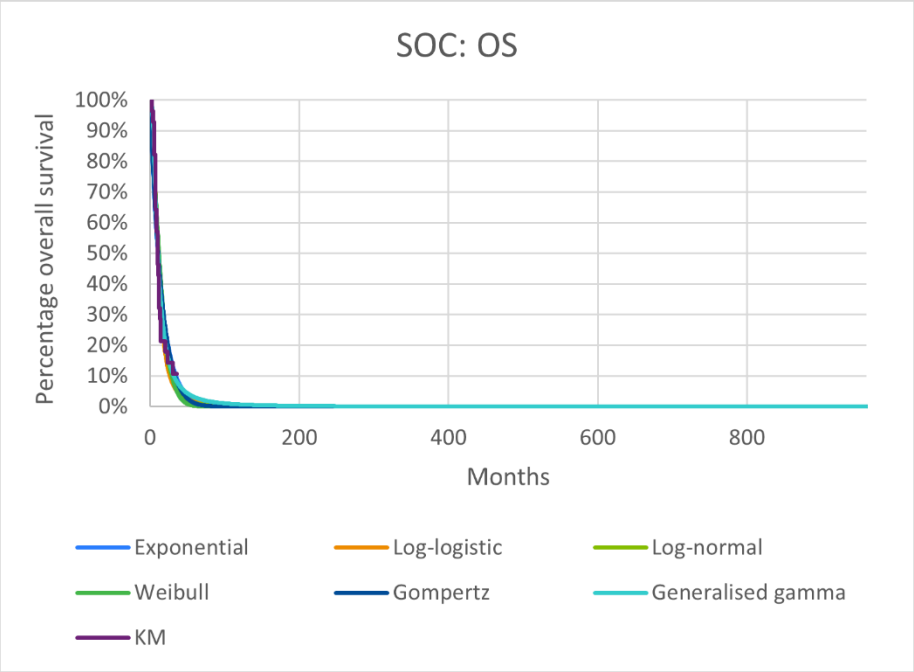


Figure 30 Extrapolation model for overall survival (OS) for SoC, Bokemeyer et al., aggregated RWD (80 years)

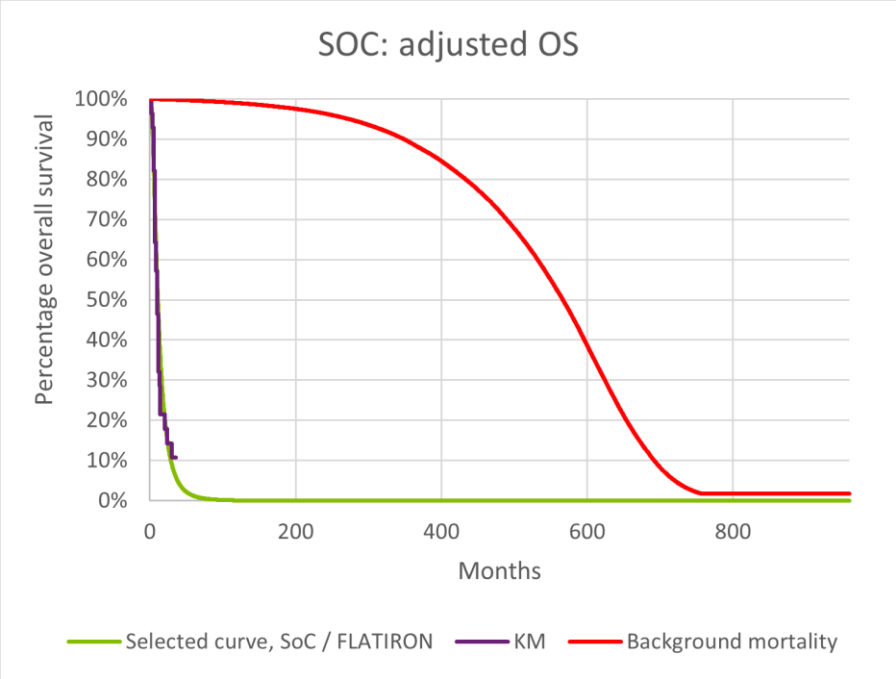


Figure 31 Extrapolation model for adjusted overall survival (OS) for SoC, Bokemeyer et al., aggregated RWD (80 years)

D.1.6 Evaluation of hazard functions

Smoothed hazard plots for larotrectinib and SoC from the parametric survival models are shown in Figure 32 and Figure 33, respectively.

Larotrectinib

For larotrectinib, the hazard based on the observed data initially increases slightly, followed by a decrease, and then continuously decreases approximating zero at the end of the curve. None of the hazard profiles closely match the observed hazards: all profiles overestimate the hazard in the beginning of the curve. The exponential model by definition produced constant hazards over time. The Gompertz model somewhat follows this pattern although elevated hazards are predicted between months 0 and 20. The Generalized Gamma model starts at a relatively high level followed by a decrease followed by a plateau at a quite low level. Based on visual fit presented in Figure 32 the hazard profile of the Gompertz distribution seems most like that of the observed data. However, the Gompertz distribution is considered to be optimistic.

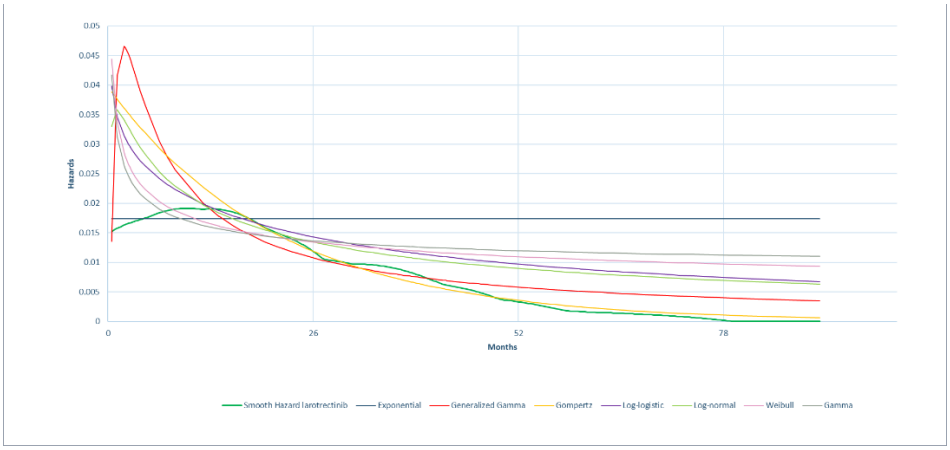


Figure 32 OS larotrectinib smoothed hazards distribution

SoC/FLATIRON

For SoC/FLATIRON, the hazard based on the observed data rises rapidly followed by a decrease. The exponential model (by definition) produced constant hazards over time. The Log-normal, Generalized Gamma, and the Log-logistic models yield relatively similar hazard profiles, characterized by a rapid initial increase in hazards followed by a decline; however, the Generalized Gamma model tends to align more closely with the overall trend of the observed data. All other hazard profiles showed a continuous increase and overestimated the hazards over nearly the entire time period.

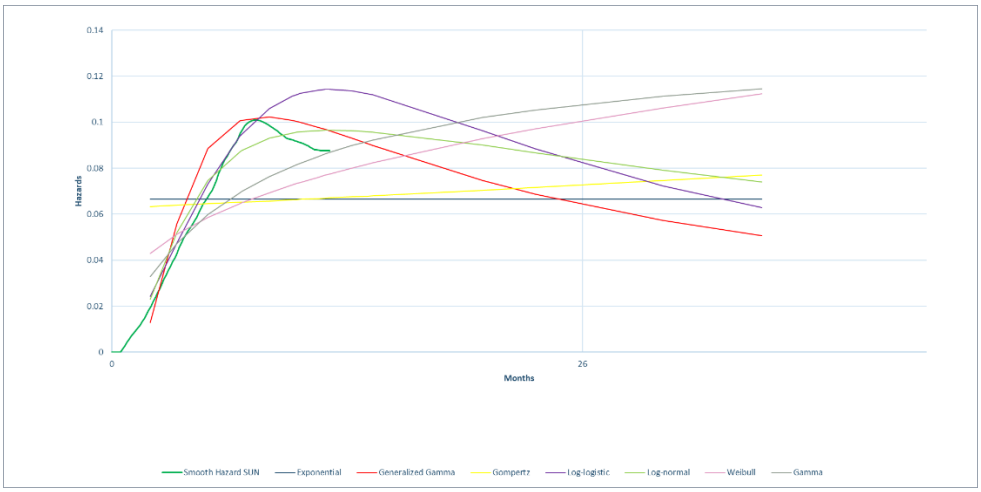


Figure 33 OS SoC smoothed hazard distribution

D.1.7 Validation and discussion of extrapolated curves

Larotrectinib

Based on visual inspection and statistical fit (AIC and BIC), the Gompertz model generally seems to provide a better fit to the observed data compared to the other parametric models. However, as previously described, the Gompertz model provides a highly optimistic fit, as the curve plateaus around xx months (see Figure 28.). As mentioned in Section 4, larotrectinib has potential for curative effect. This is tested using Gompertz and Generalised Gamma for OS, refer to Section 12.2.1.

However, the Log-normal was chosen in the base case in order to not select an overly optimistic extrapolation, and was expected to be the most clinically plausible.

SoC/FLATIRON

Based on the visual fit provided in Figure 30 all models demonstrated similar fit. Thus, all the curves were considered equally clinically plausible. The statistical fit (AIC and BIC) the Log-normal model showed the best fit to observed data. For this reason, a pragmatic approach was adopted, and the Log-normal model was selected to extrapolate OS in the SoC allowing both arms to be extrapolated in the same way.

D.1.8 Adjustment of background mortality

Throughout the model, the survival hazard rate is set to be at least that of the age- and sex-adjusted general population in Denmark (i.e. ensuring that patients survive at the same or worse rate compared to the Danish general population), using the DMC source: "Nøgletalsopslyninger inkl. general dødelighed for den danske befolkning".

D.1.9 Adjustment for treatment switching/cross-over

Not applicable.

D.1.10 Waning effect

Not applicable.

D.1.11 Cure-point

Not applicable.

D.2 Extrapolation of progression-free survival

D.2.1 Data input

Larotrectinib

As for OS, progression-free survival in the larotrectinib arm was assessed and extrapolated using MAIC weights derived from Bokemeyer et al., which were applied to re-weight the ePAS8 dataset (DCO: 20 July 2023) obtained from the larotrectinib trials.

SoC/FLATIRON

No PFS data could be obtained from Bokemeyer et al. to inform the SoC/FLATIRON arm. As a result, the PFS of the SoC/FLATIRON arm was generated using the ratio of OS to PFS from the intervention arm as a conservative assumption (the re-weighted ePAS8 data the PFS curves were inferred by using the ratio of OS to PFS from the weighted ePAS8 data (5).

D.2.2 Model

As for OS, extrapolation of PFS was generated using a standard parametric model.

For the larotrectinib arm the following distributions were used:

- Exponential
- Weibull
- Gompertz
- Log-normal
- Log-logistic
- Generalised gamma

The log-normal parametric model was selected to model PFS for the larotrectinib arm (this will be justified in the following subsections).

D.2.3 Proportional hazards

Not applicable.

D.2.4 Evaluation of statistical fit (AIC and BIC)

Table 62 presents the statistical fit of each PFS parametric model for larotrectinib. No estimates were available for the SoC/FLATIRON arm.

Table 63 PFS statistical fit, AIC and BIC for parametric survival models

Model	Larotrectinib (reweighted ePAS8)	
	AIC	AIC
Exponential	399.67	402.11
Gompertz	371.23	376.12
Log-logistic	374.44	379.33
Log-normal	377.87	382.76
Weibull	355.69	363.02
Generalised gamma	384.54	389.42

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival

Larotrectinib

The Weibull model has the best statistical fit according to both the AIC and BIC statistics.

SoC/FLATIRON

Not applicable.

D.2.5 Evaluation of visual fit

The visual fits for all fitted standard parametric models for PFS for larotrectinib are shown in Figure 28. The Weibull, the log-normal, and the log-logistic models demonstrate similar, good, visual fits. However, the Weibull model offers a somewhat more pessimistic fit

compared to the log-normal and log-logistic models. The Gompertz and Generalised Gamma models consistently overestimate survival, maintaining a fixed survival rate beyond the 50 month throughout the projected time frame. In contrast, the Exponential model tend to underestimate the survival rates around 50 months.

Clinical plausibility must be taken into consideration when selecting the most appropriate model, and the log-normal model provide a middle ground whilst having a very similar visual fit to the KM data.

The selected log-normal model for the base case extrapolation of larotrectinib PFS adjusted for the general mortality rate is shown in Figure 35.

No graphical representation is available for the SoC/FLATRION arm.

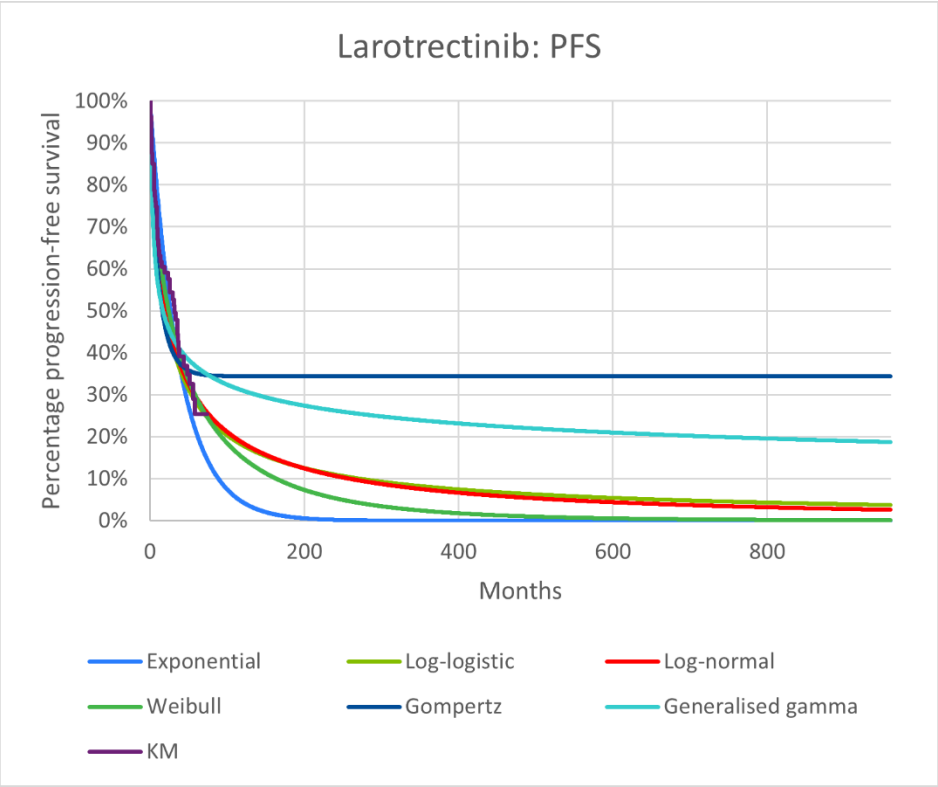


Figure 34 Extrapolation model for progression-free survival (PFS) larotrectinib, reweighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al (80 years)

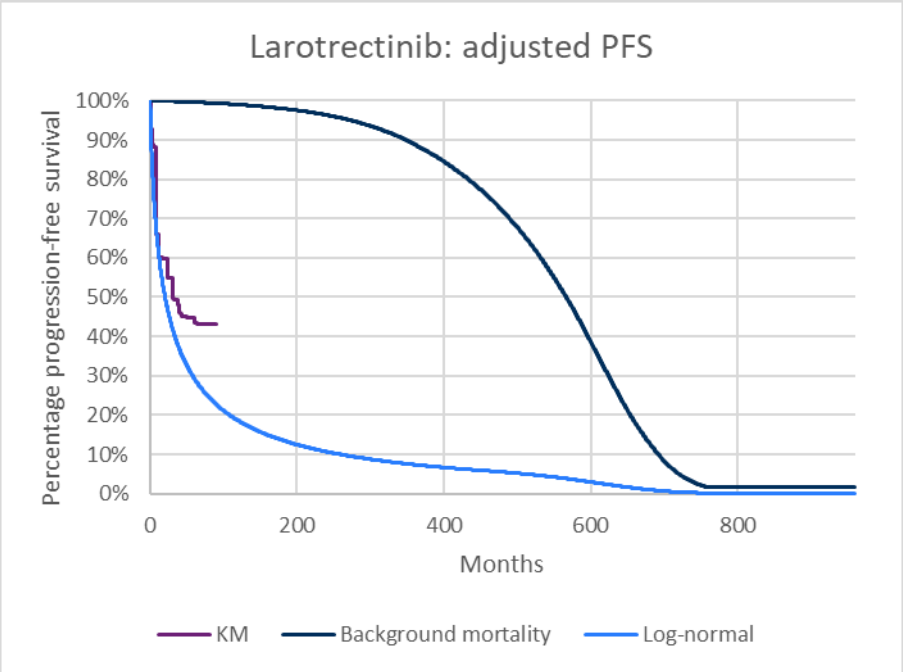


Figure 35 Extrapolation model for adjusted progression-free survival (PFS) for larotrectinib, re-weighted IPD from ePAS8 using MAIC derived weights informed by Bokemeyer et al. (80 years)

D.2.6 Evaluation of hazard functions

Smoothed hazard plots for larotrectinib from the parametric progression-free survival models are shown in Figure 36.

For larotrectinib, the hazard derived from the observed data initially remains constant, then decreases, followed by a slight increase, and subsequently declines steadily, approaching zero towards the end of the curve. None of the hazard profiles closely correspond to the observed patterns; except for the exponential model, all models tend to overestimate the hazard in the early stages of the curve. The exponential model produced constant hazards over time. By approximately month 13, all models converge closely with the observed data (refer to Figure 36).

As previously described, no graphical representation is available for the SoC/FLATRION arm.

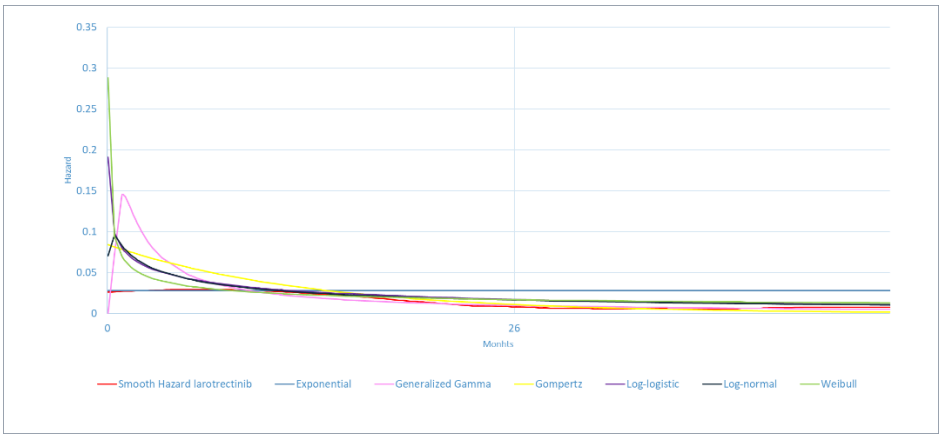


Figure 36 PFS larotrectinib smoothed hazards distribution

D.2.7 Validation and discussion of extrapolated curves

Larotrectinib

Based on the statistical fit (AIC and BIC), the Weibull model generally seems to provide a better fit to the observed data compared to the other parametric models. The Weibull, the log-logistic, and the log-normal model produced very similar, good, visual fits and produced somewhat identical long-term extrapolations. The Weibull model demonstrates a slightly more conservative fit compared to the log-normal and log-logistic models. The log-normal model provides a middle ground whilst having a very similar visual fit to the KM data. Furthermore, the selection of the log-normal model ensured consistent modelling of both PFS and OS.

Consequently, for larotrectinib PFS, the base case extrapolation is using a log-normal function.

SoC/FLATIRON arm

Not applicable.

D.2.8 Adjustment of background mortality

Throughout the model, the survival hazard rate is set to be at least that of the age- and sex-adjusted general population in Denmark (i.e. ensuring that patients survive at the same or worse rate compared to the Danish general population), using the DMC source: "Nøgletalsopslyninger inkl. general dødelighed for den danske befolkning".

D.2.9 Adjustment for treatment switching/cross-over

Not applicable.

D.2.10 Waning effect

Not applicable.

D.2.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

E.1 Serious adverse events

Table 64 Serious adverse events, ePAS8 (DCO 2023)

	Safety analysis set (n=302), patient incidence (%)	Overall analysis set (n=444), patient incidence (%)
Serious TEAE		
All	136 (45)	201 (45)
Related to larotrectinib	25 (8)	34 (8)

Abbreviation: TEAE = treatment-emergent adverse event.

In the Overall safety analysis set, 201 (45%) patients had at least 1 treatment emergent SAE. Most SAEs were not considered by the Investigator to be related to the study drug, with 34 (8%) patients who had at least 1 drug-related SAE.

The same proportion of patients had at least 1 treatment emergent SAE in the NTRK gene fusion analysis set and the Efficacy-evaluable NTRK gene fusion analysis set (45% in each). That said, serious adverse events from the ePAS8 population are not provided.

Table 65 Treatment-emergent serious adverse events, overall safety analysis set

Overall safety analysis set (n=444), patient incidence (%)	All	Study drug-related
Any treatment-emergent SAE	201 (45)	34 (8)
Pneumonia	19 (4)	1 (<1)
Pyrexia	15 (3)	1 (<1)
Dyspnoea	10 (2)	0
Diarrhoea	8 (2)	1 (<1)
Vomiting	7 (2)	2 (<1)
Hypoxia	6 (1)	0
Seizure	6 (1)	0
Sepsis	6 (1)	0
Abdominal pain	5 (1)	1 (<1)
Muscular weakness	5 (1)	1 (<1)
Pneumonia aspiration	5 (1)	0
Pulmonary embolism	5 (1)	0
Respiratory failure	5 (1)	0
Acute kidney injury	4 (<1)	0
ALT increased	4 (<1)	4 (<1)
Cellulitis	4 (<1)	0
Dizziness	4 (<1)	1 (<1)
Gait disturbance	4 (<1)	1 (<1)
Gastroenteritis	4 (<1)	0
Influenza	4 (<1)	0
Pericardial effusion	4 (<1)	0
Skin infection	4 (<1)	0
Viral infection	4 (<1)	0
Ascites	3 (<1)	0

AST increased	3 (<1)	3 (<1)
Constipation	3 (<1)	0
Dehydration	3 (<1)	0
Fall	3 (<1)	0
Fatigue	3 (<1)	0
Headache	3 (<1)	1 (<1)
Hydrocephalus	3 (<1)	0
Hyponatraemia	3 (<1)	1 (<1)
Joint dislocation	3 (<1)	0
Malaise	3 (<1)	1 (<1)
Malignant neoplasm progression	3 (<1)	0
Osteomyelitis	3 (<1)	0
Pleural effusion	3 (<1)	0
Pyelonephritis	3 (<1)	0
Urinary tract infection	3 (<1)	0
Wound infection	3 (<1)	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients with event/in category; SAE = serious adverse event
Note: Patients were counted once within each preferred term.
Reported adverse event terms were coded using MedDRA (Version 26.0).
Adverse events are sorted in decreasing order of frequency based on the overall safety analysis set for all patients.
Percentages were calculated based on the number of patients in the column heading as the denominator.
Status as of 20 JUL 2023.

E.2 Other common adverse events

Table 66 Other common treatment emergent adverse events, ePAS8 (DCO 2023), all grades

Safety analysis set (n=302), patient incidence (%)	Grade 1	Grade 2	Grade 3	Grade 4
Any TEAE	23 (8)	84 (28)	131 (43)	30 (10)
ALT increased	71 (24)	21 (7)	13 (4)	4 (1)
AST increased	68 (23)	18 (6)	11 (4)	3 (<1)
Vomiting	72 (24)	23 (8)	2 (<1)	0
Anaemia	43 (14)	28 (9)	22 (7)	0
Cough	75 (25)	15 (5)	2 (<1)	0
Constipation	75 (25)	17 (6)	1 (<1)	0
Pyrexia	54 (18)	27 (9)	8 (3)	1 (<1)
Fatigue	48 (16)	21 (7)	3 (<1)	0
Diarrhoea	57 (19)	21 (7)	11 (4)	0
Nausea	63 (21)	16 (5)	1 (<1)	0
Dizziness	55 (18)	9 (3)	3 (<1)	0
Myalgia	43 (14)	18 (6)	2 (<1)	0
Upper respiratory tract infection	14 (5)	43 (14)	3 (<1)	0
Arthralgia	37 (12)	18 (6)	3 (<1)	0
Headache	39 (13)	13 (4)	2 (<1)	0
Weight increased	26 (9)	21 (7)	16 (5)	0
Neutrophil count decreased	13 (4)	17 (6)	24 (8)	7 (2)
Dyspnoea	28 (9)	10 (3)	8 (3)	0
Oedema peripheral	39 (13)	8 (3)	2 (<1)	0
Abdominal pain	30 (10)	15 (5)	3 (<1)	0

Decreased appetite	34 (11)	7 (2)	1 (<1)	0
Leukocyte count decreased	36 (12)	10 (3)	4 (1)	2 (<1)
Pain in extremity	30 (10)	13 (4)	4 (1)	0
Urinary tract infection	2 (<1)	37 (12)	4 (1)	0
Lymphocyte count decreased	20 (7)	6 (2)	7 (2)	3 (<1)
Back pain	27 (9)	12 (4)	3 (<1)	0
Blood creatinine increased	22 (7)	11 (4)	1 (<1)	0
Hypoalbuminemia	22 (7)	8 (3)	1 (<1)	0
Nasopharyngitis	26 (9)	13 (4)	0	0
Nasal congestion	28 (9)	4 (1)	0	0
Rash	32 (11)	4 (1)	0	0
Blood alkaline phosphatase increased	17 (6)	7 (2)	3 (<1)	2 (<1)
Hyperglycaemia	22 (7)	3 (<1)	2 (<1)	1 (<1)
Abdominal pain upper	24 (8)	8 (3)	1 (<1)	0
Hypertension	10 (3)	11 (4)	6 (2)	0
Dry skin	25 (8)	4 (1)	0	0
Insomnia	20 (7)	7 (2)	0	0
Muscular weakness	14 (5)	7 (2)	3 (<1)	0
Pneumonia	3 (<1)	13 (4)	10 (3)	1 (<1)
COVID-19	15 (5)	13 (4)	0	0
Pain	13 (4)	13 (4)	3 (<1)	0
Platelet count decreased	18 (6)	4 (1)	2 (<1)	1 (<1)
Hyperkalaemia	11 (4)	13 (4)	2 (<1)	0
Hypocalcaemia	10 (3)	9 (3)	3 (<1)	2 (<1)
Hypokalaemia	13 (4)	3 (<1)	7 (2)	0
Pruritus	20 (7)	4 (1)	0	0
Fall	10 (3)	5 (2)	3 (<1)	0
Hypotension	13 (4)	5 (2)	6 (2)	0
Oropharyngeal pain	15 (5)	2 (<1)	0	0
Asthenia	13 (4)	6 (2)	2 (<1)	0
Rash maculo-papular	17 (6)	4 (1)	0	0
Weight decreased	15 (5)	6 (2)	1 (<1)	0
Haematuria	21 (7)	0	1 (<1)	0
Hyponatraemia	9 (3)	0	8 (3)	1 (<1)
Abdominal distension	13 (4)	5 (2)	0	0
Conjunctivitis	6 (2)	12 (4)	0	0
Gait disturbance	6 (2)	5 (2)	3 (<1)	0
Proteinuria	13 (4)	6 (2)	0	0
Gastroenteritis	8 (3)	10 (3)	1 (<1)	0
Hypernatremia	17 (6)	0	0	1 (<1)
Hypertriglyceridemia	12 (4)	6 (2)	2 (<1)	2 (<1)
Paraesthesia	15 (5)	1 (<1)	3 (<1)	0
Blood cholesterol increased	16 (5)	1 (<1)	0	0
Dysgeusia	13 (4)	2 (<1)	0	0
Hot flush	15 (5)	1 (<1)	0	0
Muscle spasms	14 (5)	8 (3)	0	0
Anxiety	7 (2)	5 (2)	2 (<1)	0
Dehydration	5 (2)	9 (3)	1 (<1)	0
Dysphagia	9 (3)	3 (<1)	2 (<1)	0
Hypophosphataemia	5 (2)	2 (<1)	7 (2)	0
Neuropathy peripheral	12 (4)	5 (2)	1 (<1)	0
Flatulence	17 (6)	3 (<1)	0	0

Influenza like illness	6 (2)	7 (2)	0	0
Skin infection	5 (2)	5 (2)	4 (1)	0
Blood lactate dehydrogenase increased	13 (4)	1 (<1)	0	0
Dyspepsia	8 (3)	4 (1)	0	0
Hypoglycaemia	9 (3)	4 (1)	1 (<1)	1 (<1)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; Gr = grade; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients with event/in category; NTRK = neurotrophic tyrosine kinase receptor; PT = preferred term; TEAE = treatment-emergent adverse event.
a The Efficacy-evaluable NTRK Gene Fusion Safety Analysis Set does not include patients with primary CNS tumours.
b Includes 29 patients with Grade 5 TEAEs.
c Includes 36 patients with Grade 5 TEAEs.
d Includes 44 patients with Grade 5 TEAEs.
Note: Among the patients with common TEAEs (≥5%), one Grade 5 TEAE (pneumonia) was reported in 1 patient. All Grade 5 TEAEs are discussed in Section 2.1.2
Patients with multiple severity ratings for a given TEAE are counted once under maximum severity.
Reported adverse event terms were coded using MedDRA (Version 26.0).
Severity grade assignment based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (fatal).
Status as of 20 JUL 2023

E.3 Study Drug-related adverse events

Table 67 Other common treatment emergent adverse events, ePAS8 (DCO 2023), all grades

Safety analysis set (n=302), patient incidence (%)	Grade 1	Grade 2	Grade 3	Grade 4
At least 1 related TEAE	89 (29)	102 (34)	56 (19)	12 (4)
ALT increased	62 (21)	20 (7)	9 (3)	4 (1)
AST increased	61 (20)	17 (6)	7 (2)	3 (<1)
Dizziness	37 (12)	7 (2)	1 (<1)	0
Nausea	38 (13)	3 (<1)	1 (<1)	0
Fatigue	27 (9)	10 (3)	1 (<1)	0
Myalgia	24 (8)	15 (5)	1 (<1)	0
Neutrophil count decreased	11 (4)	17 (6)	13 (4)	4 (1)
Constipation	38 (13)	5 (2)	1 (<1)	0
Weight increased	21 (7)	15 (5)	7 (2)	0
Anaemia	20 (7)	10 (3)	3 (<1)	0
Leukocyte count decreased	30 (10)	6 (2)	2 (<1)	0
Vomiting	23 (8)	4 (1)	1 (<1)	0
Diarrhoea	14 (5)	8 (3)	2 (<1)	0
Hypoalbuminemia	15 (5)	2 (<1)	0	0
Oedema peripheral	16 (5)	1 (<1)	0	0
Arthralgia	7 (2)	6 (2)	1 (<1)	0
Lymphocyte count decreased	11 (4)	4 (1)	1 (<1)	0
Blood alkaline phosphatase increased	8 (3)	4 (1)	1 (<1)	2 (<1)
Decreased appetite	14 (5)	2 (<1)	0	0
Dysgeusia	11 (4)	2 (<1)	0	0
Headache	10 (3)	6 (2)	1 (<1)	0
Platelet count decreased	11 (4)	4 (1)	2 (<1)	0
Blood creatinine increased	9 (3)	3 (<1)	0	0
Rash	13 (4)	0	0	0
Asthenia	8 (3)	2 (<1)	1 (<1)	0

Abdominal pain upper	8 (3)	3 (<1)	0	0
Hot flush	8 (3)	1 (<1)	0	0
Neuropathy peripheral	7 (2)	2 (<1)	1 (<1)	0
Paraesthesia	8 (3)	1 (<1)	1 (<1)	0
Pruritus	8 (3)	1 (<1)	0	0
Abdominal pain	6 (2)	2 (<1)	1 (<1)	0
Gamma-glutamyltransferase increased	6 (2)	1 (<1)	1 (<1)	0
Hyperglycaemia	8 (3)	0	0	0
Muscle spasms	7 (2)	5 (2)	0	0
Pain in extremity	7 (2)	3 (<1)	0	0
Muscular weakness	3 (<1)	2 (<1)	1 (<1)	0
Blood creatine phosphoki-nase increased	6 (2)	4 (1)	0	0
Gait disturbance	2 (<1)	3 (<1)	0	0
Hypertension	3 (<1)	4 (1)	0	0
Hypertriglyceridemia	7 (2)	2 (<1)	0	0
Pain	2 (<1)	3 (<1)	0	0
Proteinuria	6 (2)	0	0	0
Weight decreased	5 (2)	2 (<1)	0	0
Dry skin	4 (1)	1 (<1)	0	0
Flatulence	9 (3)	0	0	0
Increased appetite	7 (2)	0	0	0
Malaise	4 (1)	2 (<1)	0	0
Taste disorder	5 (2)	2 (<1)	0	0
Dyspepsia	4 (1)	1 (<1)	0	0
Hyperkalaemia	4 (1)	2 (<1)	0	0
Peripheral sensory neuropa-thy	3 (<1)	4 (1)	0	0
Dry mouth	4 (1)	0	0	0
Hypothyroidism	3 (<1)	2 (<1)	0	0
Memory impairment	1 (<1)	1 (<1)	0	0
Rash maculo-papular	6 (2)	0	0	0

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; Gr = grade; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of patients (100%); n = number of patients with event/in category; NTRK = neurotrophic tyrosine kinase receptor; PT = preferred term; TEAE = treatment-emergent adverse event

a The Efficacy-evaluable NTRK Gene Fusion Safety Analysis Set does not include patients with primary CNS tumours.

Note: There were no study-drug related Grade 5 TEAEs reported.

Note: Patients with multiple severity ratings for a given AE were counted once under the maximum severity. Reported adverse events were coded using MedDRA (Version 26.0).

Severity grade assignment was based on CTCAE (v4.03): Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), Grade 5 (fatal).

Status as of 20 JUL 2023:

Appendix F. Health-related quality of life

15.1.1.1 Tumour-specific utilities

A summary of the health state utility values used to generate a weighted average for SoC/FLATIRON is presented in Appendix O.2.

Appendix G. Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was performed to account for multivariate and stochastic uncertainty in the model. The uncertainties in the individual parameters for treatment effect, costs, and utilities were characterised using probability distributions and analysed using a Monte Carlo simulation using 1,000 simulations.

The following groups of parameter values were included in the PSA:

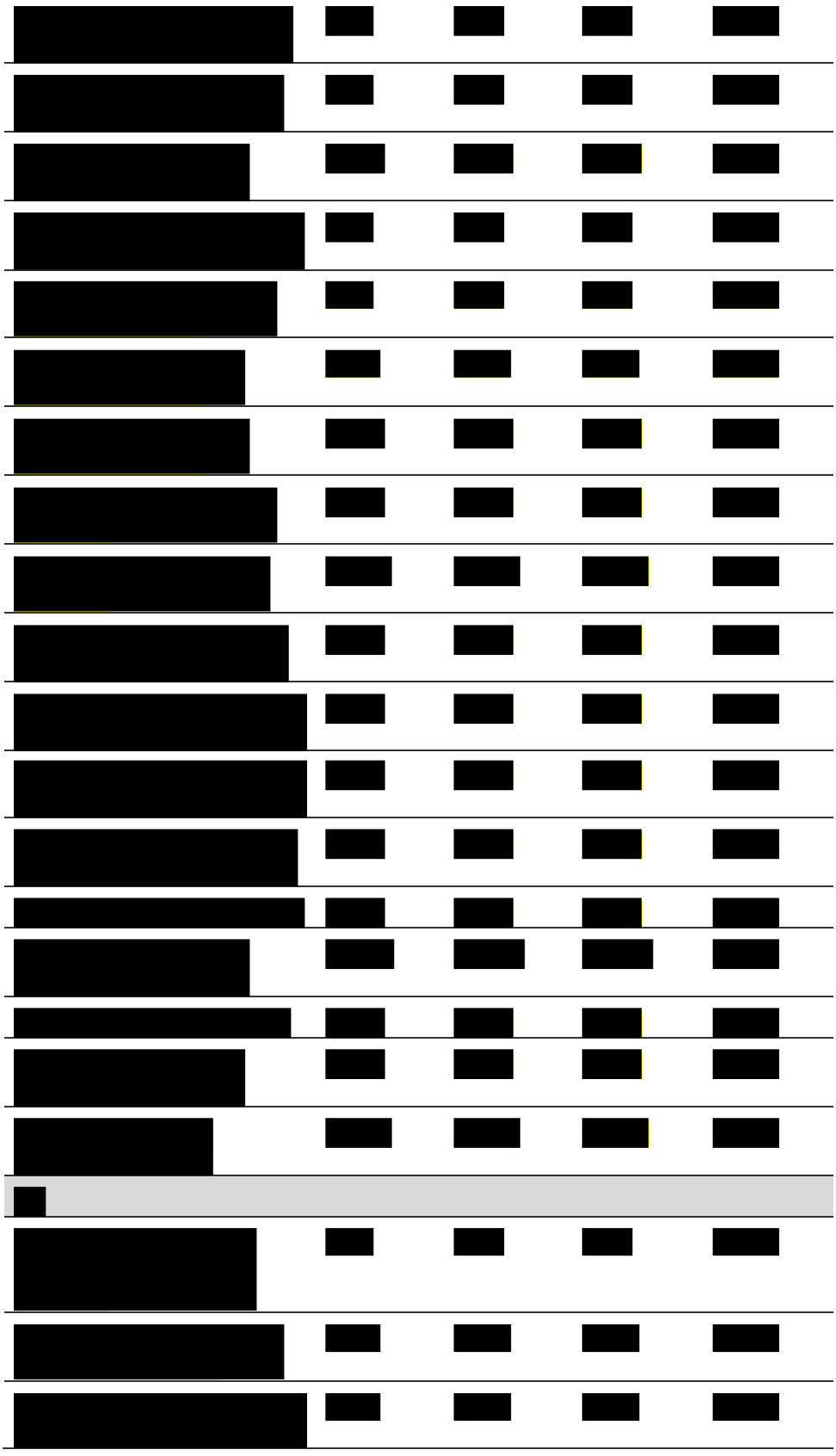
- Model characteristics (discount rate, time horizon, age)
- Parametric survival models
- Adverse event costs, disutilities
- Health state utilities
- Health state costs

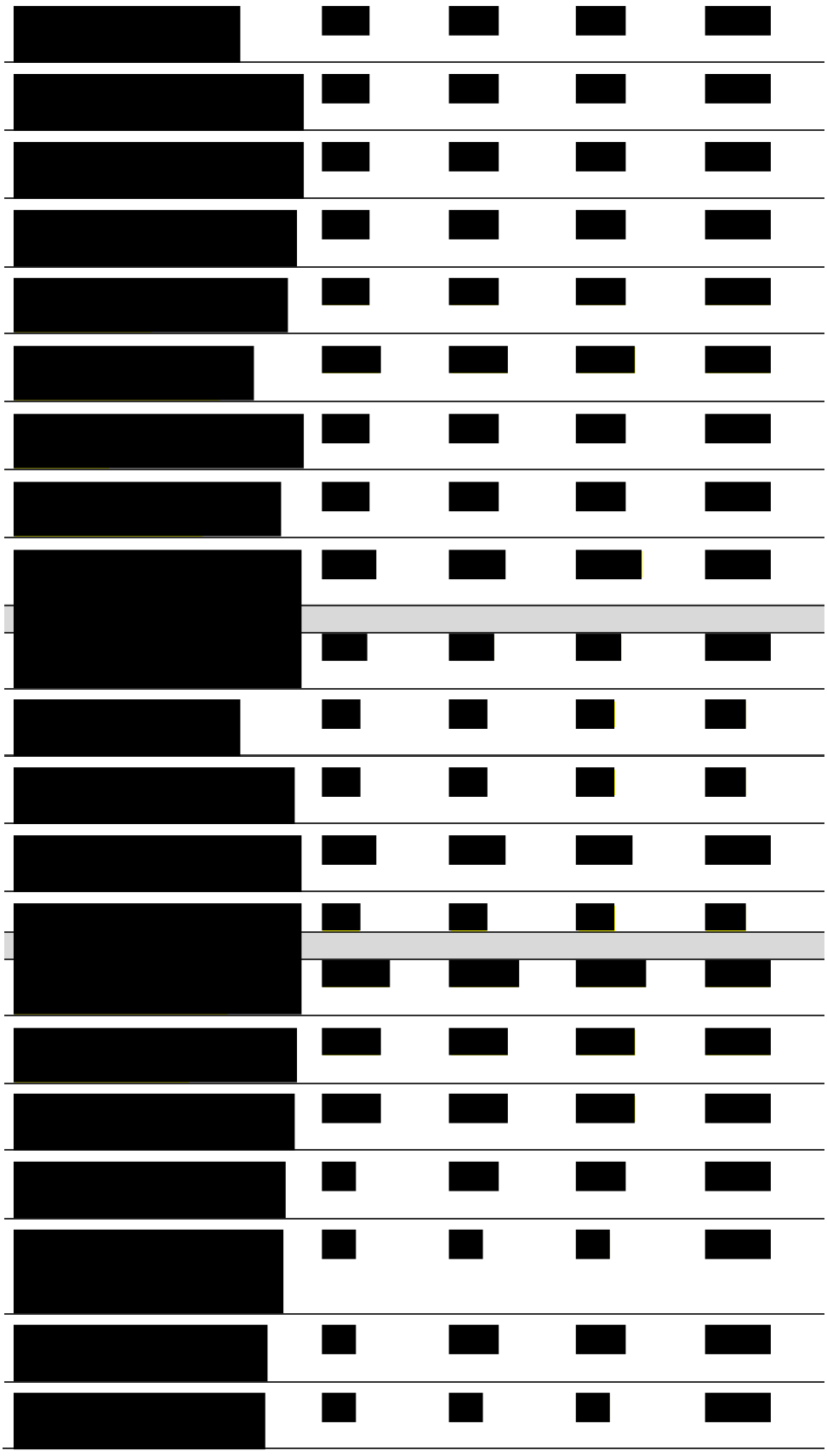
Disutilities, survival parameters, health state costs were assumed to follow a normal distribution. Utilities were assumed to follow a Beta distribution.

Table 68 shows the distributional assumptions of the model parameters (point estimate, and lower and upper bound).

Table 68. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
[redacted]				





Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

A clinical SLR was conducted which aimed to address the following research question:

- What is the clinical efficacy, real-world effectiveness, and safety outcomes for patients with NTRK fusion-positive solid tumours who are treated with NTRK-fusion-targeted therapies?

As detailed in Table 69 and Table 70, the SLR search was conducted during August 2020. The searches were performed in the following indexed databases:

- Embase and MEDLINE® (via Embase.com)
- Embase and MEDLINE® (via PubMed)
- Cochrane databases (via CochraneLibrary.com)

All databases were either unlimited searched or from 1947 to 2018 to retrieve comprehensive evidence. Search strategies for Embase® and MEDLINE® were implemented using Embase.com, MEDLINE® In-Process using the PubMed platform, and the Cochrane library using CochraneLibrary. The search was not restricted by countries or English language. However, the search was restricted to not including no editorials/letters, as these er typically narrative texts, therefore the study designs of interest was interventional studies, prospective cohort studies, cross-sectional surveys and registries. Animal studies were also excluded from the SLR as the population of interest is humans (paediatrics and adults) with NTRK fusion-positive solid tumours.

Conference abstracts from relevant conference websites were captured in the Embase database searches, from the last 2 years (2018-2020). In addition, relevant conferences that was not indexed were hand-searched in the following:

- American Association for Cancer Research (AACR)
- American Society of Clinical Oncology (ASCO)

Bibliographies of additional, published, relevant systematic review articles were examined to obtain references. Bibliographies of accepted studies were reviewed to obtain further relevant references. Additionally, the following clinical trials registers and clinical trials platforms were searched:

- ClinicalTrials.gov via https://clinicaltrials.gov/
- EU Clinical Trials Register via https://www.clinicaltrialsregister.eu/

The data identified through electronic and manual searches were supplemented by the data available on health technology assessment (HTA) websites. The following international HTA websites were searched to identify any relevant HTAs:

- National Institute for Health and Care Excellence (NICE)
- Canadian Agency for Drugs and Technologies in Health (CADTH)
- Haute Autorite de Sante (HAS)

Table 69 Bibliographic databases included in the clinical literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase and Medline	Embase.com	1947-2018	06 August 2020
Embase and Medline	PubMed	Unlimited	06 August 2020
Cochrane	CochraneLibrary.com	Unlimited	07 August 2020

Abbreviations: Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online

Table 70 Other sources included in the clinical literature search

Source name	Location/source	Search strategy	Date of search
United States NLM	Clinicaltrials.gov	NTRK/TRK with Larotrectinib/entrectinib	20 August 2020
EU Clinical Trials Register	Clinicaltrialsregister.eu	NTRK/TRK with Larotrectinib/entrectinib	20 August 2020
NICE	www.nice.org.uk	NTRK/TRK with Larotrectinib/entrectinib	N/A
CADTH	https://www.cda-amc.ca/search	NTRK/TRK with Larotrectinib/entrectinib	N/A
HAS	https://www.has-sante.fr/jcms/pprd_2986129/en/home	NTRK/TRK with Larotrectinib/entrectinib	N/A

Abbreviations: NLM, National Library of Medicine; NICE, National Institute for Health and Care Excellence, CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorite de Sante; N/A, not available / not applicable

Table 71 Conference material included in the clinical literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
AACR	https://www.aacr.org/	Manual search	Neurotrophic tyrosine, kinase, Neurotrophic, Tyrosine kinase, TRK, NTRK, Tumor-agnostic, Tumour-independent, Pan-tumour, Fusio, Larotrectinib, loxo10, arry 470, entrectinib, nms e628, nmse628, rxdx 101, repo-trectinib, ropo-trectinib, cabozantinib, Cabomety, Mo-metriq, bms907351, xl184, sitravatinib, mg 516, mg 91516, merestinib, ly 2801653, loxo195, ono 7579	N/A
ASCO	https://www.asco.org/	Manual search		N/A

Abbreviations: AACR, American Association for Cancer Research; ASCO, American Society of Clinical Oncology; N/A, not available / not applicable

H.1.1 Search strategies

The search strategies were based on the population, interventions/comparators, outcomes and study design (PICOS) developed for this clinical SLR**,** Table **75**.

Table **72** to Table **74** present the search hits in Embase, PubMed and Cochrane databases.

Table 72 Clinical search strategy table for Embase and MEDLINE (via Embase.com)

No.	Query	Results
#1	'neurotrophic tyrosine kinase*':ab,ti OR ntrk*:ab,ti OR ((trk* NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)):ab,ti) OR ((tyrosine OR tropomyosin) NEAR/2 kinase NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*))	4,673
#2	'larotrectinib'/exp OR larotrectinib:ab,ti OR loxo101:ab,ti OR 'loxo 101':ab,ti OR 'arry 470':ab,ti OR arry470:ab,ti OR 'entrectinib'/exp OR entrectinib:ab,ti OR 'nms e 628':ab,ti OR 'nms e628':ab,ti OR nmse628:ab,ti OR 'rxdx 101':ab,ti OR rxdx101:ab,ti OR 'repotrectinib'/exp OR ropotrectinib:ab,ti OR 'cabozantinib'/exp OR cabozantinib:ab,ti OR cabometyx*:ab,ti OR mometriq*:ab,ti OR bms907351:ab,ti OR 'bms 907351':ab,ti OR xl184:ab,ti OR 'xl 184':ab,ti OR 'sitravatinib'/exp OR sitravatinib:ab,ti OR 'mg 516':ab,ti OR mg516:ab,ti OR 'mg 91516':ab,ti OR mg91516:ab,ti OR mgcd516:ab,ti OR 'mgcd 516':ab,ti OR 'merestinib'/exp OR merestinib:ab,ti OR 'ly 2801653':ab,ti OR ly2801653:ab,ti OR loxo195:ab,ti OR 'loxo 195':ab,ti OR 'ono 7579':ab,ti OR ono7579:ab,ti OR ((trk* NEAR/3 inhibit*):ab,ti) OR (((tyrosine OR tropomyosin) NEAR/3 inhibit*):ab,ti) OR (((tissue OR tumour OR tumour OR histology) NEAR/2 (agnostic OR independent)):ab,ti)	66,150

No.	Query	Results
#3	#1 AND #2	1,192
#4	#3 NOT (letter:it OR editorial:it)	1,184
#5	#4 NOT ('animals'/exp NOT 'humans'/exp)	1,102
#6	[conference abstract]/lim AND [1947-2018]/py	3,371,237
#7	#5 NOT #6	742

Table 73 Clinical search strategy table for Embase and MEDLINE (via PubMed)

No.	Query	Results
#1	“neurotrophic tyrosine kinase*”[tiab] OR ntrk*[tiab] OR (trk[tiab] AND (mutat*[tiab] OR fusion*[tiab] OR translocation*[tiab] OR recombina*[tiab] OR rearrang*[tiab])) OR (tropomyosin[tiab] AND kinase[tiab] AND (mutat*[tiab] OR fusion*[tiab] OR translocation*[tiab] OR recombina*[tiab] OR rearrang*[tiab])) OR tyrosine kinase mutat*[tiab] OR tyrosine receptor kinase mutat*[tiab] OR tyrosine kinase fusion*[tiab] OR tyrosine receptor kinase fusion*[tiab] OR tyrosine kinase translocation*[tiab] OR tyrosine receptor kinase translocation*[tiab] OR tyrosine kinase recombina*[tiab] OR tyrosine receptor kinase recombina*[tiab] OR tyrosine kinase rearrang*[tiab] OR tyrosine receptor kinase rearrang*[tiab]	2,314
#2	"larotrectinib"[Supplementary Concept] OR larotrectinib[tiab] OR loxo101[tiab] OR “loxo 101”[tiab] OR “arry 470”[tiab] OR arry470[tiab] OR "entrectinib" [Supplementary Concept] OR entrectinib[tiab] OR “nms e 628”[tiab] OR “nms e628”[tiab] OR nmse628[tiab] OR “rxdx 101”[tiab] OR rxdx101[tiab] OR "repotrectinib" [Supplementary Concept] OR ropotrectinib[tiab] OR "cabozantinib" [Supplementary Concept] OR cabozantinib[tiab] OR cabometyx*[tiab] OR mometriq*[tiab] OR bms907351[tiab] OR “bms 907351”[tiab] OR xl184[tiab] OR “xl 184”[tiab] OR "sitravatinib" [Supplementary Concept] OR sitravatinib[tiab] OR “mg 516”[tiab] OR mg516[tiab] OR “mg 91516”[tiab] OR mg91516[tiab] OR mgcd516[tiab] OR “mgcd 516”[tiab] OR merestinib[tiab] OR “ly 2801653”[tiab] OR ly2801653[tiab] OR loxo195[tiab] OR “loxo 195”[tiab] OR “ono 7579”[tiab] OR ono7579[tiab] OR (trk[tiab] AND inhibit*[tiab]) OR ((tyrosine[tiab] OR tropomyosin[tiab]) AND inhibit*[tiab]) OR ((tissue[tiab] OR tumour[tiab] OR tumour[tiab] OR histology[tiab]) AND agnostic[tiab]) OR tissue independent[tiab] OR tumour independent[tiab] OR tumour independent[tiab] OR histology independent[tiab]	83,999
#3	#1 AND #2	659
#4	#3 NOT (letter[pt] OR editorial[pt])	653
#5	#4 NOT (“animals”[Mesh] NOT “humans”[Mesh])	556

Table 74 Clinical search strategy table for Cochrane via CochraneLibrary.com

No.	Query	Results
#1	("neurotrophic tyrosine":ab,ti NEXT kinase*:ab,ti) OR ntrk*:ab,ti OR ((trk* NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)):ab,ti) OR ((tyrosine OR tropomyosin) NEAR/2 kinase NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)) OR *TRK*	286
#2	larotrectinib:ab,ti OR loxo101:ab,ti OR "loxo 101":ab,ti OR "arry 470":ab,ti OR arry470:ab,ti OR entrectinib:ab,ti OR "nms e 628":ab,ti OR "nms e628":ab,ti OR nmse628:ab,ti OR "rxdx 101":ab,ti OR rxdx101:ab,ti OR ropotrectinib:ab,ti OR cabozantinib:ab,ti OR cabometyx*:ab,ti OR mo-metriq*:ab,ti OR bms907351:ab,ti OR "bms 907351":ab,ti OR xl184:ab,ti OR "xl 184":ab,ti OR sitravatinib:ab,ti OR "mg 516":ab,ti OR mg516:ab,ti OR "mg 91516":ab,ti OR mg91516:ab,ti OR mgcd516:ab,ti OR "mgcd 516":ab,ti OR merestinib:ab,ti OR "ly 2801653":ab,ti OR ly2801653:ab,ti OR loxo195:ab,ti OR "loxo 195":ab,ti OR "ono 7579":ab,ti OR ono7579:ab,ti OR ((trk* NEAR/3 inhibit*):ab,ti) OR (((tyrosine OR tropo-myosin) NEAR/3 inhibit*):ab,ti) OR (((tissue OR tumour OR tumour OR histology) NEAR/2 (agnostic OR independent)):ab,ti)	2,629
#3	#1 AND #2	53 trials, 1 SLR proto-col

H.1.2 Systematic selection of studies

All SLR search algorithms were generated using PICOS-related elements outlined in Table 75 below. These were generated from the research question pertinent to each section.

