Medicinrådet

Bilag til Medicinrådets vurdering af selpercatinib til 1.linjebeh. af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. selpercatinib til 1.linjebeh. af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft
2. Ansøgers endelige ansøgning vedr. selpercatinib til 1.linjebeh. af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

23.01.2026

LSC/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	18.02.2026
Leverandør	Eli Lilly
Lægemiddel	Retsevmo (selpercatinib)
Ansøgt indikation	Selpercatinib til behandling af voksne med RET-fusionspositiv fremskreden ikke-småcellet lungekræft (NSCLC), som ikke tidligere er behandlet med en RET-hæmmer
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet nedenstående pris på Retsevmo (selpercatinib), Tabel 1. [redacted]

Tabel 1: Forhandlingsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Retsevmo	40 mg (56 stk.)	17.258,11	[redacted]	[redacted]
Retsevmo	80 mg (56 stk.)	34.516,25	[redacted]	[redacted]

Amgros har på nuværende tidspunkt nedenstående aftalepris på Retsevmo (selpercatinib) [redacted]

Tabel 2: Udbudspris [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Retsevmo	40 mg (168 stk.)	53.100,00	[redacted]	[redacted]
Retsevmo	80 mg (112 stk.)	70.802,54	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

I dansk klinisk praksis får patienter platinbaseret kemoterapi, i enkelte tilfælde i kombination med immunterapi. I anden linje er standardbehandlingen Retsevmo.

Tabel 3 viser lægemiddeludgiften for Retsevmo for et års behandling. [redacted]

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Retsevmo	40 mg (168 stk.)	Under 50 kg: 120 mg to gange dagligt, oralt	[redacted]	[redacted]
		50 kg eller derover: 160 mg to gange dagligt, oralt	[redacted]	[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet		Link til vurdering
England	Delvist anbefalet		Link til vurdering
Sverige	Ikke vurderet	Vurderes ikke nationalt	Link til vurdering

Opsummering

[redacted]

Application for the assessment of selpercatinib (Retsevmo®) for patients with treatment-naïve RET fusion-positive non-small cell lung cancer (NSCLC)

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information

Contact information

Contact information	
Name	**Anders Troelsgaard Buchholt**
Title	Pricing & Access Manager Denmark
Phone number	[redacted]
E-mail	[redacted]
Name (External representation)	**N/A**
Title	N/A
Phone number	
E-mail	

Table of contents

Tables and Figures

Abbreviations

Abbreviation	Definition
AE	Adverse event
AIC	Akaike information criteria
AIP	Apotekernes indkøbspris (Pharmacy purchasing price)
ALK	Anaplastic lymphoma kinase
BIC	Bayesian information criteria
BICR	Blinded independent central review
BOR	Best overall response
BSA	Body surface area
CEM	Cost-effectiveness model
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CUA	Cost-utility analysis
DCO	Data cutoff
DCR	Disease control rate
DKK	Danish Krone
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRG	Diagnosis-related groups
DSU	Decision support unit
ECG	Electrocardiogram
ECOG	Easter cooperative oncology group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European organisation for research and treatment of cancer
EORTC-8D	European organisation for research and treatment of cancer 8-Dimensions
EQ-5D	EuroQol 5-Dimensions
EQ-5D-5L	EuroQol 5-Dimensions 5-Level
EQ-5D-VAS	EuroQol 5-Dimension visual analogue scale
ESS	Effective sample size
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IRC	Independent review committee
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KOL	Key opinion leader
MAIC	Matched-adjusted indirect comparison
MRI	Magnetic resonance imaging
MTC	Medullary thyroid carcinoma
N/A	Not available or applicable
NE	Not estimated
NICE	National Institute for Health and Care Excellence
NMB	Net monetary benefit

Abbreviation	Definition
NR	Not reached
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD-L1	Programmed-death ligand 1
PFS	Progression-free survival
PR	Partial response
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PT	Preferred terminology
QALY	Quality-adjusted life-years
QLQ-C30	Quality of life questionnaire-core 30
QoL	Quality of life
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection
RKKP	Regionernes Kliniske Kvalitetsudviklingsprogram
RNA	Ribonucleic acid
ROS-1	ROS proto-oncogene 1
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TA	Technology appraisal
TC	Thyroid carcinoma
TEAE	Treatment-emergent adverse event

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Retsevmo
Generic name	Selpercatinib
Therapeutic indication as defined by EMA	Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion positive non-small cell lung cancer (NSCLC) not previously treated with a rearranged during transfection (RET) inhibitor.
Marketing authorization holder in Denmark	Eli Lilly and Company
ATC code	L01EX22
Combination therapy and/or co-medication	Given as monotherapy
(Expected) Date of EC approval	April 2022
Has the medicine received a conditional marketing authorization?	A European Commission Decision (approval) for a conditional marketing authorisation for selpercatinib as monotherapy for the treatment of patients with advanced RET fusion-positive NSCLC, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy was granted in February 2021.
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Retsevmo as monotherapy is indicated for the treatment of adults with: • Advanced RET fusion positive NSCLC not previously treated with a RET inhibitor • Advanced RET fusion positive solid tumours, when treatment options not targeting RET provide limited clinical benefit, or have been exhausted Retsevmo as monotherapy is indicated for the treatment of adults and adolescents 12 years and older with: • Advanced RET fusion positive thyroid cancer who are radioactive iodine-refractory (if radioactive iodine is appropriate) • Advanced RET mutant medullary thyroid cancer (MTC)
Other indications that have been evaluated by the DMC (yes/no)	Yes. Assessed and partially recommended for RET positive thyroid cancer or NSCLC (2022 reassessment) (1).
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If no, why not? Different treatment practices across the countries
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Selpercatinib (Retsevmo®) – film coated tablets in the following package sizes: 40 mg x 56 pcs

Overview of the medicine	
	40 mg x 168 pcs 80 mg x 112 pcs

Abbreviations: NSCLC, non-small cell lung cancer; RET, rearranged during transfection; MTC, medullary thyroid carcinoma

2. Summary table

Summary	
Indication relevant for the assessment	Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion positive non-small cell lung cancer (NSCLC) not previously treated with a RET inhibitor.
Dosage regimen and administration	Oral. The recommended dose of Retsevmo based on body weight is: • Less than 50 kg: 120 mg twice daily. • 50 kg or greater: 160 mg twice daily.
Choice of comparator	Pemetrexed + carboplatin ± pembrolizumab
Prognosis with current treatment (comparator)	NSCLC accounts for 80-85% of the approximately 5,000 annual lung cancer cases in Denmark, with 55% of patients presenting metastatic, incurable disease at diagnosis. The 1-year survival rate for lung cancer is 52% (per 2022), and the 5-year survival rate is 18% (per 2022) (2). RET alterations, found in 1-5% of NSCLC cases (mostly non-squamous), are common in younger, healthier, non-smoking patients and rarely co-occur with EGFR or ALK mutations. While the prognostic impact of RET alterations is unclear, they are associated with favourable factors like non-squamous histology and better general health. It is estimated that 20-30 Danes annually are diagnosed with incurable RET-positive NSCLC (3) (1).
Type of evidence for the clinical evaluation	The main efficacy and safety evidence for selpercatinib is derived from the LIBRETTO-431 trial (ITT-pembrolizumab population, n=261). This trial is a randomized controlled phase 3 study, which compared selpercatinib against platinum-based and pemetrexed therapy with or without pembrolizumab (4). However, due to immature OS data from the LIBRETTO-431 trial, LIBRETTO-001 and KEYNOTE-189 have been used in order to compare long-term survival of patients in LIBRETTO-001 to survival of patients treated with platinum-based chemotherapy + pembrolizumab in KEYNOTE-189 study.
Most important efficacy endpoints (Difference/gain compared to comparator)	**Overall response rate (ORR)** (DCO May 2023): • Selpercatinib (n=159): 133 (84.6%) (CI, 77.0 – 89.0) • Pemetrexed + platinum ± pembrolizumab (n=102): 64 (62.7%) (CI, 52.6 -72.1) **Median overall survival (OS)** • LIBRETTO-431, 159 patients in the selpercatinib arm: 33.05 months (95% CI, 33.05-NE); 2-year OS rate = 74.1% (CI, 64.7, 81.4) vs 102 patients in the pemetrexed + platinum ± pembrolizumab arm: NE; 2-year OS rate = 80.0% (CI, 69.4, 87.2) • LIBRETTO-001 / KEYNOTE-189 (MAIC, refer to Section 7.1.3), NR (37.8, NR); HR = 0.48 (CI, 0.34, 0.66) **Median progression-free survival (PFS)** • LIBRETTO-431, 159 patients in the selpercatinib arm: 24.8 months (16.89, NE); 2-year PFS rate =52.2% (CI, 42.5, 61.0) vs 102 patients in the pemetrexed + platinum ±

Summary	
	pembrolizumab arm: 11.17 (CI, 8.77, 16.76); 2-year OS rate = 32.6% (CI, 21.5, 44.2) **Duration of response (DOR)** • LIBRETTO-431, 133 patients in the selpercatinib arm: 24.2 months (17.9-NE); 2-year PFS rate =57.2% (46.1, 66.8) vs 64 patients in the pemetrexed + platinum ± pembrolizumab arm: 11.99 months (9.7-23.3); 2-year OS rate = 28.2% (11.0, 48.4)
Most important serious adverse events for the intervention and comparator	The most frequently reported (≥2%) any-Grade SAEs by preferred terminology (PT) in the selpercatinib arm were: • Pleural effusion (4.4%), and • Hepatic function abnormal (2.5%). The most frequently reported (≥2%) any-Grade SAEs by in the control arm were: • Anaemia (2.0%) • Intestinal obstruction (2.0%) • Neutropenia (2.0%) • Platelet count decreased (2.0%) • Pneumonia (2.0%) • Pyrexia (2.0%), and • Spinal cord compression (2.0%).
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L was collected for patients in the LIBRETTO-431 study. Health economic model: For progression-free: EQ-5D 0.861 (SD, 0.155), progressed: EQ-5D 0.826 (SD, 0.208). Utility values is equal in both treatment arms (LIBRETTO-431)
Type of economic analysis that is submitted	Cost-utility analysis. Partitioned survival model
Data sources used to model the clinical effects	Head-to-head data from LIBRETTTO-431 (PFS data and some OS data available) and more mature OS data from the LIBRETTO-001 and KEYNOTE-189 trial (data cut January 2023), refer to Section 8.
Data sources used to model the health-related quality of life	EQ-5D-5L collected in the LIBRETTO-431 trial. Danish weighted EQ-5D estimates from the LIBRETTO-431 trial were applied in the model
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Parameters with largest impact on the ICER includes discount rates (for outcomes and costs), HSUVs for PD, diagnostic costs, followed by the health state costs for PD.
Number of eligible patients in Denmark	Eli Lilly estimates that fewer than 10 (≥10) RET fusion-positive patients are identified per year in Denmark.
Budget impact (in year 5)	[redacted]

Abbreviations: NSCLC, non-small cell lung cancer; RET, rearranged during transfection; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; OS, overall survival; PFS, progression-free survival; ORR, overall response rate; DOR, duration of response; SAE, serious adverse event; PT, preferred term; NE, not estimated; NR, not reached; EQ-5D-5L; SD, standard deviation

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

3.1 The medical condition

Lung cancer is termed “primary” when tumours first originate in lung tissue, usually in the cells lining the bronchi and other parts of the lung (e.g. bronchioles or alveoli). Lung cancer is divided into two main subtypes based upon the microscopic appearance of the tumour cells: small cell lung cancer and non-small cell lung cancer (NSCLC) (5). These subtypes progress and are treated in different ways, making their distinction clinically important. NSCLC accounts for the majority (80–85%) of lung cancer cases in Denmark and can be sub-divided further into three histological groups: adenocarcinoma (the most common subtype in both men and women), large-cell undifferentiated carcinoma and squamous cell carcinoma. While the treatment for these subtypes is generally similar, there are still some differences (5).

NSCLC accounts for 80-85% of Denmark's approximately 5,000 annual lung cancer cases, with 55% diagnosed as incurable. The 1-year survival rate is 52%, and 5-year survival is 18% (2). NSCLC can be further classified by genetic markers such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocation and ROS proto-oncogene 1 (ROS-1) rearrangements (6). RET fusion is one such marker, and overall, RET alterations are observed in approximately 0.5–2% of tumour tissues across cancer types (1, 7). Within lung cancer, RET alterations are found almost exclusively in non-squamous NSCLC (in approximately 1–5%) but are also present in other histologies (1). Data from Aarhus University Hospital indicate that the incidence of RET fusion in NSCLC in Denmark is at the lower end of this range (8). RET fusions are most commonly seen in adenocarcinoma but have also been reported in mixed adenosquamous histology (9).

Based on the latest Danish Medicines Council (DMC) assessment within this specific indication (RET fusion-positive NSCLC) (pralsetinib, 2023 (8)), it has been reported that recent studies have identified several molecular alterations and biomarkers in NSCLC, including oncogenic drivers like EGFR, ALK, ROS1, and RET fusions. RET fusion occurs in 1-2% of NSCLC cases, a similar frequency to ALK and ROS1 mutations. RET fusion-positive patients are typically younger, female, non-smokers or light smokers, and often have lung adenocarcinoma. Common RET fusion partners in NSCLC include KIF5B and CCDC6, with less common partners such as NCOA4, TRIM33, and others.

With approximately 5,000 diagnosed lung cancer patients, with 55% having stage IIIb-IV disease (2,750 patients). Around 85% of these cases were non-small cell lung cancer (approximately 2,338 patients), and 75% of them were non-squamous (1,758 patients. Assuming 1-2% of NSCLC cases have RET fusions and a test frequency of 100%, this would result in 18-35 RET fusion-positive patients. However, reported in the submission, clinicians in Denmark have reported that, although some NSCLC patients are tested for

RET fusions, only a few RET fusion-positive cases are identified each year. Additionally, the frequency of ALK- and ROS1-positive NSCLC cases in Denmark appears to be slightly lower than in the literature, suggesting that the incidence of RET fusions in NSCLC patients may be around 1.5% in Denmark, lower than the 1-2% prevalence reported globally (8). In addition, based on the DMC assessment of selpercatinib from 2022, the expert committee estimated that around 20-30 Danish patients annually are estimated diagnosed with incurable RET-positive NSCLC, where targeted therapies like selpercatinib may improve outcomes (1).

3.1.1 Rearranged during transfection (RET)

RET is a transmembrane receptor protein tyrosine kinase, which is present on the surface of several tissue types. The RET protein is encoded by the RET gene, which under normal circumstances plays a role in cell growth, division and specialisation. Abnormal RET activation occurs through two mechanisms associated with malignancy: mutations and fusions, with the latter typically present in NSCLC (9). RET mutations and RET fusions are two different mechanisms of alterations leading to the overactivation of the RET protein, which can act as an oncogenic driver (1). Fusions are generated by an inversion of the short and long arms of chromosome 10 (10). Chromosomal rearrangement in this way leads to the joining of a partner gene and the RET intracellular kinase domain, which is preserved and activated in the resulting protein (11).

3.1.2 Patient characteristics and prognosis

Both EGFR and ALK alterations can occur alongside RET fusion in NSCLC, though both have a very low probability (1-3% of RET-positive cases). Therefore, the majority of patients diagnosed with RET fusion will not have concurrent targetable EGFR or ALK alterations (8).

Patients exhibiting RET fusion-positive NSCLC share many clinical features with those patients who have tumours driven by other oncogenic mutations, such as ALK, ROS-1 and EGFR (12). Patients with RET fusion-positive NSCLC are typically of a younger age (≤65 years) with minimal or no prior history of smoking (5) (9) (13). Data from a retrospective real-world registry study (IMMUNOTARGET registry, including patients from Europe, the US, Israel and Australia), found that 66.7% of patients with RET fusion-positive tumours had never smoked (compared with 6.7% who were current smokers) and that the median patient age was 54.5 years (range: 29–71) (14). RET fusions in NSCLC tumours have also been found to be associated with female gender and Asian ethnicity (14).

The prognostic significance of RET alterations in NSCLC is unknown. Data from a registry study showed that patients with RET alterations had significantly improved overall survival, but this difference became statistically insignificant after adjusting for differences between the populations. RET alterations were thus associated with favourable prognostic factors, such as non-squamous histology, younger age, lower frequency of smokers, and better overall performance status (1). However, based on current evidence the real prognostic influence of RET mutations remains unclear (13).

3.1.3 Clinical symptoms and burden of disease

NSCLC represents a humanistic and economic burden on society. Disease symptoms caused by NSCLC, and the various therapies used to cure or manage them, impact the

emotional and physical functioning of patients. However, there is a paucity of data on the HRQoL impact of RET fusion-positive NSCLC specifically. As such, these data presented relate to NSCLC, regardless of genomic alteration and/or biomarker expression, although they are anticipated to reflect the experience of patients with RET fusion-positive NSCLC.

The symptomatic and health-related quality of life (HRQoL) burden of NSCLC are closely related. The earliest stage of NSCLC is often asymptomatic (15). However, as NSCLC progresses, patients experience greater symptom burden and subsequently lower quality of life (QoL) (16).

Common physical symptoms of NSCLC include fatigue (98%), loss of appetite (98%), respiratory problems (94%), cough (93%), pain (90%) and blood in sputum (70%) (17). At advanced stages, the cancer may spread to the lymph nodes, brain, liver, adrenal glands or the bones, bringing additional symptoms associated with the secondary tumour's location (18). Brain metastases occur frequently in patients with RET rearrangements, with an estimated lifetime prevalence of 46% in Stage IV disease, resulting in additional symptoms (e.g. confusion, headaches and changes in behaviour), complications to treatment and poorer patient prognosis and quality of life (19).

The health-related quality of life (HRQoL) in patients with NSCLC is significantly lower than that of the general population. A recent study by Hvidberg et al. (2023) (20) reported a mean EuroQol 5-Dimensions (EQ-5D) utility score of 0.684 among Danish patients with malignant neoplasm of the bronchi or lung. In comparison, the general population in Denmark has higher utility scores, with age-specific averages of 0.902 (16–24 years), 0.893 (25–34 years), 0.874 (35–44 years), 0.839 (45–54 years), 0.832 (55–64 years), 0.798 (65–74 years), and 0.749 (75+ years). The health state utility values used in the model (refer to Section 10) reflect this decline. These figures highlight the substantial impact of NSCLC on HRQoL, even when disease progression is controlled.

3.2 Patient population

As previous mentioned in Section 3.1, RET alterations are found almost exclusively in non-squamous NSCLC (in approximately 1-2%). However, according to the DMC and data, suggesting that the incidence of RET fusions in NSCLC patients may be around 1.5% in Denmark, lower than the 1-2% prevalence reported globally (8). Assuming 1-2% of NSCLC cases have RET fusions and a test frequency of 100%, this would result in 18-35 RET fusion-positive patients. However, reported in the submission, clinicians in Denmark have reported that, although some NSCLC patients are tested for RET fusions, only a few RET fusion-positive cases are identified each year. In addition, the applicant of the pralsetinib assessment from 2023 states that a project by Regionernes Kliniske Kvalitetsudviklingsprogram (RKKP) Denmark from 2018-2020 found that only 6% of NSCLC patients were tested for RET fusions, identifying 13 RET fusion-positive cases. Most testing occurred at Vejle Hospital, but there was a lack of consistent reporting across sites. Given missing data and the absence of RET fusion inclusion in annual reports, Eli Lilly estimates that fewer than 10 RET fusion-positive patients are identified per year in Denmark.

Table 1 Incidence and prevalence in the past 5 years

Year	2020	2021	2022	2023	2024
Incidence in Denmark	10	10	10	10	10

Year	2020	2021	2022	2023	2024
Prevalence in Denmark	1.5%	1.5%	1.5%	1.5%	1.5%
Global prevalence *	1-2%	1-2%	1-2%	1-2%	1-2%

Source: DMC, Selpercatinib 2022; DMC, pralsetinib 2023(1, 3) (8)

The economic analysis focused on treatment-naïve adults with RET fusion-positive advanced or metastatic nonsquamous NSCLC, informed by the LIBRETTO-431 trial. Based on prior assessments from the DMC, it was estimated that 20–30 RET-positive patients are diagnosed annually in Denmark (1) (8). Programmed death-ligand 1 (PD-L1) expression is an important factor in treatment decisions, with patients having PD-L1 ≥50 typically considered for immunotherapy and those with lower expression being less likely to benefit. The previous assessment estimated that 8 patients would have PD-L1 ≥50 and 16 would have PD-L1 <50. Combining these estimates, it was concluded that approximately 10 patients annually would be eligible for treatment with selpercatinib as first-line therapy for NSCLC in Denmark.

This aligns with the earlier estimation that RET fusion-positive patients are relatively low in number due to the limited testing and underreporting in Denmark, with fewer than 10 RET fusion-positive NSCLC cases being identified annually (refer to Table 1).. As testing becomes routine, the number of eligible patients for selpercatinib treatment is expected to increase.

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	10	10	10	10	10

3.3 Current treatment options

Patients with incurable NSCLC and RET fusion are currently offered first-line treatment according to the same algorithm as comparable patients without a mutation allowing for targeted treatment. Since RET fusion is predominantly seen in adenocarcinomas, the treatment approach is based on how this subgroup of patients with NSCLC is currently managed.

The DMC's latest guidelines on NSCLC treatment do not specifically address patients with RET fusion, as they are focused more on mutations that allow targeted therapies (such as EGFR, ALK, or ROS1) (21). While there has been recent progress in the availability of RET-targeted therapies, such as selpercatinib, these guidelines are primarily designed for broader mutation categories. Nevertheless, RET fusion-positive patients are gradually being integrated into these evolving treatment frameworks as new therapies and indications are considered.

Therefore, based on the latest DMC assessment in RET fusion positive NSCLC from 2023 (8), the treatment algorithm is described as follows: in the first line, patients with PD-L1 expression ≥50% are offered monotherapy with a checkpoint inhibitor (atezolizumab, cemiplimab, and pembrolizumab are considered equivalent in the DMC’s drug recommendations for incurable NSCLC (21)). Patients with PD-L1 expression <50% are offered pembrolizumab in combination with platinum-based chemotherapy and pemetrexed.

In the second line, patients with NSCLC and RET fusion can be treated with selpercatinib, which is currently indicated for use after platinum-based chemotherapy and/or immunotherapy. On March 23, 2022, the DMC recommended selpercatinib as a potential standard treatment for patients who have experienced progression after previous platinum-based chemotherapy, typically those who have not received monotherapy with a checkpoint inhibitor in the first line (1).

3.4 The intervention

Selpercatinib is a highly selective inhibitor of fusion, mutant and wild-type products involving the proto-oncogene receptor tyrosine kinase RET. The drug acts as an inhibitor that controls the RET kinase enzyme and prevents tumour cell growth (1) (22). Selpercatinib has shown promising activity in advanced RET-positive solid tumours and is approximately 250-fold more selective for RET relative to other kinases (23).

An EC Decision (approval) for a conditional marketing authorisation for selpercatinib as monotherapy for the treatment of patients with advanced RET fusion-positive NSCLC, who require systemic therapy following prior treatment with immunotherapy and/or platinum-based chemotherapy was granted in February 2021.

Table 3 Key descriptive information of selpercatinib

Overview of intervention	
Indication relevant for the assessment	The EMA approved indication is: Retsevmo as monotherapy is indicated for the treatment of adults with advanced RET fusion positive NSCLC not previously treated with a RET inhibitor.
ATMP	N/A
Method of administration	Selpercatinib was administered in oral form
Dosing	The maximum recommended dose is as follows (22): • Less than 50 kg body weight: 120 mg twice daily. • 50 kg body weight or greater: 160 mg twice daily
Dosing in the health economic model (including relative dose intensity)	Patients received 160 mg of selpercatinib twice daily (starting dose) in the LIBRETTO-431. Dose distribution in LIBRETTO-431
Should the medicine be administered with other medicines?	No. Selpercatinib is monotherapy.
Treatment duration / criteria for end of treatment	Treatment should be continued until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	N/A
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	RET-fusion positive patients are identified via genetic testing. The transition to next generation sequencing panel tests for common oncogenic drivers (ALK translocation, EGFR mutation, ROS-1 rearrangements and RET) are currently being performed at most of the treating university hospitals in Denmark and is expected to be standard practice in most hospitals.
Package size(s)	Selpercatinib (Retsevmo®) – film coated tablets in the following package sizes (24): 40 mg x 56 pcs 40 mg x 168 pcs

Overview of intervention
80 mg x 112 pcs

Abbreviations: EMA, European Medicines Agency; RET, rearranged during transfection; NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; ROS, ROS protooncogene; EGR, epidermal growth factor receptor

3.4.1 The intervention in relation to Danish clinical practice

As previously mentioned, the DMC's treatment guidelines for incurable NSCLC do not include specific recommendations for RET fusion-positive patients. These patients are treated using broader algorithms, such as monotherapy with checkpoint inhibitors for PD-L1 ≥50% or combinations of platinum-based chemotherapy with pembrolizumab and pemetrexed for PD-L1 <50%. These regimens are not tailored to the specific biology of RET fusion, potentially leading to suboptimal outcomes for this subgroup. The EMA's recent approval of selpercatinib for first-line use provides an opportunity to introduce a mutation-targeted therapy earlier in the treatment pathway, aligning with the growing emphasis on personalized oncology care.

3.5 Choice of comparator(s)

In accordance with the treatment guidelines published by the DMC and the recent DMC assessment of RET fusion positive NSCLC, the relevant comparators for this assessment are pembrolizumab alone or in combination with platin based chemotherapy. In this submission, the chosen comparator is pemetrexed + carboplatin ± pembrolizumab (8, 21). Table 4 the key descriptive information of the comparator treatments.

Table 4 Key descriptive information of pemetrexed + carboplatin ± pembrolizumab

Overview of comparator	
Generic name	Pemetrexed + carboplatin ± pembrolizumab
ATC code	Pemetrexed: L01BA04 Carboplatin: L01XA02 Pembrolizumab: L01FF02
Mechanism of action	Pemetrexed: Pemetrexed is a folate analogue metabolic inhibitor that exerts its action by disrupting key enzymatic pathways essential for DNA and RNA synthesis. It targets thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT), which are crucial for purine and thymidine nucleotide synthesis. By blocking these enzymes, pemetrexed induces cell cycle arrest and apoptosis, particularly in rapidly dividing cancer cells. Carboplatin: Carboplatin predominantly acts by attaching alkyl groups to the nucleotides, leading to the formation of monoadducts, and DNA fragmenting when repair enzymes attempt to correct the error. 2% of carboplatin's activity comes from DNA cross-linking from a base on one strand to a base on another, preventing DNA strands from separating for synthesis or transcription. Pembrolizumab: pembrolizumab is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment

Method of administration	Pemetrexed: intravenously Carboplatin: intravenously Pembrolizumab: intravenously
Dosing	Pemetrexed: Pemetrexed is administered intravenously as an infusion over ten minutes, typically on a three-week cycle. The standard dose is 500 mg/m² of body surface area. Carboplatin: Usually 400 mg/m^2 body surface area once every fourth weeks. Pembrolizumab: IV administered, typically over thirty minutes- Dosing regimens include either a fixed dose of 200 mg every three weeks or 400 mg every six weeks. It is used alone or in combination with chemotherapy, such as pemetrexed and a platinum agent (e.g., cisplatin or carboplatin)
Dosing in the health economic model (including relative dose intensity)	Pemetrexed: 500 mg/m^2, once every 3 weeks (dose intensity of 88.6%) Carboplatin: 400 mg/m^2, once every 3 weeks, limited to 4 cycles (dose intensity of 90.8%) Pembrolizumab: 200mg every third weeks (dose distribution in LIBRETTO-431)
Should the medicine be administered with other medicines?	Combination therapy regimen: Pemetrexed + carboplatin ± pembrolizumab
Treatment duration/ criteria for end of treatment	Pemetrexed: (given indefinitely) or until disease progression, unacceptable toxicity, or other reason for discontinuation Carboplatin: up to 4 cycles Pembrolizumab: 21-day cycles of pembrolizumab (up to 35 cycles, 2 years)
Need for diagnostics or other tests (i.e. companion diagnostics)	Pemetrexed: N/A Carboplatin: N/A Pembrolizumab: N/A
Package size(s)	Pemetrexed: Several package sizes, including IV use vial (glass) 10 mg/ml x 10ml and 50ml vials IV use vial (glass) 25 mg/ml x 4ml and 20ml vials IV use vial (glass) 100 mg in one vial IV use vial (glass) 500 mg in one vial Carboplatin: Several package sizes, including IV use vial (glass) 10 mg/ml x 15 ml and 45 ml vials Pembrolizumab: IV use vial (glass) 25 mg/ml of 4 ml vials.

Abbreviations:N/A, not avaialble or applicable; IV, intravenous; DNA, deoxyribonuclic acid; RNA, ribonucleic avid; PD-L1, programmed death-ligand 1
Source: EMA amlita; EMA keytruda; Promedicin.dk (25-29)

3.6 Cost-effectiveness of the comparator(s)

Selpercatinib has been assessed by DMC in 2021 for treatment of RET-altered thyroid cancer or non-small cell lung cancer and received a negative recommendation, and was reassessed in 2022, after which a positive (but partly) recommendation followed. Selpercatinib for RET fusion positive NSCLC in second line was compared with platin-based chemotherapy. For NSCLC, the DMC assessed that, despite the uncertain data, it is likely that patients live longer when treated with selpercatinib compared to treatment with docetaxel, which is the current standard treatment for this patient group (1).

Pembrolizumab in combination with platinum and pemetrexed is recommended in the DMC treatment guidelines as a first-line therapy for patients with NSCLC (21) (8). As such, pembrolizumab/platinum/pemetrexed can be reasonably considered cost-effective and aligns with the DMC's criteria for recommended treatments.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Overall survival (OS), progression-free survival (PFS), duration of response (DOR) and overall response rate (ORR) are the most relevant outcomes for this assessment.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS)	1 May 2023	LIBRETTO-431: Overall survival was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data was censored on the last date the participant is known to be alive.	Kaplan-Meier (KM) estimates were used for analyses.
	13 January 2023	LIBRETTO-001: Overall survival is defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause).	KM estimates were used for analyses.
	8 March 2022	KEYNOTE-189: Overall survival was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data was censored on the last date the participant is known to be alive.	KM estimates were used for analyses.
Progression-free survival (PFS)	1 May 2023	PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease	Blinded Independent Central Review (BICR) assessment and by investigator assessment. KM estimates were used for analyses.
Overall response rate (ORR)	1 May 2023	ORR is defined as the number of participants who achieve a best overall response (BOR) of complete response (CR) or partial response (PR) divided by the total number of participants randomized to each treatment arm.	BICR assessment
Duration of response (DOR)	1 May 2023	DoR was defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or documented disease progression was observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR according to both	BICR assessment. KM estimates were used for analyses

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		BICR and investigator-assessed BOR was evaluated per RECIST 1.1 criteria.	

Abbreviations: OS, overall survival; PFS, progression-free survival, ORR, overall response rate; DOR, duration of response; KM, Kaplan-Meier; BICR, blinded independent central review; BOR, best overall response; CR, complete response; PR, partial response

Validity of outcomes

OS, PFS and ORR are standard clinical study endpoints, which are reliable and relevant for this submission and have previously been used by the DMC for multiple oncology submission dossiers.

4. Health economic analysis

A cost-utility analysis (CUA) was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model (CEM). The objective of the economic model is to estimate the cost-effectiveness of selpercatinib in treatment-naïve NSCLC with RET gene fusion, based on data from the LIBRETTO-431 trial. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A survival partition model consisting of 3 health states was used: progression free, progressed, and dead (30). The approach is presented in Figure 1. The health states are defined as follows:

- Progression-free: Patient's disease is in a stable or responding state and not actively progressing. Patients in this state are assumed to incur costs associated with treatment, administration, medical management of the condition, and the management of grade 3/4 adverse events (AEs). Patients with progression-free disease also experience higher utility than patients with progressed disease.
- Progression: Patients have met Response Evaluation Criteria in Solid Tumors (RECIST) for disease progression. Patients in this state may continue their allocated therapy for a time and/or have subsequent anticancer therapy and incur costs associated with treatment, administration, medical management of the condition, and terminal care. Patients with progressive disease also experience a lower utility than patients with progression-free disease.
- Dead

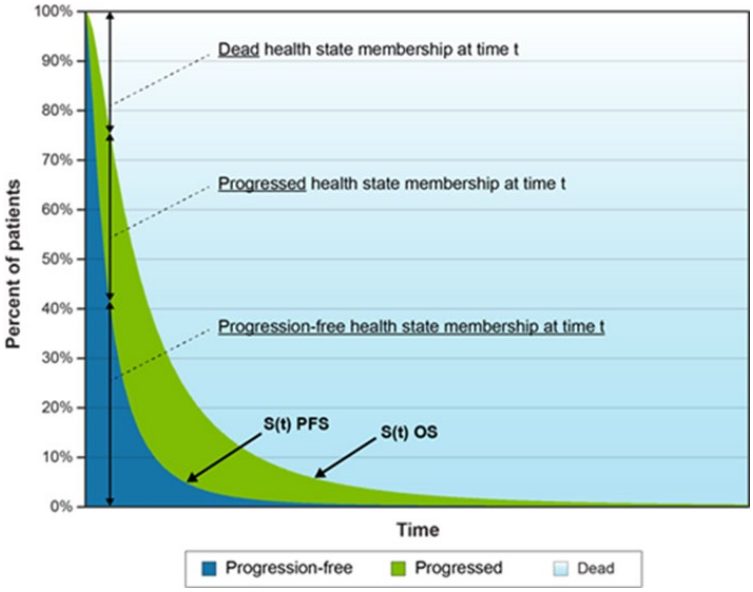


Figure 1 Model structure

OS = overall survival; PFS = progression-free survival.

Notes: The data in the figure are fictitious and used for illustrative purposes only. S(t) PFS is the survival function describing the probability that a patient remains in the progression-free health state beyond a specific timepoint (t) from model entry. S(t) OS is the survival function describing the probability that a patient survives in the progression-free or progressed health states beyond a specific timepoint (t) from model entry. Membership in the progressed health state is determined by subtracting the progression-free state membership from the dead state membership.

The model structure is consistent with that used in previous economic evaluations in NSCLC (31-35).

4.2 Model features

Table 6 describe the model features.

Table 6 Features of the economic model

Model features	Description	Justification
Patient population	The population of interest is adults with treatment-naïve advanced or metastatic RET fusion-positive non-squamous NSCLC	No deviations from Section 3.2
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (25 years)	To capture all health benefits and costs in line with DMC guidelines (36). Consistent with previous assessed selpercatinib submission (1).
Cycle length	1 week	A 1-week cycle provides the flexibility to accommodate treatment regimens with different schedules
Half-cycle correction	No	Cycle length is only one week. For simplicity, not applied.
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years
Intervention	Selpercatinib 160 mg twice daily	LIBRETTO-431

Model features	Description	Justification
Comparator(s)	Pemetrexed + carboplatin + pembrolizumab (Pembrolizumab: 200 mg: Pemetrexed: 500 mg/m2; Carboplatin: 400 mg/m2)	According to national treatment guideline, refer to Section 3.5.
Outcomes	OS, PFS, TTD	

Abbreviations: NSCLC, non-small cell lung cancer; DMC, Danish Medicines Council; OS, overall survival; PFS, progression-free survival; TTD, time-to-treatment discontinuation

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical assessment of selpercatinib is based on the LIBRETTO-431 trial (head-to-head) and LIBRETTO-001 (single-arm) and KEYNOTE-189. Systematic literature reviews (SLRs) to identify efficacy and safety data for selpercatinib and comparators (37). Furthermore, an SLR identifying prognostic factors and predictive factors (treatment-effect modifiers) to inform indirect treatment comparisons using the single-arm LIBRETTO-001 study and surrogate analyses to identify data to support modelling of survival from response or PFS data. The source of studies to inform the ITC is based on a SLR (4 May 2023) (Lilly data on file, 2023).

Table 7 below lists the literature used in the clinical assessment. In addition, the LIBRETTO-431 trial is available as a publication published by Zhou et al. The matched-adjusted indirect comparison (MAIC) is available as a publication and a technical report (data on file).

Table 7 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Eli Lilly, data on file (LIBRETTO-431), data cutoff 1 May 2023 (clinical study report) (38) Zhou, Caicun, Benjamin Solomon, Herbert H. Loong, Keunchil Park, Maurice Pérol, Edurne Arriola, Silvia Novello et al. "First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion–positive NSCLC." New England Journal of Medicine 389, no. 20 (2023): 1839-1850. (4)	LIBRETTO-431	NCT04194944	Start: 17/02/2020 Completion, primary: 01/05/2023 Overall study completion: February 2026 Data cut-off: 01/05/2023 Future data cut-offs: final OS data cut off is currently unknown	Direct head-to-head study: Selpercatinib vs. pemetrexed + platinum ± pembrolizumab
Eli Lilly, data on file (LIBRETTO-001), data cutoff 13 January 2023 (clinical study report) (39) 35P Final data from phase I/II LIBRETTO-001 trial of selpercatinib in RET fusion-positive non-small cell lung cancer Gautschi, O. et al. ESMO Open, Volume 9, 102614 (40) Wirth, L. J., Sherman, E., Robinson, B., Solomon, B., Kang, H., Lorch, J., Worden, F., Brose, M., Patel, J., Leboulleux, S., Godbert, Y., Barlesi, F., Morris, J. C., Owonikoko, T. K., Tan, D. S. W., Gautschi, O., Weiss, J., de la Fouchardiere, C., Burkard, M. E., . . . Cabanillas, M. E. (2020). Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med, 383(9), 825-835.(41) Wirth, L. J., Subbiah, V., Worden, F., Solomon, B., Robinson, A. G., Hadoux, J., Tomasini, P., Weiler, D., Deschler-Baier, B., Tan, D., Lin, Y., Bayt, T., Maeda, P., Drilon, A., & Cassier, P. (2023). Updated safety and efficacy of selpercatinib in patients with RET-activated thyroid cancer: data from LIBRETTO-001. Ann Oncol. (42) Drilon, A. (2022, 30 March-2 April). Durability of efficacy and safety with selpercatinib in patients (pts) with RET fusion+ non-small-cell	LIBRETTO-001	NCT03157128	Start: 02/05/2017 Completion, primary: 28/02/2025 Overall study completion: 28/02/2026 Data cut-off: 13/01/2023 Future data cut-offs: N/A	Single-arm trial of selpercatinib. Used for MAIC analysis (on OS): to compare long-term survival of patients in LIBRETTO-001 to survival of patients treated with platinum-based chemotherapy + pembrolizumab in KEYNOTE-189 study

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
lung cancer (NSCLC): LIBRETTO-001 [poster] European Lung Cancer Conference, Prague, Czech Republic (43) Drilon, A., Oxnard, G., Wirth, L., Besse, B., Gautschi, O., Tan, D. S. W., & al., e. (2019, 7-10 September). Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET fusion-positive lung cancers World Conference on Lung Cancer, Barcelona, Spain. (44) Drilon, A., Oxnard, G. R., Tan, D. S. W., Loong, H. H. F., Johnson, M., Gainor, J., McCoach, C. E., Gautschi, O., Besse, B., Cho, B. C., Peled, N., Weiss, J., Kim, Y. J., Ohe, Y., Nishio, M., Park, K., Patel, J., Seto, T., Sakamoto, T., . . . Subbiah, V. (2020). Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med, 383(9), 813-824. (45)				
Garassino, M. C., Gadgeel, S., Speranza, G., Felip, E., Esteban, E., Dómine, M., . . . Rodríguez-Abreu, D. (2023). Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes from the Phase 3 KEYNOTE-189 Study. 41(11), 1992-1998. doi:10.1200/jco.22.01989 (46)	KEYNOTE-189	NCT02578680	Start: 15/01/2016 Completion, primary: 08/11/2017 Overall study completion: 22/06/2023 Data cut-off: 08/03/2022 Future data cut-offs:N/A	Pembrolizumab + pemetrexed + platinum chemotherapy against control group. Used for MAIC analysis (on OS): to compare long-term survival of patients in LIBRETTO-001 to survival of patients treated with platinum-based chemotherapy + pembrolizumab in KEYNOTE-189 study. The hazard ratio (HR) for selpercatinib versus the pemetrexed + platinum + pembrolizumab arm of the KEYNOTE-189 trial was estimated using the most recent available data cut for KEYNOTE-189. However, the HR was applied to the proportional hazard survival functions fitted to the LIBRETTO-001 OS data only (i.e., the KEYNOTE-19 data were not included in the survival analysis). Refer to Section 8.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Analysis Plan to Estimate the Relative Treatment Effect in Overall Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431: Treatment Switching and Extrapolation. Data on file (Eli Lilly) February 2024(47)	LIBRETTO-431	N/A	N/A	Selpercatinib vs. pemetrexed + platinum ± pembrolizumab. Refer to
Analysis Plan to Estimate the Relative Treatment Effect in Progression-Free Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431. Data on file (Eli Lilly) 29 January 2024 (48)	LIBRETTO-431	N/A	N/A	Selpercatinib vs. pemetrexed + platinum ± pembrolizumab. Refer to K.1
Data on file Unpublished data 2024, Comparative efficacy of Selpercatinib vs Pembrolizumab + Platinum doublet chemotherapy in 1L NSCLC. A matching-adjusted indirect comparison (MAIC) of LIBRETTO-001 and KEYNOTE-189 2024 (49)	LIBRETTO-001	N/A	N/A	For time to event outcome analysis, Kaplan-Meier (KM) curves for OS and PFS from KEYNOTE-189 were digitized first to get the IPD with censoring status. After digitization, MAIC weights were incorporated in the KM method to estimate the median OS and PFS and Cox proportional hazards model was used to estimate the hazard ratio. Refer to Section 7 and Section 8.

Abbreviations: MAIC, matched-adjusted indirect comparison; OS, overall survival; PFS, progression-free survival; KM, Kaplan-Meier; IPD, individual patient data; HR, hazard ratio

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

The assessment of HRQoL in relation to health states is based on the LIBRETTO-431 study (head-to-head), hence no SLR would be considered needed. However, existing health utility estimates from the LIBRETTO-001 is also provided for comparison. An economic TLR was updated in 2024, which also cover utility estimates, refer to Appendix I. Disutility values in relation to adverse events were sourced from standard publications. The literature used for health-related quality of life is listed in Table 8.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Eli Lilly, data on file (LIBRETTO-431), PRO SAP report 2023 (50) Eli Lilly, data on file (LIBRETTO-431), PRO analysis report 2023 (51) Eli Lilly, data on file (LIBRETTO-431), EQ-5D-5L Denmark analysis 2023 (DCO 2024) (52)	Danish weighted EQ-5D estimates from the LIBRETTO-431	Provided in Section 10
Eli Lilly, data on file (LIBRETTO-001), PRO analysis (DCO January 2023) (39)	HSUVs for comparison	Provided in Section 10
Nafees, B., Stafford, M., Gavriel, S., Bhalla, S., & Watkins, J. (2008). Health state utilities for non-small cell lung cancer. Health and quality of life outcomes, 6, 1-15. (53)	Disutility for diarrhoea; asthenia; neutropenia; anaemia; febrile neutropenia	Provided in Section 10.2.2
National Institute for Health and Care Excellence, Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428) 2017(54)	Disutility for hypertension; decreased appetite; hyponatraemia; pleural effusion	Provided in Section 10.2.2
Martí, S. G., Colantonio, L., Bardach, A., Galante, J., Lopez, A., Caporale, J., ... & Pichon-Riviere, A. (2013). A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. Cost effectiveness and resource allocation, 11, 1-17. (55)	Disutility for pneumonia	Provided in Section 10.2.2
Doyle, S., Lloyd, A., & Walker, M. (2008). Health state utility scores in advanced non-small cell lung cancer. Lung Cancer, 62(3), 374-380. (56)	Disutility for cardiac failure	Provided in Section 10.2.2
National Institute for Health and Care Excellence, Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347) 2015 (57)	Disutility for decreased white blood cell count	Provided in Section 10.2.2

Abbreviations: EQ-5D, EuroQol 5-Dimensions; HSUV, health state utility value; PRO, patient-reported outcome; SAP, statistical analysis plan

5.3 Literature used for inputs for the health economic model

Model inputs were sourced from the LIBRETTO-431 trials as well as based on the targeted literature review of relevant and previously accepted technology appraisals (TA) by National Institute for Health and Care Excellence (NICE) for first line treatments in patients with advanced and/or metastatic NSCLC. An economic TLR was updated in 2024, which also cover cost estimates, refer to Appendix J. Table 9 below lists the literature used for input to the economic model.

Table 9 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
Eli Lilly, data on file (LIBRETTO-431), data cutoff 1 May 2023 (Clinical study report) (38)	Adverse event rates; subsequent treatment; dosing regimen and intensity	In trial	Section 9.2.
Sireci, A., Morosini, D., & Rothenberg, S. (2019). P1. 01-101 efficacy of immune checkpoint inhibition in RET fusion positive non-small cell lung cancer patients. Journal of Thoracic Oncology, 14(10), S401. (58)	Screen-positive rate	TLR	Section 11
National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. Technology Appraisal. NICE; 2018. (32)	Body surface area, m^2 Monitoring costs	TLR	Section 11
The Danish Medicines Council, assessment report of Retsevmo®, Bilag til Medicinrådets anbefaling vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke småcellet lungekræft – Revurdering (2022) (1)	Monitoring costs	Prior DMC assessment	Section 11
National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. Technology Appraisal NICE; 2019 (TA584) (34) National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. NICE; 2018 (TA531) (59) National Institute for Health and Care Excellence. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy. NICE; 2021 (TA713 previously TA484) (60)	Pattern of subsequent therapies	TLR	Section 11

Abbreviations: DMC, Danish Medicines Council; TA, technology appraisal; TLR, targeted literature review

6. Efficacy

6.1 Efficacy of selpercatinib compared to pemetrexed + carboplatin ± pembrolizumab for RET fusion positive NSCLC 1L patients

6.1.1 Relevant studies

Selpercatinib has previously been evaluated in a single-arm global study (LOXO-RET-17001, or LIBRETTO-001) initiated in May 2017. The study recruited patients with a variety of advanced solid tumours, including NSCLC, medullary thyroid carcinoma (MTC), and thyroid carcinoma (TC) with activating RET alterations (gene fusions and/or mutations). The study included a dose-escalation phase (Phase 1) and a dose-expansion phase (Phase 2). Results of the LIBRETTO-001 trial have been presented at the World Conference on Lung Cancer and the European Society for Medical Oncology (42, 44, 61), the European Lung Cancer Conference (40, 43), and in peer-reviewed journal articles (41, 43, 45).

Recently, positive interim results for selpercatinib were disclosed from a randomised controlled Phase 3 study (LIBRETTO-431) (38), which compares selpercatinib against platinum-based and pemetrexed therapy with or without pembrolizumab (4). Patients were stratified for randomisation according to whether the investigator had intended (before randomisation) to treat the patient with or without pembrolizumab (as well as by geographic region and brain metastases at baseline) (4). Crossover to selpercatinib is allowed for control-arm patients who have disease progression, details regarding the crossover are specified in Appendix L. The data cutoff (DCO) used in the model was 1 May 2023.

However, since the OS data from LIBRETTO-431 are particularly immature and data for the control arm are confounded by treatment switching, more mature OS data from LIBRETTO-001 and an estimated control arm based on the KEYNOTE-189 trial will be presented in the following section. Refer to Section 7 for further information regarding the OS approach using the most recent DCO from the KEYNOTE-189 (MAIC).