Table 75 PICOS used for assessment of clinical studies

PICOS	Inclusion criteria	Exclusion criteria
Population	Individuals (paediatrics and adults) with NTRK fusion-positive solid tumours	Tumours other than solid tumours (e.g., haemato-logical)
Intervention/Com-parators	Any treatment (or treatment combination) specifically targeting NTRK fusion-positive solid tumours (e.g., larotrectinib, en-trectinib)	• Studies not assessing an NTRK fusion-posi-tive targeted inter-vention • Studies evaluating surgical procedures only
Outcomes	None	
Study design/publi-cation type	• Interventional studies (e.g., ran-domized controlled trials, single-arm trials, pragmatic trials)	• Narrative reviews

	• Prospective cohort studies, cross-sectional surveys, registries • Any relevant published systematic literature reviews and meta-analyses will be included for hand-searching of the reference lists.	• Opinion, editorial, commentary, letter • Case reports, case series (N≤10) • Retrospective studies • Preclinical studies • In vitro studies
Language restrictions	No limits	None

The PRISMA flow diagram for the clinical SLR is shown in Figure 37 below. Out of 1,037 publications initially identified and screened from multiple databases, 954 were excluded based on title and abstract, leaving 83 publications for further eligibility assessment. Following full-text screening, 46 publications were excluded for the reasons detailed in Table 77. Consequently, 37 publications were included in the report, comprising:

- 6 full texts
- 31 abstracts

After a grey literature search from additional bibliography check another 10 publication were included (6 abstracts and 4 HTA submissions), resulting in in a total of 47 publications included in the clinical SLR.

Details of the included studies from the clinical SLR are provided in Table 76. Please note that abstracts are not included in this table, as they lack the detailed information required for this context.

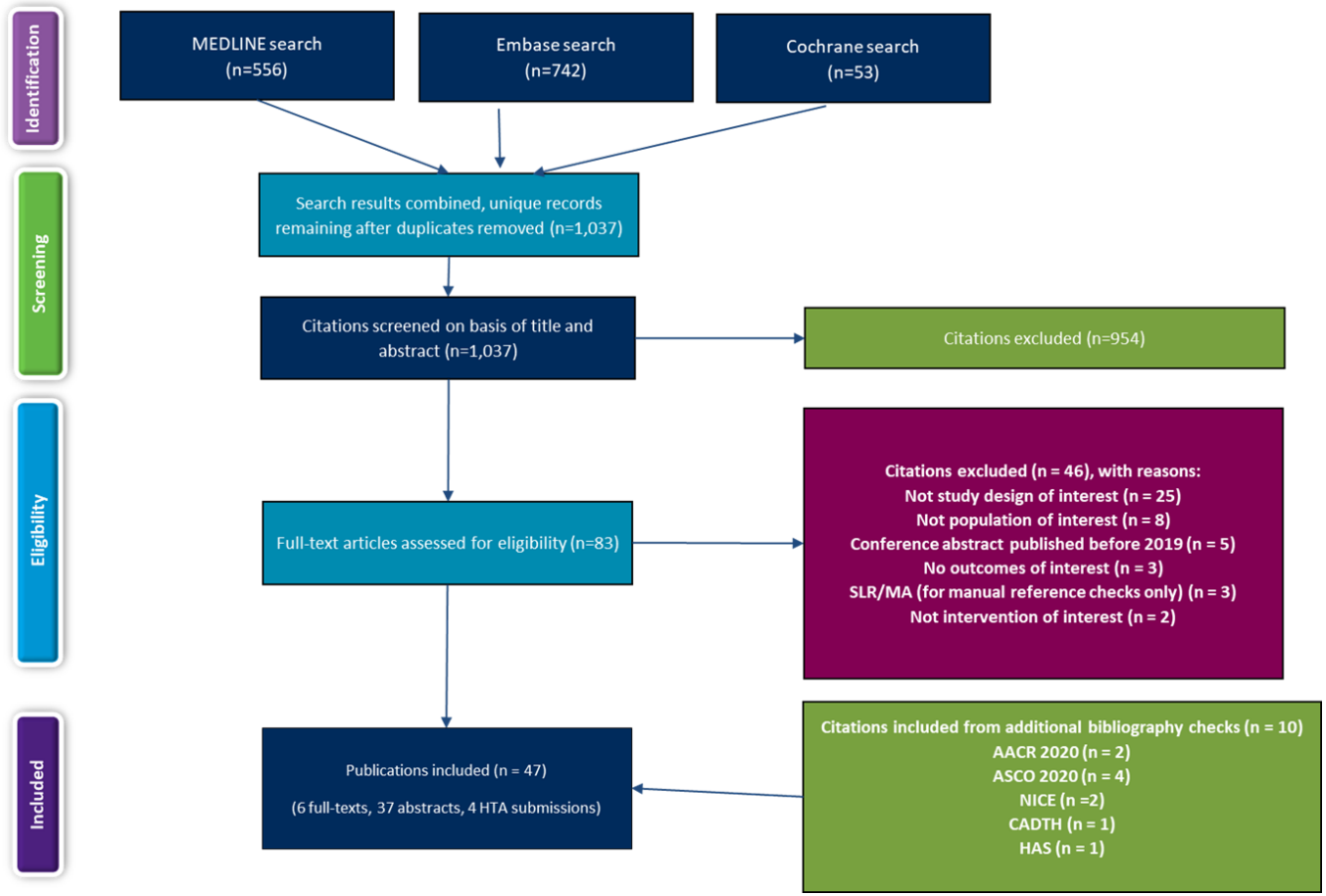


Figure 37 PRISMA flow chart for the SLR on clinical efficacy

Table 76 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Entrectinib publications						
Drilon, A et al., 2017 (ALKA-372-001 and STARTRK-1)	Evaluate the safety and antitumour activity of entrectinib, a pan-TRK, ROS1, and ALK inhibitor	Two Phase I clinical trials involving escalating dose levels of entrectinib using a 3+3 design	Patients with advanced/metastatic solid tumours harbouring NTRK1/2/3, ROS1, or ALK molecular alterations, TKI-treatment naïve, and who had no alternative effective standard therapy	Entrectinib was the intervention; no direct comparator as this was a single-arm dose-escalation study. Patients received entrectinib orally with either intermittent or continuous dosing	MTD or RP2D. The follow-up varied, but assessments were conducted every 8 weeks	Secondary outcomes evaluated anti-tumour activity, including ORR, PFS, and OS, with follow-ups extending beyond 15 months and responses lasting up to 2.5 years
Doebele, R. C. et al., 2020 (ALKA-372-001, STARTRK-1, STARTRK-2)	Assess the efficacy and safety of entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours	Integrated analysis of three Phase I/II trials using entrectinib.	Patients with advanced/metastatic NTRK fusion-positive solid tumours, TRK inhibitor-naive, aged 18 years or older	Entrectinib treatment; no comparator in a single-arm study (n = 54 efficacy-evaluable patients)	ORR of 57%, with a median follow-up of 12.9 months. Median duration of response was 10 months	Safety, including treatment-related AEs such as weight gain (10%) and anaemia (12%), with no treatment-related deaths reported
NICE HTA [ID1512]	Evidence-based recommendations on entrectinib (Rozlytrek) for treating NTRK fusion-positive solid tumours.	HTA	-	-	-	-

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Larotrectinib publications						
Drilon, A. et al., 2018 (NCT02122913, NCT02637687, NCT02576431)	Assess the efficacy and safety of larotrectinib, a highly selective TRK inhibitor, in adults and children with TRK fusion–positive cancers.	Integrated analysis of three trials (Phase 1 in adults, Phase 1-2 in children, and Phase 2 in adolescents/adults).	55 patients (aged 4 months to 76 years) with 17 unique TRK fusion-positive tumour types.	Larotrectinib treatment (n = 55), no comparator.	ORR of 75%, with a median follow-up of 9.4 months. At 1 year, 71% of responses were ongoing.	PFS and DoR not reached at DCO. Safety data showed predominantly grade 1 adverse events
Laetsch, T. W., et al., 2018	Assess the safety of larotrectinib in paediatric patients with solid tumours harbouring TRK fusions and to determine the recommended phase 2 dose.	Multicentre, open-label, phase 1 trial.	Infants, children, and adolescents aged 1 month to 21 years with locally advanced or metastatic solid or CNS tumours, regardless of TRK fusion status.	Larotrectinib was administered orally twice daily in three dose cohorts. The sample size was 24 patients, 17 with TRK fusion-positive cancers and 7 without TRK fusions.	Safety, including DLT. The follow-up period varied but median follow-up for patients with TRK fusions was 8.2 months.	Determination of MTD, pharmacokinetics, and assessment of antitumour activity (ORR).
Hong, D. S., et al., 2020	Evaluate the efficacy and long-term safety of larotrectinib in a larger population of patients with TRK fusion-positive solid tumours	Pooled analysis of three phase 1/2 clinical trials (adult phase 1, paediatric phase 1/2, and adolescent/adult phase 2).	Patients aged 1 month to 84 years, with locally advanced or metastatic TRK fusion-positive solid tumours who had previously	Larotrectinib was administered orally in capsule or liquid form. The dosing regimen was mostly 100 mg twice daily for adults and 100	ORR as assessed by local investigators, based on RECIST criteria. At a median follow-up of 12.9 months, 79% (121/153) of patients	DoR, PFS and OS. At a median follow-up of 12.9 months, the median duration of response was 35.2 months, and the

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
			received standard therapy.	mg/m² for paediatric patients. The primary analysis included 153 evaluable patients for response out of 159 enrolled.	had an objective response, with 16% (24/153) achieving complete response	median PFS was 28.3 months
NICE CA [ID1299]	Evidence-based recommendations on larotrectinib for NTRK fusion-positive solid tumours in adults and children	HTA	-	-	-	-
pan-Canadian Oncology Drug Review, 2020	Larotrectinib for NTRK Locally Advanced or Metastatic Solid Tumours	HTA	-	-	-	-
commission De La Transparence Avis, 2020	Larotrectinib 25 and 100 mg, capsule; larotrectinib 20 mg/ml, oral solution. First evaluation	HTA	-	-	-	-
TRK-Targeted therapy publication						

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Rosen, E. Y., et al., 2020	To conduct an integrated analysis of clinical and genomic characteristics of TRK fusion-positive cancers, focusing on their outcomes and response to alternative standard therapies	Retrospective design, analysing data from a centre-wide screening program that included over 26,000 patients who had undergone prospective sequencing	The study included 76 paediatric and adult patients with confirmed TRK fusions. The median age of the patients was 52 years, with an age range spanning from 1 week to 78 years.	The primary intervention in this study was TRK-targeted therapies (e.g., larotrectinib). Comparators included non-TRK therapies such as chemotherapy and immunotherapy.	The primary outcome was ORR to both TRK inhibitors and alternative standard therapies. The follow-up period varied, with a median follow-up time for survivors of 3.1 years.	Secondary outcomes included PFS, which was 9.1 months and OS from initial diagnosis, which was 19.8 years. The follow-up periods were reported in relation to these outcomes.

Abbreviations: NTRK, Neurotrophic Tyrosine Receptor Kinase; TRK, tropomyosin receptor kinase; ROS1, ROS proto-oncogene 1; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitors; MTD, maximum tolerated dose; RP2D, recommended Phase II dose; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HTA, Health Technology Assessment; DoR, duration of response; AEs, advers events; DLT, dose-limiting toxicity, RECIST, Response Evaluation Criteria in Solid Tumours

H.1.3 Excluded studies

Table 77 provides an overview of the publications excluded with reasons

Table 77 Overview of publications excluded at full-text screening from the clinical SLR

No.	Publication	Exclusion reason
#1	Tan, et al. Larotrectinib efficacy and safety in TRK fusion cancer: An expanded clinical dataset showing consistency in an age and tumour agnostic approach. Annals of Oncology. 2018. 29:ix23	Conference abstract published before 2019
#2	Demetri, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: Pooled analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. Annals of Oncology. 2018. 29:ix175	Conference abstract published before 2019
#3	Lassen, et al. Larotrectinib efficacy and safety in TRK fusion cancer: An expanded clinical dataset showing consistency in an age and tumour agnostic approach. Annals of oncology : official journal of the European Society for Medical Oncology. 2018. 29:viii133	Conference abstract published before 2019
#4	Demetri, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive (NTRK-fp) Tumours: Pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001. Annals of oncology : official journal of the European Society for Medical Oncology. 2018. 29:viii713	Conference abstract published before 2019
#5	Nathenson, et al. Activity of larotrectinib in patients with TRK fusion GI malignancies. Annals of Oncology. 2018. 29:v107	Conference abstract published before 2019
#6	Roth, et al. The Potential Long-Term Comparative Effectiveness of larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer. J Manag Care Spec Pharm. 2020. 26:981-986.	No outcomes of interest
#7	Mercier, et al. Exposure-response analysis of entrectinib supports the recommended dose in patients with advanced/metastatic solid tumours. Clinical Pharmacology and Therapeutics. 2020. 107:S50.	No outcomes of interest
#8	Bellone, et al. PCN147 Entrectinib in Ntrk tumour agnostic indication compared to different standard of care in various tumours types: a cost-effectiveness analysis in Italian patients. Value in Health. 2019. 22:S464.	No outcomes of interest

No.	Publication	Exclusion reason
#9	Farago, et al. Clinicopathologic Features of Non-Small-Cell Lung Cancer Harboring an NTRK Gene Fusion. JCO Precis Oncol. 2018. 2018.	Not an intervention of interest
#10	Park, et al. NTRK1 fusions for the therapeutic intervention of Korean patients with colon cancer. Oncotarget. 2016. 7:8399-8412	Not an intervention of interest
#11	Danilenko, et al. Targeting Tropomyosin Receptor Kinase in Cutaneous CYLD Defective Tumours With Pegcantratinib: The TRAC Randomized Clinical Trial. JAMA Dermatol. 2018. 154:913-921.	Not a population of interest
#12	Lin, et al. A phase 1, open-label, dose-escalation trial of oral TSR-011 in patients with advanced solid tumours and lymphomas. Br J Cancer. 2019. 121:131-138.	Not a population of interest
#13	Ross, et al. Enrichment of kinase fusions in ESR1 wild-type, metastatic breast cancer revealed by a systematic analysis of 4854 patients. Ann Oncol. 2020. 31:991-1000.	Not a population of interest
#14	Papadopoulos, et al. U.S. Phase I First-in-human Study of Taletrectinib (DS-6051b/AB-106), a ROS1/TRK Inhibitor, in Patients with Advanced Solid Tumours. Clin Cancer Res. 2020. #volume#.	Not a population of interest
#15	Liu, et al. Characterization of on-target adverse events caused by TRK inhibitor therapy. Ann Oncol. 2020. #volume#.	Not a population of interest
#16	Yano, et al. Foretinib circumvents the NTRK1 G667C mutation-associated entrectinib-resistance in the brain and liver metastases produced by NTRK1 fusion-positive tumour cells. Annals of oncology : official journal of the European Society for Medical Oncology. 2018. 29:viii653	Not a population of interest
#17	Moses, et al. Multiple Genetic Alterations in Papillary Thyroid Cancer are Associated with Younger Age at Presentation. Journal of Surgical Research. 2010. 160:179-183	Not a population of interest
#18	Weiss, et al. Phase i study of the safety, tolerability and pharmacokinetics of PHA-848125AC, a dual tropomyosin receptor kinase A and cyclin-dependent kinase inhibitor, in patients with advanced solid malignancies. Investigational new drugs. 2012. 30:2334-2343.	Not a population of interest
#19	Chu, et al. Systematic review of neurotrophic tropomyosin-related kinase inhibition as a tumour-agnostic management strategy. Future Oncol. 2020. 16:61-74.	SLR/MA (for manual reference checks only)

No.	Publication	Exclusion reason
#20	Naito, et al. Japan society of clinical oncology/Japanese society of medical oncology-led clinical recommendations on the diagnosis and use of tropomyosin receptor kinase inhibitors in adult and paediatric patients with neurotrophic receptor tyrosine kinase fusion-positive advanced solid tumours, cooperated by the Japanese society of paediatric hematology/oncology. Int J Clin Oncol. 2020. 25:403-417.	SLR/MA (for manual reference checks only)
#21	Sohal, et al. Metastatic Pancreatic Cancer: ASCO Guideline Update. J Clin Oncol. 2020. #volume#:JCO2001364.	SLR/MA (for manual reference checks only)
#22	Drilon, et al. Safety and Antitumour Activity of the Multitargeted Pan-TRK, ROS1, and ALK Inhibitor Entrectinib: Combined Results from Two Phase I Trials (ALKA-372-001 and STARTRK-1). Cancer Discov. 2017. 7:400-409.	Not a study design of interest
#23	Cocco, et al. Resistance to TRK inhibition mediated by convergent MAPK pathway activation. Nat Med. 2019. 25:1422-1427.	Not a study design of interest
#24	Entrectinib Effective across NTRK Fusion-Positive Cancers. Cancer Discov. 2019. 9:OF4.	Not a study design of interest
#25	Entrectinib Shows Pediatric Potential. Cancer Discov. 2019. 9:OF4.	Not a study design of interest
#26	Burki, et al. Larotrectinib in TRK fusion-positive cancers. Lancet Oncol. 2018. 19:e187.	Not a study design of interest
#27	Sidaway, et al. Targeted therapy: Larotrectinib effective against TRK-fusion-positive cancers. Nat Rev Clin Oncol. 2018. 15:264.	Not a study design of interest
#28	Combating Acquired TRK Inhibitor Resistance. Cancer Discov. 2019. 9:684-685.	Not a study design of interest
#29	Lassen, et al. Entrectinib for ROS1 fusion-positive NSCLC and NTRK fusion-positive solid tumours. Lancet Oncol. 2020. 21:193-194.	Not a study design of interest
#30	Landman, et al. Rapid Response to larotrectinib (LOXO-101) in an Adult Chemotherapy-Naive Patients With Advanced Triple-Negative Secretory Breast Cancer Expressing ETV6-NTRK3 Fusion. Clin Breast Cancer. 2018. 18:e267-e270.	Not a study design of interest
#31	Bailey, et al. Tropomyosin receptor kinase inhibitors: an updated patent review for 2016-2019. Expert Opin Ther Pat. 2020. 30:325-339.	Not a study design of interest

No.	Publication	Exclusion reason
#32	TRK Inhibitor Shows Early Promise. Cancer Discov. 2016. 6:OF4.	Not a study design of interest
#33	Wilson, et al. Larotrectinib in NTRK-Rearranged Solid Tumours(Published as part of the Biochemistry series "Biochemistry to Bedside"). Biochemistry. 2019. 58:1555-1557.	Not a study design of interest
#34	Wang, et al. Durable Clinical Response to Crizotinib in IRF2BP2-NTRK1 Non-small-cell Lung Cancer. Clin Lung Cancer. 2019. 20:e233-e237.	Not a study design of interest
#35	Hemming, et al. Response and mechanisms of resistance to larotrectinib and selitrectinib in metastatic undifferentiated sarcoma harbouring oncogenic fusion of NTRK1. JCO Precis Oncol. 2020. 4:79-90.	Not a study design of interest
#36	Okimoto, et al. Tracking Down Response and Resistance to TRK Inhibitors. Cancer Discov. 2016. 6:14-6.	Not a study design of interest
#37	Shukla, et al. Successful Targeted Therapy of Refractory Pediatric ETV6-NTRK3 Fusion-Positive Secretory Breast Carcinoma. JCO Precis Oncol. 2017. 2017.	Not a study design of interest
#38	Robinson, et al. Entrectinib in children and adolescents with recurrent or refractory solid tumours including primary CNS tumours. Neuro-Oncology. 2019. 21:vi186.	Not a study design of interest
#40	Wang, et al. Study of a selective kinase inhibitor entrectinib targeting NTRK, ROS1 and ALK fusion-positive solid tumours. Chinese Journal of New Drugs. 2019. 28:2360-2366	Not a study design of interest
#41	Drilon, et al. Safety and preliminary clinical activity of repotrectinib in patients with advanced ROS1/TRK fusion-positive solid tumours (TRIDENT-1 study). Annals of Oncology. 2019. 30:v162.	Not a study design of interest
#42	Robinson, et al. Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumours including central nervous system (CNS) tumours. Journal of Clinical Oncology. 2019. 37.	Not a study design of interest
#43	Rosen, et al. Larotrectinib demonstrates CNS efficacy in Trk fusion-positive solid tumours. JCO Precision Oncology. 2019. 3.	Not a study design of interest
#44	Pishvaian, et al. Entrectinib in TRK and ROS1 fusion-positive metastatic pancreatic cancer. JCO Precision Oncology. 2018. 2.	Not a study design of interest

No.	Publication	Exclusion reason
#45	Sartore-Bianchi, et al. Pooled Analysis of Clinical Outcome of Patients with Chemorefractory Metastatic Colorectal Cancer Treated within Phase I/II Clinical Studies Based on Individual Biomarkers of Susceptibility: A Single-Institution Experience. Targeted Oncology. 2017. 12:525-533.	Not a study design of interest
#46	Raez, et al. Neurotrophic tyrosine kinase gene fusions: Another opportunity for targeting in lung cancer. Lung Cancer Management. 2016. 5:1-4	Not a study design of interest

H.1.4 Quality assessment

The quality assessment for the included full-text publications was evaluated using a checklist in Table 78. Each item in this checklist is checked as 'yes', 'no', or as a 'score of 0 to 5'. The quality assessment is only available for 2 publications.

Table 78 Quality assessment for the clinical assessment

Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Study name																												
Drilon, A et al., 2017															N/A													
Doebele, R. C. et al., 2020	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	N	N	Y	N	N	Y	N	Y	Y	Y	N	Y	N	N	N	N	2[a]
Drilon, A. et al., 2018															N/A													
Laetsch, T. W., et al., 2018															N/A													
Hong, D. S., et al., 2020	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	Y	N	Y	N	N	N	N	Y	Y	Y	N	Y	N	N	N	N	0[a]
Rosen, E. Y., et al., 2020															N/A													

Abbreviations: N = no; Y = yes; N/A, not available / not applicable

1. Is the objective of the study clear?
2. Are the main outcomes clearly described in the Introduction or Methods?
3. Are characteristics of the patients included in the study clearly described?
4. Are the interventions clearly described?
5. Are the distributions of principal confounders in each group of subjects clearly described?
6. Are the main findings of the study clearly described?
7. Does the study estimate random variability in data for main outcomes?
8. Have all the important adverse events consequential to the intervention been reported?
9. Have characteristics of patients lost to follow-up been described?
10. Have actual probability values been reported for the main outcomes except probability < 0.001?
11. Is the source of funding clearly stated?
12. Were subjects who were asked to participate in the study representative of the entire population recruited?
13. Were those subjects who were prepared to participate representative of the recruited population?
14. Were staff, places, and facilities where patients were treated representative of treatment most received?

15. Was an attempt made to blind study subjects to the intervention?
16. Was an attempt made to blind those measuring the main outcomes?
17. If any of the results of the study were based on data dredging, was this made clear?
18. Was the time period between intervention and outcome the same for intervention and control groups or adjusted for?
19. Were the statistical tests used to assess main outcomes appropriate?
20. Was compliance with the interventions reliable?
21. Were main outcome measures used accurate (valid and reliable)?
22. Were patients in different intervention groups recruited from the same population?
23. Were study subjects in different intervention groups recruited over the same period of time?
24. Were study subjects randomized to intervention groups?
25. Was the randomized intervention assignment concealed from patients and staff until recruitment was complete?
26. Was there adequate adjustment for confounding in the analyses from which main findings were drawn?
27. Were losses of patients to follow-up taken into account?
28. Was the study sufficiently powered to detect clinically important effects where the probability value for a difference due to chance is < 5%?

[a] Size of smallest Intervention Group Score of 0 to 5

H.1.5 Unpublished data

No unpublished literature is used to inform the clinical section of the dossier.

H.1.6 Local adaptation

No adaption was done to the current application.

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

The health-related quality-of-life search is outlined below:

- Previous conducted SLR, submitted to NICE
- Updated SLR, per August 2020

I.2 Health-related quality-of-life search submission to NICE

To generate relevant comparator clinical evidence for this appraisal, a series of SLRs was undertaken in tumour sites / locations known to harbour NTRK gene fusions, reflective of those of patients so far investigated within larotrectinib clinical studies. The SLR methodology is briefly described below. Further details are available on request.

For each tumour type, SLRs were performed by searching MEDLINE (via PubMed), Embase, and the Cochrane Library (including: Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], HTA database, National Health Service [NHS] Economic Evaluation Database [EED], and Cochrane Methodology Register) (from database inception to date of search execution) for potentially relevant articles. The exact search strings for each tumour site are available on request since the information amounts to over 160 pages. Additionally, grey literature sources (conference proceedings, registers of ongoing trials, and HTA-published reports) were also reviewed. Tumour-specific inclusion/exclusion criteria were applied by 2 independent reviewers (with resolution of any conflicts by an independent third reviewer) to screen the search results and ultimately identify the relevant studies.

The pertinent data were extracted from the included studies by a single researcher, with full review and validation of all extracted data by a second independent researcher (disagreements were arbitrated by an independent third reviewer). The extracted data were then synthesized and summarized for each tumour type. A quality assessment of the included studies was also conducted as an integral component of the SLR. Quality

assessment was undertaken by 2 separate reviewers, and discrepancies in ratings were resolved by a third reviewer.

Databases searched for HRQoL evidence:

- MEDLINE (via Cochrane Library)
- Embase, and the Cochrane Library (including: Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], HTA database, National Health Service [NHS] Economic Evaluation Database [EED], and Cochrane Methodology Register)

Databases were searched from database inception to date of search execution. The date of each search is documented alongside each search string (available on request); Initial searches were performed May – August 2018 and updated in January – March 2019.

The literature search methodology as described in this section was applied to all tumour sites, except when noted otherwise. Also listed are grey literature sources, which include conference proceedings, registers of on-going trials, and HTA-published reports. The limits for human studies and specific publication types were applied to the Embase searches. No other limits were applied to the searches. The search results were combined in an EndNote database, and duplicate records were removed

Table 79 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Cochrane Library	N/A	January 2019 – March 2019
Medline	Cochrane Library	N/A	January 2019 – March 2019

Clinical Trials Databases - Clinical trials databases were searched to identify treatments currently being investigated or treatments that were investigated and abandoned. The databases included:

- Clinicaltrials.gov
- International Standard Randomised Controlled Trial Number Register (ISRCTN)
- Clinical Trials Register - International Clinical Trials Registry Platform (ICTRP)
- Clinicaltrialsregister.eu
- KlinischePrüfungen (PharmNet.Bund, AMIS - Öffentlicher Teil)

Conference proceedings - Conference abstracts from the below 3 conferences were searched for all tumour sites.:

- ASCO Annual Meeting
- ESMO Annual Meeting
- International Society for Pharmacoeconomics and Outcomes Research (ISPOR) International and European Annual Meetings

Table 80 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	N/A	January 2019 – March 2019
ISRCTN	https://www.isrctn.com/	N/A	January 2019 – March 2019
ICTRP	https://trialsearch.who.int/Default.aspx	N/A	January 2019 – March 2019
Clinicaltrialsregister.eu	https://www.clinicaltrialsregister.eu/	N/A	January 2019 – March 2019
KlinischePrüfungen	https://www.bfarm.de/DE/Arzneimittel/Klinische-Pruefung/_node.html	N/A	January 2019 – March 2019

Table 81 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://www.asco.org/	N/A	N/A	January 2019 – March 2019
ESMO	https://www.esmo.org/	N/A	N/A	January 2019 – March 2019
ISPOR	https://www.ispor.org/	N/A	N/A	January 2019 – March 2019

HTA Websites - HTA websites were searched to identify and collect information relating to applications and decisions of the relevant HTA for comparators of interest:

- Agency for Healthcare Research and Quality (AHRQ)
- All Wales Medicines Strategy Group (AWMSG)
- EMA
- Federal Joint Committee (G-BA)
- HAS
- Institute for Quality and Efficiency in Health Care (IQWIG)
- National Institute for Health and Care Excellence (NICE)
- CADTH
- Scottish Medicines Consortium (SMC)
- National Centre for Pharmacoeconomics (NCPE)

I.2.1 Search strategies

Studies were included if they met the PICOS criteria presented in Table 82 and the criteria in Table 83.

Table 82 Eligibility criteria used in the SLR strategy

PICOS	Inclusion criteria	Exclusion criteria
Population	See Table 93 for specific criteria according to each tumour included in the SLR	• Healthy volunteers • Patients with disease other than tumour in focus • Disease stage other than advanced/metastatic (i.e., early-stage) • Studies of mixed populations that do not provide outcome data stratified for the population of interest • Patients with 1st-line NSCLC • Patients treated with <2nd-line therapy for CRC, melanoma, pancreatic cancer, glioma (if treated for utilities) • Any other populations not specified in the Inclusion columns None for STS (Infantile Fibrosarcoma, Infantile Myofibromatosis, myopericytoma, Spindle Cell Sarcoma, Inflammatory Myofibroblastic Tumour, Peripheral Nerve Sheath Tumour), secretory breast cancer
Intervention/ Comparators	No limits for interventions or comparators (except for appendix cancer: Update 01 February 2019: Interventions and comparators will not include surgical interventions (except those that are conducted in conjunction with pharmacology therapy, e.g., CRS-HIPEC))	None
Outcomes	Health state utility values or disutility values (standard gamble, time trade off, etc) • EuroQoL 5D (EQ-5D) For thyroid cancer, glioma, biliary, GIST, salivary gland also: • SF-36 and its variations (e.g. SF-12, SF-6D) • Health utilities index (HUI) • FACT (general and disease-specific scales) • EORTC QLQ C30 (general and disease-specific scales)	Outcomes other than those specified in the inclusion column
Study design/ publication type	All study design (RCTs, observational, non-RCTs) reporting utility/disutility data (EQ-5D, standard gamble, time trade off, etc.) SLRs and meta-analyses for hand searching of reference lists	• Non-systematic reviews • Case reports • Case series • Conference abstracts prior to 2017 (NSCLC only) • Animal studies • Letters

Table 83 Population criteria for HRQoL SLR for relevant tumours

Tumour	Population included in the SLR
NSCLC	Patients with advanced / metastatic NSCLC (adults and paediatrics) being treated with ≥2nd-line therapy
CRC	Patients with locally advanced or metastatic CRC being treated with ≥2nd line therapy
Melanoma	Patients with locally advanced or metastatic malignant melanoma being treated with ≥2nd line therapy
Pancreatic cancer	Patients with locally advanced or metastatic pancreatic cancer being treated with ≥2nd line therapy
Thyroid cancer	Patients with locally advanced or metastatic anaplastic, follicular, or papillary thyroid cancers
Glioma	Patients with locally advanced or metastatic gliomas being treated with ≥2nd-line therapy
Biliary cancer	Patients with locally advanced or metastatic biliary cancer Updated 16 July 2018: • Biliary cancer does not include biliary strictures (malignant or benign) or periampullary cancer (of pancreatic origin)
GIST	Patients with locally advanced or metastatic GIST
Infantile Fibrosarcoma, Infantile Myofibromatosis, Myopericytoma	Infantile fibrosarcoma (Update 18 June 2018: n≥10) Infantile myofibromatosis (Update 18 June 2018: n≥10) Myopericytoma (Update 18 June 2018: n≥10)
STS: spindle cell sarcoma, inflammatory myofibroblastic tumour, and peripheral nerve sheath tumour	Infantile myofibromatosis (Update 18 June 2018: n≥10) Inflammatory myofibroblastic tumour (Update 18 June 2018: n≥10) Peripheral nerve sheath tumour (Update 18 June 2018: n≥10)
Salivary gland cancers	Patients with salivary gland cancers
Bone sarcoma	Patients with locally advanced or metastatic chondrosarcoma (conventional, clear cell, dedifferentiated, or mesenchymal) (n≥5)
Appendix Cancer	Locally advanced or metastatic appendix cancer (n≥5) Updated 01 February 2019: Subtypes not included: Pseudomyxoma peritonei (PMP), neuroendocrine tumours (carcinoids) of the ap-appendix
Secretory breast carcinoma	Secretory breast carcinoma
CMN	Locally advanced or metastatic congenital mesoblastic nephroma (n≥5)

Title/abstract screening of the citations resulting from the searches, using the inclusion and exclusion criteria detailed in tables above, was conducted by two independent reviewers with resolution of any conflicts by an independent third reviewer. Any other items that required an additional reviewer were flagged and discussed by the project team. A preliminary list of included studies was generated following title/abstract review, and based on this list, full-text articles were obtained. Two independent reviewers conducted the full-text review and narrowed the results to the final list of included studies. The

reference lists of any identified SLRs and meta-analyses were checked against the final list of studies.

Flow diagrams of the number of records included and excluded at each stage for each of the tumours studied have been summarised into a table, in order to minimise the number of pages (see Table 94).PRISMA flow diagrams are available on request. List of studies excluded at full-text review by exclusion reason is available on request.

After approval of the study citation lists for the SLRs, the data extraction step began. The list of data extraction elements was aligned with input from Bayer's economic model partner. A data extraction table shell was provided prior to commencing the data extraction phase of the review. Data extraction was conducted by a single reviewer, with full data validation conducted by a second reviewer, and conflicts resolved by a third, senior reviewer. Full data extraction tables are available on request

Table 84 Summary of PRISMA flow diagrams of the included studies for tumours included in the SLR

Screening step ► / ▼Tumour		Citations identified via: Medline (Pubmed)	Embase	Cochrane Library	Other sources [a]	**Unique citations after removal of duplicates. Title / abstract screened.**	Publications excluded during title / abstract screening	**Full text publications reviewed**	Records excluded during full text review	*Publications retrieved from manual search of SLRs & meta-analyses / conferences & registries*	**Publications included in evidence synthesis**
NSCLC		2725	2324	1428		**5315**	5138	**177**	132	*11*	**56**
CRC		1586	1366	541		**2436**	2289	**147**	120	*0*	**27**
Melanoma		463	782	634		**1106**	1001	**105**	91	*1*	**14**
Pancreatic cancer		660	647	245		**1117**	1050	**67**	61	*0*	**6**
Thyroid cancer			3403		14	**2568**	2473	**95**	76	*0*	**19**
Glioma		210	230	1		**331**	316	**15**	10	*0*	**5**
Biliary cancer		129	106	21		**201**	185	**16**	14	*0*	**2**
GIST		71	129	4		**148**	137	**11**	9	*0*	**2**
Infantile Fibrosarcoma (IFS), Infantile Myofibromatosis (IM), Myopericytoma (MP)	**IFS** / **IM** / **MP**	**See clinical evidence PRISMA table**									
Soft tissue sarcoma: spindle cell sarcoma (SC), inflammatory myofibroblastic tumour (IMT), and peripheral nerve sheath tumour (PNST)	**SC** / **IMT** / **PNST**	**See clinical evidence PRISMA table**									
Salivary gland cancers			1763		0	**1382**	1337	**45**	43	*0*	**2**
Bone sarcoma		**See clinical evidence PRISMA table**									
Appendix Cancer		**See clinical evidence PRISMA table**									
Secretory breast carcinoma (SBC)		**See clinical evidence PRISMA table**									
Congenital mesoblastic nephroma (CMN)		**See clinical evidence PRISMA table**									

[a] e.g. clinical trials, Health Technology Appraisal reports

The search string is available on request

Table 85 Search strategy for SLR

No.	Query	Results
#1	N/A	N/A

I.2.2 Summary of HRQoL publications

NSCLC

The humanistic burden of advanced NSCLC was described in 56 included publications. Nearly all studies reporting data for HRQoL and health state utilities were conducted in North America and Europe. Mean EQ-5D index scores for health states pre- and post-progression varied widely. Many of the included studies did not describe the methods of elicitation of utility values, but studies using the standard gamble approach reported fairly consistent values across several geographic settings.

Colorectal cancer

HRQoL and utilities were identified in 27 included studies of patients with advanced CRC. Treatment with panitumumab was associated with a positive impact on QoL; however, compared with BSC or chemotherapy alone, no significant differences were generally reported. Similar findings were assessed in studies of regorafenib and second-line aflibercept plus folinic acid, fluorouracil and irinotecan hydrochloride (FOLFIRI).

Melanoma

A total of 11 studies reported on HRQoL and utilities in patients with advanced melanoma. Development of late metastases, PD, and presence of key AEs resulted in lower QoL scores. Utility values were variable. The general public associated a PR or SD with favourable utility, and second-line treatment with nivolumab in melanoma patients led to improved utility values. However, second-line treatment with ipilimumab led to a utility decrement.

Pancreatic cancer

Five studies were identified reporting on the humanistic burden of pancreatic cancer, of which 4 reported on HRQoL and 4 on health utilities. Pancreatic cancer patients responded positively to therapy as assessed by QoL and returned from a decreased value to that similar to a normal population. The utility values ranged from 0.6 to 0.8 in pancreatic cancer patients, with slight differences reported between genders, geographic regions, and disease states.

Thyroid cancer

A total of 19 publications evaluated HRQoL and utilities in patients with thyroid cancer. QoL was decreased following surgical intervention and treatment with radioiodine. Utilities were similarly decreased with PD states compared with SD states.

Glioma

No utility studies were identified in this review; however, 8 studies reporting on HRQoL were included. While the QoL scales and patient populations differed across the studies, 1 study that assessed HRQoL prior to and after therapy found that HRQoL was maintained or improved after active treatment.

Biliary cancer

No true utility studies were identified by this review; however, 2 studies reporting on QoL were included. Both studies found that for a subset of patients, HRQoL was maintained or improved during active treatment.

STS: Infantile Fibrosarcoma, Infantile Myofibromatosis, and Myopericytoma

No studies reported on QoL, and no utility studies were identified.

STS: Spindle Cell, Inflammatory Myofibroblastic Tumour, Peripheral Nerve Sheath Tumour

Three studies on peripheral nerve sheath tumour reported on QoL and did not find any significant change due to treatment with sirolimus. No utility studies were identified.

Gastrointestinal Stromal Tumours

HRQoL and utilities were evaluated in 2 studies of patients with advanced GIST. Generally, no significant differences were reported for QoL scores, and decrements in utility scores were associated with progressive disease

Salivary Gland Cancer

No true utility studies were identified by this review; however, 2 studies reporting on QoL were included. These studies reported on the Quality of Life Questionnaire-Core 30 (QLQ-C30) and Quality of Life Questionnaire-Core Head and Neck Cancer 35 (QLQ-H&N35) in a cross-sectional manner.

Bone Sarcoma

No data were captured for the humanistic or economic burden of this disease.

Appendix cancer

No QoL studies were identified.

Secretory breast cancer

No QoL studies were identified.

Congenital Mesoblastic Nephroma

No studies reporting on the humanistic or economic burden of CMN were identified.

I.2.3 Quality assessment and generalizability of estimates

N/A

I.2.4 Unpublished data

N/A

I.3 Health-related quality-of-life search update in 2020

The HRQoL SLR search aimed to address the following research question:

- What is the health-related quality of life and health state utility data for patients with NTRK fusion-positive solid tumours?

As detailed in Table 86, the SLR search was conducted during August 2020. The searches were performed in the following indexed databases:

- Embase and Medline (via Embase.com)
- MEDLINE ® (via PubMed)
- Cochrane databases (via CochraneLibrary.com)

All databases were either unlimited searched or from 1947 to 2018 to retrieve comprehensive evidence. Search strategies for Embase® and MEDLINE® were implemented using Embase.com, MEDLINE® In-Process using the PubMed platform, and the Cochrane library using CochraneLibrary. The search was not restricted by countries or English language. However, the search was restricted to not including no editorials/letters, as these er typically narrative texts, therefore the study designs of interest was interventional studies, prospective cohort studies, cross-sectional surveys and registries. Animal studies were also excluded from the SLR as the population of interest is humans (paediatrics and adults) with NTRK fusion-positive solid tumours.

Conference abstracts, other bibliographic sources and HTA submissions were screened according to the methods detailed in Appendix H.

Table 86 Bibliographic databases included in the HRQoL literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase and Medline	Embase.com	1947-2018	06 August 2020
Medline	PubMed	Unlimited	06 August 2020
Cochrane	CochraneLibrary.com	Unlimited	07 August 2020

Abbreviations: Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online

I.3.1 Search strategies

All HRQoL SLR search algorithms were generated using PICOS-related elements outlined in, Table 87. These were generated from det research question pertinent to each section.

Table 87 PICOS used for assessment of HRQoL studies

PICOS	Inclusion criteria	Exclusion criteria
Population	Individuals (paediatrics and adults) with NTRK fusion-positive solid tumours	Tumours other than solid tumours (e.g., haematological)
Intervention/Comparators	None	None
Outcomes*	HRQoL and health state utilities	

Study design/publication type	• Studies reporting utility data • Economic evaluations reporting patients' utility values	• Letters, comments, and editorials
Language restrictions	No limits	None

*All studies meeting the inclusion criteria and reporting ≥1 outcome of interest was included in the review.

Table 88 to Table 90 present the search hits in Embase, PubMed and Cochrane databases.

Table 88 HRQoL search strategy for Embase and MEDLINE (via Embase.com)

No.	Query	Results
#1	'neurotrophic tyrosine kinase*':ab,ti OR ntrk*:ab,ti OR ((trk* NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)):ab,ti) OR ((tyrosine OR tropomyosin) NEAR/2 kinase NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*))	4,673
#2	'quality of life'/exp OR 'quality of life':ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'short form36':ab,ti OR shortform36:ab,ti OR sf6:ab,ti OR 'sf 6':ab,ti OR 'short form 6':ab,ti OR sf6d:ab,ti OR 'sf 6d':ab,ti OR 'short form 6d':ab,ti OR sf8:ab,ti OR 'sf 8':ab,ti OR 'short form 8':ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR sf16:ab,ti OR 'sf 16':ab,ti OR sf20:ab,ti OR 'sf 20':ab,ti OR 'short form 20':ab,ti OR hql:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR 'hr qol':ab,ti OR hye:ab,ti OR hyes:ab,ti OR ((health* NEAR/2 year* NEAR/2 equivalent*):ab,ti) OR pqol:ab,ti OR qls:ab,ti OR 'quality of well being':ab,ti OR 'index of wellbeing':ab,ti OR qwb:ab,ti OR 'sickness impact profile':ab,ti OR 'health status indicator'/exp OR 'health utilit*':ab,ti OR 'health status':ab,ti OR disutilit*:ab,ti OR 'activities of daily living':ab,ti OR adl:ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR euroqual:ab,ti OR 'euro qual':ab,ti OR 'duke health profile':ab,ti OR 'functional status':ab,ti OR disabilit*:ab,ti OR (utilit*:ab,ti AND (valu*:ab,ti OR measur*:ab,ti OR health:ab,ti OR life:ab,ti OR estimat*:ab,ti OR elicit*:ab,ti OR disease:ab,ti OR score*:ab,ti OR weight:ab,ti)) OR ((preference* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR instrument OR instruments)):ab,ti)	1,134,753
#3	#1 AND #2	124
#4	#3 NOT (letter:it OR editorial:it)	124
#5	#4 NOT ('animals'/exp NOT 'humans'/exp)	118
#6	[conference abstract]/lim AND [1947-2018]/py	3,371,237
#7	#5 NOT #6	83

Table 89 HRQoL search strategy for Medline via PubMed

No.	Query	Results
#1	"neurotrophic tyrosine kinase*"[tiab] OR ntrk*[tiab] OR (trk[tiab] AND (mutat*[tiab] OR fusion*[tiab] OR translocation*[tiab] OR recombina*[tiab] OR rearrang*[tiab])) OR (tropomyosin[tiab] AND kinase[tiab] AND (mutat*[tiab] OR fusion*[tiab] OR translocation*[tiab] OR recombina*[tiab] OR rearrang*[tiab])) OR tyrosine kinase mutat*[tiab] OR tyrosine receptor kinase mutat*[tiab] OR tyrosine kinase fusion*[tiab] OR tyrosine receptor kinase fusion*[tiab] OR tyrosine kinase translocation*[tiab] OR tyrosine receptor kinase translocation*[tiab] OR tyrosine kinase recombina*[tiab] OR tyrosine receptor kinase recombina*[tiab] OR tyrosine kinase rearrang*[tiab] OR tyrosine receptor kinase rearrang*[tiab]	2,314
#2	"Quality of Life"[Mesh] OR "quality of life"[tiab] OR sf36[tiab] OR "sf 36"[tiab] OR "short form 36"[tiab] OR "shortform 36"[tiab] OR "short form36"[tiab] OR shortform36[tiab] OR sf6[tiab] OR "sf 6"[tiab] OR "short form 6"[tiab] OR sf6d[tiab] OR "sf 6d"[tiab] OR "short form 6d"[tiab] OR sf8[tiab] OR "sf 8"[tiab] OR "short form 8"[tiab] OR sf12[tiab] OR "sf 12"[tiab] OR "short form 12"[tiab] OR sf16[tiab] OR "sf 16"[tiab] OR sf20[tiab] OR "sf 20"[tiab] OR "short form 20"[tiab] OR hql[tiab] OR hqol[tiab] OR hrqol[tiab] OR "hr qol"[tiab] OR hye[tiab] OR hyes[tiab] OR pqol[tiab] OR qls[tiab] OR "quality of well being"[tiab] OR "index of well-being"[tiab] OR qwb[tiab] OR "sickness impact profile"[tiab] OR "Health Status Indicators"[Mesh] OR "health utilit*"[tiab] OR "health status"[tiab] OR disutilit*[tiab] OR "activities of daily living"[tiab] OR adl[tiab] OR hui[tiab] OR hui1[tiab] OR hui2[tiab] OR hui3[tiab] OR euroqol[tiab] OR "euro qol"[tiab] OR eq5d[tiab] OR "eq 5d"[tiab] OR euroqual[tiab] OR "euro qual"[tiab] OR "duke health profile"[tiab] OR "functional status"[tiab] OR disabilit*[tiab] OR (utilit*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR weight[tiab])) OR (health*[tiab] AND year*[tiab] AND equivalent*[tiab]) OR (preference*[tiab] AND (valu*[tiab] OR measur*[tiab] OR health[tiab] OR life[tiab] OR estimat*[tiab] OR elicit*[tiab] OR disease[tiab] OR score*[tiab] OR instrument[tiab] OR instruments[tiab]))	1,026,790
#3	#1 AND #2	53
#4	#3 NOT (letter[pt] OR editorial[pt])	53
#5	#4 NOT ("animals"[Mesh] NOT "humans"[Mesh])	49

Table 90 HRQoL search strategy for Cochrane via CochraneLibrary.com

No.	Query	Results
#1	("neurotrophic tyrosine":ab,ti NEXT kinase*:ab,ti) OR ntrk*:ab,ti OR ((trk* NEAR/3 (mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)):ab,ti) OR ((tyrosine OR tropomyosin) NEAR/2 kinase NEAR/3	286

No.	Query	Results
	(mutat* OR fusion* OR translocation* OR recombina* OR rearrang*)) OR *TRK*	
#2	[mh "Quality of Life"] OR 'quality of life':ab,ti OR sf36:ab,ti OR 'sf 36':ab,ti OR 'short form 36':ab,ti OR 'shortform 36':ab,ti OR 'short form36':ab,ti OR shortform36:ab,ti OR sf6:ab,ti OR 'sf 6':ab,ti OR 'short form 6':ab,ti OR sf6d:ab,ti OR 'sf 6d':ab,ti OR 'short form 6d':ab,ti OR sf8:ab,ti OR 'sf 8':ab,ti OR 'short form 8':ab,ti OR sf12:ab,ti OR 'sf 12':ab,ti OR 'short form 12':ab,ti OR sf16:ab,ti OR 'sf 16':ab,ti OR sf20:ab,ti OR 'sf 20':ab,ti OR 'short form 20':ab,ti OR hql:ab,ti OR hqol:ab,ti OR hrqol:ab,ti OR 'hr qol':ab,ti OR hye:ab,ti OR hyes:ab,ti OR ((health* NEAR/2 year* NEAR/2 equivalent*):ab,ti) OR pqol:ab,ti OR qls:ab,ti OR 'quality of well being':ab,ti OR 'index of wellbeing':ab,ti OR qwb:ab,ti OR 'sickness impact profile':ab,ti OR [mh "Health Status Indicators"] OR 'health utilit*':ab,ti OR 'health status':ab,ti OR disutilit*:ab,ti OR 'activities of daily living':ab,ti OR adl:ab,ti OR hui:ab,ti OR hui1:ab,ti OR hui2:ab,ti OR hui3:ab,ti OR euroqol:ab,ti OR 'euro qol':ab,ti OR eq5d:ab,ti OR 'eq 5d':ab,ti OR euroqual:ab,ti OR 'euro qual':ab,ti OR 'duke health profile':ab,ti OR 'functional status':ab,ti OR disabilit*:ab,ti OR (utilit*:ab,ti AND (valu*:ab,ti OR measur*:ab,ti OR health:ab,ti OR life:ab,ti OR estimat*:ab,ti OR elicit*:ab,ti OR disease:ab,ti OR score*:ab,ti OR weight:ab,ti)) OR ((preference* NEAR/3 (valu* OR measur* OR health OR life OR estimat* OR elicit* OR disease OR score* OR instrument OR instruments)):ab,ti)	198,174
#3	#1 AND #2	33 trials, 10 SLRs, 2 SLR protocols

The PRISMA flow diagram of the HRQoL SLR is presented in Figure 38 below. Among the 130 publications initially identified and screened from multiple databases, 121 were excluded, leaving 9 publications for further evaluation of eligibility. Upon assessment, further 7 publications were excluded for the reasons detailed in Table 87. Consequently, 2 publications were included in the report, comprising:

- 2 abstracts

After a grey literature search from additional bibliography check another 5 publication were included (1 abstract and 4 HTA submissions), resulting in in a total of 7 included in the final SLR.