Table 10 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 time
LIBRETTO-431 (38) NCT04194944 Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, et al. First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion–positive NSCLC. New England Journal of Medicine. 2023;389(20):1839-50. (4)	Randomized phase III / open-label / placebo-control/ active comparator-control	17th of February 2020 to estimated study completion on 18th of June 2026	The intention-to-treat–pembrolizumab population included 212 patients who had been randomly assigned to receive selpercatinib (129 patients) or chemotherapy plus pembrolizumab (83 patients)	Selpercatinib. 160 milligram (mg) Selpercatinib administered orally twice daily (BID) continuously in 21-day cycles.	Pemetrexed and Platinum with or without Pembrolizumab. Pemetrexed 500 milligrams per meter squared (mg/m2) administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose of 750 mg] IV), or cisplatin (75 mg/m2 cisplatin IV) on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.	Primary outcomes: PFS assessed according to BICR (with pembrolizumab) and (with or without pembrolizumab) and by investigator assessment. Secondary outcomes selection: PFS per RCISTS 1.1. by investigator; DCR by BICR (with pembrolizumab) and (with or without pembrolizumab); PFS2 (with pembrolizumab) and (with or without pembrolizumab); ORR PFS2 (with pembrolizumab) and (with or without pembrolizumab); DOR by BICR PFS2 (with pembrolizumab) and (with or without pembrolizumab); OS (with pembrolizumab) and (with or without pembrolizumab). Time frames for outcomes: • PFS (BICR): baseline to progressive disease or death from any cause up to 31 months • DCR (BICR): baseline to progressive disease or death from any cause up to 31 months • PFS2: baseline to second disease progression or death from any cause up to 38 months • ORR: baseline to progressive disease or death from any cause up to 31 months • DOR (BICR): date of CR or PR to date of disease progression or death due to any cause up to 31 months • OS: baseline to second disease progression or death from any cause up to 38 months OS: up to approximately data cut off (DCO): 1 May 2023. Median follow-up time was approximately 19 months (DCO 1 May 2023)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
LIBRETTO-001 (39) NCT03157128	Single arm. Open-label, multi-centre Phase 1/2 study consisting of 2 parts: 1) Phase 1 - dose escalation and expansion, and 2) Phase 2 - dose expansion	9th of May 2017 to 13 January 2023. Individual patients continued selpercatinib dosing until PD, unacceptable toxicity, or other reason for treatment discontinuation	Patients with advanced solid tumours, including: 1) RET fusion-positive solid tumours such as NSCLC, thyroid, pancreas, and colorectal cancer, 2) RET-mutant MTC, and 3) other tumours with RET activation such as mutations in other tumour types or other evidence of RET activation. NSCLC population, efficacy analysis set n= 356 Treatment naïve patients, n= 69	The recommended Phase 2 dose of selpercatinib is 160 mg BID in an oral form. This dose was selected by the Safety Review Committee in Phase 1 and was used as the starting dose for patients in the Phase 2 dose-expansion phase of the study.	N/A	Primary outcome (phase 2): ORR, per IRC assessment. DCO 13 Jan 2023. Secondary outcomes (phase 2): DCO 13 Jan 2023. • ORR by investigator assessment • best change in tumour size from baseline by IRC and • investigator assessment • DOR by IRC and investigator assessment • CNS ORR by IRC assessment • CNS DOR by IRC assessment • time to any and best response by IRC and investigator • assessment • CBR by IRC and investigator assessment • PFS by IRC and investigator assessment, and • OS Time frames for outcomes: • ORR (IRC): Approximately every 8 weeks for one year, then every 12 weeks, and 7 days after the last dose (for up to 2 years) in participants who have not progressed. • ORR: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • Best change in tumour size from baseline by IRC and: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						• DOR: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • CNS ORR and DOR; time to any and best response; CBR: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • PFC (IRC): Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • OS: Approximately every 8 weeks for one year, then every 12 weeks, 7 days after the last dose (for up to 2 years) in participants who have not progressed • SAEs: From the time of informed consent, for approximately 24 months (or earlier if the participant discontinues from the study), and through Safety Follow-up (28 days after the last dose) Duration of follow-up (median in months) for the IRC assessed population. • Treatment naïve = 37.1 • Platinum chemotherapy = 39.5 Duration of follow-up (PFS) (median in months) for the IRC assessed population. • Treatment naïve = 38.9 • Platinum chemotherapy = 41.2¨

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						Duration of follow-up (OS) (median in months) for the IRC assessed population. • Treatment naïve = 41.9 • Platinum chemotherapy = 44.6
KEYNOTE-189 NCT02578680 Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, Hochmair MJ, Powell SF, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Kurata T, Gray JE, Schwarzenberger P, Jensen E, Pietanza MC, Rodríguez-Abreu D. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023 Apr 10;41(11):1992-1998. doi: 10.1200/JCO.22.01989. Epub 2023 Feb 21.	RCT (randomised in a 2:1 ratio), double-blinded, phase 3 trial	Study start: 15 of January 2016, actually study completion: 22 of June 2023	Patients with advanced or metastatic non-squamous NSCLC without sensitizing *EGFR* or *ALK* mutations who have not previously received systemic therapy for advanced disease. A total of 616 patients were randomised (in a 2:1 ratio) to receive pemetrexed and a platinum-based drug plus either 200 mg of pembrolizumab or placebo every 3 weeks for 4 cycles, followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy	Patients were randomly assigned 2:1 to pembrolizumab 200 mg or placebo once every 3 weeks for up to 35 cycles (approximately 2 years). Patients also received pemetrexed 500 mg/m2 plus cisplatin 75 mg/m2 or carboplatin area under the curve 5 mg/mL/min once every 3 weeks for four cycles followed by pemetrexed maintenance therapy.	Placebo. Patients in the placebo plus pemetrexed-platinum group could cross over to receive pembrolizumab monotherapy upon documented progressive disease (PD) per RECIST v1.1 by blinded independent central review (BICR) if eligibility criteria were met.	Patients could receive a second course of pembrolizumab monotherapy for up to 17 cycles (approximately 1 year) upon PD after either completing 35 cycles of pembrolizumab with a best overall response of stable disease or better or having achieved confirmed investigator-assessed complete response (CR) after receiving ≥ 8 cycles of pembrolizumab and ≥ 2 cycles beyond the initial CR assessment. Primary end points were PFS per RECIST v1.1 by BICR and OS. Secondary end points were objective response rate (ORR) and duration of response (DOR) per RECIST v1.1 by BICR and safety. Time frames for outcomes: • PFS: up to approximately 21 months • OS: up to approximately 21 months • ORR: up to approximately 21 months • DOR: up to approximately 21 months • AE: up to approximately 21 months Data cut off: 8 March 2022 Among 616 randomly assigned patients (n = 410, pembrolizumab plus pemetrexed-platinum; n = 206, placebo plus pemetrexed-platinum), median time from random assignment to data cutoff (March 8, 2022) was 64.6 (range, 60.1-72.4) months.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
PMID: 36809080; PMCID: PMC10082311 (46).			Patients used in this submission, n= 189			

Abbreviations: IV, intravenous; BICR, blinded independent central review; PFS, progression-free survival; OS, overall survival, ORR, overall response rate; RECIST, response evaluation criteria in solid tumours; IRC, independent review committee; DCR, disease control rate; DCO; data cutoff; CR; complete response; PD, progressive disease; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; SAE, serious adverse event; CNS, central nervous system; CBR, clinical benefit rate; PFC, progression-free survival censoring;

6.1.2 Comparability of studies

Because of the immature OS data in the LIBRETTO-431 trial, the base-case analysis in the model uses OS data from the LIBRETTO-001 and KEYNOTE-189 trials, refer to Section 8. Therefore, the following section will outline efficacy results from the three trials following trials that have been included in the evidence base as previously outlined: LIBRETTO-431, LIBRETTO-001, and KEYNOTE-189 (an HR (not adjusted for MAIC) is applied to these data (LIBRETTO-001 and KEYNOTE-189) to provide a more conservative estimate for the difference in OS between selpercatinib and pemetrexed + platinum + pembrolizumab). Table 11 presents and compares the inclusion criteria for each study.

Table 11 Inclusion criteria across trials

Inclusion criteria	LIBRETTO-431	LIBRETTO-001	KEYNOTE-189
Histologically or cytologically confirmed NSCLC	✓	✓	✓
Stage IV NSCLC	✓	✓	✓
RET gene alteration / fusion	✓	✓	X
ECOG performance status of 0-1	✓	✓ (0-2)	✓ (0-1)
Measurable or non-measurable disease	✓	✓	✓
Adequate organ function	✓	✓	✓
Life expectancy of at least 3 months	Not stated	✓	✓
No prior systemic therapy for metastatic disease	✓	Not explicitly stated	✓
Ability to provide tumour tissue	Not stated	✓	✓
Ability to swallow capsules or tablets.	✓	Not stated	Not stated

Abbreviations: NSCLC, non-small cell lung cancer; RET, rearranged during transfection; ECOG, Eastern Cooperative oncology group performance status

6.1.2.1 Comparability of patients across studies

Table 12 presents patient baseline characteristics informed by the LIBRETTO-431 trial (n=261) for the ITT-pembrolizumab population. Overall, demographic and baseline disease characteristics and the distribution of RET fusion partners were well balanced between treatment arms and consistent between the ITT-Pembrolizumab Population and the ITT Population (4, 38). More East Asian patients were enrolled in the selpercatinib arm compared to the control arm (58.1% versus 49.4%). The key prognostic factors of smoking status, ECOG, and the presence of brain metastases were similar between the selpercatinib arm and the control arm. More patients in the selpercatinib arm were programmed cell death receptor ligand 1 (PD-L1) negative (24.0%) compared to the control arm (14.5%). Overall, 38.6% of patients in the control arm and 33.3% in the selpercatinib arm had missing PD-L1 status. 0 presents a summary of treatments administered to patients in the ITT-Pembrolizumab population following disease progression.

Table 13 presents patient baseline characteristics informed by the LIBRETTO-001 trial (n=69) (39). Table 14 presents the baseline characteristics informed by the KEYNOTE-189 used for the MAIC analysis (46) (refer to Section 7).

Table 12 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety – LIBRETTO-431 ITT-pembrolizumab

Characteristics	LIBRETTO-431 Total (n=261)	Selpercatinib (n=129)	Pemetrexed + platinum + pembrolizumab (n = 83)
Female, n (%)	113 (53.3)	65 (50.4)	55 (57.8)
Median age (range), years	61.5 (31-84)	60.0 (31-84)	62.0 (31-83)
Race, n (%)			
Asian	117 (56.3)	76 (58.9)	41 (51.9)
White	86 (41.3)	49 (38.0)	37 (46.8)
Black	2 (1.0)	2 (1.6)	0
Stage at diagnosis, n (%)			
IA	6 (2.8)	6 (4.7)	0
IB	4 (1.9)	2 (1.6)	2 (2.4)
IIB	4 (1.9)	2 (1.6)	2 (2.4)
IIIA	11 (5.2)	3 (2.3)	8 (9.6)
IIIB	13 (6.1)	8 (6.2)	5 (6.0)
IVA	78 (36.8)	49 (38.0)	29 (34.9)
IVB	94 (44.3)	57 (44.2)	37 (44.6)
Missing	2 (0.9)	2 (1.6)	0
ECOG performance status, n (%)			
0	72 (34.0)	45 (34.9)	27 (32.5)
1	133 (62.7)	81 (62.8)	52 (62.7)
2	7 (3.3)	3 (2.3)	4 (4.8)
Histologic type (NSCLC), n %			
Adenocarcinoma	208 (98.1)	128 (99.2)	80 (96.4)
NSCLC not otherwise specified	4 (1.9)	1 (0.8)	3 (3.6)
Prior anticancer therapy, n (%)	66 (31.1)	38 (29.5)	28 (33.7)
PD-L1 status, n (%)			
Negative	43 (20.3)	31 (24.0)	12 (14.5)
Positive	95 (44.3)	55 (42.6)	39 (47.0)
<1%	16 (7.5)	8 (6.2)	8 (9.6)
1-49%	42 (19.8)	25 (19.4)	17 (20.5)
>50%	36 (17.0)	22 (17.1)	14 (16.9)
Missing data	75 (35.4)	43 (33.3)	32 (38.6)
RET-fusion results, n (%)			
POSITIVE	89 (42.0)	58 (45.0)	31 (37.3)
KIF5B	95 (44.8)	54 (41.9)	41 (49.4)
CCDC6	21 (9.9)	13 (10.1)	8 (9.6)
NCOA4	1 (0.5)	0	1 (1.2)
KIF13A	1 (0.5)	0	1 (1.2)
KIAA1549L	1 (0.5)	1 (0.8)	0
KIAA1468	1 (0.5)	1 (0.8)	0
PRKAR1A	1 (0.5)	0	1 (1.2)
OTHER	2 (0.9)	2 (1.6)	0
Brain metastases, n (%)	43 (20.3)	25 (19.4)	18 (21.7)
Study entry disease stage, n (%)			
Stage IIIB	12 (5.7)	7 (5.4)	5 (6.0)

Characteristics	LIBRETTO-431 Total (n=261)	Selpercatinib (n=129)	Pemetrexed + platinum + pembrolizumab (n = 83)
Stage IIIC	2 (0.9)	0	2 (2.4)
Stage IVA	86 (40.6)	51 (39.5)	35 (42.2)
Stage IVB	112 (52.8)	71 (55.0)	41 (49.4)
Smoking history, n (%)			
Never smoked	114 (67.9)	85 (65.9)	59 (71.1)
Former smoker	62 (29.2)	50 (31.0)	22 (26.5)
Current smoker	6 (2.8)	4 (3.1)	2 (2.4)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer; ITT, intention-to-treat; RET, rearranged during transfection; PD-L1; programmed-death ligand 1
Source: Lilly data on file, 2023 L-431 (38)

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety - LIBRETTO-001

Characteristics	LIBRETTO-001 (ITT) Platinum chemotherapy (n=247)	Treatment naïve (n=69)
Female, n (%)	140 (56.7)	43 (62.3)
Median age (range), years	61 (23-81)	63 (23-92)
Race, n (%)		
Asian	118 (47.8)	13 (18.8)
White	108 (43.3)	48 (69.6)
Black	12 (4.9)	4 (5.8)
ECOG performance status, n (%)		
0	90 (36.4)	25 (36.2)
1	150 (60.7)	40 (58.0)
2	7 (2.8)	4 (5.8)
Prior anticancer therapy, n (%)	237 (100.00)	N/A
RET-fusion partner, n (%)		
KIF5B	153 (61.9)	48 (69.6)
CCDC6	53 (21.5)	10 (14.5)
NCOA4	5 (2.0)	1 (1.4)
Other	15 (6.1)	2 (2.9)
Unknown	22 (8.9)	8 (11.6)
Brain metastases, n (%)	77 (31.2)	16 (23.2)
Study entry disease stage, n (%)		
Stage I	3 (1.2)	1 (1.4)
Stage II	2 (0.8)	1 (1.4)
Stage III	14 (5.7)	3 (4.3)
Stage IV	223 (92.3)	63 (91.3)
Missing	0	1 (1.4)
Smoking history, n (%)		
Never smoked	165 (66.8)	48 (69.6)
Former smoker	78 (31.6)	19 (27.5)
Current smoker	4 (1.6)	2 (2.9)
Missing	0	0

Abbreviations: ECOG = Eastern Cooperative Oncology Group; NSCLC = non–small cell lung cancer.
Source: Lilly data on file, 2023 L-001 (39)

Table 14 KEYNOTE-189 Baseline Characteristics

Characteristics	Pembrolizumab combination (n=410)	Placebo combination (n=206)	Completed 2 years of pembrolizumab n=56
Mean age, years	65.0 (34–84)	63.5 (34–84)	65.5 (42–82)
Sex (female %)	156 (38.0)	97 (47.1)	23 (41.1)
ECOG PS			
0	185 (45.1)	80 (38.8)	35 (62.5)
1	221 (53.9)	135 (60.7)	21 (37.5)
2	1 (0.2)	0	0
Missing	3 (0.07)	1 (0.5)	0
Histology			
Adenocarcinoma	394 (96.1)	199 (96.6)	56 (100.0)
NSCLC not otherwise specified	10 (2.4)	4 (1.9)	0
Other	6 (1.5)	3 (1.5)	
Brain metastases at baseline n (%)	73 (17.8)	35 (17.0)	6 (10.7)
Previously treated	43 (10.0)	23 (11.0)	3 (5.4)
Liver metastases	66 (16.1)	50 (24.3)	8 (14.3)
PD-L1 TPS, n (%)			
<1%	127 (31.0)	63 (30.6)	6 (10.7)
≥1%	260 (63.4)	128 (62.1)	47 (83.9)
Could not be evaluated	23 (5.6)	15 (7.3)	3 (5.4)
Previous therapy			
Thoracic radiotherapy	29 (7.1)	20 (9.7)	5 (8.9)
Neoadjuvant therapy	5 (1.2)	6 (2.9)	0
Adjuvant therapy	25 (6.1)	14 (6.8)	5 (8.9)
Metastasis, n (%)			
M0	2 (0.5)	1 (0.5)	0
M1a	123 (30.0)	53 (25.7)	24 (42.9)
M1b	285 (69.5)	152 (73.8)	32 (57.1)
Smoking history, n (%)			
Never smoked	48 (11.7)	25 (12.1)	5 (8.9)

ECOG PS, Eastern Cooperative Oncology Group performance score; NSCLC, non–small cell lung cancer; sd. standard deviation.

Source: Garassino et al Rodríguez-Abreu et al., 2021, Supplementary materials Table S1/ and Eli Lilly data on file (ITC / MAIC report) (46) (49)

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

As described previously, RET fusion-positive NSCLC patients are expected to have similar characteristics as patients with ALK and ROS1 positive NSCLC. Thus, patients are more likely to have lung adenocarcinoma and to be younger than wildtype NSCLC patients. Also, a higher proportion of RET fusion-positive patients are expected to be female and/or never or light smokers compared to wildtype NSCLC patients, refer to Section 3.1.2.

The characteristics of the patients included in the LIBRETTO-431 trial seem to reflect the Danish population well. Table 15 shows characteristics in the relevant population in Danish clinical practice and the values used in the health economic model.

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

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	62 years (median) (4)	60 years (start age)
Gender	54.8% (4)	53.3% (38)

6.2 Efficacy – results per LIBRETTO-431

The outcomes from the LIBRETTO-431 trial are presented in the section below. The source of the primary data from the trial presented for this submission is presented by Eli Lilly's data on file (clinical study report (CSR), etc. at DCO, 1 May 2023 (38)), which presents data from the ITT population (n=261) and ITT-pembrolizumab population (n=212). All outcomes included in the application is also presented in Appendix B.

6.2.1 Overall response rate (1 May 2023)

The ORR was one of the secondary endpoints in LIBRETTO-431 (by blinded independent central review (BICR) assessment). With a median follow-up time of approximately 19 months, the median (±SD) time spent receiving treatment was 16.7±8.3 months in the selpercatinib group and 9.8±7.2 months in the control group (pemetrexed + platinum ± pembrolizumab (n = 102) group). Table 16 below presents the response rates from the LIBRETTO-trial at DCO, 1 May 2023 (38).

Table 16 Response rates from the LIBRETTO-431 trial

Response, n (%)	Selpercatinib (n=129)	Pemetrexed + platinum + pembrolizumab (n = 83)
ORR (95% CI) [complete response or partial response]	108 (83.7%) (76.2-89.6)	54 (65.1%) (53.8-75.2)
Complete response	9 (7%) (3.2-12.8)	5 (6.0%) (2.0-13.5)
Partial response	99 (76.7%) (68.5-83.7)	49 (59.0%) (47.7-69.7)
Stable disease	14 (10.9%) (6.1-17.5)	20 (24.1%) (15.4-34.7)
Progressive disease	2 (1.6%) (0.2-5.5)	5 (6.0%) (2.0-13.5)
Not evaluable	5 (3.9%) (1.3-8.8	4 (4.8%) (1.3-11.9)

Abbreviations: ORR, overall response rate

Source: Eli Lilly, data on file (data cut 1 May 2023 CSR L-431) (38)

6.2.2 Overall survival (1 May 2023)

OS is a secondary outcome in LIBRETTO-431. The OS results in the ITT-Pembrolizumab Population are immature, with a censoring rate of 80.6% in the selpercatinib arm and 81.9% in the control arm. The median follow-up time for OS was 21.65 months and 21.22 months for selpercatinib and the control arm, respectively (1 May 2023 DCO). Table 18 below presents the OS survival rates based on the 1 May 2023 DCO. The Kaplan-Meier (KM)-curve for OS is presented in Figure 2.

Table 17 OS results from the LIBRETTO-431 trial

Results	Overall ITT Population		ITT-Pembrolizumab Population	
	Selpercatinib (n=159)	Pemetrexed + platinum +/- pembrolizumab (n = 102)	Selpercatinib (n=129)	Pemetrexed + platinum + pembrolizumab (n = 83)
Number of follow-up events, n (%)	[redacted]	[redacted]	104 (80.6)	68 (81.9)
Number of censors (deaths), n (%)	[redacted]	[redacted]	25 (19.4)	15 (18.1)
Median OS, months (95% CI)	[redacted]	[redacted]	NE	NE
Follow-up time, months	[redacted]	[redacted]	21.65 (19.71, 22.57)	21.22 (17.68, 22.74)
Hazard ratio (95% CI)				
Stratified	[redacted]		0.961 (0.503, 1.835)	
Unstratified	[redacted]		0.989 (0.521, 1.877)	

Abbreviations: OS, overall survival, NE, not estimated; CI, confidence interval

Table 18 OS - Survival rates from the LIBRETTO-431 trial

Survival (%) (CI)	Overall ITT Population		ITT-Pembrolizumab Population	
	Selpercatinib (n=159)	Control (+/- pembrolizumab) (n = 102)	Selpercatinib (n=129)	Control (+pembrolizumab) (n = 83)
6 months	[redacted]	[redacted]	95.3 (89.9, 97.9)	95.1 (87.4, 98.1)
12 months	[redacted]	[redacted]	93.0 (87.0, 96.3)	85.9 (75.9, 91.9)
18 months	[redacted]	[redacted]	82.4 (73.9, 88.3)	79.0 (67.3, 86.9)
24 months	[redacted]	[redacted]	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)
30 months	[redacted]	[redacted]	75.2 (65.0, 82.8)	79.0 (67.3, 86.9)

Source: Eli Lilly, data on file (data cut 1 May 2023 CSR L-431) (38)

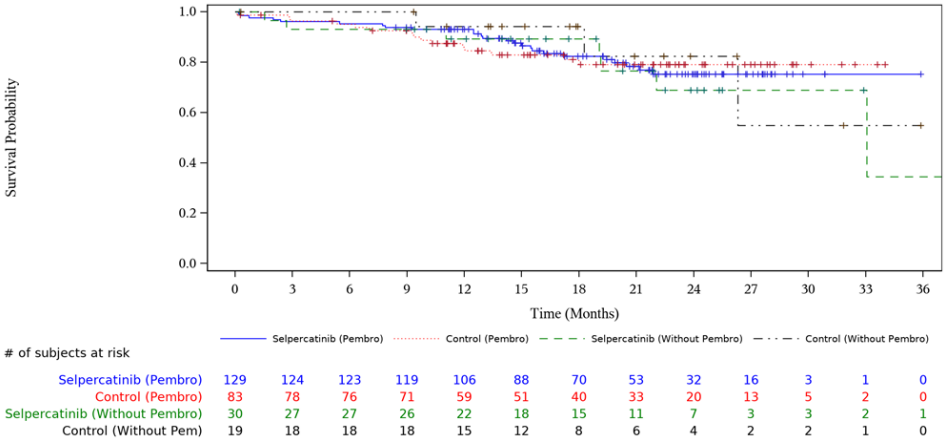


Figure 2 Kaplan-Meier curves of OS for the selpercatinib and control arm, LIBRETTO-431 trial (separated by ITT with pembrolizumab)

Source: Eli Lilly, data on file (data cut 1 May 2023), CSR L-431 (38)

Figure 3 Kaplan Meier plot of overall survival (ITT population)

Abbreviations: CI, confidence interval; HR, hazard ratio; TRT A, Selpercatinib; TRT B, Carboplatin or Cisplatin+Pemetrexed+/-Pembrolizumab.

Source: Eli Lilly, data on file (data cut 1 May 2023), CSR L-431 (38)

6.2.3 Progression-free survival (1 May 2023)

PFS is the primary outcome in LIBRETTO-431 (by BICR assessment). The median PFS was 24.8 and 11.2 months for selpercatinib vs the control arm, respectively (BICR assessment 1 May 2023 DCO). The PFS follow-up time for PFS was 19.4 months and 18.9 months for selpercatinib and the control arm, respectively (BICR assessment 1 May 2023 DCO). Table 20 below presents the PFS survival rates based on the 1 May 2023 DCO. The KM-curve for OS is presented in Figure 4.

Table 19 PFS – PFS results from the LIBRETTO-431 trial

	Overall ITT Population		ITT-Pembrolizumab Population	
Results	**Selpercatinib (n=159)**	**Control (+/- pembrolizumab) (n = 102)**	**Selpercatinib (n=129)**	**Control (+pembrolizumab) (n = 83)**
Number of events, n (%)	[redacted]	[redacted]	49 (38.0)	49 (59.0)
PD	[redacted]	[redacted]	44 (34.1)	46 (55.4)
Death without PD	[redacted]	[redacted]	4 (3.9)	3 (3.6)
Median PFS, months (95% CI)	[redacted]	[redacted]	24.8 (16.89, NE)	11.17 (8.77, 16.76)
Follow-up time, months	[redacted]	[redacted]	19.38 (16.72, 19.71)	18.86 (14.16, 22.34)
Hazard ratio (95% CI)				
Stratified	[redacted]		0.465 (0.309, 0.699)	
Unstratified	[redacted]		0.488 (0.327, 0.726)	

Abbreviations: PFS, progression-free survival; NE, not estimated; CI, confidence interval

Table 20 PFS - Survival rates from the LIBRETTO-431 trial

	Overall ITT Population		ITT-Pembrolizumab Population	
Survival (%) (CI)	**Selpercatinib (n=159)**	**Control (+/- pembrolizumab) (n = 102)**	**Selpercatinib (n=129)**	**Control (+pembrolizumab) (n = 83)**
6 months	[redacted]	[redacted]	87.2 (80.0, 92.0)	72.1 (60.8, 80.7)
12 months	[redacted]	[redacted]	71.2 (62.0,78.5)	47.8 (35.9, 58.8)
18 months	[redacted]	[redacted]	58.6 (48.3, 67.5)	34.0 (22.4, 45.9)
24 months	[redacted]	[redacted]	54.2 (43.6, 63.6)	31.6 (20.1, 43.7)
30 months	[redacted]	[redacted]	49.7 (36.6, 61.4)	-

Source: Eli Lilly, data on file (data cut 1 May 2023, CSR L-431) (38)

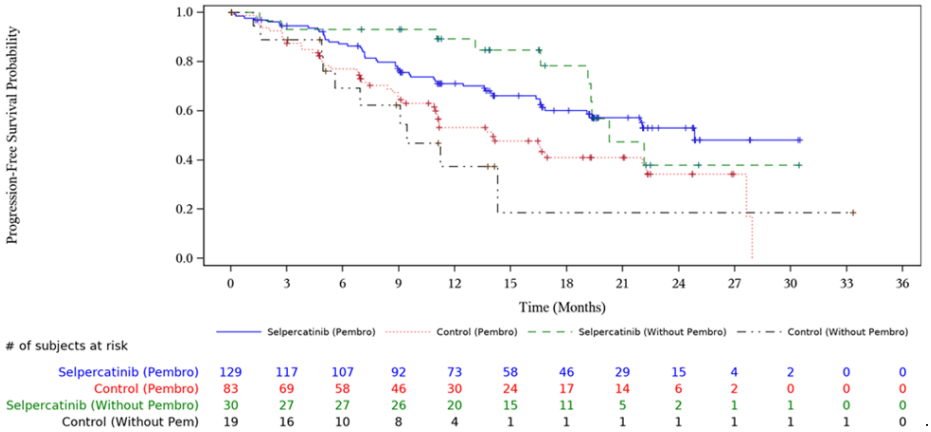


Figure 4 Kaplan-Meier curves of PFS for the selpercatinib and control arm, LIBRETTO-431 trial (separated by ITT with pembrolizumab) (BICR assessment)

Source: Eli Lilly, data on file (data cut 1 May 2023), CSR L-431 (38)

Figure 5 Kaplan-Meier plot of progression-free survival by BICR assessment (ITT Population)

Source: Eli Lilly, data on file (data cut 1 May 2023), CSR L-431 (38)

Median PFS in the selpercatinib group was more than 2 years, which was more than double the PFS in the control group. This is particularly noteworthy given that outcomes in the control group were similar to or better than those previously reported in the KEYNOTE-189 trial.

6.2.4 Duration of response (1 May 2023)

The results for DOR in the ITT Population by investigator assessment were consistent with those observed by BICR assessment. Responses were durable, as indicated by a median response duration of 24.2 months (95% CI, 17.9 to not estimable) in the selpercatinib group, as compared with 11.5 months (95% CI, 9.7 to 23.3) in the control group (refer to Table 21 (BICR assessed DOR)).

Table 22 presents the DOR survival rates on the 1 May 2023 DCO. The KM-curve for OS is presented in Figure 6.

Table 21 Duration of response data from the LIBRETTO-431 trial

Duration of response	Selpercatinib (n=129)	Pemetrexed + platinum + pembrolizumab (n = 83)
Patients with a response, n	108	54
Patients with a response and censored data, n (%)	34 (31.5)	29 (53.7)
Median duration of response, months (CI)	24.18 (17.9-NE)	11.47 (9.66-23.26)
Median duration of follow-up, months (CI)	17.9 (16.46, 19.52)	14.55 (11.24-19.81)

Abbreviations: NE, not estimated; CI, confidence interval

Table 22 DOR – survival rates from the LIBRETTO-431 trial

Survival (%) (CI)	Selpercatinib (n=108)	Pemetrexed + platinum + pembrolizumab (n = 54)
6 months	92.2 (84.9, 96.0)	77.0 (63.0, 86.2)
12 months	78.8 (69.0, 85.8)	45.7 (30.3, 59.8)
18 months	61.6 (49.9, 71.4)	39.2 (24.0, 54.0)
24 months	59.6 (47.5, 69.8)	22.8 (6.3, 45.5)
30 months	N/A	N/A

Source: Eli Lilly, data on file (data cut 1 May 2023, CSR L-431) (38)

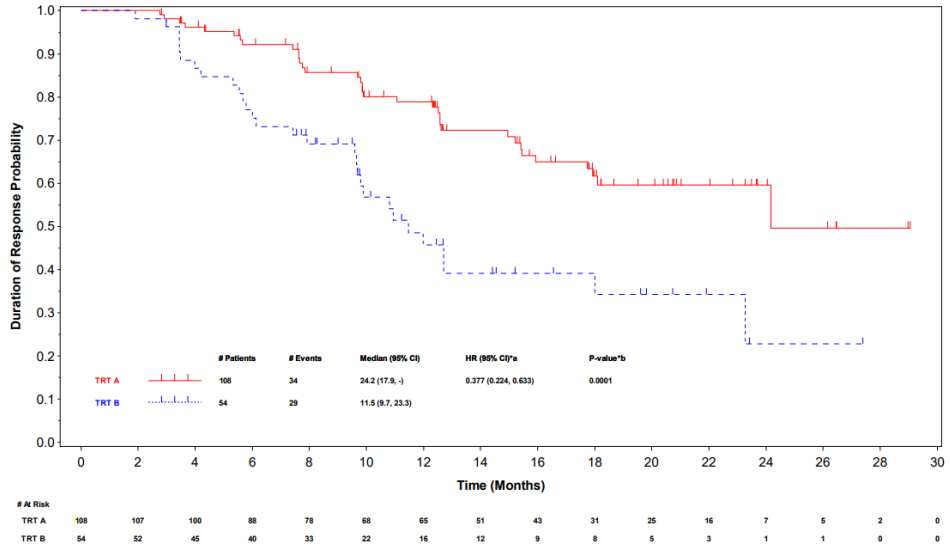


Figure 6 Kaplan-Meier curves of DOR for the selpercatinib and control arm, LIBRETTO-431 trial (ITT population) (BICR assessment).

Source: Eli Lilly, data on file (data cut 1 May 2023), CSR L-431 (38)

6.3 Efficacy – results per LIBRETTO-001

The outcomes from the LIBRETTO-001 trial are presented in the section below. The source of the primary data from the trial presented for this submission is presented by Eli Lilly's data on file (CSR, etc. at DCO, 13 January 2023), which presents data from the treatment naïve SAS1 population (n=69). All outcomes included in the application is also presented in Appendix B (in the Appendix, both the treatment naïve patient group and the PlatChemo patient group from LIBRETTO-001 is presented).

6.3.1 Overall response rate (January 2023)

The ORR was one of the primary endpoints in LIBRETTO-001. ORR was defined as the proportion of patients with best overall response (BOR) of confirmed complete response (CR) or confirmed partial response (PR) based on RECIST version 1.1. Table 23 below

presents the response rates from the LIBRETTO-trial at DCO, 13 January 2023. The ORR by IRC assessment was 82.6% (95% CI: 71.6, 90.7) for treatment naïve patients (n=69).

Table 23 Response rates from the LIBRETTO-001 trial

Response, n (%)	Treatment naïve (n=69)
ORR (95% CI) [complete response or partial response]	82.6 (71.6, 90.7)
Complete response, n (%)	5 (7.2)
Partial response, n (%)	52 (75.4)
Stable disease, n (%)	7 (10.1)
Progressive disease, n (%)	3 (4.3)
Not evaluable, n (%)	2 (2.9)

Abbreviations: ORR, overall response rate; CI, confidence interval
Source: Eli Lilly, data on file (2023) on ICR ORR L-001 (39)

6.3.2 Overall survival (January 2023)

OS is a secondary outcome in LIBRETTO-001. Most patients were alive as of the DCO date, and at 3 years 65.6 of the treatment naïve patients were alive. However, OS was not estimable (NE (95% CI: 37.8, NE) at the DCO. The median follow-up time for OS was 41.9 months for the treatment naïve patient group (13 January 2023 DCO). Table 25 below presents the OS survival rates based on the 13 January 2023 DCO. The KM-curve for OS is presented in Figure 7.

Table 24 OS results from the LIBRETTO-001 trial

Results	Treatment naïve (n=69)
Median OS, months (95% CI)	NE
Follow-up time, months	41.9

Abbreviations: OS, overall survival, NE, not estimated; CI, confidence interval

Table 25 OS - Survival rates from the LIBRETTO-001 trial

Survival (%) (CI)	Treatment naïve (n=69)
≥12 months	94.1 (85.1, 97.8)
≥24 months	74.3 (61.9, 83.1)
≥36 months	65.6 (52.4, 75.9)
≥48 months	52.3 (36.2, 66.1)
≥60 months	52.3 (36.2, 66.1)

Source: Eli Lilly data on file 2023 L-001 (39)

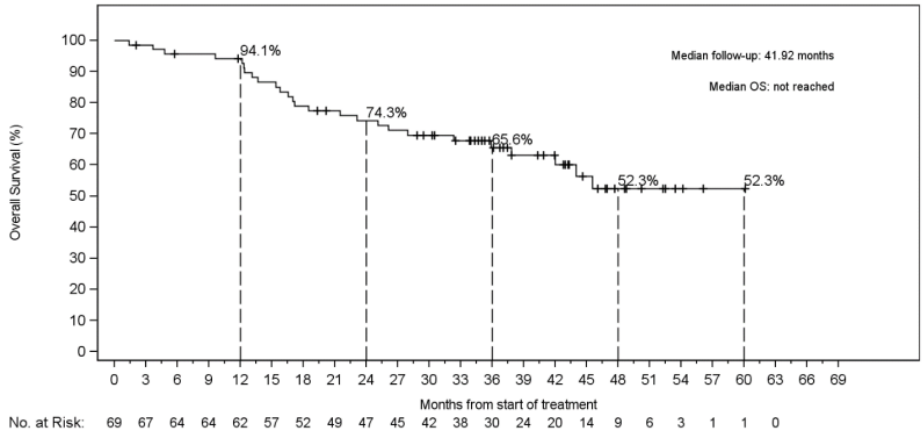


Figure 7 Kaplan-Meier curve of OS from LIBRETTO-001, treatment naive NSCLC (Jan 2023)

Abbreviations: OS, overall survival
Source: Eli Lilly, data on file (figure JZJA.5.8, data cutoff 13 Jan 2023) L-001 (39)

6.3.3 Progression-free survival (January 2023)

PFS is secondary outcome in LIBRETTO-001. The median duration of PFS by IRC assessment was 22.0 months (95% CI: 16.5, 24.9) for treatment naïve patients, with a median follow-up of 38.9 months (95% CI: 19.4, 46.9). At the time of DCO, 20.3% of the patients were still on treatment with no documented disease progression. Table 27 below presents the PFS survival rates based on the 13 January 2023 DCO. The KM-curve for OS is presented in Figure 8.

Table 26 PFS results from the LIBRETTO-001 trial

Results	Treatment naïve (n=69)
Median PFS, months (95% CI)	22.0. (16.5, 24.9)
Follow-up time, months	38.9

Abbreviations: PFS, progression-free survival

Table 27 PFS - Survival rates from the LIBRETTO-001 trial

Survival (%) (CI)	Treatment naïve (n=69)
≥12 months	70.8 (58.0, 80.3)
≥24 months	44.9 (31.8, 57.3)
≥36 months	34.6 (22.3, 47.3)
≥48 months	34.6 (22.3, 47.3)
≥60 months	NE (NE, NE)

Source: Eli Lilly data on file 2023 L-001 (39)

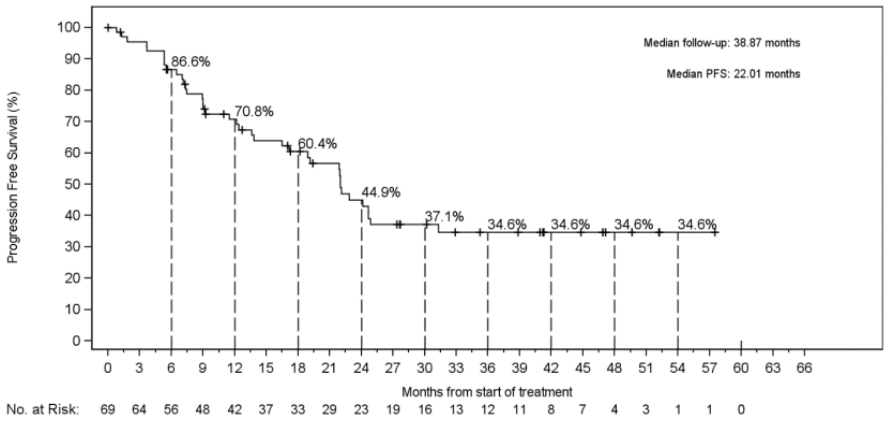


Figure 8 Kaplan-Meier curve of PFS from LIBRETTO-001, treatment naive NSCLC (Jan 2023)

Abbreviations: OS, overall survival

Source: Eli Lilly, data on file (figure JZJA.5.8, data cutoff 13 Jan 2023) L-001 (39)

6.3.4 Duration of response (January 2023)

DOR was calculated for patients who achieved CR or PR. For such patients, DOR was defined as the number of months from the start date of CR or PR (whichever response status was observed first) and subsequently confirmed, to the first date that recurrent or progressive disease was objectively documented. The median DOR by IRC assessment was 20.3 months (95% CI: 15.4, 29.5) for treatment naïve patients, with a median follow-up of 37.1 months (95% CI: 24.0, 45.1). At the time of DCO, 22.8% of patients were still on treatment with no documented disease progression. Table 29 presents the DOR survival rates on the 13 January 2023 DCO. The KM-curve for OS is presented in Figure 9.

Table 28 Duration of response data from the LIBRETTO-001 trial

Duration of response	Treatment naïve (n=69)
Patients with a response, n	57
Censored, n (%)	25 (43.9)

Median duration of response, months (CI)	20.3 (15.4, 29.5)
Median duration of follow-up, months	37.1

Table 29 DOR – survival rates from the LIBRETTO-001 trial

Survival (%) (CI)	Treatment naïve (n=69)
≥12 months	66.7 (52.4, 77.6)
≥24 months	38.1 (24.5, 51.6)
≥36 months	35.4 (22.0, 49.0)
≥48 months	35.4 (22.0, 49.0)
≥60 months	NE (NE, NE)

Abbreviations: NE, not estimated
Source: Eli Lilly data on file 2023 L-001 (39)

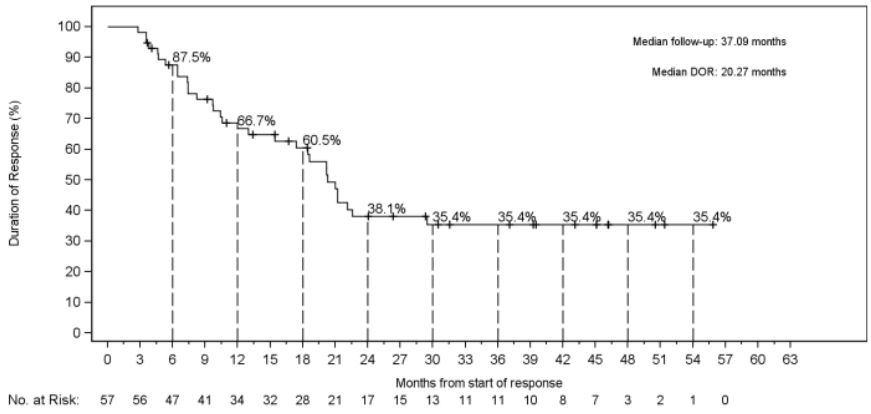


Figure 9 Kaplan-Meier curve of DOR from LIBRETTO-001, treatment naive NSCLC (Jan 2023)
Abbreviations: OS, overall survival
Source: Eli Lilly, data on file (figure JZJA.5.8, data cutoff 13 Jan 2023) L-001 (39)

6.4 Efficacy – results per KEYNOTE-189

The outcomes from the KEYNOTE-189 trial are presented in the section below. The source of the primary data from KEYNOTE-189 presented for this submission is reported in the publication by Garassino et al (2023) (with DCO, 8 March 2022) (46). All outcomes included in the application is also presented in Appendix B.

6.4.1 Efficacy outcomes (8 March 2022)

Primary endpoints were PFS per RECIST v1.1 by BICR and OS. Secondary end points were ORR and DOR per RECIST v1.1 by BICR. Median time from random assignment to DCO was 64.6 (range, 60.1-72.4) months. In the ITT population, HRs (95% CI) for pembrolizumab plus pemetrexed-platinum versus placebo plus pemetrexed-platinum were 0.60 (0.50 to 0.72) for OS and 0.50 (0.42 to 0.60) for PFS. Five-year OS rates were 19.4% versus 11.3%, and 5-year PFS rates were 7.5% versus 0.6%. ORR (95% CI) was 48.3% (43.4 to 53.2) and 19.9% (14.7 to 26.0), respectively. Median (range) DOR was 12.7 (1.1+ to 68.3+) and 7.1 (2.4 to 31.5) months, respectively.

Sections below presents the tumour response data from KEYNOTE-189 as well as the KM-curves of OS (Figure 10), PFS (Figure 11), and DOR (Figure 12), respectively.

6.4.2 Overall response rate (8 March 2022)

The ORR by IRC assessment was 48.3% (95% CI: 43.4, 53.2) for ITT population (n=410).

Table 30 Response rates from the LIBRETTO-001 trial

Response, n (%)	ITT population (n=410)
ORR (95% CI) [complete response or partial response]	48.3 (43.4, 53.2)
Complete response, n (%)	10 (2.4)
Partial response, n (%)	188 (45.9)
Stable disease, n (%)	149 (36.3)
Progressive disease, n (%)	37 (9.0)
Not evaluable, n (%)	12 (2.9)
No assessment, n (%)	14 (3.4)

Abbreviations: ORR, overall response rate; CI, confidence interval
Source: Garassino et al 2023 (46)

6.4.3 Overall survival (8 March 2022)

Figure 10 presents the KM-estimates of OS from KEYNOTE-189 (DCO: 8 March 2022).

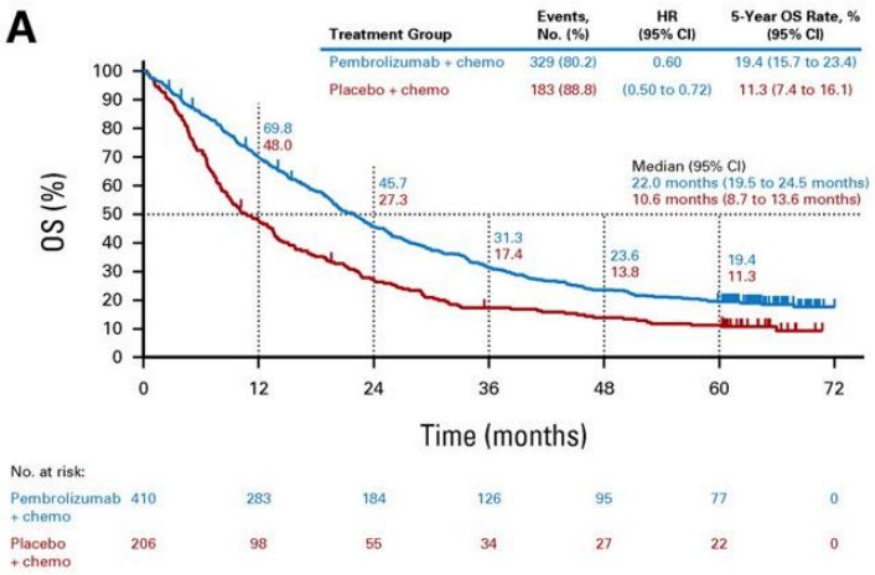


Figure 10 Kaplan-Meier curves from KEYNOTE-189 OS - ITT population (Garassino et al 2023)
Source: Garassino et al (2023) (46)

6.4.4 Progression-free survival (8 March 2022)

Figure 11 presents the KM-estimates of PFS from KEYNOTE-189 (DCO: 8 March 2022).

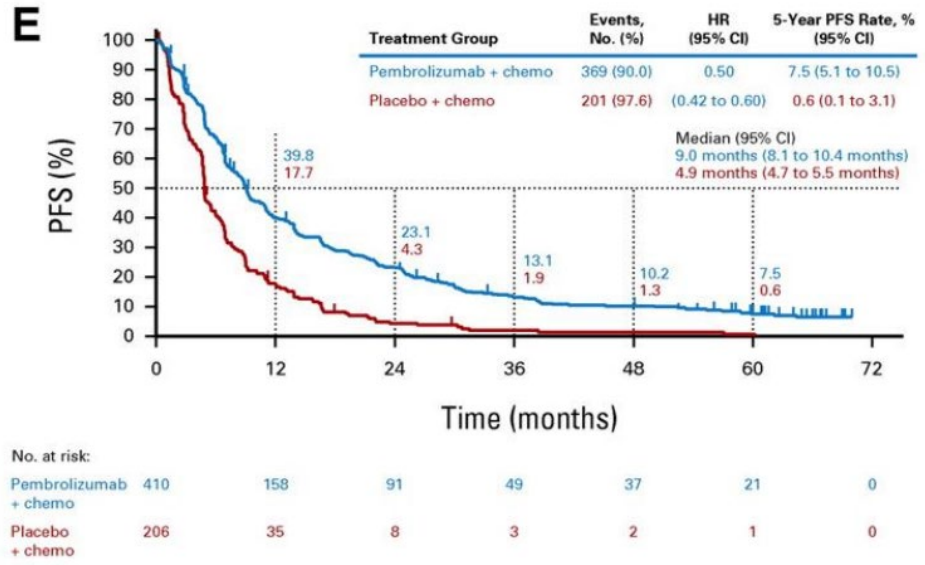


Figure 11 Kaplan-Meier curves from KEYNOTE-189 PFS - ITT population (Garassino et al 2023)
Source: Garassino et al (2023) (46)

6.4.5 Duration of response (8 March 2022)

Median DOR was 12.7 months (95% CI: 1.1, 68.3). Figure 12 presents the KM-estimates of DOR from KEYNOTE-189 (DCO: 8 March 2022).

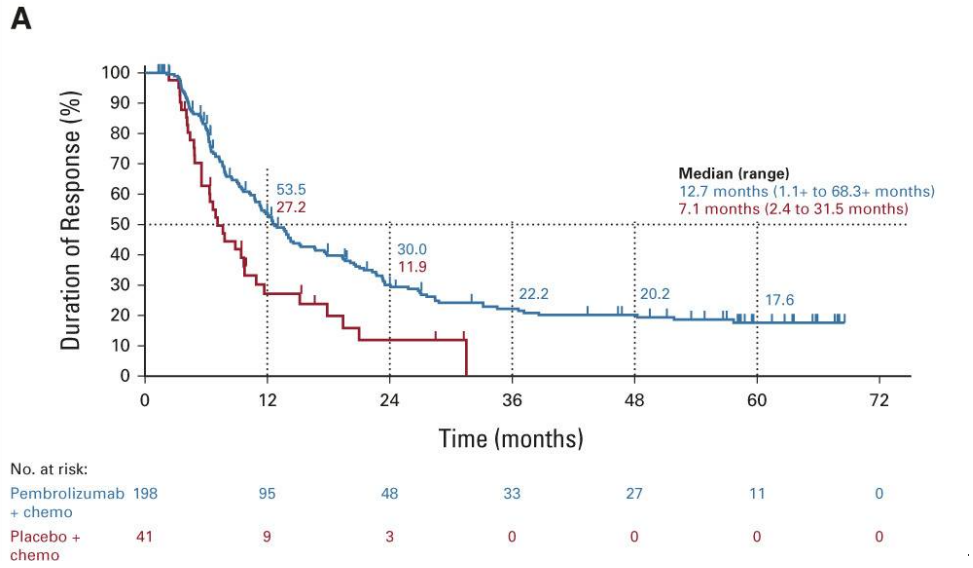


Figure 12 Kaplan-Meier curves from KEYNOTE-189 DOR - ITT population (Garassino et al 2023)
Source: Garassino et al (2023) (46)

7. Comparative analyses of efficacy

As previously mentioned, pemetrexed + carboplatin ± pembrolizumab is included in the LIBRETTO-431 trial as a part of the comparator / control arm. Selpercatinib monotherapy

as first line treatment for patients with RET fusion-positive advanced NSCLC has recently been proved to have superior efficacy versus platinum doublet chemotherapy ± pembrolizumab in phase 3 randomized clinical trial LIBRETTO-431.1 At the time of the interim analysis (DCO 1st May 2023), the preplanned criterion for primary efficacy endpoint was met (98 progression events), but OS data was still immature. Patients were allowed to crossover from the control group to selpercatinib group if progression as assessed by blinded independent central review occurred during control treatment. Therefore, the OS data are both immature and confounded by the high proportion of patients who crossed over within the trial or started commercially available selective RET inhibitor outside the trial. The availability of mature OS data for analysis are only expected after several years.