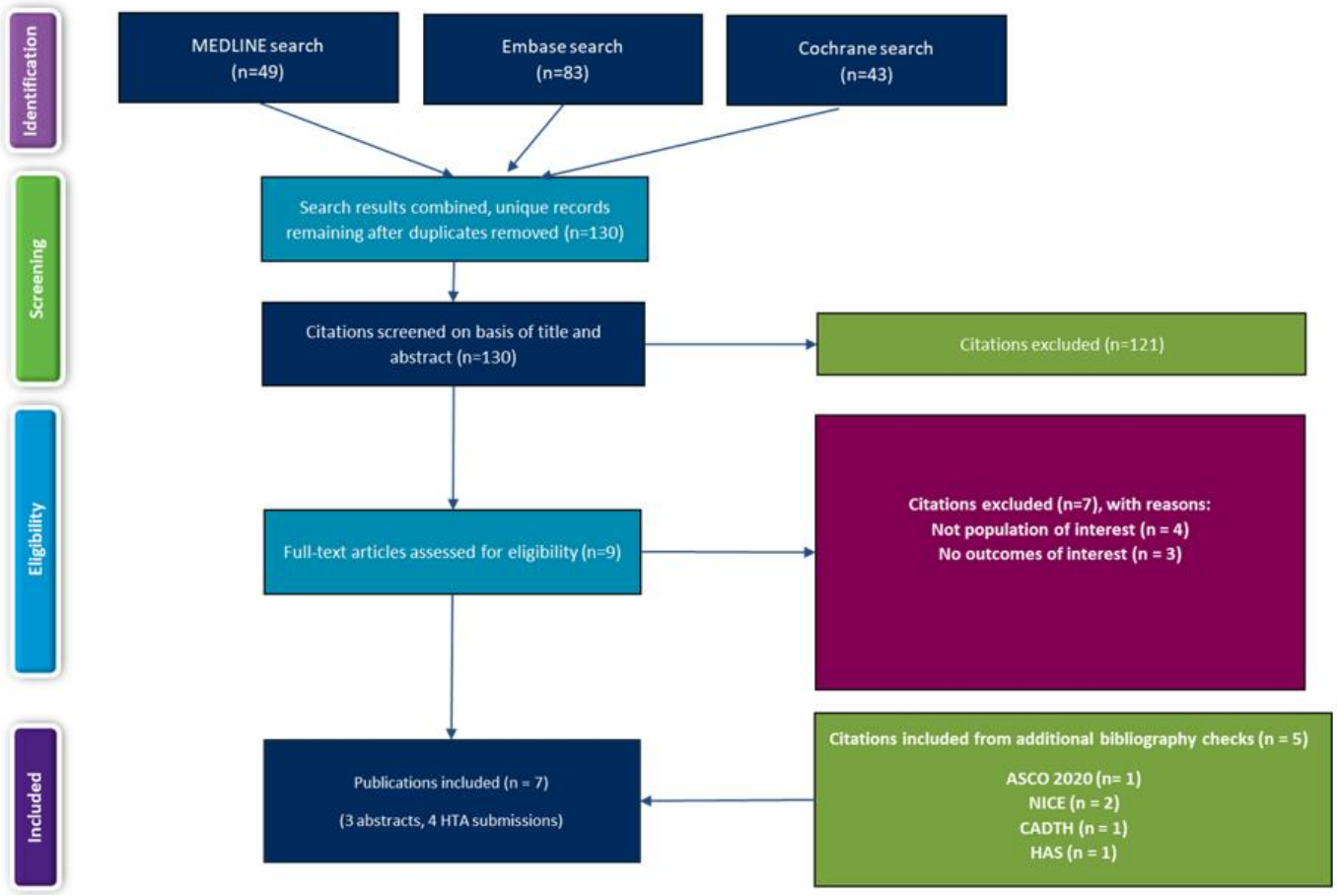


Figure 38 PRISMA flow chart for the SLR on HRQoL

Table 91 Overview of publications excluded at full-text screening from the HRQoL SLR

No.	Publication	Exclusion reason
#1	Immunohistochemical expression of neurotrophic tyrosine kinase receptors 1 and 2 in lung carcinoma: potential discriminators between squamous and nonsquamous subtypes.	No outcomes of interest
#2	The Potential Long-Term Comparative Effectiveness of larotrectinib and Entrectinib for Second-Line Treatment of TRK Fusion-Positive Metastatic Lung Cancer	No outcomes of interest
#3	Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. Eur J Cancer	No outcomes of interest
#4	Variations in COMT and NTRK2 Influence Symptom Burden in Women Undergoing Breast Cancer Treatment	Not a population of interest
#5	Gastrointestinal stromal tumours (GIST) in young adult (18 40 years) patients: A report from the Dutch GIST registry	Not a population of interest
#6	Health-related quality of life in non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (EGFR) mutation with tyrosine kinase inhibitors treatment: A systematic review	Not a population of interest
#7	Cisplatin versus carboplatin in combination with third-generation drugs for advanced non-small cell lung cancer	Not a population of interest

I.3.2 Quality assessment and generalizability of estimates

Not applicable.

I.3.3 Unpublished data

No unpublished literature is used to inform the HRQoL section of the dossier.

I.3.4 Local adaptation

No adaption was done to the current application.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

External literature for input to the health economic model is outlined below:

- Previous conducted SLR, submitted to NICE
- Updated SLR, per 2019

J.2 Health economic SLR previously submitted to NICE

To generate relevant comparator clinical evidence for this appraisal, a series of SLRs was undertaken in tumour sites / locations known to harbour NTRK gene fusions, reflective of those of patients so far investigated within larotrectinib clinical studies. The SLR methodology is briefly described below.

For each tumour site, SLRs were performed by searching MEDLINE (via PubMed), Embase, and the Cochrane Library (including: Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], HTA database, National Health Service [NHS] Economic Evaluation Database [EED], and Cochrane Methodology Register) (from database inception to date of search execution) for potentially relevant articles. The exact search strings for each tumour type are available on request since the information amounts to over 160 pages. Additionally, grey literature sources (conference proceedings, registers of ongoing trials, and health technology assessment [HTA]-published reports) were also reviewed. Tumour-specific inclusion/exclusion criteria were applied by 2 independent reviewers (with resolution of any conflicts by an independent third reviewer) to screen the search results and ultimately identify the relevant studies.

The pertinent data were extracted from the included studies by a single researcher, with full review and validation of all extracted data by a second independent researcher (disagreements were arbitrated by an independent third reviewer). The extracted data were then synthesized and summarized for each tumour type. A quality assessment of the studies included was also conducted as an integral component of the SLR. Quality assessment was undertaken by 2 separate reviewers, and discrepancies in ratings were resolved by a third reviewer.

Databases searched for resource use evidence:

- MEDLINE (via PubMed)
- Embase, and the Cochrane Library (including: Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR], Database of

Abstracts of Reviews of Effects [DARE], HTA database, National Health Service [NHS] Economic Evaluation Database [EED], and Cochrane Methodology Register)

Databases were searched from database inception to date of search execution. The date of each search is documented alongside each search string (available on request); Initial searches were performed May – August 2018 and updated in January – March 2019.

The literature search methodology as described in this section was applied to all tumour sites, except when noted otherwise. Also listed are grey literature sources, which include conference proceedings, registers of on-going trials, and HTA-published reports. The limits for human studies and specific publication types were applied to the Embase searches. No other limits were applied to the searches. The search results were combined in an EndNote database, and duplicate records were removed.

Table 92 Bibliographic databases included in the search

Database	Platform	Relevant period for the search	Date of search completion
Medline	PubMed	N/A	January 2019 – March 2019
Cochrane	CochraneLibrary.com	N/A	January 2019 – March 2019

Abbreviations: Embase, Excerpta Medica Database; MEDLINE, Medical Literature Analysis and Retrieval System Online

Clinical trials databases were searched to identify treatments currently being investigated or treatments that were investigated and abandoned. The databases included:

- Clinicaltrials.gov
- ISRCTN
- ICTRP
- Clinicaltrialsregister.eu
- KlinischePrüfungen (PharmNet.Bund, AMIS - Öffentlicher Teil)

Conference abstracts from the below 3 conferences were searched for all tumour sites:

- ASCO Annual Meeting
- European Society for Medical Oncology (ESMO) Annual Meeting
- ISPOR International and European Annual Meetings

Table 93 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
Clinicaltrials.gov	https://clinicaltrials.gov/	N/A	January 2019 – March 2019
ISRCTN	https://www.isrctn.com/	N/A	January 2019 – March 2019

Source name	Location/source	Search strategy	Date of search
ICTRP	https://trialsearch.who.int/Default.aspx	N/A	January 2019 – March 2019
Clinicaltrialsregister.eu	https://www.clinicaltrialsregister.eu/	N/A	January 2019 – March 2019
KlinischePrüfungen	https://www.bfarm.de/DE/Arzneimittel/Klinische-Pruefung/_node.html	N/A	January 2019 – March 2019

Table 94 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	https://www.asco.org/	N/A	N/A	January 2019 – March 2019
ESMO	https://www.esmo.org/	N/A	N/A	January 2019 – March 2019
ISPOR	https://www.ispor.org/	N/A	N/A	January 2019 – March 2019

HTA websites were searched to identify and collect information relating to applications and decisions of the relevant HTA for comparators of interest:

- AHRQ
- AWMSG
- EMA
- Federal Joint Committee (G-BA)
- HAS
- IQWIG
- National Institute for Health and Care Excellence (NICE)
- CADTH
- SMC
- NCPE

J.2.1 Search strategies

Studies were included if they met the PICOS criteria presented in Table 95 and specific population criteria for relevant tumours in Table 96.

Table 95 Eligibility criteria used in the cost and resource use SLR strategy

PICOS	Inclusion criteria	Exclusion criteria

Population	See Table 96 in NICE submission TA630 (39)	• Healthy volunteers • Patients with disease other than tumour in focus • Disease stage other than advanced/metastatic (i.e., early-stage) None for STS (Infantile Fibrosarcoma, Infantile Myofibromatosis, myopericytoma, Spindle Cell Sarcoma, Inflammatory Myofibroblastic Tumour, Peripheral Nerve Sheath Tumour), secretory breast cancer
Intervention/ Comparators	• Any/all/ no interventions or comparators For salivary gland cancer: Update 26 June 2018: any pharmacological interventions and comparators will be eligible for inclusion (surgery and radiotherapy will not be included) For appendix cancer: Update 01 February 2019: Interventions and comparators will not include surgical interventions (except those that are conducted in conjunction with pharmacology therapy, e.g., CRS-HIPEC)	Interventions/ comparators other than those listed in Table 96
Outcomes	• Direct costs (e.g., drug costs/ pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/income for patient and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care, inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	All outcomes other than those specified in the inclusion columns
Study design/ publication type	Cost and resource use studies (NSCLC): • Cost studies • Resource use studies • Economic evaluations reporting costs or resource use All other tumours:	• Non-systematic reviews • Case reports • Case series • Animal studies • Letters • Editorials

	• SLRs and meta-analyses will be included for hand searching of reference lists • RCTs • Non-randomized interventional studies • Observational studies (retrospective, prospective, cross-sectional, registries)	
Country (only NSCLC)	Studies conducted in the US, Canada, EU5 (United Kingdom, France, Germany, Italy, Spain), Japan, and Brazil healthcare setting will be extracted	Countries other than those specified in the inclusion columns
Time limits (only NSCLC)	• Studies published 2008 onwards • Conference abstracts 2017 onwards	• Studies published prior to 2008 will be excluded • Conference abstracts prior to 2017 will be excluded

Table 96 Population criteria for HRQoL SLR for relevant tumours

Tumour	Population included in the SLR
NSCLC	Patients with advanced / metastatic NSCLC (adults and paediatrics) being treated with ≥2nd-line therapy
CRC	Patients with locally advanced or metastatic CRC being treated with ≥2nd line therapy
Melanoma	Patients with locally advanced or metastatic malignant melanoma being treated with ≥2nd line therapy
Pancreatic cancer	Patients with locally advanced or metastatic pancreatic cancer being treated with ≥2nd line therapy
Thyroid cancer	Patients with locally advanced or metastatic anaplastic, follicular, or papillary thyroid cancers
Glioma	Patients with locally advanced or metastatic gliomas being treated with ≥2nd-line therapy
Biliary cancer	Patients with locally advanced or metastatic biliary cancer Updated 16 July, 2018: • Biliary cancer does not include biliary strictures (malignant or benign) or periampullary cancer (of pancreatic origin)
GIST	Patients with locally advanced or metastatic GIST
Infantile Fibrosarcoma, Infantile Myofibromatosis, Myopericytoma	Infantile fibrosarcoma (Update 18 June 2018: n≥10) Infantile myofibromatosis (Update 18 June 2018: n≥10) Myopericytoma (Update 18 June 2018: n≥10)
STS: spindle cell sarcoma, inflammatory myofibroblastic tumour, and peripheral nerve sheath tumour	Infantile myofibromatosis (Update 18 June 2018: n≥10) Inflammatory myofibroblastic tumour (Update 18 June 2018: n≥10) Peripheral nerve sheath tumour (Update 18 June 2018: n≥10)
Salivary gland cancers	Patients with salivary gland cancers
Bone sarcoma	Patients with locally advanced or metastatic chondrosarcoma (conventional, clear cell, dedifferentiated, or mesenchymal) (n≥5)
Appendix Cancer	Locally advanced or metastatic appendix cancer (n≥5)

	Updated 01 February 2019: Subtypes not included: Pseudomyxoma peritonei (PMP), neuroendocrine tumours (carcinoids) of the ap-appendix
Secretory breast carcinoma	Secretory breast carcinoma
CMN	Locally advanced or metastatic congenital mesoblastic nephroma (n≥5)

Title/abstract screening of the citations resulting from the searches, using the inclusion and exclusion criteria detailed in the tables presented above, was conducted by two independent reviewers with resolution of any conflicts by an independent third reviewer. Any other items that required an additional reviewer were flagged and discussed by the project team. A preliminary list of included studies was generated following title/abstract review, and based on this list, full-text articles were obtained. Two independent reviewers conducted the full-text review and narrowed the results to the final list of included studies. The reference lists of any identified SLRs and meta-analyses were checked against the final list of studies.

Flow diagrams of the number of records included and excluded at each stage for each of the tumours studied have been summarised into a table, to minimise the number of pages. PRISMA flow diagrams are available on request. List of studies excluded at full-text review by exclusion reason is available on request.

After approval of the study citation lists for the SLRs, the data extraction step began. The list of data extraction elements was aligned with input from Bayer's economic model partner. A data extraction table shell was provided prior to commencing the data extraction phase of the review. Data extraction was conducted by a single reviewer, with full data validation conducted by a second reviewer, and conflicts resolved by a third, senior reviewer.

Screening step ►		Citations identified via:				**Unique citations after removal of duplicates. Title / abstract screened.**	Publications excluded during title / abstract screening	**Full text publications reviewed**	Records excluded during full text review	*Publications retrieved from manual search of SLRs & meta-analyses / conferences & registries*	**Publications included in evidence synthesis**
▼Tumour		Medline (Pubmed)	Embase	Cochrane Library	Other sources [a]						
NSCLC		1648	2566	1541		**4639**	4253	**386**	312	*23*	**97**
CRC		1066	1869	563		**2265**	2095	**170**	121	*0*	**49**
Melanoma		412	928	134		**1009**	929	**80**	53	*0*	**27**
Pancreatic cancer		251	571	123		**660**	571	**89**	71	*0*	**18**
Thyroid cancer			2957		0	**2061**	1974	**87**	63	*0*	**24**
Glioma		137	169	1		**249**	225	**24**	21	*0*	**3**
Biliary cancer		126	98	50		**195**	184	**29**	21	*0*	**8**
GIST		62	102	22		**127**	95	**32**	28	*0*	**4**
Infantile Fibrosarcoma (IFS), Infantile Myofibromatosis (IM), Myopericytoma (MP)	**IFS**	**See clinical evidence PRISMA table**									
	IM										
	MP										
Soft tissue sarcoma: spindle cell sarcoma (SC), inflammatory myofibroblastic tumour (IMT), and peripheral nerve sheath tumour (PNST)	**SC**	**See clinical evidence PRISMA table**									
	IMT										
	PNST										
Salivary gland cancers			1763		0	**1382**	1337	**45**	43	*0*	**2**
Bone sarcoma		**See clinical evidence PRISMA table**									
Appendix Cancer		**See clinical evidence PRISMA table**									
Secretory breast carcinoma (SBC)		**See clinical evidence PRISMA table**									
Congenital mesoblastic nephroma (CMN)		**See clinical evidence PRISMA table**									

[a] e.g. clinical trials, Health Technology Appraisal reports

Figure 39 Summary of PRISMA flow diagrams of the included studies for tumours included in the economic costs and resource use SLR

J.2.2 Summary of cost and resource use publications

NSCLC

Ninety-seven publications reported HCRU or cost data for advanced NSCLC. Most of the studies evaluating HCRU assessed patients in the US or the UK, while some publications compared healthcare visits and length of stay in hospital across several countries. Direct costs varied considerably, depending on specific interventions and geographic setting. No studies reporting indirect cost data were identified.

Colorectal cancer

A total of 49 studies evaluated HCRU and costs in patients with advanced CRC across diverse geographies. The rate of hospitalizations among patients was variable, ranging from 22% to 100%, and the mean length of stay varied from 5.0 to 17.0 days. Greater HCRU was reported for patients with longer survival. Total direct costs were substantial, ranging up to $61,360 [USD] (total healthcare costs during second-line therapy). Notable drivers of total healthcare or medical costs were hospitalizations and outpatient-based care.

Melanoma

Costs and HCRU were reported in 30 publications, including 16 publications on resource use and 20 publications on direct costs. No data on indirect costs were reported. Commonly reported measures of HCRU included hospitalizations, outpatient visits, and emergency department visits. Nearly all studies did not report on HCRU associated with specific interventions. Resource use tended to increase with increasing line of therapy. Costs varied significantly across geographies.

Pancreatic cancer

Eighteen studies reported on costs and HCRU, of which 14 reported on resource use, 8 on direct costs, and none on indirect costs. Resource use varied widely across studies, suggesting that the specifics of the study design and population may contribute to determining specifics of hospitalizations. In the US and Japan, costs varied by disease stage and drug type, respectively.

Thyroid cancer

HCRU and costs were evaluated in 24 publications in patients with advanced thyroid cancers. Reporting on utilization in the US, Europe, and Asia, outcomes focused on hospitalizations, costs, resource use associated with surgical interventions, and drug costs.

Glioma

Three HCRU studies were included; no studies reporting on direct or indirect costs were included. Much of the data on HCRU were obtained from studies comparing outcomes for different stages of glioma, varying treatment interventions, and different lines of therapy. While patients receiving treatment for advanced glioma required varying lengths of hospitalization that led to variable costs, 1 study reported that, among patients receiving

treatment for advanced glioma, approximately 20% and 12% required hospital readmission or reoperation, respectively.

Biliary cancer

Eight cost and HCRU studies were included, of which 7 studies reported on HCRU, 6 on direct costs, and 0 on indirect costs. Much of the data on HCRU and costs were obtained from studies comparing outcomes for different stents and stenting procedures or surgery for unresectable disease. Patients receiving stents for treatment of the symptoms of cholangiocarcinoma have lengthy hospital stays and incur high costs.

STS: Infantile Fibrosarcoma, Infantile Myofibromatosis, and Myopericytoma

No cost and HCRU studies were identified reporting on patients with STSs.

STS: Spindle Cell, Inflammatory Myofibroblastic Tumour, Peripheral Nerve Sheath Tumour

No cost and HCRU studies were identified reporting on patients with STSs.

Gastrointestinal Stromal Tumours

The economic burden in advanced GIST was evaluated in 4 studies, with higher direct costs attributed to treatment with sunitinib and imatinib compared with BSC.

Salivary gland cancer

One study reported HCRU and direct cost data. Patients in France undergoing chemotherapy and radiotherapy had a high number of hospital stays with higher costs in the public sector compared with the private sector.

Bone Sarcoma

No data were captured for the humanistic or economic burden of this disease.

Appendix cancer

No cost or resource studies were identified.

Secretory breast cancer

No cost or resource studies were identified.

Congenital Mesoblastic Nephroma

No studies reporting on the humanistic or economic burden of CMN were identified.

J.3 SLR updated (economic) in 2019

No economic evaluations or cost-effectiveness publications considering a NTRK Fusion population were identified.

The series of cost effectiveness SLRs conducted by tumour site, identified publications which provided comparator specific inputs and assumptions. Cost-effectiveness results were not suitable for informing decision making, however inputs and assumptions for relevant comparators were utilised in the model development.

The review of previous oncology NICE TAs did not identify any existing approaches or available economic models that considered multiple tumour sites in a single-arm trial.

The findings from the reviews were used to help inform model design and are discussed in the sections below.

A series of SLRs was conducted to address NTRK fusion-positive solid tumours as a whole and for a variety of specific solid tumours known to harbour NTRK gene fusions, as listed in Table 97. Studies on treatments (approved and in development) for each tumour localization were identified and the available economic evidence was synthesized. The evidence generated from the SLRs will support the launch of larotrectinib, including pricing and reimbursement submissions and will populate parameters for an economic model.

Table 97 Tumour types

Cohort	Tumour type
NSCLC	NSCLC
Colorectal cancer	Colorectal cancer
Melanoma	Melanoma
Pancreatic cancer	Pancreatic cancer
Thyroid cancer	Anaplastic thyroid cancer Follicular thyroid cancer Papillary thyroid cancer
Sarcoma	IFS Infantile myofibromatosis Myopericytoma Spindle cell sarcoma Inflammatory myofibroblastic tumour Peripheral nerve sheath tumour GIST
Biliary cancer	Cholangiocarcinoma
Salivary gland cancer	MASC of the salivary glands
Secretory breast cancer	Secretory breast cancer

Abbreviations: IFS, infantile fibrosarcoma; GIST, gastrointestinal stromal tumour; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer.

The literature search for inputs to the health economic model is specified for every tumour type in Section J.3.6-J.3.17

J.3.1 Objective

The objective of this research was to conduct the SLR for all pivotal studies for each tumour localization, synthesizing the available economic evidence on approved agents.

The following key research question were identified to guide the search process for the literature reviews:

> What is the economic burden (direct and indirect costs) of the solid tumours of interest?

- What is the resource use and cost data associated with treatment of these tumours?
- What cost-effectiveness analyses and health technology assessments have been published for the interventions used to treat solid tumours of interest based on their clinical trials1?

J.3.2 Methods

MEDLINE, Embase and the Cochrane Library (including: Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews [CDSR], Database of Abstracts of Reviews of Effects [DARE], HTA database, National Health Service [NHS] Economic Evaluation Database [EED], and Cochrane Methodology Register) were searched from database inception to date of search execution, specified in Table 98.

The literature search methodology was applied to all tumour types, except when noted otherwise; tumour-specific search criteria can be found in their respective subsections. The search results were combined in an EndNote database, and duplicate records were removed. The exact search strings for each tumour type can be found in the tumour-specific subsections.

Table 98 Sources included in the health economic search for tumour specific SLRs

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	2008 - 2018	18.05.2018 – 28.08.2018
Medline	via PubMed	2008 - 2018	18.05.2018 – 28.08.2018
Cochrane Library	N/A	2008 - 2018	18.05.2018 – 28.08.2018

Abbreviations: Embase, Excerpta Medica Database; N/A, not available / not applicable

In addition, conference abstracts from 3 conferences in Table 99 were searched for all tumour types. The search strings found in their respective subsections were utilized to identify all conference-related publications indexed in Embase. Except for pancreatic cancer, colorectal cancer, and melanoma, additional conferences were evaluated for each of the tumour types as detailed in an earlier document.

Table 99 Conference material included in the health economic search tumour specific SLRs

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO	Embase (Ovid)	Electronic search	Not applicable	18.05.2018 – 28.08.2018
ESMO	Embase (Ovid)	Electronic search	Not applicable	18.05.2018 – 28.08.2018
ISPOR	Embase (Ovid)	Electronic search	Not applicable	18.05.2018 – 28.08.2018

Abbreviations: Embase, Excerpta Medica Database; ASCO, American Society of Clinical Oncology; ESMO, European Society for Medical Oncology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research

Another SLR was undertaken to identify any cost-effectiveness models or research around treatment of NTRK fusion-positive solid tumours, see page 208. Searches were conducted in the databases stated in Table 100.

Table 100 Sources included in the health economic search for NTRK fusion-positive solid tumours SLRs

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Proquest Dialog interface	1947 - 2019	05.05.2019
Medline	Proquest Dialog interface	1946 - 2019	05.05.2019
EconLit	Proquest Dialog interface	1886 - 2019	05.05.2019
Northern Lights Life Sciences Conference Abstracts	Proquest Dialog interface	2010 - 2019	05.05.2019
Cochrane Library	Proquest Dialog interface	N/A	05.05.2019

Abbreviations: Embase, Excerpta Medica Database; N/A, not available / not applicable

J.3.3 Study selection criteria

Inclusion and exclusion criteria that were applied during title/abstract and full-text screening are provided in tumour-specific subsections. Title/abstract screening was conducted by 2 independent reviewers with resolution of any conflicts by an independent third reviewer. Any other items that required an additional reviewer were flagged and discussed by the project team. A preliminary list of included studies was generated following title/abstract review, and based on this list, full-text articles were obtained. Two independent reviewers conducted the full-text review and narrowed the results to the final list of included studies. The reference lists of any identified SLRs and meta-analyses were checked against the final list of studies.

After the study citation lists for the SLRs were approved, the data extraction step began. The list of data extraction elements was aligned with input from Bayer's economic model partner. A data extraction table shell was provided prior to commencing the data extraction phase of the review.

Data extraction was conducted by a single reviewer, with full data validation conducted by a second reviewer, and conflicts resolved by a third, senior reviewer.

J.3.4 Quality assessment

Economic modelling studies identified in the global SLRs were assessed using the British Medical Journal (BMJ) Study Checklist or the Drummond's checklist.

J.3.5 Local adaptation

A local adaptation of the global SLR was not conducted, as the HCRU and economic data from the SLR were considered comprehensive for the model in a Danish setting. The global SLR data were used solely to calculate ORR, presented as a weighted average. HCRU inputs were primarily based on data from NICE TAs, which informed key assumptions. For tumour sites without a specific NICE TA, data collection for HCRU inputs relied on the SLR

output where possible; in cases where no evidence was found in the SLR, broader targeted searches for published articles were conducted to supplement the findings.

J.3.6 NTRK cost effectiveness models

The list of publications was screened by two independent reviewers. Any disagreements were to be resolved by a third reviewer. All citations identified in the search (n=108) were independently screened against the PICOS inclusion/exclusion criteria, based on their titles only. Excluded citations were disregarded (n=106). Abstracts of retained citations (n=2) were reviewed. Neither abstract was identified as relevant to the search on cost-effectiveness models / studies in NTRK fusion-positive cancer and were excluded.

A flow diagram of the number of records included and excluded at each stage is provided in Figure 40.

No cost-effectiveness models or studies were identified in the literature on the treatment of NTRK fusion-positive cancer.

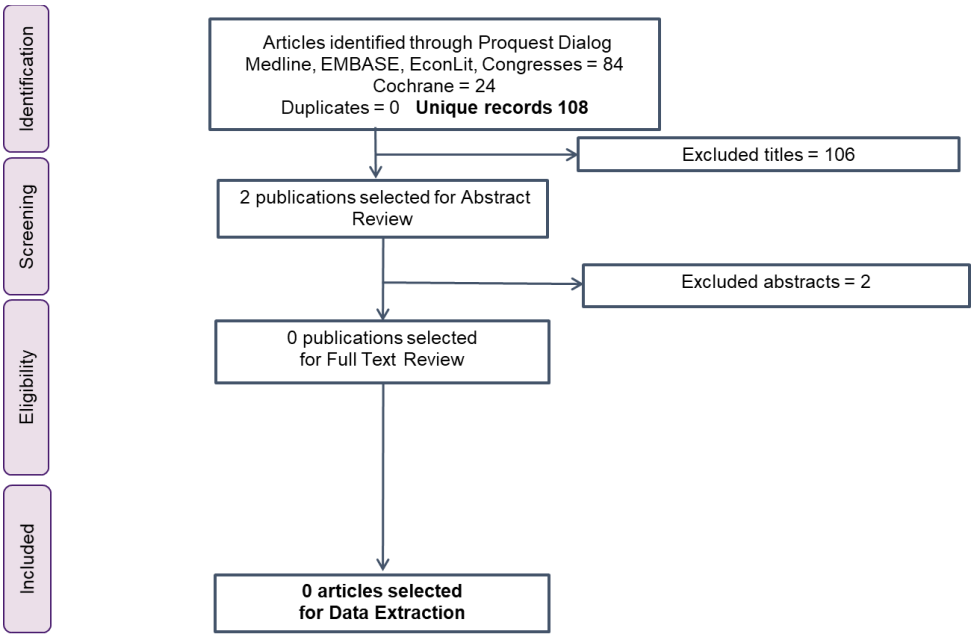


Figure 40 PRISMA flow diagram of the included health economic studies in NTRK fusion-positive treatment

J.3.6.1 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and HCRU in the NTRK fusion-positive cancer reviews are detailed using the PICOS framework in Table 140.

Table 101 Inclusion and exclusion criteria for economic evaluations/resource use reviews in NTRK fusion-positive tumours

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with NTRK fusion-positive solid tumours	None-human

Interventions/ Comparators	Any treatment or treatment combination specifically targeting NTRK fusion-positive solid tumours	None
Outcomes	No restrictions	
Study design (s)	Cost-effectiveness and cost-utility studies Budget impact analyses Costing studies reporting cost or resource use by treatment	Studies solely focussing on screening for NTRK-positive tumours rather than treatment.

Abbreviations: NTRK, neurotrophic tyrosine receptor kinase.

J.3.6.2 Search strategy

The full search strategies are presented in Table 102 and Table 103. The search strategies were kept intentionally broad owing to the multiple ways 'NTRK gene fusion' can be referred to in the literature. There were also no language or geographic restrictions.

Table 102 Medline, Embase, EconLit and Congress abstracts search strategy for HRQoL/PROs/utilities and economic evaluations/resource use in NTRK fusion-positive tumours

#	Query	Results from 5 May 2019
1	AB,TI(decision NEAR/1 (tree* or analy* or model*))	55172*
2	AB,TI(qaly or qalys or qale or qales)	28752*
3	AB,TI("sensitivity analys?s" or "willingness to pay" or "quality-adjusted life year*" or "quality adjusted life" or "quality of life")	748630*
4	("markov chain*" or "monte carlo")	136243*
5	AB,TI(cost*effective*)	5283*
6	AB,TI("cost effective*")	313089*
7	AB,TI(economic NEAR/2 evaluation)	30171*
8	AB,TI("cost benefit analysis")	10625*
9	AB,TI("cost* utilit* analys*")	7439*
10	AB,TI("cost* benefit analys*")	12279*
11	AB,TI(eq5d or "eq 5d" or euroqol)	28087*
12	AB,TI(hui or hui2 or "hui 2" or hui3 or "hui 3")	5470*
13	TI(cost or costs or costly or costing*)	301989*
14	AB,TI(economic$ or price$ or pricing or pharmacoeconomic$)	925085*
15	EMB.EXACT.EXPLODE("cost benefit analysis") OR SU.EXACT("Allocative Efficiency; Cost-Benefit Analysis (D61)") OR MESH.EXACT.EXPLODE("Cost-Benefit Analysis")	166022*
16	MESH.EXACT.EXPLODE("Economics, Medical") OR EMB.EXACT.EXPLODE("health economics")	848848*
17	"decision analytic model*"	5128*

18	"decision model*"	6836*
19	"simulation model*"	37348*
20	"markov model*"	25871*
21	"state transition model*"	868°
22	"markov cohort model*"	363°
23	("discrete event simulation" or "DES model")	1305°
24	#23 OR #22 OR #21 OR #20 OR #19 OR #18 OR #17 OR #16 OR #15 OR #14 OR #13 OR #12 OR #11 OR #10 OR #9 OR #8 OR #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1	2863377*
25	*trk*	32479*
26	#25 AND #24	294°
27	cancer* or *sarcoma* or *carcinoma* or malign* or melanoma* or nephroma* or *cytoma* or *glioma* or *blastoma* or tumour* or tumour* or Neoplas* or lymphoma* or ependymoma* or histiocytosis or granuloma* or myeloma* or glioblastoma*	11576224*
28	#27 AND #26	84°

Table 103 Cochrane Library search strategy for HRQoL/PROs/utilities and economic evaluations/resource use in NTRK fusion-positive tumours

#	Query	Results from 5 May 2019
1	cost benefit analys*	14524
2	eq5d or eq 5d or euroqol	7821
3	hui or hui2 or hui 2 or hui3 or hui 3	1720
4	cost or costs or costly or costing*	66509
5	economic* or price* or pricing or pharmacoeconomic*	34158
6	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	6420
7	MeSH descriptor: [Economics, Medical] explode all trees	61
8	decision analytic model*	975
9	decision model*	8743
10	simulation model*	4129
11	markov model*	1266
12	state transition model*	485
13	markov cohort model*	283
14	(discrete event simulation or DES model)	592
15	MeSH descriptor: [Models, Economic] explode all trees	317
16	(OR #1-#15)	93519
17	*trk*	201
18	#17 AND #16	24

J.3.6.3 Quality assessment

N/A

J.3.7 Non-small cell lung cancer

J.3.7.1 Healthcare resource use and costs

Fifty-eight studies described in 66 publications reported HCRU or cost data for advanced NSCLC. Most of the studies evaluating HCRU assessed patients in the US or the UK, while some publications compared healthcare visits and length of stay in hospital across several countries. Direct costs varied considerably, depending on specific interventions and geographic setting. No studies reporting indirect cost data were identified. The PRISMA flow diagram for economic costs and healthcare resource in NSCLC is presented in Figure 41.

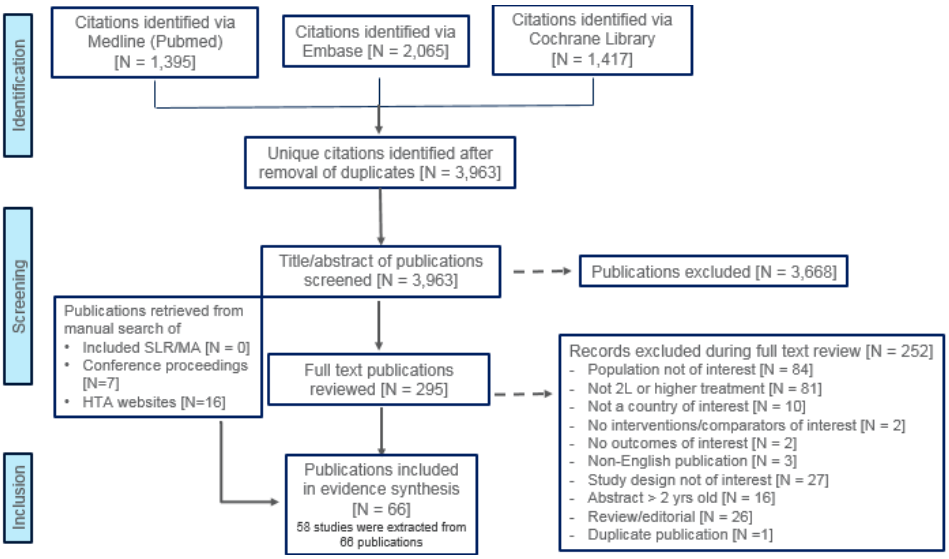


Figure 41 Literature selection and review process for economic costs and healthcare resource utilization in NSCLC

Abbreviations: 2L, second line; HTA, health technology assessment; MA, meta-analysis; NSCLC, non-small cell lung cancer; SLR, systematic literature review.

J.3.7.2 Systematic selection of studies

Selection of studies for inclusion was determined using the PICOS framework. The inclusion and exclusion criteria of the NSCLC reviews are presented in Table 104.

Table 104 Inclusion and exclusion criteria for costs and resource use reviews in NSCLC

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with advanced or metastatic NSCLC being treated with ≥2nd-line therapy	• Healthy volunteers • Patients with diseases other than NSCLC • Patients with early stage NSCLC

		• Patients with 1st-line NSCLC
Interventions	Any/all/no interventions*	None
Comparators	Any/all/no comparators	None
Outcomes	• Direct costs (e.g., drug costs/ pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/income for patient and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care, inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	All outcomes other than those specified in the inclusion columns
Study design (s]	Cost and resource use studies: • Cost studies • Resource use studies • Economic evaluations reporting costs or resource use	• Non-systematic reviews • Case reports • Case series • Animal studies • Letters • Editorials
Country	Studies conducted in the US, Canada, EU5 (United Kingdom, France, Germany, Italy, Spain), Japan, and Brazil healthcare setting will be extracted	Countries other than those specified in the inclusion columns
Time limits	• Studies published 2008 onwards • Conference abstracts 2017 onwards[a]	• Studies published prior to 2008 will be excluded • Conference abstracts prior to 2017 will be excluded

[a] Conferences identified in Table 99 will be included for evaluation.
* Studies of no intervention, mixed interventions or class of therapy, interventions not specified, etc, will be included, along with studies of the interventions of interest listed under economic modeling review. However, utility and cost/resource use data assessing specifically treatments not of interest will not be used for the cost-effectiveness analyse (CEA) inputs and will be excluded during screening

J.3.7.3 Search strategy

Table 105 Embase search strategy for economic costs and resource use in NSCLC Table 105, Table 106 and Table 107 present the search hits in Embase, Medline and Cochrane databases.

Table 105 Embase search strategy for economic costs and resource use in NSCLC

#	Query	Results from 23 August 2018
1	('non small cell lung cancer' OR 'non small cell lung cancer'/syn OR 'non small cell lung cancer'/exp OR nsclc OR 'non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR (lung NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumour* OR squamous OR adenocarcinoma*)):ab,ti OR ('lung'/exp AND ('neoplasm'/exp OR 'cancer'/exp OR 'carcinoma'/exp OR 'malignancy'/exp OR 'tumour'/exp))) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	106,118
2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR 'fee'/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR 'expenditures'/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR 'health care utilization':ab,ti OR 'health care utilisation':ab,ti OR 'absenteeism'/exp OR absenteeism:ab,ti OR 'presenteeism'/exp OR presenteeism:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR 'medical leave'/exp OR 'medical leave':ab,ti	1,930,522
3	#1 AND #2	4,555
4	#3 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	4,147
5	#3 AND [conference abstract]/lim AND [humans]/lim AND [2015-2018]/py	961
6	#4 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2008-2018]/py	1,073
7	#5 or #6	2,065

Table 106 Medline search strategy for economic costs and resource use in NSCLC

#	Query	Results from 23 August 2018
1	((((((("non small cell lung cancer" OR nsclc)) OR Carcinoma, Non-Small-Cell Lung[MeSH Terms]) OR (((Neoplasms[MeSH Terms]) OR Carcinoma[MeSH Terms]) AND Lung[MeSH Terms])) OR ("non-small-cell" OR "non-small cell" OR "non small cell" OR "nonsmall cell")) OR ((lung[Title/Abstract]) AND (cancer[Title/Abstract] OR carcinoma[Title/Abstract] OR neoplasm[Title/Abstract] OR tumour[Title/Abstract] OR tumour[Title/Abstract] OR squamous[Title/Abstract] OR adenocarcinoma[Title/Abstract]))) AND (advanced OR inoperable OR unresectable OR metasta*)	81,448
2	(Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR	1,444,307

	economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab] OR "health care utilization"[tiab] OR "health care utilisation"[tiab])	
3	#1 AND #2	2,408
4	#3: Filters: published in the last 10 years	1,395

Table 107 Cochrane Library search strategy for economic costs and resource use in NSCLC

#	Query	Results from 23 August 2018
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	3,526
2	non small cell lung cancer or nsclc	9,645
3	#1 or #2	9,699
4	MeSH descriptor: [Lung] explode all trees	3,906
5	MeSH descriptor: [Neoplasms] explode all trees	67,072
6	MeSH descriptor: [Carcinoma] explode all trees	11,554
7	#5 or #6	67,072
8	#4 and #7	244
9	non-small-cell or non-small cell or non small cell or nonsmall cell	14,455
10	(lung near/3 (cancer* or carcin* or neoplasm* or tumour* or tumour* or squamous or adenocarcinoma*)):ti,ab	15,112
11	#3 or #8 or #9 or #10	21,149
12	advanced OR inoperable OR unresectable OR metasta*	77,965
13	#11 and #12	8,830
14	MeSH descriptor: [Costs and Cost Analysis] explode all trees	9,439
15	MeSH descriptor: [Fees and Charges] explode all trees	245
16	MeSH descriptor: [Health Expenditures] explode all trees	174
17	MeSH descriptor: [Cost of Illness] explode all trees	769
18	MeSH descriptor: [Absenteeism] explode all trees	466
19	MeSH descriptor: [Presenteeism] explode all trees	15
20	MeSH descriptor: [Health Care Costs] explode all trees	3,188
21	(cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or health care utilization or healthcare utilisation or health care utilisation or absenteeism or presenteeism or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave):ti,ab,kw	144,575

22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	144,577
23	#13 AND #22	1,417
24	#23 in Cochrane Reviews and Protocols with Publication Year from 2008 to 2018	1,052
25	#23 in Trials with Publication Year from 2008 to 2018	365
26	#23 in Clinical Answers with Publication Year from 2008 to 2018	0
27	#23 in Editorials with Publication Year from 2008 to 2018	0
28	#23 in Special collections with Publication Year from 2008 to 2018	0

Note: Word variations have been searched for all queries

J.3.7.4 Quality assessment

N/A

J.3.7.5 Economic evaluations

The cost-effectiveness of various treatments in second-line or higher advanced NSCLC was investigated in 29 publications. Nearly all the analyses assessed checkpoint inhibitors, most frequently comparing them to treatment with docetaxel. Nivolumab was deemed cost-effective in Spain, the UK, Scotland, and Canada but not in the US, Germany, or Ireland. Similarly, pembrolizumab was found to be cost-effective vs docetaxel in 5 of 8 studies. Atezolizumab also was considered cost-effective in most studies when compared with nivolumab, pembrolizumab, or docetaxel. The PRISMA flow diagram for economic evaluations in NSCLC is presented in Figure 42.

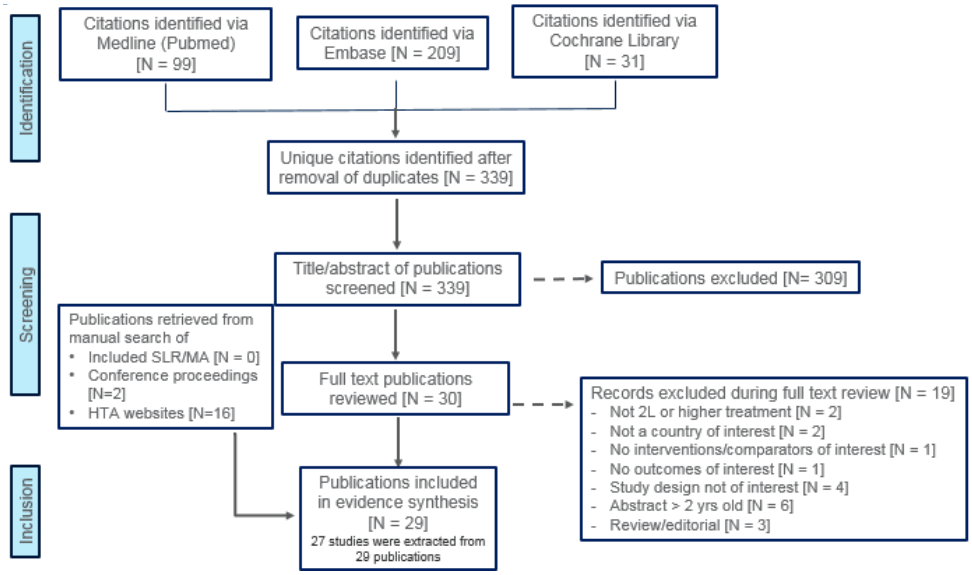


Figure 42 Literature selection and review process for economic evaluations in NSCLC
Abbreviations: 2L, second line; HTA, health technology assessment; MA, meta-analysis; NSCLC, non-small cell lung cancer; SLR, systematic literature review.

J.3.7.5.1 Systematic selection of studies

The inclusion and exclusion criteria for economic evaluations in the NSCLC reviews are detailed using the PICOS framework in Table 108.

Table 108 Inclusion and exclusion criteria for economic evaluations in NSCLC

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with advanced or metastatic NSCLC being treated with ≥2nd-line therapy	• Healthy volunteers • Patients with diseases other than NSCLC • Patients with early-stage NSCLC • Patients with 1st-line NSCLC
Interventions	Monotherapies: • Docetaxel • Gemcitabine • Pemetrexed • Larotrectinib • Pembrolizumab • Nivolumab • Atezolizumab Combination treatments: • Ramucirumab + docetaxel	Interventions other than those listed in inclusion column
Comparators	Monotherapies: • Docetaxel • Gemcitabine • Pemetrexed • Larotrectinib • Pembrolizumab • Nivolumab • Atezolizumab • Placebo • SoC/BSC (author defined) Combination treatments: • Ramucirumab + docetaxel	Comparators other than those listed in the inclusion column
Outcomes	• Overall costs (results of modelled analyses) • Quality-adjusted outcomes (e.g., quality-adjusted life-months, quality-adjusted life-years, quality-adjusted life expectancy, quality-time without symptoms or toxicity) • Disutility-adjusted outcomes (e.g., disutility-adjusted life years) • Incremental cost-effectiveness ratios	All outcomes other than those specified in the inclusion columns

	• Treatment dominance	
Study design (s]	Full economic evaluations:* • Cost-consequence • Cost-minimization • Cost-effectiveness • Cost-utility • Cost-benefit • Budget impact	• Non-systematic reviews • Case reports • Case series • Animal studies • Letters • Editorials
Country	Studies conducted in the US, Canada, EU5 (United Kingdom, France, Germany, Italy, Spain), Japan, and Brazil healthcare setting will be extracted	Countries other than those specified in the inclusion columns
Time limits	• Studies published 2008 onwards • Conference abstracts 2017 onwards[a]	• Studies published prior to 2008 will be excluded • Conference abstracts prior to 2017 will be excluded

[a] Conferences identified in Table 99 will be included for evaluation.
* The cost-minimization and BI studies will be extracted in the cost-resource use review, since these studies do not provide any argument on cost-effectiveness conclusions

J.3.7.5.2 Search strategy

Table 109, Table 110 and Table 111 present the search hits in Embase, Medline and Cochrane databases.