Therefore, since the OS data from the LIBRETTO-431 trial is immature, more mature OS data from LIBRETTO-001 an estimated control arm based on the KEYNOTE-189 trial will be presented and used in this analysis, refer to Table 10. For this purpose, this approach uses the most recent DCO from the KEYNOTE-189 trial (as per 8 March 2022) and focuses on the pembrolizumab arm to provide a more conservative estimate. The hazard ratio (HR) for selpercatinib versus the pemetrexed + platinum + pembrolizumab arm of the KEYNOTE-189 trial (pembro+PC) was estimated using the most recent available DCO for KEYNOTE-189 (aggregated data were used because the patient-level data were not available for the latest DCO).

When using KEYNOTE-189 data, the model assumes that outcomes are equivalent with and without pembrolizumab, refer to Section 8.

7.1.1 Differences in definitions of outcomes between studies

The OS was deemed comparable between LIBRETTO-001 and KEYNOTE-189. A summary of the definition of each endpoint considered for the MAIC is presented in Table 31.

Table 31 Definition of outcomes from LIBRETTO-001 and KEYNOTE-189 (and LIBRETTO-431)

Inclusion criteria	LIBRETTO-431	LIBRETTO-001	KEYNOTE-189
OS	Overall survival was defined as the time from randomization until death from any cause.	Overall survival is defined as the number of months elapsed between the date of the first dose of selpercatinib and the date of death (whatever the cause).	OS was defined as the time from randomization to death due to any cause.

Abbreviations: OS, overall survival

7.1.2 Method of synthesis

As the LIBRETTO-001 trial is a single-arm clinical trial, there is no head-to-head evidence to compare the clinical efficacy of selpercatinib and the chosen comparator. For this reason, a MAIC using LIBRETTO-001 and KEYNOTE-189 has been conducted to assess the relative efficacy. An overview of the methods used is provided below. The full methos are available in Appendix C.

The evidence base was composed of individual patient level data (IPD) from treatment naïve patients (n=69) based on January 2023 DCO in the LIBRETTO-001 trial (will inform

the SELPE data). The most recent publications reporting the outcomes of interest from KEYNOTE-189 will inform the pembro+PC data (refer to Table 10) using a DCO from 8 March 2022. Adjusting for the following baseline characteristics from KEYNOTE-189 is proposed in Table 14. In addition, adjusting for PD-L1 is considered, but LIBRETTO-001 has not collected these data and therefore the adjustment is not possible. Refer to Section 6 for KM-curves from LIBRETTO-001 and KEYNOTE-189.

7.1.2.1 Unanchored MAIC of selpercatinib (SELPE) vs comparator (pembro+PC)

As described, the MAIC will use IPD from LIBRETTO-001 (DCO January 2023) for the naïve NSCLC cohort (n=69). This IPD cohort will then be matched with the baseline summary statistics reported in the pembro+PC arm of KEYNOTE-189 (ITT population). Patients in LIBRETTO -001 will be reweighted such that their weighted mean baseline characteristics match to those reported in the publication (Garassino et al (2023)). The list of baseline covariates that will be used are listed here (also refer to Table 32):

- Age (mean, standard deviation, derived from median and range if not reported)
- Gender (% female)
- ECOG (% 0)
- Smoking status (% never)
- Brain metastases (% yes)

7.1.2.2 Distribution of MAIC weights

This approach is a form of propensity score weighting in which group with IPD are weighted by their inverse odds of being in that group versus the other treatment group (trial with only published aggregate data). For time to event outcome analysis, KM-curves for OS and PFS from KEYNOTE-189 need to be digitized first to get the IPD with censoring status. After digitization, MAIC weights will be incorporated in the KM method to estimate the median OS and PFS and Cox proportional hazards model to estimate the hazard ratio. Note that the outcome data is not used when calculating MAIC weights. More details of the MAIC methodology are available in Signorovitch et al (62).

Figure 13 Distribution of raw weights
Source: Eli Lilly, data on file (ITC / MAIC reports) 2024

Figure 14 Distribution of MAIC rescaled weights

Notes: The rescaled weights are relative to the original unit weights of each individual (a rescaled weight > 1 means that an individual carries more weight in the re-weighted population than the original data, and that a rescaled weight < 1 means that an individual carries less weight in the re-weighted population than the original data).

Source: Eli Lilly, data on file (ITC / MAIC reports) 2024

There we no extreme weights as seen in the histogram. Majority of the weights were less than 0.5.

7.1.2.3 Baseline characteristics before and after weighting

Table 32 presents selected baseline characteristics informed by a MAIC. Patients in LIBRETTO-001 were reweighted such that their weighted mean baseline characteristics matched to those reported in the publication. Refer to section 6.1.2.1 for tables showing the baseline characteristics of patients from LIBRETTO-001 (treatment-naïve, n=69) and KEYNOTE-189. The list of baseline covariates that were used is listed in the previous slide.

It is noteworthy to mention that the data for selpercatinib comes from LIBRETTO-001 study restricted to RET fusion-positive patients. Furthermore, the comparator data have no information on RET status, and hence, majority of patients is expected to be RET fusion-negative since only 1-2% of NSCLC is RET positive.

Sample size for selpercatinib in the treatment naïve subgroup of patients is small (n=69) so adjusting for all these prognostic factors may reduce effective sample size (ESS) too much. There is no procedure that would allow stepwise adjustment. We will evaluate the weights distribution based on the 5 specified factors and if we see extreme weights (>10) or drastic reduction in the effective sample size, we will explore what covariate drives the weights and consider removing it from the algorithm.

Table 32 Baseline Characteristics in Treatment-Naïve Patients in the LIBRETTO-001 (Before and After Weighting) and KEYNOTE-189 Trials

Characteristics	LIBRETTO-001 before weighting SAS1 treatment naïve (n=69)	LIBRETTO-001 after weighting [a] SAS1 treatment naïve (n=22)	KEYNOTE-189 Pem + plat-based drugs (n=410)
Mean age, years	61.5 (13.01)	65.0 (5.43)	65.0 (8.33)[b]

Characteristics	LIBRETTO-001 before weighting SAS1 treatment naïve (n=69)	LIBRETTO-001 after weighting [a] SAS1 treatment naïve (n=22)	KEYNOTE-189 Pem + plat-based drugs (n=410)
Sex (female %)	43 (62.32%)	11 (38.05%)	156 (38.0%)
ECOG PS			
0	25 (36.23%)	13 (45.12%)	185 (45.1%)
1	40 (57.97%)	15 (51.36%)	221 (53.9%)
2	4 (5.80%)	1 (3.52%)	1 (0.2%)
Brain metastases at baseline	16 (23.19%)	5 (17.81%)	73 (17.8%)
Smoking history, n (%)			
Never smoked	48 (69.57%)	3 (11.71%)	48 (11.7%)

ECOG PS = Eastern Cooperative Oncology Group performance score; NSCLC = non–small cell lung cancer; sd = standard deviation.

Notes: a, effective sample size across the entire data set; b, mean age for KN-189 is assumed to be equal to median age, sd is calculated as range divided by 6.

The large difference in smoking status between the groups was a key contributor to the reduction of ESS, which increased the uncertainty relative effectiveness estimates (wider 95%CIs). Furthermore, adjustment was only possible for characteristics reported/collected in both studies (e.g., PD-L1 expression was not collected in LIBRETTO-001); therefore, some unbalances might be present.

7.1.2.4 Standardized difference plot and variance ratio plot

The standardized difference plot and variance ratio plot were used to assess the balance of baseline characteristics between the populations after re-weighting in the MAIC analysis, refer to Figure 15 and Figure 16.

Figure 15 Standardized difference plot, LIBRETTO-001 vs KEYNOTE-189

Figure 16 Variance ratio plot, LIBRETTO-001 vs KEYNOTE-189

7.1.3 Results from the comparative analysis

For time to event outcome analysis, KM- curves for OS and PFS from KEYNOTE-189 were digitized first to get the IPD with censoring status. After digitization, MAIC weights were incorporated in the KM method to estimate the median OS and PFS and Cox proportional hazards model was used to estimate the hazard ratio.

Table 33 and Table 34 present the unadjusted and MAIC adjusted analysis of OS and PFS for selpercatinib vs pembro+PC. Weighting had minimal impact on selpercatinib effectiveness estimates, and increased uncertainty by widening confidence intervals. Therefore, for the purposes of modelling OS in the health economic analysis, unadjusted results is used in the base case analysis.

Table 33 Results from the comparative analysis of selpercatinib vs. pembro+PC before weighting

Outcome measure	Selpercatinib	Pembro+PC
Treatment naïve – OS		
Median OS (95% CI)		
Hazard ratio		
P value		
Treatment naïve – PFS		
Median PFS		
Hazard ratio		
P value		

Abbreviations: OS, overall survival; NR, not reached; PFS, progression-free survival; pembro+PC, pembrolizumab and platinum chemotherapies

Table 34 Results from the comparative analysis of selpercatinib vs. pembro+PC after weighting

Outcome measure	Selpercatinib	Pembro+PC
Treatment naïve – OS		
Median OS (95% CI)		
Hazard ratio		
P value		
Treatment naïve – PFS		
Median PFS		
Hazard ratio		
P value		

Abbreviations: OS, overall; NR, not reached; pembro+PC, pembrolizumab and platinum chemotherapies

7.1.4 Efficacy – results per overall survival

The median OS and HR for both the unadjusted and adjusted analyses are reported in Table 33 and Table 34 in the section above. Results were similar in both unweighted and weighted (MAIC) analyses. Consistency of MAIC PFS results with Ph3 RCT increases confidence to OS results which are not available from LIBRETTO-431 at the time of interim analysis due to immature data and high rate of crossover.

Figure 17 Kaplan-Meier curves of OS for selpercatinib vs pembro+PC

Note: The TRT=Libretto-001 weighted curve represents the weighted number at risk at each time point.
Source: Eli Lilly, data on file (2024) ITC / MAIC report

7.1.5 Efficacy – results per progression-free survival

The median OS and HR for both the unadjusted and adjusted analyses are reported in Table 33 and Table 34 in the section above. Results for PFS were consistent with Ph3 randomized controlled trial LIBRETTO-431 which reported PFS HR of [redacted] for selpercatinib vs pembro+PC arm (refer to Appendix D.2.1).

Figure 18 Kaplan-Meier curves of PFS for selpercatinib vs pembro+PC
Source: Eli Lilly, data on file (2024) ITC / MAIC report (49)

8. Modelling of efficacy in the health economic analysis

Because of the immature OS data in the LIBRETTO-431 trial, the base-case analysis in the model uses OS data from the LIBRETTO-001 and KEYNOTE-189 trials. An HR (not adjusted for MAIC) is applied to these data to provide a more conservative estimate for the difference in OS between selpercatinib and pemetrexed + platinum + pembrolizumab. As mentioned in Section 7, a MAIC was performed (63) to match the LIBRETTO-001 population characteristics to those of the KEYNOTE-189 trial. This was conducted in order to extrapolate OS, providing this analysis with more mature OS data (from LIBRETTO-001). The following section will describe the extrapolation approach applied in the analysis.

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

LIBRETTO-431

Progression-free survival and some OS data are available for selpercatinib and comparators from the LIBRETTO-431 trial (ITT-pembrolizumab, n = 261), refer to Figure 19.

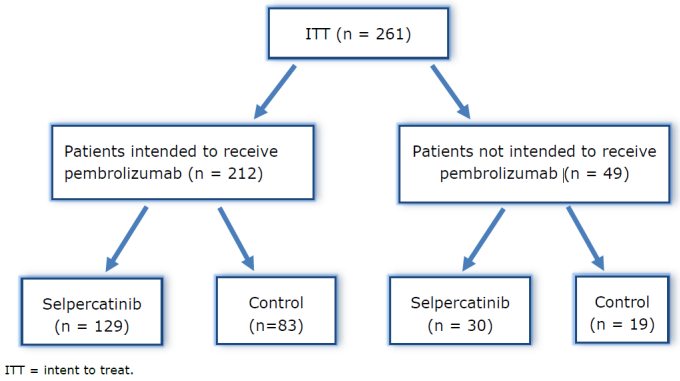


Figure 19 Randomisation and treatment arms in LIBRETTO-431

The LIBRETTO-431 included randomisation to the following 2 treatment arms:

- Selpercatinib (n=159)
- Standard of care: pemetrexed + carboplatin or cisplatin ± pembrolizumab (n = 102) (control n=83 + control n=19)

The analysis uses data from the overall populations with a covariate for ITT with pembrolizumab (assuming that there is no treatment-effect interaction for intention to receive pembrolizumab but allow the survival in the patient populations to differ by ITT with pembrolizumab (n = 261), please refer to Appendix D.2 for further information.

LIBRETTO-001 and KEYNOTE-189 (MAIC)

More mature OS data for selpercatinib are available from the LIBRETTO-001 trial (January 2023 DCO; SAS1, n = 69). Data for comparator treatments were identified by the SLR (Pfeiffer et al., 2017). The MAIC approach uses the most recent DCO from the KEYNOTE-189 trial (aggregate data due to unavailability of IPD data) and focuses on the pembrolizumab arm to provide a more conservative estimate for the comparison of selpercatinib versus pemetrexed + platinum + pembrolizumab.

8.1.1 Extrapolation of efficacy data

For PFS, OS, and TTD, survival functions were fitted to the LIBRETTO-431 data.

Table 35 Survival estimation approaches

Method/approach	Description/assumption
Survival functions fitted to LIBRETTO-431 data separated by intention to treat with pembrolizumab	Survival functions fitted to trial PFS, OS, and TTD data with intention to treat with pembrolizumab (n=261) as a variable, such that functions are available for selpercatinib vs. pemetrexed + platinum + pembrolizumab

Abbreviations: NSCLC = non–small cell lung cancer; OS = overall survival; PFS = progression-free survival; TTD = time to treatment discontinuation.

Parametric survival functions were fitted to KM data as recommended by the NICE Decision Support Unit (DSU) (Latimer, 2011) (64). Stratified functions and unstratified functions (with treatment as an indicator variable) were fitted. Stratified functions were used rather than separate functions for each treatment arm to allow comparison of model fit statistics (Akaike information criterion (AIC) and Bayesian information criterion (BIC)) with those for the unstratified functions. The visual fit to the data was evaluated by comparison of the parametric curves overlaid with the KM curves.

Because the OS data from LIBRETTO-431 are particularly immature and data for the control arm are confounded by treatment switching, additional scenarios using different survival data and approaches are available in the model. These include:

- OS survival data from LIBRETTO-431, adjusted for treatment switching and using clinical expert expectation for survival.
- More mature OS data from LIBRETTO-001 and an estimated control arm based on the KEYNOTE-189 trial (with the options outlined in Appendix D). The HR for selpercatinib versus the pemetrexed + platinum + pembrolizumab arm of the KEYNOTE-189 trial, estimated using the most recent available DCO for KEYNOTE-189, was applied in the base case.
- PFS used as a surrogate. Specifically, the difference in median OS for selpercatinib versus the estimated control arm (pemetrexed plus platinum plus pembrolizumab) was estimated based on the difference in median PFS (estimated from the PFS functions) and a published regression analysis for the association between overall response rate, PFS, and OS) (Pfeiffer et al., 2017) (65). The HR for OS was estimated from the ratio of median OS (Cortés et al., 2014) (66) Overall survival for selpercatinib was estimated by applying the HR for OS to the OS function for pemetrexed + carboplatin + pembrolizumab.

Overall survival is capped in the model using general population mortality rates, adjusted using a mortality ratio for patients with cancer (mortality ratio of 1.00 is assumed). Progression-free survival and TTD are capped by OS in the model.

Summary of the approaches to estimation of PFS and OS in the cost-effectiveness model is provided in the table below.

Table 36 Summary of approaches for the estimation of PFS and OS in the CEM.

Selpercatinib and comparator arm	LIBRETTO-431
Sample size	A total of 261 patients were enrolled in the study who were randomised 2:1 to receive selpercatinib (159 patients) versus standard of care (102 patients). Patients that progressed in the control arm were given the choice to receive selpercatinib.
PFS available	Yes
OS available	LIBRETTO-001 and hazard ratio (HR) vs KEYNOTE-189 pemetrexed + platinum + pembrolizumab arm: (latest KEYNOTE-189 DCO (8 March 2022), functions fitted to the LIBRETTO-001 only); HR options: MAIC adjusted or unadjusted.
Comparative effectiveness approach for the primary analysis	Survival functions for selpercatinib and the pemetrexed + platinum + pembrolizumab arm from the LIBRETTO-431 trial.

Abbreviations: PFS, progression-free survival; OS, overall survival ; MAIC, matched-adjusted indirect comparison; HR, hazard ratio, DCO, data cutoff

8.1.1.1 Extrapolation of Overall Survival (OS)

For the base-case analysis, in order to use the latest data available for the KEYNOTE-189 study to the selpercatinib OS function, a range of parametric proportional hazards functions were fitted to the selpercatinib data from LIBRETTO-001 for this analysis.

Summary of the survival estimation approach based on the MAIC

Overall survival data for the pemetrexed + platinum + pembrolizumab arm were digitised, and patient-level data were simulated. A MAIC was performed (Signorovitch et al 2019) to match the LIBRETTO-001 population characteristics to those of the KEYNOTE-189 trial. Hazard ratios were estimated using a Cox model comparing the adjusted and unadjusted OS for selpercatinib with those for pemetrexed + platinum + pembrolizumab.
The HR was applied to proportional hazards survival functions fitted to the LIBRETTO-001 OS data to estimate OS for pemetrexed + platinum + pembrolizumab. Options are available in the CEM to apply the HR estimated after MAIC adjustment and the HR without any adjustment (naïve indirect comparison), which provides a more conservative estimate, refer to Section 7, Table 33 and Table 34.

Results from the MAIC for selpercatinib (LIBRETTO-001) and pemetrexed + platinum + pembrolizumab (KEYNOTE-189, most recent DCO) are provided in Section 7. Variance ratio and standardised differences plots are also available. Table 37 below presents the key assumptions associated with the extrapolation of OS derived from the IPD from the SAS1 (n=69) population in LIBRETTO-001 and aggregate data from the ITT (n=410) population in KEYNOTE-189.

The LIBRETTO-431 OS data are also available as a scenario in the model with the option to adjust the data for treatment switching and clinical expert opinion.

Table 37 Summary of assumptions associated with extrapolation of Overall Survival (OS)

Method/approach	Description/assumption
Data input	KEYNOTE-189 (data cutoff 8 March 2022)(46) and LIBRETTO-001 (data cutoff 13 January 2023)(39) was used in the MAIC analysis (49). LIBRETTO-001 & HR vs. KEYNOTE-189 pemetrexed +platinum + pembrolizumab arm: (latest K-189 data cut, functions fitted to L-001 only); HR option: MAIC unadjusted.
Model	For the base-case analysis, in order to use the latest data available for the KEYNOTE-189 study to the selpercatinib OS function, a range of parametric proportional hazards functions were fitted to the selpercatinib data from LIBRETTO-001 for this analysis (including Exponential, Weibull, and Gompertz).
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Selpercatinib: Exponential Comparator: N/A
Function with best BIC fit	Selpercatinib: Exponential Comparator: N/A
Function with best visual fit	Selpercatinib: All distributions have good visual fit. Comparator: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Not applicable
Validation of selected extrapolated curves (external evidence)	Survival prediction beyond trial follow-up is provided by clinical experts (derived from clinical expert meetings June 2022), refer to Appendix D.1.7).

Method/approach	Description/assumption
Function with the best fit according to external evidence	Not available
Selected parametric function in base case analysis	Selpercatinib: Exponential function fitted to LIBRETTO-001 OS data Comparator: Exponential. HR for LIBRETTTO-001 vs KEYNOTE-189 pembrolizumab arm (not MAIC adjusted) applied to selpercatinib function.
Adjustment of background mortality with data from Statistics Denmark	Overall survival is capped in the model using general population mortality rates, adjusted using a mortality ratio for patients with cancer.
Adjustment for treatment switching/cross-over	Not in the base case. Only applicable when using OS survival data from LIBRETTO-431 (adjusted for treatment switching and using clinical expert expectation for survival, refer to K.2)
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: N/A, not applicable or available; OS, overall survival; MAIC, matched-adjusted indirect comparison; HR, hazard ratio

Refer to Figure 17 for the MAIC derived observed time-to-event data for selpercatinib (LIBRETTO-001 unweighted).

Figure 20 presents the extrapolated OS curves applied in the base case long-term projections. In the selpercatinib arm, an exponential function is used to present the LIBRETTTO-001 OS data. For the comparator arm, OS was modelled by applying the unadjusted HR from LIBRETTTO-001 versus the KEYNOTE-189 pemetrexed +platinum + pembrolizumab arm (latest K-189 data cut) to the selpercatinib exponential survival function.

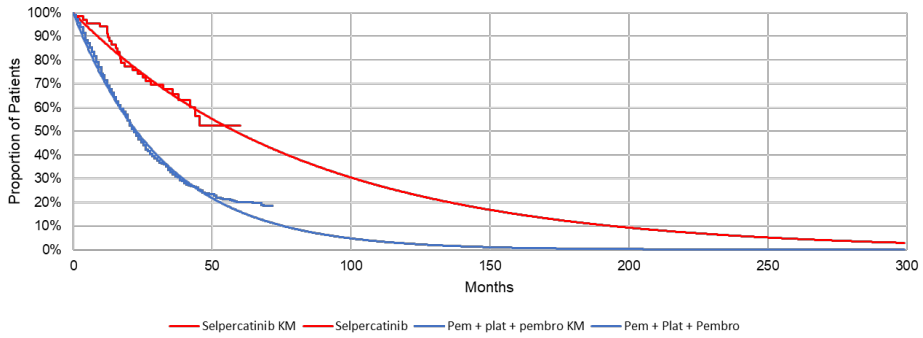


Figure 20 Extrapolation of OS (LIBRETTO-001) including KM-data

Abbreviations: OS, overall survival; KM, Kaplan-Meier

Source: Eli Lilly data on file 2024

Note: only the chosen distribution is shown in the figure (for both intervention and comparator)

8.1.1.2 Extrapolation of Progression-free Survival (PFS)

PFS from LIBRETTO-431 was analysed, including intention to treat with pembrolizumab as a variable to provide estimates for selpercatinib versus pemetrexed + platinum + pembrolizumab treatments in the control arm. Table 38 below provides a summary of the assumptions associated with extrapolation of PFS.

Table 38 Summary of assumptions associated with extrapolation of Progression-free Survival (PFS)

Method/approach	Description/assumption
Data input	Progression-free survival from LIBRETTO-431 was analysed, including intention to treat with pembrolizumab as a variable to provide estimates for selpercatinib versus pemetrexed + platinum + pembrolizumab treatments in the control arm.
Model	A range of parametric functions were fitted to the PFS data: • Exponential • Weibull • Log-normal • Log-logistic • Gompertz • Gamma • Spline/knot = 1 • Spline/knot = 2 • Spline/knot = 3 • Gen-gamma • Stratified Weibull • Stratified log-normal • Stratified log-logistic • Stratified Gompertz • Stratified gamma • Stratified spline/knot = 1 • Stratified spline/knot = 2 • Stratified spline/knot = 3 • Stratified Gen-gamma
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Selpercatinib: Log-logistic Pemetrexed + carboplatin ± pembrolizumab: Log-logistic
Function with best BIC fit	Selpercatinib: Exponential Pemetrexed + carboplatin ± pembrolizumab: Exponential
Function with best visual fit	Selpercatinib: Quite similar fit across parametric functions Pemetrexed + carboplatin ± pembrolizumab: Quite similar fit across parametric functions
Function with best fit according to evaluation of smoothed hazard assumptions	Not available
Validation of selected extrapolated curves (external evidence)	Survival prediction beyond trial follow-up is provided by clinical experts (derived from clinical expert meetings June 2022), refer to Appendix D.1.7).
Function with the best fit according to external evidence	Not available
Selected parametric function in base case analysis	Selpercatinib: Exponential Pemetrexed + carboplatin ± pembrolizumab: Exponential
Adjustment of background mortality with data from Statistics Denmark	Progression-free survival and TTD are capped by OS in the model.

Method/approach	Description/assumption
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: OS, overall survival; KM, Kaplan-Meier
Source: Eli Lilly data on file 2024
Note: only the chosen distribution is shown in the figure (for both intervention and comparator)

Figure 21 shows the extrapolated PFS curves applied in the base case (exponential model) long-term projection derived from the LIBRETTO-431 data.

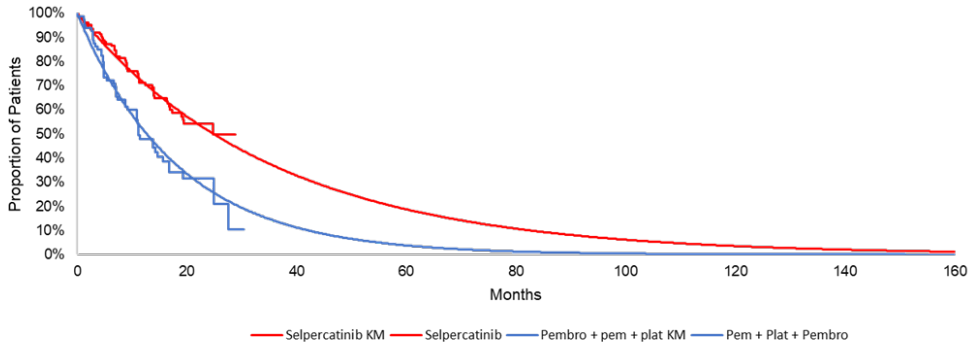


Figure 21 Extrapolation of PFS (LIBRETTO-431) including KM-data
Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier

8.1.1.3 Extrapolation of Time to Treatment Discontinuation (TTD)

In the base case, TTD for selpercatinib is extrapolated by using the PFS curve. For the comparator arm a range of standard parametric distributions to extrapolate TTD data from the LIBRETTO-431 trial. This was conducted to estimate DOR for the comparator in the model. Table 39 below provides a summary of the assumptions associated with extrapolation of TTD in the base case.

Table 39 Summary of assumptions associated with extrapolation of Time to Treatment Discontinuation (TTD)

Method/approach	Description/assumption
Data input	TTD for selpercatinib: uses the PFS curve (base case) For comparator, TTD data from LIBRETTO-431 was analysed (DOR data), including intention to treat with pembrolizumab as a variable to provide estimates for selpercatinib versus pemetrexed + platinum + pembrolizumab treatments in the control arm.
Model	Refer to PFS
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	Selpercatinib: Exponential Pemetrexed + carboplatin ± pembrolizumab: Exponential
Function with best BIC fit	Selpercatinib: Exponential Pemetrexed + carboplatin ± pembrolizumab: Exponential
Function with best visual fit	Selpercatinib: Quite similar fit across parametric functions Pemetrexed + carboplatin ± pembrolizumab: Quite similar fit across parametric functions

Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	Not available
Validation of selected extrapolated curves (external evidence)	Not available
Function with the best fit according to external evidence	Not available
Selected parametric function in base case analysis	Selpercatinib: Use PFS curve Pemetrexed + carboplatin ± pembrolizumab: Exponential
Adjustment of background mortality with data from Statistics Denmark	Progression-free survival and TTD are capped by OS in the model.
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	No

Abbreviations: OS, overall survival; KM, Kaplan-Meier
Source: Eli Lilly data on file 2024
Note: only the chosen distribution is shown in the figure (for both intervention and comparator)

Figure 22 shows the extrapolated TTD curves applied in the base case (exponential model) long-term projections derived from the LIBRETTO-431 data. The selpercatinib arm is modelled using the PFS curve (refer to 8.1.1.2). For the comparator arm, TTD data from LIBRETTO-431 was analysed (DOR data), including intention to treat with pembrolizumab as a variable to provide estimates for selpercatinib versus pemetrexed + platinum + pembrolizumab treatments in the control arm.

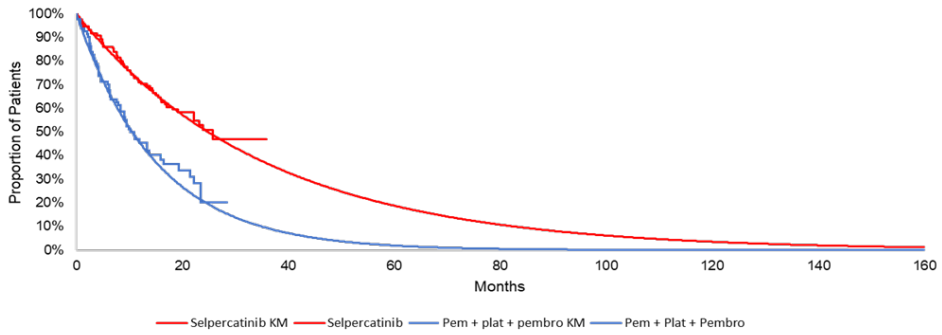


Figure 22 Extrapolation of TTD (LIBRETTO-431) including KM-data
Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier

8.1.2 Calculation of transition probabilities

Not applicable.

Table 40 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
N/A	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Refer to Section 11.6.

8.4 Other assumptions regarding efficacy in the model

Not applicable.

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

Table 41 and Table 42 presents the estimates in the model for the modelled average OS and PFS, respectively. The modelled estimates are discounted, without half-cycle correction and adjusted for background mortality of the Danish population (as per DMC's guidelines).

Table 41 Estimates in the model - OS

	Modelled average OS	Modelled median OS	Observed median OS from relevant study
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed + carboplatin ± pembrolizumab	[redacted]	[redacted]	[redacted]

Abbreviations: OS, overall survival, NR, not reached, L-431, LIBRETTO-431 trial; L-001, LIBRETTO-001 trial; MAIC, matched-adjusted indirect comparison
Notes: in the model, refer to the model sheet "Partitioned Survival Model"

Table 42 Estimates in the model - PFS

	Modelled average PFS	Modelled median PFS	Observed median PFS from relevant study
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed + carboplatin ± pembrolizumab	[redacted]	[redacted]	[redacted]

Abbreviations: PFS, progression-free survival, N/A, not available; L-431, LIBRETTO-431 trial; L-001, LIBRETTO-001 trial; MAIC, matched-adjusted indirect comparison
Notes: in the model, refer to the model sheet "Partitioned Survival Model"

Table 43 presents the modelled average treatment length and time in model health states.

Table 43 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]
Selpercatinib	[redacted]	[redacted]	[redacted]
Pemetrexed + carboplatin ± pembrolizumab	[redacted]	[redacted]	[redacted]

Abbreviations: PF, progression-free; PD, progressive disease
Notes: in the model, refer to the model sheet "Partitioned Survival Model"

9. Safety

9.1 Safety data from the clinical documentation

The safety profile of selpercatinib in this submission is based on the analysis of AEs that occurred in the phase 3 trial, LIBRETTO-431. The safety-pembrolizumab population is considered the relevant population (n=209). Safety was evaluated in patients who received at least 1 dose of study treatment as of 01 May 2023.

- Safety-Overall Population (N=256)
- Safety-Pembrolizumab Population (N=209)

No clinically meaningful difference in the safety profile between the Safety-Overall Population and the Safety-Pembrolizumab Population was observed. All patients in the selpercatinib arm and 99.0% of patients in the control arm reported at least 1 treatment-emergent adverse event (TEAE), refer to Table 44. For the safety-pembrolizumab population, the median time on treatment is 16.8 months and 10.7 months for the selpercatinib and control arm, respectively.

Table 44 Overview of safety events. LIBRETO-431 - DCO from 1 May 2023.

	Safety-Overall Population			Safety-Pembrolizumab Population		
	Selpercatinib (N=158)	Control arm (N=98)	Difference, % (95 % CI)	Selpercatinib (N=129)	Control arm (N=80)	Difference, % (95 % CI)
Number of adverse events, n	[redacted]	[redacted]		129 (100.0%)*	79 (98.8%)*	
Number and proportion of patients with ≥1 adverse events, n (%)	[redacted]	[redacted]		129 (100.0%)* [a]	79 (98.8%)* [a]	
Number of serious adverse events*, n	[redacted]	[redacted]		44 (34.1%)	22 (27.5%)	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	[redacted]	[redacted]		44 (34.1%) [a]	22 (27.5%) [a]	
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]		88 (68.2%)	49 (61.3%)	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	[redacted]	[redacted]		88 (68.2%)[a]	49 (61.3%)[a]	
Number of adverse reactions, n	[redacted]	[redacted]		N/A	N/A	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	[redacted]	[redacted]		N/A	N/A	
Number and proportion of patients who had a dose reduction, n (%)	[redacted]	[redacted]		65 (50.4%)	23 (28.8%)	
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	[redacted]	[redacted]		N/A	N/A	
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	[redacted]	[redacted]		14 (10.9%)	2 (2.5%)	
Number and proportion of patients who discontinue treatment due to serious adverse events, n (%)	[redacted]	[redacted]		7 (5.4%)	1 (1.3%)	

Abbreviations: TEAE, treatment-emergent adverse event; SAE, serious adverse event; N/A, not available or applicable; DCO, data cutoff, CTCAE, common terminology criteria for adverse event
Notes: * indicates adverse events as a treatment-emergent adverse event, TEAE; [a] indicates that the included estimate / proportion is described more than once in the table, e.g. for "Number of CTCAE grade ≥ 3 events, n" is equal to "Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)"
Source: Eli Lilly data on file 2023 (38)

Serious adverse events

The frequency of serious adverse events (SAEs) reported in the selpercatinib arm and control arm was 34.1% and 27.5%, respectively. Information regarding the most comment SAEs in the selpercatinib arm and the control arm is presented in Table 45.

Table 45 Serious adverse events- the most frequently reported (≥2%) any-grade SAEs. DCO 1 May 2023.

	Safety-Overall Population				Safety-Pembrolizumab Population			
Adverse events	Selpercatinib (N=159)		Control arm (N=98)		Selpercatinib (N=129)		Control arm (N=80)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)								
Pleural effusion	[redacted]	N/A	[redacted]	N/A	5 (3.9%)	N/A	0 (0.0%)	N/A
Hepatic function abnormal	[redacted]	N/A	[redacted]	N/A	4 (3.1%)	N/A	0 (0.0%)	N/A
Ascites	[redacted]	N/A	[redacted]	N/A	3 (2.3%)	N/A	0 (0.0%)	N/A
Anaemia	[redacted]	N/A	[redacted]	N/A	0 (0.0%)	N/A	2 (2.5%)	N/A
Intestinal obstruction	[redacted]	N/A	[redacted]	N/A	1 (0.8%)	N/A	2 (2.5%)	N/A
Neutropenia	[redacted]	N/A	[redacted]	N/A	0 (0.0%)	N/A	2 (2.5%)	N/A
Platelet count decreased	[redacted]	N/A	[redacted]	N/A	1 (0.8%)	N/A	2 (2.5%)	N/A
Pyrexia	[redacted]	N/A	[redacted]	N/A	2 (1.6%)	N/A	2 (2.5%)	N/A
Spinal cord compression	[redacted]	N/A	[redacted]	N/A	0 (0.0%)	N/A	2 (2.5%)	N/A
Pneumonia	[redacted]	N/A	[redacted]	N/A	2 (1.6%)	N/A	1 (1.3%)	N/A

Abbreviations: N/A, not available or applicable; DCO, data cutoff

Source: Eli Lilly data on file 2023

Treatment-emergent adverse events

Table 46 presents the TEAEs occurring in ≥5% patients in the selpercatinib arm and control arm. The table provided do not provide any combined column for platinum+pemetrexed patients (n=18) and platinum+pemetrexed+pembrolizumab (n=80) arms, hence the control arm consists of 80 patients.

Table 46 Summary of treatment-emergent adverse events occurring in ≥5% patients in either treatment arm. Grade ≥3 - DCO 1 May 2023.

	Safety-Overall Population		Safety-Pembrolizumab Population	
Adverse events	**Selpercatinib (N=158)**	**Control arm (N=98)**	**Selpercatinib (N=129)**	**Control arm (N=80)**
	Number of patients with adverse events	**Number of patients with adverse events**	**Number of patients with adverse events**	**Number of patients with adverse events**
Adverse event, n (%)	[redacted]	[redacted]	89(56.3%)	37(46.3%)
Hypertension	[redacted]	[redacted]	31(19.6%)	0 (0%)
ECG QT prolonged	[redacted]	[redacted]	14(8.9%)	0 (0%)
Alanine aminotransferase increased	[redacted]	[redacted]	32(20.3%)	1 (1.3%)
Aspartate aminotransferase increased	[redacted]	[redacted]	19(12.0%)	1 (1.3%)
Neutropenia	[redacted]	[redacted]	0(0.0%)	9 (11.3%)
Anaemia	[redacted]	[redacted]	0(0.0%)	7 (8.8%)
Leukopenia	[redacted]	[redacted]	0(0.0%)	3 (3.8%)
Decreased platelet count	[redacted]	[redacted]	4(2.5%)	5 (6.3%)
Decreased neutrophil count	[redacted]	[redacted]	3(1.9%)	12 (15.0%)
Decreased white blood cell count	[redacted]	[redacted]	2(1.3%)	4 (5.0%)

Abbreviations: ECG, electrocardiogram; DCO, data cutoff
Source: Eli Lilly, data on file (CSR L-431) (38)

Health economic model

Probabilities of individual AEs for each intervention were based on data from LIBRETTO-431 (selpercatinib, n=159 vs control arm, n=98). To focus on AEs, grade ≥ 3 AEs with at least a 2% difference in frequency between interventions (as reported in the source trials) were included. Costs and utility decrements (if any) associated with each AE were included in the model and were attributed to the first model cycle. The incidence data for AEs are presented in Table 47. In the probabilistic sensitivity analysis (PSA), AE probabilities were sampled from a beta distribution based on the number of patients with an event and the number at risk, refer to Appendix G.

Table 47 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 events	Intervention	Comparator		
Adverse event, n (%)	n= 158	n= 80	LIBRETTO-431 (for all)	Incidence of grade ≥ 3 in 2% or more of the patients.
Diarrhoea	0.63%	2.50%		
Hypertension	19.62%	0.00%		
ECG QT prolonged	8.86%	0.00%		
Decreased appetite	0.00%	2.50%		
Asthenia	0.00%	1.25%		
Alanine aminotransferase increased	20.25%	1.25%		
Aspartate aminotransferase increased	12.03%	1.25%		
Cardiac failure	0.63%	2.50%		
Thrombocytopenia	0.00%	2.50%		
Neutropenia	0.00%	11.25%		
Anaemia	0.00%	8.75%		
Febrile neutropenia	0.00%	2.50%		
Hepatitis Lab abnormalities	3.16%	1.25%		
Lymphocyte count decreased	1.90%	2.50%		
Leukopenia	0.00%	3.75%		
Gamma-glutamyltransferase increased	2.53%	0.00%		
Decreased platelet count	2.53%	6.25%		
Decreased neutrophil count	1.90%	15.00%		
Decreased white blood cell count	1.27%	5.00%		

Abbreviations: ECG, electrocardiogram
Source: Eli Lilly, data on file (CSR L-431) (38)

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

Not applicable.

Table 48 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 applicable or available

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

In the LIBRETTO-431 trial, scores for EuroQol 5-Dimensions 5-Level (EQ-5D-5L) were obtained and Danish weighted EQ-5D estimates were applied in the cost-effectiveness model. As per the Danish guidelines, the model uses utilities with Danish tariff (using the value set informed by Jensen et al). Utility estimates from the LIBRETTO-001 trial are also shown in the table for comparison (Quality of Life Questionnaire - Core 30 (QLQ-C30) was mapped into EQ-5D-3L scores using a mapping algorithm by Young et al).

The AE utility decrements were sourced from previous NICE appraisals and published literature.

Table 49 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	LIBRETTO-431	HSUV for progression-free and progressed. Danish weighted values. Used for the base case analysis
QLQ-C30	LIBRETTO-001	HSUV for progression-free and progressed. Scenario analysis

Abbreviations: EQ-5D-5L, ; QLQ-C30, ; HSUV, health-state utility value

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments]

10.1.1 Study design and measuring instrument

The instrument EQ-5D-5L was the most transferable and informative for the decision problem, as this is a widely accepted measure of HRQoL and allows for direct estimation of Danish utility values in line with the DMC guidelines.

EQ-5D-5L was measured at baseline (day 1, cycle 1) and every three weeks. This has two components, the EQ 5D descriptive system and the EuroQol 5-Dimensions visual analog scale (EQ-5D-VAS).

As LIBRETTO-431 is a head-to-head trial, EQ-5D-5L data is available for both the selpercatinib and control arm (pemetrexed + carboplatin ± pembrolizumab) (n=261). The patient-reported outcome (PRO) evaluation patient population in the LIBRETTO-431 is n=159 ad n=102 for selpercatinib and control arm, respectively, refer to Table 50.

Table 50 Patient populations

Population	Selpercatinib (n=159)	Pemetrexed + platinum + pembrolizumab (n=102)	Overall (n=261)
ITT	159	102	261
PRO evaluable	159 (100%)	102 (100%)	261 (100%)
ITT-pembrolizumab	129 (81.1%)	83 (81.4%)	212 (81.2%)
Safety	158 (99.4%)	98 (96.1%)	256 (98.1%)

Abbreviations: ITT, intention-to-treat; PRO, patient-reported outcomes

10.1.2 Data collection

The EQ-5D-5L questionnaire was administrated on day 1 of every three-week cycle, and at the short-term (30 +/7 days) and long-term (90 +/- 7 days) follow-up visits (completed at clinic site).

As mentioned in Table 50, all patients in both the selpercatinib and control arm of LIBRETTO-431 were PRO evaluable patients. Of the 159 selpercatinib and 102 control patients who PRO evaluable in the LIBRETTO-431 trial, 147 and 87 had a baseline assessment (week 1), respectively.

From the LIBRETTO-431, available data rates is defined as the proportion of patients who completed the questionnaire at that time point using the number of patients in the PRO evaluable population as denominator (fixed denominator); and completion rates is defined as the proportion of patients who completed the questionnaire at that time point using the number of patients expected to have an assessment at the respective time point as the denominator (variable denominator). No further information can be provided. Table 51 presents the completion data for selpercatinib. Table 52 presents the completion data for the control arm (both EQ-5D-5L completion rates by timepoint for the PRO evaluable population). Appendix F presents the available rates for selpercatinib and control arm.

Table 51 Pattern of missing data and completion, PRO evaluable population, selpercatinib

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Week 1	159	12 (7.5%)	159	147 (92.5%)
Week 4	159	21 (13.2%)	155	138 (89.0%)
Week 7	159	33 (20.8%)	150	126 (84.0%)
Week 10	159	35 (22.0%)	150	124 (82.7%)
Week 13	159	33 (20.8%)	145	126 (86.9%)
Week 16	159	30 (18.9%)	145	129 (89.0%)
Week 19	159	33 (20.8%)	144	126 (87.5%)
Week 22	159	30 (18.9%)	142	129 (90.8%)
Week 25	159	34 (21.4%)	138	125 (90.6%)
Week 28	159	36 (22.6%)	138	123 (89.1%)
Week 31	159	34 (21.4%)	138	125 (90.6%)
Week 34	159	38 (23.9%)	135	121 (89.6%)
Week 37	159	45 (28.3%)	132	114 (86.4%)
Week 40	159	47 (29.6%)	125	112 (89.6%)
Week 43	159	54 (34.0%)	121	105 (86.8%)
Week 46	159	58 (36.5%)	118	101 (85.6%)
Week 49	159	63 (39.6%)	114	96 (84.2%)
Week 52	159	74 (46.5%)	106	85 (80.2%)
Week 55	159	73 (45.9%)	101	86 (85.1%)
Week 58	159	82 (51.6%)	99	77 (77.8%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 61	159	76 (47.8%)	96	83 (86.5%)
Week 64	159	85 (53.5%)	89	74 (83.1%)
Week 67	159	87 (54.7%)	85	72 (84.7%)
Week 70	159	92 (57.9%)	80	67 (83.8%)
Week 73	159	105 (66.0%)	74	54 (71.0%)
Week 76	159	104 (65.4%)	67	55 (82.1%)
Week 79	159	105 (66.0%)	66	54 (81.8%)
Week 82	159	103 (64.8%)	63	56 (88.9%)
Week 85	159	112 (70.4%)	56	47 (83.9%)
Week 88	159	115 (72.3%)	51	44 (86.3%)
Week 91	159	124 (78.0%)	47	35 (74.5%)
Week 94	159	124 (78.0%)	44	35 (79.5%)
Week 97	159	126 (79.2%)	39	33 (84.6%)
Week 100	159	130 (81.8%)	34	29 (85.3%)
Week 103	159	135 (84.9%)	31	24 (77.4%)
Week 106	159	141 (88.7%)	24	18 (75.0%)
Week 109	159	142 (89.3%)	20	17 (85.0%)
Week 112	159	144 (90.6%)	15	15 (100.0%)
Week 115	159	145 (91.2%)	14	14 (100.0%)
Week 118	159	148 (93.1%)	12	11 (91.7%)
Week 121	159	151 (95.0%)	8	8 (100.0%)
Week 124	159	153 (96.2%)	6	6 (100.0%)
Week 127	159	154 (96.9%)	5	5 (100.0%)
Week 130	159	154 (96.9%)	5	5 (100.0%)
Week 133	159	154 (96.9%)	5	5 (100.0%)
Week 136	159	156 (98.1%)	3	3 (100.0%)
Week 139	159	156 (98.1%)	3	3 (100.0%)
Week 142	159	156 (98.1%)	3	3 (100.0%)
Week 145	159	157 (98.7%)	2	2 (100.0%)
Week 148	159	157 (98.7%)	2	2 (100.0%)
Week 151	159	157 (98.7%)	2	2 (100.0%)
Week 154	159	157 (98.7%)	2	2 (100.0%)
Week 157	159	158 (99.4%)	1	1 (100.0%)
Week 160	159	158 (99.4%)	1	1 (100.0%)
Week 163	159	158 (99.4%)	1	1 (100.0%)

Source: Eli Lilly data on file, 2023 data cut (LIBRETTO-431) Table 2.2.4

Notes: Available Rate - Percentage of patients completed PRO instrument out of the number of randomized patients in the PRO evaluable population.

Table 52 Pattern of missing data and completion, PRO evaluable population, control arm

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Week 1	102	15 (14.7%)	102	87 (85.3%)
Week 4	102	20 (19.6%)	95	82 (86.3%)
Week 7	102	27 (26.5%)	91	75 (82.4%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 10	102	28 (27.5%)	90	74 (82.2%)
Week 13	102	35 (34.3%)	84	67 (79.8%)
Week 16	102	33 (32.4%)	80	69 (86.3%)
Week 19	102	38 (37.3%)	77	64 (83.1%)
Week 22	102	43 (42.2%)	68	59 (86.8%)
Week 25	102	46 (45.1%)	67	56 (83.6%)
Week 28	102	48 (47.1%)	65	54 (83.1%)
Week 31	102	50 (49.0%)	60	52 (86.7%)
Week 34	102	53 (52.0%)	60	49 (81.7%)
Week 37	102	59 (57.8%)	57	43 (75.4%)
Week 40	102	61 (59.8%)	52	41 (78.8%)
Week 43	102	63 (61.8%)	46	39 (84.8%)
Week 46	102	67 (65.7%)	44	35 (79.5%)
Week 49	102	70 (68.6%)	36	32 (88.9%)
Week 52	102	73 (71.6%)	35	29 (82.9%)
Week 55	102	75 (73.5%)	31	27 (87.1%)
Week 58	102	79 (77.5%)	30	23 (76.7%)
Week 61	102	82 (80.4%)	24	20 (83.3%)
Week 64	102	83 (81.4%)	23	19 (82.6%)
Week 67	102	84 (82.4%)	22	18 (81.8%)
Week 70	102	86 (84.3%)	20	16 (80.0%)
Week 73	102	88 (86.3%)	18	14 (77.8%)
Week 76	102	89 (87.3%)	15	13 (86.7%)
Week 79	102	90 (88.2%)	15	12 (80.0%)
Week 82	102	89 (87.3%)	14	13 (92.9%)
Week 85	102	89 (87.3%)	14	13 (92.9%)
Week 88	102	90 (88.2%)	13	12 (92.3%)
Week 91	102	91 (89.2%)	13	11 (84.6%)
Week 94	102	92 (90.2%)	13	10 (76.9%)
Week 97	102	95 (93.1%)	11	7 (63.6%)
Week 100	102	96 (94.1%)	9	6 (66.7%)
Week 103	102	97 (95.1%)	7	5 (71.4%)
Week 106	102	99 (97.1%)	5	3 (60.0%)
Week 109	102	99 (97.1%)	4	3 (75.0%)
Week 112	102	98 (96.1%)	4	4 (100.0%)
Week 115	102	100 (98.0%)	2	2 (100.0%)
Week 118	102	101 (99.0%)	1	1 (100.0%)
Week 121	102	101 (99.0%)	1	1 (100.0%)
Week 124	102	102 (100.0%)	1	0 (0.0%)
Week 127	102	102 (100.0%)	0	0 (0.0%)
Week 130	102	102 (100.0%)	0	0 (0.0%)
Week 133	102	102 (100.0%)	0	0 (0.0%)
Week 136	102	102 (100.0%)	0	0 (0.0%)
Week 139	102	102 (100.0%)	0	0 (0.0%)
Week 142	102	102 (100.0%)	0	0 (0.0%)
Week 145	102	102 (100.0%)	0	0 (0.0%)
Week 148	102	102 (100.0%)	0	0 (0.0%)
Week 151	102	102 (100.0%)	0	0 (0.0%)
Week 154	102	102 (100.0%)	0	0 (0.0%)
Week 157	102	102 (100.0%)	0	0 (0.0%)

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 160	102	102 (100.0%)	0	0 (0.0%)
Week 163	102	102 (100.0%)	0	0 (0.0%)

Source: Eli Lilly data on file, 2023 data cut (LIBRETTO-431). Table 2.2.4
Notes: Available Rate - Percentage of patients completed PRO instrument out of the number of randomized patients in the PRO evaluable population.