Table 109 Embase search strategy for economic evaluations in NSCLC

#	Query	Results from 28 August 2018
1	('non small cell lung cancer' OR 'non small cell lung cancer'/syn OR 'non small cell lung cancer'/exp OR nsclc OR 'non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR (lung NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumour* OR squamous OR adenocarcinoma*)):ab,ti OR ('lung'/exp AND ('neoplasm'/exp OR 'cancer'/exp OR 'carcinoma'/exp OR 'malignancy'/exp OR 'tumour'/exp))) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	106,118
2	('docetaxel'/syn OR 'docetaxel'/exp OR docetaxel OR docefrez OR taxotere OR docecad OR 'rx 56976' OR 'gemcitabine'/syn OR 'gemcitabine'/exp OR gemcitabine OR gemzar OR 'ly188011' OR 'ly-188011' OR 'pemetrexed'/syn OR 'pemetrexed'/exp OR pemetrexed OR alimta OR 'ly231514' OR 'pembrolizumab'/syn OR 'pembrolizumab'/exp OR pembrolizumab OR keytruda OR 'mk-3475' OR 'sch 900475' OR 'nivolumab'/syn OR 'nivolumab'/exp OR nivolumab OR opdivo OR 'bms-936558' OR 'mdx-1106' OR 'ono-4538' OR 'atezolizumab'/syn OR 'atezolizumab'/exp OR atezolizumab OR tecentriq OR mpdl3280a OR 'rg7446' OR 'ro5541267' OR 'ramucirumab'/syn OR 'ramucirumab'/exp OR ramucirumab OR cyramza or 'imc-1121b' OR ly3009806 OR	107,159

	'larotrectinib'/syn OR 'larotrectinib'/exp OR 'larotrectinib' OR 'loxo 101'/exp OR 'loxo 101' OR 'loxo101' OR 'loxo101'	
3	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	413,686
4	#1 AND #2 AND #3	456
5	#4 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	371
6	#5 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2008-2018]/py	142
7	#5 or #6	209

Table 110 Medline search strategy for economic evaluations in NSCLC

#	Query	Results from 28 August 2018
1	((((((("non small cell lung cancer" OR nsclc)) OR Carcinoma, Non-Small-Cell Lung[MeSH Terms]) OR (((Neoplasms[MeSH Terms]) OR Carcinoma[MeSH Terms]) AND Lung[MeSH Terms])) OR ("non-small-cell" OR "non-small cell" OR "non small cell" OR "nonsmall cell")) OR ((lung[Title/Abstract]) AND (cancer[Title/Abstract] OR carcinoma[Title/Abstract] OR neoplasm[Title/Abstract] OR tumour[Title/Abstract] OR tumour[Title/Abstract] OR squamous[Title/Abstract] OR adenocarcinoma[Title/Abstract]))) AND (advanced OR inoperable OR unresectable OR metasta*)	81,448
2	(((((((((docetaxel or docefrez or taxotere or docecad or "rx 56976" or gemcitabine or gemzar or "ly188011" or "ly-188011" or pemetrexed or alimta or ly231514 or pembrolizumab or keytruda or "mk-3475" or "sch 900475" or nivolumab or opdivo or "bms-936558" or "mdx-1106" or "ono-4538" or atezolizumab or tecentriq or mpdl3280a or rg7446 or ro5541267 or ramucirumab or cyramza or "imc-1121b" or ly3009806 or larotrectinib or "loxo-101" or loxo101 or "loxo 101")) OR Docetaxel[MeSH Terms]) OR gemcitabine[MeSH Terms]) OR pemetrexed[MeSH Terms]) OR pembrolizumab[MeSH Terms]) OR nivolumab[MeSH Terms]) OR atezolizumab[MeSH Terms]) OR ramucirumab[MeSH Terms]) OR larotrectinib[MeSH Terms]	33,938
3	("Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget	369,100

	impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab])	
4	#1 AND #2 AND #3	142
5	#4: Filters: published in the last 10 years	99

Table 111 Cochrane Library search strategy for economic evaluations in NSCLC

#	Query	Results from 28 August 2018
1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	3,526
2	non small cell lung cancer or nsclc	9,645
3	#1 or #2	9,699
4	MeSH descriptor: [Lung] explode all trees	3,906
5	MeSH descriptor: [Neoplasms] explode all trees	67,072
6	MeSH descriptor: [Carcinoma] explode all trees	11,554
7	#5 or #6	67,072
8	#4 and #7	244
9	non-small-cell or non-small cell or non small cell or nonsmall cell	14,455
10	(lung near/3 (cancer* or carcin* or neoplasm* or tumour* or tumour* or squamous or adenocarcinoma*)):ti,ab	15,112
11	#3 or #8 or #9 or #10	21,149
12	advanced OR inoperable OR unresectable OR metasta*	77,965
13	#11 and #12	8,830
14	MeSH descriptor: [Models, Economic] explode all trees	295
15	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	6,124
16	MeSH descriptor: [Costs and Cost Analysis] explode all trees	9,439
17	MeSH descriptor: [Decision Theory] explode all trees	162
18	MeSH descriptor: [Decision Trees] explode all trees	156
19	MeSH descriptor: [Decision Support Techniques] explode all trees	2,332
20	(Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR decision analys* OR decision analyt* OR decision model*):ti,ab,kw	48,493
21	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	51,467
22	docetaxel or docefrez or taxotere or docecad or rx 56976 or gemcitabine or gemzar or ly188011 or ly-188011 or pemetrexed or alimta or ly231514 or pembrolizumab or keytruda or mk-3475 or sch 900475 or nivolumab or opdivo or bms-936558 or mdx-1106 or ono-4538 or	10,519

	atezolizumab or tecentriq or mpdl3280a or rg7446 or ro5541267 or ramucirumab or cyramza or imc-1121b or ly3009806 or larotrectinib or loxo-101 or loxo101 or loxo 101	
23	MeSH descriptor: [Pemetrexed] explode all trees	444
24	#22 OR #23	10,519
25	#13 AND #21 AND #24	31
26	#25 in Cochrane Reviews and Protocols with Publication Year from 2008 to 2018	1
27	#25 in Trials with Publication Year from 2008 to 2018	30
28	#25 in Clinical Answers with Publication Year from 2008 to 2018	0
29	#25 in Editorials with Publication Year from 2008 to 2018	0
30	#25 in Special collections with Publication Year from 2008 to 2018	0

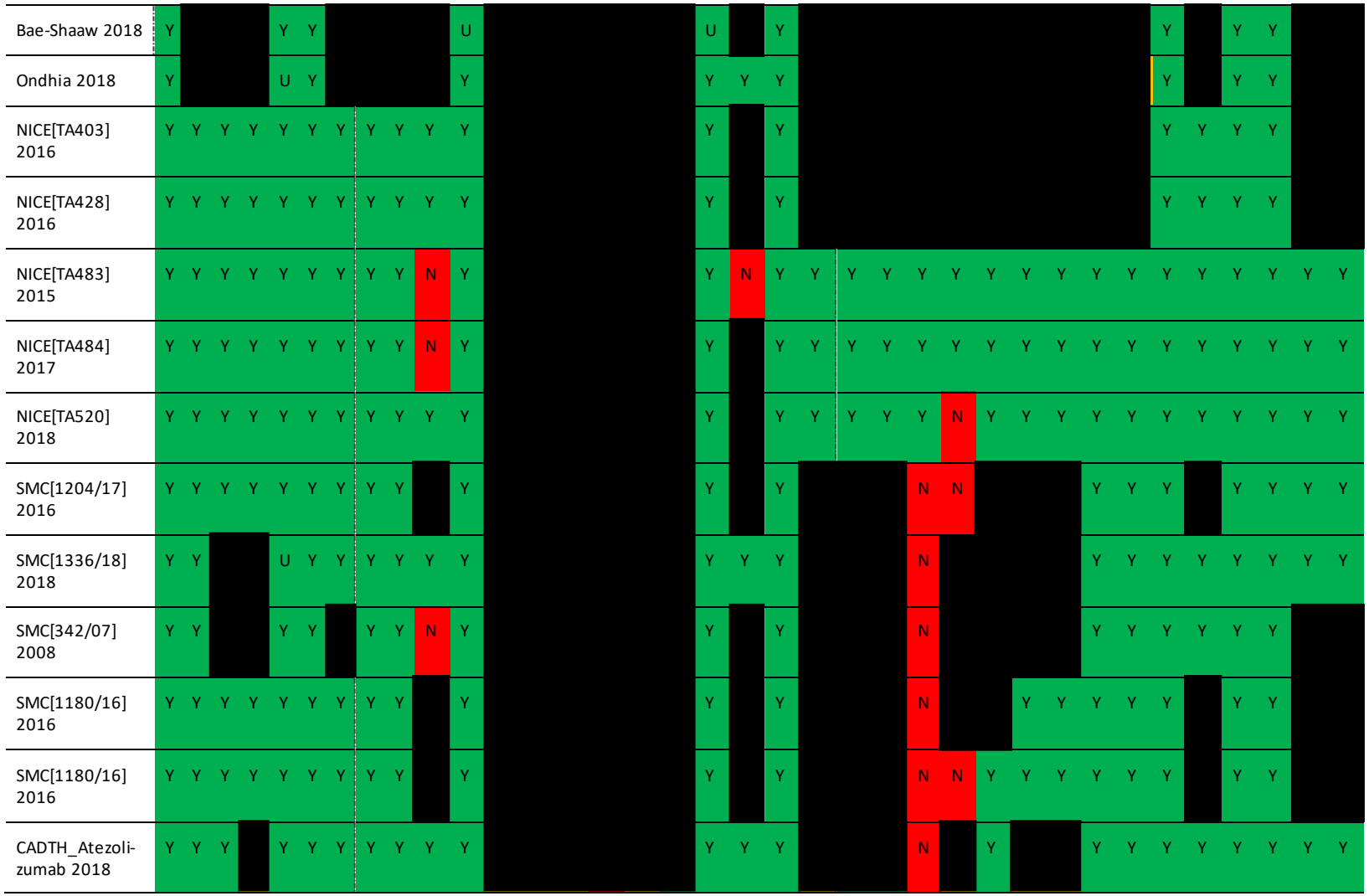
Note: Word variations have been searched for all queries

J.3.7.5.3 Quality assessment

The 27 included cost-effectiveness studies were generally of high quality based on the Drummond's checklist with respect to study design, data collection and analysis, and interpretation of results. However, most of the CEAs did not include indirect costs, and justification was not provided for adjustments for inflation, choice of model used, or discount rate.

Table 112 Quality assessment of the economic evaluations: NSCLC

Question no.	Study design							Data collection												Analysis and interpretation of results															
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36
Publication																																				
Asukai 2010	Y	Y	Y	Y	Y	Y		Y										Y												Y	Y	Y	Y	Y		
Carlson 2008	Y	Y	Y	Y	Y	Y		U										Y												Y	Y	Y	Y	Y		
Román 2018	Y				Y	Y		U										U												Y	Y		Y	Y		
Goeree 2016	Y	Y	Y	Y	Y	Y	Y	Y										Y												Y	Y	Y	Y	Y	Y	Y
González 2017	Y				Y	Y	Y	Y										U												Y	Y	Y	Y	Y		
Huang 2017	Y	Y	Y	Y	Y	Y	Y	Y										Y												Y	Y	Y	Y	Y	Y	Y
Kuhlmann 2017	Y	Y	Y		U	Y	Y	Y										U												Y	Y	Y	Y			
Langella 2017	Y		Y		U	Y	Y	Y										U												Y	Y		Y			
Vergnenegre 2011	Y	Y	Y	Y	Y	Y	Y	Y										Y												Y	Y	Y	Y	Y	Y	Y


Bae-Shaaw 2018
Ondhia 2018
NICE[TA403] 2016
NICE[TA428] 2016
NICE[TA483] 2015
NICE[TA484] 2017
NICE[TA520] 2018
SMC[1204/17] 2016
SMC[1336/18] 2018
SMC[342/07] 2008
SMC[1180/16] 2016
SMC[1180/16] 2016
CADTH_Atezoli-zumab 2018

CADTH_Nivolumab 2016	Y	Y	Y	Y	Y	[redacted]		Y	Y	[redacted]		Y	Y	[redacted]	Y	[redacted]	Y	[redacted]	Y	[redacted]	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
CADTH_Pem-brolizumab 2016	Y	Y	Y	Y	Y	[redacted]		Y	Y	[redacted]		Y	Y	[redacted]	Y	[redacted]	Y	Y	Y	[redacted]	N	[redacted]					Y	Y	Y	Y	Y	Y	Y
NCPE_Nivolumab 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	[redacted]	Y	[redacted]	Y	Y	Y	[redacted]	N	[redacted]					Y	Y	Y	Y	Y	Y	Y
NCPE_Pembroli-zumab 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	[redacted]	Y	[redacted]	Y	Y	Y	[redacted]	N	[redacted]					Y	Y	Y	Y	Y	Y	Y
NCPE_Nivolumab (Nn-squamous) 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	[redacted]	Y	[redacted]	Y	Y	Y	[redacted]	N	[redacted]					Y	Y	Y	Y	Y	Y	Y

Abbviation: N, no; U, unclear; Y, yes.

1. Was the research question stated?
2. Was the economic importance of the research question stated?
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?
5. Were the alternatives being compared clearly described?
6. Was the form of economic evaluation stated?
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?
8. Was/were the source(s) of effectiveness estimates used stated?
9. Were details of the design and results of the effectiveness study given (if based on a single study)?
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?
12. Were the methods used to value health states and other benefits stated?
13. Were the details of the subjects from whom valuations were obtained given?
14. Were productivity changes (if included) reported separately?
15. Was the relevance of productivity changes to the study question discussed?
16. Were quantities of resources reported separately from their unit cost?
17. Were the methods for the estimation of quantities and unit costs described?
18. Were currency and price data recorded?
19. Were details of price adjustments for inflation or currency conversion given?
20. Were details of any model used given?
21. Was there a justification for the choice of model used and the key parameters on which it was based?

22. Was the time horizon of cost and benefits stated?
23. Was the discount rate stated?
24. Was the choice of rate justified?
25. Was an explanation given if cost or benefits were not discounted?
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?
27. Was the approach to sensitivity analysis described?
28. Was the choice of variables for sensitivity analysis justified?
29. Were the ranges over which the parameters were varied stated?
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)
31. Was an incremental analysis reported?
32. Were major outcomes presented in a disaggregated as well as aggregated form?
33. Was the answer to the study question given?
34. Did conclusions follow from the data reported?
35. Were conclusions accompanied by the appropriate caveats?
36. Were the generalisability issues addressed?

J.3.8 Colorectal cancer

J.3.8.1 Healthcare resource use and costs

A total of 42 trials evaluated HCRU and costs in patients with advanced CRC across diverse geographies. The rate of hospitalizations among patients was variable, ranging from 22% to 95%, and the mean length of stay varied from 5.0 to 8.3 days. Greater HCRU was reported for patients with longer survival. Total direct costs were substantial, ranging up to $61,360 (USD) (total healthcare costs during second-line therapy). Notable drivers of total healthcare or medical costs were hospitalizations and outpatient-based care. The PRISMA flow diagram for economic costs and healthcare resource in colorectal cancer is shown in Figure 43.

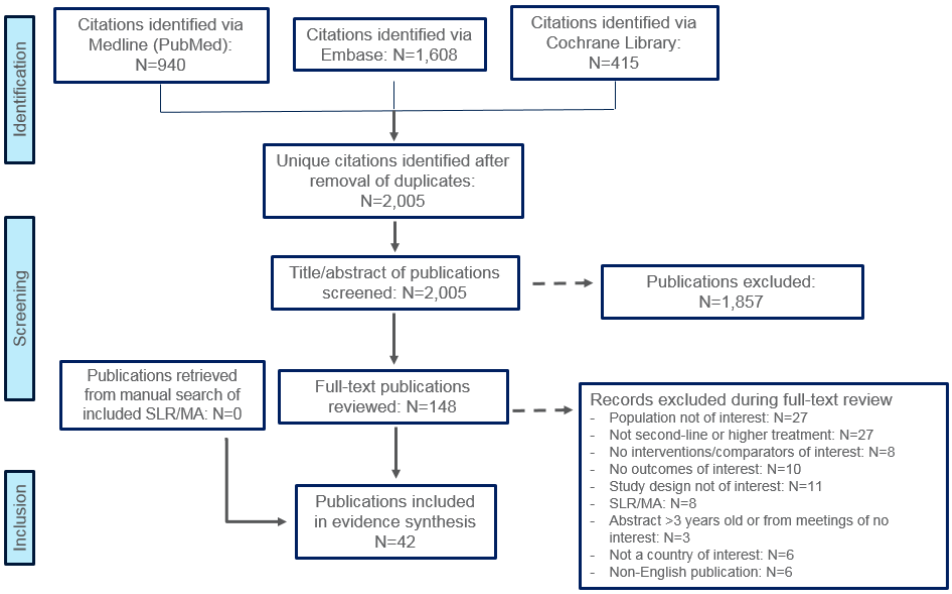


Figure 43 Literature selection and review process for economic costs and healthcare resource utilization in colorectal cancer

Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.8.2 Systematic selection of studies

The inclusion and exclusion criteria for costs and resource use in the colorectal cancer reviews are detailed using the PICOS framework in Table 113.

Table 113 Inclusion and exclusion criteria for costs and resource use reviews in colorectal cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic CRC ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than CRC • Patients with early-stage CRC

Interventions	Any/all/no interventions	None
Comparators	Any/all/no interventions	None
Outcomes	• Direct costs (e.g., drug costs/pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/ income for patients and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care, inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies (retrospective, prospective, cross-sectional, registries)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials • Other study designs not specified in Inclusion column

Abbreviations: CRC, colorectal cancer; RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.8.3 Search strategy

Table 114, Table 115 and Table 116 present the search hits in Embase, Medline and Cochrane databases.

Table 114 Embase search strategy for economic costs and resource use in colorectal cancer

#	Query	Results from 29 July 2018
1	('colorectal cancer'/exp OR 'colorectal cancer':ab,ti OR 'colon cancer':ab,ti OR 'rectal cancer':ab,ti OR 'colorectal tumour':ab,ti OR 'colorectal tumour':ab,ti OR 'colon tumour':ab,ti OR 'colon tumour':ab,ti OR 'rectal tumour':ab,ti OR 'rectal tumour':ab,ti OR 'colorectal carcinoma':ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	78,030

2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR fee/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR expenditures/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR 'health care utilization':ab,ti OR 'health care utilisation':ab,ti OR absenteeism/exp OR absenteeism:ab,ti OR presenteeism/exp OR presenteeism:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR 'medical leave'/exp OR 'medical leave':ab,ti	1.9m
3	#1 AND #2	3,603
4	#3 AND Humans	3,270
5	#4 AND Limits: Articles, Reviews, Articles in Press	1,962
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	1,548
7	#6 AND Publication 2008-2018	1,035
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	573
9	#6 OR #7	1,608

Table 115 Medline search strategy for economic costs and resource use in colorectal cancer

#	Query	Results from 29 July 2018
1	("colorectal neoplasms"[mesh] OR "colorectal cancer"[tiab] OR "colon cancer"[tiab] OR "rectal cancer"[tiab] OR "colorectal tumour"[tiab] OR "colorectal tumour"[tiab] OR "colon tumour"[tiab] OR "colon tumour"[tiab] OR "rectal tumour"[tiab] OR "rectal tumour"[tiab] OR "colorectal carcinoma"[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	57,628
2	Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR "health care utilization"[tiab] OR "health care utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab]	1.4m
3	#1 AND #2	1,929
4	#3 NOT (animals[mh] NOT humans[mh])	1,906
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	1,779
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	1,448

7	#6 Publication date from 2008-2018	940

Table 116 Cochrane Library search strategy for economic costs and resource use in colorectal cancer

#	Query	Results from 29 July 2018
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	8,199
2	(colorectal cancer OR colon cancer OR rectal cancer OR colorectal tumour OR colorectal tumour OR colon tumour OR colon tumour OR rectal tumour OR rectal tumour OR colorectal carcinoma)ti,ab,kw (Word variations have been searched)	16,546
3	#1 OR #2	17,850
4	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087
5	#3 AND #4	6,741
6	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
7	MeSH descriptor: [Fees and Charges] explode all trees	519
8	MeSH descriptor: [Health Expenditures] explode all trees	354
9	MeSH descriptor: [Cost of Illness] explode all trees	1,390
10	MeSH descriptor: [Absenteeism] explode all trees	550
11	MeSH descriptor: [Presenteeism] explode all trees	15
12	MeSH descriptor: [Health care costs] explode all trees	7,652
13	cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or healthcare utilisation or health care utilization or health care utilisation or absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave:ti,ab,kw (Word variations have been searched)	146,424
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	146,501
15	#5 AND #14	545
16	#15 Publication Dates: 2008-2018	415

J.3.8.4 Quality assessment

N/A

J.3.8.5 Economic evaluations

20 economic models reporting on the cost-effectiveness of interventions in advanced CRC were identified across a variety of countries including the US, Europe, and Canada. Several different combinations of chemotherapy were evaluated along with monotherapy

compared with placebo or BSC. Reported ICERs ranged widely from £51,194 (GBP) for trifluridine/tipiracil to $975,954 (USD) for regorafenib 160 mg and $1,036,648 (USD) for maintenance capecitabine plus bevacizumab. The PRISMA flow diagram for economic evaluations in colorectal cancer is presented in Figure 44.

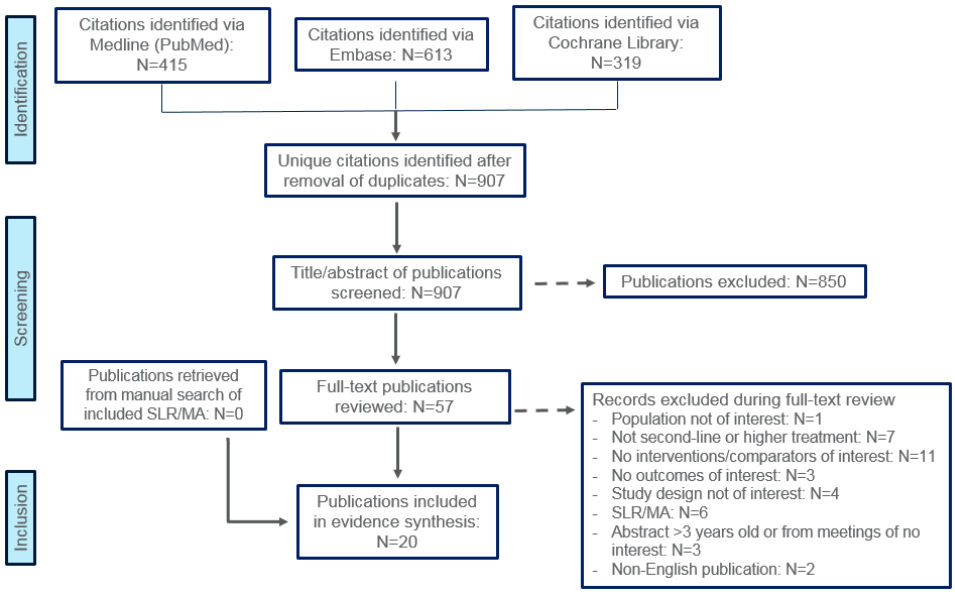


Figure 44 Literature selection and review process for economic evaluations in colorectal cancer
Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.8.5.1 Systematic selection of studies

The inclusion and exclusion criteria for economic evaluations in the colorectal cancer reviews are detailed using the PICOS framework in Table 117.

Table 117 Inclusion and exclusion criteria for economic evaluations in colorectal cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic CRC ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than CRC • Patients with early-stage CRC
Interventions	Monotherapies: • Capecitabine • Irinotecan (if FOLFOX 1st line) • Regorafenib • Larotrectinib Combination treatments: • FOLFIRI (IFL) + bevacizumab • leucovorin + fluorouracil • leucovorin + fluorouracil + bevacizumab	Interventions other than those listed in inclusion column

	• Capecitabine + bevacizumab • FOLFOX • FOLFOX + bevacizumab • FOLFIRI + ziv-aflibercept • FOLFIRI + ramucirumab • Trifluridine + tipiracil (TAS-102) • FOLFIRI (if FOLFOX or XELOX 1st line)	
Comparators	Monotherapies: • Capecitabine • Irinotecan (if FOLFOX 1st line) • Regorafenib • Larotrectinib Combination treatments: • FOLFIRI (IFL) + bevacizumab • leucovorin + fluorouracil • leucovorin + fluorouracil + bevacizumab • Capecitabine + bevacizumab • FOLFOX • FOLFOX + bevacizumab • FOLFIRI + ziv-aflibercept • FOLFIRI + ramucirumab • Trifluridine + tipiracil (TAS-102) • FOLFIRI (if FOLFOX or XELOX 1st line) Placebo: • SoC/BSC (author-defined)	Comparators other than those listed in the inclusion column
Outcomes	• Overall costs (results of modelled analyses) • Quality-adjusted outcomes (e.g., quality-adjusted life-months, quality-adjusted life-years, quality-adjusted life expectancy, quality-time without symptoms or toxicity) • Disutility-adjusted outcomes (e.g., disutility-adjusted life years) • Incremental cost-effectiveness ratios • Treatment dominance	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • Health economic studies • Cost-effectiveness • Cost-benefit • Cost-utility • Cost-consequence • Cost-minimization • Budget impact	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

- Other study designs not specified in Inclusion column

Abbreviations: BSC, best supportive care; CRC, colorectal cancer; FOLFIRI, folinic acid, fluorouracil, irinotecan hydrochloride; FOLFOX, folinic acid, fluorouracil and oxaliplatin; SLR, systematic literature review; SoC, standard of care; XELOX, oxaliplatin and capecitabine.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.8.5.2 Search strategy

Table 118, Table 119 and Table 120 present the search hits in Embase, Medline and Cochrane databases.

Table 118 Embase search strategy for economic evaluations in colorectal cancer

#	Query	Results from 30 July 2018
1	('colorectal cancer'/exp OR 'colorectal cancer':ab,ti OR 'colon cancer':ab,ti OR 'rectal cancer':ab,ti OR 'colorectal tumour':ab,ti OR 'colorectal tumour':ab,ti OR 'colon tumour':ab,ti OR 'colon tumour':ab,ti OR 'rectal tumour':ab,ti OR 'rectal tumour':ab,ti OR 'colorectal carcinoma':ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	78,030
2	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	413k
3	#1 AND #2	1,416
4	#3 AND Humans	1,302
5	#4 AND Limits: Articles, Reviews, Articles in Press	812
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	602
7	#6 AND Publication 2008-2018	407
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	206
9	#7 OR #8	613

Table 119 Medline search strategy for economic evaluations in colorectal cancer

#	Query	Results from 30 July 2018
1	("colorectal neoplasms"[mesh] OR "colorectal cancer"[tiab] OR "colon cancer"[tiab] OR "rectal cancer"[tiab] OR "colorectal tumour"[tiab] OR "colorectal tumour"[tiab] OR "colon tumour"[tiab] OR "colon tumour"[tiab] OR "rectal tumour"[tiab] OR "rectal tumour"[tiab] OR "colorectal carcinoma"[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	57,634
2	"Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab]	369k
3	#1 AND #2	773
4	#3 NOT (animals[mh] NOT humans[mh])	769
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	738
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	599
7	#6 Publication date from 2008-2018	415

Table 120 Cochrane Library search strategy for economic evaluations in colorectal cancer

#	Query	Results from 30 July 2018
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees	8,199
2	(colorectal cancer OR colon cancer OR rectal cancer OR colorectal tumour OR colorectal tumour OR colon tumour OR colon tumour OR rectal tumour OR rectal tumour OR colorectal carcinoma)ti,ab,kw	
3	(Word variations have been searched)	16,546
4	#1 OR #2	
5	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087
6	MeSH descriptor: [Models, Economic] explode all trees	2,060
7	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,942
8	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
9	MeSH descriptor: [Decision Theory] explode all trees	937
10	MeSH descriptor: [Decision Trees] explode all trees	921
11	MeSH descriptor: [Decision Analyses] explode all trees	3,796

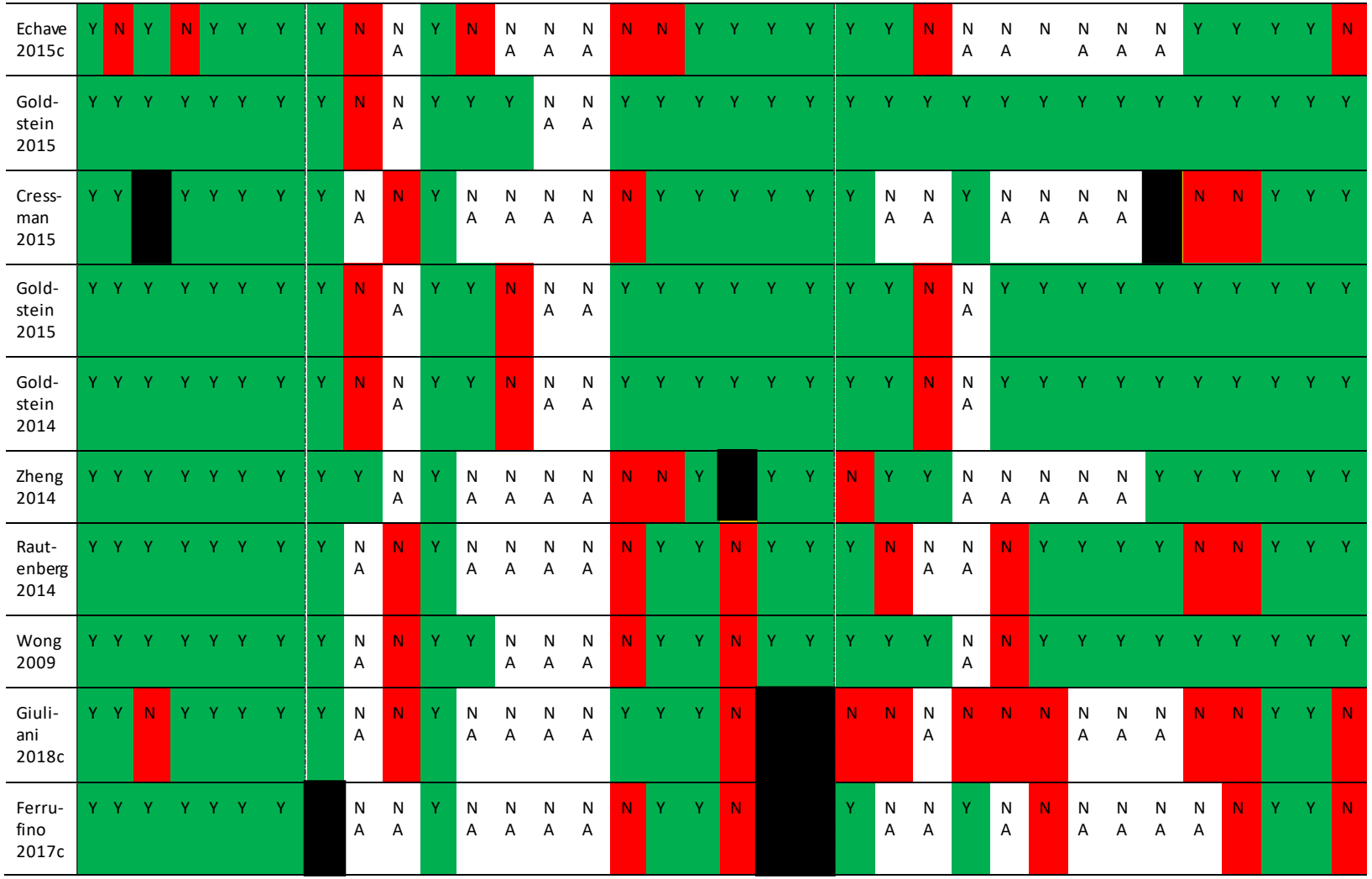
12	Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR decision analys* OR decision analyt* OR decision model* :ti,ab,kw (Word variations have been searched)	59,093
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	65,575
14	#5 AND #13	420
15	#14 Publication Dates: 2008-2018	319

J.3.8.5.3 Quality assessment

Of the 19 economic analyses assessed for quality in the CRC SLR, 8 were conference abstracts, for which it can be difficult to assess quality due to lack of information (i.e., space limitations). Among the full publications, the quality was generally high. The quality of the analyses described in the conference abstracts was also considered generally high, but the "not clear" response option was more often used (for between 1 and 6 questions out of 35 total questions).

Table 121 Quality assessment of the economic evaluations: Colorectal cancer

	Study design							Data collection														Analysis and interpretation of results																	
Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35				
Publication																																								
Giuliani 2018	Y	Y		Y	Y	NA	NA	Y	NA	Y	Y	NA	NA	NA	NA	N		Y	N	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	Y	Y	Y	Y				
Bullement 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	N	N	Y	Y	Y	Y	Y	Y				
Kimura 2016	Y	Y		Y	Y	Y	Y	Y	Y	NA	Y	NA	NA	NA	NA	N	Y	Y	N	NA	NA	NA	N	NA	NA	Y	NA	NA	NA	NA	Y	Y	Y	Y	N				
Riesco-Martiinez 2016	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	NA	NA	N	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y				


Echave 2015c
Gold-stein 2015
Cress-man 2015
Gold-stein 2015
Gold-stein 2014
Zheng 2014
Raut-enberg 2014
Wong 2009
Giuli-ani 2018c
Ferru-fino 2017c

Lange 2017c	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	N	NA	NA	N	Y	Y	N	N			N	NA	N	N					Y	N	Y	Y	N
Gonza-lez Flo-res 2016c	Y	Y	Y	Y	N	Y	Y	Y	NA	NA	Y	NA	NA	NA	NA	N	Y	Y	N	N			N	NA	NA	NA	N	NA	NA	NA	NA	NA	Y	Y	N
Whalen 2015c	Y	Y	Y	Y	Y	Y	Y	Y	N	NA	Y	NA	NA	NA	NA	N	Y	Y	N	N			Y	Y	NA	N	N	NA	NA	NA	Y	Y	Y	Y	N
Whalen 2015c	Y	Y	Y	Y	N	Y	Y	Y	N	NA	Y	NA	NA	NA	NA	N	Y	Y	N	N			N	NA	NA	NA	N	NA	NA	NA	Y	Y	Y	Y	N
Huff 2015c	Y	Y	Y	Y	Y	Y	Y		NA	N	Y	NA	NA	NA	NA	N	Y	Y	N	Y			N	NA	NA	NA					NA	NA	Y	Y	N

Abbviation: N, no; NC, not clear; Y, yes; NA, not avalible.
Note: Used BMJ Study Checklist for Economic Studies (Drummond 1996)

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoint(s) of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed
8. The source(s) of effectiveness estimates used are stated
9. Details of the design and results of effectiveness study are given (if based on a single study)
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11. The primary outcome measure(s) for the economic evaluation are clearly stated
12. Methods to value health states and other benefits are stated
13. Details of the subjects from whom valuations were obtained are given

14. Productivity changes (if included) are reported separately
15. The relevance of productivity changes to the study question is discussed
16. Quantities of resources are reported separately from their unit costs
17. Methods for the estimation of quantities and unit costs are described
18. Currency and price data are recorded
19. Details of currency or price adjustments for inflation or currency conversion are given
20. Details of any model used are given
21. The choice of model used and the key parameters on which it is based are justified
22. Time horizon of costs and benefits is stated
23. The discount rate(s) is stated
24. The choice of rate(s) is justified
25. An explanation is given if costs or benefits are not discounted
26. Details of statistical tests and confidence intervals are given for stochastic data
27. The approach to sensitivity analysis is given
28. The choice of variables for sensitivity analysis is justified
29. The ranges over which the variables are varied are stated
30. Relevant alternatives are compared
31. Incremental analysis is reported
32. Major outcomes are presented in a disaggregated as well as aggregated form
33. The answer to the study question is given
34. Conclusions follow from the data reported
35. Conclusions are accompanied by the appropriate caveats

J.3.9 Melanoma

J.3.9.1 Healthcare resource use and costs

Cost and HCRU were reported in 25 publications including 14 publications on resource use and 17 publications on direct costs. No data on indirect costs were reported. Commonly reported measures of HCRU included hospitalizations, outpatient visits, and emergency department visits. Nearly all studies did not report on HCRU associated with specific interventions. Resource use tended to increase with increasing line of therapy. Costs varied significantly across geographies. The PRISMA flow diagram for economic costs and healthcare resource in melanoma is shown in Figure 45.

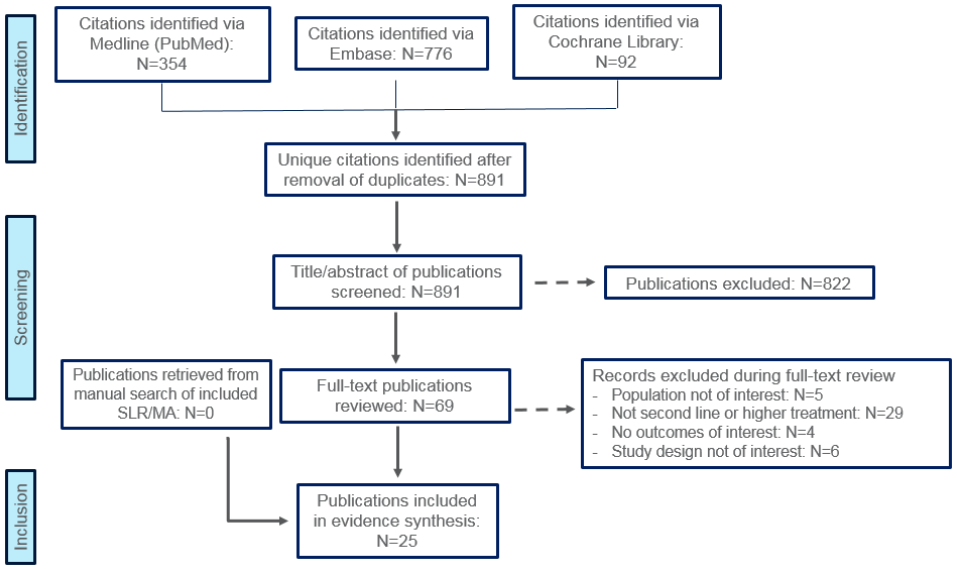


Figure 45 Literature selection and review process for economic costs and healthcare resource utilization in melanoma

Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.9.2 Systematic selection of studies

The inclusion and exclusion criteria for costs and resource use in the melanoma reviews are detailed using the PICOS framework in Table 122.

Table 122 Inclusion and exclusion criteria for costs and resource use reviews in melanoma

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic malignant melanoma ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than malignant melanoma • Patients with early-stage malignant melanoma

Interventions	Any/all/no interventions	None
Comparators	Any/all/no interventions	None
Outcomes	• Direct costs (e.g., drug costs/pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/ income for patients and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care, inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies (retrospective, prospective, cross-sectional, registries)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

Abbreviations: RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.9.3 Search strategy

Table 123, Table 124 and Table 125 present the search hits in Embase, Medline and Cochrane databases.

Table 123 Embase search strategy for economic costs and resource use in melanoma

#	Query	Results from 26 July 2018
1	('melanoma'/exp OR melanoma:ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	56,157
2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR fee/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR expenditures/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR 'health care utilization':ab,ti OR 'health care utilisation':ab,ti OR absenteeism/exp OR absenteeism:ab,ti OR presenteeism/exp OR	1.9m

	presenteeism:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR 'medical leave'/exp OR 'medical leave':ab,ti	
3	#1 AND #2	1,725
4	#3 AND Humans	1,538
5	#4 AND Limits: Articles, Reviews, Articles in Press	830
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	636
7	#6 AND Publication 2008-2018	421
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	355
9	#6 OR #7	776

Table 124 Medline search strategy for economic costs and resource use in melanoma

#	Query	Results from 26 July 2018
1	("Melanoma"[Mesh] OR melanoma[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	36,824
2	Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR "health care utilization"[tiab] OR "health care utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab]	1.4m
3	#1 AND #2	787
4	#3 NOT (animals[mh] NOT humans[mh])	745
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	688
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	547
7	#6 Publication date from 2008-2018	354

Table 125 Cochrane Library search strategy for economic costs and resource use in melanoma

#	Query	Results from 26 July 2018
1	MeSH descriptor: [Melanoma] explode all trees	1,719
2	melanoma:ti,ab	3,865
3	#1 OR #2	4,010
4	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087

5	#3 AND #4	2,129
6	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
7	MeSH descriptor: [Fees and Charges] explode all trees	519
8	MeSH descriptor: [Health Expenditures] explode all trees	354
9	MeSH descriptor: [Cost of Illness] explode all trees	1,390
10	MeSH descriptor: [Absenteeism] explode all trees	550
11	MeSH descriptor: [Presenteeism] explode all trees	15
12	MeSH descriptor: [Health care costs] explode all trees	7,652
13	cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or healthcare utilisation or health care utilization or health care utilisation or absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave:ti,ab,kw (Word variations have been searched)	146,423
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	146,500
15	#5 AND #14	107
16	#15 Publication Dates: 2008-2018	92

J.3.9.4 Quality assessment

N/A

J.3.9.5 Economic evaluations

Six economic models were identified, of which 5 reported on the cost-effectiveness of different interventions in patients with advanced melanoma. The PRISMA flow diagram for economic evaluations in melanoma is presented in Figure 46.

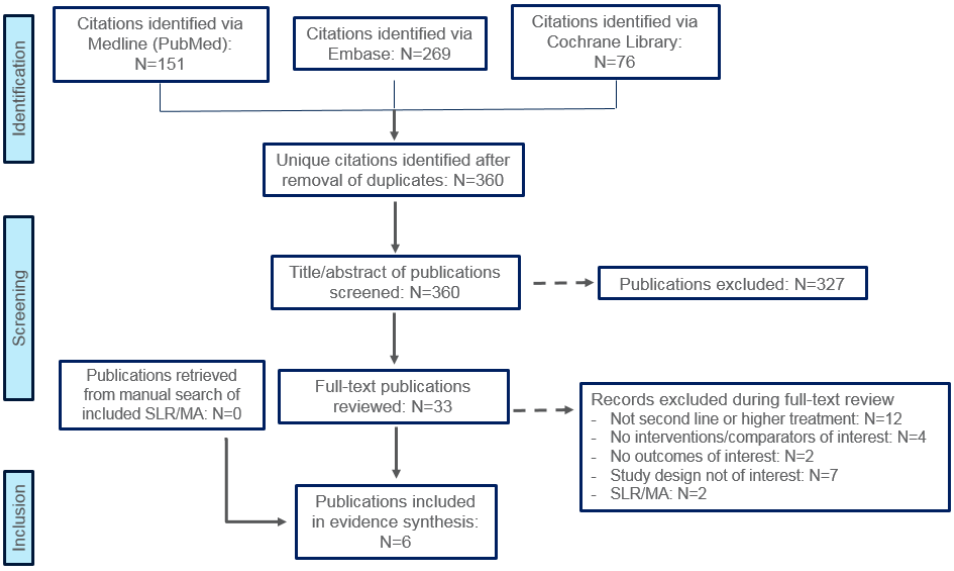


Figure 46 Literature selection and review process for economic evaluations in melanoma
Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.9.5.1 Systematic selection of studies

The inclusion and exclusion criteria for economic evaluations in the melanoma reviews are detailed using the PICOS framework in Table 126.

Table 126 Inclusion and exclusion criteria for economic evaluations in melanoma

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic malignant melanoma ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than malignant melanoma • Patients with early-stage malignant melanoma
Interventions	Monotherapies: • Pembrolizumab • Nivolumab • Ipilimumab • Dacarbazine • Larotrectinib Combination treatments: • Nivolumab + ipilimumab	Interventions other than those listed in inclusion column
Comparators	Monotherapies: • Pembrolizumab • Nivolumab • Ipilimumab	Comparators other than those listed in the inclusion column

	• Dacarbazine • Larotrectinib • Combination treatments: • Nivolumab + ipilimumab Placebo: • SoC/BSC (author-defined)	
Outcomes	• Overall costs (results of modelled analyses) • Quality-adjusted outcomes (e.g., quality-adjusted life-months, quality-adjusted life-years, quality-adjusted life expectancy, quality-time without symptoms or toxicity) • Disutility-adjusted outcomes (e.g., disutility-adjusted life years) • Incremental cost-effectiveness ratios • Treatment dominance	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • Health economic studies • Cost-effectiveness • Cost-benefit • Cost-utility • Cost-consequence • Cost-minimization • Budget impact	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials • Other study designs not specified in Inclusion column

Abbreviations: BSC, best supportive care; SLR, systematic literature review; SoC, standard of care.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.9.5.2 Search strategy

Table 127, Table 128 and Table 129 present the search hits in Embase, Medline and Cochrane databases.

Table 127 Embase search strategy for economic evaluations in melanoma

#	Query	Results from 27 July 2018
1	('melanoma'/exp OR melanoma:ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	56,170
2	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost	413k

	minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	
3	#1 AND #2	576
4	#3 AND Humans	532
5	#4 AND Limits: Articles, Reviews, Articles in Press	303
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	225
7	#6 AND Publication 2008-2018	154
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	115
9	#6 OR #7	269

Table 128 Medline search strategy for economic evaluations in melanoma

#	Query	Results from 27 July 2018
1	("Melanoma"[Mesh] OR melanoma[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	36,830
2	"Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab]	368k
3	#1 AND #2	280
4	#3 NOT (animals[mh] NOT humans[mh])	276
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	263
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	215
7	#6 Publication date from 2008-2018	151

Table 129 Cochrane Library search strategy for economic evaluations in melanoma

#	Query	Results from 27 July 2018
1	MeSH descriptor: [Melanoma] explode all trees	1,719
2	melanoma:ti,ab	3,865
3	#1 OR #2	4,010

4	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087
5	#3 AND #4	2,129
6	MeSH descriptor: [Models, Economic] explode all trees	2,060
7	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,942
8	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
9	MeSH descriptor: [Decision Theory] explode all trees	937
10	MeSH descriptor: [Decision Trees] explode all trees	921
11	MeSH descriptor: [Decision Analyses] explode all trees	3,796
12	Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR de-cision analys* OR decision analyt* OR decision model* :ti,ab,kw (Word variations have been searched)	59,093
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	65,575
14	#5 AND #13	83
15	#14 Publication Dates: 2008-2018	76

J.3.9.5.3 Quality assessment

Two of the 6 economic analyses were conference abstracts. In general, the economic analyses were considered of moderate to high quality, with very few questions being answered "not clear." The publications were assessed as being of high quality in study design and of variable quality in data collection and analysis/interpretation of results.

Table 130 Quality assessment of the economic evaluations: Melanoma

	Study design							Data collection													Analysis and interpretation of results														
Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Publication																																			
Guglieri-Lopez 2016	Y	Y	Y	Y				Y	Y	NA	Y	NA	NA	NA	NA	Y	Y	Y	N	NA	N	Y	NA	NA	NA	Y	Y	Y	Y	N	NA	Y	Y	Y	N
Marriott 2015b	Y	N	N	N				Y	N	NA	Y	Y	N		N	N	N	N	N	N		Y	N	NA	N	N	N	N	N	N	Y	N	Y	Y	N
Huo 2014	Y	Y	Y	Y	Y	Y	N	Y	Y	NA	Y	NA	NA	NA	NA	N	Y	Y	N	Y	N	Y	Y	NA	Y	Y	N	NA	NA	NA	Y	N	Y	Y	N
Barzey 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	Y	NA	NA	N	Y	Y	N	Y	Y	Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Alex-an-drescu 2009	Y	Y	NA		NA		NA		Y	Y	N	NA		NA		Y	NA		NA		Y	N	N	N	Y	N	Y	Y	Y	NA		NA		NA		Y	NA		NA		NA		NA		Y	Y	Y	Y
Zeich-ner 2016 b	Y	Y	Y		Y		N		Y	N	Y	NA		NA		Y	N		N		Y	N	N	N	Y	N	N	N	Y	N		NA		NA		N		N		N		N		Y	Y	Y	Y	N

Abbviation: N, no; NC, not clear; Y, yes; NA, not avalible.
Note: Used BMJ Study Checklist for Economic Studies (Drummond 1996)

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoint(s) of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed
8. The source(s) of effectiveness estimates used are stated
9. Details of the design and results of effectiveness study are given (if based on a single study)
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11. The primary outcome measure(s) for the economic evaluation are clearly stated
12. Methods to value health states and other benefits are stated
13. Details of the subjects from whom valuations were obtained are given
14. Productivity changes (if included) are reported separately
15. The relevance of productivity changes to the study question is discussed
16. Quantities of resources are reported separately from their unit costs
17. Methods for the estimation of quantities and unit costs are described
18. Currency and price data are recorded
19. Details of currency or price adjustments for inflation or currency conversion are given

20. Details of any model used are given
21. The choice of model used and the key parameters on which it is based are justified
22. Time horizon of costs and benefits is stated
23. The discount rate(s) is stated
24. The choice of rate(s) is justified
25. An explanation is given if costs or benefits are not discounted
26. Details of statistical tests and confidence intervals are given for stochastic data
27. The approach to sensitivity analysis is given
28. The choice of variables for sensitivity analysis is justified
29. The ranges over which the variables are varied are stated
30. Relevant alternatives are compared
31. Incremental analysis is reported
32. Major outcomes are presented in a disaggregated as well as aggregated form
33. The answer to the study question is given
34. Conclusions follow from the data reported
35. Conclusions are accompanied by the appropriate cave

J.3.10 Pancreatic cancer

J.3.10.1 Healthcare resource use and costs

Fourteen studies reported on costs and HCRU, of which 11 reported on resource use, 5 on direct costs, and none on indirect costs. Resource use varied widely across studies, suggesting that the specifics of the study design and population may contribute to determining specifics of hospitalizations. In the US and Japan, costs varied by disease stage and drug type, respectively. The PRISMA flow diagram for economic costs and healthcare resource in pancreatic cancer is shown in Figure 47.

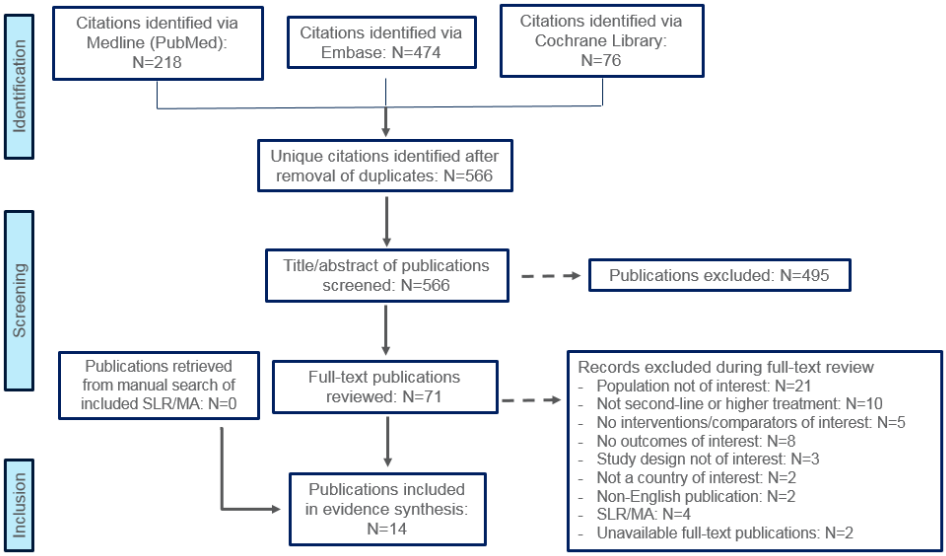


Figure 47 Literature selection and review process for economic costs and healthcare resource utilization in pancreatic cancer

Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.10.2 Systematic selection of studies

The inclusion and exclusion criteria for costs and resource use in the pancreatic cancer reviews are detailed using the PICOS framework in Table 131.

Table 131 Inclusion and exclusion criteria for costs and resource use reviews in pancreatic cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic pancreatic cancer ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than pancreatic cancer • Patients with early stage pancreatic cancer
Interventions	Any/all/no interventions	None

Comparators	Any/all/no interventions	None
Outcomes	• Direct costs (e.g., drug costs/pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/income for patients and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care, inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies (retrospective, prospective, cross-sectional, registries)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

Abbreviations: RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.10.3 Search strategy

Table 132, Table 133 and Table 134 present the search hits in Embase, Medline and Cochrane databases.