10.1.3 HRQoL results

EQ 5D 5L health states, defined by the EQ 5D 5L descriptive system, may be converted into a single summary index by applying a formula that essentially attaches values (weights) to each of the levels in each dimension. The index can be calculated by deducting the appropriate weights from 1, the value for full health (i.e., state 11111). Value sets have been derived for EQ 5D 5L in several countries using the EQ 5D VAS valuation technique or the time trade-off valuation technique. The United Kingdom (UK) Measurement and Valuation of Health study value set is generally considered the base case scoring function for the purposes of publication. Therefore, all EQ 5D utility index scores results by timepoint presented in Table 53 are based on UK values. However, the Danish value set informed by Jensen et al (2021) has been applied to utility indices, as per requested by the DMC. Please refer to Table 55.

Table 53 presents the EQ-5D-5L results by timepoint, starting from week 1 to week 94, with three weeks between each timepoint, as previously described. Please note that the index results are based on the patient number reported in Appendix F showing the available rates.

Figure 23 displays the mean change (with error bars showing the 95 % confidence intervals) from baseline through the different data collection time points for both the intervention and comparator.

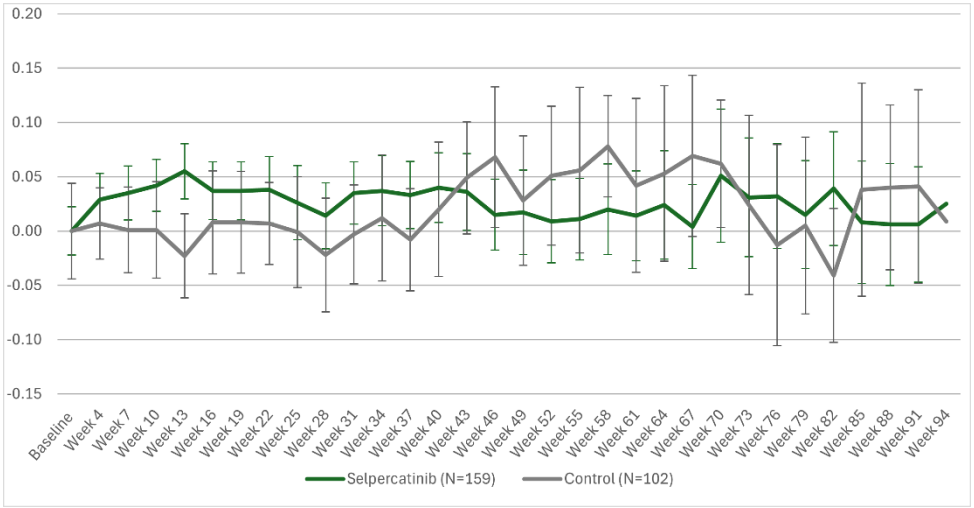


Figure 23 Mean change in EQ-5D-5L (UK) from baseline to week 94, both arms (LIBRETTO-431)
Note: for divided figure (one for selpercatinib and one for control arm, refer to Appendix F)

Table 53 HRQoL EQ-5D-5L summary statistics, UK value set

	Selpercatinib (n=159)		Control (n=102)		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (SE)
Week 1	147	0.841 (0.012)	87	0.835 (0.015)	0.006 (0.010)
Week 4	139	0.872 (0.011)	82	0.851 (0.019)	0.021 (-0.040)
Week 7	126	0.871 (0.012)	75	0.836 (0.016)	0.035 (0.000)
Week 10	124	0.879 (0.011)	74	0.850 (0.017)	0.029 (-0.030)
Week 13	126	0.895 (0.009)	67	0.833 (0.220)	0.062 (-1.700)
Week 16	129	0.876 (0.011)	69	0.859 (0.017)	0.017 (-0.020)
Week 19	126	0.869 (0.012)	64	0.861 (0.021)	0.008 (-0.040)
Week 22	129	0.875 (0.011)	59	0.856 (0.020)	0.019 (-0.020)
Week 25	125	0.865 (0.012)	56	0.849 (0.016)	0.0.016 (0.010)
Week 28	123	0.858 (0.015)	54	0.840 (0.027)	0.018 (-0.030)
Week 31	125	0.875 (0.012)	52	0.847 (0.024)	0.028 (-0.040)
Week 34	121	0.886 (0.010)	49	0.869 (0.023)	0.017 (-0.050)
Week 37	114	0.880 (0.012)	43	0.846 (0.030)	0.034 (-0.070)
Week 40	112	0.884 (0.012)	41	0.873 (0.022)	0.011 (-0.010)
Week 43	106	0.888 (0.013)	39	0.892 (0.021)	-0.004 (0.000)
Week 46	101	0.867 (0.015)	35	0.899 (0.017)	-0.032 (0.050)
Week 49	96	0.867 (0.014)	32	0.870 (0.025)	-0.003 (0.000)
Week 52	85	0.856 (0.015)	29	0.884 (0.028)	-0.028 (-0.010)
Week 55	86	0.861 (0.016)	27	0.883 (0.021)	-0.022 (0.040)
Week 58	77	0.883 (0.015)	23	0.888 (0.027)	-0.005 (0.000)
Week 61	84	0.872 (0.016)	20	0.885 (0.029)	-0.013 (0.020)
Week 64	74	0.870 (0.019)	19	0.854 (0.028)	0.016 (0.040)
Week 67	72	0.863 (0.022)	18	0.870 (0.026)	-0.007 (0.080)
Week 70	68	0.905 (0.013)	16	0.862 (0.033)	0.043 (-0.020)
Week 73	54	0.875 (0.023)	14	0.867 (0.040)	0.008 (0.020)
Week 76	55	0.875 (0.023)	13	0.840 (0.058)	0.035 (-0.040)
Week 79	54	0.865 (0.020)	12	0.831 (0.061)	0.034 (-0.060)
Week 82	56	0.881 (0.019)	13	0.795 (0.055)	0.086 (-0.060)
Week 85	48	0.877 (0.020)	13	0.893 (0.028)	-0.016 (0.040)
Week 88	44	0.866 (0.027)	12	0.880 (0.040)	-0.014 (0.040)
Week 91	35	0.870 (0.025)	11	0.878 (0.030)	-0.008 (0.050)
Week 94	35	0.884 (0.019)	10	0.855 (0.032)	0.029 (0.010)

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

10.2.1 HSUV calculation

As described in Section 10, the HSUVs applied in the cost-effectiveness model for the health states: progression-free and progressed disease is based on EQ-5D-5L data from the LIBRETTO-431 trial. The base case analysis of the economic model uses the HSUV using Danish tariffs, using the methodology provided by Jensen et al (67). The Danish weighted HSUVs used for progression-free and progressed disease is estimated based on the overall population, refer to Table 54 below.

Table 54 HRQoL EQ-5D-5L summary statistics, DK value set

	Selpercatinib (n=159)		Control (n=102)		Overall (n=261)	
	N	Mean (95 % CI)	N	Mean (95 % CI)	N	Mean (95 % CI)
Baseline	129	0.854 (0.826; 0.883)	82	0.845 (0.812; 0.880)	211	0.850 (0.829; 0.873)
All pre-progression assessments	157	0.866 (0.843; 0.890)	95	0.845 (0.814; 0.876)	252	0.858 (0.840; 0.877)
All post-bl pre-progression assessments	156	0.869 (0.846; 0.893)	93	0.845 (0.811; 0.880)	249	**0.861 (0.841; 0.880)**
All post-progression assessments	44	0.857 (0.693; 0.880)	45	0.7949 (0.761; 0.895)	89	**0.826 (0.782; 0.870)**

Abbreviations: bl, baseline; SE, standard error
Source: Eli Lilly, data on file. Data cut May 2023

Age adjustment to the utility values has been applied in accordance with DMC's guidance and source: "*Appendiks: Aldersjustering for sundhedsrelateret livskvalitet*" (68).

For scenario analysis, QLQ-C30 was collected in the LIBRETTO-001 trial and was mapped into EQ-5D-3L scores using a mapping algorithm by Young et al. Refer to Section 10.3 for further information regarding the LIBRETTO-001 derived health state utility values (HSUVs).

10.2.1.1 Mapping

For the base case, mapping of utility values was needed as UK values were estimated directly from LIBRETTO-431 EQ-5D-5L observations using the UK value set. To align with the DMC guidelines, Danish values has been obtained using the Danish value set informed by Jensen et al. (2021).

For scenario analysis, the LIBRETTO-001 collected QLQ-C30 data, which has been converted to EQ-5D-3L (UK tariffs) using the mapping algorithm provided by Young et al. (2015). Since the HSUVs derived from the LIBRETTO-001 is only used for scenario analysis, the mapping description of Young et al. can be found in Appendix F.

10.2.2 Disutility calculation

Not applicable. Disutility calculations were derived from external literature.

10.2.3 HSUV results

Table 55 presents an overview of HSUVs applied in the model (base case and scenario analysis).

Table 55 Overview of health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Base case analysis				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Progression-free	0.861 [0.841;0.880]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms (overall population, n=261). All post-baseline pre-progression assessments
Progressed	0.826 [0.782;0.870]	EQ-5D-5L	DK	Estimate is based on mean of both trial arms (overall population, n=261). All post-progression assessments
Scenario analysis				
Progression-free	0.85 [N/A]	EQ-5D-3L	UK	LIBRETTO-001
Progressed	0.79 [N/A]	EQ-5D-3L	UK	LIBRETTO-001
Disutilities				
Diarrhoea	−0.047	N/A	N/A	Disutility: Nafees, Stafford (69)
Decreased appetite	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)
Asthenia	−0.074	N/A	N/A	Disutility: Nafees, Stafford (69)
Hyponatraemia	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)
Pneumonia	−0.008	N/A	N/A	Disutility: (Marti et al., 2013)
Cardiac failure	−0.069	N/A	N/A	Disutility: Doyle, Lloyd and Walker (2008)
Thrombocytopenia	0.000	N/A	N/A	Assumed no disutility
Neutropenia	−0.090	N/A	N/A	Disutility: Nafees, Stafford (69)
Anaemia	−0.073	N/A	N/A	Disutility: Nafees, Stafford (69)
Pleural effusion	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)
Febrile neutropenia	−0.090	N/A	N/A	Disutility: Nafees, Stafford (69)
Lymphocyte count decreased	0.000	N/A	N/A	Assumed no disutility
Leukopenia	−0.090	N/A	N/A	Assumed equal to neutropenia
Gamma-glutamyltransferase increased	−0.090	N/A	N/A	Assumed equal to neutropenia
Decreased platelet count	0.000	N/A	N/A	Assumed no disutility
Decreased neutrophil count	0.000	N/A	N/A	Assumed no disutility
Decreased white blood cell count	0.000	N/A	N/A	Assumed no disutility

Abbreviations: N/A, not available or applicable; NICE, National Institute of Health and Care Excellence

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

The LIBRETTO-001 derived HSUVs will be explored in scenario analyses.

10.3.1 Study design

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 was collected for patients aged 18 years and older in the LIBRETTO-001 study.

10.3.2 Data collection

The questionnaires were to be answered by the participant to the best of their ability within 7 days of each radiologic assessment (approximately every 8 weeks in year 1 and every 12 weeks thereafter), preferably before learning the results of the radiologic disease assessment), and at the post-discontinuation follow-up visit. Few data were collected for patients in the progressed health state because most patients in the study are still receiving treatment and in the pre-progression state. In addition, for most of the discontinued patients, only 1 post-progression evaluation was planned. Collection data from the LIBRETTO-001 (DCO January 2023) will not be provided in this submission.

10.3.3 HRQoL Results

Utility was estimated from the EORTC QLQ-C30 data using the EORTC−Eight Dimensions (EORTC-8D) valuation (Rowen et al., 2011) and mapping algorithms reported by Young et al. (2015) (70), Kontodimopoulos et al. (2009) (71), and Marriott et al. (2017) (72). For simplicity, the EQ-5D-3L values derived by using the mapping algorithm informed by Young et al (2015) has been considered in this submission.

Because most responses to treatment were partial responses, it seems unlikely that there would be an important improvement in quality of life for responders. Therefore, no adjustment to the progression-free utility weight was made to reflect response.

10.3.4 HSUV and disutility results

Table 56 presents the HSUVs derived from LIBRETTO-001 (refer also to Table 55).

As previously mentioned, AE utility decrements applied in the model is based on previous NICE appraisals and published literature, refer to Table 57.

Table 56 Overview of health state utility values – LIBRETTO-001

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Scenario analysis				
Progression-free	0.85 [N/A]	EQ-5D-3L	UK	Estimate is based on mean of both trial arms.
Progressed	0.79 [N/A]	EQ-5D-3L	UK	Estimate is based on mean of both trial arms.

Table 57 Overview of literature-based disutility values

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Diarrhoea	−0.047	N/A	N/A	Disutility: Nafees, Stafford (69)
Decreased appetite	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)
Asthenia	−0.074	N/A	N/A	Disutility: Nafees, Stafford (69)
Hyponatraemia	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Pneumonia	−0.008	N/A	N/A	Disutility: (Marti et al., 2013)
Cardiac failure	−0.069	N/A	N/A	Disutility: Doyle, Lloyd and Walker (2008)
Thrombocytopenia	0.000	N/A	N/A	Assumed no disutility
Neutropenia	−0.090	N/A	N/A	Disutility: Nafees, Stafford (69)
Anaemia	−0.073	N/A	N/A	Disutility: Nafees, Stafford (69)
Pleural effusion	−0.085	N/A	N/A	Disutility: National Institute for Health and Care Excellence (54)
Febrile neutropenia	−0.090	N/A	N/A	Disutility: Nafees, Stafford (69)
Lymphocyte count decreased	0.000	N/A	N/A	Assumed no disutility
Leukopenia	−0.090	N/A	N/A	Assumed equal to neutropenia
Gamma-glutamyltransferase increased	−0.090	N/A	N/A	Assumed equal to neutropenia
Decreased platelet count	0.000	N/A	N/A	Assumed no disutility
Decreased neutrophil count	0.000	N/A	N/A	Assumed no disutility
Decreased white blood cell count	0.000	N/A	N/A	Assumed no disutility

Abbreviations: N/A, not available or applicable; NICE; National Institute for Health and Care Excellence

11. Resource use and associated costs

The model includes direct medical costs, as well as patient time and transportation costs, consistent with the restricted societal perspective as described in the DMC guidelines. All costs are valued in 2024 Danish Krone (DKK).

Drug costs are sourced from Medicinpriser.dk and applied as pharmacy purchasing prices (AIP). Disease management and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024 and DMC catalogue for unit costs (2024). Patient and transportation costs are based on the DMC catalogue for unit costs and are resented in a separate section covering all patient- and transportation costs for all health states.

11.1 Medicines - intervention and comparator

Drug acquisition costs of selpercatinib and the relevant comparators were based on their list price extracted from Medicinpriser.dk. Prices for each vial/package size were applied and are presented in Table 58. The drug acquisition costs are presented in Table 59.

The model allows for 100% dose intensity, however, in the base case analysis, clinical trial specific dose is considered. The proportion receiving pembrolizumab is 81% in the model (this can be explored in scenario analyses).

Table 58 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Selpercatinib	160 mg 80 mg	83.3% 16.7%	Every day Twice daily, 4-week cycles	Drug wastage is included
Pembrolizumab	200mg	95.3%	Once every 3 weeks (up to 2 years or progression)	Drug wastage is included
Pemetrexed	500 mg/m^2	88.6%	Once every 3 weeks	Drug wastage is included
Carboplatin	400 mg/ m^2	90.8%	Once every 3 weeks, limited to 4 cycles	Drug wastage is included

Notes: trial-specific dose intensities is sourced from LIBRETTO-431. Because the dose intensities for pemetrexed and carboplatin have minimal impact on the results, the mean dose based on the LIBRETTO-431 trial is applied without adjusting for the percentage on each dose
Source: LIBRETTO-431

Table 59 Drug acquisition costs

Medicine	Strength /unit	Pack size	Cost per pack	Source
Selpercatinib	40mg	56	17,258.11	Medicinpriser.dk
Pembrolizumab	25 mg/ml	4 ml	21,573.58	Medicinpriser.dk
Pemetrexed	25 mg/ml	20 ml	552.49	Medicinpriser.dk
Carboplatin	10 mg/ml	45ml	226.00	Medicinpriser.dk

Source: Medicinpriser.dk (73)

The body weight and body surface area (BSA) estimates that are used for adjusted-dose interventions are presented in Table 60.

Table 60 Body weight and body surface area

Parameter	NSCLC with RET gene fusion
Mean weight (kg)	67.1
BSA (m^2)	1.81

Abbreviations: BSA, body surface area; NSCLC, non-small cell lung cancer; RET, rearranged during transfection
Source: weight – Eli Lilly data on file, BSA – NICE (2018), TA520, p. 279 (74)

The treatment duration for selpercatinib and comparators was predicted using parametric functions fitted to the TTD in LIBRETTO-431 (treatment exposure in the LIBRETTO-431 trial data may not be used directly because many patients had not discontinued treatment during trial follow-up). The TTD functions are presented in Section 8. Additionally, an option was included that uses the mean time from progression to treatment discontinuation observed in the LIBRETTO-431 trial (among those patients who had discontinued within trial follow-up). The proportion of selpercatinib and pembrolizumab administrations at each dose level was based on the recorded doses received in the LIBRETTO-431 trial, adjusted to reflect the available tablet and vial sizes. Separate data were applied for the initial dose distribution (applied for the first 4 weeks) and thereafter. Because the dose intensities for pemetrexed and carboplatin have minimal impact on the

results, the mean dose based on the LIBRETTO-431 trial is applied without adjusting for the percentage on each dose.

Alternative scenarios are available in the model to include or exclude drug wastage. For intravenous drugs, if wastage is included in the model, it is assumed that any unused drug in opened vials is discarded (base case). The weight and BSA distribution of the population are modelled, and the lowest cost vial combination is determined according to each weight or BSA category. The cost of each whole vial combination is calculated, and the weighted average cost across the population is calculated using the proportion of patients in each weight or BSA category. For oral drugs, the drug wastage scenario assumes the minimum cost of whole tablet combinations to provide the required dose. It is assumed that oral drugs are dispensed as 4-week prescriptions, i.e., patients discontinuing during the 4 weeks after a prescription will be assigned the full cost of that prescription. A 1-week option is also available as a scenario analysis.

11.2 Medicines– co-administration

An option is available in the model to include the cost of screening to identify patients with RET-altered tumours in the selpercatinib arm. This option may be switched off (or hidden) to allow the cost of the diagnostic test to be excluded from the analysis.

Estimates of the screen-positive rate in each population and the cost of the test are presented in Table 61.

Table 61 Diagnostic test parameters

Parameter	NSCLC with RET gene fusion
Screen-positive rate	1.5% (Sireci, Morosini, & Rothenberg, 2019)
RET test cost	DKK 5,000.00 (DMC 2024)

Abbreviations: DMC, Danish Medicines Council; RET, rearranged during transfection

11.3 Administration costs

For selpercatinib, administration cost was considered for only first cycle and no cost was applied for remaining cycles (one-off cost applied in the model). For the comparator, IV administration costs has been applied every third week. This is consistent with the DMC assessment of selpercatinib from 2022 (1).

Table 62 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Selpercatinib administration	Once only	1756.00	10MA01	DRG 2024
Comparator administration, simple (IV)	Every third week	1311.00	04MA98	DRG 2024
Comparator administration, complex (IV)	Every third week	20822.00	27MP21	DRG 2024

Abbreviations: IV, intravenous; DRG, diagnose-related groups

During treatment, patients were assumed to have 1 oncologist visit every 13 weeks (consistent with previous assessment of selpercatinib, 2021 (3) and consistent with previous NICE TA520 (74)). In addition to this, cost for 7 electrocardiograms (ECGs) were added to selpercatinib monitoring costs for the first 6 months, in line with the updated

label (consistent with the product characteristics) (22). Monitoring costs related to the treatment is listed below in Table 63.

Table 63 Monitoring costs used in the model – treatment administration

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Oncologist visit	Every 13 weeks	1311.00	04MA98	DRG 2024
ECG	7 ECGs for the first 6 months	1311.00	04MA98	DRG 2024

Abbreviations: ECG, electrocardiogram

11.4 Disease management costs

Best supportive care was assumed to be monitoring and palliative care, as included in the health-state costs. The resource and frequency of use in the progression-free and progressed health states for pretreated NSCLC was based on key opinion leader (KOL) feedback, refer to Table 64. The costs associated with palliative terminal care for the last month of life were not included in the Danish settings.

Table 64 Resource use per 30-day period, by health state

Item	Progression-free	Progressed	Unit cost (DKK)	Source
Outpatient visit	1.0	1.0	1,756.00	DRG 2024, 10MA01
CT scan (chest)	1.0	1.0	3,620.00	DRG 2024, 36PR07
Full blood test	1.0	1.0	112.00	Rigshospitalets Labportal, NPU19654, NPU19651, NPU19658 and NPU19857
Liver function test	1.0	1.0	30.00	Rigshospitalets Labportal, NPU19651 and NPU1965
Brain MRI	1.0	1.0	2,511.00	DRG 2024, 30PR02

Abbreviations: DRG, diagnosis-related groups; MRI, magnetic resonance imaging; CT, computerised tomography

11.5 Costs associated with management of adverse events

Probabilities of individual AEs for each intervention were based on data from LIBRETTO-431. Modelled AEs are defined in Section 9, refer to the incidence data for AEs presented in Table 47. Costs and associated with each AE were included in the model and were attributed to the first model cycle. Unit costs for AEs are presented below in Table 65.

Table 65 Cost associated with management of adverse events

	DRG code	Unit cost/DRG tariff	Duration (days)	Source (duration)
Diarrhoea	DRG 2024, 06MA11	7,818.00	5.5	NICE (2017a)
Decreased appetite	DRG 2024, 10MA04	1,736.00	15.0	Assumption
Asthenia	DRG 2024, 23MA03	5,103.00	23.8	Assumed same as fatigue
Hyponatraemia	DRG 2024, 10MA98	1,847.00	15.0	Assumption
Pneumonia	DRG 2024, 04MA98	1,311.00	15.0	Assumption
Cardiac failure	DRG 2024, 05MA04	39,083.00	31.0	Assumed the same as pain (NICE, 2023a)
Thrombocytopenia	DRG 2024, 04MA98	2,111.00	0.0	-
Neutropenia	DRG 2024, 16MA98	2,111.00	15.0	Assumption
Anaemia	DRG 2024, 16MA98	2,111.00	23.8	Assumed same as fatigue
Pleural effusion	DRG 2024, 16MA98	1,311.00	15.0	Assumption

	DRG code	Unit cost/DRG tariff	Duration (days)	Source (duration)
Febrile neutropenia	DRG 2024, 16MA03	2,240.00	15.0	Assumption
Hepatitis Lab abnormalities	DRG 2024, 07MA98	1,947.00	0.0	-
Lymphocyte count decreased	DRG 2024, 10MA98	2,111.00	15.0	Assumed equal to neutropenia
Leukopenia	DRG 2024, 16MA98	2,111.00	15.0	Assumed equal to neutropenia
Gamma-glutamyltransferase increased	DRG 2024, 10MA98	1,847.00	0.0	-
Decreased platelet count	DRG 2024, 16MA98	2,111.00	0.0	-
Decreased neutrophil count	DRG 2024, 16MA98	2,111.00	0.0	-
Decreased white blood cell count	DRG 2024, 16MA98	2,111.00	15.0	Assumption

Abbreviations: DRG, diagnosis-related groups
Notes: AE inclusion threshold 2%

Duration (days) of each adverse event has been informed by previous NICE appraisals, when possible, which has been included in the table above as well.

11.6 Subsequent treatment costs

The cost of subsequent systemic treatment is assumed to be independent of survival post-progression and is applied in the model as a one-off cost at the time of disease progression. The pattern of therapies is based on TA584 (34), TA531 (59), and TA484 (60). For selpercatinib, estimates are based on subsequent treatments applied to other targeted treatments in non-squamous NSCLC. The cost considers the time on treatment for subsequent therapy, associated administration costs, and the fraction of the patients receiving each post-progression therapy. The estimates are presented in Table 66.

Table 66 Subsequent Therapy Distribution Following First-line Treatment for NSCLC

Therapy	% of patients after selpercatinib	% of patients after pemetrexed + carboplatin + pembrolizumab	% of patients after pemetrexed + carboplatin	% of patients after pemetrexed + carboplatin ± pembrolizumab
Docetaxel	56.0%	100.00%	15%	84%
Pemetrexed + Carboplatin	44.0%	0.0%	0.0%	0.0%
Pemetrexed	0.0%	0.0%	0.0%	0.0%

Sources: Eli Lilly data on file (21 March 2024)

Table 67 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Docetaxel	75mg	100.00%	Once every 3 weeks	No
Pemetrexed + Carboplatin	500mg + 490mg	100.00%	Once every 3 weeks	No
Pemetrexed	500mg	100.00%	Once every 3 weeks	No

Source: assumption

For simplicity, drug wastage was not accounted for in the subsequent systemic treatment costs unless the treatment was also a comparator and, therefore, drug wastage calculations were available for that purpose.

Key assumption

The cost of subsequent systemic treatment is assumed to be independent of survival post-progression and is applied in the model as a one-off cost at the time of progression. For simplicity, the timing was not adjusted in analyses where selpercatinib treatment is continued beyond disease progression. This approach may result in subsequent treatment costs occurring earlier in the model time horizon than they would. This is expected to be a conservative assumption, as less discounting will be applied for the costs of subsequent systemic treatment.

11.7 Patient costs

Cost associated with patient time and transport was also included in the health state cost (consistent with the DMC guidelines). Based on DMC's unit cost catalogue (2024), a unit cost of 3.79 DKK per km was applied to all visits and healthcare activities in the model to account for travel expenses, and a unit cost of 188 DKK was used for all patient hours associated with health state related activities.

The input values are provided below in Table 68. Patient time loss was calculated by multiplying the hourly wages and the number of hours lost by hospital visit due to progressive disease. Transportation costs loss was calculated by multiplying the transportation cost per kilometre by the number of visits and the mean distance travelled per hospital visit. These costs were then multiplied by the proportion of patients in the progressive disease state at each model cycle.

Table 68 Patient costs related inputs in the model

Activity	Time spent
Number of visits to the hospital	24 visits
Time taken per visit	2 hours
Mean distance per hospital visit	40 km

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

The costs associated with palliative terminal care for the last month of life were not included in the Danish settings, refer to Section 11.4.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 69.

Table 69 Base case overview

Feature	Description
Comparator	Pemetrexed + carboplatin ± pembrolizumab
Type of model	Partitioned survival model
Time horizon	25 years (life time)
Treatment line	1st line. Subsequent treatment lines are included.

Feature	Description
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study LIBRETTO-431. Danish population weights were used to estimate health-state utility values.
Costs included	Medicine costs Diagnostics cost Administration costs Hospital costs Costs of adverse events Patient costs Best supportive care costs / health state costs Subsequent treatment costs
Dosage of medicine	Based on weight. BSA on 1.81 m2
Average time on treatment	[redacted]
Parametric function for PFS	Selpercatinib: Exponential Pemetrexed + platinum + pembrolizumab: Exponential
Parametric function for OS	Selpercatinib: Exponential Pemetrexed + platinum + pembrolizumab: Exponential
Inclusion of waste	No included
Average time in model health state PF PD	Selpercatinib vs comparator [redacted] [redacted]

Abbreviations: EQ-5D-5L, EuroQol 5-Dimensions 5-Level; BSA, body surface area; PF, progression-free; PD, progressed disease

12.1.1 Base case results

In the model base case, discounted results are presented in Table 70. The incremental expected total life-year gain amounts to [redacted] years (discounted). The discounted incremental costs of [redacted] DKK and incremental QALYs of [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] / QALY versus standard of care.

Table 70 Base case results, discounted estimates

	Selpercatinib	Pembrolizumab + pemetrexed + carboplatin	Difference
Medicine costs	[redacted]	[redacted]	[redacted]
Medicine costs – co-administration	[redacted]	[redacted]	[redacted]
Administration	[redacted]	[redacted]	[redacted]
Monitoring costs	[redacted]	[redacted]	[redacted]
Diagnostic test costs	[redacted]	[redacted]	[redacted]
General disease management	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained PF	[redacted]	[redacted]	[redacted]
Life years gained PD	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs PF	[redacted]	[redacted]	[redacted]
QALYs PD	[redacted]	[redacted]	[redacted]

	Selpercatinib	Pembrolizumab + pemetrexed + carboplatin	Difference
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained xxxxxx [redacted]			
Incremental cost per QALY gained (ICER) [redacted]			

12.2 Sensitivity analyses

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

12.2.1 Deterministic sensitivity analyses

Univariate sensitivity analyses were performed to identify the parameters that have the most influence on the ICER. 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 ±10% 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 71 and as a tornado diagram in Figure 24.

Table 71 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
Lower bound					
Discount Rate Outcomes	[redacted]	Range of impact on the base case ICER	[redacted]	[redacted]	[redacted]
Discount Rate Costs	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progressed disease	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Diagnostic costs - Cost of testing	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Costs - Average Weekly Costs - Progressed disease	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progression-free - Selpercatinib	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Costs - Average Weekly Costs - Progression-free	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Subsequent Active Systemic Anticancer Therapy - % after pem + pembro + plat - Docetaxel	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Drug Administration Costs - Pembrolizumab + pemetrexed + carboplatin	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progression-free - Pembrolizumab + pemetrexed + carboplatin	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Upper bound	[redacted]		[redacted]	[redacted]	[redacted]
Discount Rate Outcomes	[redacted]	Range of impact on the base case ICER	[redacted]	[redacted]	[redacted]
Discount Rate Costs	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progressed disease	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Diagnostic costs - Cost of testing	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Costs - Average Weekly Costs - Progressed disease	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progression-free - Selpercatinib	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Costs - Average Weekly Costs - Progression-free	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Subsequent Active Systemic Anticancer Therapy - % after pem + pembro + plat - Docetaxel	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Drug Administration Costs - Pembrolizumab + pemetrexed + carboplatin	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Health State Utility Weights - Progression-free - Pembrolizumab + pemetrexed + carboplatin	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

Abbreviations: ICER, incremental cost-effectiveness ratio

Figure 24 Tornado diagram

Abbreviations: ICER, incremental cost-effectiveness ratio; DKK, Danish Krone; QALY, quality-adjusted life-years

12.2.1.1 Scenario analyses

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings, refer to Table 72.

Table 72 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case			[redacted]	[redacted]	[redacted]
Drug wastage excluded	[redacted]	Not considering drug wastage	[redacted]	[redacted]	[redacted]
Oral treatment cycle, 1 week	[redacted]	Alternative oral drugs dispensing prescription	[redacted]	[redacted]	[redacted]
PFS function selpercatinib: Log-log	[redacted]	Alternative PFS function	[redacted]	[redacted]	[redacted]
PFS function estimated control (pemetrexed + platinum + pembrolizumab): Log-log	[redacted]	Alternative PFS function	[redacted]	[redacted]	[redacted]
TTD function selpercatinib: Exponential	[redacted]	Alternative TTD approach	[redacted]	[redacted]	[redacted]
HR MAIC adjusted	[redacted]	Less conservative approach.	[redacted]	[redacted]	[redacted]
OS function selpercatinib: Weibull	[redacted]	Alternative OS function	[redacted]	[redacted]	[redacted]
OSS function estimated control (pemetrexed + platinum + pembrolizumab): Weibull	[redacted]	Alternative OS function	[redacted]	[redacted]	[redacted]
OS function selpercatinib: Gompertz	[redacted]	Alternative OS function	[redacted]	[redacted]	[redacted]
OSS function estimated control (pemetrexed + platinum + pembrolizumab): Gompertz	[redacted]	Alternative OS function	[redacted]	[redacted]	[redacted]

Abbreviations: QALY, quality-adjusted life-years; DKK, Danish Krone; ICER, incremental cost-effectiveness ratio;

12.2.2 Probabilistic sensitivity analyses

The PSA include all model parameters; estimates of uncertainty were based on the uncertainty in the source data (where data availability permits). Where no such data were

available, the model applies a user-defined percentage of the mean value as the standard error.

Parameters are sampled from appropriate statistical distributions (Briggs, 2005), such as the following:

- Survival function parameters are sampled from correlated distributions defined by their mean, standard error, and covariance using the Cholesky decomposition or from Bayesian posterior distributions.
- HRs are sampled from a log-normal distribution.
- Mean utility weights may be converted to decrements and sampled from a gamma distribution of the parameter as defined by the mean and standard error.
- Mean costs may be sampled from a gamma distribution defined by the mean and standard error.

All distributions are fully documented within the model.

The PSA is performed by estimating the net monetary benefit (NMB) for each simulation of the probabilistic model at a series of ICER thresholds according to the following formula:

$$NMB = \Delta b \times ICERt - \Delta c,$$

where NMB is the NMB, Δb is the incremental benefit, ICERt is the ICER threshold, and Δc is the incremental cost.

The probability of CE at each ICER threshold is estimated as the percentage of the simulations with NMB greater than zero. The probabilistic estimate of the mean ICER is calculated as the difference in the probabilistic mean cost divided by the difference in the probabilistic mean outcome (life-year or QALY).

A scatter plot of 1,000 simulations, including a 95% confidence cloud, is presented in Figure 25, with a cost-effectiveness acceptability curve presented in Figure 26. The full set of parameters included in the model (including details of distributional forms) and the PSA analysis are presented in Appendix G.

Table 73 PSA ICER results

	ICER QALY
Selpercatinib vs pemetrexed + carboplatin + pembrolizumab	[redacted]

Figure 25 Scatter plot, 1,000 iterations (incremental costs and QALYs)
Abbreviations: QALY, quality-adjusted life-years

Figure 26 Cost-effectiveness acceptability curve (incremental costs and QALYs)
Abbreviations: QALY, quality-adjusted life-years

Figure 27 Convergence plot, ICER
Abbreviations: ICER, incremental cost-effectiveness ratio

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending selpercatinib for treatment of RET fusion positive NSCLC 1L 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 would 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 cost and transportation cost have not been included as per the guidelines by the DMC. The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where selpercatinib is recommended and the scenario where selpercatinib is not recommended. The total budget impact per year is the difference between the two scenarios.

Number of patients (including assumptions of market share)

As previously mentioned, (refer to Section 3.2), the assumed numbers of [redacted] The market shares used for this budget impact analysis [redacted] market share if selpercatinib is not recommended. This market share uptake is based on previous statements found in the DMC assessment report of selpercatinib, 2022, in which the expert committee suggested a higher market share that previously submitted (1).

Table 74 Number of new patients expected to be treated over the next five-year period if is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Selpercatinib	[redacted]				
Pemetrexed + carboplatin ± pembrolizumab	[redacted]				
			Non-recommendation		
Selpercatinib	[redacted]				
Pemetrexed + carboplatin ± pembrolizumab	[redacted]				

Budget impact

The budget impact estimated in Table 75is based on non-discounted cost outputs (2024 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of selpercatinib in both scenarios.

Table 75 Expected budget impact of recommending selpercatinib for RET fusion positive NSCLC 1L (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Selpercatinib is recommended	[redacted]				
Selpercatinib is NOT recommended	[redacted]				

	Year 1	Year 2	Year 3	Year 4	Year 5
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

14. List of experts

N/A

15. References

1. Danish Medicines Council. Bilag til Medicinrådets anbefaling vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke småcellet lungekræft - Revurdering. DMC; 2022.
2. Kvalitetsudviklingsprogram RK. Dansk Lunge Cancer Register Årsrapport 2022. Annual report RKKP; 2023 June 2023.
3. Danish Medicines Council. Bilag til Medicinrådets anbefaling vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller ikke småcellet lungekræft. 2021.
4. Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, et al. First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion–positive NSCLC. New England Journal of Medicine. 2023;389(20):1839-50.
5. Bekæmpelse K. Undersøgelser og diagnose - Lungekræft Cancer.dk: Cancer.dk; 2024 [Available from: https://www.cancer.dk/lungekraeft-lungecancer/undersoegelser-og-diagnose/.
6. Gruppe DLC. Lungecancer - Visitation, Diagnose, Stadie. Clinical guideline. DMCG: DCLG; 2024.
7. National Institute of Health and Care Excellence. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer. Committee Papers NICE; 2022.
8. Danish Medicines Council. Medicinrådets anbefaling vedr. pralsetinib til behandling af RET-fusionspositiv, fremskreden ikke-småcellet lungekræft. DMC; 2023.
9. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer. Committee Papers NICE; 2022.
10. Gridelli C, Losanno T. About rearranged during transfection in non-small cell lung cancer. Translational Cancer Research. 2017;6(Suppl 7).
11. Ferrara R, Auger N, Auclin E, Besse B. Clinical and translational implications of RET rearrangements in non–small cell lung cancer. Journal of Thoracic Oncology. 2018;13(1):27-45.
12. Shen T, Pu X, Wang L, Yu Z, Li J, Zhang Y, et al. Association between RET fusions and efficacy of pemetrexed-based chemotherapy for patients with advanced NSCLC in China: a multicenter retrospective study. Clinical Lung Cancer. 2020;21(5):e349-e54.
13. Hess LM, Han Y, Zhu YE, Bhandari NR, Sireci A. Characteristics and outcomes of patients with RET-fusion positive non-small lung cancer in real-world practice in the United States. BMC cancer. 2021;21:1-12.
14. O'Leary C, Xu W, Pavlakis N, Richard D, O'Byrne K. Rearranged during transfection fusions in non-small cell lung cancer. Cancers. 2019;11(5):620.
15. Bradley SH, Kennedy MP, Neal RD. Recognising lung cancer in primary care. Advances in therapy. 2019;36(1):19-30.
16. Williams L, Shi Q, El Ferjani B, Hirschmann M, Ponce D, Dibaj S, et al. MA19. 03 Differences in Symptom Burden Between Responsive and Progressive Disease in

Advanced Non-Small Cell Lung Cancer (aNSCLC). Journal of Thoracic Oncology. 2019;14(10):S327.
17. Polanski J, Jankowska-Polanska B, Rosinczuk J, Chabowski M, Szymanska-Chabowska A. Quality of life of patients with lung cancer. OncoTargets and therapy. 2016:1023-8.
18. UK CR. Symptoms of metastatic lung cancer [updated Mar 2023. Available from: https://www.cancerresearchuk.org/about-cancer/lung-cancer/metastatic/symptoms.
19. Drilon A, Lin JJ, Filleron T, Ni A, Milia J, Bergagnini I, et al. Frequency of brain metastases and multikinase inhibitor outcomes in patients with RET–rearranged lung cancers. Journal of Thoracic Oncology. 2018;13(10):1595-601.
20. Hvidberg MF, Petersen KD, Davidsen M, Witt Udsen F, Frølich A, Ehlers L, et al. Catalog of EQ-5D-3L health-related quality-of-life scores for 199 chronic conditions and health risks in Denmark. MDM Policy & Practice. 2023;8(1):23814683231159023.
21. Council DM. Medicinrådets lægemiddelrekommandation vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet. DMC; 2024.
22. European Medicines Agency. Retsevmo: EPAR - product information EMA; 2021.
23. Drilon AE, Subbiah V, Oxnard GR, Bauer TM, Velcheti V, Lakhani NJ, et al. A phase 1 study of LOXO-292, a potent and highly selective RET inhibitor, in patients with RET-altered cancers. American Society of Clinical Oncology; 2018.
24. Medicinpriser.dk. Pharmaceutical costs 2024 [Available from: https://www.medicinpriser.dk/Default.aspx.
25. Agency EM. Amlita: EPAR - Product information EMA; 2009.
26. Agency EM. Keytruda: EPAR - Product information EMA; 2015.
27. Pemetrexed "Accord" [Internet]. Pro.medicin.dk. 2024 [cited December 2024]. Available from: https://pro.medicin.dk/Medicin/Praeparater/10346.
28. Keytruda [Internet]. Pro.medicin.dk. 2024 [cited December 2024]. Available from: https://pro.medicin.dk/Medicin/Praeparater/7830.
29. Carboplatin "Accord" [Internet]. Pro.medicin.dk. 2024 [cited December 2024]. Available from: https://pro.medicin.dk/Medicin/Praeparater/7395.
30. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU Technical Support Document 19: Partitioned Survival Analysis for Decision Modelling in. 2017.
31. National Institute for Health and Care Excellence. Cabozantinib for treating medullary thyroid cancer. Technology Appraisal. NICE; 2017.
32. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. Technology Appraisal. NICE; 2018.
33. National Institute for Health and Care Excellence. Lenvatinib and sorafenib for treating differentiated thyroid cancer after radioactive iodine. Technology Appraisal NICE; 2018.
34. National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. Technology Appraisal NICE; 2019.
35. National Institute for Health and Care Excellence. Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer. Technology Appraisal. NICE; 2023.
36. Danish Medicines Council. The Danish Medicines Council methods guide for assessing new pharmaceuticals 2021 [v1.2:[Available from: https://medicinraadet.dk/media/5eibukbr/the-danish-medicines-council-methods-guide-for-assessing-new-pharmaceuticals-version-1-3.pdf.
37. Eli Lilly. Systematic literature reviews of clinical evidence and safety. 2019.
38. Eli Lilly. Interim Clinical Study Report LIBRETTO-431 (J2G-MC-JZJC) (NSCLC; 01 May 2023). 2023.
39. Eli Lilly. A Phase 1/2 Study of Oral LOXO-292 in Patients with Advanced Solid Tumors, Including RET Fusion-Positive Solid Tumors, Medullary Thyroid Cancer and Other Tumors with RET Activation (LIBRETTO-001). 2023.

40. Gautschi O, Drilon A, Solomon B, Tomasini P, Loong H, De Braud F, et al. 35P Final data from phase I/II LIBRETTO-001 trial of selpercatinib in RET fusion-positive non-small cell lung cancer. ESMO Open. 2024;9.
41. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, et al. Efficacy of selpercatinib in RET-altered thyroid cancers. New England Journal of Medicine. 2020;383(9):825-35.
42. Wirth L, Subbiah V, Worden F, Solomon B, Robinson B, Hadoux J, et al. 2229P Updated safety and efficacy of selpercatinib in patients (pts) with RET-activated thyroid cancer: Data from LIBRETTO-001. Annals of Oncology. 2023;34:S1147-S8.
43. Drilon A, Subbiah V, Gautschi O, Tomasini P, De Braud F, Solomon B, et al. 27P Durability of efficacy and safety with selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC). Annals of Oncology. 2022;33:S43.
44. Drilon A, Oxnard G, Wirth L. Registrational results of LIBRETTO-001: a phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET fusion-positive lung cancers. Talk presented at: 20th Annual World Conference on Lung Cancer (WCLC); September 7-10, 2019; Barcelona, Spain. 2019.
45. Drilon A, Oxnard GR, Tan DS, Loong HH, Johnson M, Gainor J, et al. Efficacy of selpercatinib in RET fusion–positive non–small-cell lung cancer. New England Journal of Medicine. 2020;383(9):813-24.
46. Garassino MC, Gadgeel S, Speranza G, Felip E, Esteban E, Dómine M, et al. Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol. 2023;41(11):1992-8.
47. Eli Lilly. Analysis Plan to Estimate the Relative Treatment Effect in Overall Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431: Treatment Switching and Extrapolation. . 2024.
48. Eli Lilly. Analysis Plan to Estimate the Relative Treatment Effect in Progression-Free Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung

Cancer Using Data From LIBRETTO-431. . 2024.
49. Eli Lilly. Comparative efficacy of Selpercatinib vs Pembrolizumab + Platinum doublet chemotherapy in 1L NSCLC (MAIC). MAIC 2024 May 2024.
50. Eli Lilly. Utility data: PRO SAP Final report. 2023.
51. Eli Lilly. Utility report: PRO report, interim analysis. 2023.
52. Eli Lilly. Utility data: EQ-5D-5L Denmark analysis 2023.
53. 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.
54. National Institute for Health and Care Excellence. Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy. National Institute for Health and Care Excellence; 2017.
55. Martí SG, Colantonio L, Bardach A, Galante J, Lopez A, Caporale J, et al. A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. Cost effectiveness and resource allocation. 2013;11:1-17.
56. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008;62(3):374-80.
57. National Institute for Health and Care Excellence. Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. NICE; 2015 December 2024.
58. Sireci A, Morosini D, Rothenberg S. P1. 01-101 efficacy of immune checkpoint inhibition in RET fusion positive non-small cell lung cancer patients. Journal of Thoracic Oncology. 2019;14(10):S401.
59. National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. NICE; 2018.

60. National Institute for Health and Care Excellence. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy. NICE; 2021.
61. Wirth L, Sherman E, Drilon A, Solomon B, Robinson B, Lorch J, et al. Registrational results of LOXO-292 in patients with RET-altered thyroid cancers. Annals of Oncology. 2019;30:v933.
62. Signorovitch JE, Sikirica V, Erder MH, Xie J, Lu M, Hodgkins PS, et al. Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. Value in Health. 2012;15(6):940-7.
63. Signorovitch J, Zhou Z, Ryan J, Anhorn R, Chawla A. Budget impact analysis of comprehensive genomic profiling in patients with advanced non-small cell lung cancer. Journal of medical economics. 2019;22(2):140-50.
64. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. Report by the Decision Support Unit. 2011.
65. Pfeiffer B, Hashim M, Bartsch R, Postma M, Heeg B. Objective response rate and progression-free survival as surrogate endpoints for overall survival and the impact of crossover and unbalanced post-progression treatments: A systematic review and meta-analysis in second-and further-line therapy of advanced non-small cell lung cancer. American Society of Clinical Oncology; 2017.
https://www.medicinpriser.dk/default.aspx.

Appendix A. Main characteristics of studies included

Table 76 Main characteristic of studies included (LIBRETTO-431)

Trial name: LIBRETTO-431	**NCT number: NCT04194944**
Objective	This study is being conducted to see if selpercatinib compared to a standard treatment is effective and safe in participants with rearranged during transfection (RET) fusion-positive non-squamous non-small cell lung cancer (NSCLC) that has spread to other parts of the body. Participants who are assigned to the standard treatment and discontinue due to progressive disease have the option to potentially crossover to selpercatinib.
Publications – title, author, journal, year	Zhou C, Solomon B, Loong HH, Park K, Pérol M, Arriola E, et al. First-line selpercatinib or chemotherapy and pembrolizumab in RET fusion–positive NSCLC. New England Journal of Medicine. 2023;389(20):1839-50. (4) Claerhout S, Lehnert S, Vander Borght S, Spans L, Dooms C, Wauters E, Vansteenkiste J, Weynand B, Deraedt K, Bourgain C, Vanden Bempt I. Targeted RNA sequencing for upfront analysis of actionable driver alterations in non-small cell lung cancer. Lung Cancer. 2022 Apr;166:242-249. doi: 10.1016/j.lungcan.2022.02.013. Epub 2022 Mar 1. Solomon BJ, Zhou CC, Drilon A, Park K, Wolf J, Elamin Y, Davis HM, Soldatenkova V, Sashegyi A, Lin AB, Lin BK, F Loong HH, Novello S, Arriola E, Perol M, Goto K, Santini FC. Phase III study of selpercatinib versus chemotherapy +/- pembrolizumab in untreated RET positive non-small-cell lung cancer. Future Oncol. 2021 Mar;17(7):763-773. doi: 10.2217/fon-2020-0935. Epub 2020 Nov 5.
Study type and design	A Multicenter, Randomized, Open-Label, Phase 3 Trial Comparing Selpercatinib to Platinum-Based and Pemetrexed Therapy With or Without Pembrolizumab as Initial Treatment of Advanced or Metastatic RET Fusion-Positive Non-Small Cell Lung Cancer
Sample size (n)	Total, N = 261 (ITT) population Intervention, N = 159 Comparator, N = 102 *ITT population-pembrolizumab population, n=212 with 129 patients treated with selpercatinib and 83 patients assgined to platinum-based pemetrexed treatment + pembrolizumab*
Main inclusion criteria	Histologically or cytologically confirmed, Stage IIIB-IIIC or Stage IV non-squamous NSCLC that is not suitable for radical surgery or radiation therapy. A RET gene fusion in tumor and/or blood from a qualified laboratory.

Trial name: LIBRETTO-431	NCT number: NCT04194944
	Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Adequate hematologic, hepatic and renal function. Willingness of men and women of reproductive potential to observe conventional and highly effective birth control for the duration of treatment and for 6 months after. Ability to swallow capsules.
Main exclusion criteria	Additional validated oncogenic drivers in NSCLC if known. Prior systemic therapy for metastatic disease. Treatment (chemotherapy, immunotherapy, or biological therapy) in the adjuvant/neoadjuvant setting is permitted if it was completed at least 6 months prior to randomization. Major surgery within 3 weeks prior to planned start of selpercatinib. Radiotherapy for palliation within 1 week of the first dose of study treatment or any radiotherapy within 6 months prior to the first dose of study treatment if more than 30 Gy to the lung. Symptomatic central nervous system (CNS) metastases, carcinomatous meningitis, or untreated spinal cord compression. Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of selpercatinib or prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF) > 470 milliseconds. Active uncontrolled systemic bacterial, viral, or fungal infection or serious ongoing intercurrent illness, such as hypertension or diabetes, despite optimal treatment. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of the study drug. Pregnancy or lactation. Other malignancy unless nonmelanoma skin cancer, carcinoma in situ of the cervix or other in situ cancers or a malignancy diagnosed ≥2 years previously and not currently active. Uncontrolled, disease related pericardial effusion or pleural effusion. Requiring chronic treatment with steroids. **Exclusion criteria for participants receiving pembrolizumab:** History of interstitial lung disease or interstitial pneumonitis. Active autoimmune disease or any illness or treatment that could compromise the immune system.
Intervention	159 participants treated with 160 mg Selpercatinib administered orally twice daily (BID) continuously in 21-day cycles.

Trial name: LIBRETTO-431	NCT number: NCT04194944
Comparator(s)	102 participants treated with pemetrexed 500 mg/m^2 administered intravenously (IV) on Day 1, every 3 weeks (Q3W), plus investigator's choice of carboplatin area under the concentration versus time curve 5 (AUC 5 [maximum dose of 750 mg] IV), or cisplatin (75 mg/m2 cisplatin IV) on Day 1 Q3W for 4 cycles, plus investigator's choice with or without 200 mg pembrolizumab IV on Day 1 Q3W up to 35 cycles.
Follow-up time	Median follow-up time was approximately 19 months (DCO 1 May 2023)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Primary endpoints • Progression Free Survival (PFS) by Blinded Independent Central Review (BICR) (With Pembrolizumab) • PFS by BICR (With or Without Pembrolizumab) *Secondary endpoints:* • Percentage of Participant with Disease Control Rate (DCR) by BICR (With Pembrolizumab) • Percentage of Participant with DCR by BICR (With or Without Pembrolizumab) • PFS2 (With Pembrolizumab) • PFS2 (With or Without Pembrolizumab) • Overall Response Rate (ORR): Percentage of Participants with Complete Response (CR) or Partial Response (PR) by BICR (With Pembrolizumab) • ORR: Percentage of Participants with CR or PR by BICR (With or Without Pembrolizumab) • Duration of Response (DoR) by BICR (With Pembrolizumab) • DOR by BICR (With or Without Pembrolizumab) • Overall Survival (OS) (With Pembrolizumab) • OS (With or Without Pembrolizumab) • Intracranial ORR: Percentage of Participants with Intracranial CR or PR Per RECIST (Response Evaluation Criteria in Solid Tumors) 1.1 by BICR (With Pembrolizumab) • Intracranial ORR: Percentage of Participants with Intracranial CR or PR Per RECIST 1.1 by BICR (With or Without Pembrolizumab)

Trial name: LIBRETTO-431	NCT number: NCT04194944
	• Median Intracranial DOR Per RECIST 1.1 by BICR (With Pembrolizumab) • Median Intracranial DOR Per RECIST 1.1 by BICR (With or Without Pembrolizumab) • Time to Deterioration of Pulmonary Symptoms (With Pembrolizumab) • Time to Deterioration of Pulmonary Symptoms (With or Without Pembrolizumab) • The Concordance of the Local Lab and the Central Lab RET Results: Percentage of Participants With RET-Positive Specimens as Called by the Central Lab, which is Also RET-Positive as Called by a Local Lab (Positive Percent Agreement) • Median Time to CNS Progression Per RECIST 1.1 by BICR (With Pembrolizumab) • Median Time to CNS Progression Per RECIST 1.1 by BICR (With or Without Pembrolizumab) • Intracranial ORR: Percentage of Participants with Intracranial CR or PR Per Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) by BICR (With Pembrolizumab) • Intracranial ORR: Percentage of Participants with Intracranial CR or PR Per RANO-BM by BICR (With or Without Pembrolizumab) • Intracranial DOR Per RANO-BM by BICR (With Pembrolizumab) • Intracranial DOR Per RANO-BM by BICR (With or Without Pembrolizumab) **Endpoints included in this application:** • ORR • OS • PFS • Duration of response
Method of analysis	ITT population, n=261 All efficacy analyses were intention-to-treat analyses. We used the Kaplan–Meier method to estimate rates of progression-free survival and overall survival (and DOR) Overall response rate (confirmed) by BICR assessment, intention to treat population.
Subgroup analyses	Not subgroup analysis has been included for this submission. However, Eli Lilly is primarily interested in the population that was not intended to receive pembrolizumab (n=49, refer to Figure 19). However, this is problematic because this population is small compared with the patient

Trial name: LIBRETTO-431	NCT number: NCT04194944
	population that received pembrolizumab. ITT-pembrolizumab population has been included in this submission
Other relevant information	N/A

Abbreviations: RET, rearranged during transfection; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; N/A, not available or applicable; ORR; overall response rate; ITT, intention to treat; OS, overall survival; DOR, duration of response; PFS, progression-free survival; BICR, blinded independent central review; DCO, data cutoff; DCR, disease control rate; CNS, central nervous system; IV, intravenous; CR, complete response; PR, partial response; RECIST, response evaluation criteria in solid tumours.

Table 77 Main characteristic of studies included (LIBRETTO-001)

Trial name: LIBRETTO-001	NCT number: NCT03157128
Objective	This is an open-label, multi-center Phase 1/2 study in participants with advanced solid tumors, including RET fusion-positive solid tumors, MTC, and other tumors with RET activation. The trial will be conducted in 2 parts: Phase 1 (dose escalation - completed) and phase 2 (dose expansion). Participants with advanced cancer are eligible if they have progressed on or are intolerant to available standard therapies, or no standard or available curative therapy exists, or in the opinion of the Investigator, they would be unlikely to tolerate or derive significant clinical benefit from appropriate standard of care therapy, or they declined standard therapy. A dose of 160 milligrams (mg) twice a day (BID) has been selected as the recommended phase 2 dose (RP2D). Approximately 875 participants with advanced solid tumors harboring a RET gene alteration in tumor and/or blood will be enrolled to one of seven phase 2 cohorts: Cohort 1: Advanced RET fusion positive solid tumor other than NSCLC or thyroid cancer for participants who progressed on or intolerant to first line therapy (open) Cohort 2: Advanced RET fusion positive solid tumor other than NSCLC or thyroid cancer for treatment naïve participants (open) Cohort 3: Advanced RET-mutant MTC participants who progressed on or intolerant to first line therapy (closed) Cohort 4: Advanced RET-mutant MTC participants who are treatment naïve (closed) Cohort 5: Advanced RET-altered solid tumor for participants other than NSCLC or thyroid cancer and RET-mutant MEN2 spectrum tumors (e.g. pheochromocytoma) otherwise ineligible for cohorts 1-4. See details in inclusion/exclusion criteria (open) Cohort 6: Participants otherwise eligible for Cohorts 1-5 who discontinued another RET inhibitor due to intolerance may be eligible with prior Sponsor approval (closed) Cohort 7: RET fusion positive early-stage non-small cell lung cancer (NSCLC) participants who are candidates for definitive surgery.

Trial name: LIBRETTO-001	NCT number: NCT03157128
	Participants will receive selpercatinib in a neoadjuvant and adjuvant setting. Participants will be followed for disease recurrence for up to 5 years from the date of surgery (closed)
Publications – title, author, journal, year	Subbiah V, Wolf J, Konda B, Kang H, Spira A, Weiss J, Takeda M, Ohe Y, Khan S, Ohashi K, Soldatenkova V, Szymczak S, Sullivan L, Wright J, Drilon A. Tumour-agnostic efficacy and safety of selpercatinib in patients with RET fusion-positive solid tumours other than lung or thyroid tumours (LIBRETTO-001): a phase 1/2, open-label, basket trial. Lancet Oncol. 2022 Oct;23(10):1261-1273. doi: 10.1016/S1470-2045(22)00541-1. Epub 2022 Sep 12. Rolfo C, Hess LM, Jen MH, Peterson P, Li X, Liu H, Lai Y, Sugihara T, Kiiskinen U, Vickers A, Summers Y. External control cohorts for the single-arm LIBRETTO-001 trial of selpercatinib in RET+ non-small-cell lung cancer. ESMO Open. 2022 Aug;7(4):100551. doi: 10.1016/j.esmoop.2022.100551. Epub 2022 Aug 2. Subbiah V, Gainor JF, Oxnard GR, Tan DSW, Owen DH, Cho BC, Loong HH, McCoach CE, Weiss J, Kim YJ, Bazhenova L, Park K, Daga H, Besse B, Gautschi O, Rolfo C, Zhu EY, Kherani JF, Huang X, Kang S, Drilon A. Intracranial Efficacy of Selpercatinib in RET Fusion-Positive Non-Small Cell Lung Cancers on the LIBRETTO-001 Trial. Clin Cancer Res. 2021 Aug 1;27(15):4160-4167. doi: 10.1158/1078-0432.CCR-21-0800. Epub 2021 Jun 4. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, Godbert Y, Barlesi F, Morris JC, Owonikoko TK, Tan DSW, Gautschi O, Weiss J, de la Fouchardiere C, Burkard ME, Laskin J, Taylor MH, Kroiss M, Medioni J, Goldman JW, Bauer TM, Levy B, Zhu VW, Lakhani N, Moreno V, Ebata K, Nguyen M, Heirich D, Zhu EY, Huang X, Yang L, Kherani J, Rothenberg SM, Drilon A, Subbiah V, Shah MH, Cabanillas ME. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. N Engl J Med. 2020 Aug 27;383(9):825-835. doi: 10.1056/NEJMoa2005651. Drilon A, Oxnard GR, Tan DSW, Loong HHF, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC, Peled N, Weiss J, Kim YJ, Ohe Y, Nishio M, Park K, Patel J, Seto T, Sakamoto T, Rosen E, Shah MH, Barlesi F, Cassier PA, Bazhenova L, De Braud F, Garralda E, Velcheti V, Satouchi M, Ohashi K, Pennell NA, Reckamp KL, Dy GK, Wolf J, Solomon B, Falchook G, Ebata K, Nguyen M, Nair B, Zhu EY, Yang L, Huang X, Olek E, Rothenberg SM, Goto K, Subbiah V. Efficacy of Selpercatinib in RET Fusion-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2020 Aug 27;383(9):813-824. doi: 10.1056/NEJMoa2005653.
Study type and design	Single arm. Open-label, multi-centre Phase 1/2 study consisting of 2 parts: 1) Phase 1 - dose escalation and expansion, and 2) Phase 2 - dose expansion.
Sample size (n)	Enrolled patients, n= 968 (all patients screened) Treated with selpercatinib, n=837 (all patients treated regardless of tumor type)

Trial name: LIBRETTO-001	NCT number: NCT03157128
	All patients continuing study intervention, n=369 RET fusion positive cancers, n=483 RET fusion-positive NSCLC (safety analysis set), n=362 NSCLC efficacy analysis set, n=356 • Treatment naïve, n=69 (SAS) • Platinum chemotherapy, n=247
Main inclusion criteria	**For phase 1:** Participants with a locally advanced or metastatic solid tumor that: Has progressed on or is intolerant to standard therapy, or For which no standard therapy exists, or in the opinion of the Investigator, are not candidates for or would be unlikely to tolerate or derive significant clinical benefit from standard therapy, or Decline standard therapy Prior multikinase inhibitors (MKIs) with anti-RET activity are allowed A RET gene alteration is not required initially. Once adequate PK exposure is achieved, evidence of RET gene alteration in tumor and/or blood is required as identified through molecular assays, as performed for clinical evaluation Measurable or non-measurable disease as determined by RECIST 1.1 or RANO as appropriate to tumor type Eastern Cooperative Oncology Group (ECOG) score of 0, 1, or 2 or Lansky Performance Score (LPS) greater than or equal to (≥) 40 percent (%) (age less than [<] 16 years) with no sudden deterioration 2 weeks prior to the first dose of study treatment Adequate hematologic, hepatic and renal function Life expectancy of at least 3 months **For phase 2: As for phase 1 with the following modifications:** <u>For Cohort 1:</u> Participants must have received prior standard therapy appropriate for their tumor type and stage of disease, or in the opinion of the Investigator, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy <u>Cohorts 1 and 2:</u> Enrollment will be restricted to participants with evidence of a RET gene alteration in tumor At least one measurable lesion as defined by RECIST 1.1 or RANO, as appropriate to tumor type and not previously irradiated <u>Cohorts 3 and 4:</u> Enrollment closed

Trial name: LIBRETTO-001	NCT number: NCT03157128

	Cohort 5: Cohorts 1-4 without measurable disease MCT not meeting the requirements for Cohorts 3 or 4 MTC syndrome spectrum cancers (e.g., MTC, pheochromocytoma), cancers with neuroendocrine features/differentiation, or poorly differentiated thyroid cancers with other RET alteration/activation may be allowed with prior Sponsor approval cfDNA positive for a RET gene alteration not known to be present in a tumor sample Cohort 6: Participants who otherwise are eligible for Cohorts 1, 2 or 5 who discontinued another RET inhibitor may be eligible with prior Sponsor approval Cohort 7: Participants with a histologically confirmed stage IB-IIIA NSCLC and a RET fusion; determined to be medically operable and tumor deemed resectable by a thoracic surgical oncologist, without prior systemic treatment for NSCLC
Main exclusion criteria	**Key exclusion criteria (phase 1 and hase 2):** Phase 2 Cohorts 1 and 2: An additional well-known oncogenic driver Cohorts 3 and 4: Enrollment closed Cohorts 1, 2 and 5: prior treatment with a selective RET inhibitor Notes: Participants otherwise eligible for Cohorts 1, 2, and 5 who discontinued another selective RET inhibitor may be eligible for Phase 2 Cohort 6 with prior Sponsor approval Investigational agent or anticancer therapy (including chemotherapy, biologic therapy, immunotherapy, anticancer Chinese medicine or other anticancer herbal remedy) within 5 half-lives or 2 weeks (whichever is shorter) prior to planned start of LOXO-292 (selpercatinib). In addition, no concurrent investigational anti-cancer therapy is permitted Note: Potential exception for this exclusion criterion will require a valid scientific justification and approval from the Sponsor Major surgery (excluding placement of vascular access) within 2 weeks prior to planned start of LOXO-292 (selpercatinib) Radiotherapy with a limited field of radiation for palliation within 1 week of planned start of LOXO-292 (selpercatinib), with the exception of participants receiving radiation to more than 30% of the bone

Trial name: LIBRETTO-001	NCT number: NCT03157128
	marrow or with a wide field of radiation, which must be completed at least 4 weeks prior to the first dose of study treatment Any unresolved toxicities from prior therapy greater than Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy Symptomatic primary CNS tumor, metastases, leptomeningeal carcinomatosis, or untreated spinal cord compression. Participants are eligible if neurological symptoms and CNS imaging are stable and steroid dose is stable for 14 days prior to the first dose of LOXO-292 (selpercatinib) and no CNS surgery or radiation has been performed for 28 days, 14 days if stereotactic radiosurgery (SRS) Clinically significant active cardiovascular disease or history of myocardial infarction within 6 months prior to planned start of LOXO-292 (selpercatinib) or prolongation of the QT interval corrected (QTcF) greater than (>) 470 milliseconds (msec) • Participants with implanted pacemakers may enter the study without meeting QTc criteria due to nonevaluable measurement if it is possible to monitor QT changes. • Participants with bundle branch block may be considered for study entry if QTc is appropriate by a formula other than Fridericia's and if it is possible to monitor for QT changes. Required treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and certain prohibited concomitant medications Phase 2 Cohort 7 (neoadjuvant treatment): Participant must not have received prior systemic therapy for NSCLC.
Intervention	The recommended Phase 2 dose of selpercatinib is 160 mg BID in an oral form. This dose was selected by the Safety Review Committee in Phase 1 and was used as the starting dose for patients in the Phase 2 dose-expansion phase of the study.
Comparator(s)	N/A
Follow-up time	The first patient was treated on 9th May 2017. At the latest data cut-off of 15th June 2021, the median follow-up was 25.2 months for OS and 21.9 months for PFS for SAS1 (treatment-naïve) patients
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	*Primary endpoints* • Phase 1: MTD • Phase 1: RP2D

Trial name: LIBRETTO-001	NCT number: NCT03157128
	• Phase 2: Objective Response Rate *Secondary endpoints:* • Phase 1: Number of Participants with a Treatment-Related Adverse Event(s) (TRAE[s]) • Phase 1: Number of Participants with an Abnormal Laboratory or Physical Exam Result(s) • Phase 1: Overall Response Rate (ORR) based on RECIST 1.1 or RANO, as Appropriate to Tumor Type • Phase 2: ORR (by Investigator) • Phase 2: Best Change in Tumor Size from Baseline (by IRC and Investigator) • Phase 2: Duration of Response (DOR; by IRC and Investigator) • Phase 2: Central Nervous System (CNS) ORR (by IRC) • Phase 2: CNS DOR (by IRC) • Phase 2: Time to Any and Best Response (by IRC and Investigator) • Phase 2: CBR (by IRC and Investigator) • Phase 2: PFS (by IRC and Investigator) • Phase 2: Overall Survival (OS) • Phase 2: Percentage of Participants with any Serious Adverse Event (SAE[s]) • Phase 1 and 2: Pharmacokinetics (PK): Area Under the Plasma Concentration-Time Curve of LOXO-292 (Selpercatinib) • Phase 1 and 2: PK: Maximum Concentration (Cmax) of LOXO-292 (Selpercatinib) **Endpoints included in this application:** • ORR • OS • PFS • Duration of response
Method of analysis	SAS1 population, n=69 (treatment naïve RET fusion-positive patients NSCLC), refer to Figure 28. Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival (and DOR) Refer to Section 7. LIBRETTO-001 (n=69) was compared with KEYNOTE-189. Hazard ratios were estimated using a Cox model comparing the adjusted and unadjusted OS for selpercatinib with those for pemetrexed + platinum + pembrolizumab (KEYNOTE-189). The HR was

Trial name: LIBRETTO-001		NCT number: NCT03157128
	applied to proportional hazards survival functions fitted to the LIBRETTO-001 OS data	
Subgroup analyses	N/A	
Other relevant information	N/A	

Abbreviations: RET, rearranged during transfection; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; N/A, not available or applicable; ORR; overall response rate; ITT, intention to treat; OS, overall survival; DOR, duration of response; PFS, progression-free survival; BICR, blinded independent central review; DCO, data cutoff; DCR, disease control rate; CNS, central nervous system; IV, intravenous; CR, complete response; PR, partial response; RECIST, response evaluation criteria in solid tumours; MTC, medullary thyroid carcinoma; MKR, multikinase inhibtor; CTCAE, common terminology criteria for adverse events.

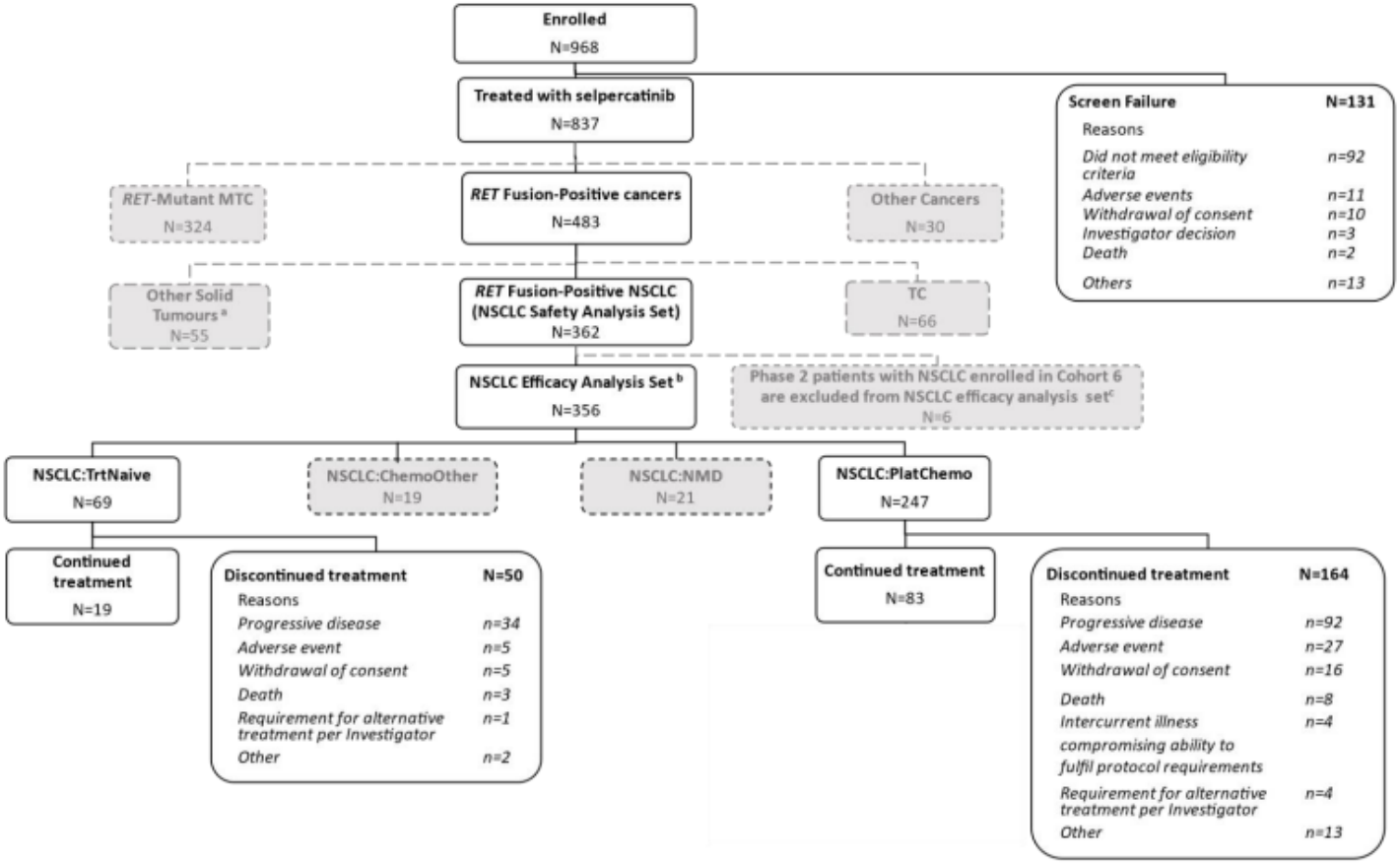


Figure 28 LIBRETTO-001 diagram presenting the patient disposition for RET fusion-positive NSCLC efficacy analysis DCO 13 January 202

Table 78 Main characteristic of studies included (KEYNOTE-189)

Trial name: KEYNOTE-189	NCT number: NCT02578680
Objective	This is an efficacy and safety study of pembrolizumab (MK-3475) combined with pemetrexed/platinum chemotherapy versus pemetrexed/platinum chemotherapy alone in participants with advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC) who have not previously received systemic therapy for advanced disease. Participants will be randomly assigned to receive pembrolizumab combined with pemetrexed/platinum (Investigators choice of cisplatin or carboplatin), OR pemetrexed/platinum (Investigators choice of cisplatin or carboplatin).
Publications – title, author, journal, year	Garon EB, Aerts J, Kim JS, Muehlenbein CE, Peterson P, Rizzo MT, Gadgeel SM. Safety of pemetrexed plus platinum in combination with pembrolizumab for metastatic nonsquamous non-small cell lung cancer: A post hoc analysis of KEYNOTE-189. Lung Cancer. 2021 May;155:53-60. doi: 10.1016/j.lungcan.2021.02.021. Epub 2021 Feb 19. Erratum In: Lung Cancer. 2023 Sep;183:107285. doi: 10.1016/j.lungcan.2023.107285. Gadgeel S, Rodriguez-Abreu D, Speranza G, Esteban E, Felip E, Domine M, Hui R, Hochmair MJ, Clingan P, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Garon EB, Novello S, Rubio-Viqueira B, Boyer M, Kurata T, Gray JE, Yang J, Bas T, Pietanza MC, Garassino MC. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer. J Clin Oncol. 2020 May 10;38(14):1505-1517. doi: 10.1200/JCO.19.03136. Epub 2020 Mar 9. Garassino MC, Gadgeel S, Esteban E, Felip E, Speranza G, Domine M, Hochmair MJ, Powell S, Cheng SY, Bischoff HG, Peled N, Reck M, Hui R, Garon EB, Boyer M, Wei Z, Burke T, Pietanza MC, Rodriguez-Abreu D. Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol. 2020 Mar;21(3):387-397. doi: 10.1016/S1470-2045(19)30801-0. Epub 2020 Feb 6. Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF, Cheng SY, Bischoff HG, Peled N, Grossi F, Jennens RR, Reck M, Hui R, Garon EB, Boyer M, Rubio-Viqueira B, Novello S, Kurata T, Gray JE, Vida J, Wei Z, Yang J, Raftopoulos H, Pietanza MC, Garassino MC; KEYNOTE-189 Investigators. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078-2092. doi: 10.1056/NEJMoa1801005. Epub 2018 Apr 16.
Study type and design	A Randomized, Double-Blind, Phase III Study of Platinum+Pemetrexed Chemotherapy With or Without Pembrolizumab (MK-3475) in First Line

Trial name: KEYNOTE-189	NCT number: NCT02578680
	Metastatic Non-squamous Non-small Cell Lung Cancer Subjects (KEYNOTE-189)
Sample size (n)	Total, N = 616 Intervention, N = 410 Comparator, N = 206
Main inclusion criteria	Has a histologically-confirmed or cytologically confirmed diagnosis of stage IV nonsquamous NSCLC. Has confirmation that epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)-directed therapy is not indicated. Has measurable disease. Has not received prior systemic treatment for their advanced/metastatic NSCLC. Can provide tumor tissue. Has a life expectancy of at least 3 months. Has a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Status. Has adequate organ function If female of childbearing potential, is willing to use adequate contraception for the course of the study through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents. If male with a female partner(s) of child-bearing potential, must agree to use adequate contraception starting with the first dose of study medication through 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.
Main exclusion criteria	Has predominantly squamous cell histology NSCLC. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks prior to administration of pembrolizumab. Before the first dose of study medication: a) Has received prior systemic cytotoxic chemotherapy for metastatic disease, b) Has received antineoplastic biological therapy (e.g., erlotinib, crizotinib, cetuximab), c) Had major surgery (<3 weeks prior to first dose) Received radiation therapy to the lung that is >30 Gray (Gy) within 6 months of the first dose of study medication. Completed palliative radiotherapy within 7 days of the first dose of study medication.

Trial name: KEYNOTE-189	NCT number: NCT02578680

Is expected to require any other form of antineoplastic therapy while on study.

Received a live-virus vaccination within 30 days of planned start of study medication.

Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction, peritoneal carcinomatosis.

Known history of prior malignancy except if participant has undergone potentially curative therapy with no evidence of that disease recurrence for 5 years since initiation of that therapy, except for successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

Previously had a severe hypersensitivity reaction to treatment with another monoclonal antibody (mAb).

Known sensitivity to any component of cisplatin, carboplatin or pemetrexed.

Has active autoimmune disease that has required systemic treatment in past 2 years.

Is on chronic systemic steroids.

Is unable to interrupt aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs), other than an aspirin dose ≤1.3 g per day, for a 5-day period (8-day period for long-acting agents, such as piroxicam).

Is unable or unwilling to take folic acid or vitamin B12 supplementation.

Had prior treatment with any other anti-programmed cell death-1 (PD-1), or PD-ligand 1 (PD-L1) or PD-L2 agent or an antibody targeting other immuno-regulatory receptors or mechanisms. Has participated in any other pembrolizumab study and has been treated with pembrolizumab.

Has an active infection requiring therapy.

Has known history of Human Immunodeficiency Virus (HIV).

Has known active Hepatitis B or C.

Has known psychiatric or substance abuse disorder that would interfere with cooperation with the requirements of the trial.

Is a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol).

Has symptomatic ascites or pleural effusion.

Has interstitial lung disease or a history of pneumonitis that required oral of IV glucocorticoids to assist with management.

Trial name: KEYNOTE-189	NCT number: NCT02578680
	Is pregnant or breastfeeding, or expecting to conceive or father children prior to 120 days after the last dose of study medication or through 180 days after last dose of chemotherapeutic agents.
Intervention	Pembrolizumab+Pemetrexed+Platinum Chemotherapy Followed by Pembrolizumab+Pemetrexed Participants receive pembrolizumab 200 mg intravenously (IV) PLUS pemetrexed 500 mg/m^2 IV (with vitamin supplementation) PLUS cisplatin 75 mg/m^2 IV OR carboplatin Area Under the Curve (AUC) 5 IV on Day 1 of every 3-week cycle (Q3W) for 4 cycles followed by pembrolizumab 200 mg IV PLUS pemetrexed 500 mg/m^2 IV Q3W until progression. (Participants who receive pembrolizumab 200 mg IV Q3W for up to 2 years but experience disease progression, will be eligible to receive a second course of pembrolizumab monotherapy 200 mg IV Q3W, at the investigator's discretion, for up to 1 additional year.)
Comparator(s)	Participants receive saline placebo IV PLUS pemetrexed 500 mg/m^2 IV (with vitamin supplementation) PLUS cisplatin 75 mg/m^2 IV OR carboplatin AUC 5 IV on Day 1 of every 3-week cycle (Q3W) for 4 cycles followed by saline placebo IV PLUS pemetrexed 500 mg/m^2 IV Q3W until progression. (Effective 23-Dec-2019, participants will discontinue saline placebo. If documented progression occurs, participants may be able to receive pembrolizumab monotherapy Q3W for the remainder of the study.)
Follow-up time	[redacted]
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	*Primary endpoints* • Progression-Free Survival (PFS) Per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as Assessed by Blinded Central Imaging • Overall Survival (OS) *Secondary endpoints:* • Overall Response Rate (ORR) Per RECIST 1.1 as Assessed by Blinded Central Imaging • Duration of Response (DOR) Per RECIST 1.1 as Assessed by Blinded Central Imaging • Number of Participants Who Experienced an Adverse Event (AE) • Number of Participants Who Discontinued Any Study Drug Due to an AE *Other outcome measures:*

Trial name: KEYNOTE-189	NCT number: NCT02578680
	• Progression-Free Survival (PFS) as Assessed by Investigator Immune-related RECIST (irRECIST) Response Criteria **Endpoints included in this application:** • ORR • OS • PFS • Duration of response
Method of analysis	Pembro+PC population, n=410 Kaplan–Meier method was used to estimate rates of progression-free survival and overall survival Refer to Section 7. LIBRETTO-001 (n=69) was compared with KEYNOTE-189 (n=410). Hazard ratios were estimated using a Cox model comparing the adjusted and unadjusted OS for selpercatinib with those for pemetrexed + platinum + pembrolizumab (KEYNOTE-189). The HR was applied to proportional hazards survival functions fitted to the LIBRETTO-001 OS data
Subgroup analyses	N/A
Other relevant information	N/A

Abbreviations: RET, rearranged during transfection; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; N/A, not available or applicable; ORR; overall response rate; ITT, intention to treat; OS, overall survival; DOR, duration of response; PFS, progression-free survival; BICR, blinded independent central review; DCO, data cutoff; DCR, disease control rate; CNS, central nervous system; IV, intravenous; CR, complete response; PR, partial response; RECIST, response evaluation criteria in solid tumours; MTC, medullary thyroid carcinoma; MKR, multikinase inhibtor; CTCAE, common terminology criteria for adverse events.

Appendix B. Efficacy results per study

Results per study

Results of the LIBRETTO-431, LIBRETTO-001 and KEYNOTE-189 trial is presented in Table 79 / Table 80 (for full ITT or ITT-pembrolizumab, respectively), Table 81 and Table 82, below. All results are based on the latest efficacy data cut.

Table 79 Results per study (LIBRETTO-431) ITT-population

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR per RECIST 1.1 by BICR (DCO 1 May 2023)	Selpercatinib	159	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	ORR is defined as the number of participants who achieve a BOR of CR or PR divided by the total number of participants randomized to each treatment arm. The OR is stratified by Geography (East Asian vs. non-East Asian) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS, and Brain metastases (presence or absence) - IWRS. The P-value is calculated using the Exact Cochran-Mantel-Haenszel test, stratified by the	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	102	[redacted]								Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										randomization strata Geography (East Asian vs. non-East Asian) - IWRS, Brain metastases (presence or absence) - IWRS, and Investigator's intent to treat with pembrolizumab - IWRS. Where a p-value is 'NC', the computations were not performed because there were fewer than 2 non-missing levels in the data.	
OS (DCO 1 May 2023)	Selpercatinib	159	[redacted]	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]	OS was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the participant is known to be alive. The log rank tesyt used for the p-value was stratified by geography (East Asian vs.	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	102	N/A (N/A – N/A)								Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										non-East Asian) - IWRS, Brain metastases (presence or absence/unknown) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS.	
PFS per RECIST 1.1 by BICR (DCO 1 May 2023)	Selpercatinib	159	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	PFS is defined as the time from randomization until the occurrence of documented disease progression by the BICR, per RECIST version 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease. The log rank test used for the p-value was stratified by geography (East Asian vs. non-East Asian) - IWRS, Brain metastases (presence or absence/unknown) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS.	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	102	[redacted]								Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N (%)**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
DOR per RECIST 1.1 by BICR (DCO 1 May 2023)	Selpercatinib	133	[redacted]	[redacted]	N/A	N/A	[redacted]	[redacted]	[redacted]	DoR was defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or documented disease progression was observed, or the date of death from any cause in the absence of documented disease progression or recurrence. The DOR according to both BICR and investigator-assessed BOR was evaluated per RECIST 1.1 criteria.	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	64	[redacted]								Eli Lilly, 2023 (38)

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; DOR, duration of response; HR, hazard ratio; IWRS, Interactive Web Response System; NC, not computable; N/A, not applicable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; TRT A, experimental: selpercatinib; TRT B, pemetrexed and platinum with or without pembrolizumab.

Table 80 Results per study (LIBRETTO-431) ITT-pembrolizumab

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N (%)**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
ORR per RECIST 1.1 by BICR	Selpercatinib	129	108 (83.7%) (76.2-89.6)	N/A	N/A	N/A	OR: 2.7	1.4-5.1	0.0028	ORR is defined as the number of participants who achieve a BOR of CR or PR divided by the total number of participants randomized to each treatment arm. The OR is stratified by Geography (East Asian vs. non-East Asian) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS, and Brain metastases (presence or absence) - IWRS. The P-value is calculated using the Exact Cochran-Mantel-Haenszel test, stratified by the randomization strata Geography (East Asian vs. non-East Asian) - IWRS, Brain metastases (presence or absence) - IWRS, and Investigator's intent to treat with pembrolizumab - IWRS. Where a p-value is 'NC', the	Eli Lilly, 2023 (38)
(DCO 1 May 2023)	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	83	54 (65.1%) (53.8–75.2)								Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										computations were not performed because there were fewer than 2 non-missing levels in the data.	
OS (DCO 1 May 2023)	Selpercatinib	129	N/A	N/A	N/A	N/A	HR: 0.961	0.503-1.835	0.9033	OS was defined as the time from randomization until death from any cause. If the participant was alive or lost to follow-up at the time of data analysis, OS data will be censored on the last date the participant is known to be alive. The log rank tesyt used for the p-value was stratified by geography (East Asian vs. non-East Asian) - IWRS, Brain metastases (presence or absence/unknown) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS.	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	83	N/A								Eli Lilly, 2023 (38)
	Selpercatinib	129	24.84 (16.89, N/A)	13.63	N/A	N/A	HR: 0.465	(0.31, 0.69)	0.0002	PFS is defined as the time from randomization until the	Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS per RECIST 1.1 by BICR (DCO 1 May 2023)	Carboplatin/ cisplatin + pemetrexed +/- pembrolizumab	83	11.17 (8.77, 16.76)							occurrence of documented disease progression by the BICR, per RECIST version 1.1 criteria, or death from any cause in the absence of BICR-documented progressive disease. The log rank test used for the p-value was stratified by geography (East Asian vs. non-East Asian) - IWRS, Brain metastases (presence or absence/unknown) - IWRS, Investigator's intent to treat with pembrolizumab - IWRS.	Eli Lilly, 2023 (38)
DOR per RECIST 1.1 by BICR (DCO 1 May 2023)	Selpercatinib	108	24.18 (17.94, N/A)	12.71	N/A	N/A	HR: 0.377	(0.224, 0.633)	0.0001	DoR was defined as the time from the date that measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or documented disease progression was observed, or the date of death	Eli Lilly, 2023 (38)
	Carboplatin/ cisplatin + pemetrexed +/-	54	11.47 (9.66, 23.26)								Eli Lilly, 2023 (38)

Results of [LIBRETTO-431 (NCT04194944)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N (%)	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	pembrolizumab									from any cause in the absence of documented disease progression or recurrence. The DOR according to both BICR and investigator-assessed BOR was evaluated per RECIST 1.1 criteria.	

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CR, complete response; DOR, duration of response; HR, hazard ratio; IWRS, Interactive Web Response System; NC, not computable; N/A, not applicable; OR, odds ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumors; TRT A, experimental: selpercatinib; TRT B, pemetrexed and platinum with or without pembrolizumab.

Table 81 Results per study (LIBRETTO-001)

Results of [LIBRETTO-001 (NCT03157128)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS per RECISTv1.1 byBICR (DCO 13 January 2023)	TrtNaive (SAS1 population)	69	22.0 (16.5–24.9) months	4.2 months	N/A	N/A	N/A	N/A	N/A	PFS was defined as the time, in months, from the date of the first dose of selpercatinib to the earliest date of documented PD or death from any cause. Unless specified otherwise, the analytical methods described for DOR were applied to PFS. PFS estimates were calculated using the KM method, and 95% CIs were derived using the Brookmeyer and Crowley method	Eli Lilly, 2023 (39)
	PlatChemo	247	26.2 (19.3–35.7) months								Eli Lilly, 2023 (39)
OS (DCO 13 January 2023)	TrtNaive (SAS1 population)	69	N/A (37.8-N/A)	N/A	N/A	N/A	N/A	N/A	N/A	OS was defined as the time, in months, from the date of the first dose of selpercatinib to the date of death from any cause. Patients who were alive or lost to follow-up at the data cutoff date were right-censored, with the censoring date corresponding to the last	Eli Lilly, 2023 (39)
	PlatChemo	247	47.6 (35.9-N/A)								Eli Lilly, 2023 (39)

Results of [LIBRETTO-001 (NCT03157128)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										date the patient was known to be alive. OS estimates were calculated using the KM method, and 95% Cls were derived using the Brookmeyer and Crowley method.	
ORR per RECIST v1.1 by BICR and safety (DCO 13 January 2023)	TrtNaive (SAS1 population)	69	57 (82.6%) (71.6-90.7)	21.1%	N/A	N/A	N/A	N/A	N/A	ORR was estimated using the maximum likelihood estimator, representing the crude proportion of patients with a BOR of confirmed CR or PR. A two-sided 95% exact binomial CI was calculated using the Clopper-Pearson method. Responses were confirmed by a repeat assessment conducted at least 28 days later.	Eli Lilly, 2023 (39)
	PlatChemo	247	152 (61.5%) (55.2-67.6)								Eli Lilly, 2023 (39)
DOR per RECIST v1.1 by	TrtNaive (SAS1 population)	69	20.3 (15.4-29.5)	11.3 months	N/A	N/A	N/A	N/A	N/A	DOR was calculated for patients who achieved a confirmed CR or PR. DOR was	Eli Lilly, 2023 (39)

Results of [LIBRETTO-001 (NCT03157128)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
BICR and safety (DCO 13 January 2023)	PlatChemo	247	31.6 (20.4-42.3)							defined as the time, in months, from the start date of the first observed and confirmed CR or PR to the first documented date of recurrent or progressive disease. If a patient died, irrespective of cause, without prior documentation of recurrent or progressive disease, the date of death was used as the response end date. DOR was summarised descriptively using the KM method, and median follow-up was estimated based on the KM estimate of potential follow-up.	Eli Lilly, 2023 (39)

Abbreviations: BICR, blinded independent central review; BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; KM, Kaplan-Meier; N/A, not available; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PlatChemo, patients previously treated with platinum-based chemotherapy; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TrtNaive, treatment-naïve patients.

Table 82 Results per study (KEYNOTE-189)

Results of [KEYNOTE-189 (NCT02578680)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS per RECISTv1.1 byBICR (DCO 8 March 2022)	Pembro+PC	410	8.8 months (7.6-9.2)	3.9 months	N/A	N/A	HR: 0.52	0.43-0.64	<0.00001	PFS was defined as the time from randomization to the first documented PD or death due to any cause, whichever occurred first. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. The PFS per RECIST 1.1 is presented. Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs.	Gandhi et al. (75)
	Control	206	4.9 months (4.7-5.5)								Gandhi et al. (75)

Results of [KEYNOTE-189 (NCT02578680)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										carboplatin) & smoking status (never vs. former/current). Pembrolizumab=numerator; Control=denominator.	
OS (DCO 8 March 2022)	Pembro+PC	410	N/A (N/A-N/A)	N/A	N/A	N/A	HR: 0.49	0.38-0.64	<0.00001	OS was defined as the time from randomization to death due to any cause. Participants without documented death at the time of the interim analysis were censored at the date of the last follow-up. The OS is presented. Based on Cox regression model with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) & smoking status (never vs. former/current). Pembrolizumab=numerator; Control=denominator.	Gandhi et al. (75)
	Control	206	11.3 months (8.7-15.1)								Gandhi et al. (75)

Results of [KEYNOTE-189 (NCT02578680)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
ORR per RECIST v1.1 by BICR and safety (DCO 8 March 2022)	Pembro+PC	410	48.3 (43.4-53.2)	28.4	N/A	N/A	N/A	N/A	N/A	ORR was defined as the percentage of participants in the analysis population who had a Complete Response (CR: Disappearance of all target lesions) or a Partial Response (PR: ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters) per RECIST 1.1. The percentage of participants who experienced a CR or PR is presented. Miettinen and Nurminen method with treatment as a covariate stratified by PD-L1 status (≥1% vs. <1%), platinum chemotherapy (cisplatin vs. carboplatin) & smoking status (never vs. former/current). Pembrolizumab=numerator; Control=denominator. In Difference in Percentage vs. Control	Garassino et al. (46)
	Control	206	19.9 (14.7-26.0)								Garassino et al. (46)

Results of [KEYNOTE-189 (NCT02578680)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
DOR per RECIST v1.1 by BICR and safety (DCO 8 March 2022)	Pembro+PC	410	12.7 (1.1-68.3)	5.6 months	N/A	N/A	N/A	N/A	N/A	For participants who demonstrated a confirmed CR or PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1, DOR was defined as the time from first documented evidence of a CR or PR until PD or death. DOR for participants who had not progressed or died at the time of analysis was to be censored at the date of their last tumour assessment. Per RECIST 1.1, PD was defined as ≥20% increase in the sum of diameters of target lesions. In addition to the relative increase of 20%, the sum must also have demonstrated an absolute increase of ≥5 mm. Note: The appearance of one or more new lesions was also considered PD. DOR assessments were based on blinded central imaging review	Garassino et al. (46)
	Control	206	7.1 (2.4-31.5)								Garassino et al. (46)

Results of [KEYNOTE-189 (NCT02578680)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										with confirmation. The DOR per RECIST 1.1 for all participants who experienced a confirmed CR or PR is presented. This is on basis of On the basis of Kaplan-Meier estimate	

Abbreviations: BICR, blinded independent central review; CR, complete response; DOR, duration of response; HR, hazard ratio; N/A, not applicable; ORR, objective response rate; OS, overall survival; PD, progressive disease; Pembro+PC, pembrolizumab + pemetrexed + platinum chemotherapy followed by pembrolizumab + pemetrexed; PFS, progression-free survival; PR, partial response; RECIST, response evaluation criteria in solid tumours.

Appendix C. Comparative analysis of efficacy

Full information is provided in Section 7.

Table 83 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome			Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Weighted / unweighted	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
Median OS	Weighted	LIBRETTO-001 (data cutoff January 2023) KEYNOTE-189 (data cutoff 8 March 2022)	[redacted]	NE	NE	[redacted]	[redacted]	[redacted]	Cox proportional hazards model was used to estimate the hazard ratio	No
Median PFS	Weighted	LIBRETTO-001 (data cutoff January 2023) KEYNOTE-189 (data cutoff 8 March 2022)	[redacted]	NE	NE	[redacted]	[redacted]	[redacted]	Cox proportional hazards model was used to estimate the hazard ratio	No
Median OS	Unweighted	LIBRETTO-001 (data cutoff January 2023) KEYNOTE-189 (data cutoff 8 March 2022)	[redacted]	NE	NE	[redacted]	[redacted]	[redacted]	Cox proportional hazards model was used to estimate the hazard ratio	Yes

Outcome	Weighted / unweighted	Studies included in the analysis	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 PFS	Unweighted	LIBRETTO-001 (data cutoff January 2023) KEYNOTE-189 (data cutoff 8 March 2022)	[redacted]	NE	NE	[redacted]	[redacted]	[redacted]	Cox proportional hazards model was used to estimate the hazard ratio	Yes

Abbreviations:
Source: Eli Lilly, data on file (2024) ITC / MAIC report

Appendix D. Extrapolation

Because the OS data from LIBRETTO-431 are particularly immature and data for the control arm are confounded by treatment switching, additional scenarios using different survival data and approaches are available in the model. These include:

- OS survival data from LIBRETTO-431, adjusted for treatment switching and using clinical expert expectation for survival.
- More mature OS data from LIBRETTO-001 and an estimated control arm based on the KEYNOTE-189 trial (Section 8), with the following option:

  L-001 & HR vs. KN-189 pem+plat+pembro (latest K-189 data cut – functions fitted to L-001 only): This approach uses the most recent data cut (8 March 2022) from the KEYNOTE-189 trial and focuses on the pembrolizumab arm to provide a more conservative estimate (46). The hazard ratio (HR) for selpercatinib versus the pemetrexed + platinum + pembrolizumab arm of the KEYNOTE-189 trial was estimated using the most recent available data cut for KEYNOTE-189 (aggregated data were used because the patient-level data were not available for the latest data cut). The HR was applied to the proportional hazard survival functions fitted to the LIBRETTO-001 OS data only (i.e., the KEYNOTE-19 data were not included in the survival analysis). Options are available to apply an HR estimated after MAIC adjustment and an HR without any adjustment (naïve indirect comparison), which provides a more conservative estimate. This approach is applied as the base case in the cost-effectiveness model.

- For the approaches using KEYNOTE-189 data, the model assumes that outcomes are equivalent with and without pembrolizumab.

D.1 Extrapolation of Overall Survival

Extrapolation of OS is based on more mature OS data from LIBRETTO-001 and an estimated control arm based on the KEYNOTE-189 trial.

D.1.1 Data input

Overall survival data for the pemetrexed + platinum + pembrolizumab arm were digitised, and patient-level data were simulated. A MAIC was performed (Signorovitch et al 2019) to match the LIBRETTO-001 population characteristics to those of the KEYNOTE-189 trial. Hazard ratios were estimated using a Cox model comparing the adjusted and unadjusted OS for selpercatinib with those for pemetrexed + platinum + pembrolizumab.
The HR was applied to proportional hazards survival functions fitted to the LIBRETTO-001 OS data to estimate OS for pemetrexed + platinum + pembrolizumab. Options are available in the CEM to apply the HR estimated after MAIC adjustment and the HR without any adjustment (naïve indirect comparison), which provides a more conservative estimate, refer to Section 7, Table 33 and Table 34.

Results from the MAIC for selpercatinib (LIBRETTO-001) and pemetrexed + platinum + pembrolizumab (KEYNOTE-189, most recent data cut) are provided in Section 7. Variance ratio and standardised differences plots are also available.

Table 37 below presents the key assumptions associated with the extrapolation of OS derived from the IPD from the SAS1 (n=69) population in LIBRETTO-001 and aggregate data from the ITT (n=410) population in KEYNOTE-189.

D.1.2 Model

For the base-case analysis, in order to use the latest data available for the KEYNOTE-189 study to the selpercatinib OS function, a range of parametric proportional hazards functions were fitted to the selpercatinib data from LIBRETTO-001 for this analysis (including Exponential, Weibull, and Gompertz).