Table 132 Embase search strategy for economic costs and resource use in pancreatic cancer

#	Query	Results from 28 July 2018
1	('pancreas cancer'/exp OR 'pancreatic cancer':ab,ti OR 'pancreas cancer':ab,ti OR 'cancer of the pancreas':ab,ti OR 'pancreatic tumour':ab,ti OR 'pancreatic tumour':ab,ti OR 'pancreatic carcinoma':ab,ti OR 'pancreatic adenocarcinoma':ab,ti OR 'pancreatic exocrine cancer':ab,ti OR 'pancreatic endocrine cancer':ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	31,663
2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR fee/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR expenditures/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti	1.9m

	OR 'health care utilization':ab,ti OR 'health care utilisation':ab,ti OR absenteeism/exp OR absenteeism:ab,ti OR presenteeism/exp OR presenteeism:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR 'medical leave'/exp OR 'medical leave':ab,ti	
3	#1 AND #2	1,053
4	#3 AND Humans	956
5	#4 AND Limits: Articles, Reviews, Articles in Press	556
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	433
7	#6 AND Publication 2008-2018	285
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	189
9	#6 OR #7	474

Table 133 Medline search strategy for economic costs and resource use in pancreatic cancer

#	Query	Results from 28 July 2018
1	(pancreatic neoplasms[mesh] OR "pancreatic cancer"[tiab] OR "pancreas cancer"[tiab] OR "cancer of the pancreas"[tiab] OR "pancreatic tumour"[tiab] OR "pancreatic tumour"[tiab] OR "pancreatic carcinoma"[tiab] OR "pancreatic adenocarcinoma"[tiab] OR "pancreatic exocrine cancer"[tiab] OR "pancreatic endocrine cancer"[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	20,656
2	Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR "health care utilization"[tiab] OR "health care utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab]	1.4m
3	#1 AND #2	506
4	#3 NOT (animals[mh] NOT humans[mh])	500
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	460
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	370
7	#6 Publication date from 2008-2018	218

Table 134 Cochrane search strategy for economic costs and resource use in pancreatic cancer

#	Query	Results from 28 July 2018
1	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	1,686
2	(pancreatic cancer OR pancreas cancer OR cancer of the pancreas OR pancreatic tumour OR pancreatic tumour OR pancreatic carcinoma OR pancreatic adenocarcinoma OR pancreatic exocrine cancer OR pancreatic endocrine cancer)ti,ab,kw (Word variations have been searched)	4,315
3	#1 OR #2	4,545
4	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087
5	#3 AND #4	2,331
6	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
7	MeSH descriptor: [Fees and Charges] explode all trees	519
8	MeSH descriptor: [Health Expenditures] explode all trees	354
9	MeSH descriptor: [Cost of Illness] explode all trees	1,390
10	MeSH descriptor: [Absenteeism] explode all trees	550
11	MeSH descriptor: [Presenteeism] explode all trees	15
12	MeSH descriptor: [Health care costs] explode all trees	7,652
13	cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or healthcare utilisation or health care utilization or health care utilisation or absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave:ti,ab,kw (Word variations have been searched)	146,424
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	146,501
15	#5 AND #14	102
16	#15 Publication Dates: 2008-2018	76

J.3.10.4 Quality assessment

N/A

J.3.10.5 Economic evaluations

Five economic analyses were identified in the literature review including 2 CEAs from Japan and Italy and a budget impact model from the US. In Japan the most cost-effective treatment was S-1 followed by gemcitabine; nab-paclitaxel plus gemcitabine; and fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX). In Italy, nab-paclitaxel plus gemcitabine was found to have an ICER of €46,022 when compared to gemcitabine alone. A budget impact model developed from the US payer perspective reported nano liposomal

irinotecan plus 5-fluouracil plus leucovorin to have a total incremental annual cost of $74,629. The PRISMA flow diagram for economic evaluations in pancreatic cancer is presented in Figure 48.

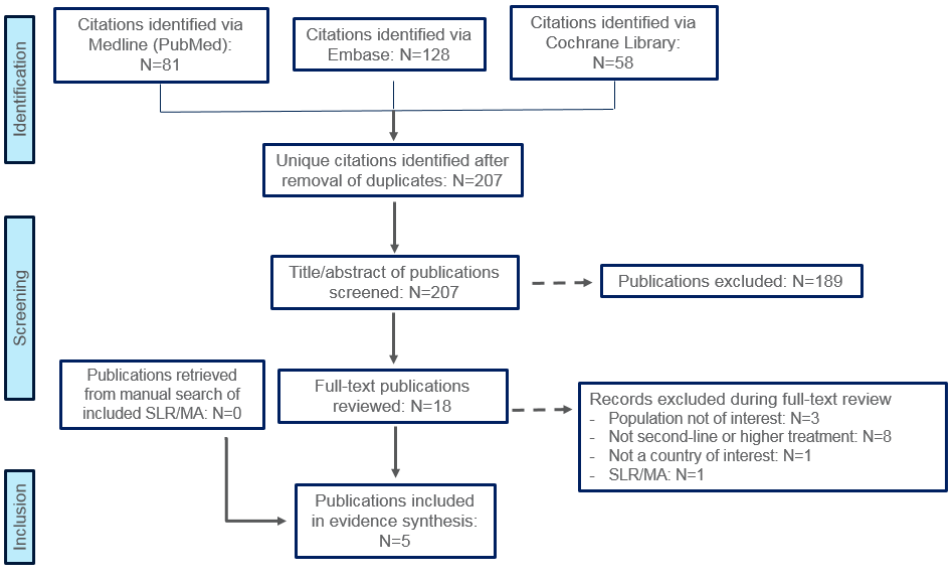


Figure 48 Literature selection and review process for economic evaluations in pancreatic cancer
Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.10.5.1 Systematic selection of studies

The inclusion and exclusion criteria for economic evaluations in the pancreatic cancer reviews are detailed using the PICOS framework in Table 135.

Table 135 Inclusion and exclusion criteria for economic evaluations in pancreatic cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with locally advanced or metastatic pancreatic cancer ○ If treated, treated with ≥2nd line therapy	• Healthy volunteers • Patients with diseases other than pancreatic cancer • Patients with early stage pancreatic cancer
Interventions	Monotherapies: • Gemcitabine • Fluorouracil • Larotrectinib Combination treatments: • Gemcitabine + erlotinib • Gemcitabine + nab-paclitaxel • Leucovorin + fluorouracil + liposomal irinotecan	Interventions other than those listed in inclusion column

	• Leucovorin + fluorouracil + oxaliplatin	
Comparators	Monotherapies: • Gemcitabine • Fluorouracil • Larotrectinib Combination treatments: • Gemcitabine + erlotinib • Gemcitabine + nab-paclitaxel • Leucovorin + fluorouracil + liposomal irinotecan • Leucovorin + fluorouracil + oxaliplatin Placebo: • SoC/BSC (author-defined)	Comparators other than those listed in the inclusion column
Outcomes	• Overall costs (results of modelled analyses) • Quality-adjusted outcomes (e.g., quality-adjusted life months], quality-adjusted life years, quality-adjusted life expectancy, quality time without symptoms or toxicity) • Disutility-adjusted outcomes (e.g., disutility-adjusted life-years) • ICERs • Treatment dominance	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • Health economic studies • Cost-effectiveness • Cost-benefit • Cost-utility • Cost-consequence • Cost-minimization • Budget impact	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials • Other study designs not specified in Inclusion column

Abbreviations: ICER, incremental cost-effectiveness; RCT, randomized controlled trial; SLR, systematic literature review; SoC, standard of care; BSC, best suportive care.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.10.5.2 Search strategy

Table 136, Table 137 and Table 138 present the search hits in Embase, Medline and Cochrane databases.

Table 136 Embase search strategy for economic evaluations in pancreatic cancer

#	Query	Results from 29 July 2018
1	('pancreas cancer'/exp OR 'pancreatic cancer':ab,ti OR 'pancreas cancer':ab,ti OR 'cancer of the pancreas':ab,ti OR 'pancreatic tumour':ab,ti OR 'pancreatic tumour':ab,ti OR 'pancreatic carcinoma':ab,ti OR 'pancreatic adenocarcinoma':ab,ti OR 'pancreatic exocrine cancer':ab,ti OR 'pancreatic endocrine cancer':ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	31,663
2	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	413k
3	#1 AND #2	342
4	#3 AND Humans	315
5	#4 AND Limits: Articles, Reviews, Articles in Press	212
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	142
7	#6 AND Publication 2008-2018	88
8	#4 AND Limit: Publication Type: Conference Abstracts; Limit: Publication Dates (2015-2018)	40
9	#6 OR #7	128

Table 137 Medline search strategy for economic evaluations in pancreatic cancer

#	Query	Results from 29 July 2018
1	(pancreatic neoplasms[mesh] OR "pancreatic cancer"[tiab] OR "pancreas cancer"[tiab] OR "cancer of the pancreas"[tiab] OR "pancreatic tumour"[tiab] OR "pancreatic tumour"[tiab] OR "pancreatic carcinoma"[tiab] OR "pancreatic adenocarcinoma"[tiab] OR "pancreatic exocrine cancer"[tiab] OR "pancreatic endocrine cancer"[tiab]) AND (advanced[tiab] OR inoperable[tiab] OR unresectable[tiab] OR metasta*[tiab])	20,658
2	"Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision	369k

	Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab]	
3	#1 AND #2	182
4	#3 NOT (animals[mh] NOT humans[mh])	182
5	#4 NOT (case reports[pt] OR editorial[pt] OR letter[pt] OR comment[pt])	178
6	#5 NOT (review[pt) NOT (systematic OR (meta AND analy*)))	141
8	#6 Publication date from 2008-2018	81

Table 138 Cochrane search strategy for economic evaluations in pancreatic cancer

#	Query	Results from 29 July 2018
1	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	1,686
2	(pancreatic cancer OR pancreas cancer OR cancer of the pancreas OR pancreatic tumour OR pancreatic tumour OR pancreatic carcinoma OR pancreatic adenocarcinoma OR pancreatic exocrine cancer OR pancreatic endocrine cancer)ti,ab,kw (Word variations have been searched)	4,315
3	#1 OR #2	4,545
4	advanced:ti,ab OR inoperable:ti,ab OR unresectable:ti,ab OR metasta*:ti,ab	60,087
5	#3 AND #4	2,331
6	MeSH descriptor: [Models, Economic] explode all trees	2,060
7	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,942
8	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
9	MeSH descriptor: [Decision Theory] explode all trees	937
10	MeSH descriptor: [Decision Trees] explode all trees	921
11	MeSH descriptor: [Decision Analyses] explode all trees	3,796
12	Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR decision analys* OR decision analyt* OR decision model* :ti,ab,kw (Word variations have been searched)	59,093
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	65,575
14	#5 AND #13	81
15	#14 Publication Dates: 2008-2018	58

J.3.10.5.3 Quality assessment

Three of the 5 economic analyses were conference abstracts, for which it can be difficult to assess quality due to lack of information (i.e., space limitations). In general, the economic analyses were considered of moderate to high quality, with a varying number of questions answered as "Not clear" (between 0 and 4 out of 35 questions, depending on publication, meaning that not enough information was available in the publication to answer the question). The publications were assessed as being of high quality in study design, generally of high quality in data collection, and of variable quality with the analysis and interpretation of results.

Table 139 Quality assessment of the economic evaluations: Pancreatic cancer

	Study design							Data collection													Analysis and interpretation of results																	
Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35		
Publication																																					
Kurimoto 2017	Y	Y	N	Y	Y	Y	N					NA	NA	NA	NA	NA	Y	Y	N	NA	NA	N	N	NA	NA	Y	NA	NA	NA	Y	Y	Y	Y	Y	N		
MacEwan 2017	Y	Y	NA	Y			N	Y	Y	NA	NA	NA	NA	NA	NA	NA	Y	Y	Y			Y	Y	Y	NA	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Becker 2016a	Y	Y	Y	N			Y	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y		N			N	NA	NA	NA	NA	N	NA	NA	NA	NA	N	Y	Y	N		

NA Laz-zaro 2016a	Y	N	Y	Y	Y	Y	Y	Y	N	NA	Y	Y	NA	NA	NA	NA	N	Y	N	Y	Y	Y	N	NA	NA	N	Y	N	N	Y	Y	Y	Y	Y	N
Chan 2015a	Y	Y	Y	Y	Y	Y	Y	Y	NA	N	Y	Y	NA	NA	NA	NA	N	Y	Y	Y	Y	Y	Y	N	NA	N	N	N	N	N	Y	N	Y	Y	N

Abbviation: N, no; NC, not clear; Y, yes; NA, not avalible.
Note: Used BMJ Study Checklist for Economic Studies (Drummond 1996)

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoint(s) of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed
8. The source(s) of effectiveness estimates used are stated
9. Details of the design and results of effectiveness study are given (if based on a single study)
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11. The primary outcome measure(s) for the economic evaluation are clearly stated
12. Methods to value health states and other benefits are stated
13. Details of the subjects from whom valuations were obtained are given
14. Productivity changes (if included) are reported separately
15. The relevance of productivity changes to the study question is discussed
16. Quantities of resources are reported separately from their unit costs
17. Methods for the estimation of quantities and unit costs are described
18. Currency and price data are recorded
19. Details of currency or price adjustments for inflation or currency conversion are given
20. Details of any model used are given
21. The choice of model used and the key parameters on which it is based are justified

22. Time horizon of costs and benefits is stated
23. The discount rate(s) is stated
24. The choice of rate(s) is justified
25. An explanation is given if costs or benefits are not discounted
26. Details of statistical tests and confidence intervals are given for stochastic data
27. The approach to sensitivity analysis is given
28. The choice of variables for sensitivity analysis is justified
29. The ranges over which the variables are varied are stated
30. Relevant alternatives are compared
31. Incremental analysis is reported
32. Major outcomes are presented in a disaggregated as well as aggregated form
33. The answer to the study question is given
34. Conclusions follow from the data reported
35. Conclusions are accompanied by the appropriate cave

J.3.11 Thyroid Cancer

J.3.11.1 Healthcare resource use and costs

HCRU and costs were evaluated in 18 studies in patients with advanced thyroid cancers. Reporting on utilization in the US, Europe, and Asia, outcomes focused on hospitalizations, costs, resource use associated with surgical interventions, and drug costs. The PRISMA flow diagram for economic costs and healthcare resource in thyroid cancer is shown in

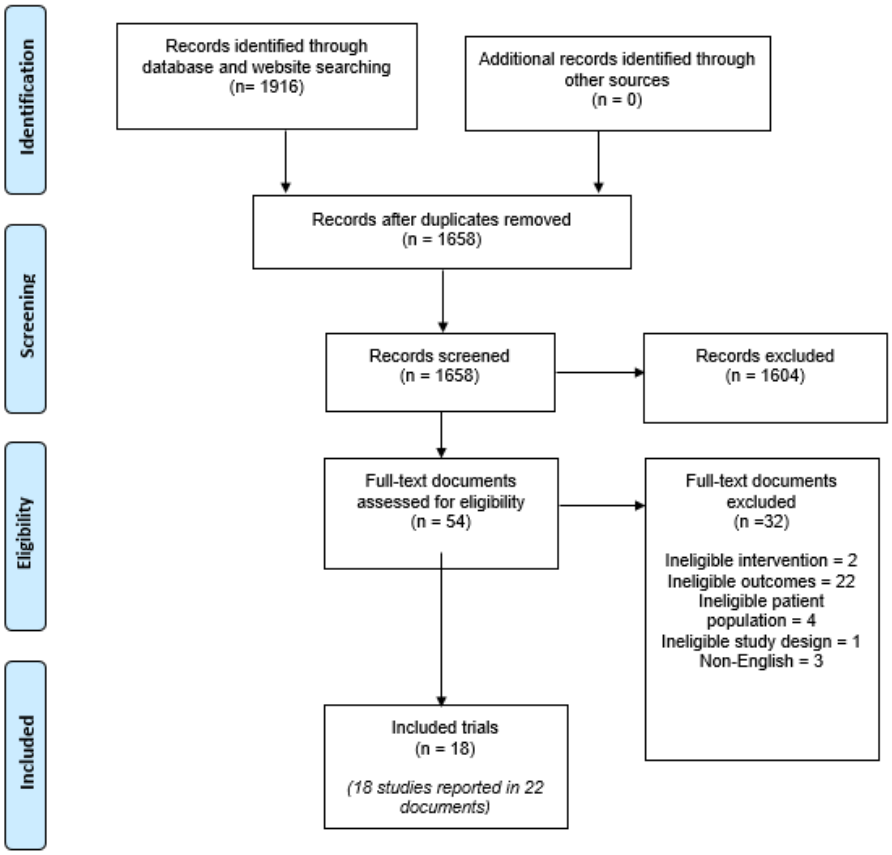


Figure 49.

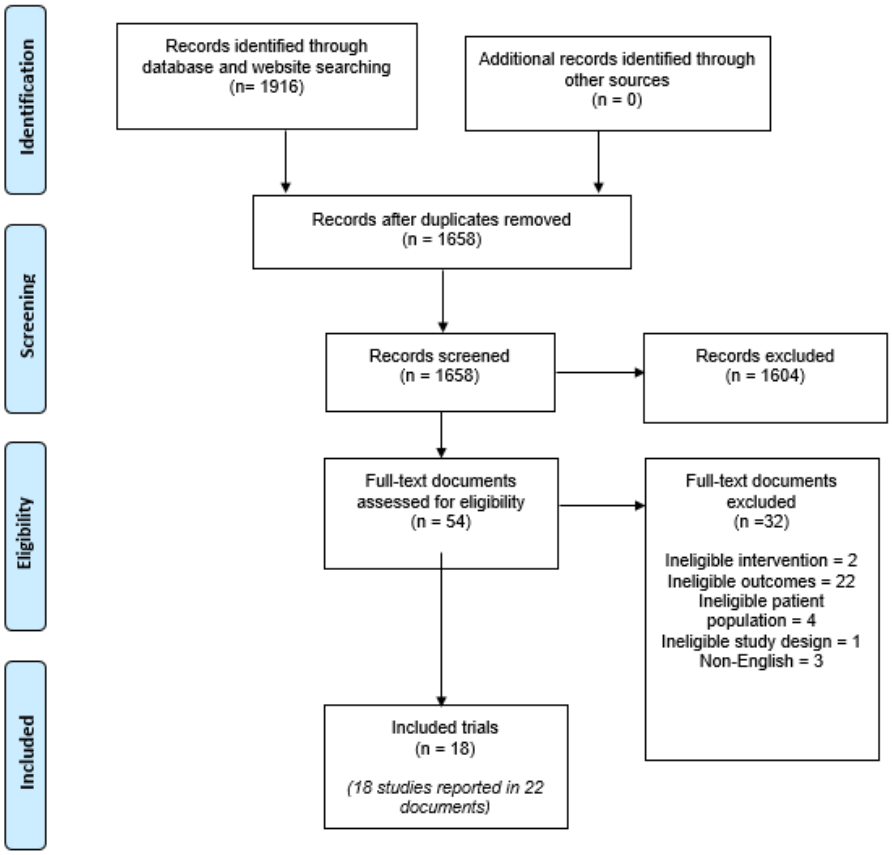


Figure 49 Literature selection and review process for economic costs and healthcare resource utilization in thyroid cancer

J.3.11.2 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and HCRU in the thyroid cancer reviews are detailed using the PICOS framework in Table 140.

Table 140 Inclusion and exclusion criteria for economic evaluations/resource use reviews in thyroid cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Thyroid cancers (anaplastic, follicular, and papillary)	None
Interventions	• For anaplastic thyroid cancer, cost-effectiveness, resource use, and cost outcomes for any interventions • For cost-effectiveness studies of follicular and papillary thyroid cancers, economic outcomes for larotrectinib, lenvatinib and sorafenib • For cost and resource use studies of follicular and papillary thyroid cancers, any interventions	None

Comparators	Any comparators	None
Outcomes	• Healthcare resource utilization • Direct costs[a] • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/ analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s]	• SLRs and meta-analyses[b] • RCTs • Non-randomized interventional studies • Observational studies; Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[c] • Animal studies • Letters • Editorials

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review.
[a] Direct costs to include costs related to monitoring, inpatient/outpatient visits, emergency visits, general practice visits, adverse events, death, and drugs.
[b] SLRs and meta-analyses will be included for hand-searching of reference lists.
[c] Conferences identified in Table 99 will be included for evaluation.

J.3.11.3 Search strategy

Table 141, Table 142 and Table 143 present the search hits in Embase, Medline and Cochrane databases.

Table 141 Embase search strategy for HRQoL/PROs/utilities and economic evaluations/resource use in thyroid cancer

#	Query	Results from 25 July 2018
1	anaplastic thyroid carcinoma/	247
2	anaplastic carcinoma/ and thyroid gland/	214
3	((anaplastic or undifferentiated) and (thyroid$ cancer$ or thyroid$ neoplasm$ or thyroid$ neoplasia$ or thyroid$ carcinoma$ or thyroid$ adenocarcinoma$ or thyroid$ tumour$ or thyroid$ tumour$ or thyroid$ malignan$ or thyroid$ gland cancer$ or thyroid$ gland neoplasm$ or thyroid$ gland neoplasia$ or thyroid$ gland carcinoma$ or thyroid$ gland adenocarcinoma$ or thyroid$ gland tumour$ or thyroid$ gland tumour$ or thyroid$ gland malignan$)).ti,ab,kw.	4,829
4	or/1-3	4,930
5	thyroid follicular carcinoma/	4,447
6	Hurthle cell carcinoma/	68

7	(follicle$ cancer$ or follicle$ neoplasm$ or follicle$ neoplasia$ or follicle$ carcinoma$ or follicle$ adenocarcinoma$ or follicle$ tumour$ or follicle$ tumour$ or follicle$ malignan$ or follicular cancer$ or follicular neoplasm$ or follicular neoplasia$ or follicular carcinoma$ or follicular adenocarcinoma$ or follicular tumour$ or follicular tumour$ or follicular malignan$).ti,ab,kw.	5,842
8	(Hurthle$ cancer$ or Hurthle$ neoplasm$ or Hurthle$ neoplasia$ or Hurthle$ carcinoma$ or Hurthle$ adenocarcinoma$ or Hurthle$ tumour$ or Hurthle$ tumour$ or Hurthle$ malignan$ or Huerthle$ cancer$ or Huerthle$ neoplasm$ or Huerthle$ neoplasia$ or Huerthle$ carcinoma$ or Huerthle$ adenocarcinoma$ or Huerthle$ tumour$ or Huerthle$ tumour$ or Huerthle$ malignan$ or Oxyphilic cancer$ or Oxyphilic neoplasm$ or Oxyphilic neoplasia$ or Oxyphilic carcinoma$ or Oxyphilic adenocarcinoma$ or Oxyphilic tumour$ or Oxyphilic tumour$ or Oxyphilic malignan$ or Hurthle$ cell cancer$ or Hurthle$ cell neoplasm$ or Hurthle$ cell neoplasia$ or Hurthle$ cell carcinoma$ or Hurthle$ cell adenocarcinoma$ or Hurthle$ cell tumour$ or Hurthle$ cell tumour$ or Hurthle$ cell malignan$ or Huerthle$ cell cancer$ or Huerthle$ cell neoplasm$ or Huerthle$ cell neoplasia$ or Huerthle$ cell carcinoma$ or Huerthle$ cell adenocarcinoma$ or Huerthle$ cell tumour$ or Huerthle$ cell tumour$ or Huerthle$ cell malignan$ or Oxyphilic cell cancer$ or Oxyphilic cell neoplasm$ or Oxyphilic cell neoplasia$ or Oxyphilic cell carcinoma$ or Oxyphilic cell adenocarcinoma$ or Oxyphilic cell tumour$ or Oxyphilic cell tumour$ or Oxyphilic cell malignan$).ti,ab,kw.	1,265
9	or/5-8	9,272
10	thyroid papillary carcinoma/	9,198
11	papillary carcinoma/ and thyroid gland/	1,199
12	(papilla$ cancer$ or papilla$ neoplasm$ or papilla$ neoplasia$ or papilla$ carcinoma$ or papilla$ adenocarcinoma$ or papilla$ tumour$ or papilla$ tumour$ or papilla$ malignan$).ti,ab,kw.	14,422
13	or/10-12	21,163
14	(utilit$ or disutilit$ or eq 5d or eq5d or sf 36 or sf36 or sf 12 or sf12 or hui or fact or qlq c30).ti,ab. or eq-5d/ or exp short form 36/ or eortc qlq c30/	575,616
15	(4 or 9 or 13) and 14	944
16	exp cost/	322,070
17	exp cost effectiveness analysis/	133,751
18	(cost$ or fee$ or budget$ or expenditure$).ti,ab.	1,327,403
19	exp cost of illness/	17,595
20	cost of illness.ti,ab.	2,166
21	("resource use" or resource utilization or resource utilisation).ti,ab.	23,832
22	(economic$ or pharmacoeconomic$).ti,ab.	289,491
23	exp health care utilization/	60,055
24	(healthcare utilization or healthcare utilisation).ti,ab.	5,926

25	(absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day).ti,ab.	139,067
26	exp health care cost/	264,507
27	(hospitalization or hospitalisation).ti,ab.	187,968
28	or/16-27	1,999,391
29	(4 or 9 or 13) and 28	729
30	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5,914,489
31	editorial.pt. or case report.ti.	832,457
32	15 not (30 or 31)	911
33	remove duplicates from 32	886*
34	29 not (30 or 31)	694
35	remove duplicates from 34	678**

* Results downloaded for HRQoL/PROs/utilities
** Results downloaded for economics/resource use

Table 142 Medline search strategy for HRQoL/PROs/utilities and economic evaluations/resource use in pancreatic cancer

#	Query	Results from 27 July 2018
1	Search "Thyroid Carcinoma, Anaplastic" [mh:noexp]	461
2	Search Carcinoma [mh:noexp] AND "Thyroid Gland" [mh:noexp] AND (anaplastic[tiab] OR undifferentiated[tiab])	191
3	Search ((anaplastic[tiab] OR undifferentiated[tiab]) AND thyroid*[tiab] AND (cancer*[tiab] OR neoplasm*[tiab] OR neoplasia*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR malignan*[tiab]))	4,021
4	Search (#1 OR #2 OR #3)	4,047
5	Search "Adenocarcinoma, Follicular" [mh:noexp]	3,468
6	Search "Adenoma, Oxyphilic" [mh:noexp]	1,910
7	Search ((follicle*[tiab] OR follicular[tiab]) AND (cancer*[tiab] OR neoplasm*[tiab] OR neoplasia*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR malignan*[tiab]))	23,876
8	Search ((hurthle*[tiab] OR huerthle*[tiab] OR oxyphilic[tiab]) AND (cancer*[tiab] OR neoplasm*[tiab] OR neoplasia*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR malignan*[tiab]))	1,556
9	Search (#5 OR #6 OR #7 OR #8)	26,908
10	Search "Carcinoma, Papillary" [mh:noexp]	17,578
11	Search (papilla*[tiab] AND (cancer*[tiab] OR neoplasm*[tiab] OR neoplasia*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR malignan*[tiab]))	36,587

12	Search (#10 OR #11)	42,518
13	Search utilit* [tiab] OR disutilit* [tiab] OR "eq 5d" [tiab] OR eq5d [tiab] OR "sf 36" [tiab] OR sf36 [tiab] OR "sf 12" OR sf12 [tiab] OR hui [tiab] OR fact [tiab] OR "qlq c30" [tiab] OR quality-adjusted life years [mesh: no-exp] OR quality of life [mesh: noexp]	559,813
14	Search ((#4 OR #9 OR #12) AND #13)	1,668
15	Search "costs and cost analysis" [mesh]	215,922
16	Search Cost [tiab] OR costs [tiab] OR costing [tiab] OR budget* [tiab] OR expenditure* [tiab]	517,710
17	Search "resource use" [tiab] OR "resource utilisation" [tiab] OR "resource utilisation" [tiab]	7,961
18	Search Economic* [tiab] OR pharmacoeconomic* [tiab]	244,133
19	Search "healthcare utilization" [tiab] OR "healthcare utilisation" [tiab]	3,504
20	Search (absenteeism [tiab] OR presenteeism [tiab] OR productivity [tiab] OR "work loss" [tiab] OR employment [tiab] OR retirement [tiab] OR "sick leave" [tiab] or "sick day" [tiab])	116,936
21	Search (Hospitalization [tiab] OR hospitalisation [tiab])	115,914
22	Search (#15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21)	976,031
23	Search ((#4 OR #9 OR #12) AND #22)	696
24	Search (animals[mh] NOT humans[mh:noexp])	4,468,364
25	Search editorial[pt] OR case report[ti]	668,842
26	Search (#14 NOT (#24 OR #25))	1,582 *
27	Search (#23 NOT (#24 OR #25))	666 **

* Results downloaded for HRQoL/PRO/Utilities
** Results downloaded for economic evaluations / resource use

Table 143 Cochrane Library search strategy for HRQoL/PROs/utilities and economic evaluations/resource use in pancreatic cancer

#	Query	Results from 25 July 2018
1	[mh ^"Thyroid Carcinoma, Anaplastic"]	6
2	[mh ^Carcinoma] and [mh ^"Thyroid Gland"] and (anaplastic or undifferentiated)	0
3	((anaplastic or undifferentiated) and (thyroid* next cancer* or thyroid* next neoplasm* or thyroid* next neoplasia* or thyroid* next carcinoma* or thyroid* next adenocarcinoma* or thyroid* next tumour* or thyroid* next tumour* or thyroid* next malignan* or thyroid* next gland next cancer* or thyroid* next gland next neoplasm* or thyroid* next gland next neoplasia* or thyroid* next gland next carcinoma* or thyroid* next gland next adenocarcinoma* or thyroid* next gland next tumour* or thyroid* next gland next tumour* or thyroid* next gland next malignan*))	41
4	#1 or #2 or #3	41

5	[mh ^"Adenocarcinoma, Follicular"]	42
6	[mh ^"Adenoma, Oxyphilic"]	7
7	(follicle* next cancer* or follicle* next neoplasm* or follicle* next neoplasia* or follicle* next carcinoma* or follicle* next adenocarcinoma* or follicle* next tumour* or follicle* next tumour* or follicle* next malignan* or follicular next cancer* or follicular next neoplasm* or follicular next neoplasia* or follicular next carcinoma* or follicular next adenocarcinoma* or follicular next tumour* or follicular next tumour* or follicular next malignan*)	82
8	(Hurthle* next cancer* or Hurthle* next neoplasm* or Hurthle* next neoplasia* or Hurthle* next carcinoma* or Hurthle* next adenocarcinoma* or Hurthle* next tumour* or Hurthle* next tumour* or Hurthle* next malignan* or Huerthle* next cancer* or Huerthle* next neoplasm* or Huerthle* next neoplasia* or Huerthle* next carcinoma* or Huerthle* next adenocarcinoma* or Huerthle* next tumour* or Huerthle* next tumour* or Huerthle* next malignan* or Oxyphilic next cancer* or Oxyphilic next neoplasm* or Oxyphilic next neoplasia* or Oxyphilic next carcinoma* or Oxyphilic next adenocarcinoma* or Oxyphilic next tumour* or Oxyphilic next tumour* or Oxyphilic next malignan* or Hurthle* next cell next cancer* or Hurthle* next cell next neoplasm* or Hurthle* next cell next neoplasia* or Hurthle* next cell next carcinoma* or Hurthle* next cell next adenocarcinoma* or Hurthle* next cell next tumour* or Hurthle* next cell next tumour* or Hurthle* next cell next malignan* or Huerthle* next cell next cancer* or Huerthle* next cell next neoplasm* or Huerthle* next cell next neoplasia* or Huerthle* next cell next carcinoma* or Huerthle* next cell next adenocarcinoma* or Huerthle* next cell next tumour* or Huerthle* next cell next tumour* or Huerthle* next cell next malignan* or Oxyphilic next cell next cancer* or Oxyphilic next cell next neoplasm* or Oxyphilic next cell next neoplasia* or Oxyphilic next cell next carcinoma* or Oxyphilic next cell next adenocarcinoma* or Oxyphilic next cell next tumour* or Oxyphilic next cell next tumour* or Oxyphilic next cell next malignan*)	16
9	#5 or #6 or #7 or #8	120
10	[mh ^"Carcinoma, Papillary"]	146
11	(papilla* next cancer* or papilla* next neoplasm* or papilla* next neoplasia* or papilla* next carcinoma* or papilla* next adenocarcinoma* or papilla* next tumour* or papilla* next tumour* or papilla* next malignan*)	271
12	#10 or #11	394
13	#4 or #9 or #12	480
14	#13 in Technology Assessments	2 *
15	#13 in Economic Evaluations	14 **
16	#13 in Methods Studies	0
17	#13 in Other Reviews	23 ***
18	#13 in Trials	415 ****
19	#13 in Cochrane Reviews (Reviews and Protocols)	26*****

* Results from HTA database. 2 records were for HRQoL/PRO/Utilities and 2 for Economics / Resource Use.
** Results from NHS EED. 14 records were for HRQoL/PRO/Utilities and 14 for Economics / Resource Use.
*** Results from DARE. 23 records were for HRQoL/PRO/Utilities and 23 for Economics / Resource Use.
**** Results from CENTRAL. 415 records were for HRQoL/PRO/Utilities and 415 for Economics / Resource Use.
***** Results from CDSR. 26 records were for HRQoL/PRO/Utilities and 26 for Economics / Resource Use.

J.3.11.4 Quality assessment

N/A

J.3.11.5 Economic evaluations

Economic evaluations were identified in 6 HTAs of Lenvatinib or Sorafenib in DTC and papillary thyroid cancer. From the perspectives of the UK, Scotland and Wales, and Canada, both interventions represented cost-effective interventions for the identified patient populations. The PRISMA flow diagram for economic evaluations in thyroid cancer is presented in Figure 50.

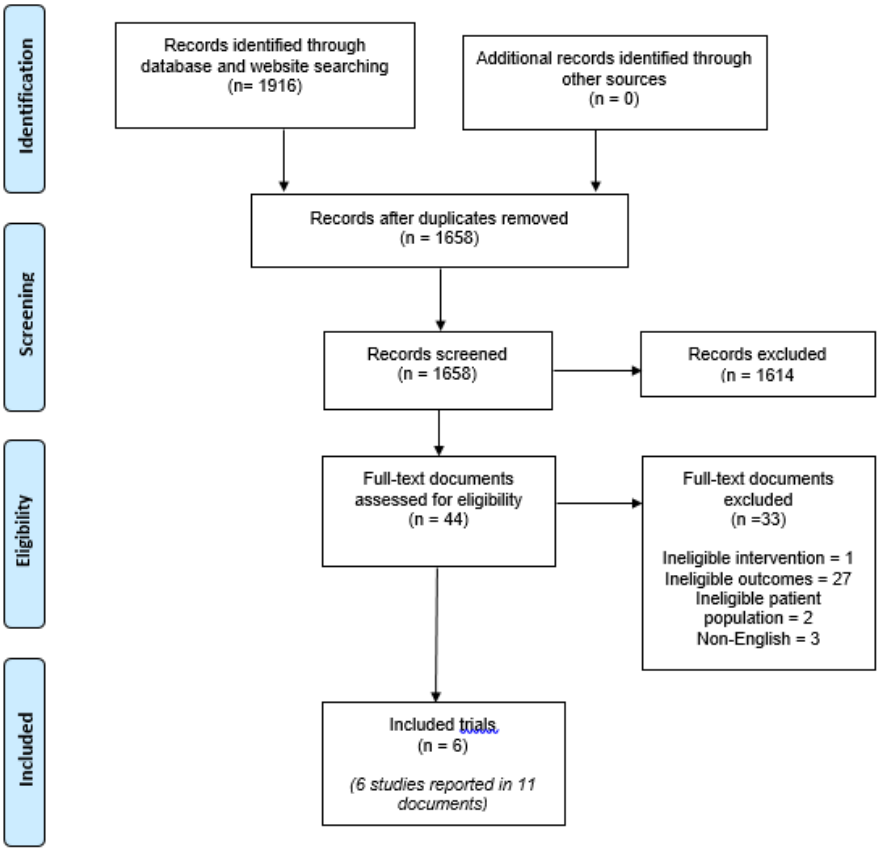


Figure 50 Literature selection and review process for economic evaluations in thyroid cancer

J.3.11.5.1 Systematic selection of studies

See Table 140

J.3.11.5.2 Search strategy

See Table 141, Table 142 and Table 143.

J.3.11.5.3 Quality assessment

N/A

J.3.12 Soft tissue sarcomas: Infantile fibrosarcoma, infantile myofibromatosis, myopericytoma

No economic burden literature (evaluating HCRU and costs) was identified on any sarcomas of interest and no economic analyses were identified reporting on STSs.

J.3.12.1 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and HCRU in the reviews of infantile fibrosarcoma, infantile myofibromatosis and myopericytoma are detailed using the PICOS framework in Table 154.

Table 144 Inclusion and exclusion criteria for economic evaluations/resource use reviews in soft tissue sarcoma: infantile fibrosarcoma, infantile myofibromatosis and myopericytoma

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Infantile fibrosarcoma • Infantile myofibromatosis • Myopericytoma	None
Interventions	No restrictions (any/all)	None
Comparators	No restrictions (any/all)	None
Outcomes	• Healthcare resource utilization • Direct costs (to include costs related to monitoring, inpatient/ outpatient visits, emergency visits, general practice visits, adverse events, death, drugs) • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies • Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b]

- Animal studies
- Letters
- Editorials

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.12.2 Search strategy: Infantile fibrosarcoma

Table 145, Table 146 and Table 147 present the search results from Embase, Medline, and Cochrane databases within the SLR clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile fibrosarcoma.

Table 145 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile fibrosarcoma

#	Query	Results from 18 May 2018
1	infantile fibrosarcoma'/exp OR 'infantile fibrosarcoma':ab,ti OR 'congenital fibrosarcoma'/exp OR 'congenital fibrosarcoma':ab,ti	465
2	• Publication types: Articles, Conference Abstracts, Reviews, Articles in Press • Humans	375
3	#2 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	331

Table 146 Medline Search Strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile fibrosarcoma

#	Query	Results from 18 May 2018
1	"infantile fibrosarcoma"[tiab] OR "congenital fibrosarcoma"[tiab]	347
2	#1 NOT (animals [MH] NOT humans [MH])	344
3	#2 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	141
4	#3 NOT (review[pt] NOT (systematic OR meta-analysis))	116

Table 147 Cochrane Library Search Strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile fibrosarcoma

#	Query	Results from 18 May 2018
1	"infantile fibrosarcoma" or "congenital fibrosarcoma":ti,ab	2

J.3.12.3 Search strategy: Infantile Myofibromatosis

Table 148, Table 149 and Table 150 present the search results from Embase, Medline, and Cochrane databases within the SLR for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile myofibromatosis.

Table 148 Embase Search Strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile myofibromatosis

#	Query	Results from 18 May 2018
1	infantile myofibromatosis'/exp OR 'infantile myofibromatosis':ab,ti OR 'infantile myofibroma'/exp OR 'infantile myofibroma':ab,ti OR 'congenital myofibromatosis' OR 'congenital myofibromatosis':ab,ti	439
2	Publication types: Articles, Conference Abstracts, Reviews, Articles in Press AND Humans	386
3	#2 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	356

Table 149 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile myofibromatosis

#	Query	Results from 18 May 2018
1	("Myofibromatosis"[Mesh] AND (infantile OR congenital)) OR "infantile myofibromatosis"[tiab] OR "infantile myofibroma"[tiab] OR "congenital myofibromatosis"[tiab]	384
2	#1 NOT (animals [MH] NOT humans [MH])	384
3	#2 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	102
4	#3 NOT (review[pt] NOT (systematic OR meta-analysis))	86

Table 150 Cochrane Library search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in infantile myofibromatosis

#	Query	Results from 18 May 2018
1	"Myofibromatosis"[Mesh]	1
2	infantile OR congenital	9,000
3	#1 AND #2	0
4	"infantile myofibromatosis" OR "infantile myofibroma" OR "congenital myofibromatosis":ab,ti	0
5	#3 OR #4	0

J.3.12.4 Search strategy: Myopericytoma

Table 151, Table 152 and Table 153 present the search results from Embase, Medline, and Cochrane databases within the SLR clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in myopericytoma.

Table 151 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in myopericytoma

#	Query	Results from 18 May 2018
1	myopericytoma'/exp OR myopericytoma:ab,ti OR 'glomangiopericytoma'/exp OR glomangiopericytoma:ab,ti	246
2	Publication types: Articles, Conference Abstracts, Reviews, Articles in Press AND Humans	208
3	#2 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	185

Table 152 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in myopericytoma

#	Query	Results from 18 May 2018
1	"myopericytoma"[tiab] OR "glomangiopericytoma"[tiab]	187
2	#1 NOT (animals [MH] NOT humans [MH])	185
3	#2 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	89
4	#3 NOT (review[pt] NOT (systematic OR meta-analysis))	77

Table 153 Cochrane Library search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in myopericytoma

#	Query	Results from 18 May 2018
1	"myopericytoma" OR "glomangiopericytoma":ab,ti	0

J.3.12.5 Quality assessment

N/A

J.3.13 Soft tissue sarcomas: Spindle cell sarcoma, inflammatory myofibroblastic tumour, and peripheral nerve sheath tumour

No economic burden literature (evaluating HCRU and costs) was identified on any sarcomas of interest and no economic analyses were identified reporting on STSs.

J.3.13.1 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and healthcare resource use in the reviews of Spindle cell sarcoma, inflammatory myofibroblastic tumour and peripheral nerve sheath tumour are detailed using the PICOS framework in Table 154.

Table 154 Inclusion and exclusion criteria for economic evaluations/resource use reviews in soft tissue sarcoma: Spindle cell sarcoma, inflammatory myofibroblastic tumour and peripheral nerve sheath tumour

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Spindle cell sarcoma • Inflammatory myofibroblastic tumour • Peripheral nerve sheath tumour	None
Interventions	No restrictions (any/all)	None
Comparators	No restrictions (any/all)	None
Outcomes	• Healthcare resource utilization • Direct costs (to include costs related to monitoring, inpatient/outpatient visits, emergency visits, general practice visits, adverse events, death, and drugs) • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/ analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies • Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.13.2 Search strategy: Spindle cell sarcoma

Table 155, Table 156 and Table 157 present the search results from Embase, Medline, and Cochrane databases within the SLR for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in spindle cell sarcoma.

Table 155 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in spindle cell sarcoma

#	Query	Results from 31 May 2018
1	spindle cell sarcoma'/exp OR 'spindle cell sarcoma':ab,ti	1,437

2	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR 'adverse event':ab,ti OR tolerability:ab,ti OR 'adverse effect':ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	3.4m
3	#1 AND #2	113
4	quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti OR 'well being':ab,ti OR 'health status':ab,ti OR 'health state':ab,ti OR adl:ab,ti OR 'activities of daily living':ab,ti OR 'patient burden' OR 'patient-reported outcome'/exp OR pro:ab,ti OR 'patient preference':ab,ti OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	1.8m
5	#1 AND #4	70
6	cost'/exp OR 'cost effectiveness analysis'/exp OR cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	2m
7	#1 AND #6	15
8	#3 OR #5 OR #7	178
9	#8 AND Limit: Humans	158
10	#9 AND Limit: Articles, Reviews, Articles in Press	113
11	#10 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	106
12	Conference abstracts	38
13	Total	144

Table 156 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in spindle cell sarcoma

#	Query	Results from 31 May 2018
1	"spindle cell sarcoma"[tiab]	583
2	efficacy[tiab] OR safety[tiab] OR effectiveness[tiab] OR "adverse event"[tiab] OR tolerability[tiab] OR "adverse effect"[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR controlled[tiab] OR blind*[tiab] OR trial[tiab] OR allocat*[tiab] OR assign*[tiab]	2.5m
3	#1 AND #2	25
4	"Quality of Life"[Mesh] OR "quality of life"[tiab] OR qol[tiab] OR "well being"[tiab] OR "health status"[tiab] OR "health state"[tiab] OR adl[tiab] OR "activities of daily living"[tiab] OR "patient burden" OR "Patient-Reported Outcome Measures"[Mesh] OR pro[tiab] OR "patient preference"[tiab] OR psychosocial[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR	1.2m

	disabilit*[tiab] OR ((patient[tiab] OR caregiver[tiab]) AND (burden[tiab] OR preference[tiab] OR satisfaction[tiab] OR function*[tiab])) OR (symptom*[tiab] AND burden[tiab])	
5	#1 AND #4	22
6	"Costs and Cost Analysis"[Mesh] OR cost*[tiab] OR fee*[tiab] OR budget*[tiab] OR expenditure*[tiab] OR "cost of illness"[tiab] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "Patient Acceptance of Health Care"[Mesh] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR absenteeism[tiab] OR presenteeism[tiab] OR productivity[tiab] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR hospitalization*[tiab] OR hospitalisation*[tiab]	1.5m
7	#1 AND #6	1
8	#3 OR #5 OR #7	46
9	#8 NOT (animals [MH] NOT humans [MH])	45
10	#9 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	37
11	#10 NOT (review[pt] NOT (systematic OR meta-analysis))	36

Table 157 Cochrane Library search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in spindle cell sarcoma

#	Query	Results from 31 May 2018
1	"spindle cell sarcoma":ab,ti	3
2	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR "adverse event":ab,ti OR tolerability:ab,ti OR "adverse effect":ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	892,826
3	#1 AND #2	2
4	"Quality of Life"[Mesh]	22,088
5	"Patient-Reported Outcome Measures"[Mesh]	162
6	"quality of life":ab,ti OR qol:ab,ti OR "well being":ab,ti OR "health status":ab,ti OR "health state":ab,ti OR adl:ab,ti OR "activities of daily living":ab,ti OR "patient burden" OR pro:ab,ti OR "patient preference":ab,ti OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	139,298
7	#4 OR #5 OR #6	143,752
8	#1 AND #7	0
9	"Costs and Cost Analysis"[Mesh]	26,088
10	"Patient Acceptance of Health Care"[Mesh]	14,086

11	cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR "cost of illness":ab,ti OR "resource use":ab,ti OR "resource utilization":ab,ti OR "resource utilisation":ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR "healthcare utilization":ab,ti OR "healthcare utilisation":ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR "work loss":ab,ti OR employment:ab,ti OR retirement:ab,ti OR "sick leave":ab,ti OR "sick day":ab,ti OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	115,943
12	#9 OR #10 OR #11	132,291
13	#1 AND #12	0
14	#3 OR #8 OR #13	2

J.3.13.3 Search strategy: Inflammatory myofibroblastic tumour

Table 158, Table 159 and Table 160 present the search results from Embase, Medline, and Cochrane databases within the SLR clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in inflammatory myofibroblastic tumour.

Table 158 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in inflammatory myofibroblastic tumour

#	Query	Results from 31 May 2018
1	inflammatory myofibroblastic tumour'/exp OR 'inflammatory myofibroblastic':ab,ti	3,837
2	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR 'adverse event':ab,ti OR tolerability:ab,ti OR 'adverse effect':ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	3.4m
3	#1 AND #2	172
4	quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti OR 'well being':ab,ti OR 'health status':ab,ti OR 'health state':ab,ti OR adl:ab,ti OR 'activities of daily living':ab,ti OR 'patient burden' OR 'patient-reported outcome'/exp OR pro:ab,ti OR 'patient preference':ab,ti OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	1.8m
5	#1 AND #4	127
6	'cost'/exp OR 'cost effectiveness analysis'/exp OR cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	2m

7	#1 AND #6	49
8	#3 OR #5 OR #7	322
9	#8 AND Limit: Humans	301
10	#9 AND Limit: Articles, Reviews, Articles in Press	182
11	#10 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	152
12	Conference abstracts	107
13	Total	259

Table 159 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in inflammatory myofibroblastic tumour

#	Query	Results from 31 May 2018
1	"inflammatory myofibroblastic"[tiab]	1,401
2	efficacy[tiab] OR safety[tiab] OR effectiveness[tiab] OR "adverse event"[tiab] OR tolerability[tiab] OR "adverse effect"[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR controlled[tiab] OR blind*[tiab] OR trial[tiab] OR allocat*[tiab] OR assign*[tiab]	2.5m
3	#1 AND #2	47
4	"Quality of Life"[Mesh] OR "quality of life"[tiab] OR qol[tiab] OR "well being"[tiab] OR "health status"[tiab] OR "health state"[tiab] OR adl[tiab] OR "activities of daily living"[tiab] OR "patient burden" OR "Patient-Reported Outcome Measures"[Mesh] OR pro[tiab] OR "patient preference"[tiab] OR psychosocial[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR disabilit*[tiab] OR ((patient[tiab] OR caregiver[tiab]) AND (burden[tiab] OR preference[tiab] OR satisfaction[tiab] OR function*[tiab])) OR (symptom*[tiab] AND burden[tiab])	1.2m
5	#1 AND #4	28
6	"Costs and Cost Analysis"[Mesh] OR cost*[tiab] OR fee*[tiab] OR budget*[tiab] OR expenditure*[tiab] OR "cost of illness"[tiab] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "Patient Acceptance of Health Care"[Mesh] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR absenteeism[tiab] OR presenteeism[tiab] OR productivity[tiab] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR hospitalization*[tiab] OR hospitalisation*[tiab]	1.5m
7	#1 AND #6	9
8	#3 OR #5 OR #7	80
9	#8 NOT (animals [MH] NOT humans [MH])	78
10	#9 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	46
11	#10 NOT (review[pt] NOT (systematic OR meta-analysis))	37

Table 160 Cochrane Library search strategy clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in inflammatory myofibroblastic tumour

#	Query	Results from 31 May 2018
1	"inflammatory myofibroblastic":ab,ti	7
2	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR "adverse event":ab,ti OR tolerability:ab,ti OR "adverse effect":ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	892,826
3	#1 AND #2	5
4	"Quality of Life"[Mesh]	22,088
5	"Patient-Reported Outcome Measures"[Mesh]	162
6	"quality of life":ab,ti OR qol:ab,ti OR "well being":ab,ti OR "health status":ab,ti OR "health state":ab,ti OR adl:ab,ti OR "activities of daily living":ab,ti OR "patient burden" OR pro:ab,ti OR "patient preference":ab,ti OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	139,298
7	#4 OR #5 OR #6	143,752
8	#1 AND #7	1
9	"Costs and Cost Analysis"[Mesh]	26,088
10	"Patient Acceptance of Health Care"[Mesh]	14,086
11	cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR "cost of illness":ab,ti OR "resource use":ab,ti OR "resource utilization":ab,ti OR "resource utilisation":ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR "healthcare utilization":ab,ti OR "healthcare utilisation":ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR "work loss":ab,ti OR employment:ab,ti OR retirement:ab,ti OR "sick leave":ab,ti OR "sick day":ab,ti OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	115,943
12	#9 OR #10 OR #11	132,291
13	#1 AND #12	0
14	#3 OR #8 OR #13	5

J.3.13.4 Search strategy: Peripheral nerve sheath tumour

Table 161, Table 162 and Table 163 present the search results from Embase, Medline, and Cochrane databases within the SLR for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in peripheral nerve sheath tumour.

Table 161 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in peripheral nerve sheath tumour

#	Query	Results from 31 May 2018

1	peripheral nerve sheath tumour'/exp OR ('peripheral nerve sheath':ab,ti AND (tumour*:ab,ti OR tumour*:ab,ti OR sarcoma*:ab,ti))	3,454
2	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR 'adverse event':ab,ti OR tolerability:ab,ti OR 'adverse effect':ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	3.4m
3	#1 AND #2	220
4	quality of life'/exp OR 'quality of life':ab,ti OR qol:ab,ti OR 'well being':ab,ti OR 'health status':ab,ti OR 'health state':ab,ti OR adl:ab,ti OR 'activities of daily living':ab,ti OR 'patient burden' OR 'patient-reported outcome'/exp OR pro:ab,ti OR 'patient preference':ab,ti OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	1.8m
5	#1 AND #4	234
6	'cost'/exp OR 'cost effectiveness analysis'/exp OR cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	2m
7	#1 AND #6	60
8	#3 OR #5 OR #7	472
9	#8 AND Limit: Humans	380
10	#9 AND Limit: Articles, Reviews, Articles in Press	233
11	#10 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	203
12	Conference abstracts	136
13	Total	339

Table 162 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in peripheral nerve sheath tumour

#	Query	Results from 31 May 2018
1	("Nerve Sheath Neoplasms"[Mesh] AND peripheral[tiab]) OR ("peripheral nerve sheath"[tiab] AND (tumour*[tiab] OR tumour*[tiab] OR sarcoma*[tiab]))	4,561
2	efficacy[tiab] OR safety[tiab] OR effectiveness[tiab] OR "adverse event"[tiab] OR tolerability[tiab] OR "adverse effect"[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR controlled[tiab] OR blind*[tiab] OR trial[tiab] OR allocat*[tiab] OR assign*[tiab]	2.5m
3	#1 AND #2	160

4	"Quality of Life"[Mesh] OR "quality of life"[tiab] OR qol[tiab] OR "well being"[tiab] OR "health status"[tiab] OR "health state"[tiab] OR adl[tiab] OR "activities of daily living"[tiab] OR "patient burden" OR "Patient-Reported Outcome Measures"[Mesh] OR pro[tiab] OR "patient preference"[tiab] OR psychosocial[tiab] OR utilit*[tiab] OR disutilit*[tiab] OR disabilit*[tiab] OR ((patient[tiab] OR caregiver[tiab]) AND (burden[tiab] OR preference[tiab] OR satisfaction[tiab] OR function*[tiab])) OR (symptom*[tiab] AND burden[tiab])	1.2m
5	#1 AND #4	240
6	"Costs and Cost Analysis"[Mesh] OR cost*[tiab] OR fee*[tiab] OR budget*[tiab] OR expenditure*[tiab] OR "cost of illness"[tiab] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "Patient Acceptance of Health Care"[Mesh] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR absenteeism[tiab] OR presenteeism[tiab] OR productivity[tiab] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR hospitalization*[tiab] OR hospitalisation*[tiab]	1.5m
7	#1 AND #6	55
8	#3 OR #5 OR #7	428
9	#8 NOT (animals [MH] NOT humans [MH])	396
10	#9 NOT (case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])	296
11	#10 NOT (review[pt] NOT (systematic OR meta-analysis))	241

Table 163 Cochrane Library search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in peripheral nerve sheath tumour

#	Query	Results from 31 May 2018
1	"Nerve Sheath Neoplasms"[Mesh]	159
2	peripheral:ab,ti	29,675
3	#1 AND #2	12
4	("peripheral nerve sheath":ab,ti AND (tumour*:ab,ti OR tumour*:ab,ti OR sarcoma*:ab,ti))	13
5	#3 OR #4	21
6	efficacy:ab,ti OR safety:ab,ti OR effectiveness:ab,ti OR "adverse event":ab,ti OR tolerability:ab,ti OR "adverse effect":ab,ti OR randomized:ab,ti OR randomised:ab,ti OR placebo:ab,ti OR controlled:ab,ti OR blind*:ab,ti OR trial:ab,ti OR allocat*:ab,ti OR assign*:ab,ti	892,826
7	#5 AND #6	11
8	"Quality of Life"[Mesh]	22,088
9	"Patient-Reported Outcome Measures"[Mesh]	162
10	"quality of life":ab,ti OR qol:ab,ti OR "well being":ab,ti OR "health status":ab,ti OR "health state":ab,ti OR adl:ab,ti OR "activities of daily living":ab,ti OR "patient burden" OR pro:ab,ti OR "patient preference":ab,ti	139,298

	OR psychosocial:ab,ti OR utilit*:ab,ti OR disutilit*:ab,ti OR disabilit*:ab,ti OR ((patient:ab,ti OR caregiver:ab,ti) AND (burden:ab,ti OR preference:ab,ti OR satisfaction:ab,ti OR function*:ab,ti)) OR (symptom*:ab,ti AND burden:ab,ti)	
11	#8 OR #9 OR #10	143,752
12	#5 AND #11	0
13	"Costs and Cost Analysis"[Mesh]	26,088
14	"Patient Acceptance of Health Care"[Mesh]	14,086
15	cost*:ab,ti OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR "cost of illness":ab,ti OR "resource use":ab,ti OR "resource utilization":ab,ti OR "resource utilisation":ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR "healthcare utilization":ab,ti OR "healthcare utilisation":ab,ti OR absenteeism:ab,ti OR presenteeism:ab,ti OR productivity:ab,ti OR "work loss":ab,ti OR employment:ab,ti OR retirement:ab,ti OR "sick leave":ab,ti OR "sick day":ab,ti OR hospitalization*:ab,ti OR hospitalisation*:ab,ti	115,943
16	#13 OR #14 OR #15	132,291
17	#5 AND #16	1
18	#7 OR #12 OR #17	11

J.3.13.5 Quality assessment

N/A

J.3.14 Gastrointestinal stromal tumours

J.3.14.1 Healthcare resource use and costs

The economic burden in advanced GIST was evaluated in 4 studies, with higher direct costs attributed to treatment with sunitinib and imatinib compared with BSC. The PRISMA flow diagram for economic costs and healthcare resource in GIST is shown in Figure 51.

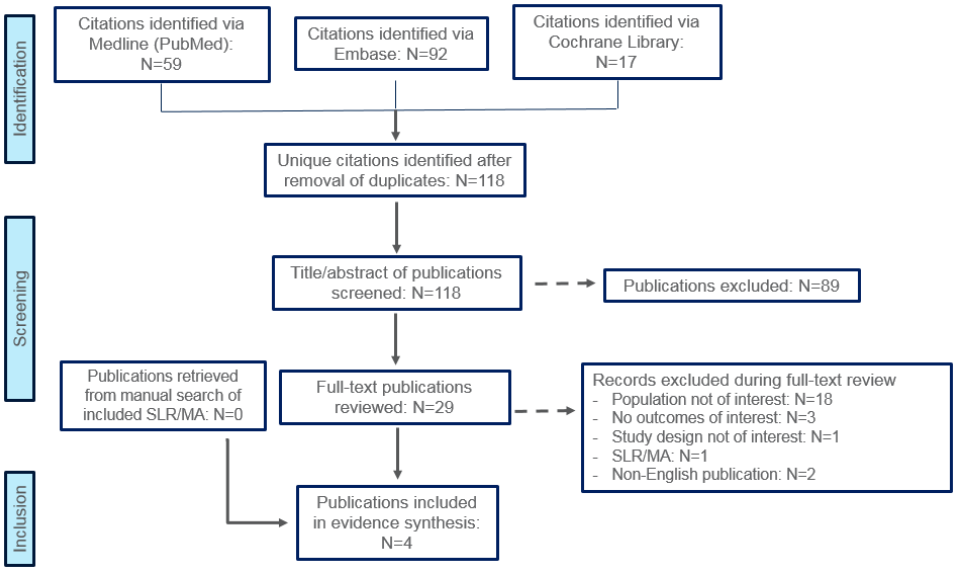


Figure 51 Literature selection and review process for economic costs and healthcare resource utilization in GIST

Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.14.2 Systematic selection of studies

The inclusion and exclusion criteria for costs and resource use in the GIST reviews are detailed using the PICOS framework in Table 164.

Table 164 Inclusion and exclusion criteria for costs and resource use reviews in GIST

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with locally advanced or metastatic GIST	• Healthy volunteers • Patients with diseases other than GIST • Patients with early stage GIST
Interventions	Any/all/no comparators	None
Comparators	Any/all/no comparators	None
Outcomes	• Direct costs (e.g., drug costs/pharmacy costs, medical supply costs, hospital costs, insurance costs/payer expenses, patient out-of-pocket expenses) • Indirect costs (e.g., lost productivity/ income for patients and/or carers/family members, travel time to appointments, loss of potential lifetime earnings, loss of future educational opportunities, need for additional financial/social support) • Resource use (e.g., physician visits [specialist and/or general practitioners], outpatient visits, home nursing care,	All outcomes other than those specified in the inclusion columns

	inpatient hospitalizations, length of stay in hospital, physician/nursing contact time, medical supplies, hospice or palliative care)	
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies (retrospective, prospective, cross-sectional, registries)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

Abbreviations: GIST, gastrointestinal stromal tumour; RCT, randomized controlled trial; SLR, systematic literature review.

[a] SLRs and meta-analyses will be included for hand-searching of reference lists.

[b] Conferences identified in Table 99 will be included for evaluation.

J.3.14.3 Search strategy

Table 165, Table 166 and Table 167 present the search results from Embase, Medline, and Cochrane databases within the SLR for economic costs and resource use in gastrointestinal stromal tumours.

Table 165 Embase search strategy for economic costs and resource use in GIST

#	Query	Results from 24 July 2018
1	('gastrointestinal stromal tumour'/exp OR 'gastrointestinal stromal tumour*':ab,ti OR 'gastrointestinal stromal tumour*':ab,ti OR 'gastrointestinal stroma tumour*':ab,ti OR 'gastrointestinal stroma tumour*':ab,ti OR 'gastrointestinal stromal neoplasm*':ab,ti OR gist:ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	5,565
2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR fee/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR expenditures/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR absenteeism/exp OR absenteeism:ab,ti OR presenteeism/exp OR presenteeism:ab,ti OR productivity:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR ‘medical leave’/exp OR ‘medical leave’:ab,ti	2.0m
3	#1 AND #2	171
4	#3 AND Humans	162
5	#4 AND Limits: Articles, Reviews (No Articles in Press)	94
6	#5 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	67
7	#4 AND Limit: Publication Type: Conference Abstracts (2015-2018)	25

8	#6 OR #7	92

Table 166 Medline search strategy for economic costs and resource use in GIST

#	Query	Results from 24 July 2018
1	("gastrointestinal stromal tumours"[mesh] OR "gastrointestinal stromal tumour"[tiab] OR "gastrointestinal stromal neoplasm"[tiab] OR "gastrointestinal stromal tumour"[tiab] OR "gastrointestinal stroma tumour"[tiab] OR "gastrointestinal stroma tumour"[tiab] OR GIST[tiab]) AND (advanced[tiab] OR unresectable[tiab] OR inoperable[tiab] OR metasta*[tiab])	2,756
2	Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR productivity[tiab] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab]	1.5m
3	#1 AND #2	59

Table 167 Cochrane search strategy for economic costs and resource use in GIST

#	Query	Results from 24 July 2018
1	MeSH descriptor: [Gastrointestinal stromal tumours] explode all trees	169
2	(gastrointestinal stromal tumour OR gastrointestinal stromal tumour OR gastrointestinal stroma tumour OR gastrointestinal stroma tumour OR gastrointestinal stromal neoplasm OR gist)ti,ab,kw (Word variations have been searched)	527
3	(advanced OR inoperable OR unresectable OR metasta*)ti,ab,kw (Word variations have been searched)	69,095
4	#1 OR #2	527
5	#3 AND #4	220
6	MeSH descriptor: [Costs and cost analysis] explode all trees	26,144
7	MeSH descriptor: [Fees and charges] explode all trees	519
8	MeSH descriptor: [Health expenditures] explode all trees	354
9	MeSH descriptor: [Cost of illness] explode all trees	1,390
10	MeSH descriptor: [Absenteeism] explode all trees	550
11	MeSH descriptor: [Presenteeism] explode all trees	15
12	MeSH descriptor: [Health care costs] explode all trees	7,652

13	cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or healthcare utilisation or absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave:ti,ab,kw (Word variations have been searched)	145,004
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	145,082
15	#5 AND #14	17

J.3.14.4 Quality assessment

N/A

J.3.14.5 Economic evaluations

Across 15 cost-effectiveness studies evaluating imatinib, regorafenib, and sunitinib, active treatment was generally reported to be cost-effective compared with BSC, controls, or no treatment. Evaluated in various geographies from a range of perspectives and time horizons, the ICERs indicated favourability toward treatment as values were below commonly reported willingness-to-pay (WTP) thresholds. The PRISMA flow diagram for economic evaluations in GIST is presented in Figure 52.

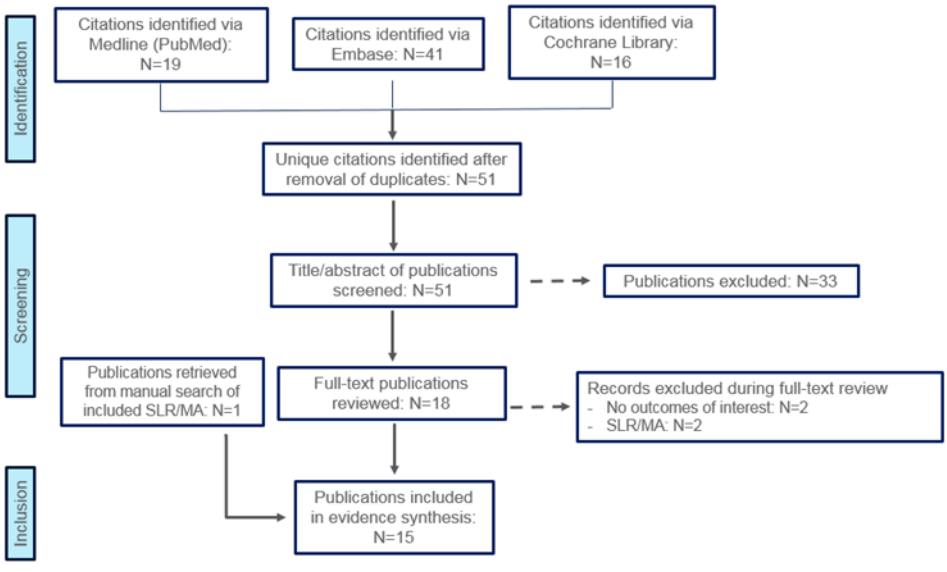


Figure 52 Literature selection and review process for economic evaluations in GIST
Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.14.5.1 Systematic selection of studies

The inclusion and exclusion criteria for economic evaluations in the GIST reviews are detailed using the PICOS framework in Table 168.

Table 168 Inclusion and Exclusion Criteria for economic evaluations in GIST

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients with locally advanced or metastatic GIST	• Healthy volunteers • Patients with diseases other than GIST • Patients with early stage GIST
Interventions	Monotherapies: • Larotrectinib • Imatinib • Sunitinib • Regorafenib	Interventions other than those listed in Inclusion column
Comparators	Monotherapies: • Larotrectinib • Imatinib • Sunitinib • Regorafenib Placebo SoC/BSC (author-defined)	Comparators other than those listed in the Inclusion column
Outcomes	• Overall costs (results of modelled analyses) • Quality-adjusted outcomes (e.g., quality-adjusted life months, quality-adjusted life years, quality-adjusted life expectancy, quality time without symptoms or toxicity) • Disutility-adjusted outcomes (e.g., disutility-adjusted life years) • Incremental cost-effectiveness ratios • Treatment dominance	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • Health economic studies • Cost-effectiveness • Cost-benefit • Cost-utility • Cost-consequence • Cost-minimization • Budget impact	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials • Other study designs not specified in Inclusion column

Abbreviations: BSC, best supportive care; GIST, gastrointestinal stromal tumour; SLR, systematic literature review; SoC, standard of care.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
b Conferences identified in Table 99 will be included for evaluation.

J.3.14.5.2 Search strategy

Table 169, Table 170 and Table 171 present the search results from Embase, Medline, and Cochrane databases within the SLR for economic evaluations in gastrointestinal stromal tumours.

Table 169 Embase search strategy for economic evaluations in GIST

#	Query	Results from 25 July 2018
1	('gastrointestinal stromal tumour'/exp OR 'gastrointestinal stromal tumour*':ab,ti OR 'gastrointestinal stromal tumour*':ab,ti OR 'gastrointestinal stroma tumour*':ab,ti OR 'gastrointestinal stroma tumour*':ab,ti OR 'gastrointestinal stromal neoplasm*':ab,ti OR gist:ab,ti) AND (advanced:ab,ti OR inoperable:ab,ti OR unresectable:ab,ti OR metasta*:ab,ti)	5,568
2	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	413k
3	#1 AND #2	54
4	#3 AND Humans	46
5	#4 AND Limits: Articles, Reviews (No Articles in Press)	32
6	#4 AND Limit: Publication Type: Conference Abstracts (2015-2018)	9
7	#5 OR #6	41

Table 170 Medline search strategy for economic evaluations in GIST

#	Query	Results from 25 July 2018
1	("gastrointestinal stromal tumours"[mesh] OR "gastrointestinal stromal tumour"[tiab] OR "gastrointestinal stromal neoplasm"[tiab] OR "gastrointestinal stromal tumour"[tiab] OR "gastrointestinal stroma tumour"[tiab] OR "gastrointestinal stroma tumour"[tiab] OR GIST[tiab]) AND (advanced[tiab] OR unresectable[tiab] OR inoperable[tiab] OR metasta*[tiab])	2,757
2	"Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget	368k

	impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab]	
3	#1 AND #2	19

Table 171 Cochrane search strategy for economic evaluations in GIST

#	Query	Results from 24 July 2018
1	MeSH descriptor: [Gastrointestinal stromal tumours] explode all trees	169
2	(gastrointestinal stromal tumour OR gastrointestinal stromal tumour OR gastrointestinal stroma tumour OR gastrointestinal stroma tumour OR gastrointestinal stromal neoplasm OR gist)ti,ab,kw (Word variations have been searched)	527
3	(advanced OR inoperable OR unresectable OR metasta*)ti,ab,kw (Word variations have been searched)	69,095
4	#1 OR #2	527
5	#3 AND #4	220
6	MeSH descriptor: [Models, Economic] explode all trees	2,060
7	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,942
8	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
9	MeSH descriptor: [Decision Theory] explode all trees	937
10	MeSH descriptor: [Decision Trees] explode all trees	921
11	MeSH descriptor: [Decision Analyses] explode all trees	3,796
12	Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR decision analys* OR decision analyt* OR decision model* :ti,ab,kw (Word variations have been searched)	59,093
13	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12	65,575
14	#5 AND #13	16

J.3.14.5.3 Quality assessment

Of the 15 included studies, only 2 are documented in Table 172; the remaining 13 studies are unavailable for assessment. The 2 economic analyses assessed, 1 was described in a conference abstract and the quality was considered good, while the other was a full publication that was considered of very high quality.

Table 172 Quality assessment of the economic evaluations: GIST

	Study design							Data collection														Analysis and interpretation of results															
Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
Publica-tion																																					
Kurimoto 2017	Y	N	Y	N	Y	Y	Y	Y	N	NA	Y	N	N	NA	NA	N	Y	Y	N	Y	N	N	N	NA		N	N	NA	NA	NA	Y	Y	Y	Y	N
MacEwan 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	Y	N	NA	NA	N	Y	Y	Y	Y	Y	Y	Y	N	NA	N	Y	Y	N	Y	Y	Y	Y	Y	Y

Abbviation: N, no; NC, not clear; Y, yes; NA, not avalible.
Note: Used BMJ Study Checklist for Economic Studies (Drummond 1996)

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoint(s) of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed
8. The source(s) of effectiveness estimates used are stated
9. Details of the design and results of effectiveness study are given (if based on a single study)

10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11. The primary outcome measure(s) for the economic evaluation are clearly stated
12. Methods to value health states and other benefits are stated
13. Details of the subjects from whom valuations were obtained are given
14. Productivity changes (if included) are reported separately
15. The relevance of productivity changes to the study question is discussed
16. Quantities of resources are reported separately from their unit costs
17. Methods for the estimation of quantities and unit costs are described
18. Currency and price data are recorded
19. Details of currency or price adjustments for inflation or currency conversion are given
20. Details of any model used are given
21. The choice of model used and the key parameters on which it is based are justified
22. Time horizon of costs and benefits is stated
23. The discount rate(s) is stated
24. The choice of rate(s) is justified
25. An explanation is given if costs or benefits are not discounted
26. Details of statistical tests and confidence intervals are given for stochastic data
27. The approach to sensitivity analysis is given
28. The choice of variables for sensitivity analysis is justified
29. The ranges over which the variables are varied are stated
30. Relevant alternatives are compared
31. Incremental analysis is reported
32. Major outcomes are presented in a disaggregated as well as aggregated form
33. The answer to the study question is given
34. Conclusions follow from the data reported
35. Conclusions are accompanied by the appropriate cave

J.3.15 Biliary Cancer

J.3.15.1 Healthcare resource use and costs

Eight cost and HCRU studies were included, of which 7 studies reported on HCRU, 6 on direct costs, and 0 on indirect costs. Much of the data on HCRU and costs were obtained from studies comparing outcomes for different stents and stenting procedures or surgery for unresectable disease. Patients receiving stents for treatment of the symptoms of cholangiocarcinoma have lengthy hospital stays and incur high costs. The PRISMA flow diagram for economic costs and healthcare resource in biliary cancer is shown in Figure 53.

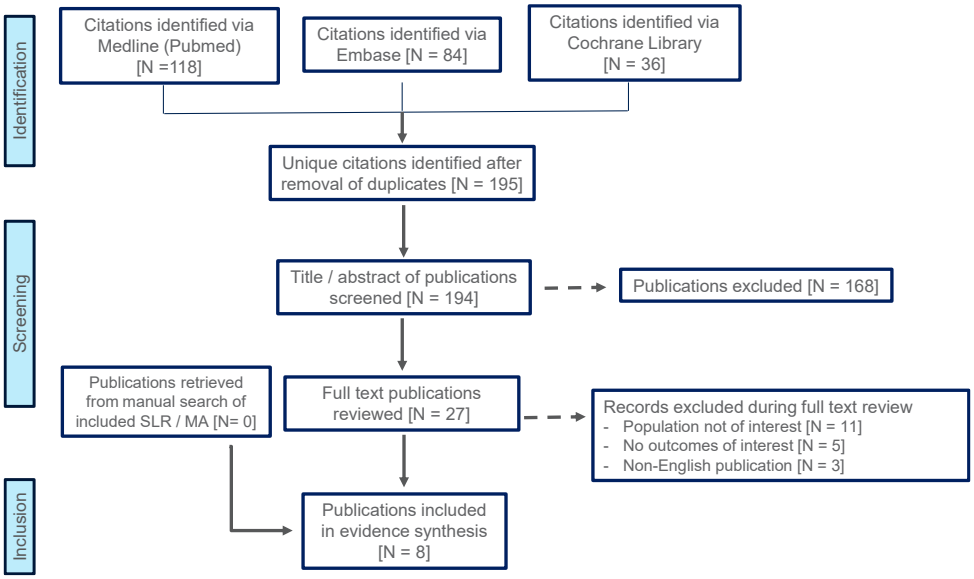


Figure 53 Literature selection and review process for economic costs and healthcare resource utilization in biliary cancer

Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.15.2 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and HCRU in the biliary cancer reviews are detailed using the PICOS framework in Table 173.

Table 173 Inclusion and exclusion criteria for economic evaluations/resource use reviews in biliary cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Biliary cancer	None
Interventions	• Larotrectinib • Oxaliplatin • Cisplatin • Capecitabine • Gemcitabine • Fluorouracil	None

	• Pembrolizumab	
Comparators	• Larotrectinib • Oxaliplatin • Cisplatin • Capecitabine • Gemcitabine • Fluorouracil • Pembrolizumab • Placebo • SoC	None
Outcomes	• Healthcare resource utilization • Direct costs[a] • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/ analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s]	• SLRs and meta-analyses[b] • RCTs • Non-randomized interventional studies • Observational studies • Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstractsc • Animal studies • Letters • Editorials

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QoL, quality of life; SLR, systematic literature review.
[a] Direct costs to include costs related to monitoring; inpatient/outpatient visits; emergency visits; general practice visits; adverse events; death; drugs.
[b] SLRs and meta-analyses will be included for hand-searching of reference lists.
[c] Conferences identified in Table 99 will be included for evaluation.

J.3.15.3 Search strategy

Table 174, Table 175 and Table 176 present the search results from Embase, Medline, and Cochrane databases within the SLR for economic costs and resource use in biliary cancer.

Table 174 Embase search strategy for economic costs and resource use in biliary cancer

#	Query	Results from 25 July 2018
1	('bile duct carcinoma'/exp OR 'bile duct carcinoma':ab,ti OR 'cholangiocarcinoma'/exp OR cholangiocarcinoma:ab,ti) AND (advanced:ab,ti OR unresectable:ab,ti OR inoperable:ab,ti OR metasta*ab,ti)	3,912

2	'cost'/exp OR cost:ab,ti OR costs:ab,ti OR costing:ab,ti OR fee/exp OR fee*:ab,ti OR budget*:ab,ti OR expenditure*:ab,ti OR expenditures/exp OR 'cost of illness'/exp OR 'cost of illness':ab,ti OR 'resource use':ab,ti OR 'resource utilization':ab,ti OR 'resource utilisation':ab,ti OR economic*:ab,ti OR pharmacoeconomic*:ab,ti OR 'healthcare utilization'/exp OR 'healthcare utilization':ab,ti OR 'healthcare utilisation':ab,ti OR 'health care utilization':ab,ti OR 'health care utilisation':ab,ti OR absenteeism/exp OR absenteeism:ab,ti OR presenteeism/exp OR presenteeism:ab,ti OR 'work loss':ab,ti OR employment:ab,ti OR retirement:ab,ti OR 'sick leave':ab,ti OR 'sick day':ab,ti OR 'health care cost'/exp OR hospitalization*:ab,ti OR hospitalisation*:ab,ti OR 'medical leave'/exp OR 'medical leave':ab,ti	1.9m
3	#1 AND #2	125
4	#3 AND Humans	118
5	#4 AND Limits: Articles, Reviews (No Articles in Press)	57
6	#4 AND Limit: Publication Type: Conference Abstracts (2015-2018)	27
7	#5 OR #6	84

Table 175 Medline search strategy for economic costs and resource use in biliary cancer

#	Query	Results from 25 July 2018
1	("bile duct neoplasms"[mesh] OR "bile duct neoplasm"[tiab] OR "bile duct carcinoma"[tiab] OR cholangiocarcinoma[mesh] OR cholangiocarcinoma[tiab]) AND (advanced[tiab] OR unresectable[tiab] OR inoperable[tiab] OR metasta*[tiab])	5,780
2	Cost[tiab] OR costs[tiab] OR costing[tiab] OR "Costs and Cost Analysis"[mesh] OR fee*[tiab] OR "Fees and Charges"[mesh] OR budget*[tiab] OR expenditure*[tiab] OR "Health Expenditures"[mesh] OR "cost of illness"[tiab] OR "Cost of Illness"[mesh] OR "resource use"[tiab] OR "resource utilization"[tiab] OR "resource utilisation"[tiab] OR economic*[tiab] OR pharmacoeconomic*[tiab] OR "healthcare utilization"[tiab] OR "healthcare utilisation"[tiab] OR "health care utilization"[tiab] OR "health care utilisation"[tiab] OR absenteeism[tiab] OR absenteeism[mesh] OR presenteeism[tiab] OR presenteeism[mesh] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] OR "sick day"[tiab] OR "Health Care Costs"[mesh] OR hospitalization*[tiab] OR hospitalisation*[tiab] OR "medical leave"[tiab]	1.4m
3	#1 AND #2	118

Table 176 Cochrane search strategy for economic costs and resource use in biliary cancer

#	Query	Results from 25 July 2018
1	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	239
2	MeSH descriptor: [Cholangiocarcinoma] explode all trees	182
3	(bile duct neoplasm OR bile duct carcinoma OR cholangiocarcinoma)ti,ab,kw (Word variations have been searched)	882

4	#1 OR #2 OR #3	884
5	(advanced OR inoperable OR unresectable OR metasta*)ti,ab,kw (Word variations have been searched)	69,095
6	#4 AND #5	405
7	MeSH descriptor: [Costs and cost analysis] explode all trees	26,144
8	MeSH descriptor: [Fees and charges] explode all trees	519
9	MeSH descriptor: [Health expenditures] explode all trees	354
10	MeSH descriptor: [Cost of illness] explode all trees	1390
11	MeSH descriptor: [Absenteeism] explode all trees	550
12	MeSH descriptor: [Presenteeism] explode all trees	15
13	MeSH descriptor: [Health care costs] explode all trees	7652
14	cost or costs or costing or fee* or budget* or expenditure* or cost of illness or resource use or resource utilization or resource utilisation or economic* or pharmacoeconomic* or healthcare utilization or healthcare utilisation or health care utilization or health care utilisation or absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day or hospitalization* or hospitalisation* or medical leave:ti,ab,kw (Word variations have been searched)	146,423
15	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	146,500
16	#6 AND #15	36

J.3.15.4 Quality assessment

N/A

J.3.15.5 Economic evaluations

The single identified cost-utility analysis compared 2 standard cholangiocarcinoma treatment strategies: hepatic resection as primary treatment followed by adjuvant systemic chemotherapy vs systemic chemotherapy with gemcitabine plus cisplatin followed by curative hepatic resection in patients who responded to systemic chemotherapy. The most cost-effective strategy was dependent on the specific subtype of cholangiocarcinoma. The PRISMA flow diagram for economic evaluations in biliary cancer is presented in Figure 54.

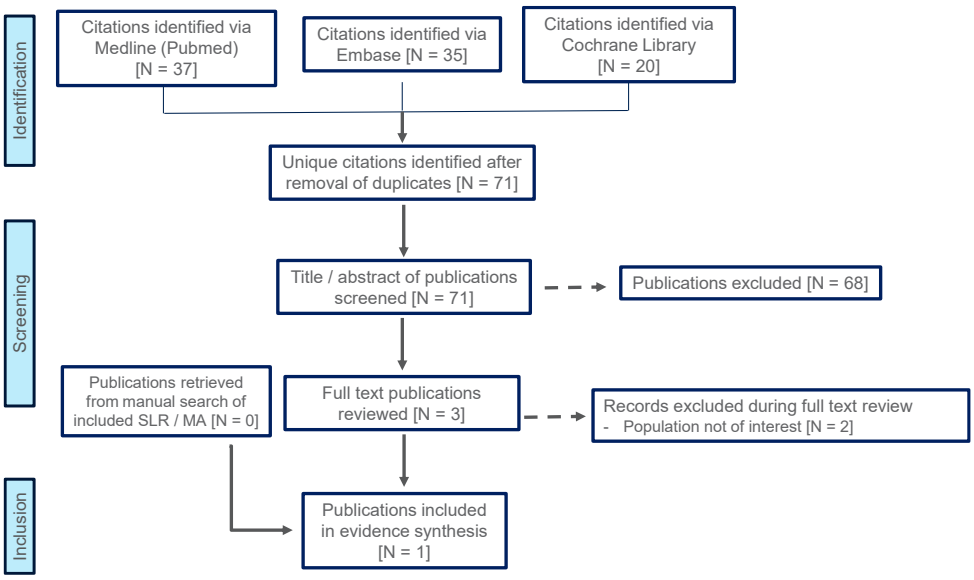


Figure 54 Literature selection and review process for economic evaluations in biliary cancer
Abbreviations: MA, meta-analysis; SLR, systematic literature review.

J.3.15.5.1 Systematic selection of studies

See Table 173.

J.3.15.5.2 Search strategy

Table 177, Table 178 and Table 179 present the search results from Embase, Medline, and Cochrane databases within the SLR for economic evaluations in biliary cancer.

Table 177 Embase search strategy for economic evaluations in biliary cancer

#	Query	Results from 26 July 2018
1	('bile duct carcinoma'/exp OR 'bile duct carcinoma':ab,ti OR 'cholangiocarcinoma'/exp OR cholangiocarcinoma:ab,ti) AND (advanced:ab,ti OR unresectable:ab,ti OR inoperable:ab,ti OR metasta*ab,ti)	3,912
2	'economic evaluation'/exp OR 'economic evaluation*':ab,ti OR 'economic model*':ab,ti OR 'cost effectiveness analysis'/exp OR 'cost effective*':ab,ti OR cost-effective*:ab,ti OR 'cost benefit analysis'/exp OR 'cost benefit':ab,ti OR cost-benefit:ab,ti OR 'cost utility analysis'/exp OR 'cost utility':ab,ti OR cost-utility:ab,ti OR 'cost minimization analysis'/exp OR 'cost minimization':ab,ti OR cost-minimization:ab,ti OR 'cost minimisation':ab,ti OR cost-minimisation:ab,ti OR 'budget impact analysis'/exp OR 'budget impact':ab,ti OR Markov:ab,ti OR 'Monte Carlo':ab,ti OR 'decision theory'/exp OR 'decision theory':ab,ti OR 'decision tree'/exp OR 'decision tree*':ab,ti OR 'decision analytic model'/exp OR 'decision analysis'/exp OR 'decision analysis model'/exp OR 'decision analys*':ab,ti OR 'decision analyt*':ab,ti OR 'decision model'/exp OR 'decision model*':ab,ti	413K
3	#1 AND #2	47
4	#3 AND Humans	46

5	#4 AND Limits: Articles, Reviews (No Articles in Press)	29
6	#4 AND Limit: Publication Type: Conference Abstracts (2015-2018)	6
7	#5 OR #6	35

Table 178 Medline search strategy for economic evaluations in biliary cancer

#	Query	Results from 26 July 2018
1	("bile duct neoplasms"[mesh] OR "bile duct neoplasm"[tiab] OR "bile duct carcinoma"[tiab] OR cholangiocarcinoma[mesh] OR cholangiocarcinoma[tiab]) AND (advanced[tiab] OR unresectable[tiab] OR inoperable[tiab] OR metasta*[tiab])	5,782
2	"Models, Economic"[mesh] OR "economic evaluation*"[tiab] OR "economic model*"[tiab] OR "Cost-Benefit Analysis"[mesh] OR "cost effective*"[tiab] OR cost-effective*[tiab] OR "cost benefit"[tiab] OR cost-benefit[tiab] OR "cost utility"[tiab] OR cost-utility[tiab] OR "Costs and Cost Analysis"[mesh] OR "cost minimization"[tiab] OR cost-minimization[tiab] OR "cost minimisation"[tiab] OR cost-minimisation[tiab] OR "budget impact"[tiab] OR Markov[tiab] OR "Monte Carlo"[tiab] OR "Decision Theory"[mesh] OR "decision theory"[tiab] OR "Decision Trees"[mesh] OR "decision tree*"[tiab] OR "Decision Analyses"[mesh] OR "decision analys*"[tiab] OR "decision analyt*"[tiab] OR "decision model*"[tiab]	368K
3	#1 AND #2	37

Table 179 Cochrane search strategy for economic evaluations in biliary cancer

#	Query	Results from 26 July 2018
1	MeSH descriptor: [Bile Duct Neoplasms] explode all trees	239
2	MeSH descriptor: [Cholangiocarcinoma] explode all trees	182
3	(bile duct neoplasm OR bile duct carcinoma OR cholangiocarcinoma)ti,ab,kw (Word variations have been searched)	882
4	#1 OR #2 OR #3	884
5	(advanced OR inoperable OR unresectable OR metasta*)ti,ab,kw (Word variations have been searched)	69,095
6	#4 AND #5	405
7	MeSH descriptor: [Models, Economic] explode all trees	2,060
8	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	18,942
9	MeSH descriptor: [Costs and Cost Analysis] explode all trees	26,144
10	MeSH descriptor: [Decision Theory] explode all trees	937
11	MeSH descriptor: [Decision Trees] explode all trees	921
12	MeSH descriptor: [Decision Analyses] explode all trees	3,796
13	Economic evaluation* OR economic model* OR cost effective* OR cost-effective* OR cost benefit OR cost-benefit OR cost utility OR cost-utility	59,093

	OR cost minimization OR cost-minimization OR cost minimisation OR cost-minimisation OR budget impact OR Markov OR Monte Carlo OR decision analys* OR decision analyt* OR decision model* :ti,ab,kw (Word variations have been searched)	
14	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	65,575
15	#6 AND #14	20

J.3.15.5.3 Quality assessment

The quality of the economic model was generally of high quality based on the assessment.

Table 180 Quality assessment for the economic evaluations: Pancreatic cancer

	Study design							Data collection													Analysis and interpretation of results																	
Question no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35		
Publication																																					
Kurimoto 2017	Y	Y	N	Y	Y	Y	N					NA	NA	NA	NA	NA	Y	Y	N	NA	NA	N	N	NA	NA	Y	NA	NA	NA	Y	Y	Y	Y	Y	N		

Abbviation: N, no; NC, not clear; Y, yes; NA, not avalible.
Note: Used BMJ Study Checklist for Economic Studies (Drummond 1996)

1. The research question is stated
2. The economic importance of the research question is stated
3. The viewpoint(s) of the analysis are clearly stated and justified
4. The rationale for choosing the alternative programmes or interventions compared is stated
5. The alternatives being compared are clearly described
6. The form of economic evaluation used is stated
7. The choice of form of economic evaluation is justified in relation to the questions addressed
8. The source(s) of effectiveness estimates used are stated
9. Details of the design and results of effectiveness study are given (if based on a single study)
10. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)
11. The primary outcome measure(s) for the economic evaluation are clearly stated
12. Methods to value health states and other benefits are stated

13. Details of the subjects from whom valuations were obtained are given
14. Productivity changes (if included) are reported separately
15. The relevance of productivity changes to the study question is discussed
16. Quantities of resources are reported separately from their unit costs
17. Methods for the estimation of quantities and unit costs are described
18. Currency and price data are recorded
19. Details of currency or price adjustments for inflation or currency conversion are given
20. Details of any model used are given
21. The choice of model used and the key parameters on which it is based are justified
22. Time horizon of costs and benefits is stated
23. The discount rate(s) is stated
24. The choice of rate(s) is justified
25. An explanation is given if costs or benefits are not discounted
26. Details of statistical tests and confidence intervals are given for stochastic data
27. The approach to sensitivity analysis is given
28. The choice of variables for sensitivity analysis is justified
29. The ranges over which the variables are varied are stated
30. Relevant alternatives are compared
31. Incremental analysis is reported
32. Major outcomes are presented in a disaggregated as well as aggregated form
33. The answer to the study question is given
34. Conclusions follow from the data reported
35. Conclusions are accompanied by the appropriate cave

J.3.16 Salivary Gland Cancer

J.3.16.1 Healthcare resource use and costs

One study reported HCRU and direct cost data. Patients in France undergoing chemotherapy and radiotherapy had a high number of hospital stays with higher costs in the public sector compared with the private sector. The PRISMA flow diagram for economic costs and healthcare resource in salivary gland cancer is shown in Figure 55.

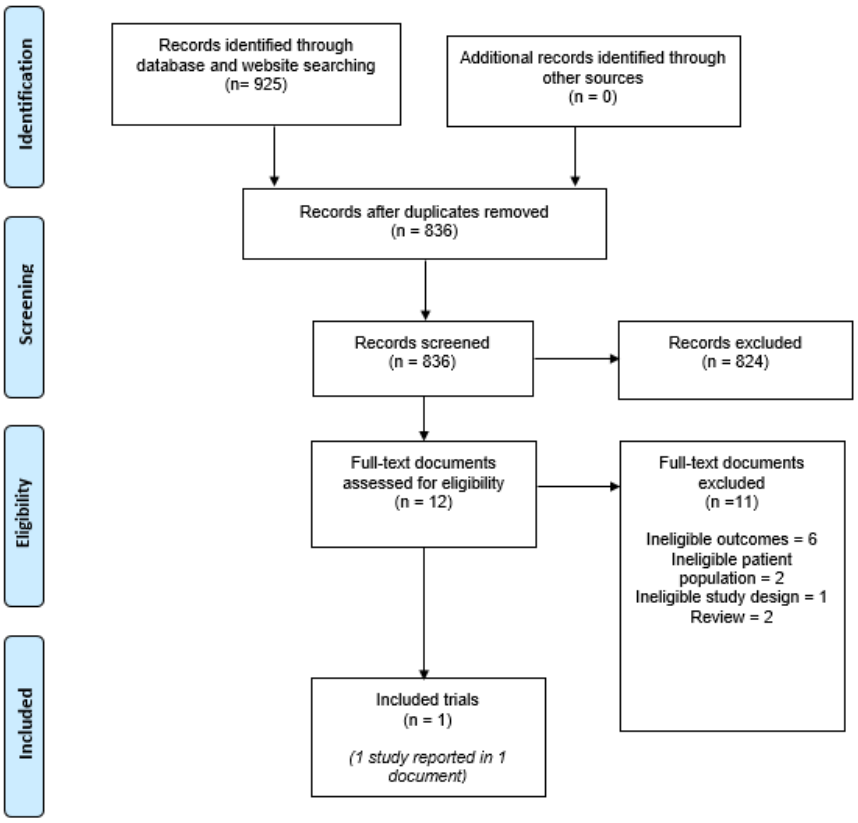


Figure 55 Literature selection and review process for economic costs and healthcare resource utilization in salivary gland cancer

J.3.16.2 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and healthcare resource use in the salivary gland cancer reviews are detailed using the PICOS framework in Table 181.

Table 181 Inclusion and exclusion criteria for economic evaluations/resource use reviews in salivary gland cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Salivary gland cancer	None
Interventions	Any interventions	None

Comparators	Any interventions	None
Outcomes	• Healthcare resource utilization • Direct costs[a] • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/ analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[b] • RCTs • Non-randomized interventional studies • Observational studies • Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[c] • Animal studies • Letters • Editorials

Abbreviations: ICER, incremental cost effectiveness ratio; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review.
[a] Direct costs to include costs related to monitoring; inpatient/outpatient visits; emergency visits; general practice visits; adverse events; death; drugs.
[b] SLRs and meta-analyses will be included for hand-searching of reference lists.
[c] Conferences identified in Table 99 will be included for evaluation.

J.3.16.3 Search strategy

Table 182, Table 183 and Table 184 present the search results from Embase, Medline, and Cochrane databases within the SLR for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in salivary gland cancer.

Table 182 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in salivary gland cancer

#	Query	Results from 25 June 2018
1	salivary gland tumour/ or exp parotid gland tumour/ or exp salivary gland cancer/	19,163
2	(saliva cancer$ or saliva neoplasm$ or saliva neoplasia$ or saliva carcinoma$ or saliva adenocarcinoma$ or saliva tumour$ or saliva tumour$ or saliva malignan$ or salivary cancer$ or salivary neoplasm$ or salivary neoplasia$ or salivary carcinoma$ or salivary adenocarcinoma$ or salivary tumour$ or salivary tumour$ or salivary malignan$ or parotis cancer$ or parotis neoplasm$ or parotis neoplasia$ or parotis carcinoma$ or parotis adenocarcinoma$ or parotis tumour$ or parotis tumour$ or parotis malignan$ or parotid$ cancer$ or parotid$ neoplasm$ or parotid$ neoplasia$ or parotid$ carcinoma$ or parotid$ adenocarcinoma$ or parotid$ tumour$ or parotid$ tumour$ or parotid$ malignan$ or sublingual$ cancer$ or sublingual$ neoplasm$ or sublingual$ neoplasia$ or	10,067

	sublingual$ carcinoma$ or sublingual$ adenocarcinoma$ or sublingual$ tumour$ or sublingual$ tumour$ or sublingual$ malignan$ or submandibul$ cancer$ or submandibul$ neoplasm$ or submandibul$ neoplasia$ or submandibul$ carcinoma$ or submandibul$ adenocarcinoma$ or submandibul$ tumour$ or submandibul$ tumour$ or submandibul$ malignan$ or saliva gland cancer$ or saliva gland neoplasm$ or saliva gland neoplasia$ or saliva gland carcinoma$ or saliva gland adenocarcinoma$ or saliva gland tumour$ or saliva gland tumour$ or saliva gland malignan$ or salivary gland cancer$ or salivary gland neoplasm$ or salivary gland neoplasia$ or salivary gland carcinoma$ or salivary gland adenocarcinoma$ or salivary gland tumour$ or salivary gland tumour$ or salivary gland malignan$ or parotis gland cancer$ or parotis gland neoplasm$ or parotis gland neoplasia$ or parotis gland carcinoma$ or parotis gland adenocarcinoma$ or parotis gland tumour$ or parotis gland tumour$ or parotis gland malignan$ or parotid$ gland cancer$ or parotid$ gland neoplasm$ or parotid$ gland neoplasia$ or parotid$ gland carcinoma$ or parotid$ gland adenocarcinoma$ or parotid$ gland tumour$ or parotid$ gland tumour$ or parotid$ gland malignan$ or sublingual$ gland cancer$ or sublingual$ gland neoplasm$ or sublingual$ gland neoplasia$ or sublingual$ gland carcinoma$ or sublingual$ gland adenocarcinoma$ or sublingual$ gland tumour$ or sublingual$ gland tumour$ or sublingual$ gland malignan$ or submandibul$ gland cancer$ or submandibul$ gland neoplasm$ or submandibul$ gland neoplasia$ or submandibul$ gland carcinoma$ or submandibul$ gland adenocarcinoma$ or submandibul$ gland tumour$ or submandibul$ gland tumour$ or submandibul$ gland malignan$).ti,ab,kw.	
3	(mammary analogue secretory carcinoma$ or MASC or MASCSG).ti,ab,kw.	705
4	or/1-3	21,879
5	(utilit$ or disutilit$ or eq 5d or eq5d or sf 36 or sf36 or sf 12 or sf12 or hui or fact or qlq c30).ti,ab. or eq-5d/ or exp short form 36/ or eortc qlq c30/	575,616
6	4 and 5	430
7	exp cost/	322,070
8	exp cost effectiveness analysis/	133,751
9	(cost$ or fee$ or budget$ or expenditure$).ti,ab.	1,327,403
10	exp cost of illness/	17,595
11	cost of illness.ti,ab.	2,166
12	("resource use" or resource utilization or resource utilisation).ti,ab.	23,832
13	(economic$ or pharmacoeconomic$).ti,ab.	289,491
14	exp health care utilization/	60,055
15	(healthcare utilization or healthcare utilisation).ti,ab.	5,926
16	(absenteeism or presenteeism or productivity or work loss or employment or retirement or sick leave or sick day).ti,ab.	139,067
17	exp health care cost/	264,507
18	(hospitalization or hospitalisation).ti,ab.	187,968

19	or/7-18	1,999,391
20	4 and 19	347
21	(efficacy or safety or effectiveness or adverse event or tolerability or adverse effect or randomized or randomised or placebo or controlled or blind$ or trial or allocat$ or assign$).ti,ab.	3,459,631
22	4 and 21	1,147
23	(animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/) not exp human/	5,914,489
24	editorial.pt. or case report.ti.	832,457
25	6 not (23 or 24)	410
26	remove duplicates from 25	401 *
27	20 not (23 or 24)	332
28	remove duplicates from 27	326 **
29	22 not (23 or 24)	1,088
30	remove duplicates from 29	1,071 ***

* Results downloaded for HRQoL/PRO/Utilities
** Results downloaded for economic evaluations / resource use
*** Results downloaded for efficacy and safety

Table 183 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in salivary gland cancer

#	Query	Results from 28 June 2018
1	Salivary Gland Neoplasms[mh:noexp] OR Parotid Neoplasms[mh:noexp] OR Sublingual Gland Neoplasms[mh:noexp] OR Submandibular Gland Neoplasms[mh:noexp]	16,381
2	(saliva[tiab] OR salivary[tiab] OR parotis[tiab] OR parotid*[tiab] OR sublingual*[tiab] OR submandibul*[tiab]) AND (cancer*[tiab] OR neoplasm*[tiab] OR neoplasia*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR tumour*[tiab] OR tumour*[tiab] OR malignan*[tiab])	26,001
3	Mammary Analogue Secretory Carcinoma[mh:noexp]	46
4	“mammary analogue secretory carcinoma*”[tiab] OR MASC[tiab] OR MASCSG[tiab]	459
5	#1 OR #2 OR #3 OR #4	30,754
6	utilit*[tiab] OR disutilit*[tiab] OR "eq 5d"[tiab] OR eq5d[tiab] OR "sf 36"[tiab] OR sf36[tiab] OR "sf 12"[tiab] OR sf12[tiab] OR hui[tiab] OR fact[tiab] OR "qlq c30"[tiab] OR eortcqlq*[tiab] OR "eortc qlq*"[tiab] OR Quality-Adjusted Life Years[mh:noexp] OR Quality of Life[mh:noexp]	559,960
7	#5 AND #6	933
8	"Costs and Cost Analysis"[mh]	215,922
9	cost[tiab] OR costs[tiab] OR costing[tiab] OR budget*[tiab] OR expenditure*[tiab]	517,710

10	"resource use"[tiab] OR "resource utilisation"[tiab] OR "resource utilisation"[tiab]	7,961
11	economic*[tiab] OR pharmacoeconomic*[tiab]	244,133
12	"healthcare utilization"[tiab] OR "healthcare utilisation"[tiab]	3,504
13	absenteeism[tiab] OR presenteeism[tiab] OR productivity[tiab] OR "work loss"[tiab] OR employment[tiab] OR retirement[tiab] OR "sick leave"[tiab] or "sick day"[tiab]	116,936
14	hospitalization[tiab] OR hospitalisation[tiab]	115,914
15	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14	976,031
16	#5 AND #15	355
17	efficacy[tiab] OR safety[tiab] OR effectiveness[tiab] OR "adverse event"[tiab] OR "adverse events"[tiab] OR tolerability[tiab] OR "adverse effect"[tiab] OR "adverse effects"[tiab] OR randomized[tiab] OR randomised[tiab] OR placebo[tiab] OR controlled[tiab] OR blind*[tiab] OR trial[tiab] OR allocat*[tiab] OR assign*[tiab]	2,656,668
18	#5 AND #17	2,013
19	animals[mh] NOT humans[mh:noexp]	4,468,364
20	editorial[pt] OR case report[ti]	668,842
21	#7 NOT (#19 OR #20)	905*
22	#16 NOT (#19 OR #20)	340**
23	#18 NOT (#19 OR #20)	1,909***

* Results downloaded for HRQoL/PRO/Utilities
** Results downloaded for economic evaluations / resource use
*** Results downloaded for efficacy and safety

Table 184 Cochrane search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in salivary gland cancer

#	Query	Results from 26 June 2018
1	[mh ^"Salivary Gland Neoplasms"] or [mh ^"Parotid Neoplasms"] or [mh ^"Sublingual Gland Neoplasms"] or [mh ^"Submandibular Gland Neoplasms"]	90
2	saliva next cancer* or saliva next neoplasm* or saliva next neoplasia* or saliva next carcinoma* or saliva next adenocarcinoma* or saliva next tumour* or saliva next tumour* or saliva next malignan* or salivary next cancer* or salivary next neoplasm* or salivary next neoplasia* or salivary next carcinoma* or salivary next adenocarcinoma* or salivary next tumour* or salivary next tumour* or salivary next malignan* or parotis next cancer* or parotis next neoplasm* or parotis next neoplasia* or parotis next carcinoma* or parotis next adenocarcinoma* or parotis next tumour* or parotis next tumour* or parotis next malignan* or parotid* next cancer* or parotid* next neoplasm* or parotid* next neoplasia* or parotid* next carcinoma* or parotid* next adenocarcinoma* or parotid* next tumour* or parotid* next tumour* or parotid* next malignan* or sublingual* next cancer* or sublingual* next neoplasm* or sublingual* next neoplasia* or sublingual* next carcinoma* or	203

	sublingual* next adenocarcinoma* or sublingual* next tumour* or sublingual* next tumour* or sublingual* next malignan* or submandibul* next cancer* or submandibul* next neoplasm* or submandibul* next neoplasia* or submandibul* next carcinoma* or submandibul* next adenocarcinoma* or submandibul* next tumour* or submandibul* next tumour* or submandibul* next malignan* or "saliva gland" next cancer* or "saliva gland" next neoplasm* or "saliva gland" next neoplasia* or "saliva gland" next carcinoma* or "saliva gland" next adenocarcinoma* or "saliva gland" next tumour* or "saliva gland" next tumour* or "saliva gland" next malignan* or "salivary gland" next cancer* or "salivary gland" next neoplasm* or "salivary gland" next neoplasia* or "salivary gland" next carcinoma* or "salivary gland" next adenocarcinoma* or "salivary gland" next tumour* or "salivary gland" next tumour* or "salivary gland" next malignan* or "parotis gland" next cancer* or "parotis gland" next neoplasm* or "parotis gland" next neoplasia* or "parotis gland" next carcinoma* or "parotis gland" next adenocarcinoma* or "parotis gland" next tumour* or "parotis gland" next tumour* or "parotis gland" next malignan* or parotid* next gland next cancer* or parotid* next gland next neoplasm* or parotid* next gland next neoplasia* or parotid* next gland next carcinoma* or parotid* next gland next adenocarcinoma* or parotid* next gland next tumour* or parotid* next gland next tumour* or parotid* next gland next malignan* or sublingual* next gland next cancer* or sublingual* next gland next neoplasm* or sublingual* next gland next neoplasia* or sublingual* next gland next carcinoma* or sublingual* next gland next adenocarcinoma* or sublingual* next gland next tumour* or sublingual* next gland next tumour* or sublingual* next gland next malignan* or submandibul* next gland next cancer* or submandibul* next gland next neoplasm* or submandibul* next gland next neoplasia* or submandibul* next gland next carcinoma* or submandibul* next gland next adenocarcinoma* or submandibul* next gland next tumour* or submandibul* next gland next tumour* or submandibul* next gland next malignan*	
3	[mh ^"Mammary Analogue Secretory Carcinoma"]	0
4	"mammary analogue secretory" next carcinoma* or MASC or MASCSG	46
5	#1 or #2 or #3 or #4	249
6	#1 or #2 or #3 or #4 in Methods Studies	0
7	#1 or #2 or #3 or #4 in Technology Assessments	1*
8	#1 or #2 or #3 or #4 in Economic Evaluations	4**
9	#1 or #2 or #3 or #4 in Trials	205***
10	#1 or #2 or #3 or #4 in Other Reviews	15****
11	#1 or #2 or #3 or #4 in Cochrane Reviews (Reviews and Protocols)	24*****

* Results downloaded from HTA Database
** Results downloaded from NHS EED
*** Results downloaded from CENTRAL
**** Results downloaded from DARE
***** Results downloaded from CDSR

J.3.16.4 Quality assessment

N/A

J.3.16.5 Economic evaluations

No economic analyses were identified. The PRISMA flow diagram for economic evaluations in salivary gland cancer is presented in Figure 56.