D.1.3 Proportional hazards

The HR was applied to proportional hazards survival functions fitted to the LIBRETTO-001 OS data to estimate OS for pemetrexed + platinum + pembrolizumab. Schoenfeld residuals and log-cumulative hazard plots without MAIC are presented in Figure 29 and Figure 30. The global test of Schoenfeld residuals over time yielded a non-significant result (p = 0.351). Schoenfeld residuals and log-cumulative hazard plots after MAIC are presented in Figure 31 and Figure 32. Similarly, the global test of Schoenfeld residuals over time produced a non-significant outcome (p = 0.301)

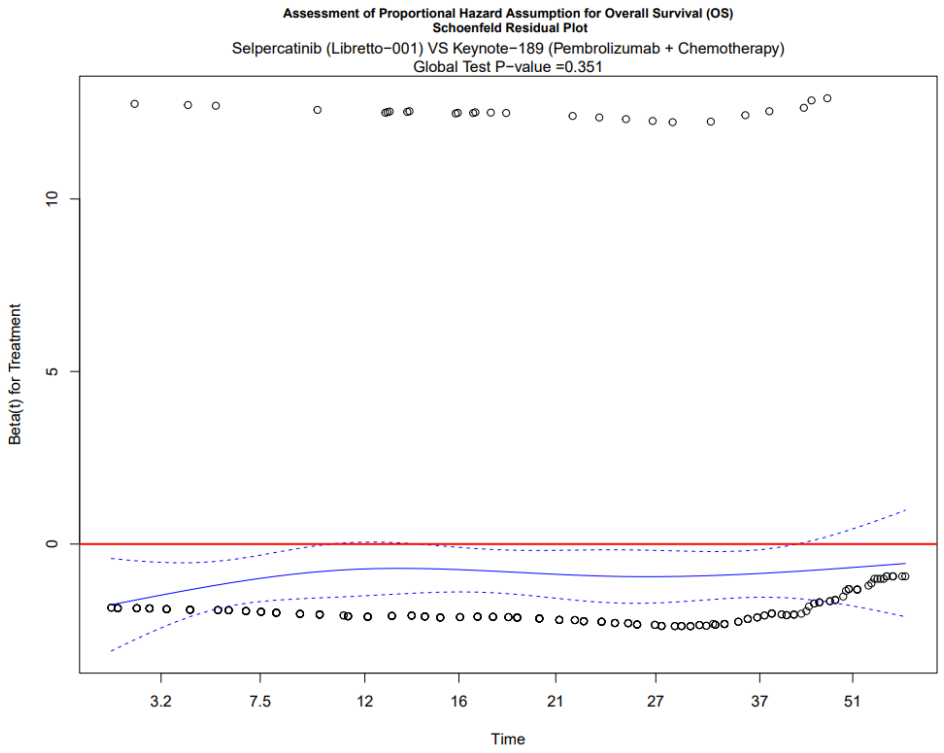


Figure 29 Schoenfeld residual plot – overall survival

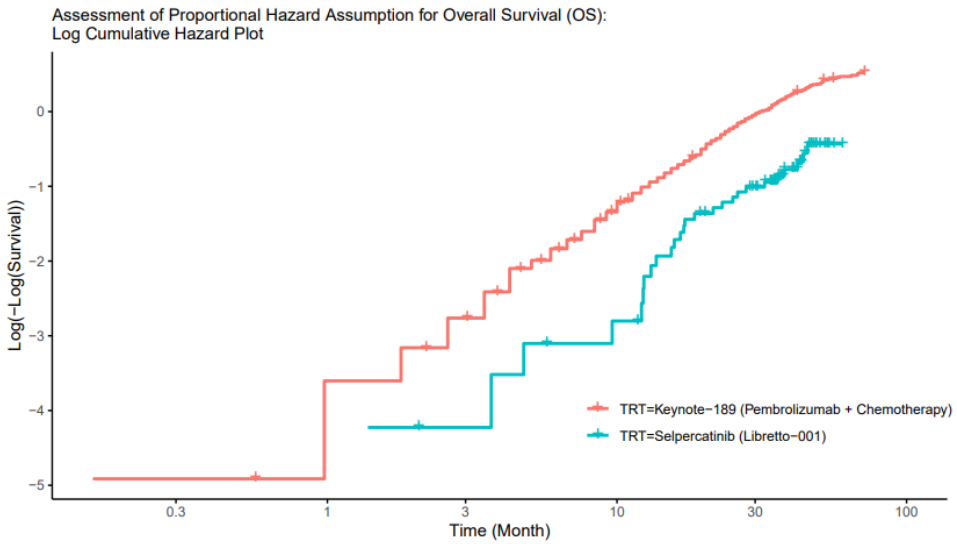


Figure 30 Log cumulative hazard plot – overall survival

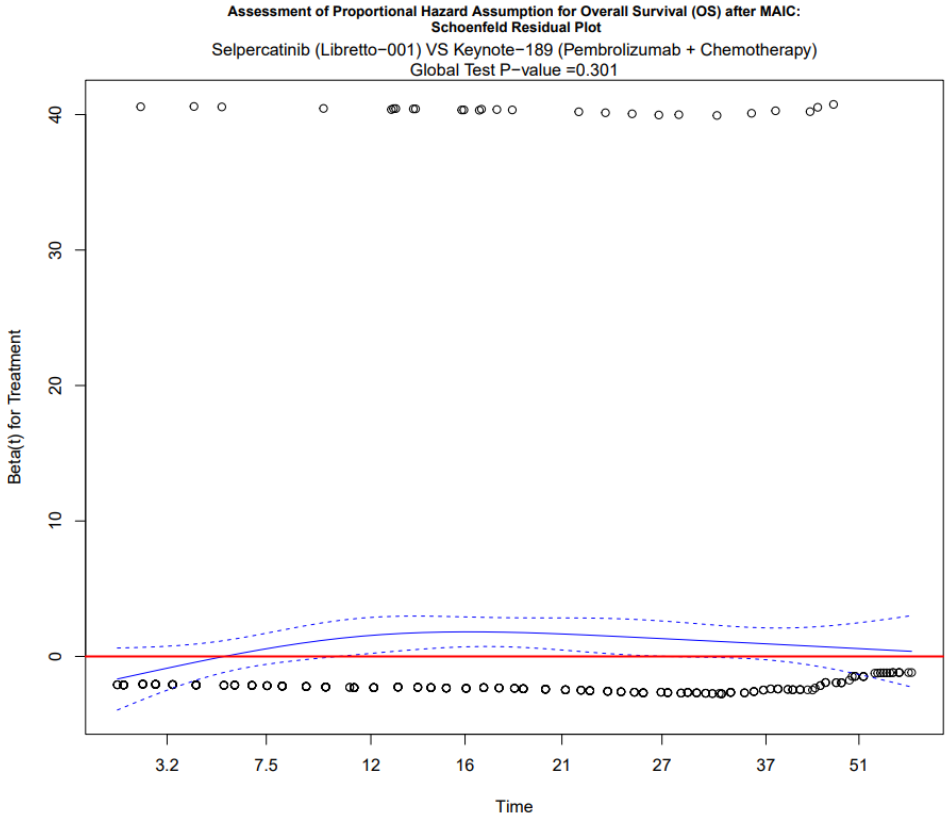


Figure 31 Schoenfeld residual plot – overall survival after MAIC

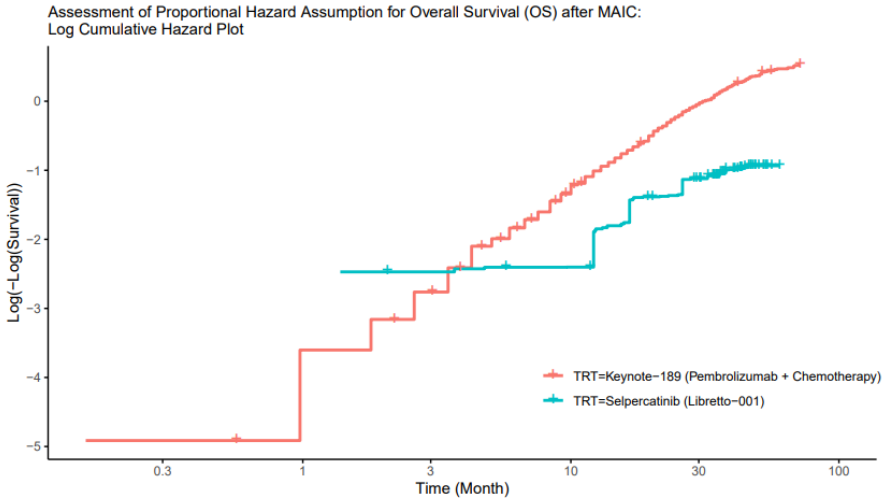


Figure 32 Log cumulative hazard plot – overall survival after MAIC

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

For OS, the fit test results are presented in Table 84 below.

Table 84 Overall Survival Model Evaluation Results for the Selpercatinib

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	284.5	286.7	1	1
Weibull	285.2	289.7	2	2
Gompertz	286.1	290.6	3	3

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: Eli Lilly 2024 (MAIC report), data on file

The Exponential distribution provides the best statistical fit, both based on AIC and BIC statistics. However, the statistical fits for all included distributions are quite close to each other.

D.1.5 Evaluation of visual fit

Visual fit to the KM data is presented in figures below.

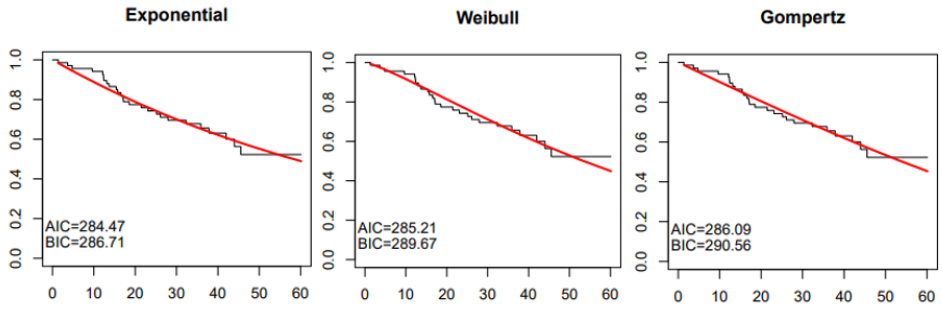


Figure 33 Overall survival proportional hazard function fit for the selpercatinib arm (LIBRETTO-001 13 Jan 2023)

AIC = Akaike information criterion; BIC = Bayesian information criterion.
Source: Lilly data on file (11 July 2024): tx-naive-paramsurv-unstratified-OS.

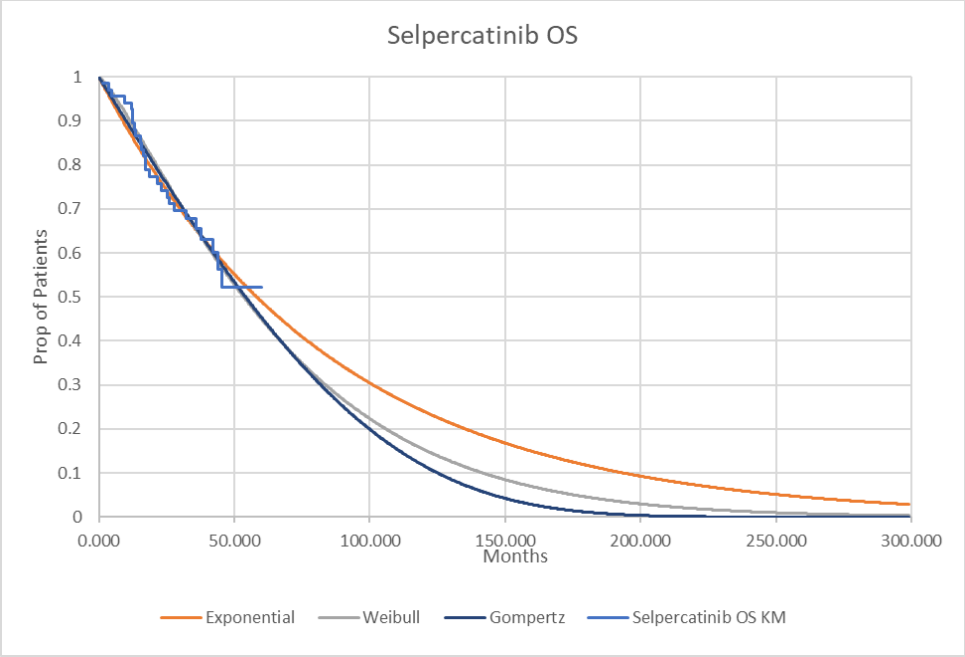


Figure 34 Extrapolation models for overall survival for the selpercatinib arm (LIBRETTO-001)

Abbreviations: OS, overall survival; KM, Kaplan-Meier
Source: Eli Lilly data on file 2024

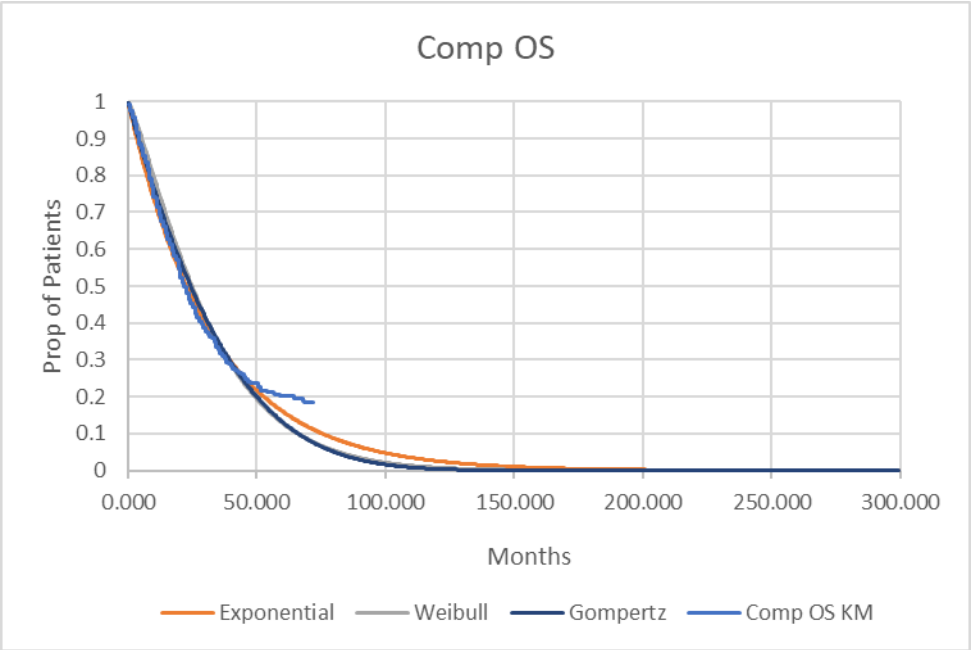


Figure 35 Extrapolation models for overall survival for the comparator arm (HR for LIBRETTTO-001 vs KEYNOTE-189 pembrolizumab arm (not MAIC adjusted) applied to selpercatinib function)

Abbreviations: Comp, pemetrexed +platinum + pembrolizumab arm; OS, overall survival; KM, Kaplan-Meier
Source: Eli Lilly data on file 2024

D.1.6 Evaluation of hazard functions

Not applicable

D.1.7 Validation and discussion of extrapolated curves

Validation of the curve selection cannot be provided. However, based on communication with clinical experts, the extrapolated OS results presented in Section 8.1.1 (refer to the extrapolation models) can be considered clinically plausible when looking on the following clinical expert survival estimates below in Table 85. The estimates provided by clinical experts are based on personal communications (clinical expert meetings) conducted in June 2022. Please also refer to the extrapolation section regarding PFS.

Table 85 Clinical expert opinion for survival prediction beyond trial follow-up - OS

Time point (years)	Selpercatinib OS (%)		Pemetrexed + platinum ± pembrolizumab OS (%)	
	CE1	CE2	CE1	CE2
3	NA	60	25	40
5	50	45	6-7	17
10	20	20	< 1	5
20	5-10	1-2	< 1	0
Median (years)	60-72	50	12-18	24

Source: personal communications, clinical expert meetings June 2022

D.1.8 Adjustment of background mortality

Overall survival is capped in the model using general population mortality rates (provided by the DMC), adjusted using a mortality ratio for patients with cancer (mortality ratio of 1.00).

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

Extrapolation of PFS is based on LIBRETTO-431 (data cutoff 1 May 2023). PFS is based on the BICR data on PFS. The base case analysis uses the ITT population. However, survival appears to be better in the patient population that was intended to receive pembrolizumab. It is possible that patients benefited from this treatment and/or the physicians selected healthier patients to receive this treatment.

Table 86 Hazard ratios for selpercatinib versus the control for PFS (BICR) by treatment and patient populations (intent to prescribe pembrolizumab)

Population	Selpercatinib, n	Pembro+PC, n	Hazard ratio (95% CI)
ITT	159	102	0.493 (0.343-0.710)
Intent to prescribe pembrolizumab	159	83	0.488 (0.327-0.726)
Intent not to prescribe pembrolizumab	30	19	0.495 (0.194-1.259)

Abbreviations: BICR = blinded independent central review; CI = confidence interval; ITT = intent to treat; PFS = progression-free survival.

For further information, please refer to Appendix K.

D.2.2 Model

A variety of parametric models has been included and explored to extrapolate PFS. Fitted to the LIBRETTO-431 data. Parametric models include:

- Exponential
- Weibull
- Log-normal
- Log-logistic
- Gompertz
- Gamma
- Spline/knot = 1
- Spline/knot = 2

- Spline/knot = 3
- Gen-gamma
- Stratified Weibull
- Stratified log-normal
- Stratified log-logistic
- Stratified Gompertz
- Stratified gamma
- Stratified spline/knot = 1
- Stratified spline/knot = 2
- Stratified spline/knot = 3
- Stratified Gen-gamma

D.2.3 Proportional hazards

No plots or statistical tests are currently provided.

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

For PFS, the fit test results are presented in Table 87 below.

Table 87 Progression-Free Survival Model Evaluation Results for the Selpercatinib and Control Arm (Pemetrexed Plus Platinum Plus Pembrolizumab)

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	1,009.3	1,020.0	2	1
Weibull	1,009.7	1,024.0	4	4
Log-normal	1,016.5	1,030.8	16	12
Log-logistic	1,008.3	1,022.6	1	2
Gompertz	1,011.0	1,025.3	7	5
Gamma	1,009.4	1,023.6	3	3
Spline/knot = 1	1,011.2	1,029.0	8	8
Spline/knot = 2	1,012.9	1,034.3	12	13
Spline/knot = 3	1,014.2	1,039.2	15	17
Gengamma	1,010.9	1,028.8	6	7
Stratified Weibull	1,011.7	1,029.5	10	10
Stratified log-normal	1,017.1	1,034.9	17	14
Stratified log-logistic	1,009.9	1,027.8	5	6
Stratified Gompertz	1,012.8	1,030.6	11	11
Stratified gamma	1,011.4	1,029.2	9	9
Stratified spline/knot = 1	1,013.8	1,038.8	13	15
Stratified spline/knot = 2	1,017.5	1,049.5	18	18
Stratified spline/knot = 3	1,020.4	1,059.6	19	19
Stratified gengamma	1,014.1	1,039.0	14	16

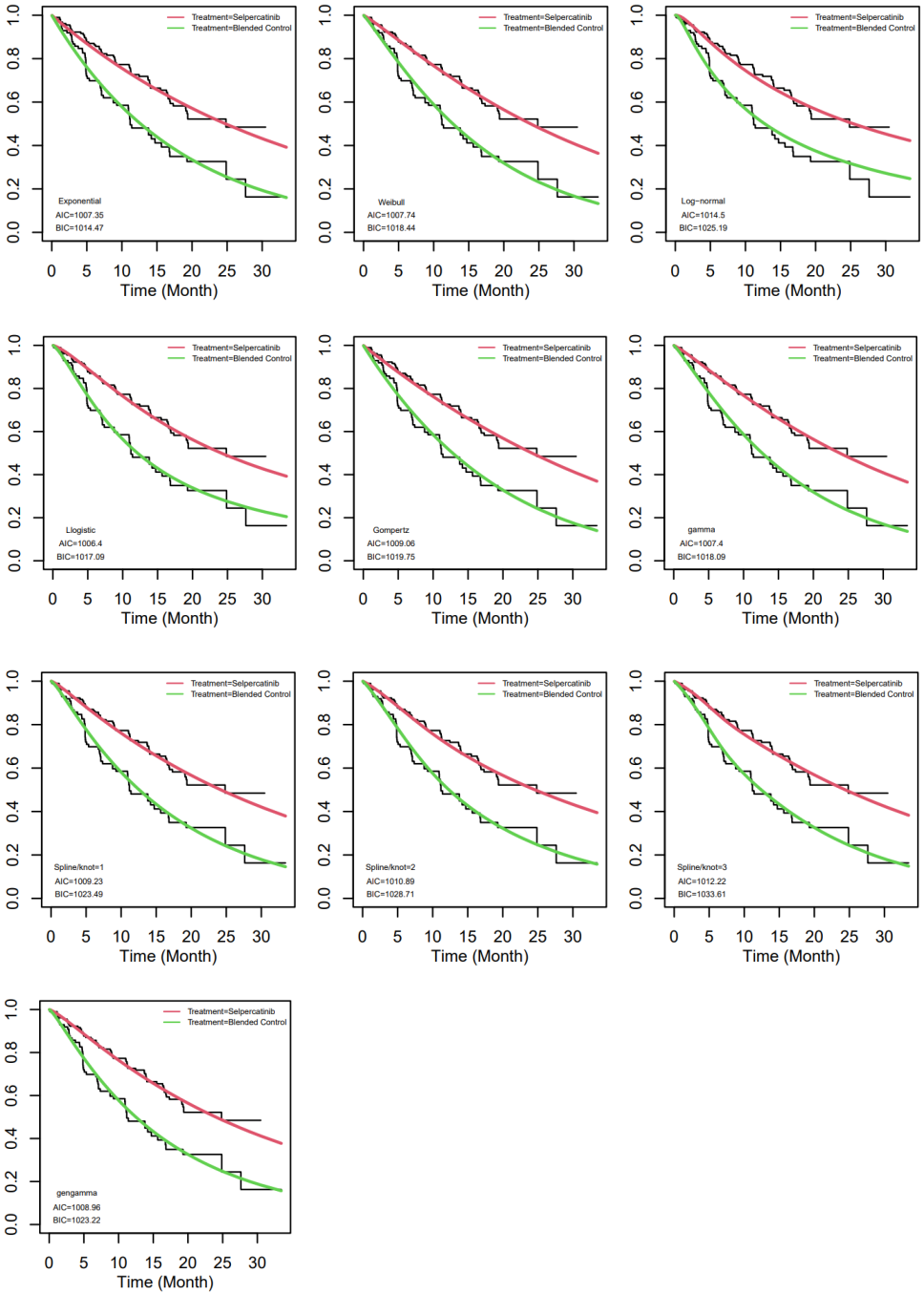
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: Eli Lilly, data on file

The Log-logistic distribution provides the best AIC fit, while the Exponential distribution provides the best BIC fit.

D.2.5 Evaluation of visual fit

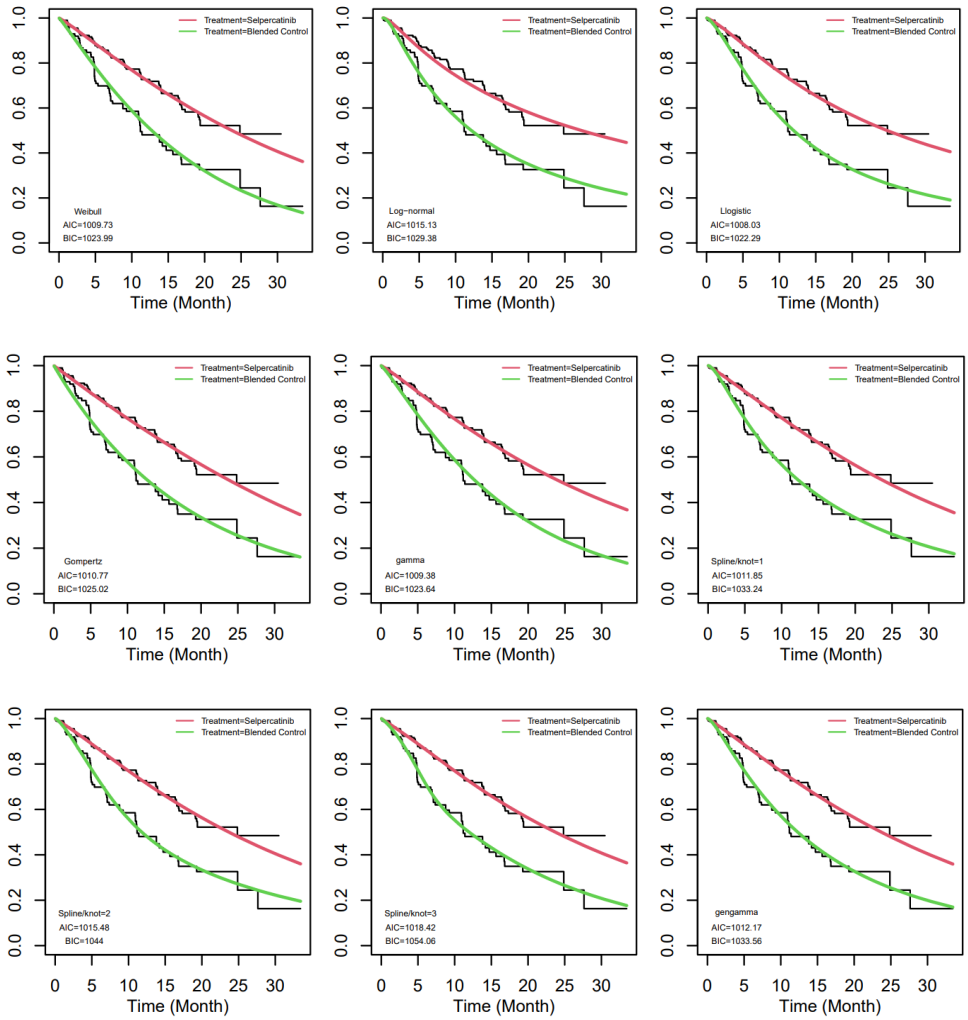
For PFS, the visual fit to the KM data is presented in the following figures below.

(A) Unstratified functions (fitted with a treatment indicator [Selpercatinib, control] and intention to treat with pembrolizumab as a covariate)



AIC = Akaike information criterion; BIC = Bayesian information criterion.
Source: Eli Lilly data on file (14 March 2024)

(B) Stratified functions (selpercatinib treatment included as stratification factor):



AIC = Akaike information criterion; BIC = Bayesian information criterion.
Source: Eli Lilly data on file (14 March 2024)

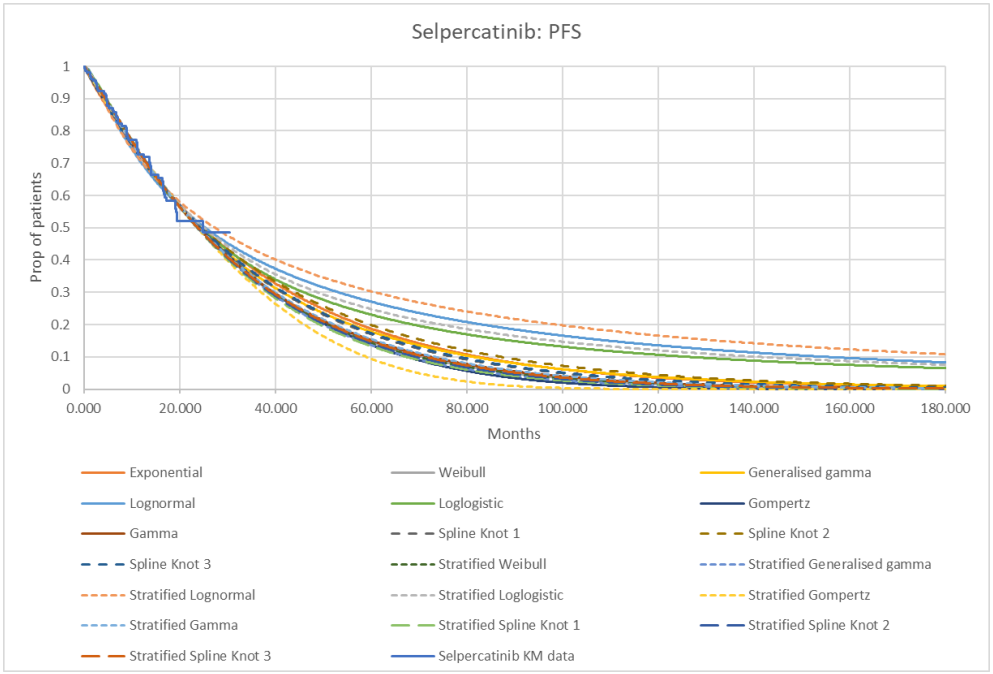


Figure 36 Extrapolation models for progression-free survival for the selpercatinib arm (LIBRETTO-431)

Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier

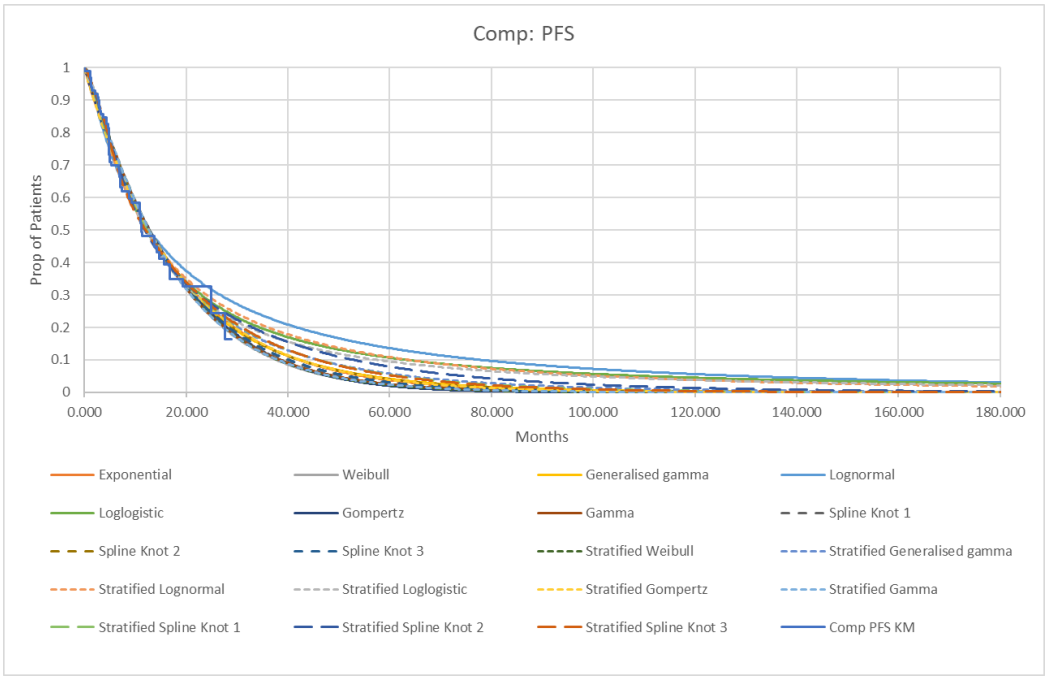


Figure 37 Extrapolation models for progression-free survival for the comparator arm (LIBRETTO-431)

Abbreviations: Comp, pemetrexed + platinum + pembrolizumab, ; PFS, progression-free survival; KM, Kaplan-Meier

D.2.6 Evaluation of hazard functions

Not applicable

D.2.7 Validation and discussion of extrapolated curves

Validation of the curve selection cannot be provided. However, as previously mentioned, clinical expert meetings were conducted in June 2022, resulting in some survival predictions for both OS and PFS. Based on the communication with clinical experts, the extrapolated PFS results presented in Section 8.1.1 (refer to the extrapolation models) can be considered clinically plausible when looking on the following clinical expert survival estimates below in Table 88.

Table 88 Clinical expert opinion for survival prediction beyond trial follow-up - PFS

Time point (years)	Selpercatinib PFS (%)		Pemetrexed + platinum ± pembrolizumab PFS (%)	
	CE1	CE2	CE1	CE2
3	30	30-35	NA	15
5	15	15	< 5	5
10	5	3	< 1	0
20	5	1-2	< 1	0
Median (years)	21	See KM data	6-10	11

Source: personal communications, clinical expert meetings June 2022

D.2.8 Adjustment of background mortality

Progression-free survival and TTD are capped by OS in the model.

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.

D.3 Extrapolation of Time-to-Treatment Discontinuation

D.3.1 Data input

Extrapolation of TDD is based on LIBRETTO-431 (data cutoff 1 May 2023). TTD is based on the BICR data on DOR. The base case analysis uses the ITT population. The treatment duration for selpercatinib and comparators was predicted using parametric functions fitted to the TTD in LIBRETTO-431 (treatment exposure in the LIBRETTO-431 trial data may not be used directly because many patients had not discontinued treatment during trial follow-up). In the base case analysis, the function selected for TTD for selpercatinib is “use PFS curve”

D.3.2 Model

Refer to PFS section.

D.3.3 Proportional hazards

No plots or statistical tests are currently provided.

D.3.4 Evaluation of statistical fit (AIC and BIC)

For TTD, the fit test results are presented in Table 89 below.

Table 89 Time-to-treatment discontinuation Model Evaluation Results for the Selpercatinib and Control Arm (Pemetrexed Plus Platinum Plus Pembrolizumab)

Function	AIC	BIC	Rank (AIC)	Rank (BIC)
Exponential	1,111.1	1,118.2	1	1
Weibull	1,113.0	1,123.6	2	2
Log-normal	1,131.6	1,142.2	18	16
Log-logistic	1,116.3	1,126.9	11	5
Gompertz	1,113.0	1,123.7	2	3
Gamma	1,113.0	1,123.7	2	3
Spline/knot = 1	1,114.6	1,128.8	5	6
Spline/knot = 2	1,116.2	1,133.9	10	12
Spline/knot = 3	1,118.2	1,139.4	13	13
Gengamma	1,115.0	1,129.2	7	8
Stratified Weibull	1,115.0	1,129.2	7	8
Stratified Log-normal	1,133.1	1,147.3	19	17
Stratified Log-logistic	1,117.8	1,132.0	12	11
Stratified Gompertz	1,114.9	1,129.0	6	7
Stratified Gamma	1,115.0	1,129.2	7	8
Stratified Spline/knot = 1	1,118.6	1,139.9	14	14
Stratified Spline/knot = 2	1,120.3	1,148.6	16	18
Stratified Spline/knot = 3	1,122.9	1,158.4	17	19
Stratified Gengamma	1,118.7	1,140.0	15	15

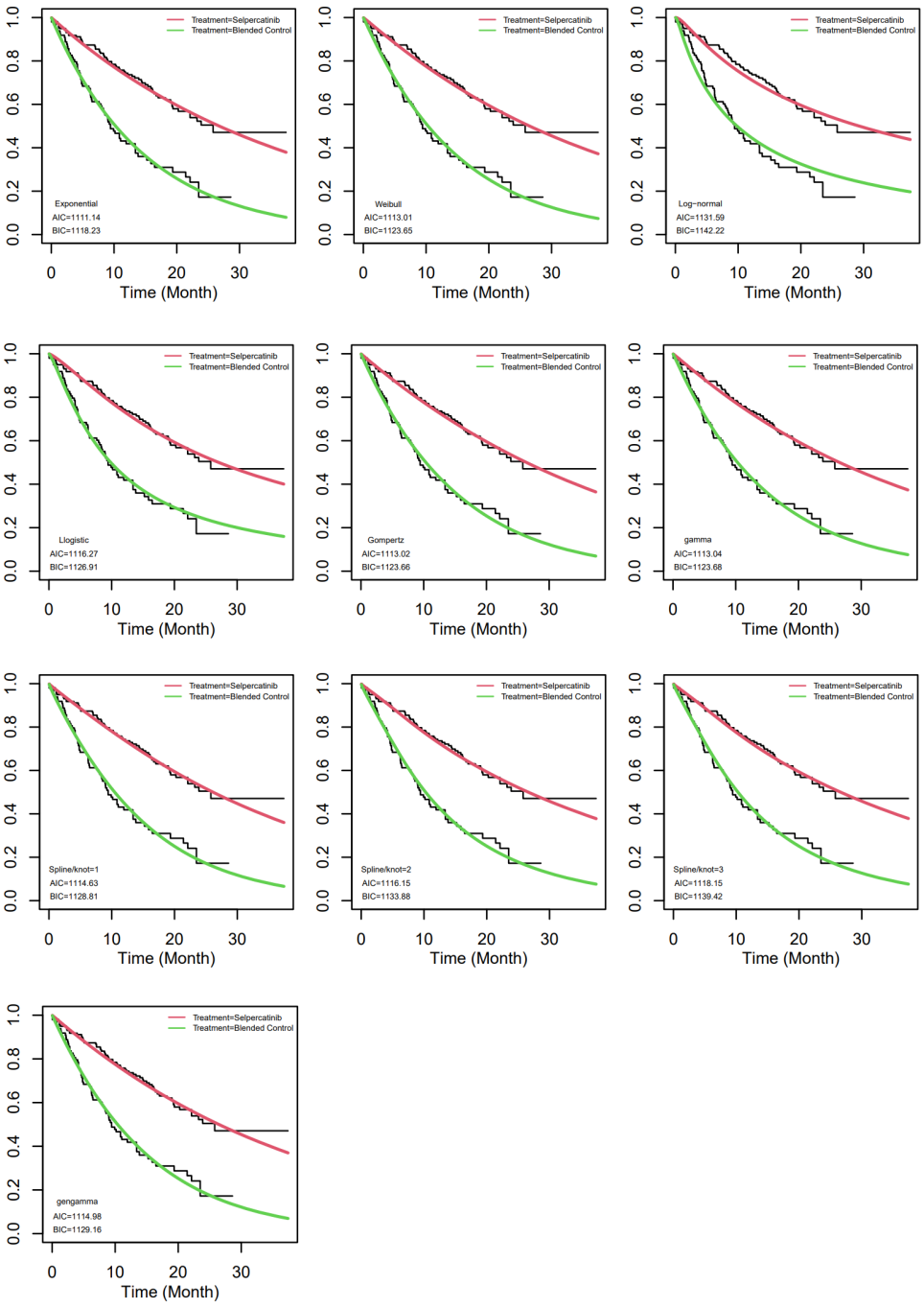
Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion
Source: Eli Lilly, data on file

The Exponential distribution provides the best statistical fit, both based on AIC and BIC statistics.

D.3.5 Evaluation of visual fit

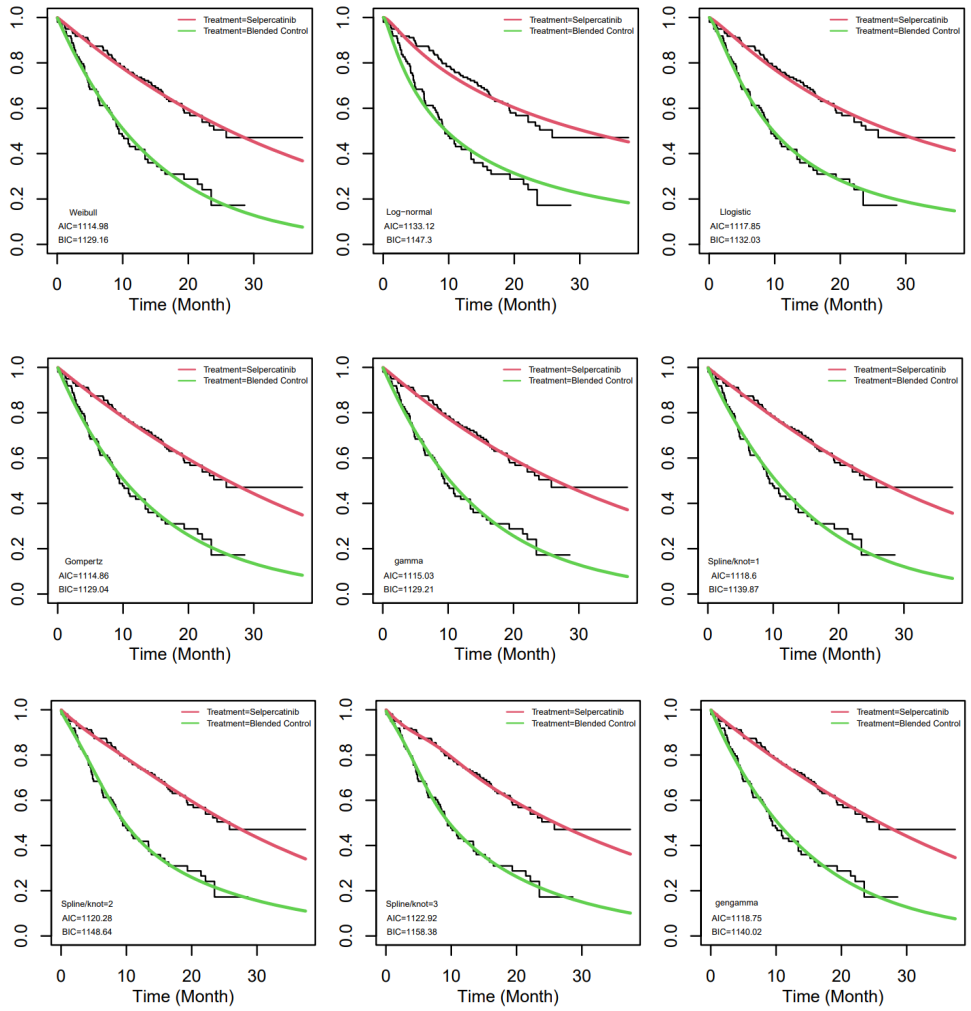
For TTD, the visual fit to the KM data is presented in the following figures below.

(A) Unstratified functions (fitted with a treatment indicator [Selpercatinib, control] and intention to treat with pembrolizumab as a covariate)



AIC = Akaike information criterion; BIC = Bayesian information criterion.
Source: Eli Lilly data on file (14 March 2024)

(B) Stratified functions (selpercatinib treatment included as stratification factor):



AIC = Akaike information criterion; BIC = Bayesian information criterion.

Source: Eli Lilly data on file (14 March 2024)

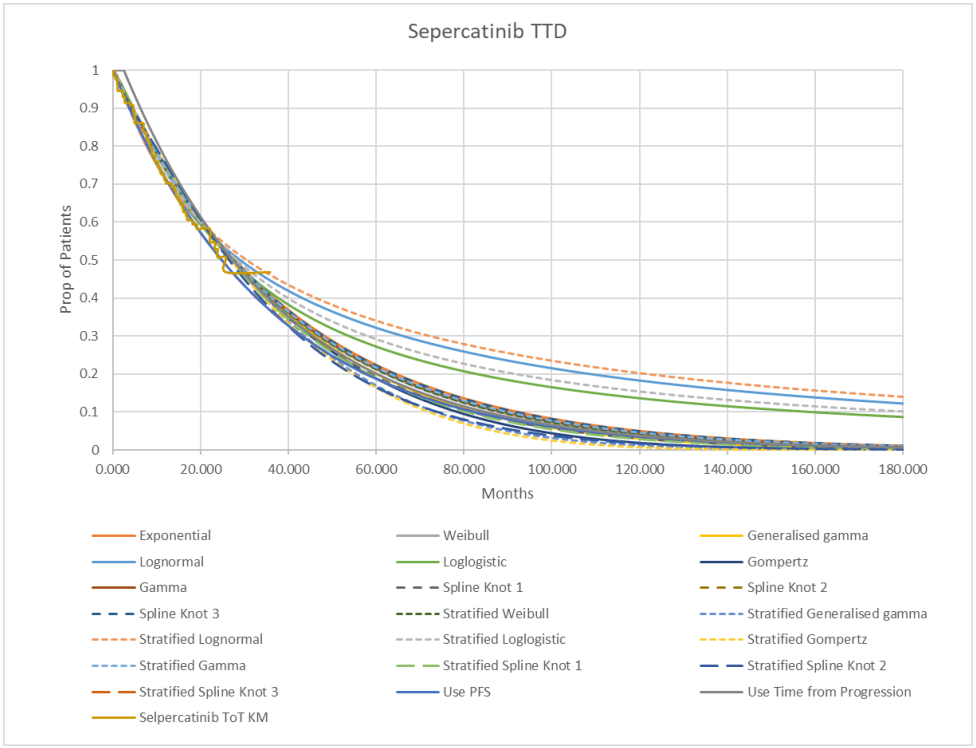


Figure 38 Extrapolation models for time to treatment discontinuation (TTD) for the sepercatinib arm (LIBRETTO-431)

Abbreviations: KM, Kaplan-Meier; TTD, time to treatment discontinuation

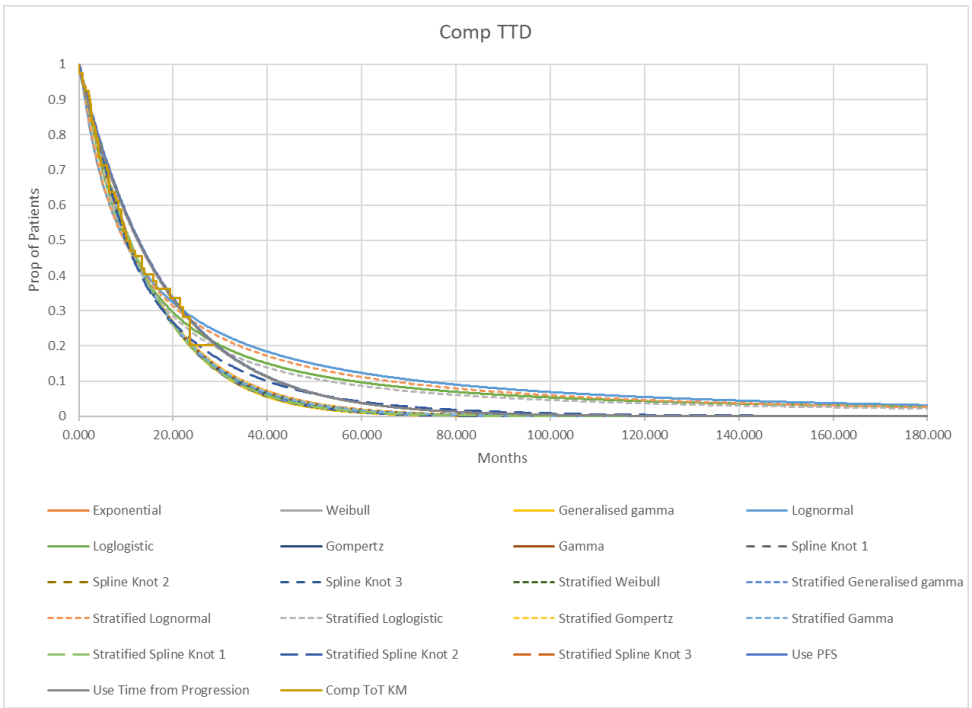


Figure 39 Extrapolation models for time to treatment discontinuation (TTD) for the comparator arm (LIBRETTO-431)

Abbreviations: Comp, pemetrexed + platinum + pembrolizumab; KM, Kaplan-Meier; TTD, time to treatment discontinuation

D.3.6 Evaluation of hazard functions

Not applicable

D.3.7 Validation and discussion of extrapolated curves

Not available

D.3.8 Adjustment of background mortality

Progression-free survival and TTD are capped by OS in the model.

D.3.9 Adjustment for treatment switching/cross-over

Not applicable.

D.3.10 Waning effect

Not applicable.

D.3.11 Cure-point

Not applicable.

Appendix E. Serious adverse events

All SAEs are reported in Table 90. In this application, as stated, safety data (AEs) are presented as TEAEs.

Table 90 Serious adverse events

Preferred term	Selpercatinib (N=158)	Control arm (N=98)
Subjects with >=1 serious TEAE	**55 (34.8)**	**23 (23.5)**
Pleural effusion	7 (4.4)	0 (0.0)
Hepatic function abnormal	4 (2.5)	0 (0.0)
Ascites	3 (1.9)	0 (0.0)
Cholecystitis	3 (1.9)	0 (0.0)
Pneumonia	3 (1.9)	2 (2.0)
Decreased appetite	2 (1.3)	0 (0.0)
Dyspnoea	2 (1.3)	1 (1.0)
Immune-mediated hepatic disorder	2 (1.3)	0 (0.0)
Malignant pleural effusion	2 (1.3)	1 (1.0)
Myocardial infarction	2 (1.3)	1 (1.0)
Pericardial effusion	2 (1.3)	0 (0.0)
Pyrexia	2 (1.3)	2 (2.0)
Abdominal pain	1 (0.6)	0 (0.0)
Acute kidney injury	1 (0.6)	0 (0.0)
Acute respiratory failure	1 (0.6)	0 (0.0)
Alanine aminotransferase increased	1 (0.6)	0 (0.0)
Anaphylactic shock	1 (0.6)	0 (0.0)
Angina pectoris	1 (0.6)	0 (0.0)
Aspartate aminotransferase increased	1 (0.6)	0 (0.0)
Back pain	1 (0.6)	0 (0.0)
COVID-19	1 (0.6)	0 (0.0)
COVID-19 pneumonia	1 (0.6)	0 (0.0)
Cardiac arrest	1 (0.6)	0 (0.0)
Chylothorax	1 (0.6)	0 (0.0)
Dermatitis	1 (0.6)	0 (0.0)
Dizziness	1 (0.6)	0 (0.0)
Drug eruption	1 (0.6)	0 (0.0)
Enterocolitis	1 (0.6)	0 (0.0)
Femur fracture	1 (0.6)	0 (0.0)
Gastritis erosive	1 (0.6)	0 (0.0)
Haematemesis	1 (0.6)	0 (0.0)

Hepatic enzyme increased	1 (0.6)	0 (0.0)
Hyperglycaemia	1 (0.6)	1 (1.0)
Hypersensitivity	1 (0.6)	0 (0.0)
Hypertension	1 (0.6)	0 (0.0)
Hypokalaemia	1 (0.6)	0 (0.0)
Hyponatraemia	1 (0.6)	0 (0.0)
Ileus	1 (0.6)	0 (0.0)
Infectious pleural effusion	1 (0.6)	0 (0.0)
Inguinal hernia	1 (0.6)	0 (0.0)
Interstitial lung disease	1 (0.6)	0 (0.0)
Intestinal obstruction	1 (0.6)	2 (2.0)
Jugular vein thrombosis	1 (0.6)	0 (0.0)
Malaise	1 (0.6)	0 (0.0)
Malnutrition	1 (0.6)	0 (0.0)
Meningitis	1 (0.6)	0 (0.0)
Myocardial ischaemia	1 (0.6)	0 (0.0)
Oedema peripheral	1 (0.6)	0 (0.0)
Pancreatitis	1 (0.6)	0 (0.0)
Peritonitis	1 (0.6)	0 (0.0)
Platelet count decreased	1 (0.6)	2 (2.0)
Pneumonia viral	1 (0.6)	0 (0.0)
Pulmonary embolism	1 (0.6)	1 (1.0)
Respiratory failure	1 (0.6)	0 (0.0)
Soft tissue infection	1 (0.6)	0 (0.0)
Sudden death	1 (0.6)	0 (0.0)
Urinary tract infection	1 (0.6)	0 (0.0)
Urosepsis	1 (0.6)	0 (0.0)
Venous thrombosis limb	1 (0.6)	0 (0.0)
Volvulus	1 (0.6)	0 (0.0)
Anaemia	0 (0.0)	2 (2.0)
Asthenia	0 (0.0)	1 (1.0)
Atrial fibrillation	0 (0.0)	1 (1.0)
Blood creatinine increased	0 (0.0)	1 (1.0)
Cardiac failure	0 (0.0)	1 (1.0)
Chest pain	0 (0.0)	1 (1.0)
Electrocardiogram T wave abnormal	0 (0.0)	1 (1.0)
Electrolyte imbalance	0 (0.0)	1 (1.0)
Erysipelas	0 (0.0)	1 (1.0)
Febrile neutropenia	0 (0.0)	1 (1.0)
Herpes zoster	0 (0.0)	1 (1.0)
Hypocalcaemia	0 (0.0)	1 (1.0)

Hypomagnesaemia	0 (0.0)	1 (1.0)
Neutropenia	0 (0.0)	2 (2.0)
Neutrophil count decreased	0 (0.0)	1 (1.0)
Pancreatitis acute	0 (0.0)	1 (1.0)
Procedural haemorrhage	0 (0.0)	1 (1.0)
Small intestinal haemorrhage	0 (0.0)	1 (1.0)
Spinal cord compression	0 (0.0)	2 (2.0)
Transitional cell carcinoma	0 (0.0)	1 (1.0)

Source: Eli Lilly data on file 2023(76)

Appendix F. Health-related quality of life

LIBRETTO-431

As previously reported, the available rates from the EQ-5D-5L collection in LIBRETTO-431 is reported here in the following table.