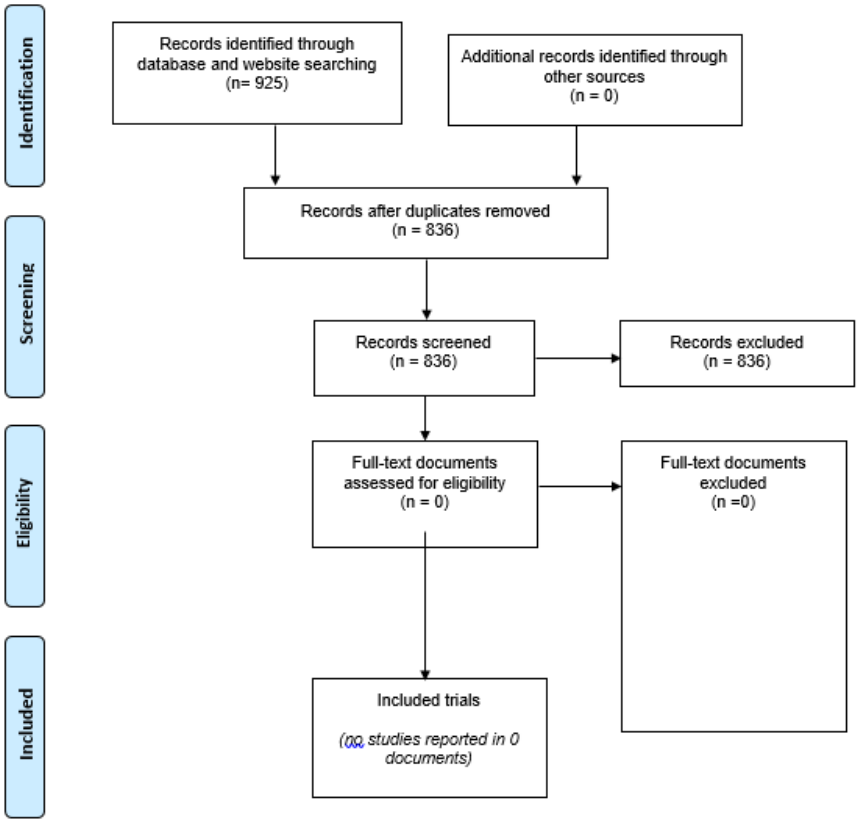


Figure 56 Literature selection and review process for economic evaluations in salivary gland cancer

J.3.16.5.1 Systematic selection of studies

See Table 181.

J.3.16.5.2 Search strategy

See Table 182, Table 183 and Table 184.

J.3.16.5.3 Quality assessment

N/A

J.3.17 Secretory Breast Cancer

J.3.17.1 Healthcare resource use and costs

No data was identified for any economic burden outcomes, including HCRU, direct costs, and indirect costs.

J.3.17.2 Systematic selection of studies

The inclusion and exclusion criteria for both economic evaluations and healthcare resource use in the salivary gland cancer reviews are detailed using the PICOS framework in Table 185.

Table 185 Inclusion and exclusion criteria for economic evaluations/resource use reviews in secretory breast cancer

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Secretory breast cancer	None
Interventions	Any interventions	None
Comparators	Any interventions	None
Outcomes	• Healthcare resource utilization • Direct costs (to include costs related to monitoring, inpatient/ outpatient visits; emergency visits; general practice visits; adverse events; death; drugs. • Indirect costs • Cost-effectiveness • QoL/utility values (stratified by metastatic status where available) • Economic models, including budget impact models/analyses • QALYs • ICERs	All outcomes other than those specified in the inclusion columns
Study design (s)	• SLRs and meta-analyses[a] • RCTs • Non-randomized interventional studies • Observational studies • Health economic studies (e.g., cost-effectiveness analyses)	• Non-systematic reviews • Case reports • Case series • Conference abstracts[b] • Animal studies • Letters • Editorials

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; QoL, quality of life; RCT, randomized controlled trial; SLR, systematic literature review.
[a] SLRs and meta-analyses will be included for hand-searching of reference lists.
[b] Conferences identified in Table 99 will be included for evaluation.

J.3.17.3 Search strategy

Table 186, Table 187 and Table 188 present the search results from Embase, Medline, and Cochrane databases within the SLR for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in secretory breast cancer

Table 186 Embase search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in salivary gland cancer in secretory breast cancer

#	Query	Results from 24 May 2018
1	Search secretory AND breast AND 'carcinoma'/exp	803
2	'secretory breast carcinoma':ab,ti	69
3	('secretory carcinoma':ab,ti OR 'secretory carcinoma'/exp) AND 'breast':ab,ti	216
4	#1 OR #2 OR #3	837
5	#4 AND ('article'/it OR 'article in press'/it OR 'conference abstract'/it OR 'review'/it)	787
6	#5 AND [humans]/lim AND [embase]/lim	564
7	#6 NOT ([review]/lim NOT (systematic OR (meta AND analy*)))	488

Table 187 Medline search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in secretory breast cancer

#	Query	Results from 24 May 2018
1	Search "Secretory breast carcinoma" [Supplementary Concept] Sort by: Best Match	53
2	Search ((((secretory) AND breast)) AND carcinoma[MeSH Terms]) Sort by: Best Match	387
3	Search "secretory breast carcinoma"	95
4	Search (("secretory carcinoma"[Title/Abstract]) AND breast[Title/Abstract])	173
5	Search ((("Secretory breast carcinoma" [Supplementary Concept]) OR (((((secretory) AND breast)) AND carcinoma[MeSH Terms])))) OR "secretory breast carcinoma") OR ((("secretory carcinoma"[Title/Abstract]) AND breast[Title/Abstract])) Sort by: Best Match	456
6	NOT (((case reports [pt] OR editorial [pt] OR letter [pt] OR comment [pt])))) NOT (((review [pt] NOT (systematic OR meta-analysis)))) NOT animal studies	268

Table 188 Cochrane Library search strategy for clinical efficacy, HRQoL/PROs/utilities and economic evaluations/resource use in secretory breast cancer

#	Query	Results from 23 May 2018
1	MeSH descriptor: [Carcinoma] explode all trees	10,789
2	secretory and breast (Word variations have been searched)	96
3	#1 and #2	0

4	"secretory breast carcinoma" (Word variations have been searched)	1
5	"secretory carcinoma":ti or "secretory carcinoma":ab (Word variations have been searched)	3
6	breast:ti or breast:ab (Word variations have been searched)	29,984
7	#5 and #6	1
8	secretory:ti,ab,kw (Word variations have been searched)	2,263
9	breast:ti,ab,kw (Word variations have been searched)	33,541
10	#8 and #9	57
11	secretory (Word variations have been searched)	2,395
12	breast (Word variations have been searched)	35,463
13	#11 and #12	96
14	#13 and #1	0
15	#4 or #7	1

J.3.17.4 Quality assessment

N/A

J.3.17.5 Economic evaluations

No economic analyses were identified reporting on secretory breast cancer.

J.3.17.5.1 Systematic selection of studies

See Table 185.

J.3.17.5.2 Search strategy

See Table 186, Table 187 and Table 188.

J.3.17.5.3 Quality assessment

N/A

Appendix L. Literature searches conducted by Lassen et al

L.1 Efficacy for the SoC arm

An SLR was conducted in Medline, Embase, Cochrane, and PubMed to identify studies comparing the OS of patients with NTRK gene fusion-positive vs NTRK gene fusion-negative tumours. The aim of this meta-analysis was to provide a more robust estimate of the prognostic value of NTRK+ status in patients in a real-world setting.

L.1.1 Search strategies

The systematic review and meta-analysis were reported by Lassen et al (2023) (26) were performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. Studies published up to 11 August, 2022, were retrieved from:

- Medline
- Embase
- Cochrane
- PubMed

No restrictions based on language, time, study design, or article type were made.

TABLE A1. Search Strategy

ID	Search Query	Results
Medline and Embase		
#1	'tropomyosin receptor kinase'/exp	77
#2	(('*NTRK*' OR 'tropomyosin receptor kinase') NEAR/3 (gene OR fusion OR inhibition)):ti,ab	778
#3	#1 OR #2	843
#4	'cancer survival':de,ti,ab OR 'OS':de,ti,ab OR 'mortality':de,ti,ab	2,379,883
#5	#3 AND #4	164
#6	#5 AND [embase]/lim	162
#7	#5 AND ([medline]/lim OR [preprint]/lim OR [pubmed-not-medline]/lim)	38
Cochrane		
#1	(('*NTRK*' OR "tropomyosin receptor kinase") NEAR/3 (gene OR fusion OR inhibition)):ti,ab,kw	15
#2	("cancer survival" OR "OS" OR 'mortality'):ti,ab,kw	148,113
#3	#1 and #2	9
PubMed		
#1	tropomyosin receptor kinase[MeSH Major Topic]	944
#2	('*NTRK*'[Title/Abstract] OR 'tropomyosin receptor kinase'[Title/Abstract])	1,708
#3	(gene[Title/Abstract] OR fusion[Title/Abstract] OR inhibition[Title/Abstract])	2,950,961
#4	#1 OR (#2 AND #3)	1,679
#5	'cancer survival'[Title/Abstract] OR 'OS'[Title/Abstract] OR 'mortality'[Title/Abstract]	1,110,209
#6	#4 AND #5	50

Abbreviation: MeSH, Medical Subject Headings; *NTRK*, neurotrophic tyrosine receptor kinase; OS, overall survival.

Figure 57 Search strategy reported by Lassen et al (2023)

L.1.2 Selection criteria

Articles were included in the review if they satisfied the following eligibility criteria:

- Population included patients with NTRK+ solid tumours

- OS was included as an outcome
- Comparative results with NTRK- tumours were provided

The results from the electronic databases were combined, and duplicates were removed. Two reviewers independently assessed abstracts against eligibility criteria, classifying them as include, exclude, or unsure. Discrepancies were resolved by consensus or a third reviewer. For included abstracts, the full-text articles underwent the same double-review process. Reasons for exclusion were documented at each stage. Bibliographies of included articles were hand-searched for additional eligible studies. Only unique patient cohorts were included in the meta-analysis.

L.1.3 Data extraction

The following data items were extracted from the full-text articles of included studies and clinical study reports (if available), or from conference abstracts and posters if full texts were unavailable:

- Study details
- Patient cohort
- Sample size
- Study design
- Data source
- Country
- Patient demographics
- Practice type
- ECOG Performance Status
- NTRK fusion status
- Index date
- Censoring
- Follow-up time
- Event count
- OS rate
- Covariate adjustment

Data were entered into a form and independently validated. Availability of KM curves was noted, and further data points were extracted using digitizing software and a published algorithm if needed.

L.1.4 Risk of bias assessment

Risk of bias was independently assessed by two reviewers using the Risk of Bias Assessment tool for Non-randomized Studies. This tool, known for its validity and reliability, evaluates six domains of methodological quality: participant selection, confounding control, exposure measurement, outcome assessment, incomplete outcome data, and selective outcome reporting. Each domain was rated as low, high, or unclear.

L.1.5 Data synthesis

Study characteristics and endpoint data availability were assessed to determine the feasibility of quantitative evidence synthesis. Log HRs were pooled using a fixed-effects model, with statistical heterogeneity evaluated by I^2. The fixed-effects model assumes a common NTRK gene fusion effect across studies, which may not hold if heterogeneity exists. Due to the limited number of studies, a Bayesian random-effects model was also fitted, incorporating suitable prior distributions for between-study heterogeneity. Models were compared using leave-one-out information criteria, and results from the best-fitting model were presented in a forest plot, showing the posterior mean log HR with 95% credible intervals. A funnel plot was examined for reporting bias, though no asymmetry test was conducted due to the small study number. Analysis was performed using RStudio version 4.2.1 with the meta and brms packages.

L.1.6 Results

The search strategy, conducted on 11 August 2022, retrieved 265 articles (Fig 1). After removing duplicates, 198 abstracts were screened, and 187 were excluded based on eligibility criteria. The full texts of the remaining 11 articles were reviewed, leading to the exclusion of six more: four lacked an NTRK comparison group, one did not report the appropriate survival outcome, and one was a duplicate study. The remaining articles were further assessed for inclusion in the quantitative synthesis. The full article by Bridgewater et al. was published on 23 August 2022.

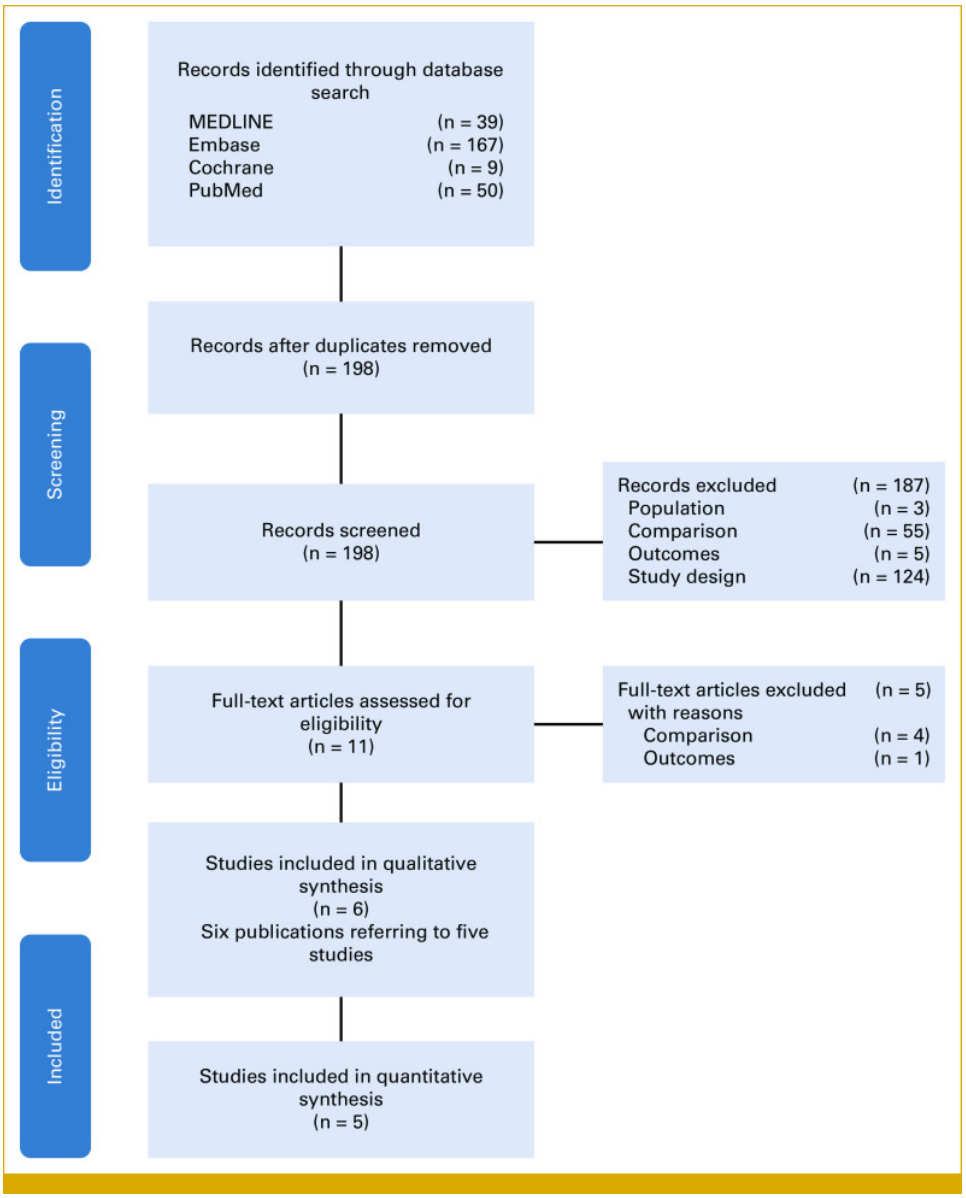


Figure 58 PRISMA, reported by Lassen et al (2023)

Five retrospective matched case-control studies published before 11 August 2022, were assessed for inclusion. Please refer to the figure below.

TABLE 1. Study and Patient Characteristics of the Five Studies Assessed for Quantitative Synthesis

Study	Country	Study Design	Data Source (period)	Patient Cohort	Sample Size, No.	Male Sex, No. (%)	Median Age (range), Years	ECOG, %	Practice Type, %
								0-1/2-4/ Unknown	Academic/ Community
Bazhenova et al[9]	United States	Retrospective, matched (1:4) on age, ECOG performance status, albumin, antineoplastic use, practice type, year of report	FH-FMI real-world Clinico-Genomic Database (January 1, 2011-July 31, 2018)	*NTRK*+	27	13 (44.8)	60 (49-65)	17.2/0/82.8	20.7/79.3
				NTRK wild-type	107	45 (42.1)	63 (55-70)	22.4/0/77.6	19.6/80.4
Bridgewater et al[10,19]	United Kingdom	Retrospective, matched (1:4) on type of primary tumor, disease type, histology, stage at diagnosis, sex, age at diagnosis, year of diagnosis, CCI score	Genomics England database v9.0 (March 2016-July 2019)	*NTRK*+	18	3 (16.7)	58.5 (12-79)	13.3/6.7/80	NR
				NTRK−	72	12 (16.7)	60 (9-83)	18.1/0/81.9	NR
Hibar et al[11]	United States	Retrospective, matched (1:10) on cancer type and propensity score (estimated using age, smoking status, practice type, lines of therapy, stage at diagnosis, time from diagnosis to report)	FH-FMI real-world Clinico-Genomic Database (January 1, 2011-December 31, 2019)	*NTRK*+	28	10 (35.7)	18-64: 60.7% ≥65: 39.3%	50.0/7.1/42.9	14.3/85.7
				NTRK−	280	149 (53.2)	18-64: 56.1% ≥65: 43.9%	45.0/11.4/43.6	18.9/81.1
Santi et al[12]	The Netherlands	Retrospective, matched (1:4) on age, sex, and number of previous lines of therapy plus others not reported	Hartwig Medical Foundation database from 44 hospitals (2012-2020)	*NTRK*+	23	10 (43.5)	59 (28-75)	NR	NR
				NTRK−	92	34 (37.0)	61 (36-83)	NR	NR
Zhu et al[13]	United States	Retrospective, matched (1:5) on histology, stage at diagnosis, and sex	MDACC patients with *NTRK*+ fusions Patients in TCGA database with *NTRK*− fusions	*NTRK*+	25	11 (44)	16 (4-72)	NR	NR
				NTRK−	122	7 (5.7)	56 (36-87)	NR	NR

Abbreviation: CCI, Charlson Comorbidity Index; CGP, comprehensive genomic profiling; ECOG, Eastern Cooperative Oncology Group; FH-FMI, Flatiron Health-Foundation Medicine; MDACC, University of Texas MD Anderson Cancer Center; NR, not reported; *NTRK*, neurotrophic tyrosine receptor kinase; TCGA, The Cancer Genome Atlas.

The study by Bazhenova et al. was excluded from data synthesis because it used the same database as the study by Hibar et al., and thus did not provide a unique, independent sample. The data from Hibar et al. were retained due to a longer, more up-to-date study period (1 January 2011 – 31 December 2019, vs. 31 July 2018) and a larger number of cases and controls. Three studies were included in the meta-analysis. The median OS was not estimable in the studies by Bridgewater et al and Zhu et al because of a lack of events, but in the three other studies, it ranged from 10 to 16.5 months. Refer to the figure below.

TABLE 2. Statistical Methods and Results of the Five Studies Assessed for Quantitative Synthesis

Study	Index Date	Statistical Model and Covariate Adjustment	PH Assumption Satisfied	Censoring	*NTRK*	Median Follow-Up (range), months	Events, No. (%)	Median OS (95% CI), months	KM Curves Reported	HR OS (95% CI)
Bazhenova et al[9]	Primary: date of CGP report Secondary: date of first systemic cancer therapy	Unadjusted Cox PH model	Yes	Last activity date or at the day after the primary index date if no later activity date	29 positive 107 negative	7.5[a] (2.2-12.5) 7.6[a] (2.2-16.2)	11 (40.7) 45 (42.1)	12.5 (9.5 to NE) 16.5 (12.5 to 22.5)	Yes	1.44 (0.61 to 3.37)
Bridgewater et al[10,11]	First date of cancer diagnosis for the gene sequenced tumor	Unadjusted Cox PH model	Yes	Date of the last death recorded in the cohort (November 20, 2019) or on initiation of TRK inhibitor therapy	18 positive 72 negative	24.1 (6.0-49.2) 27.4 (6.0-44.4)	2 (11.1) 6 (8.3)	NE NE	Yes	1.47 (0.39 to 5.57)
Hibar et al[11]	Primary: locally advanced/metastatic/recurrent disease diagnosis Secondary: start of last available treatment line before the NGS report	Unadjusted Cox PH model	NR	Last visit date Excluded patients previously or currently receiving TRK inhibitor therapy	28 positive 280 negative	10.3 13.9	22 (79) 164 (59)	10.2 (7.2 to 14.1) 10.4 (8.7 to 14.3)	Yes	1.60 (1.02 to 2.50)
Santi et al[12]	Date of the first postbiopsy treatment	Unadjusted Cox PH model Adjusted Cox PH model (age, sex, and previous line of treatment)	Some evidence of non-PH (author communication)	NR in abstract/poster	23 positive 92 negative	NR NR	16 (69.6) 54 (59.7)	12.7 (6.3 to 17.4) 10.1 (8.0 to 17.8)	Yes	Unadjusted: 1.37 (0.78 to 2.42) Adjusted: 1.32 (0.74 to 2.35)
Zhu et al[13]	Initial diagnosis of primary tumor	Adjusted Cox PH model (stage and age at initial diagnosis)	NR	On initiation of *NTRK* inhibitor therapy	25 positive 122 negative	NR NR	NR NR	NE NE	NR	NR

Abbreviation: CGP, comprehensive genomic profiling; HR, hazard ratio; KM, Kaplan-Meier; NE, not estimable; NGS, next-generation sequencing; NR, not reported; *NTRK*, neurotrophic tyrosine receptor kinase; OS, overall survival; PH, proportional hazards; TRK, tyrosine receptor kinase.

[a]Mean.

Appendix M. VICTORIA study

Study Description: The VICTORIA study is a comparative effectiveness study of the real-world clinical benefit of TRK fusion-positive cancer patients treated with historical SoC therapies vs patients from the larotrectinib clinical trials (Bayer Data on File VICTORIA Protocol 2022) (93).

Study dates: The data collection period will vary among real-world data sources but will be from January 2013 until 01 March 2022 (subject to change) (Bayer Data on File VICTORIA Protocol 2022.

Endpoints

Primary objective: The primary objective is to describe and compare OS in adult patients with solid tumours harbouring an NTRK gene fusion who received historical SoC/BSC in the real-world setting with patients who received larotrectinib in clinical trials (for the full cohort and by tumour type if sample sizes allow it) (Bayer Data on File VICTORIA Protocol 2022).

- OS is defined as time from index date (i.e., initiation of larotrectinib or SoC/BSC therapy after matching with tumour type and larotrectinib treatment line) to the time of death (by any cause) or last observation (Bayer Data on File VICTORIA SAP 2022).

Secondary objectives: The secondary objectives include describing and comparing treatment patterns, durations of therapies, and time to next treatment between patients who received historical SoC/BSC in the real-world setting with patients who received larotrectinib in clinical trials (Bayer Data on File VICTORIA Protocol 2022).

- Line of therapy (LOT) will be defined as distinct combinations. Re-treatment with the same therapy will not increment the line. Components of the original combination may be dropped without incrementing the line. The line will be incremented if new drugs are added to the original treatment regimen (Bayer Data on File VICTORIA Protocol 2022).
- Duration of therapy for an LOT will be defined as time from initiation of treatment (which may be the index date) until permanent treatment discontinuation (defined as the end of an LOT followed by another LOT, or a therapy discontinued with a physician's note, or discontinued for a predefined gap period [e.g., >90 days]) or death for any reason (Bayer Data on File VICTORIA SAP 2022).
- Time to next treatment will be defined as the time from the index date until the date of initiation of the next line of systemic treatment (Bayer Data on File VICTORIA SAP 2022).

Exploratory objectives: Exploratory objectives include to compare real-world response rates and real-world PFS between patients who received historical SoC/BSC in the real-world setting with patients who received larotrectinib in clinical trials (Bayer Data on File VICTORIA Protocol 2022).

- Real-world response rates will be defined as the proportion of patients with a best OR of CR or PR reported by the treating physician during the index or comparative treatment period (Bayer Data on File VICTORIA Protocol 2022).
- Real-world PFS will be defined as time from the index date to the date of progression for patients for whom progression is indicated as the reason for discontinuation or death due to any cause (Bayer Data on File VICTORIA SAP 2022).

Study Design

The VICTORIA study is a retrospective comparative effectiveness study between a real-world external comparator cohort and patients in larotrectinib clinical trials (Figure 59). In order to obtain a sufficient number of patients with NTRK gene fusions, the real-world comparator cohort will include patients pooled from different data sources, such as AACR Genomics Evidence Neoplasia Information Exchange data, Cardinal study data, and global retrospective chart review data (other data sources will also be considered depending on data availability). This data collection period began 01 January 2013, and ended 01 March 2022. A comparative effectiveness analysis against the larotrectinib clinical trials will then be conducted in patients with the following 5 major tumour types of interest: NSCLC, CRC, thyroid cancer, sarcomas, and salivary gland carcinoma. The index date for comparative analyses will be the initiation of the matched LOT of larotrectinib or comparator therapy (i.e., SoC/BSC after matching with tumour type and larotrectinib treatment line). For outcomes assessments, patients will be followed from index date up to last activity, end of study period, or death, whichever occurs first (Bayer Data on File VICTORIA Protocol 2022).

Data Sources – Larotrectinib Cohort: Patient-level data was included from larotrectinib clinical trials, including a phase 1 adult clinical (NCT02122913), a phase 2 adolescent and adult clinical trial (NAVIGATE, NCT02576431), and the SCOUT paediatric trial (NCT02637687, which included 1 patient >18 years). The five most frequent tumour types from the two trials were identified and selected with July 2022 cutoff in the ePAS7 as the larotrectinib-treated cohort (Bayer Data on File CSR 2024).

Data Sources – Real-World Cohort:

The real-world cohort of patients with NTRK gene fusion-positive cancer was identified through 2 approaches: identification and evaluation of clinic-genomic databases (CGDBs) and global clinical sites survey (Bayer Data on File VICTORIA Slide Deck 2023).

- Of these 21 CGDBs identified, 4 were recommended for inclusion. 17 databases were excluded mainly due to inaccessible patient-level data (n=12), incomplete treatment or outcome information (n=8), and lack of ability to validate NTRK gene fusion status (n=3).
- The clinical sites survey was initially sent to 915 clinical sites from 25 countries covering North America, Europe, and Asia-Pacific. 49 clinical sites responded to the initial or revised survey outreach; of these, 7 clinical sites were eligible for inclusion in the patient chart review after validation of NTRK gene fusion-positive status.

Inclusion criteria: Adult patients (aged ≥18 years at date of diagnosis of advanced or metastatic cancer with NTRK gene fusion) with a diagnosis of NSCLC, CRC, thyroid cancer, sarcomas, or salivary gland carcinoma; diagnosis of advanced stage of disease or metastatic

disease on or after 01 January 2013; and diagnosis of NTRK gene fusion with valid tests including NGS or RT-PCR, PCR, or FISH studies (Bayer Data on File VICTORIA Protocol 2022).

Exclusion criteria: Patients with a second primary cancer during the study period except non-melanoma skin carcinoma or carcinoma in situ or patients involved in TRK inhibitor clinical trials will be excluded from the real-world control cohort (patients who received TRK inhibitors in the real-world setting will be allowed) (Bayer Data on File VICTORIA Protocol 2022).

Study population: The FAS will include all patients from the aggregated real-world data sources (after merging, cleaning, and de-duplication), along with the larotrectinib clinical trial patients (Figure 59). All final analyses will be performed on the FAS (Bayer Data on File VICTORIA SAP 2022).

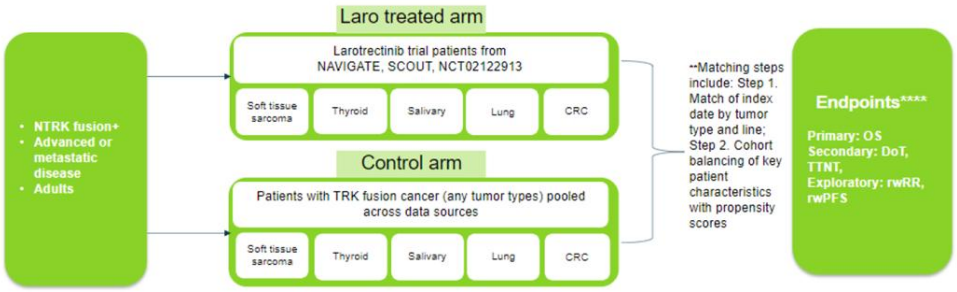


Figure 59 Study design and description of the larotrectinib trial patients and real-world patients with potential for inclusion into data analysis

Source: VICTORIA CSR 2024 (data on file)

* Numbers are from ePAS5 for the adult patients with 5 major tumour types. The most updated data available for larotrectinib were used for analysis.

** Variable set for weighting included age at index (continuous; derived), race (White, Black, Asian, Other), gender (male, female), presence of metastasis at index date, and ECOG performance status score (0, 1, 2, 3).

**** Primary, secondary and exploratory analyses utilized the matched cohorts.

Abbreviation: CRC, colorectal cancer; DoT, duration of treatment; NTRK, neurotrophic tyrosine receptor kinase; OS, overall survival; rwPFS, real-world progression-free survival; rwRR, real-world response rate; TTNT, time to next treatment.

Sample characteristics: After matching, there were 82 patients included in each of the two cohorts, and the percentage of patients treated with larotrectinib and patients from the real-world cohort were well-balanced across cancer types, including STS (28.0%), CRC (20.7%), NSCLC (18.3%), salivary gland cancer (18.3%), and thyroid cancer (14.6%). Nearly half (n=39, 47.6%) of patients were in first line therapy (as current line of therapy), a quarter in second (n=20, 24.4%) or third (n=19, 23.2%) LOT, and one in 20 (n=4, 4.9%) were in fourth line therapy. Index line of comparator therapy was active anticancer treatments in all cases (no real-world patient matched on BSC). Most of the patients from the real-world cohort (48.8%) received chemotherapy as the index line of comparator therapy, while 22 patients (26.8%) received targeted therapy (small molecule), 9 patients (11.0%) received chemotherapy + targeted therapy (other), and 8 patients (9.8%) received immune checkpoint inhibitor therapy (Bayer Data on File VICTORIA CSR 2024).

Results: A total of 82 larotrectinib trial patients were matched with 82 real-world patients based on tumour type and number of lines of systemic therapies. The primary outcome was OS. Secondary outcomes included duration of therapies (DoT) and TTNT.

Exploratory outcomes included real-world response rate and real-world PFS. Study outcomes are reported in Table 189.

Table 189 Comparative Effectiveness Estimates for Larotrectinib vs Real-World Cohort in TRK Fusion Solid Tumours

Outcome	Larotrectinib (n=82)	Real-World Cohort (n=82)
Median OS, months (95%CI)		
Unweighted[a]	63.4 (42.9, NE)	37.2 (17.4, NE)
	HR: 0.47 (95% CI: 0.26, 0.88; *P*=0.0176)	
Weighted[b]	NE (42.9, NE)	37.2 (12.5, NE)
	HR: 0.44 (95% CI: 0.23, 0.83; *P*=0.0109)	
Median DOT, months (95% CI)		
Weighted[c]	30.8 (18.2, 47.6)	3.4 (2.7, 4.7)
	HR: 0.23 (95% CI: 0.15, 0.33)	
Median TTNT, months (95% CI)		
Unweighted	58.1 (53.2, NE)	10.0 (6.7, 17.7)
	HR: 0.24 (0.14, 0.40)	
Weighted	NE (53.2, NE)	10.6 (6.1, 17.7)
	HR: 0.22 (0.13, 0.38)	
rwRR, % (95% CI)[d]		
	73.8 (62.7, 83.0)	53.8 (37.2, 69.9)
Median rwPFS, months (95% CI)		
Weighted[c]	36.8 (25.8, 58.2)	5.2 (3.5, 6.8)
	HR: 0.29 (95% CI: 0.18, 0.46)	

a OS in the FAS (N = 164) was 63.4 (95% CI: 38.7, NE).
b OS in the FAS (N = 164) was 63.4 (95% CI: 38.5, NE).
c Similar before and after weighting.
d Overall response rate was defined as the proportion of patients with best overall response of CR or PR during the index or comparative treatment period over patients with non-missing response only.
Key: Key: CI – confidence interval; DoT – duration of therapy; FAS – full analysis set; HR – hazard ratio; NE – not estimable; OS – overall survival; rwPFS – real-world progression-free survival; rwRR – real-world response rate; TTNT – time to next treatment.

Conclusion: Patients with tumour who harboured NTRK gene fusions treated with larotrectinib in clinical trials had longer median OS, DoT, TTNT, and rwPFS compared with matched real-world control patients. Also, patients treated with larotrectinib had numerically higher real-world response rates compared with real-world control patients.

Appendix N. Model structure, using the stratified comparator arm by tumour site

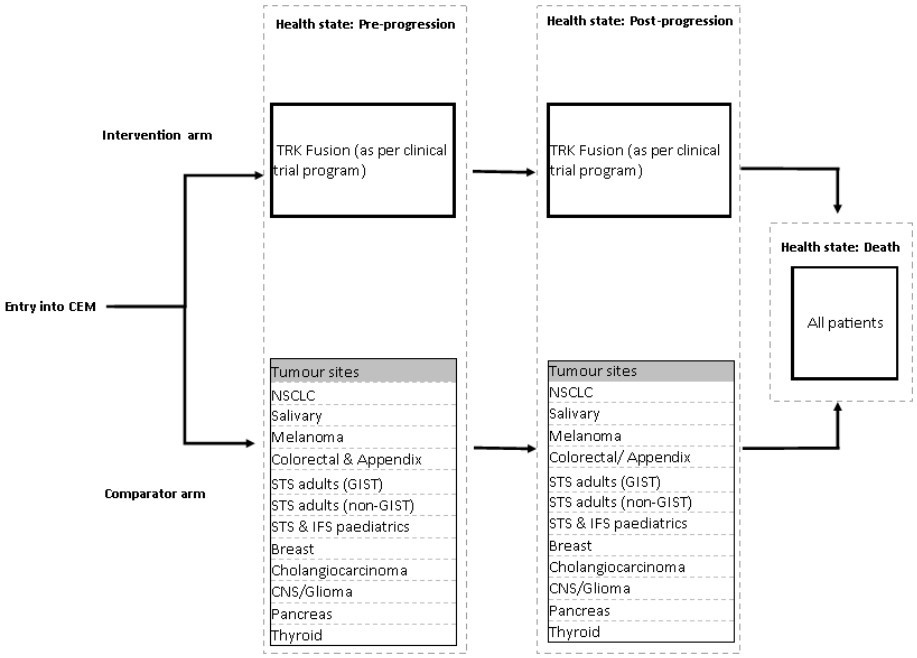


Figure 60 Economic model schematic

Appendix O. Tumour specific inputs

The included section here entails inputs and assumptions regarding the modelling of the following due to the absence of adequate input data for modelling the comparator arm: response data; health care resource use and costs; utility values and others.

The tables below outline the data sources by input parameter for individual tumour locations. Further information on e.g. costs and utilities can be found in subsection in this Appendix.

Tumour location	GIST 3L	Non-GIST 2L	Thyroid papillary/follicular 2L+	Cholangiocarcinoma 2L+
Comparator treatment	SoC	SoC	SoC	Gemcitabine+cisplatin
Main source(s)	NICE TA488; Bayer model; GRID trial	NICE TA185	RAIRDTC NICE model; NICE TA535; MTA	ABC-02 (Valle 2010), Tsukiyama 2017/Roth 2012
Treatment cost				
Treatment dosing	N/A	N/A	N/A	Valle 2010
Drug acquisition	N/A	N/A	N/A	BNF 2018
Administration costs	N/A	N/A	N/A	NHS Reference Costs
Other treatment costs	N/A	N/A	N/A	NR
Response status				
Efficacy	GRID (Demetri 2013)	NICE TA185	NICE TA535	Valle 2010
Utility	NICE TA488	NICE TA185	NICE TA535	Roth 2012
Adverse events				
Rates	NICE TA488	NICE TA185	NICE TA535	Valle 2010
Cost	Tumour agnostic AE cost per event based on past TAs (gap filled by resource use in published literature) and NHS Reference Costs			
Disutility	N/A	NICE TA185	N/A	Assumed values from TAs of CRC and NSCLC
Health state cost				
Cost for PFS and PD	NICE TA488	NICE TA185	NICE TA 535	Weighted average of other comparators

Survival				
Median PFS (only needed if curve is not available)	N/A	N/A	N/A	Valle 2010
PFS KM curves and parameters	NICE Excel model	N/A	KM from NICE TA 535 + Exponential from Guyot survival analysis	Guyot survival analysis
Median OS (only needed if curve is not available)	N/A	N/A	N/A	Valle 2010
OS KM curves and parameters	NICE Excel model	NICE TA185	KM from NICE TA 535 + Exponential from Guyot survival analysis	Guyot survival analysis

Tumour location	**Colorectal third-line**	**Salivary second-line**	**STS Paediatrics**	**NSCLC second/third-line**
Comparator treatment	SoC	Cisplatin + Vinorelbine	Irinotecan + Vincristine	SoC
Main source(s)	NICE TA405	Airoldi et al 2001; Liberato 2012	Early model: Mascarenhas et al 2010; Zuluga-Sanchez 2018; Delea 2014; Amdahl 2014; Judson 2007	NICE TA374, Sheppard 2005
Treatment cost				
Treatment dosing	N/A	Airoldi et al 2001	Mascarenhas 2010	N/A
Drug acquisition	N/A	BNF 2018	BNF 2018	N/A
Administration costs	N/A	NHS Reference Costs	NHS Reference Costs	N/A
Other treatment costs	N/A	NR	NR	N/A
Response status				
Efficacy	NICE TA405	Airoldi 2001	Mascarenhas 2010	Sheppard 2005
Utility	NICE TA405	Liberato 2012	Zuluga-Sanchez 2018; Delea 2014	NICE TA 374
Adverse events				
Rates	NICE TA405	Airoldi 2001	Mascarenhas 2010	Sheppard 2005

Cost	Tumour agnostic AE cost per event based on past TAs (gap filled by resource use in published literature) and NHS Reference Costs			
Disutility	NICE TA405	Nafees 2008 (assumption is supported by TA 490)	Swinburn 2010; Nafees 2008 (assumed the same as NSCLC)	Nafees 2008; NICE TA 374
Health state cost				
Cost for PFS and PD	NICE TA405	NICE TA 490	Amdahl 2014	NICE TA 374
Survival				
Median PFS (only needed if curve is not available)	NICE TA405	Airoldi 2001	Mascarenhas 2010	NICE TA 374
PFS KM curves and parameters	NICE TA405; Guyot survival analysis	Calculated exponential from median PFS	Guyot survival analysis	KM from NICE TA 374 + Exponential from Guyot survival analysis
Median OS (only needed if curve is not available)	NICE TA405	Airoldi 2001	Mascarenhas 2010	NICE TA 374
OS KM curves and parameters	NICE TA405; Guyot survival analysis	Guyot survival analysis (IPD created based on Airoldi 2001)	Guyot survival analysis	KM from NICE TA 374 + Exponential from Guyot survival analysis

Tumour location	**Breast**	**Melanoma second-line**	**Pancreas**	**Glioma/CNS**
Comparator treatment	Treatment of physician's choice (TPC)	SoC: Mixed chemo arm	5-fluorouracil + leucovorin	Lomustine
Main source(s)	NICE TA423	KEYNOTE-002 trials; MELODY study (Johnston et al 2012) NICE TA 357.	NICE TA440	NICE TA 23; Batchelor 2013
Treatment cost				
Treatment dosing	NICE TA 423	NICE TA 357	NICE TA 440	Batchelor 2013
Drug acquisition	BNF 2018	BNF 2018	BNF 2018	BNF 2018

Administration costs	NHS Reference Costs	NHS Reference Costs	NHS Reference Costs	NHS Reference Costs
Other treatment costs	N/A	N/A	N/A	N/A
Response status				
Efficacy	NICE TA 423	NICE TA 357	NICE TA 440	NICE TA 23
Utility	NICE TA 423	NICE TA357	NICE TA 440	NICE TA 23
Adverse events				
Rates	NICE TA 423	NICE TA 357	NICE TA 440	Batchelor 2013
Cost	Tumour agnostic AE cost per event based on past TAs (gap filled by resource use in published literature) and NHS Reference Costs			
Disutility	NICE TA 423	Assumed the same as CRC NICE TA 405	Swinburn 2010	Assumed the same as NSCLC Nafees 2008
Health state cost				
Cost for PFS and PD	NICE TA 423	NICE TA 268	NICE TA 440	NICE TA 23
Survival				
Median PFS (only needed if curve is not available)	NICE TA 423	NICE TA357	NICE TA 440	Batchelor 2013
PFS KM curves and parameters	NICE TA 423 (directly use KM data)	KM from NICE TA 357 + Gompertz from Guyot survival analysis	NICE TA 440 (directly use KM data)	Guyot survival analysis
Median OS (only needed if curve is not available)	NICE TA 423	NICE TA357	NICE TA 440	Batchelor 2013
OS KM curves and parameters	KM from NICE TA 423 + Exponential from Guyot survival analysis	Guyot survival analysis	NICE TA 440 (directly use KM data)	Guyot survival analysis

O.1 Tumour-specific clinical inputs

For comparators, data were taken from relevant technology appraisals (TAs), or publications identified to represent the efficacy of each of the tumour locations in the pooled comparator. See table below for overview of the response data used in the model to generate a weighted average for the chosen comparator, SoC (informed by Bokemeyer et al.)

Table 190 Clinical efficacy - tumour site locations from literature

Location	Response	Value (%)	Source
NSCLC	Complete response	0	Shepperd 2005 (94)
	Partial response	100	Shepperd 2005 (94)
	Stable disease	0	Shepperd 2005 (94)
	Progressive disease	0	Shepperd 2005 (94)
Salivary	Complete response	18.91	Airoldi et al., 2001 (95)
	Partial response	24.88	Airoldi et al., 2001 (95)
	Stable disease	37.31	Airoldi et al., 2001 (95)
	Progressive disease	18.91	Airoldi et al., 2001 (95)
Melanoma	Complete response	0	TA357(50)
	Partial response	5.30	TA357(50)
	Stable disease	21.67	TA357(50)
	Progressive disease	73.03	TA357(50)
Colorectal	Complete response	0.35	Pooled from Mayer 2015 (78) and Yoshino 2012 (96)
	Partial response	0	Pooled from Mayer 2015 (78) and Yoshino 2012 (96)
	Stable disease	16.38	Pooled from Mayer 2015 (78) and Yoshino 2012 (96)
	Progressive disease	83.28	Pooled from Mayer 2015 (78) and Yoshino 2012 (96)
STS adults (GIST)	Complete response	0	GIST NICE model: NICE TA488 (53)
	Partial response	4.35	GIST NICE model: NICE TA488 (53)
	Stable disease	95.65	GIST NICE model: NICE TA488 (53)
	Progressive disease	0	GIST NICE model: NICE TA488 (53)
STS adults (non-GIST)	Complete response	0	NICE TA185 (55)
	Partial response	0	NICE TA185 (55)
	Stable disease	0	NICE TA185 (55)
	Progressive disease	100	NICE TA185 (55)
STS paediatrics	Complete response	0	Mascarenhas et al 2010 (80)
	Partial response	54.85	Mascarenhas et al 2010 (80)
	Stable disease	45.15	Mascarenhas et al 2010 (80)
	Progressive disease	0	Mascarenhas et al 2010 (80)
Breast	Complete response	0	NICE TA 423 (59). EMBRACE study (page 152)
	Partial response	4.76	NICE TA 423 (59). EMBRACE study (page 152)
	Stable disease	45.49	NICE TA 423 (59). EMBRACE study (page 152)
	Progressive disease	49.75	NICE TA 423 (59). EMBRACE study (page 152)
Cholangiocarcinoma	Complete response	0.62	Valle 2010 (81)
	Partial response	25.47	Valle 2010 (81)
	Stable disease	55.28	Valle 2010 (81)
	Progressive disease	18.63	Valle 2010 (81)
CNS / glioma	Complete response	2.86	NICE TA23 (97)
	Partial response	25.71	NICE TA23 (97)
	Stable disease	71.43	NICE TA23 (97)
	Progressive disease	0	
Pancreas	Complete response	0	NICE TA440 (62)
	Partial response	3.53	NICE TA440 (62)
	Stable disease	30.59	NICE TA440 (62)
	Progressive disease	65.88	NICE TA440 (62)
Thyroid follicular and papillary	Complete response	0	Brose 2014 (98)
	Partial response	1.48	Brose 2014 (98)
	Stable disease	98.52	Brose 2014 (98)

Progressive disease	0

Abbreviations: TA = technology appraisal; NICE= National Institute for Health and Care Excellence

O.2 Tumour-specific utility values

O.2.1 HSUVs

In the absence of QoL data from the SoC/FLATIRON data (reported by Bokemeyer et al) used as the comparator in this analysis, utility values for SoC/FLATIRON arm were informed by several sources (tumour-specific utility values).

- For tumour sites with previously published NICE technology assessments, HSUVs were extracted directly from the submissions, leveraging the Committee's preferred assumptions on the values to use for the analysis. This was true for the following tumour sites: NSCLC, melanoma, colorectal, GIST, adult STS (non-GIST) (also used as proxy for bone sarcoma), breast, CNS/glioma, pancreas and thyroid.
- For cholangiocarcinoma, published health-state utility values could not be identified from the literature. Cholangiocarcinoma patients were assigned the weighted average of health state utilities for other tumour sites.
- For the remaining tumour sites (salivary, STS paediatric), targeted literature searches were conducted to identify appropriate utility information. The health state utility values for STS paediatric patients could not be identified and were set equivalent to the general STS population.
- For NSCLC, the health state utilities in the committee papers were adjusted by adverse reactions. However, an attempt to back-calculate was not successful, so this analysis uses the original health state utility values for progression-free from the cited study in the publicly available NICE appraisal documents. This approach was taken to avoid double-counting utility decrements due to adverse reactions.
- For breast cancer, the progression-free utility value was also adjusted for adverse reactions and response rates. Back-calculation was successful, so the value used for progression-free utility in this analysis only represents adjustment for response. Therefore, there was no double-counting when applying adverse reaction utility decrements.

A summary of the health state utility values used to generate a weighted average for SoC/FLATIRON is presented in Table 191.

Table 191 Tumour-specific utility values

Tumour sites	State	Value	Method or source
NSCLC	PF	0.707	NICE TA 520 (48); literature review conducted as part of submission
	PD	0.640	
Melanoma	PF	0.75	NICE TA357(50)
	PD	0.69	
Colorectal	PF	0.73	Recommended by ERG for NICE TA405 (51); Grothey 2013 (CORRECT trial) (52)
	PD	0.59	
GIST	PF	0.767	EQ-5D results from GRID (53)
	PD	0.647	
nGIST	PF	0.653	NICE TA185(55)

	PD	0.473	
Breast	PF	0.708	NICE TA423(59)
	PD	0.496	
CNS / Glioma	PF	0.6	NICE TA 23(97)
	PD	0.6	No data. Assumed the same as utility for PF state to be conservative
Pancreas	PF	0.671	NICE TA440 (62)
	PD	0.6	
Thyroid (follicular and papillary)	PF	[redacted]	[redacted]
	PD		
Salivary	PF	0.746	Liberato 2012 (49)
	PD	0.6	
STS paediatrics	PF	0.678	Zuluga-Sanchez 2018 (57); Delea 2014 (58)
	PD	0.425	
Cholangiocarcinoma	PF	0.698	Weighted average of other comparator treatments; Roth 2012(99)
	PD	0.536	

Abbreviations: PF = progression free; PD= progressive disease; STS= soft tissue sarcoma ; NICE= National Institute for Health and Care Excellence; TA= technology appraisal ; CNS= central nervous system; GIST= gastroinstestinal stromal tumour; ERG= evidence review group

O.2.2 Adverse reactions utility decrements

The model includes utility decrements for these AEs. These decrements vary by tumour site, as tumour-specific decrements were preferred. Utility decrements reported in the publicly available NICE appraisal documents and the SLR were preferred. In the absence of this data a systematic approach was taken, based on the following steps:

1. Use disutility values as reported in the committee papers by tumour site
2. Use estimates from other TAs for the same tumour site
3. Use information from a targeted literature review for the same tumour site
4. Identify a proxy from another tumour site and/or a previously used source

Utility decrements reported for the same tumour site were preferred overuse of utility decrements from other tumour site or making assumption for event proxies. The utility decrements for adverse reactions for larotrectinib were assumed to be the maximum disutility for the event across all tumour sites to conservatively account for the utility decrements.

Table 192 Tumour-specific adverse event utility decrements

Adverse event	Tumour site	Decrement	Justification
Anaemia	Larotrectinib	-0.204	Used highest utility decrement across tumour sites
	NSCLC	-0.08973	Nafees et al 2008(56)
	Melanoma	-0.085	NICE TA176 Assessment Group report, table 126 page 340 (100)
	Colorectal	-0.085	NICE TA176 AG report (100)
	Non-GIST (adults)	-0.08973	Nafees et al 2008(56)

	STS paediatrics	-0.119	Amdahl 2014(101), refers to RCC Swinburn 2010(102)
	Cholangiocarcinoma	-0.085	NICE TA176 AG report, table 126 page 340 (100)
	Pancreas	-0.204	Swinburn 2010(102)
Neutropenia	Larotrectinib	-0.08973	Used highest utility decrement across tumour sites
	Colorectal	-0.08973	Used highest utility decrement across tumour sites
	Non-GIST (adults)	-0.08973	Used highest utility decrement across tumour sites
	STS paediatrics	-0.08973	Amdahl 2014(101), refers to RCC Swinburn 2010(102)
	Breast	-0.007	NICE TA423 (59), table 51, page 212
	Cholangiocarcinoma	-0.08973	Nafees et al 2008(56)

Abbreviations: CEA: cost-effectiveness analyse, ERG: evidence review group, NSCLC: non-small cell lung cancer, STS: soft tissue sarcoma, TA: technology assessment

O.3 HCRU and costs associated with tumour-specific location

O.3.1 Tumour-specific treatment regimens

As described in Section 3.5, the approach taken to identifying the comparator is to consider SoC after patients have exhausted all satisfactory treatment options. This means later lines / last line of chemotherapy represented by the tumour specific treatment regimens presented in the tables below (by each tumour-site).

Table 193 Treatment regimen, NSCLC

Overview of comparator	
Generic name	Atezolizumab
ATC code	L01FF05
Mechanism of action	Atezolizumab is a monoclonal antibody targeting programmed death-ligand 1 (PD-L1). By inhibiting the interaction of PD-L1 with its receptors, PD-1 and B7.1, it prevents immune evasion by tumour cells, thereby restoring T-cell activation and promoting an antitumor immune response.
Method of administration	Atezolizumab is administered via intravenous infusion over 30–60 minutes, with dosing schedules typically every 2 to 4 weeks, depending on the specific clinical protocol.
Dosing	1,200 mg every 3 weeks
Dosing in the health economic model (including relative dose intensity)	1,200 mg every 3 weeks
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	1 vial (20ml) containing 1,200 mg atezolizumab

Abbreviations: N/A= not applicable
Source: EPAR atezolizumab(103) and Medicinpriser.dk(88)

Table 194 Treatment regimen, Salivary

Overview of comparator	
Generic name	Cisplatin + vinorelbine
ATC code	Cisplatin: L01XA01 Vinorelbine: L01CA04
Mechanism of action	Cisplatin: Cisplatin forms intra-strand DNA crosslinks by replacing chloride ligands with water, disrupting DNA replication and transcription, leading to cell death. Vinorelbine: Vinorelbine inhibits microtubule assembly by binding to tubulin, preventing mitotic spindle formation and causing cell cycle arrest and apoptosis.
Method of administration	Cisplatin: IV, slow infusion Vinorelbine: Is given IV as a slow infusion or orally in capsule form, with dosing schedules depending on the treatment regimen.
Dosing	Cisplatin: 50-100 mg/m² intravenously every 3 to 4 weeks. Vinorelbine: For intravenous administration, the typical dose is 25-30 mg/m² once a week or every other week, depending on the regimen and cancer type. For oral administration, the usual dose is 60-80 mg/m² once a week.
Dosing in the health economic model (including relative dose intensity)	Cisplatin: 80 mg/m2 on day 1 Vinorelbine: 25 mg/m2 on days 1 and 8 (oral)
Should the pharmaceutical be administered with other medicines?	Combination therapy
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Cisplatin: available in 50ml or 100ml of 1 mg/ml Vinorelbine: Oral Capsules: available in 20 mg, 30 mg, or 80 mg per capsule / IV: available in 1ml, 5ml, or 10 x 1ml (10 mg/ml)

Abbreviations: IV= intraveneous ; N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

Table 195 Treatment regimen, Melanoma

Overview of comparator	
Generic name	Pembrolizumab
ATC code	L01XC18

Overview of comparator	
Mechanism of action	Pembrolizumab is a monoclonal antibody targeting PD-1 (programmed cell death protein-1). By blocking the interaction of PD-1 with its ligands, PD-L1 and PD-L2, it enhances T-cell activation and restores immune-mediated tumour destruction.
Method of administration	IV use. It must be administered by infusion over 30 minutes
Dosing	The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.
Dosing in the health economic model (including relative dose intensity)	2mg/kg once every 3 weeks
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	If specified in the indication, patient selection for treatment with KEYTRUDA based on the tumour expression of PD-L1 should be confirmed by a validated test.
Package size(s)	1 vial of 4 mL of concentrate contains 100 mg of pembrolizumab.

Abbreviations: N/A= not applicable
Source: EPAR pembrolizumab (105)and Medicinpriser.dk(88)

Table 196 Treatment regimen, Colorectal

Overview of comparator	
Generic name	Trifluridine-tipiracil + bevacizumab
ATC code	Trifluridine-tipiracil: L01BC59 Bevacizumab: L01XC07
Mechanism of action	Trifluridine-tipiracil: Trifluridine is phosphorylated in cancer cells and incorporated into DNA, disrupting its function and inhibiting cell proliferation. Tipiracil inhibits thymidine phosphorylase, preventing trifluridine degradation and enhancing its bioavailability. Bevacizumab: Bevacizumab is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF), inhibiting angiogenesis and reducing tumour blood supply and growth.
Method of administration	Trifluridine-tipiracil: Oral, typically administered twice daily on days 1–5 and days 8–12 of a 28-day cycle. Bevacizumab: Intravenous infusion, typically given every 2–3 weeks, depending on the regimen. The first infusion is administered over 90 minutes, with subsequent infusions over 30–60 minutes if well tolerated.

Overview of comparator	
Dosing	Trifluridine-tipiracil: 35 mg/m2/dose administered orally twice daily on Days 1 to 5 and Days 8 to 12 of each 28-day cycle Bevacizumab: when in combination with trifluridine-tipiracil, the dose of bevacizumab is 5 mg/kg of body weight given once every 2 weeks
Dosing in the health economic model (including relative dose intensity)	Trifluridine-tipiracil: 35mg/m2 twice a day on days 1-5 and days 8-12 of 28-day cycle Bevacizumab: 5 mg/kg of body weight given once every 2 weeks
Should the pharmaceutical be administered with other medicines?	Combination therapy
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Trifluridine-tipiracil: vial of 20 pcs (oral tablets) (20mg per tab) Bevacizumab: 1 vial of 16 ml (25 mg/ml)

Abbreviations: N/A= not applicable
Source: EMA EPAR, trifluridine-tipiracil (106)and Medicinpriser.dk(88)

Table 197 Treatment regimen, STS adults - GIST

Overview of comparator	
Generic name	Regorafenib
ATC code	L01EX05
Mechanism of action	Regorafenib is a multikinase inhibitor targeting several tyrosine kinases involved in tumour angiogenesis (e.g., VEGFR1-3, TIE2), oncogenesis (e.g., KIT, RET), and the tumour microenvironment (e.g., PDGFR, FGFR). By inhibiting these pathways, it suppresses tumour growth and metastasis.
Method of administration	Oral use
Dosing	The recommended dose of regorafenib is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy.
Dosing in the health economic model (including relative dose intensity)	160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle.
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	84 pcs tablets of 40 mg

Abbreviations: N/A= not applicable
Source: EMA EPAR, Stivarga (107)and Medicinpriser.dk(88)

Table 198 Treatment regimen, STS adults – non-GIST

Overview of comparator	
Generic name	Trabectidin
ATC code	L01CX01
Mechanism of action	Trabectedin binds to the minor groove of deoxyribonucleic acid (DNA), bending the helix to the major groove. This binding to DNA triggers a cascade of events affecting several transcription factors, DNA binding proteins, and DNA repair pathways, resulting in perturbation of the cell cycle.
Method of administration	IV
Dosing	The typical dose is 1.5 mg/m² every three weeks, infused over 24 hours via a central venous line, often with corticosteroid premedication to reduce inflammation and side effects.
Dosing in the health economic model (including relative dose intensity)	1.22 mg/m2 body surface area, administered as IV over 24 hours with a 3-week interval between cycles.
Should the pharmaceutical be administered with other medicines?	20 mg of dexamethasone IV 30 minutes prior (in monotherapy). However, this is not modelled.
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	1 vial of 0.25mg/dose or 1mg/dose (powder for concentrate for solution for infusion)

Abbreviations: N/A= not applicable
Source: EMA EPAR, Yondelis (108)and Medicinpriser.dk(88)

Table 199 Treatment regimen, STS paediatrics

Overview of comparator	
Generic name	Irinotecan + vincristine
ATC code	Irinotecan: L01XX19 Vincristine: L01CA02
Mechanism of action	Irinotecan: Irinotecan is a prodrug converted into its active metabolite, SN-38, which inhibits topoisomerase I. This enzyme is essential for DNA unwinding during replication and transcription. The inhibition leads to DNA damage and apoptosis in rapidly dividing cells. Vincristine: Vincristine binds to tubulin, inhibiting microtubule formation, thereby disrupting the mitotic spindle and causing mitotic arrest and apoptosis in cancer cells.
Method of administration	Irinotecan: IV administration Vincristine: IV administration

Overview of comparator	
Dosing	Irinotecan: dose of 125-350 mg/m² every 2 or 3 weeks, depending on the regimen and cancer type. Infusion time is usually 30–90 minutes. Vincristine: dose of 1.4 mg/m² (maximum 2 mg) weekly. It is given as a slow IV injection (usually over 1 minute) or as part of a chemotherapy combination regimen.
Dosing in the health economic model (including relative dose intensity)	Irinotecan: 50 mg/m2 per day for 5 days at weeks 1, 4, 13, 25, 34, 46, 49. Vincristine: 1.5mg/m2 on day 1 of weeks 1, 2, 4, 5, 13, 14, 25, 26, 34, 35, 46, 47, 49, 50.
Should the pharmaceutical be administered with other medicines?	Combination therapy
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Irinotecan: available in vials containing 5 mL or 15ml or 25ml (20 mg/ml) and vials containing 180 ml, 200ml, 220ml or 240ml (1.5 mg/ml). Vincristine: available in 1ml or 2ml vials of 1mg/ml

Abbreviations: N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

Table 200 Treatment regimen, Breast

Overview of comparator	
Generic name	Treatment of physician's choice, including: • Vinorelbine (50 mg) – 18.38% • Vinorelbine (Oral) – 18.38% • Vinorelbine (Oral) – 18.38% • Gemcitabine (1200mg) – 27.72% • Docetaxel (80mg) – 5.97% • Paclitaxel (300mg) – 15-62%
ATC code	Vinorelbine: L01CA04 Gemcitabine: L01BC05 Docetaxel: L01CD02 Paclitaxel: L01CD01
Mechanism of action	Vinorelbine: see description for salivary (Table 194) Gemcitabine: Gemcitabine is phosphorylated intracellularly to active metabolites, which inhibit DNA synthesis by incorporating into DNA and disrupting elongation, causing apoptosis. Docetaxel: Docetaxel stabilizes microtubules by preventing depolymerization, inhibiting mitosis and inducing apoptosis in cancer cells. Paclitaxel: Paclitaxel promotes microtubule assembly and prevents disassembly, disrupting mitosis and inducing apoptosis in dividing cells.
Method of administration	Vinorelbine: see description for salivary (Table 194) Gemcitabine: IV infusion over 30 minutes. Docetaxel: IV infusion over 1 hour Paclitaxel: IV infusion over 3 hours

Overview of comparator	
Dosing	Vinorelbine: see description for salivary (Table 194) Gemcitabine (1200mg): dosing is 1000–1250 mg/m² on days 1, 8, and 15 of a 28-day cycle. Docetaxel: doses of 75–100 mg/m² every 3 weeks Paclitaxel: typically doses of 175 mg/m² every 3 weeks
Dosing in the health economic model (including relative dose intensity)	Vinorelbine (50 mg): 30 mg/m2 weekly for 6 months Vinorelbine (Oral): 60mg/m2 weekly for first 3 administrations Vinorelbine (Oral): 80mg/m2 weekly for subsequent administrations for 6 months Gemcitabine (1200mg): 1250mg/m2 two times per 21-day cycle for 6 months Docetaxel (80mg): 100mg/m2 once per 21-day cycle for 6 months Paclitaxel (300mg): 175mg/m2 once per 21-day cycle for 6 months
Should the pharmaceutical be administered with other medicines?	Docetaxel: often with corticosteroid premedication to reduce hypersensitivity (not modelled)
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Vinorelbine: see description for salivary (Table 194) Gemcitabine: available vials of 25ml or 50ml containing 40 mg/ml / or vials of 120 ml, 140ml, 160ml, 180ml, 200ml, or 220ml containing 10 mg/ml / or vials containing 1g or 2g or 26.3ml containing 28 mg/ml. Docetaxel: available vials of 1ml, 4ml, or 8ml containing mg/ml, 80mg/ml, or 160 mg/ml, respectively. Paclitaxel: available vials of (powder) 100mg or 20ml vial containing 5 mg/ml / or vials of 25ml, 50ml, 16.7 ml containing 6mg/ml.

Abbreviations: N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

Table 201 Treatment regimen, Cholangiocarcinoma

Overview of comparator	
Generic name	Gemcitabine + cisplatin
ATC code	Gemcitabine: see description for breast (Table) Cisplatin: see description for salivary (Table 194)
Mechanism of action	Gemcitabine: see description for breast (Table) Cisplatin: see description for salivary (Table 194)
Method of administration	Gemcitabine: see description for breast (Table) Cisplatin: see description for salivary (Table 194)

Overview of comparator	
Dosing	Gemcitabine: see description for breast (Table) Cisplatin: see description for salivary (Table 194)
Dosing in the health economic model (including relative dose intensity)	Gemcitabine: 1000 mg/m2 on days 1 and 8 every 3 weeks Cisplatin: 25 mg/m2 on days 1 and 8 every 3 weeks
Should the pharmaceutical be administered with other medicines?	Combination therapy
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Gemcitabine: see description for breast (Table) Cisplatin: see description for salivary (Table 194)

Abbreviations: N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

Table 202 Treatment regimen, CNS / Glioma

Overview of comparator	
Generic name	Lomustine
ATC code	L01AX01
Mechanism of action	alkylating agent that induces DNA damage by forming covalent bonds with DNA bases, leading to crosslinking and strand breakage. This inhibits DNA replication and transcription, ultimately causing cell cycle arrest and apoptosis, especially in rapidly dividing cancer cells.
Method of administration	Orally in capsule form,
Dosing	Doses of 75-130 mg/m² body surface area every 6 to 8 weeks
Dosing in the health economic model (including relative dose intensity)	110mg/m2 day on Day 1 every 6 weeks
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Available package: 20 pcs of 40mg (each)

Abbreviations: N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

Table 203 Treatment regimen, Pancreas

Overview of comparator	
Generic name	5-fluorouracil + leucovorin
ATC code	5-fluorouracil: L01BC02 Leucovorin: V03AF05

Overview of comparator	
Mechanism of action	5-fluorouracil: pyrimidine analogue that is metabolized into active metabolites, primarily 5-FdUMP, which inhibits thymidylate synthase. This blocks DNA synthesis and leads to cell death, especially in rapidly proliferating cancer cells. Leucovorin: (folinic acid) enhances the effects of 5-FU by stabilizing the binding of 5-FdUMP to thymidylate synthase, thus potentiating its cytotoxic action.
Method of administration	5-fluorouracil: IV administration Leucovorin: IV administration
Dosing	In combination (bimonthly): leucovorin: 200 mg/m² by intravenous infusion over two hours, followed by a bolus of 400 mg/m² of 5-fluorouracil and a 22-hour infusion of 5-fluorouracil (600 mg/m²) for two consecutive days, every 2 weeks on days 1 and 2."
Dosing in the health economic model (including relative dose intensity)	5-fluorouracil: bolus of 400 mg/m² of 5-fluorouracil and a 22-hour infusion of 5-fluorouracil (600 mg/m²) for two consecutive days, every 2 weeks on days 1 and 2. Leucovorin: 200mg/m^2 administered on day 2-3 (46 hours) by IV at home
Should the pharmaceutical be administered with other medicines?	Combination therapy
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	5-fluorouracil: available in vials of 10ml, 50ml, 100ml containing 50mg/ml (IV) Leucovorin: available in vials of 10 x 10ml, 10 x 35ml, 10 x100ml, 10ml, 35ml, or 100 ml containing 10 mg/ml.

Abbreviations: N/A= not applicable
Source: Aalborg University Hospital (109), Medicinpriser.dk (88) and SmpC for leucovorin-teva

Table 204 Treatment regimen, Thyroid follicular and papillary

Overview of comparator	
Generic name	Sorafenib
ATC code	L01EX02
Mechanism of action	Multikinase inhibitor that targets several key pathways involved in tumour growth and angiogenesis, including RAF kinase, VEGFR-2, VEGFR-3, PDGFR-β, and c-kit. By inhibiting these kinases, sorafenib reduces tumour cell proliferation and prevents tumour blood vessel formation.
Method of administration	Orally administered
Dosing	400 mg twice daily
Dosing in the health economic model (including relative dose intensity)	Average daily dose in DECISION: 651 mg

Overview of comparator	
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	112 pcs tablets containing 200mg per tablet.

Abbreviations: N/A= not applicable
Source: Promedicin.dk(104) and Medicinpriser.dk(88)

O.3.2 Tumour-specific cost and health care resource use identification, measurement and valuation

O.3.2.1 Drug acquisition costs

As mentioned in 11.1, the drug acquisition costs modelled for the chosen comparator, SoC/FLATIRON, is estimated based on a weighted average of tumour-specific treatment regimens, listed below in Table 205. The frequency and dosing can be found in Table 193; Table 194; Table 195; Table 196; Table 197; Table 198; Table 199; Table 200; Table 201; Table 202; Table 203; and Table 204.

Table 205 Drug dosing and total acquisition costs, tumour-specific regimens

Regimen	Administration	Dose	Relative dose intensity	Frequency	Vial sharing	Cost per treatment cycle [DKK]	Modelled cost per day [DKK]
Comparator							
NSCLC							
Atezolizumab	IV	1200 mg	N/A	Every 3rd week	No	28,953	1,379
Salivary (cisplatin plus vinorelbine)							
Cisplatin	IV	80 mg/m²	N/A	Every 3rd week	No	74	4
Vinorelbine (50 mg)	IV	25 mg/m²	N/A	Day 1 and 8 every 3 weeks	No	2,291	109
Melanoma							
Pembrolizumab	IV	2 mg/kg	N/A	Every 3rd week	No	30,203	1,438
Colorectal							
Trifluridine-tipiracil	Oral	35 mg/m²	N/A	Twice a day on days 1-5 and days 8-12 of 28-days	No	15,000	536
Bevacizumab	IV	5 mg/kg	N/A	Every 2nd week	No	8,152	582
STS adults (GIST)							
Regorafenib	Oral	160 mg	N/A	Once daily for 3 weeks followed by 1 week off therapy	No	19,218	686
STS adults (non-GIST)							
Trabectedin (1 mg)	IV	1.22 mg/m²	N/A	Every 3rd week	No	29,711	1,415

Trabectedin (0.25 mg)	IV	1.22 mg/m^2	N/A	Every 3rd week	No	3,949	188
STS paediatrics (irinotecan + vincristine)							
Irinotecan	IV	50 mg/m^2	N/A	Every day for 5 days at weeks 1, 4, 13, 25, 34, 46, 49	No	44	0.13
Vincristine	IV	1.5 mg/m^2	N/A	1.5 mg/m^2 on day 1 of weeks 1, 2, 4, 5, 13, 14, 25, 26, 34, 35, 46, 47, 49, 50	No	351	1
Breast (TPC)							
Vinorelbine	IV	30 mg/m^2	N/A	Once weekly	No	3,837	185
Vinorelbine	Oral	60 mg/m^2 for first 3 admins	N/A	Once weekly for first 3 administrations	No	371	18
		80 mg/m2 for subsequent admins	N/A	Once weekly	No	433	21
Gemcitabine	IV	1250 mg/m^2	N/A	2 times per 3 weeks	No	1,309	66
Docetaxel	IV	100 mg/m^2	N/A	Every 3rd week	No	335	16
Paclitaxel	IV	175 mg/m^2	N/A	Every 3rd week	No	300	14
Cholangiocarcinoma (gemcitabine + cisplatin)							
Gemcitabine (2000 mg)	IV	1000 mg/m^2	N/A	Day 1 and 8 every 3 weeks	No	770	37
Cisplatin	IV	25 mg/m^2	N/A	Day 1 and 8 every 3 weeks	No	200	10
Glioma/CNS							
Lomustine	Oral	110 mg/m^2	N/A	Every 6 weeks	No	982	23
Pancreas (5-fluorouracil + leucovorin)							
5-fluorouracil	IV	1000 mg/m^2	N/A	Once every 2 weeks	No	140	10
Leucovorin	IV	200 mg/m2	N/A	Day 2-3 every 2 weeks	No	136	6
Thyroid follicular and papillary							
Sorafenib	Oral	400 mg - Average daily dose in DECISION: 651 mg	N/A	Twice daily	No	642	642

Abbreviations: NSCLC, non-small cell lung cancer; IV, Intravenous; GIST, gastrointestinal stromal tumour; TPC, treatment of physician's choice; CNS, central nervous syste

Table 206 Pharmaceutical costs used in the model

Pharmaceutical	Strength	Package size	Pharmacy purchase price [DKK])(88)
Larotrectinib (oral)	100 mg	56 pcs	42,678
	25 mg	56 pcs	10,670
	2000 mg	1 bottle	15,242
Entrectinib (oral)	100 mg	30 pcs	6,934
Vinorelbine (oral)	20 mg	1 pcs	413
Trifluridine-tipiracil (oral)	20 mg	20 pcs	5,000
Lomustine (oral)	40 mg	20 pcs	4,200
Sorafenib (oral)	200 mg	112 pcs	17,980
Regorafenib (oral)	40 mg	84 pcs	19,218
5-fluorouracil (IV)	50 mg/ml	10 ml	70
Atezolizumab (IV)	1200 mg/ml	1 vial	28,953
Bevacizumab (IV)	25 mg/ml	16 ml	6,987
Cisplatin (IV)	1 mg/ml	50 ml	100
Docetaxel (IV)	20 mg/ml	4 ml	150
Gemcitabine (IV)	10 mg/ml	120 ml	310
	10 mg/ml	200 ml	385
Irinotecan (IV)	20 mg/ml	5 ml	125
Leucorovin (IV)	10 mg/ml	100 ml	340
Paclitaxel (IV)	6 mg/ml	50 ml	202
Pembrolizumab (IV)	25 mg/ml	4 ml	21,574
Trabectedin (IV)	1 mg/ml	1 vial	14,855
	0.25 mg/ml	1 vial	3949
Vinorelbine (IV)	10 mg/ml	5 ml	1,240
Vincristine (IV)	1 mg/ml	2 ml	660

Abbreviations: IV, intravenous
Source: Medicinpriser.dk

O.3.2.1.1 Tumour-specific administration costs

For some tumour sites in the stratified comparator arm, some drugs were administered through intravenous therapy (IV) route and were dosed according to average BSA. The average BSA were taken as reported in the relevant NICE TA, where applicable, or a published clinical trial informing the inputs if this information was not available in the appraisal. The dosing regimens reflects Danish recommended dosing regimen for included therapies.

Refer to Table 205 for overview of frequency and method of administration.

Table 207 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Intravenously	Refer to Table	1,550.00	11MA98	DRG-tariffs 2024 (74)
Oral	Refer to Table	0	N/A	N/A

Abbreviations: DRG= diagnosis-related groups; N/A= not applicable

O.3.2.2 Disease management cost

For the comparator arm, as per the other model inputs, healthcare resource use was modelled independently for each tumour site. Where a NICE TA was available, the approach selected was to use the HCRU inputs used to inform the Committee's preferred assumptions.

Data collection for HCRU inputs for the tumour locations without a NICE TA was based on the SLR output where possible and otherwise broader targeted searches were conducted for published articles, where no evidence was found in the SLR.

The cost of the progression-free or progressive disease health states could take the form of a one-off cost at state initiation (start-up costs) and recurrent costs per cycle.

Where a source for a tumour site provided an aggregate cost, or HCRU details for start-up costs, these were implemented in the model. If the source did not present a start-up cost, start-up costs were assumed null, remaining consistent with the replication of methodology used within the specific TA or evidence source.

All tumours except for glioma/CNS and cholangiocarcinoma reported per cycle health state costs or detailed HCRU. No HCRU source was identified for cholangiocarcinoma. Therefore, the health state costs for cholangiocarcinoma were based on a weighted average of all other tumour sites

Table 208 lists the resource use associated with the tumour-sites. These inputs are used to generate a weighted average cost for the SoC/FLATIRON arm used in the base case analysis. OBS: One cycle is one week. Table 209 lists the HCRU unit costs.

Table 208 Disease management frequency used in the model

Tumour site	Health state	Component	Frequency per cycle, start-up	Frequency per cycle	Reference
NSCLC	PF	Outpatient visit	N/A	Every 6th week	NICE TA 374 (69)
		Chest X-Ray	N/A	Every 8th week	NICE TA 374 (69)
		CT scan	N/A	Every 50th week	NICE TA 374 (69)
		ECG	N/A	Every 50th week	NICE TA 374 (69)
		Community nurse visit	N/A	Every 2nd week	NICE TA 374 (69)
		Clinical nurse specialist	N/A	Every 30th week	NICE TA 374 (69)
		GP surgery	N/A	Every 30th week	NICE TA 374 (69)
Salivary	PF	Dental visit	N/A	Every 18th week	NICE TA 490 (70)
		Depression management	N/A	Every 31st week	NICE TA 490 (70)
		Nutritional support	N/A	Every 7th week	NICE TA 490 (70)
		Pain and symptom management	N/A	Every 8th week	NICE TA 490 (70)
		Speech therapy	N/A	Every 18th week	NICE TA 490 (70)
		Hematologic growth factor/transfusion	Every 27th week	N/A	NICE TA 490 (70)

Tumour site	Health state	Component	Frequency per cycle, start-up	Frequency per cycle	Reference
		Hematologic growth factor/transfusion (follow-up)	N/A	Every 15th week	NICE TA 490 (70)
		Xerostomia management	N/A	Every 17th week	NICE TA 490 (70)
		Antiemetics	N/A	Every 7th week	NICE TA 490 (70)
		Management of oral and GI mucositis	N/A	Every 14th week	NICE TA 490 (70)
Melanoma	PF	Medical oncologist visit	N/A	Every 3rd week	NICE TA 268 (71)
		Radiation oncologist visit	N/A	Every 100th week	NICE TA 268 (71)
		GP visit	Every 13th week	Every 50th week	NICE TA 268 (71)
		Oncology inpatient visit	Every 6th week	Every 50th week	NICE TA 268 (71)
		Plastic surgeon visit	Every 33rd week	Every 100th week	NICE TA 268 (71)
		Full blood count	Every week	Every 4th week	NICE TA 268 (71)
		Complete metabolic panel	Every week	Every 4th week	NICE TA 268 (71)
		Lactate dehydrogenase	Every week	Every 4th week	NICE TA 268 (71)
		CT scan	2.46*	Every 6th week	NICE TA 268 (71)
		MRI scan	Every 17th week	Every 100th week	NICE TA 268 (71)
		Bone scan	Every 5th week	Every 1000th week	NICE TA 268 (71)
		ECG	Every 17th week	Every 100th week	NICE TA 268 (71)
		Chest x-ray	Every 5th week	Every 13th week	NICE TA 268 (71)
Colorectal	PF	Medical oncologist visit	N/A	Every 4th week	NICE TA 405 (51)
		Nurse	N/A	Every 17th week	NICE TA 405 (51)
		Blood test	N/A	Every 2nd week	TA405 (51) Nordsjællandshospital.dk (110)
		CT scan	Every week	Every 3rd week	TA405 (51) Nordsjællandshospital.dk (110)
STS adults (GIST)	PF	CT scan	Every 4th week	Every 33rd week	GRID (53)
		MRI scan	Every 100th week	Every 100th week	GRID (53)
		Full blood count	Every 2nd week	Every 17th week	GRID (53)

Tumour site	Health state	Component	Frequency per cycle, start-up	Frequency per cycle	Reference
		Liver function test	Every 2nd week	Every 20th week	NICE TA 488 (53)
STS adults (non-GIST)	PF	Reported average cost per month, based on a cost of illness study and calculated using study follow-up time.	N/A	Every week	NICE TA 185 (55)
STS paediatrics	PF	Assumed half of progressed state	N/A	Every week	Proxy values from Amdahl 2014 (73)
Breast	PF	Oncologist visit	N/A	Every 4th week	NICE TA 423 (59)
		GP visit	N/A	Every 4th week	NICE TA 423 (59)
		CT scan	N/A	Every 13th week	NICE TA 423 (59)
CNS/Glioma	PF	MRI scan	3.00**	Every 25th week	NICE TA 23 (97)
		GP visit	N/A	Every week	NICE TA23 (97)/ Rigshospitalet.dk (111)
		Full blood count	N/A	Every week	NICE TA23 (97) / Rigshospitalet.dk (111)
Pancreas	PF	Outpatient visit	Every week	Every 3rd week	NICE 440 (62)
		Nurse	N/A	Every 8th week	NICE 440 (62)
		CT scan	Every week	Every 13th week	NICE 440 (62)
		MRI scan	Every 10th week	N/A	NICE 440 (62)
		Full blood count	Every week	Every week	NICE 440 (62)
		Liver function test	Every week	Every week	NICE 440 (62)
		Ultrasound	Every 20th week	N/A	NICE 440 (62)
		Tumour marker test	N/A	Every 13th week	NICE 440 (62)
Thyroid	PF	Full blood count	N/A	Every 13th week	NICE TA 535 (63)
		Coagulation test	N/A	Every 13th week	NICE TA 535 (63)
		Urine test	N/A	Every 13th week	NICE TA 535 (63)
		Liver function test	N/A	Every 2nd week	NICE TA 535 (63)
		Thyroid function test	N/A	Every 4th week	NICE TA 535 (63)
		Protein test	N/A	Every 13th week	NICE TA 535 (63)
		Bone scan	N/A	Every 13th week	NICE TA 535 (63)
		MRI	N/A	Every 13th week	NICE TA 535 (63)
		CT scan	N/A	Every 13th week	NICE TA 535 (63)
		Oncology visit	N/A	Every 13th week	NICE TA 535 (63)

Abbreviations: N/A= not avaiable / or applicable; PF= progression-free; TA= technology appraisal; CNS= central nervous system; MRI=; CT=; GP= general practitioner;
*CT scan frequency is a weighted avarage, based on Table 32 in NICE submission (112)

**The glioma NICE TA (110), only reported a magnetic resonance imaging (MRI) procedure at baseline, after 2 treatment cycles, and at 6-month follow-up. While this was cost spread over time, it could not be implemented on a per-cycle basis. Thus, the model calculated the total cost of 3 MRIs and applied it as a one-off cost to glioma.

Table 209 Disease management costs

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Oncologist visit	Refer to Table 208	1,989	17MA98	DRG 2024 (74)
GP-visit	Refer to Table 208	156	N/A	DMC catalogue for unit cost 2024
Nurse/health specialist visit	Refer to Table 208	462	N/A	DMC catalogue for unit cost 2024
Plastic surgeon visit	Refer to Table 208	1,989	17MA98	DRG 2024 (74)
Dental visit	Refer to Table 208	558	N/A	DMC catalogue for unit cost 2024
Depression management	Refer to Table 208	558	N/A	DMC catalogue for unit cost 2024
Nutritional supportive care visit	Refer to Table 208	347	N/A	DMC catalogue for unit cost 2024
Speech therapy visit	Refer to Table 208	558	N/A	DMC catalogue for unit cost 2024
Tests				
CT scan (one area)	Refer to Table 208	2,021	30PR07	DRG 2024 (74)
CT scan (three areas)	Refer to Table 208	2,585	30PR06	DRG 2024 (74)
MRI scan	Refer to Table 208	6,887	27PR03; 30PR01; 30PR02; 30PR03; 30PR04	DRG 2024 (74)
Ultrasound	Refer to Table 208	1,930	30PR09; 30PR10; 30PR11	DRG 2024 (74)
Full blood count	Refer to Table 208	23	N/A	Takskort 2024 (90)
Liver function test	Refer to Table 208	23	N/A	Takskort 2024 (90)
Bone scan	Refer to Table 208	2,021	30PR07	DRG 2024 (74)
ECG	Refer to Table 208	5,741	30PR09; 30PR10; 30PR11; 30PR12	DRG 2024 (74)
Chest X-ray	Refer to Table 208	1,697	30PR18	DRG 2024 (74)
Total protein	Refer to Table 208	1,989	DD487; WNCNOXXXX	DRG 2024 (74)
Urinalysis	Refer to Table 208	1,989	DD487; ZZ0149	DRG 2024 (74)
Clinical/laboratory test	Refer to Table 208	1,989	DD487; ZZ0149	DRG 2024 (74)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Coagulation panel (PT/PT-INR, PTT)	Refer to Table 208	1,989	DD487: FB4303	DRG 2024 (74)
Haematologic growth factor transfusions (first cycle)	Refer to Table 208	6,723	16PR01	DRG 2024 (74)
Haematologic growth factor transfusions (subsequent cycle)	Refer to Table 208	6,723	16PR01	DRG 2024 (74)

Abbreviations: DRG = diagnosis-related groups; N/A= not applicable / or available; ECG= Electrocardiogram; PTT= Partial Thromboplastin Time, PT= Prothrombin Time, PR-INR= Prothrombin Time-International Normalized Ratio; MRI= Magnetic Resonance Imaging; CT= computer tomografi

O.3.2.3 Tumour-specific adverse event costs

Tumour agnostic AE cost per event based on past NICE TAs. Only AE incidence data reported for available tumour-sites. For missing tumour-sites, the incidence has been assumed to be 0%.

Table 210 Adverse event incidence, tumour-specific

Tumour site	Anaemia (%)	Cost (DKK)	Source	Neutropenia (%)	Cost (DKK)	Source
NSCLC	2.30 %	2,111	Rittmeyer et al. 2017 (77)	N/A	N/A	N/A
Salivary	0.60 %	2,111	NICE TA357 (50)- (trial KEYNOTE-002)	N/A	N/A	N/A
Colorectal	18.18 %	2,111	Mayer 2015(78)	37.88 %	2,111	Mayer 2015 (78)
STS adults (non-GIST)	14.41 %	2,111	Demetri et al., 2015 (79)	37.06 %	2,111	Demetri et al., 2015 (79)
STS paediatrics	28 %	2,111	Mascarenhas et al 2010 (80)	34 %	2,111	Mascarenhas et al 2010 (80)
Breast	N/A	N/A	N/A	5.26 %	2,111	NICE TA 423(59)
Cholangiocarcinoma	7.58	2,111	Valle 2010 (81)	25.25 %	164	Valle 2010 (81)
Pancreas	6.7 %	2,111	NICE TA 440(62)	N/A	N/A	N/A

Abbreviations: N/A = not available; STS= soft tissue sarcoma; GIST= gastrointestinal stromal tumour; NSCLC= non-small cell lung cancer

O.3.2.4 Patient costs

The patient costs associated with the comparator arm were estimated by calculating the weighted average of societal costs from each specific tumour site, following the same approach as reported for the larotrectinib arm in Section 11.7.

Table 211 outlines the assumptions concerning the time allocated to treatment administration and disease management activities for each tumour site. The frequency of administration of each specific tumour site is reported in Table 205.

To avoid double counting, patient time during the start-up phase was calculated based on the maximum frequency reported in previous NICE submissions (reported in the Tab 'Unit cost' in the model) for the specific tumour type. For informal care during the start-up phase, a similar calculation was employed, but with an additional hour included for transportation per hospital visit, multiplied by the frequency of visits associated with disease management during start-up.

Table 211 Patient costs associated with tumour specific sites

Activity		Time spent [hours]	Frequency
Hospital visit, NSCLC	Total patient hours:	1.67 (113)	Every 3rd week
	Informal care:	2.50	Every 3rd week
	Start-up – total patient hours:	N/A	N/A
	Start-up – informal care:	N/A	N/A
Hospital visit, Salivary	Total patient hours:	1.63 (114)	Every 3rd week
	Informal care:	2.11	Every 3rd week
	Start-up – total patient hours:	0.52	N/A
	Start-up – informal care:	0.78	N/A
Hospital visit, Melanoma	Total patient hours:	1.34 (115)	Every 3rd week
	Informal care:	2.11	Every 3rd week
	Start-up – total patient hours:	4.92	N/A
	Start-up – informal care:	7.38	N/A
Hospital visit, Colorectal	Total patient hours:	1.38 (110)	Every 2nd weeks
	Informal care:	2.08	Every 2nd weeks
	Start-up – total patient hours:	2.00	N/A
	Start-up – informal care:	1.00	N/A
Hospital visit, STS adults (GIST)	Total patient hours:	0.12 (116)	0.00
	Informal care:	N/A	N/A
	Start-up – total patient hours:	1.12	N/A
	Start-up – informal care:	0.00	N/A
Hospital visit, STS adults (non-GIST)	Total patient hours:	10.17 (117)	Every 3rd week
	Informal care:	N/A	N/A
	Start-up – total patient hours:	1.12	N/A
	Start-up – informal care:	0.00	N/A
Hospital visit, STS paediatrics	Total patient hours:	N/A	N/A
	Informal care:	4.54	Every 10th day
	Start-up – total patient hours:	N/A	N/A
	Start-up – informal care:	0.00	N/A
Hospital visit, Breast	Total patient hours:	1.43 (118, 119)	Every 12th day
	Informal care:	2.25	Every 12th day
	Start-up – total patient hours:	N/A	N/A

Activity		Time spent [hours]	Frequency
	Start-up – informal care:	N/A	N/A
Hospital visit, CNS/Glioma	Total patient hours:	2.00 (111)	Every 6th weeks
	Informal care:	3.00	Every 6th weeks
	Start-up – total patient hours:	6.00	N/A
	Start-up – informal care:	9.00	N/A
Hospital visit, Pancreas	Total patient hours:	2.13 (120)	Every 2nd weeks
	Informal care:	3.38	Every 2nd weeks
	Start-up – total patient hours:	2.00	N/A
	Start-up – informal care:	3.00	N/A
Hospital visit, Thyroid follicular and papillary	Total patient hours:	1.08 (121)	0.00
	Informal care:	1.62	0.00
	Start-up – total patient hours:	0.00	N/A
	Start-up – informal care:	0.00	N/A

** total hours + 1 hour per frequency

Abbreviations: N/A, not available / not applicable

Appendix P. DMC request regarding larotrectinib data for paediatric and adult population, ePAS8

The following appendix describes tables on the ePAS8 data, divided by paediatric and adult population (total n=302). The following tables includes data on best overall response and ORR, time to response, DOR, PFS, and OS for paediatrics and adults from the ePAS8 data set (DCO 20 July 2023).

Table 212 Best Overall response and overall response rate for paediatrics and adults based on IRC assessments (extended primary analysis set 8, ePAS8), DCO 20 July 2023

Status	Pediatrics (< 18 years) (N=99)	Adults (18 years and older) (N=203)
Best Overall Response[1,2]		
Any complete response	51 (52%)	31 (15%)
Complete response (CR)	35 (35%)	30 (15%)
Pathological complete response (pCR)	16 (16%)	1 (0%)
Partial response (PR)	34 (34%)	79 (39%)
Stable disease (SD)	9 (9%)	46 (23%)
Progressive disease (PD)	3 (3%)	29 (14%)
Not evaluable (NE)	2 (2%)	18 (9%)
Overall Response Rate[3,4]		
Number of evaluable patients	99	203
Number of patients with CR + pCR + PR	85 (86%)	110 (54%)
95% confidence interval	(77%, 92%)	(47%, 61%)

Percentages are based on the number of patients in the analysis set or subgroup.
A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.
The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.
Pathological complete response was previously referred to as surgical CR.
[1] Based on IRC assessments.
[2] Best overall response classification based on radiologist and clinician assessments.
[3] Overall response rate (%) is defined as the proportion of patients with best overall response of confirmed CR, pCR, or PR. Responses were confirmed by a repeat assessment no less than 28 days. Patients with unconfirmed CR following PR are considered confirmed responders.
[4] 95% confidence interval was calculated using Clopper-Pearson method.
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Table 213 Overall response rate for paediatrics and adults based on IRC assessment (extended primary analysis set 8, ePAS8) DCO 20 July 2023

Age Group	Number of Patients	Number of Patients with CR, pCR or PR[1]	ORR	95% CI[2]
Overall	302	195	65%	(59%, 70%)
Adults (18 years and older)	203	110	54%	(47%, 61%)
Pediatrics (< 18 years)	99	85	86%	(77%, 92%)

Percentages are based on the number of patients in the analysis set or subgroup.
A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.
The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1. Pathological complete response was previously referred to as surgical CR.
[1] CR=complete response, PR=partial response, pCR=pathological complete response.
[2] 95% confidence interval was calculated using Clopper-Pearson method. NC=Not calculated.
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Table 214 Time to response for paediatrics and adults based on IRC assessments (subgroup of extended primary analysis set 8, ePAS8, with confirmed CR, pCR or PR) DCO 20 July 2023

Status	Pediatrics (< 18 years) (N=99)	Adults (18 years and older) (N=203)
Patients with Best Response of Confirmed CR, pCR, or PR[1,2]	85	110
Time to Response (months)[3]		
Median	1.84	1.84
25th,75th percentiles	1.77, 1.94	1.74, 2.07
Minimum, Maximum	0.89, 7.29	0.92, 22.90
Time to Response		
2 months or less	66 (78%)	82 (75%)
> 2 to 4 months	13 (15%)	12 (11%)
> 4 to 6 months	5 (6%)	6 (5%)
> 6 to 9 months	1 (1%)	5 (5%)
> 9 months	0 (0%)	5 (5%)

Percentages are based on the number of patients in the analysis set or subgroup.
A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.
The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.
Pathological complete response was previously referred to as surgical CR.
[1] Based on IRC assessments.
[2] Best overall response classification based on radiologist and clinician assessments.
[3] Time to response is defined as the number of months elapsed between the date of the first dose of Larotrectinib and the first documentation of objective response (CR, pCR, or PR whichever occurred earlier) that was subsequently confirmed.
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Table 215 Duration of response for paediatrics and adults based on IRC assessments (subgroup of extended primary analysis set 8, ePAS8, with confirmed CR, pCR or PR) DCO 20 July 2023

Status	Pediatrics (< 18 years) (N=99)	Adults (18 years and older) (N=203)
Patients with Best Response of Confirmed CR, pCR, or PR[1,2]	85	110
Response Status[2,3]		
Disease progression	33 (39%)	44 (40%)
Censored	52 (61%)	66 (60%)
Reason Censored		
Alive without documented disease progression	39 (46%)	62 (56%)
Surgical resection of tumor without pCR	13 (15%)	0 (0%)
Anti-cancer therapy date before death date	0 (0%)	4 (4%)
Duration of Response		
6 months or less	25 (29%)	17 (15%)
> 6 to 12 months	8 (9%)	18 (16%)
> 12 to 18 months	6 (7%)	13 (12%)
> 18 to 24 months	6 (7%)	12 (11%)
> 24 to 36 months	16 (19%)	18 (16%)
> 36 to 48 months	11 (13%)	16 (15%)
> 48 to 60 months	6 (7%)	12 (11%)
> 60 to 72 months	4 (5%)	3 (3%)
> 72 months	3 (4%)	1 (1%)
Duration of Response (months)[4,5]		
Median	43.3	54.7
95% confidence interval for median	27.1, NE	32.5, NE
Minimum, Maximum	0.0+, 73.7+	1.9+, 72.4+
Duration of Follow-up (months)[4]		
Median	36.9	36.3
25th,75th percentiles	8.9, 54.8	19.5, 50.7
Rate (%) of Duration of Response[4,5]		
6 months or more	88%	90%
95% confidence interval	(80%, 95%)	(84%, 95%)
12 months or more	82%	77%
95% confidence interval	(73%, 91%)	(68%, 85%)
18 months or more	75%	72%
95% confidence interval	(65%, 86%)	(64%, 81%)
24 months or more	69%	66%
95% confidence interval	(57%, 80%)	(57%, 76%)
36 months or more	53%	57%
95% confidence interval	(41%, 66%)	(47%, 68%)
48 months or more	44%	51%
95% confidence interval	(30%, 59%)	(39%, 62%)
60 months or more	40%	37%
95% confidence interval	(26%, 55%)	(17%, 56%)
72 months or more	40%	37%
95% confidence interval	(26%, 55%)	(17%, 56%)

Percentages are based on the number of patients in the analysis set or subgroup.
A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.
The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1.
Pathological complete response was previously referred to as surgical CR.
[1] Based on IRC assessments.
[2] Best overall response classification based on radiologist and clinician assessments.
[3] Status as of the patient's last disease assessment on or before visit cutoff.
[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[5] 95% confidence interval was calculated using Greenwood's formula.
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Table 216 Progression-free survival for paediatrics and adults based on IRC assessments (extended primary analysis set 8, ePAS8) DCO 20 July 2023

Status	Pediatrics (< 18 years) (N=99)	Adults (18 years and older) (N=203)
Progression Status[1,2,3]		
Progressed	39 (39%)	111 (55%)
Censored	60 (61%)	92 (45%)
Reason Progressed		
Died without disease progression beforehand	3 (3%)	29 (14%)
Progressed	36 (36%)	82 (40%)
Reason Censored		
Alive without documented disease progression	43 (43%)	78 (38%)
Surgical resection of tumor without pCR	15 (15%)	0 (0%)
No evaluable postbaseline disease assessments	2 (2%)	7 (3%)
Anti-cancer therapy date before death date	0 (0%)	7 (3%)
Duration of Progression-free Survival		
6 months or less	22 (22%)	81 (40%)
> 6 to 12 months	23 (23%)	34 (17%)
> 12 to 18 months	2 (2%)	14 (7%)
> 18 to 24 months	6 (6%)	11 (5%)
> 24 to 36 months	18 (18%)	27 (13%)
> 36 to 48 months	13 (13%)	13 (6%)
> 48 to 60 months	7 (7%)	16 (8%)
> 60 to 72 months	3 (3%)	5 (2%)
> 72 months	5 (5%)	2 (1%)
Duration of Progression-free Survival (months)[4,5]		
Median	40.2	16.0
95% confidence interval for median	28.1, NE	9.9, 33.0
Minimum, Maximum	0.03+, 77.2+	0.03+, 74.3+
Duration of Follow-up (months)[4]		
Median	38.7	35.8
25th,75th percentiles	9.1, 56.7	16.6, 52.2
Rate (%) of Progression-free Survival[4,5]		
6 months or more	91%	68%
95% confidence interval	(85%, 97%)	(61%, 74%)
12 months or more	78%	54%
95% confidence interval	(69%, 87%)	(47%, 61%)
18 months or more	77%	49%
95% confidence interval	(67%, 86%)	(42%, 56%)
24 months or more	69%	47%
95% confidence interval	(59%, 80%)	(40%, 54%)
36 months or more	54%	38%
95% confidence interval	(42%, 66%)	(31%, 46%)
48 months or more	44%	37%
95% confidence interval	(31%, 58%)	(29%, 45%)
60 months or more	38%	30%
95% confidence interval	(24%, 52%)	(20%, 40%)
72 months or more	38%	24%
95% confidence interval	(24%, 52%)	(11%, 37%)

Percentages are based on the number of patients in the analysis set.
A pathological CR was a CR achieved by patients who were treated with larotrectinib and subsequently underwent surgical resection with no viable tumor cells and negative margins on postsurgical pathology evaluation.
The pre-surgical best response for these patients was reclassified pathological CR after surgery following RECIST v1.1. Pathological complete response was previously referred to as surgical CR.
[1] Based on IRC assessments.
[2] Progression status based on radiologist and clinician assessments.
[3] Status as of the patient's last disease assessment on or before visit cutoff.
[4] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[5] 95% confidence interval was calculated using Greenwood's formula.
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Table 217 Overall survival for paediatrics and adults (extended primary analysis set 8, ePAS8)

DCO 20 July 2023

Status	Pediatrics (< 18 years) (N=99)	Adults (18 years and older) (N=203)
Vital Status[1]		
Dead	11 (11%)	88 (43%)
Censored	88 (89%)	115 (57%)
Reason Censored		
Alive	80 (81%)	114 (56%)
Study discontinuation	8 (8%)	1 (0%)
Duration of Overall Survival (months)[2,3]		
Median	NE	48.7
95% confidence interval for median	NE, NE	38.3, NE
Minimum, Maximum	3.7, 87.4+	0.4, 90.2+
Duration of Follow-up (months)[2]		
Median	54.3	39.6
25th,75th percentiles	34.8, 67.6	26.3, 59.9
Rate (%) of Overall Survival[2,3]		
6 months or more	99%	87%
95% confidence interval	(97%, 100%)	(83%, 92%)
12 months or more	95%	77%
95% confidence interval	(90%, 99%)	(71%, 83%)
18 months or more	93%	68%
95% confidence interval	(87%, 98%)	(61%, 75%)
24 months or more	93%	64%
95% confidence interval	(87%, 98%)	(57%, 71%)
36 months or more	90%	59%
95% confidence interval	(84%, 96%)	(52%, 66%)
48 months or more	90%	50%
95% confidence interval	(84%, 96%)	(42%, 58%)
60 months or more	88%	46%
95% confidence interval	(80%, 95%)	(38%, 55%)
72 months or more	85%	42%
95% confidence interval	(75%, 94%)	(32%, 52%)

Percentages are based on the number of patients in the analysis set.
[1] Status as of the last contact on or before visit cutoff.
[2] Estimate based on Kaplan-Meier method. NE = Not estimable. + = Censored observation.
[3] 95% confidence interval was calculated using Greenwood's formula.
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