Table 91 Available rates, PRO evaluable population, both arms

Time point	Selpercatinib (N=159) Number completed N	% of PRO evaluable	Control arm (N=102) Number completed N	% of PRO evaluable
Week 1	147	92.5%	87	85.3%
Week 4	139	87.4%	82	80.4%
Week 7	126	79.2%	75	73.5%
Week 10	124	78.0%	74	72.5%
Week 13	126	79.2%	67	65.7%
Week 16	129	81.1%	69	67.6%
Week 19	126	79.2%	64	62.7%
Week 22	129	81.1%	59	57.8%
Week 25	125	78.6%	56	54.9%
Week 28	123	77.4%	54	52.9%
Week 31	125	78.6%	52	51.0%
Week 34	121	76.1%	49	48.0%
Week 37	114	71.7%	43	42.2%
Week 40	112	70.4%	41	40.2%
Week 43	106	66.7%	39	38.2%
Week 46	101	63.5%	35	34.3%
Week 49	96	60.4%	32	31.4%
Week 52	85	53.5%	29	28.4%
Week 55	86	54.1%	27	26.5%
Week 58	77	48.4%	23	22.5%
Week 61	84	52.8%	20	19.6%
Week 64	74	46.5%	19	18.6%
Week 67	72	45.3%	18	17.6%
Week 70	68	42.8%	16	15.7%
Week 73	54	34.0%	14	13.7%
Week 76	55	34.6%	13	12.7%
Week 79	54	34.0%	12	11.8%
Week 82	56	35.2%	13	12.7%
Week 85	48	30.2%	13	12.7%
Week 88	44	27.7%	12	11.8%
Week 91	35	22.0%	11	10.8%
Week 94	35	22.0%	10	9.8%
Week 97	33	20.8%	7	6.9%
Week 100	29	18.2%	6	5.9%
Week 103	24	15.1%	5	4.9%
Week 106	18	11.3%	3	2.9%
Week 109	17	10.7%	3	2.9%

Time point	Selpercatinib (N=159) Number completed N	% of PRO evaluable	Control arm (N=102) Number completed N	% of PRO evaluable
Week 112	15	9.4%	4	3.9%
Week 115	14	8.8%	2	2.0%
Week 118	11	6.9%	1	1.0%
Week 121	8	5.0%	1	1.0%
Week 124	6	3.8%	0	0.0%
Week 127	5	3.1%	0	0.0%
Week 130	5	3.1%	0	0.0%
Week 133	5	3.1%	0	0.0%
Week 136	3	1.9%	0	0.0%
Week 139	3	1.9%	0	0.0%
Week 142	3	1.9%	0	0.0%
Week 145	2	1.3%	0	0.0%
Week 148	2	1.3%	0	0.0%
Week 151	2	1.3%	0	0.0%
Week 154	2	1.3%	0	0.0%
Week 157	1	0.6%	0	0.0%
Week 160	1	0.6%	0	0.0%
Week 163	1	0.6%	0	0.0%

Source: Eli Lilly data on file, 2023 data cut (LIBRETTO-431) Table 2.2.1
Notes: Available Rate - Percentage of patients completed PRO instrument out of the number of randomized patients in the PRO evaluable population.

As described in Section 10.1.3, the mean change in EQ-5D-5L (collected in LIBRETTO-431) for separately selpercatinib and control arm is displayed in the following figures.

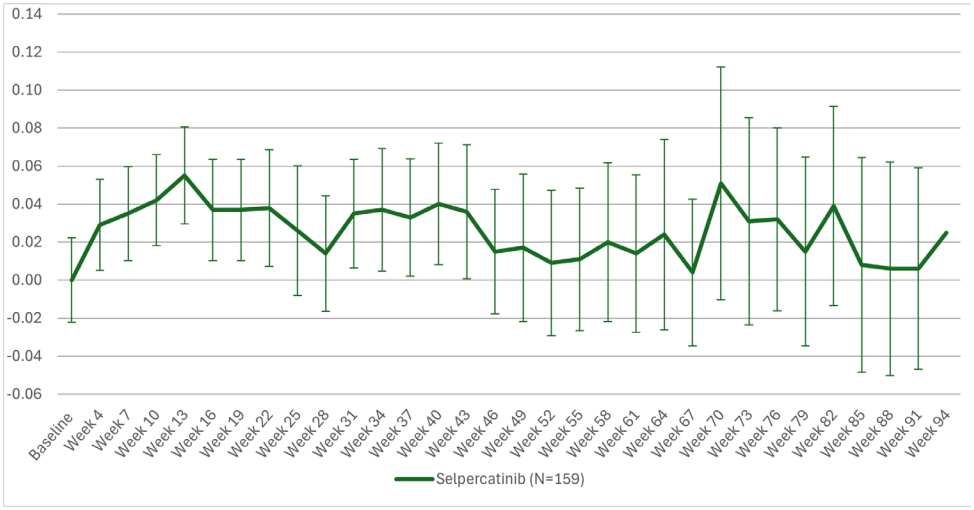


Figure 40 Mean change in EQ-5D-5L (UK) for the selpercatinib arm, LIBRETTO-431

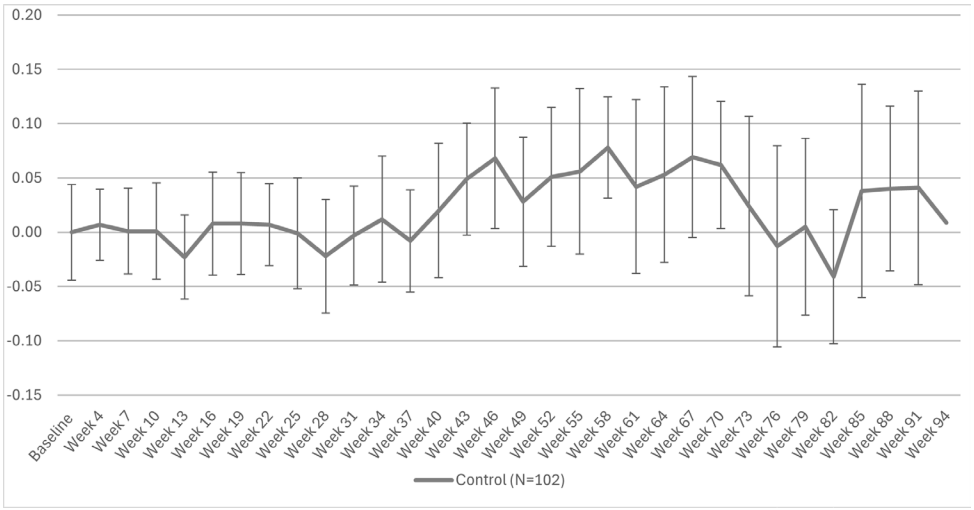


Figure 41 Mean change in EQ-5D-5L (UK) for the control arm, LIBRETTO-431

EQ-5D-5L with Danish weights

Table 92 HRQoL EQ-5D-5L summary statistics, DK value set

	Selpercatinib (n=159)		Control (n=102)		Intervention vs. comparator
	N	Mean (SD)	N	Mean (SD)	Difference (SD)
Week 1	147	0.850 (0.162)	87	0.844 (0.155)	N/A
Week 4	139	0.889 (0.128)	82	0.866 (0.206)	N/A
Week 7	126	0.884 (0.151)	75	0.857 (0.149)	N/A
Week 10	124	0.894 (0.122)	74	0.871 (0.153)	N/A
Week 13	126	0.909 (0.102)	67	0.850 (0.195)	N/A
Week 16	129	0.891 (0.119)	69	0.874 (0.148)	N/A
Week 19	126	0.879 (0.142)	64	0.870 (0.178)	N/A
Week 22	129	0.880 (0.157)	59	0.873 (0.148)	N/A
Week 25	125	0.878 (0.141)	56	0.869 (0.128)	N/A
Week 28	123	0.866 (0.184)	54	0.848 (0.220)	N/A
Week 31	125	0.886 (0.147)	52	0.858 (0.184)	N/A
Week 34	121	0.900 (0.112)	49	0.878 (0.189)	N/A

	Selpercatinib (n=159)		Control (n=102)		Intervention vs. comparator
Week 37	114	0.889 (0.147)	43	0.856 (0.207)	N/A
Week 40	112	0.897 (0.130)	41	0.886 (0.144)	N/A
Week 43	106	0.900 (0.129)	39	0.903 (0.138)	N/A
Week 46	101	0.875 (0.169)	35	0.914 (0.091)	N/A
Week 49	96	0.880 (0.142)	32	0.886 (0.146)	N/A
Week 52	85	0.863 (0.175)	29	0.891 (0.185)	N/A
Week 55	86	0.867 (0.172)	27	0.900 (0.105)	N/A
Week 58	77	0.887 (0.154)	23	0.896 (0.139)	N/A
Week 61	84	0.882 (0.156)	20	0.894 (0.144)	N/A
Week 64	74	0.880 (0.170)	19	0.851 (0.178)	N/A
Week 67	72	0.867 (0.214)	18	0.881 (0.122)	N/A
Week 70	68	0.918 (0.097)	16	0.874 (0.153)	N/A
Week 73	54	0.879 (0.217)	14	0.844 (0.215)	N/A
Week 76	55	0.879 (0.190)	13	0.830 (0.293)	N/A
Week 79	54	0.870 (0.174)	12	0.806 (0.306)	N/A
Week 82	56	0.892 (0.144)	13	0.798 (0.283)	N/A
Week 85	48	0.888 (0.153)	13	0.898 (0.111)	N/A
Week 88	44	0.874 (0.198)	12	0.879 (0.173)	N/A
Week 91	35	0.880 (0.152)	11	0.881 (0.112)	N/A
Week 94	35	0.897 (0.115)	10	0.866 (0.122)	N/A

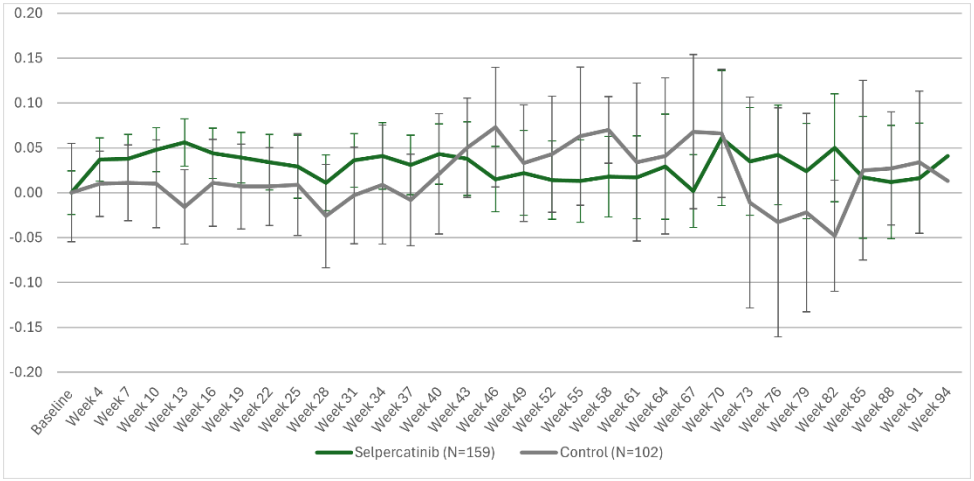


Figure 42 Mean change in EQ-5D-5L (DK) from baseline to week 94, both arms (LIBRETTO-431)

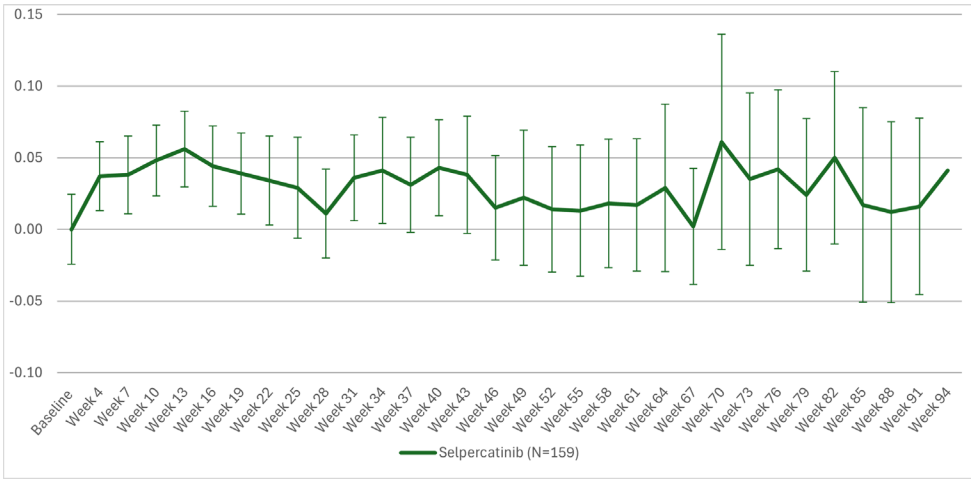


Figure 43 Mean change in EQ-5D-5L (DK) for the selpercatinib arm, LIBRETTO-431

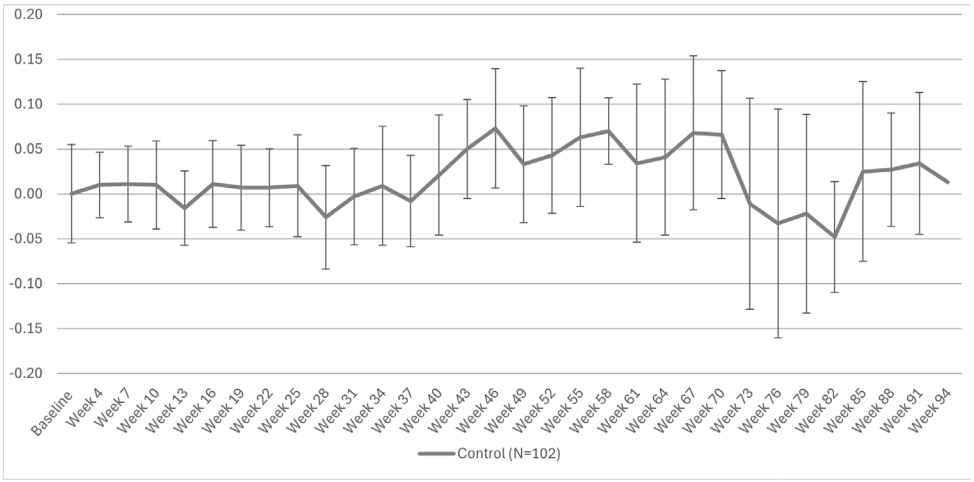


Figure 44 Mean change in EQ-5D-5L (DK) for the control arm, LIBRETTO-431

LIBRETTO-001

As mentioned in Section 10.2, QLQ-C30 data from the LIBRETTO-001 study was converted into EQ-5D-3L using the mapping algorithm provided by Young et al. The mapping description will therefore be described in this section using the original publication.

Background

Clinical trials in cancer frequently include cancer-specific measures of health but not preference-based measures such as the EQ-5D that are suitable for economic evaluation. Mapping functions have been developed to predict EQ-5D values from these measures, but there is considerable uncertainty about the most appropriate model to use, and many existing models are poor at predicting EQ-5D values. This study aims to investigate a range of potential models to develop mapping functions from 2 widely used cancer-specific measures (FACT-G and EORTC-QLQ-C30) and to identify the best model.

Methods

Mapping models are fitted to predict EQ-5D-3L values using ordinary least squares (OLS), tobit, 2-part models, splining, and to EQ-5D item-level responses using response mapping from the FACT-G and QLQ-C30. A variety of model specifications are estimated. Model performance and predictive ability are compared. Analysis is based on 530 patients with various cancers for the FACT-G and 771 patients with multiple myeloma, breast cancer, and lung cancer for the QLQ-C30.

Results

For FACT-G, OLS models most accurately predict mean EQ-5D values with the best predicting model using FACT-G items with similar results using tobit. Response mapping has low predictive ability. In contrast, for the QLQ-C30, response mapping has the most accurate predictions using QLQ-C30 dimensions. The QLQ-C30 has better predicted EQ-5D values across the range of possible values; however, few respondents in the FACT-G data set have low EQ-5D values, which reduces the accuracy at the severe end. Conclusions. OLS and tobit mapping functions perform well for both instruments. Response mapping gives the best model predictions for QLQ-C30. The generalizability of the FACT-G mapping function is limited to populations in moderate to good health.

Appendix G. Probabilistic sensitivity analyses

Table 93 shows which data/assumptions (point estimate, and lower and upper bound) that form the basis for the selected probability distributions used in the probabilistic analysis, refer to Section 12.2.2 for further description.

Table 93. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Mean starting age	60.00	59.22	60.77608719	Normal
Percentage, female	0.53	0.50	0.567284049	Beta
OS options				
Mortality ratio	1.0	0.90	1.1	Normal
Adverse events selpercatinib				
Diarrhoea	0.006	0.000	0.013	Beta
Hypertension	0.196	0.165	0.228	Beta
ECG QT prolonged	0.089	0.066	0.111	Beta
Chest pain	0.000	0.000	0.000	Beta
Fatigue	0.000	0.000	0.000	Beta
Decreased appetite	0.000	0.000	0.000	Beta
Asthenia	0.006	0.000	0.013	Beta
Vomiting	0.000	0.000	0.000	Beta
Dyspnoea	0.006	0.000	0.013	Beta
Alanine aminotransferase increased	0.203	0.171	0.235	Beta
Aspartate aminotransferase increased	0.120	0.094	0.146	Beta

Hyponatraemia	0.000	0.000	0.000	Beta
Hyperglycemia	0.000	0.000	0.000	Beta
Pneumonia	0.000	0.000	0.000	Beta
Cardiac failure	0.006	0.000	0.013	Beta
Thrombocytopenia	0.000	0.000	0.000	Beta
Neutropenia	0.000	0.000	0.000	Beta
Anaemia	0.000	0.000	0.000	Beta
Pleural effusion	0.000	0.000	0.000	Beta
Febrile neutropenia	0.000	0.000	0.000	Beta
Spinal cord compression	0.000	0.000	0.000	Beta
Pneumonitis	0.000	0.000	0.000	Beta
Nausea	0.000	0.000	0.000	Beta
Hepatitis Lab abnormalities	0.032	0.018	0.046	Beta
Lymphocyte count decreased	0.019	0.008	0.030	Beta
Leukopenia	0.000	0.000	0.000	Beta
Hypermagnesaemia	0.000	0.000	0.000	Beta
Sepsis	0.000	0.000	0.000	Beta
Acute kidney injury	0.000	0.000	0.000	Beta
Gamma-glutamyltransferase increased	0.025	0.013	0.038	Beta
Decreased platelet count	0.025	0.013	0.038	Beta
Decreased neutrophil count	0.019	0.008	0.030	Beta

Hypokalaemia	0.000	0.000	0.000	Beta
Decreased white blood cell count	0.013	0.004	0.022	Beta
Adverse events control (Pem + Pembro + Plat)				
Diarrhoea	0.020	0.006	0.035	Beta
Hypertension	0.031	0.013	0.048	Beta
ECG QT prolonged	0.000	0.000	0.000	Beta
Chest pain	0.020	0.006	0.035	Beta
Fatigue	0.000	0.000	0.000	Beta
Decreased appetite	0.020	0.006	0.035	Beta
Asthenia	0.041	0.021	0.061	Beta
Vomiting	0.000	0.000	0.000	Beta
Dyspnoea	0.041	0.021	0.061	Beta
Alanine aminotransferase increased	0.031	0.013	0.048	Beta
Aspartate aminotransferase increased	0.010	0.000	0.020	Beta
Hyponatraemia	0.000	0.000	0.000	Beta
Hyperglycemia	0.000	0.000	0.000	Beta
Pneumonia	0.000	0.000	0.000	Beta
Cardiac failure	0.020	0.006	0.035	Beta
Thrombocytopenia	0.020	0.006	0.035	Beta
Neutropenia	0.133	0.098	0.167	Beta
Anaemia	0.102	0.071	0.133	Beta
Pleural effusion	0.000	0.000	0.000	Beta

Febrile neutropenia	0.020	0.006	0.035	Beta
Spinal cord compression	0.020	0.006	0.035	Beta
Pneumonitis	0.000	0.000	0.000	Beta
Nausea	0.000	0.000	0.000	Beta
Hepatitis Lab abnormalities	0.000	0.000	0.000	Beta
Lymphocyte count decreased	0.031	0.013	0.048	Beta
Leukopenia	0.031	0.013	0.048	Beta
Hypermagnesaemia	0.000	0.000	0.000	Beta
Sepsis	0.000	0.000	0.000	Beta
Acute kidney injury	0.000	0.000	0.000	Beta
Gamma-glutamyltransferase increased	0.000	0.000	0.000	Beta
Decreased platelet count	0.051	0.029	0.073	Beta
Decreased neutrophil count	0.122	0.089	0.156	Beta
Hypokalaemia	0.031	0.013	0.048	Beta
Decreased white blood cell count	0.041	0.021	0.061	Beta
Patient time and transportation costs				
Progression-free	242.674	218.407	266.942	Gamma
Progressed disease	242.674	218.407	266.942	Gamma
Calculated per cycle cost				
Proportion receiving pembrolizumab	0.812	0.812	0.812	Beta

Diagnostic costs				
Cost of testing	5000.00	4500.00	5500.00	Gamma
Patient population to be screened	0.015	0.015	0.015	Beta
Drug administration costs				
Selpercatinib	1756.00	1580.40	1931.60	Gamma
Pembrolizumab + pemetrexed + carboplatin	22133.00	19919.70	24346.30	Gamma
Pemetrexed + carboplatin	20822.00	18739.80	22904.20	Gamma
Drug-related monitoring costs – weekly cycle				
Selpercatinib	100.57	90.51	110.63	Gamma
Pembrolizumab + pemetrexed + carboplatin	100.57	90.51	110.63	Gamma
Pemetrexed + carboplatin	100.57	90.51	110.63	Gamma
ECG (7 for selpercatinib)	1311.00	1179.90	1442.10	Gamma
Subsequent active systematic anticancer therapy costs				
Docetaxel	117913.35	106122.02	129704.69	Fixed
Pemetrexed + carboplatin	111949.61	100754.65	123144.57	Fixed
Pemetrexed	104050.63	93645.57	114455.69	Fixed
Subsequent active systematic anticancer therapy - % after selpercatinib				
Docetaxel	0.56	0.50	0.62	Beta
Pemetrexed + carboplatin	0.44	0.40	0.48	Beta
Subsequent active systematic anticancer therapy - % after pem + pembro + plat				

Docetaxel	1.00	0.90	1.10	Beta
Subsequent active systematic anticancer therapy - % after pem + plat				
Docetaxel	0.15	0.14	0.17	Beta
Nivolumab	0.34	0.31	0.37	Beta
Pembrolizumab	0.34	0.31	0.37	Beta
Atezolizumab	0.17	0.15	0.19	Beta
Subsequent Active Systemic Anticancer Therapy - % after pem + plat +/- pembro				
Docetaxel	0.84	0.76	0.92	Beta
Nivolumab	0.06	0.06	0.07	Beta
Pembrolizumab	0.06	0.06	0.07	Beta
Atezolizumab	0.03	0.03	0.04	Beta
Health state costs – weekly costs				
Progression-free	1873.43	1686.09	2060.78	Gamma
Progressed disease	1873.43	1686.09	2060.78	Gamma
Adverse event costs – per event				
Diarrhoea	7818.00	7036.20	8599.80	Gamma
Hypertension	0.00	0.00	0.00	Gamma
ECG QT prolonged	0.00	0.00	0.00	Gamma
Chest pain	0.00	0.00	0.00	Gamma
Fatigue	0.00	0.00	0.00	Gamma
Decreased appetite	1736.00	1562.40	1909.60	Gamma
Asthenia	5103.00	4592.70	5613.30	Gamma
Vomiting	0.00	0.00	0.00	Gamma
Dyspnoea	0.00	0.00	0.00	Gamma

Alanine aminotransferase increased	0.00	0.00	0.00	Gamma
Aspartate aminotransferase increased	0.00	0.00	0.00	Gamma
Hyponatraemia	1847.00	1662.30	2031.70	Gamma
Hyperglycemia	0.00	0.00	0.00	Gamma
Pneumonia	1311.00	1179.90	1442.10	Gamma
Cardiac failure	39083.00	35174.70	42991.30	Gamma
Thrombocytopenia	2111.00	1899.90	2322.10	Gamma
Neutropenia	2111.00	1899.90	2322.10	Gamma
Anaemia	2111.00	1899.90	2322.10	Gamma
Pleural effusion	1311.00	1179.90	1442.10	Gamma
Febrile neutropenia	2240.00	2016.00	2464.00	Gamma
Spinal cord compression	0.00	0.00	0.00	Gamma
Pneumonitis	0.00	0.00	0.00	Gamma
Nausea	0.00	0.00	0.00	Gamma
Hepatitis Lab abnormalities	1947.00	1752.30	2141.70	Gamma
Lymphocyte count decreased	2111.00	1899.90	2322.10	Gamma
Leukopenia	2111.00	1899.90	2322.10	Gamma
Hypermagnesaemia	0.00	0.00	0.00	Gamma
Sepsis	0.00	0.00	0.00	Gamma
Acute kidney injury	0.00	0.00	0.00	Gamma

Gamma-glutamyltransferase increased	1847.00	1662.30	2031.70	Gamma
Decreased platelet count	2111.00	1899.90	2322.10	Gamma
Decreased neutrophil count	2111.00	1899.90	2322.10	Gamma
Hypokalaemia	0.00	0.00	0.00	Gamma
Decreased white blood cell count	2111.00	1899.90	2322.10	Gamma
Health state utility weights				
Progression-free – selpercatinib	0.86	0.85	0.87	Beta
Progression-free – pembrolizumab + pemetrexed + carboplatin	0.86	0.85	0.87	Beta
Progression-free – carboplatin + pemetrexed ± pembrolizumab	0.86	0.85	0.87	Beta
Progression-free – pemetrexed + carboplatin	0.86	0.85	0.87	Beta
Progressed disease	0.83	0.81	0.84	Beta
Utility decrements for adverse events				
Diarrhoea	-0.05	-0.05	-0.04	Gamma
Hypertension	0.00	0.00	0.00	Gamma
ECG QT prolonged	0.00	0.00	0.00	Gamma
Chest pain	0.00	0.00	0.00	Gamma
Fatigue	0.00	0.00	0.00	Gamma
Decreased appetite	-0.09	-0.09	-0.08	Gamma

Asthenia	-0.07	-0.08	-0.07	Gamma
Vomiting	0.00	0.00	0.00	Gamma
Dyspnoea	0.00	0.00	0.00	Gamma
Alanine aminotransferase increased	0.00	0.00	0.00	Gamma
Aspartate aminotransferase increased	0.00	0.00	0.00	Gamma
Hyponatraemia	-0.09	-0.09	-0.08	Gamma
Hyperglycemia	0.00	0.00	0.00	Gamma
Pneumonia	-0.01	-0.01	-0.01	Gamma
Cardiac failure	-0.07	-0.08	-0.06	Gamma
Thrombocytopenia	0.00	0.00	0.00	Gamma
Neutropenia	-0.09	-0.11	-0.08	Gamma
Anaemia	-0.07	-0.08	-0.07	Gamma
Pleural effusion	-0.09	-0.09	-0.08	Gamma
Febrile neutropenia	-0.09	-0.11	-0.07	Gamma
Spinal cord compression	0.00	0.00	0.00	Gamma
Pneumonitis	0.00	0.00	0.00	Gamma
Nausea	0.00	0.00	0.00	Gamma
Hepatitis Lab abnormalities	0.00	0.00	0.00	Gamma
Lymphocyte count decreased	-0.09	-0.11	-0.08	Gamma
Leukopenia	-0.09	-0.11	-0.08	Gamma
Hypermagnesaemia	0.00	0.00	0.00	Gamma

Sepsis	0.00	0.00	0.00	Gamma
Acute kidney injury	0.00	0.00	0.00	Gamma
Gamma-glutamyltransferase increased	0.00	0.00	0.00	Gamma
Decreased platelet count	0.00	0.00	0.00	Gamma
Decreased neutrophil count	0.00	0.00	0.00	Gamma
Hypokalaemia	0.00	0.00	0.00	Gamma
Decreased white blood cell count	-0.05	-0.06	-0.04	Gamma
Duration of AEs				
Diarrhoea	5.53	4.98	6.08	Gamma
Hypertension	0.00	0.00	0.00	Gamma
ECG QT prolonged	0.00	0.00	0.00	Gamma
Chest pain	0.00	0.00	0.00	Gamma
Fatigue	0.00	0.00	0.00	Gamma
Decreased appetite	15.00	13.50	16.50	Gamma
Asthenia	23.78	21.40	26.16	Gamma
Vomiting	0.00	0.00	0.00	Gamma
Dyspnoea	0.00	0.00	0.00	Gamma
Alanine aminotransferase increased	0.00	0.00	0.00	Gamma
Aspartate aminotransferase increased	0.00	0.00	0.00	Gamma
Hyponatraemia	15.00	13.50	16.50	Gamma

Hyperglycemia	0.00	0.00	0.00	Gamma
Pneumonia	15.00	13.50	16.50	Gamma
Cardiac failure	31.00	27.90	34.10	Gamma
Thrombocytopenia	0.00	0.00	0.00	Gamma
Neutropenia	15.00	13.50	16.50	Gamma
Anaemia	23.78	21.40	26.16	Gamma
Pleural effusion	15.00	13.50	16.50	Gamma
Febrile neutropenia	15.00	13.50	16.50	Gamma
Spinal cord compression	0.00	0.00	0.00	Gamma
Pneumonitis	0.00	0.00	0.00	Gamma
Nausea	0.00	0.00	0.00	Gamma
Hepatitis Lab abnormalities	0.00	0.00	0.00	Gamma
Lymphocyte count decreased	15.00	13.50	16.50	Gamma
Leukopenia	15.00	13.50	16.50	Gamma
Hypermagnesaemia	0.00	0.00	0.00	Gamma
Sepsis	0.00	0.00	0.00	Gamma
Acute kidney injury	0.00	0.00	0.00	Gamma
Gamma-glutamyltransferase increased	0.00	0.00	0.00	Gamma
Decreased platelet count	0.00	0.00	0.00	Gamma
Decreased neutrophil count	0.00	0.00	0.00	Gamma
Hypokalaemia	0.00	0.00	0.00	Gamma

Decreased white blood cell count	15.00	13.50	16.50	Gamma

Abbreviations: OS, overall survival; ECG, electrocardiogram

Individual extrapolations of OS, PFS and TTD are included in the PSA. This can be seen in the ”Survival calculations” sheet where the covariance matrix is used to perform cholesky decomposition.

Appendix H. Literature searches for clinical efficacy

Objective

To summarise the clinical efficacy and safety of selpercatinib or comparator interventions in patients with RET fusion positive NSCLC for first-line and first-line to progression. The data has not been available for comparator interventions within patient populations with RET fusion-positive NSCLC. Therefore, RCTs in the wider patient population with nsq NSCLC (without RET fusion-positive NSCLC) were identified to ensure all potentially relevant data were collected.

Method

The SLR1 (SLR1 refers to the original SLR while SLR2, SLR3, and SLR4 were the updates of SLR1) was conducted on 12 January 2016, which covered evidence up to 2016, and it was first updated in June 2018 (SLR2). The subsequent SLR updates were carried out in July 2020 (SLR3 update 2), July 2021 (SLR4 update 3), July 2022 (SLR5 update 4), and March 2023 (SLR6 update 5) to cover the latest evidence base.

The search strings were run on different medical literature databases to identify relevant publications. Additional searches were also conducted across clinical trial registries and conference proceedings. Bibliographic lists of relevant systematic reviews and meta-analyses were searched for relevant studies that had not been identified in the electronic searches. All titles/abstracts were reviewed according to the eligibility criteria, fully described in the protocol by two systematic reviewers independently. Titles/abstracts that passed the first stage of screening were then screened at the full-text level. Any conflicts between the reviewers were referred to a third reviewer and an agreement was reached. Relevant data from included articles were collected by a single reviewer in extraction tables and then cross checked by another reviewer in a validation step. The data were extracted into a bespoke extraction sheet in Microsoft Excel®. The included studies were categorized as first-line and first-line to progression.

Finally, risk of bias assessment for each study was conducted to standards recommended by National Institute for Health and Care Excellence.6 As no validated tool to assess for quality of single-arm studies exists, the Critical Appraisal Skills Programme (CASP) cohort study checklist was used to assess all single-arm trials. Quality assessments were undertaken by two independent reviewers with conflicts referred to a third reviewer and agreements were reached.

Eligibility criteria are specified in Table 94 in terms of PICO.

Table 94 PICO statement

PICOS	Criteria
Patients	• Adult patients (≥18 years old) with locally advanced or metastatic nsq NSCLC (stage IIIB or IV) receiving first-line and first-line to progression

	• Single-arm trials or RCTs including RET-altered tumours (any tumour site, any intervention, first-line of therapy) • RCTs in first-line NSCLC
Interventions	• Selpercatinib (SEL) • Pralsetinib (PRL) • Afatinib (AFT) • Bevacizumab (BEV) • Carboplatin (CARB) • Cisplatin (CIS) • Crizotinib • Docetaxel (DOC) • Erlotinib (ERL) • Gefitinib (GEF) • Gemcitabine (GEM) • Nab-Paclitaxel (NBPAC) • Nivolumab (NIV) • Paclitaxel (PAC) • Pembrolizumab (PEMBRO) • Pemetrexed (PEM) • Ramucirumab (RAM) • Atezolizumab (ATEZ) • Durvalumab (DUR) • Ipilimumab (IPI) • Tremelimumab (TRE) • Combinations of the above
Comparators	Any active systemic therapy, placebo, best supportive care, or no treatment
Outcomes	At least one of the following outcomes: • Response • PFS • OS • Safety (Grade 3-4 AEs)
Study design	RCT**
Language	English
Time frame	• SLR1: Database inception to 12 January 2016 • SLR2: 2016 to 13 June 2018 • SLR3: 2018 to 29 July 2020 (SLR3)*** • SLR4: 2020 to 30 July 2021 • SLR5: 2021 to 20 July 2022 • SLR6: 2022 to 15 March 2023
Other considerations	Studies that included head-to-head comparisons of at least two of the treatments listed (or placebo [PBO]) were eligible for inclusion

Abbreviations: AE, adverse events; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; nsq, non-squamous; OS, overall survival; PFS, progression-free survival; PICOS, patients, interventions, comparators, outcome, and study design; RCT, randomised controlled trial; RET, rearranged during transfection; SLR, systematic literature review.

*Studies including only a mutation-positive-specific population (EGFR+, ALK+) were excluded.
**RCTs with mixed histologic populations were included when separate results for the nsq NSCLC were reported. An exception was made for CHECKMATE 227 (OS was reported for the nsq population; however, both ORR and PFS were reported for the mixed population), KEYNOTE-042, and KEYNOTE-024 trials, since these studies assessed immunotherapies which are considered as key comparators for selpercatinib, hence efficacy data for the mixed population were still extracted if not reported for nsq subgroup specifically. It is to be noted that the majority of patients were nsq NSCLC (≥60%) hence the results were considered representative of nsq NSCLC population.
***Additional search strategy to identify selpercatinib and pralsetinib (not in scope for the SLR1 or SLR2) was run on 27 August 2020.

H.1.1 Search strategies

H.1.1.1 Information sources

Search for published studies

Searches were performed in the following electronic databases:

- Medical Literature Analysis and Retrieval System Online (MEDLINE®) ALL and MEDLINE® In-Process
- Excerpta Medica Database (EMBASE®)
- Evidence-Based Medicine Reviews (Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Clinical Answers, Cochrane Central Register of Controlled Trials, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database)

These sources are consistent with the requirements of all major HTA bodies and are recommended by the Cochrane Collaboration.

The searches were conducted from database inception to March 2023.

Search for conference abstracts

To complement the search for published trials, relevant abstracts from the following key international conferences were searched:

- American Association for Cancer Research
- European Lung Cancer Conference (ELCC)
- International Association for the Study of Lung Cancer World Conference on Lung Cancer (WCLC)
- European Society for Medical Oncology (ESMO)
- ESMO Immuno Oncology Congress
- American Society for Clinical Oncology (ASCO)

Conference proceedings published since 2013 were systematically searched online for studies meeting the eligibility criteria. The keywords used for identifying relevant conference abstracts were ‘lung cancer’, ‘non-small cell lung cancer’, ‘RET’, and ‘RCT’.

At the time of development of the original SLR, proceedings for ASCO 2014 to 2017, ESMO 2015 to 2017, ELCC 2014 to 2018, and WCLC 2017 were searched through EMBASE. Search

strategies with the same disease terms and randomised controlled trial filters as used in the EMBASE search for full publications were used

Ongoing clinical trial databases

Identification of ongoing trials that are likely to publish evidence within 12 months of an indication being appraised is an important aspect of HTA submissions to inform timelines for updates of the evidence synthesis. The keywords used for identifying relevant ongoing clinical trials were 'lung cancer', 'non-small cell lung cancer', and 'studies with results'. The following trial databases were searched to identify ongoing trials:

- ClinicalTrials.gov (http://clinicaltrials.gov/)
- International Clinical Trials Registry Platform (https://ictrptest.azurewebsites.net/Default.aspx)

Bibliographic search

Reference lists of any identified systematic reviews and meta-analyses published in the last year were searched for further studies of interest. These reference lists are good sources of additional material that can supplement the articles identified in the medical literature databases. In addition, the indexed publications of relevant clinical trials were checked for further studies of interest.

Database searches were executed in March 2023, refer to Table 95 for an overview of search strategies.

Table 95 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Elsevier Platform	The inclusion and exclusion criteria were used to identify the population and disease condition, interventions, comparators, outcomes and study types (also known as the PICOS criteria). Refer to Table 94	15 March 2023
Medline	PubMed platform	The inclusion and exclusion criteria were used to identify the population and disease condition, interventions, comparators, outcomes and study types (also known as the PICOS criteria). Refer to Table 94	15 March 2023
Cochrane Library	N/A	The inclusion and exclusion criteria were used to identify the population and disease condition, interventions, comparators, outcomes and study types (also known as the PICOS criteria). Refer to Table 94	15 March 2023

Abbreviations: Embase = Excerpta Medica database; MEDLINE = Medical Literature Analysis and Retrieval System Online, N/A = not available.

Table 96 Other sources included in the literature search

Source name	Location/source	Relevant period for the search	Date of search
ClinicalTrials.gov	http://clinicaltrials.gov/	1 January 2015 to present	15 March 2023
International Clinical Trials Registry Platform	http://www.who.int/ictrp/en/	1 January 2015 to present	15 March 2023
NICE	https://www.nice.org.uk/	1 January 2015 to present	15 March 2023

Abbreviations: NICE = National Institute for Health and Care Excellence, N/A = not available.

Table 97 Conference material included in the literature search

Conference	Source of abstracts	Relevant period for the search	Date of search
American Society of Clinical Oncology	http://www.asco.org/	2017-2023	15 March 2023
European Society for Medical Oncology	http://www.esmo.org/	2017-2023	15 March 2023
International Association for the Study of Lung Cancer	https://www.iaslc.org/	2017-2023	15 March 2023
American Association for Cancer Research		2017-2023	15 March 2023
ESMO Immuno Oncology Congress		2017-2023	15 March 2023
European Lung Cancer Conference (ELCC)		2017-2023	15 March 2023

Abbreviations: N/A = not available.

H.1.1.2 Search strings

The search strings for the clinical SLRs are reported below for the SLR conducted in March 2023

Table 98 Search strategy for EMBASE for first-line NSCLC clinical trial evidence for selpercatinib and comparators (conducted on 15 March 2023)

No.	Query	Results
Population		
1	exp lung neoplasms/	472,001
2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	147,483
3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	136,421
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	414,257
5	1 or 2 or 3 or 4	577,946

No.	Query	Results
6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	1,619,946
7	5 and 6	206,779
8	(first line therapy or first-line or first line or 1st line or untreated or treatment naive or previously untreated or first-line to progression or first line to progression).tw,kw.	482,697
9	7 and 8	19,841
10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	1084
11	*cisplatin/	66,090
12	(Cisplat$ or abiplatin or bioc#splatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj2 dichloroplatinum) or cis diamin#chloroplatinum or (cis adj2 platinum) or cis plat$ or cytoplatin or cytosplat or diamine dichloroplatinum or diam?in#dichloroplatinum or dichlorodiam?ineplatinum or dichlorodiam?ine platinum or Docistin or elvecis or Kemoplat or lederplatin or Lipoplatin or mpi 5010 or mpi5010 or Neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or Platimine or platinex or Platinil or platinol or (platinum adj2 diaminodichloride) or Platinum diam?in#dichloride or (platinum adj2 dichloride) or Platiran or platistil or Platistin or platosin or Randa or romcis or Sicatem or 'spi 077' or Tecnoplatin).mp.	226,027
13	*carboplatin/	15,686
14	(Carboplat$ or blastocarb or boplatex or carbosin or carbotec or carplan or CBDCA or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or nsc 241240 or oncocarbin or paraplatin$ or nealorin or neocarbo or platinwas or ribocarbo).mp.	87,429
15	*gemcitabine/	16,343
16	(Gemcitabine or gemcite or gemzar or ly 188011 or ly188011).mp.	73,068
17	*docetaxel/	16,254
18	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	73,736
19	*pemetrexed/	3964
20	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	24,681
21	*paclitaxel/	130,222
22	(paclitaxel or 'abi 007' or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or Formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc 125973 or nsc125973 or oncogel or onxol or pacitaxel or pacxel or	140,438

No.	Query	Results
	padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan).mp.	
23	*bevacizumab/	20,218
24	(bevacizumab or altuzan or avastin or nsc 704856 or nsc704865).mp.	74,359
25	*erlotinib/	6350
26	(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.	32,594
27	*ramucirumab/	1150
28	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	4774
29	*nivolumab/	10,709
30	(nivolumab or bms 936558 or bms936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.	36,707
31	*gefitinib/	5941
32	(Gefitinib or geftinat or iressa or zd 1839 or zd1839).mp.	29,685
33	*afatinib/	2037
34	(Afatinib or bibw 2992 or bibw2992 or gilotrif or tovok or giotrif).mp.	8348
35	*crizotinib/	2550
36	(Crizotinib or 'pf 02341066' or pf 1066 or pf 2341066 or pf02341066 or pf1066 or pf2341066 or xalkori).mp.	11,422
37	*pembrolizumab/	9694
38	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch900475).mp.	35,512
39	*ipilimumab/	5272
40	(ipilimumab or bms 734016 or bms734016 or 'mdx 010' or mdx 101 or mdx010 or mdx101 or strentarga or yervoy or CTLA 4).mp.	37,494
41	*ticilimumab/	639
42	(ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206 or tremelimumab).mp.	4049
43	*durvalumab/	2082
44	(durvalumab or imfinzi or medi 4736 or medi4736).mp.	9576
45	*atezolizumab/	2902
46	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).mp.	14,462
47	or/10-46	560,906
48	9 and 47	13,322
49	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	4,347,080
50	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	11,705,664
51	49 not 50	2,344,392

No.	Query	Results
52	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	3,153,223
53	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	6,997,070
54	52 or 53	8,721,017
55	animal/ not (animal/ and human/)	1,173,907
56	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	12,485,150
57	55 or 56	13,502,471
58	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	5322
59	(9 and 58 and 54) not (51 or 57)	89
60	limit 59 to dc=20220601-20230315	27
61	(48 and 52) not (51 or 57)	4039
62	limit 61 to dc=20220601-20230315	350

Abbreviations: 2L = second line; DTC = differentiated thyroid cancer; LOT = line of therapy; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PTC = papillary thyroid cancer; RCT = randomized controlled trial; RET = rearrangements and/or mutations during transfection; SLR = systematic literature review.

Table 99 Search strategy for MEDLINE for first-line NSCLC clinical trial evidence for selpercatinib and comparators (conducted on 15 March 2023)

No.	Query	Results
Population		
1	exp lung neoplasms/	270,604
2	](non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	84,352
3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	84,149
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	284,094
5	1 or 2 or 3 or 4	369,246
6	(metasta* or advanced or stage IIIB or stage IV or stage 4 or stage four).tw,kw.	1,092,298

No.	Query	Results
7	5 and 6	112,361
8	(first line therapy or first-line or first line or 1st line or untreated or treatment naive or previously untreated or first-line to progression or first line to progression).tw,kw.	309,262
9	7 and 8	8785
10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	416
11	*cisplatin/	23,711
12	(Cisplat$ or abiplatin or bioc#splatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj2 dichloroplatinum) or cis diamin#chloroplatinum or (cis adj2 platinum) or cis plat$ or cytoplatin or cytosplat or diamine dichloroplatinum or diam?in#dichloroplatinum or dichlorodiam?ineplatinum or dichlorodiam?ine platinum or Docistin or elvecis or Kemoplat or lederplatin or Lipoplatin or mpi 5010 or mpi5010 or Neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or Platimine or platinex or Platinil or platinol or (platinum adj2 diaminodichloride) or Platinum diam?in#dichloride or (platinum adj2 dichloride) or Platiran or platistil or Platistin or platosin or Randa or romcis or Sicatem or ‘spi 077’ or Tecnoplatin).mp.	88,470
13	*carboplatin/	3578
14	(Carboplat$ or blastocarb or boplatex or carbosin or carbotec or carplan or CBDCA or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or nsc 241240 or oncocarbin or paraplatin$ or nealorin or neocarbo or platinwas or ribocarbo).mp.	20,399
15	*gemcitabine/	25
16	(Gemcitabine or gemcite or gemzar or ly 188011 or ly188011).mp.	20,402
17	*docetaxel/	902
18	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	19,712
19	*pemetrexed/	366
20	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	9440
21	*paclitaxel/	30,358
22	(paclitaxel or ‘abi 007’ or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or Formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc 125973 or nsc125973 or oncogel or onxol or pacitaxel or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan).mp.	47,683

No.	Query	Results
23	*bevacizumab/	2979
24	(bevacizumab or altuzan or avastin or nsc 704856 or nsc704865).mp.	22,438
25	*erlotinib/	793
26	(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.	7941
27	*ramucirumab/	0
28	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	1220
29	*nivolumab/	1876
30	(nivolumab or bms 936558 or bms936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.	9218
31	*gefitinib/	372
32	(Gefitinib or geftinat or iressa or zd 1839 or zd1839).mp.	8520
33	*afatinib/	240
34	(Afatinib or bibw 2992 or bibw2992 or gilotrif or tovok or giotrif).mp.	2061
35	*crizotinib/	335
36	(Crizotinib or 'pf 02341066' or pf 1066 or pf 2341066 or pf02341066 or pf1066 or pf2341066 or xalkori).mp.	3257
37	*pembrolizumab/	0
38	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch900475).mp.	8457
39	*ipilimumab/	676
40	(ipilimumab or bms 734016 or bms734016 or 'mdx 010' or mdx 101 or mdx010 or mdx101 or strentarga or yervoy or CTLA 4).mp.	16,154
41	*ticilimumab/	0
42	(ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206 or tremelimumab).mp.	485
43	*durvalumab/	0
44	(durvalumab or imfinzi or medi 4736 or medi4736).mp.	1390
45	*atezolizumab/	0
46	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).mp.	2826
47	or/10-46	228,292
48	9 and 47	5187
49	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	4,487,064
50	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	8,908,086
51	49 not 50	2,241,706

No.	Query	Results
52	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	2,252,978
53	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	1,443,561
54	52 or 53	3,144,230
55	animal/ not (animal/ and human/)	5,069,501
56	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	4,201,648
57	55 or 56	8,486,776
58	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	5120
59	(9 and 58 and 54) not (51 or 57)	28
60	limit 59 to dc=20220601-20230315	11
61	(48 and 52) not (51 or 57)	1572
62	limit 61 to dt=20220601-20230315	93

Abbreviations: 2L = second line; DTC = differentiated thyroid cancer; LOT = line of therapy; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PTC = papillary thyroid cancer; RCT = randomized controlled trial; RET = rearrangements and/or mutations during transfection; SLR = systematic literature review.

Table 100 Search strategy for EBMR for first-line NSCLC clinical trial evidence for selpercatinib and comparators (conducted on 15 March 2023)

No.	Query	Results
Population		
1	exp lung neoplasms/	10,737
2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.	16,186
3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.	15,551
4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.	27,309
5	1 or 2 or 3 or 4	29,170
6	(metasta* or advanced or stage IV or stage 4 or stage four).tw,kw.	106,951
7	5 and 6	14,845

No.	Query	Results
8	(first line therapy or first-line or first line or 1st line or untreated or treatment naive or previously untreated or first-line to progression or first line to progression).tw,kw.	53,513
9	7 and 8	3991
10	(selpercatinib or LY3527723 or LY-3527723 or LY 3527723 or LOXO-292 or LOXO 292 or LOXO292 or RETEVMOTM or RETEVMO TM or RETSEVMO or Pralsetinib or blue-667 or blue 667 or blue667 or blu 667 or blu-667 or blu667 or cs-3009 or cs 3009 or cs3009 or gavreto or RET inhibitor or RET inhibitors).mp.	43
11	*cisplatin/	0
12	(Cisplat$ or abiplatin or bioc#splatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj2 dichloroplatinum) or cis diamin#chloroplatinum or (cis adj2 platinum) or cis plat$ or cytoplatin or cytosplat or diamine dichloroplatinum or diam?in#dichloroplatinum or dichlorodiam?ineplatinum or dichlorodiam?ine platinum or Docistin or elvecis or Kemoplat or lederplatin or Lipoplatin or mpi 5010 or mpi5010 or Neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or Platimine or platinex or Platinil or platinol or (platinum adj2 diaminodichloride) or Platinum diam?in#dichloride or (platinum adj2 dichloride) or Platiran or platistil or Platistin or platosin or Randa or romcis or Sicatem or ‘spi 077’ or Tecnoplatin).mp.	16,934
13	*carboplatin/	0
14	(Carboplat$ or blastocarb or boplatex or carbosin or carbotec or carplan or CBDCA or cycloplatin or erbakar or ercar or ifacap or jm 8 or kemocarb or nsc 241240 or oncocarbin or paraplatin$ or nealorin or neocarbo or platinwas or ribocarbo).mp.	8697
15	*gemcitabine/	0
16	(Gemcitabine or gemcite or gemzar or ly 188011 or ly188011).mp.	7080
17	*docetaxel/	0
18	(docetaxel or daxotel or dexotel or docefrez or docetaxel accord or lit 976 or lit976 or n debenzoyl n tert butoxycarbonyl 10 deacetyltaxol or n tert butoxycarbonyl 10 deacetyl n debenzoyltaxol or nsc628503 or nsc 628503 or oncodocel or rp 56976 or rp56976 or taxespira or taxoter$ or taxotere or texot or taxoltere metro).mp.	8546
19	*pemetrexed/	0
20	(pemetrexed or alimta or armisarte or ciambra or elimta or ly 231514 or ly231514 or ly 231 514 or MTA or pemfexy or pemta).mp.	3307
21	*paclitaxel/	4549
22	(paclitaxel or ‘abi 007’ or abraxane or anzatax or asotax or biotax or bms 181339 or bms181339 or bristaxol or britaxol or coroxane or Formoxol or genexol or hunxol or ifaxol or infinnium or intaxel or medixel or mitotax or nsc 125973 or nsc125973 or oncogel or onxol or pacitaxel or pacxel or padexol or parexel or paxceed or paxene or paxus or praxel or taxocris or taxol or taxus or taycovit or yewtaxan).mp.	12986
23	*bevacizumab/	0

No.	Query	Results
24	(bevacizumab or altuzan or avastin or nsc 704856 or nsc704865).mp.	7717
25	*erlotinib/	0
26	(erlotinib or Tarceva or nsc 718781 or nsc718781 or osi 774 or osi774 or r 1415 or r1415 or cp 358774 or cp358774).mp.	1912
27	*ramucirumab/	0
28	(ramucirumab or cyramza or imc 1121 or imc 1121b or imc1121 b or imc1121b or ly 3009806 or ly3009806).mp.	639
29	*nivolumab/	0
30	(nivolumab or bms 936558 or bms936558 or cmab819 or cmab 819 or mdx 1106 or mdx1106 or ono 4538 or ono4538 or opdivo).mp.	2768
31	*gefitinib/	0
32	(Gefitinib or geftinat or iressa or zd 1839 or zd1839).mp.	1235
33	*afatinib/	0
34	(Afatinib or bibw 2992 or bibw2992 or gilotrif or tovok or giotrif).mp.	487
35	*crizotinib/	0
36	(Crizotinib or 'pf 02341066' or pf 1066 or pf 2341066 or pf02341066 or pf1066 or pf2341066 or xalkori).mp.	443
37	*pembrolizumab/	0
38	(Pembrolizumab or Keytruda or lambrolizumab or mk 3475 or mk3475 or sch900475 or sch900475).mp.	2744
39	*ipilimumab/	0
40	(ipilimumab or bms 734016 or bms734016 or 'mdx 010' or mdx 101 or mdx010 or mdx101 or strentarga or yervoy or CTLA 4).mp.	2171
41	*ticilimumab/	0
42	(ticilimumab or cp 675 206 or cp 675206 or cp675 206 or cp675206 or tremelimumab).mp.	406
43	*durvalumab/	0
44	(durvalumab or imfinzi or medi 4736 or medi4736).mp.	1029
45	*atezolizumab/	0
46	(atezolizumab or mpdl 3280a or mpdl3280a or rg 7446 or rg7446 or tecentriq or tecntriq).mp.	1281
47	or/10-46	51,782
48	9 and 47	3381
49	(juvenile or juvenile* or infant or child* or adolescen* or teen*).mp.	330,124
50	(adult or adults or above 19 years or >19 years or above 18 years or >18 years or aged or middle aged).mp.	1,044,767
51	49 not 50	139,679
52	(crossover procedure or double-blind procedure or randomized controlled trial or single-blind procedure or random* or factorial* or crossover* or placebo* or assign* or allocat* or volunteer*).mp.	1,484,230

No.	Query	Results
53	(single arm or single-arm or one arm or one-arm or clinical study or clinical stud* or clinical trial* or phase 2 clinical trial or prospective study).mp.	705,553
54	52 or 53	1,561,447
55	animal/ not (animal/ and human/)	16,370
56	(comment* or letter or editorial or note or short survey or conference review or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).mp.	134,954
57	55 or 56	146,914
58	(RET mutation or RET-mutation or RET mutant or RET-mutant or RET fusion or RET-fusion or RET proto oncogene or RET proto-oncogene or rearranged during transfection or oncogene RET or RET oncogene or c RET protein or c RET protein or c RET receptor tyrosine kinase or c RET tyrosine kinase or protein c RET or proto oncogene protein c RET or proto oncogene proteins c RET or proto-oncogene protein c RET or proto-oncogene proteins c RET or proto-oncogene protein c-RET or proto-oncogene proteins c-RET or proto-oncogene protein c RET or RET protein or RET receptor tyrosine kinase or RET tyrosine kinase or RET rearrangement or RET alteration RET altered or RET aberration).mp.	94
59	(9 and 58 and 54) not (51 or 57)	11
60	limit 59 to yr=‘2022 -Current’ [Limit not valid in DARE; records were retained]	2
61	(48 and 52) not (51 or 57)	2703
62	limit 61 to yr=‘2022 -Current’ [Limit not valid in DARE; records were retained]	221

Abbreviations: 2L = second line; DTC = differentiated thyroid cancer; LOT = line of therapy; MTC = medullary thyroid cancer; NSCLC = non-small cell lung cancer; PTC = papillary thyroid cancer; RCT = randomized controlled trial; RET = rearrangements and/or mutations during transfection; SLR = systematic literature review.

H.1.2 Systematic selection of studies

All abstracts were reviewed independently by two systematic reviewers using the DistillerSR® tool according to the eligibility criteria previously outlined in Table 94; any differences in opinion regarding eligibility were resolved through discussion with a third reviewer. The same process was applied to the subsequent review of full texts. The full texts were split according to the treatment line and subsequently, each treatment line was considered independently for inclusion of studies and data extraction.

A PRISMA flow diagram indicating the number of studies included and excluded at each stage of the review was developed. Studies excluded at the full-text stage were tabulated alongside the reason for exclusion in accordance with best practice guidelines.

H.1.2.1 Data extraction

Table 94 presents the inclusion and exclusion criteria the SLR. The inclusion and exclusion criteria were used to identify the population and disease condition, interventions, comparators, outcomes and study types (also known as the PICOS criteria).

Once all abstracts of potentially relevant published articles were identified, the screening of titles and abstracts was performed to determine study eligibility based on the inclusion and exclusion criteria.

Data were extracted into the extraction sheet in Microsoft Excel® by a single reviewer. For full publications included in the SLR, journal websites were cross-checked for the availability of publication corrections and electronic supplementary materials. The data from clinical trial websites were not extracted, as those data were not peer-reviewed. The extractions were independently verified and validated by a second reviewer. Any disagreements between the original extraction and validation were resolved through discussion with a third reviewer.

The following data, where reported, were extracted from each included study:

Table 101 Extraction from included studies

Data	Description of extraction

Study descriptors and treatments	• author and date of publication
	• study design (phase, location, and blinding)
	• clinical trial number
	• treatments (including schedule, median number of cycles, median time on treatment, and dosing)
	• main inclusion/exclusion criteria
	• crossover
	  ○ was crossover allowed (yes/no)
	  ○ details of crossover

Baseline characteristics	• number of patients randomised, intention-to-treat population and population used for baseline characteristics • age (mean, standard deviation, median, and range) • female (number of patients in this category [n], %) • race (n, %) • ethnicity (n, %) • mean body mass index (BMI) • smoking status (% of never smokers, current, or previous smokers) • diagnosis (staging [n, % at each American Joint Committee on Cancer (AJCC) stage], Eastern Cooperative Oncology Group/PS [n, %]) • histology (n, % of adenocarcinoma, large cell carcinoma, other [adenosquamous carcinoma and sarcomatoid carcinoma], and unknown) • biomarker status (n, % positive for anaplastic lymphoma kinase, epidermal growth factor receptor [EGFR], programmed death-ligand 1 [PD-L1], and ROS1 [c-ros oncogene])

	• tumour mutational burden (mean or median number of mutations per mega base)
Other data	• post-discontinuation therapies (% of patients in each arm with an additional line of therapy and % of patients on each type of post-discontinuation therapy) • study follow-up (median)

Efficacy endpoints	• survival (median 95% confidence interval [CI], hazard ratio 95% CI, 1- to 5-year survival rates [%], Kaplan Meier availability)
	  ○ progression-free survival (PFS) (or variants including event-free survival/failure-free survival/time to progression [TTP])
	  ○ overall survival (OS)
	• response (total number of patients analysed [N], number of patients with response [n] and %)
	  ○ overall response rate (ORR)
	  ○ complete response (CR)
	  ○ partial response (PR)
	  ○ stable disease
	  ○ progressive disease (PD)
	• subgroup analysis (PD-L1 Tumor Proportion Score [TPS] <1%, PD-L1 TPS 1-49%, PD-L1 TPS ≥50%)
	  ○ PFS (or variants including event-free survival/failure-free survival/TTP)
	  ○ OS
	  ○ ORR
	  ○ CR
	  ○ PR
	  ○ SD
	  ○ PD

Safety endpoints	• grade 3/4 adverse events (AEs) that are reported in ≥5% of patients in one or more treatment arms (N, n, and %) • overall discontinuation in the treatment phase (N, n, and %) • discontinuation due to AEs (N, n, and %)

Results

The search of electronic databases and conference proceedings was conducted from database inception to March 2023. The SLR1 was conducted on 12 January 2016, SLR2 (first update) on 13 June 2018, SLR3 (second update) on 29 July 2020, SLR4 (third update) on 30 July 2021, SLR5 (fourth update) on 20 July 2022 and SLR 6 (fifth update) on 15 March 2023. A total of 23,844 records were identified through database search, across the updates (SLR1: 15,069; SLR2: 3490; SLR3: 3169; SLR4: 700; SLR5: 752; and SLR 6: 664). In addition, 84 records were identified through conference proceedings and bibliographic searches. After de-duplication, a total of 16,396 records were screened. The abstracts of these records were reviewed for eligibility, out of which, 1069 full-text records were

assessed for further eligibility. Following a full-text review, 223 records describing 102 unique studies were included in the review.

- SLR1 and SLR2: A total of 37,118 records were identified. After de-duplication, 12,392 records were screened in level 1 and a total of 326 records were included for full-text screening. Of these, 64 records met the eligibility criteria. In addition, nine conference abstracts were also included in the review. In total, 27 studies were identified in SLR1 and 14 in SLR2.
- SLR3: A total of 3169 records were identified. After de-duplication 2229 records were screened at level 1 and a total of 61 records were included for full-text screening. Of these, 11 records met the eligibility criteria. In addition, 22 eligible conference abstracts were also included in the review. In total, eight new primary studies and 24 secondary records were identified in the SLR3.
- SLR4: A total of 700 records were identified. After de-duplication, 476 records were screened at level 1 and a total of 118 records were included for full-text screening. Of these, 33 records met the eligibility criteria. In addition, six eligible conference abstracts and one peer-reviewed article (identified through bibliographic search) were also included in the review. In total, 21 new primary studies and 18 secondary records were identified in SLR4.
- SLR5: A total of 768 records were identified. After de-duplication, 703 records were screened at level 1 and a total of 352 records were included for full-text screening. Of these, 37 records met the eligibility criteria. In total, 14 new primary studies and 23 secondary studies were identified in SLR5.
- SLR6: A total of 664 records were identified. After de-duplication, 547 records were screened at level 1 and a total of 152 records were included for full-text screening. Of these, 35 records met the eligibility criteria. In addition, 10 eligible conference abstracts and 20 studies (identified through bibliographic search) were also included in the review, making it a total of 65 records (18 new primary studies and 47 secondary studies).

Figure 45 is the PRISMA diagram describing the inclusion/ exclusion of articles at each stage of the review.

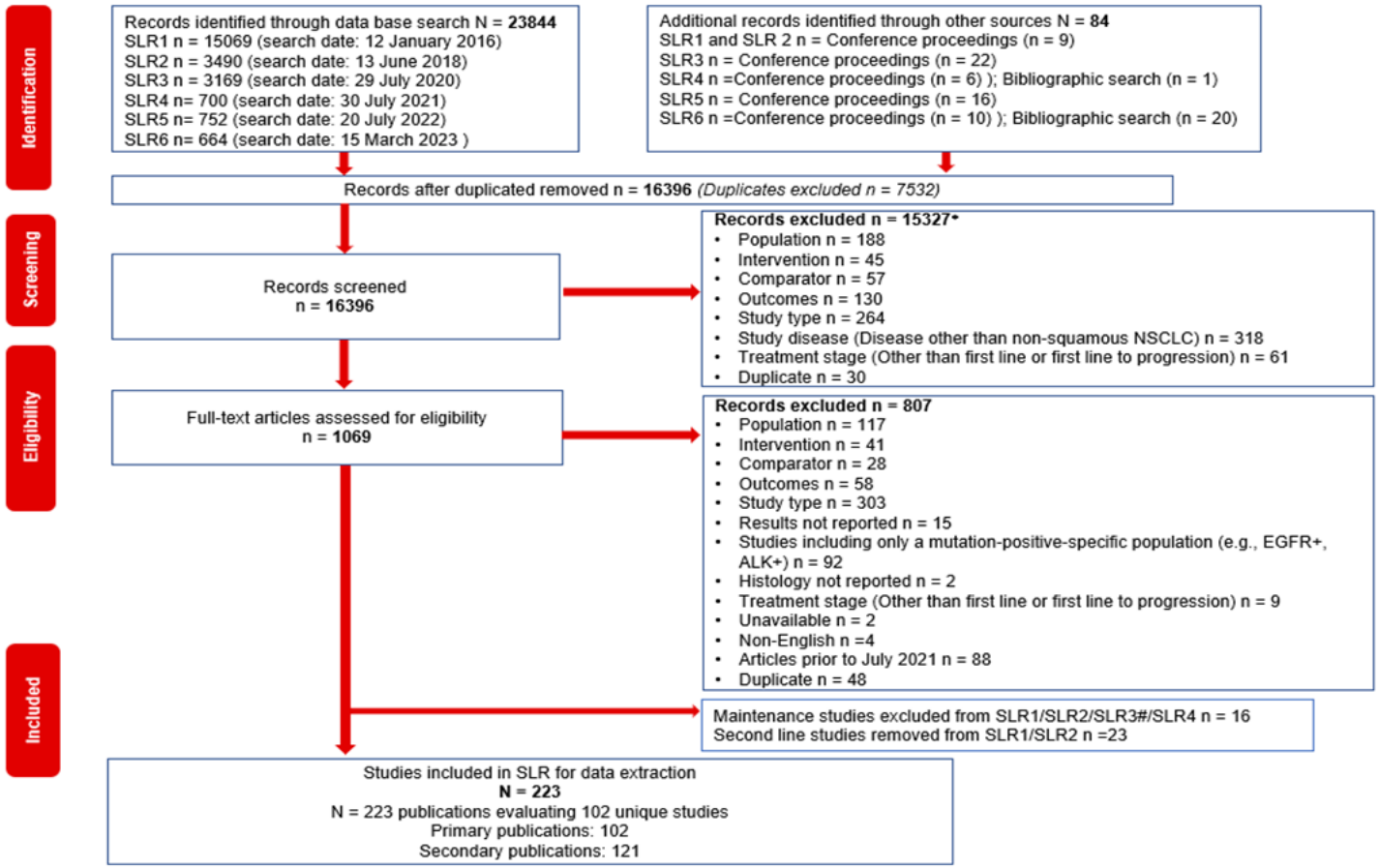


Figure 45 PRISMA flow diagram

The results of the systematic review have been structured according to the treatment line investigated:

- First-line treatment: Induction treatment is given for a fixed number of cycles.
- First-line to progression treatment: Induction treatment given for a fixed number of cycles in combination with an agent(s) given until disease progression or only agent/s given until disease progression.

Due to differences in study design, the characteristics and results of first-line to progression studies and first-line only studies are presented separately. Furthermore, the results for first-line to progression treatment were divided into studies investigating interventions in wider patients with nsq NSCLC and patients with RET fusion-positive NSCLC. Due to the presence of RET in the patient population, the characteristics and results of studies investigating first-line and first-line to progression interventions in patients with RET fusion-positive NSCLC and patients with nsq NSCLC are presented separately.

Table 102 Number of studies by population subtypes

Treatment line	SLR1	SLR2	SLR3	SLR4	SLR5	SLR6
First-line	10	2	0	0	0	0
NSCLC	10	2	0	0	0	0
RET fusion positive NSCLC	0	0	0	0	0	0
First-line to progression	17	12	8	21	16	19
NSCLC	17	12	8	19	15	19
RET fusion positive NSCLC	0	0	0	2	1	0

Table 103 Overview of studies included, first line studies

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
1	Gronberg (2009)	Grønberg BH, Bremnes RM, Fløtten O, Amundsen T, Brunsvig PF, Hjelde HH, Kaasa S, von Plessen C, Stornes F, Tollåli T, Wammer F. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. Journal of clinical oncology. 2009 Jul 1;27(19):3217-24.*	
2	Kader (2013)	Kader YA, Le Chevalier T, El-Nahas T, Sakr A. Comparative study analysing survival and safety of bevacizumab/carboplatin/paclitaxel and cisplatin/pemetrexed in chemotherapy-naive patients with advanced non-squamous bronchogenic carcinoma not harboring EGFR mutation. OncoTargets and therapy. 2013;6:803.*	
3	Rodrigues-Periera (2011)	Rodrigues-Pereira J, Kim JH, Magallanes M, Lee DH, Wang J, Ganju V, Martínez-Barrera L, Barraclough H, Van Kooten M, Orlando M. A randomised phase 3 trial comparing pemetrexed/carboplatin and docetaxel/carboplatin as first-line treatment for advanced, nonsquamous non-small cell lung cancer. Journal of Thoracic Oncology. 2011 Nov 1;6(11):1907-14.*	
4	Scagliotti (2008)	Scagliotti GV, Parikh P, Von Pawel J, Biesma B, Vansteenkiste J, Manegold C, Serwatowski P, Gatzemeier U, Digumarti R, Zukin M, Lee JS. Phase III study comparing cisplatin plus	Novello S, Pimentel FL, Douillard JY, O'Brien M, von Pawel J, Eckardt J, Liepa AM, Simms L, Visseren-Grul C, Paz-Ares L. Safety and resource utilization by non-small cell lung cancer histology: results from the randomised phase III

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. Journal of clinical oncology. 2008 Jul 20;26(21):3543-51.*	study of pemetrexed plus cisplatin versus gemcitabine plus cisplatin in chemonaive patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology. 2010 Oct 1;5(10):1602-8.*
5	Schuette (2013)	Schuette WH, Gröschel A, Sebastian M, Andreas S, Müller T, Schneller F, Guetz S, Eschbach C, Bohnet S, Leschinger MI, Reck M. A randomised phase II study of pemetrexed in combination with cisplatin or carboplatin as first-line therapy for patients with locally advanced or metastatic non–small-cell lung cancer. Clinical lung cancer. 2013 May 1;14(3):215-23.*	
6	Treat (2010)	Treat JA, Gonin R, Socinski MA, Edelman MJ, Catalano RB, Marinucci DM, Ansari R, Gillenwater HH, Rowland KM, Comis RL, Obasaju CK. A randomised, phase III multicenter trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin in patients with advanced or metastatic non-small-cell lung cancer. Annals of oncology. 2010 Mar 1;21(3):540-7.*	Treat J, Edelman MJ, Belani CP, Socinski MA, Monberg MJ, Chen R, Obasaju CK. A retrospective analysis of outcomes across histological subgroups in a three-arm phase III trial of gemcitabine in combination with carboplatin or paclitaxel versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. Lung cancer. 2010 Dec 1;70(3):340-6.*
7	Zhang (2013)	Zhang X, Lu J, Xu J, Li H, Wang J, Qin Y, Ma P, Wei L, He J. Pemetrexed plus platinum or gemcitabine plus platinum for advanced non-small cell lung cancer: final survival analysis from a multicenter randomised phase II trial in the East Asia region and a meta-analysis. Respirology. 2013 Jan;18(1):131-9.*	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
8	SICOG	Comella P, Chiuri VE, De Cataldis G, Filippelli G, Maiorino L, Vessia G, Cioffi R, Mancarella S, Putzu C, Greco E, Palmeri L. Gemcitabine combined with either pemetrexed or paclitaxel in the treatment of advanced non-small cell lung cancer: a randomised phase II SICOG trial. Lung Cancer. 2010 Apr 1;68(1):94-8.*	
9	Yu (2014)	Yu H, Zhang J, Wu X, Luo Z, Wang H, Sun S, Peng W, Qiao J, Feng Y, Wang J, Chang J. A phase II randomised trial evaluating gefitinib intercalated with pemetrexed/platinum chemotherapy or pemetrexed/platinum chemotherapy alone in unselected patients with advanced non-squamous non-small cell lung cancer. Cancer biology & therapy. 2014 Jul 1;15(7):832-9.*	
10	ET	Lee SM, Falzon M, Blackhall F, Spicer J, Nicolson M, Chaudhuri A, Middleton G, Ahmed S, Hicks J, Crosse B, Napier M. Randomised prospective biomarker trial of ERCC1 for comparing platinum and nonplatinum therapy in advanced non-small-cell lung cancer: ERCC1 trial (ET). Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2017 Feb;35(4):402-11.[#]	
11	TRAIL	Park CK, Oh IJ, Kim KS, Choi YD, Jang TW, Kim YS, Lee KH, Shin KC, Jung CY, Yang SH, Ryu JS. Randomised phase III study of docetaxel plus cisplatin versus pemetrexed plus cisplatin as first-line treatment of nonsquamous non–small-cell lung	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		cancer: a TRAIL trial. Clinical lung cancer. 2017 Jul 1;18(4):e289-96.#	
12	Kim (ESMO 2014)	Kim Y, Oh I, Kim K, Jang T, Choi YD, Kim YS, Lee K, Shin K, Jung CY, Yang S, Jang S. A randomised phase iii study of docetaxel plus cisplatin versus pemetrexed plus cisplatin in first line non-squamous non-small cell lung cancer (NSQ-NSCLC). Annals of Oncology. 2014 Sep 1;25:v1. *	
13	Ahn 2012	Ahn MJ, Yang JC, Liang J, Kang JH, Xiu Q, Chen YM, Blair JM, Peng G, Linn C, Orlando M. Randomised phase II trial of first-line treatment with pemetrexed-cisplatin, followed sequentially by gefitinib or pemetrexed, in East Asian, never-smoker patients with advanced non-small cell lung cancer. Lung cancer. 2012 Aug 1;77(2):346-52.*	
14	Boutsikou 2013	Boutsikou E, Kontakiotis T, Zarogoulidis P, Darwiche K, Eleptheriadou E, Porpodis K, Galaktidou G, Sakkas L, Hohenforst-Schmidt W, Tsakiridis K, Karaiskos T. Docetaxel-carboplatin in combination with erlotinib and/or bevacizumab in patients with non-small cell lung cancer. OncoTargets and therapy. 2013;6:125.*	
15	ERACLE	Galetta D, Cinieri S, Pisconti S, Gebbia V, Morabito A, Borsellino N, Maiello E, Febbraro A, Catino A, Rizzo P, Montrone M. Cisplatin/pemetrexed followed by maintenance pemetrexed versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in advanced nonsquamous lung cancer: the GOIM (Gruppo Oncologico	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		Italia Meridionale) ERACLE phase III randomized trial. Clinical lung cancer. 2015 Jul 1;16(4):262-73.*	
16	Johnson 2004	Johnson DH, Fehrenbacher L, Novotny WF, Herbst RS, Nemunaitis JJ, Jablons DM, Langer CJ, DeVore III RF, Gaudreault J, Damico LA, Holmgren E. Randomised phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. Journal of Clinical Oncology. 2004 Jun 1;22(11):2184-91.*	
17	Niho 2012	Niho S, Kunitoh H, Nokihara H, Horai T, Ichinose Y, Hida T, Yamamoto N, Kawahara M, Shinkai T, Nakagawa K, Matsui K. Randomised phase II study of first-line carboplatin-paclitaxel with or without bevacizumab in Japanese patients with advanced non-squamous non-small-cell lung cancer. Lung cancer. 2012 Jun 1;76(3):362-7.*	
18	Pointbreak	Patel JD, Socinski MA, Garon EB, Reynolds CH, Spigel DR, Olsen MR, Hermann RC, Jotte RM, Beck T, Richards DA, Guba SC. PointBreak: a randomised phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non–small-cell lung cancer. Journal of Clinical Oncology. 2013 Dec 1;31(34):4349.*	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
19	AVAiL	Reck M, von Pawel J, Zatloukal P, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non–small-cell lung cancer: AVAiL. Journal of Clinical Oncology. 2009 Mar 10;27(8):1227-34.*	Reck M, Von Pawel J, Zatloukal PV, Ramlau R, Gorbounova V, Hirsh V, Leighl N, Mezger J, Archer V, Moore N, Manegold C. Overall survival with cisplatin–gemcitabine and bevacizumab or placebo as first-line therapy for nonsquamous non-small-cell lung cancer: results from a randomised phase III trial (AVAiL). Annals of oncology. 2010 Sep 1;21(9):1804-9.*
			Leighl NB, Zatloukal P, Mezger J, Ramlau R, Moore N, Reck M, Manegold C. Efficacy and safety of bevacizumab-based therapy in elderly patients with advanced or recurrent nonsquamous non-small cell lung cancer in the phase III BO17704 study (AVAiL). J Thorac Oncol. 2010 Dec;5(12):1970-6. doi: 10.1097/JTO.0b013e3181f49c22. PMID: 20978447.
			Mok TS, Hsia TC, Tsai CM, Tsang K, Chang GC, Chang JW, Sirisinha T, Sriuranpong V, Thongprasert S, Chua DT, Moore N, Manegold C. Efficacy of bevacizumab with cisplatin and gemcitabine in Asian patients with advanced or recurrent non-squamous non-small cell lung cancer who have not received prior chemotherapy: a substudy of the Avastin in Lung trial. Asia Pac J Clin Oncol. 2011 Jun;7 Suppl 2:4-12. doi: 10.1111/j.1743-7563.2011.01397.x. Erratum in: Asia Pac J Clin Oncol. 2011 Sep;7(3):321. Thitiya, Sirisinha [corrected to Sirisinha, Thitiya]. PMID: 21585703.
20	Sandler 2006	Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH. Paclitaxel–carboplatin alone or with bevacizumab for non–small-cell lung cancer. New England Journal of Medicine. 2006 Dec 14;355(24):2542-50.*	Ramalingam SS, Dahlberg SE, Langer CJ, Gray R, Belani CP, Brahmer JR, Sandler AB, Schiller JH, Johnson DH; Eastern Cooperative Oncology Group. Outcomes for elderly, advanced-stage non small-cell lung cancer patients treated with bevacizumab in combination with carboplatin and paclitaxel: analysis of Eastern Cooperative Oncology Group Trial 4599. J Clin Oncol. 2008 Jan 1;26(1):60-5. doi: 10.1200/JCO.2007.13.1144. PMID: 18165641.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Sandler A, Yi J, Dahlberg S, Kolb MM, Wang L, Hambleton J, Schiller J, Johnson DH. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. J Thorac Oncol. 2010 Sep;5(9):1416-23. doi: 10.1097/JTO.0b013e3181da36f4. PMID: 20686429.
21	Socinski 2012	Socinski MA, Bondarenko I, Karaseva NA, Makhson AM, Vynnychenko I, Okamoto I, Hon JK, Hirsh V, Bhar P, Zhang H, Iglesias JL. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer: final results of a phase III trial. J Clin Oncol. 2012 Jun 10;30(17):2055-62.*	Socinski MA, Okamoto I, Hon JK, Hirsh V, Dakhil SR, Page RD, Orsini J, Yamamoto N, Zhang H, Renschler MF. Safety and efficacy analysis by histology of weekly nab-paclitaxel in combination with carboplatin as first-line therapy in patients with advanced non-small-cell lung cancer. Annals of oncology. 2013 Sep 1;24(9):2390-6.*
22	FASTACT-2	Wu YL, Lee JS, Thongprasert S, Yu CJ, Zhang L, Ladrera G, Srimuninnimit V, Sriuranpong V, Sandoval-Tan J, Zhu Y, Liao M. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. The lancet oncology. 2013 Jul 1;14(8):777-86.*	
23	BEYOND	Zhou C, Wu YL, Chen G, Liu X, Zhu Y, Lu S, Feng J, He J, Han B, Wang J, Jiang G. BEYOND: a randomised, double-blind, placebo-controlled, multicenter, phase III study of first-line carboplatin/paclitaxel plus bevacizumab or placebo in Chinese patients with advanced or recurrent nonsquamous non–small-cell lung cancer. Journal of Clinical Oncology. 2015 Jul 1;33(19):2197-204.*	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
24	PRONOUNCE	Zinner RG, Obasaju CK, Spigel DR, Weaver RW, Beck JT, Waterhouse DM, Modiano MR, Hrinczenko B, Nikolinakos PG, Liu J, Koustenis AG. PRONOUNCE: randomised, open-label, phase III study of first-line pemetrexed+carboplatin followed by maintenance pemetrexed versus paclitaxel+carboplatin+bevacizumab followed by maintenance bevacizumab in patients ith advanced nonsquamous non–small-cell lung cancer. Journal of Thoracic Oncology. 2015 Jan 1;10(1):134-42.*	
25	TASK	Ciuleanu T, Tsai CM, Tsao CJ, Milanowski J, Amoroso D, Heo DS, Groen HJ, Szczesna A, Chung CY, Chao TY, Middleton G. A phase II study of erlotinib in combination with bevacizumab versus chemotherapy plus bevacizumab in the first-line treatment of advanced non-squamous non-small cell lung cancer. Lung Cancer. 2013 Nov 1;82(2):276-81.*	
26	Doebele 2015	Doebele RC, Spigel D, Tehfe M, Thomas S, Reck M, Verma S, Eakle J, Bustin F, Goldschmidt Jr J, Cao D, Alexandris E. Phase 2, randomised, open-label study of ramucirumab in combination with first-line pemetrexed and platinum chemotherapy in patients with nonsquamous, advanced/metastatic non–small cell lung cancer. Cancer. 2015 Mar 15;121(6):883-92.*	
27	Georgoulias 2001	Georgoulias V, Papadakis EF, Alexopoulos AF, Tsiafaki X, Rapti A, Veslemes M, Palamidas P, Vlachonikolis I, Greek Oncology Cooperative Group (GOCG) for Lung Cancer. Platinum-based	Georgoulias V, Samonis G, Papadakis E, Alexopoulos A, Tsiafaki X, Rapti A, Veslemes M, Grigoratou T, Palamidas P, Kouroussis C, Mavroudis D. Comparison of docetaxel/cisplatin to docetaxel/gemcitabine as first-line

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		and non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a randomised multicenter trial. The Lancet. 2001 May 12;357(9267):1478-84.*	treatment of advanced non-small cell lung cancer: early results of a randomised trial. Lung cancer. 2001 Dec 1;34:47-51.*
28	Spigel 2012	Spigel DR, Hainsworth JD, Shipley DL, Ervin TJ, Kohler PC, Lubiner ET, Peyton JD, Waterhouse DM, Burris III HA, Greco FA. A randomised phase II trial of pemetrexed/gemcitabine/bevacizumab or pemetrexed/carboplatin/bevacizumab in the first-line treatment of elderly patients with advanced non-small cell lung cancer. Journal of Thoracic Oncology. 2012 Jan 1;7(1):196-202.*	
29	INNOVATIONS	Thomas M, Fischer J, Andreas S, Kortsik C, Grah C, Serke M, von Eiff M, Witt C, Kollmeier J, Müller E, Schenk M. Erlotinib and bevacizumab versus cisplatin, gemcitabine and bevacizumab in unselected nonsquamous nonsmall cell lung cancer. European Respiratory Journal. 2015 Jul 1;46(1):219-29.*	
30	CheckMate 227	Hellmann MD, Ciuleanu TE, Pluzanski A, Lee JS, Otterson GA, Audigier-Valette C, Minenza E, Linardou H, Burgers S, Salman P, Borghaei H. Nivolumab plus ipilimumab in lung cancer with a high tumour mutational burden. New England Journal of Medicine. 2018 May 31;378(22):2093-104.[#]	Borghaei H, Hellmann MD, Paz-Ares L, Ramalingam SS, Reck M, O'Byrne KJ, Bhagavatheeswaran P, Nathan F, Brahmer J. nivolumab+ipilimumab, nivolumab+chemotherapy, and chemotherapy in chemo-naive patients with advanced non-small cell lung cancer and< 1% tumour PD-L1 expression: results from CheckMate 227. InAmerican Society of Clinical Oncology (ASCO) 2018.*
			Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, Carcereny Costa E, Park K, Alexandru A, Lupinacci L, de la Mora Jimenez E, Sakai H.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. New England Journal of Medicine. 2019 Nov 21;381(21):2020-31.[@]
			Borghaei H, Hellmann MD, Paz-Ares LG, Ramalingam SS, Reck M, O'Byrne KJ, et al. Nivolumab (Nivo)+platinum-doublet chemotherapy (Chemo) vs chemo as first-line (1L) treatment (Tx) for advanced non-small cell lung cancer (NSCLC) with <1% tumour PD-L1 expression: Results from CheckMate 227. 2018;36(15_suppl):9001[@]
			Peters S, Ramalingam SS, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim SW, et al. LBA4_PR - Nivolumab (NIVO)+low-dose ipilimumab (IPI) vs platinum-doublet chemotherapy (chemo) as first-line (1L) treatment (tx) for advanced non-small cell lung cancer (NSCLC): CheckMate 227 part 1 final analysis. Annals of Oncology. 2019;30:v913-v4[@]
			Reck M, Hellmann MD, Paz-Ares LG, Ramalingam SS, Brahmer JR, O'Byrne KJ, et al. Nivolumab (Nivo)+Ipilimumab (Ipi) vs Platinum-Doublet Chemotherapy (Chemo) as First-line (1L) Treatment (Tx) for Advanced Non-Small Cell Lung Cancer (NSCLC): Safety Analysis and Patient-Reported Outcomes (PROs) From CheckMate 227. 2018;36(15_suppl):9020[@]
			Ramalingam SS, Ciuleanu TE, Pluzanski A, Lee JS, Schenker M, Caro RB, Lee KH, Zurawski B, Audigier-Valette C, Provencio M, Linardou H. OA03. 03 Nivolumab (NIVO)+ipilimumab (IPI) Versus Platinum-Doublet Chemotherapy (Chemo) as First-Line (1L) Treatment for Advanced Non-Small Cell Lung Cancer (aNSCLC): 3-year Update from CheckMate 227 Part 1. Journal of Thoracic Oncology. 2021 Jan 1;16(1):S2-3.[$]
			Nivolumab (N)+Low-Dose Ipilimumab (I) vs Platinum-Doublet Chemotherapy (Chemo) as First-Line (1L) Treatment (tx) for Advanced Non-Small Cell Lung

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Cancer (NSCLC): Checkmate 227 Part 1 Final Analysis. Oncol Res Treat 2020;43(suppl 1):1–265[$]
			Paz-Ares LG, Ciuleanu T-E, Lee J-S, Urban L, Caro RB, Park K, et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. 2021;39(15_suppl):9016[$]
			K.J. O'Byrne, K.H. Lee, S.-W. Kim, K. Park, M. Nishio, H. Sakai, Y. Ohe, T. Fukuhara, J.-H. Kang, H. Daga, C.-J. Yu, K. Hotta, H. Tanaka, M. Takeda, T. Yokoyama, F.E. Nathan, J.-S. Lee, First-line nivolumab + ipilimumab in advanced NSCLC: CheckMate 227 subpopulation analyses in Asian patients☆,
			ESMO Open, Volume 7, Issue 1, 2022, 100394,ISSN2059-7029, https://doi.org/10.1016/j.esmoop.2022.100394.
			Paz-Ares LG, Ramalingam SS, Ciuleanu TE, Lee JS, Urban L, Caro RB, Park K, Sakai H, Ohe Y, Nishio M, Audigier-Valette C. First-line nivolumab plus ipilimumab in advanced NSCLC: 4-year outcomes from the randomized, open-label, phase 3 CheckMate 227 part 1 trial. Journal of Thoracic Oncology. 2022 Feb 1;17(2):289-308.
			Thomas M., Ramalingam S.S., Ciuleanu T.E., Pluzanski A., Lee J.-S., Schenker M., Bernabé Caro R., Lee K.H., Zurawski B., Audigier-Valette C., Provencio M., Linardou H., Kim S.-W., Borghaei H., Hellmann M.D., O'Byrne K.J., Paz-Ares L.G., Reck M., Nathan F.E., Brahmer J.R. Nivolumab (NIVO) + ipilimumab (IPI) versus platinum-doublet chemotherapy as first-line treatment for advanced non-small cell lung cancer: Three-year update from CheckMate 227 Part 1. Oncol Res Treat 2020;43(suppl 4):140-141

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Julie R. Brahmer, Jong-Seok Lee, Tudor-Eliade Ciuleanu, Reyes Bernabe Caro, Makoto Nishio, Lazlo Urban, Clarisse Audigier-Valette, Lorena Lupinacci, Randeep S. Sangha, Luis G. Paz-Ares, Martin Reck, Hossein Borghaei, Kenneth John O'Byrne, Ravi Gupta, Judith Bushong, Li Li, Steven I. Blum, Laura Eccles, and Suresh S. Ramalingam Journal of Clinical Oncology 2022 40:17_suppl, LBA9025-LBA9025
			Martin Reck ; Julie R. Brahmer ; Jong-Seok Lee ; Tudor-Eliade Ciuleanu ; Reyes Bernabe Caro ; Makoto Nishio ; Laszlo Urban ; Clarisse Audigier-Valette ; Lorena Lupinacci ; Randeep Sangha; Luis Paz-Ares; Hossein Borghaei; Kenneth John O'byrne; Ravi G. Gupta; Judith Bushong; LI LI; Steven I. Blum; Laura Eccles; Suresh S. Ramalingam. Five-year survival outcomes with nivolumab (NIVO) + ipilimumab (IPI) vs chemotherapy (chemo) as first-line (1L) treatment for metastatic non-small cell lung cancer (mNSCLC): Results from CheckMate 227 Oncol Res Treat 2022;45(suppl 1):5 DOI: 10.1159/000521004
			H. Borghaei, J.R. Brahmer, J.-S. Lee, T.-E. Ciuleanu, R. Bernabe Caro, M. Nishio, L. Urban, C. Audigier-Valette, L. Lupinacci, R. Sangha, L.G. Paz-Ares, M. Reck, K. John O'Byrne, R.G. Gupta, J. Bushong, L. Li, S.I. Blum, L. Eccles, S.S. Ramalingam, PPD04.02 First-Line Nivolumab + Ipilimumab (NIVO+IPI) in Metastatic NSCLC: 5-Year Survival in CheckMate 227, Journal of Thoracic Oncology,Volume 18, Issue 3, Supplement, 2023,Pages e8-e9,ISSN 1556-0864, https://doi.org/10.1016/j.jtho.2022.09.024.
			Julie R. Brahmer, Jong-Seok Lee, Tudor-Eliade Ciuleanu, Reyes Bernabe Caro, Makoto Nishio, Laszlo Urban, Clarisse Audigier-Valette, Lorena Lupinacci, Randeep Sangha, Adam Pluzanski, Jacobus Burgers, Mauricio Mahave, Samreen Ahmed, Adam J. Schoenfeld, Luis G. Paz-Ares, Martin Reck, Hossein

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Borghaei, Kenneth J. O'Byrne, Ravi G. Gupta, Judith Bushong, Li Li, Steven I. Blum, Laura J. Eccles, and Suresh S. Ramalingam Journal of Clinical Oncology 2023 41:6, 1200-1212
			Reck M, Ciuleanu TE, Lee JS, Schenker M, Zurawski B, Kim SW, Mahave M, Alexandru A, Peters S, Pluzanski A, Caro RB, Linardou H, Burgers JA, Nishio M, Martinez-Marti A, Azuma K, Axelrod R, Paz-Ares LG, Ramalingam SS, Borghaei H, O'Byrne KJ, Li L, Bushong J, Gupta RG, Grootendorst DJ, Eccles LJ, Brahmer JR. Systemic and Intracranial Outcomes With First-Line Nivolumab Plus Ipilimumab in Patients With Metastatic NSCLC and Baseline Brain Metastases From CheckMate 227 Part 1. J Thorac Oncol. 2023 Aug;18(8):1055-1069. doi: 10.1016/j.jtho.2023.04.021. Epub 2023 May 3. PMID: 37146754.
31	Lynch 2012	Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, Sebastian M, Neal J, Lu H, Cuillerot JM, Reck M. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non–small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. Journal of clinical oncology. 2012 Jun 10;30(17):2046-54.[#]	
32	IMPower150	Socinski MA, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F, Finley G. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. New England Journal of Medicine. 2018 Jun 14;378(24):2288-301.[#]	Reck M, Socinski MA, Cappuzzo F, Orlandi FJ, Stroyakovskiy D, Nogami N, et al. 134PD Primary PFS and safety analyses of a randomised phase III study of carboplatin+paclitaxel+Q bevacizumab, with or without atezolizumab in 1L non-squamous metastatic NSCLC (IMpower150). 2018;13.[@]
			Socinski MA, Mok TS, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, et al. Abstract CT216: IMpower150 final analysis: Efficacy of atezolizumab (atezo)+bevacizumab (bev) and chemotherapy in first-line (1L) metastatic

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			nonsquamous (nsq) non-small cell lung cancer (NSCLC) across key subgroups. 2020;80(16 Supplement):CT216-CT.[@]
			Reck M, Wehler T, Orlandi F, Nogami N, Barone C, Moro-Sibilot D, Shtivelband M, Larriba JG, Rothenstein J, Frueh M, Shankar G. IMpower150: Clinical safety, tolerability and immune-related adverse events in a phase III study of atezolizumab (atezo)+chemotherapy (chemo)±bevacizumab (bev) vs chemo+bev in 1L nonsquamous NSCLC. Annals of Oncology. 2018 Oct 1;29:viii498-9.[@]
			Socinski MA, Jotte RM, Cappuzzo F, Orlandi FJ, Stroyakovskiy D, Nogami N, et al. Overall survival (OS) analysis of IMpower150, a randomised Ph 3 study of atezolizumab (atezo)+chemotherapy (chemo) ± bevacizumab (bev) vs chemo+bev in 1L nonsquamous (NSQ) NSCLC. 2018;36(15_suppl):9002[@]
			Socinski MA, Nishio M, Jotte RM, Cappuzzo F, Orlandi F, Stroyakovskiy D, Nogami N, Rodríguez-Abreu D, Moro-Sibilot D, Thomas CA, Barlesi F. IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Nov 1;16(11):1909-24.[$]
33	EAGLES	De Marinis F, Bidoli P, Luciani A, Amoroso D, Tonini G, Bertolini A, Brandes AA, Migliorino MR, Favaretto A, Gridelli C. EAGLES study: first-line bevacizumab in combination with chemotherapy in elderly patients with advanced, metastatic, non-squamous non-small cell lung cancer. Anticancer research. 2017 May 1;37(5):2457-64.[#]	
34	KEYNOTE-189	Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, Domine M, Clingan P, Hochmair MJ, Powell SF,	Gadgeel S, Rodríguez-Abreu D, Speranza G, Esteban E, Felip E, Dómine M, et al. Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		Cheng SY. Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer. New England journal of medicine. 2018 May 31;378(22):2078-92.[#]	Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non–Small-Cell Lung Cancer. 2020;38(14):1505-17[@]
			Gadgeel SM, Garassino MC, Esteban E, Speranza G, Felip E, Hochmair MJ, et al. KEYNOTE-189: Updated OS and progression after the next line of therapy (PFS2) with pembrolizumab (pembro) plus chemo with pemetrexed and platinum vs placebo plus chemo for metastatic nonsquamous NSCLC. 2019;37(15_suppl):9013[@]
			Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, Kasahara K, Hattori Y, Ichihara E, Adachi N, Sawada T. Safety and tolerability of pembrolizumab or placebo plus pemetrexed and platinum as first-line therapy in Japanese patients (PTS) with metastatic non-squamous non-small cell lung cancer (NSCLC) enrolled in the phase III KEYNOTE-189 study. Annals of Oncology. 2019 Apr 1;30:ii56-7.[@]
			Rodriguez Abreu D, Garassino MC, Esteban E, Speranza G, Felip E, Domine M, et al. KEYNOTE-189 study of pembrolizumab (pembro) plus pemetrexed (pem) and platinum vs placebo plus pem and platinum for untreated, metastatic, nonsquamous NSCLC: Does choice of platinum affect outcomes? Annals of Oncology. 2018;29:ix164[@]
			Gray J, Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY. FP13. 02 Pembrolizumab+Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology. 2021 Mar 1;16(3):S224.[$]
			Rodríguez-Abreu D, Powell SF, Hochmair MJ, Gadgeel S, Esteban E, Felip E, Speranza G, De Angelis F, Dómine M, Cheng SY, Bischoff HG. Pemetrexed plus

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189. Annals of Oncology. 2021 Jul 1;32(7):881-95.[$]
			Marina C. Garassino, Shirish Gadgeel, Giovanna Speranza, Enriqueta Felip, Emilio Esteban, Manuel Dómine, Maximilian J. Hochmair, Steven F. Powell, Helge G. Bischoff, Nir Peled, Francesco Grossi, Ross R. Jennens, Martin Reck, Rina Hui, Edward B. Garon, Takayasu Kurata, Jhanelle E. Gray, Paul Schwarzenberger, Erin Jensen, M. Catherine Pietanza, and Delvys Rodríguez-Abreu Journal of Clinical Oncology 2023 41:11, 1992-1998
35	KEYNOTE-189 - Japan	Horinouchi H, Nogami N, Saka H, Nishio M, Tokito T, Takahashi T, et al. Pembrolizumab plus pemetrexed-platinum for metastatic nonsquamous non-small-cell lung cancer: KEYNOTE-189 Japan Study. Cancer science. 2021;112(8):3255-65.[$]	
36	Karayama 2016#	Maintenance therapy with pemetrexed and bevacizumab versus pemetrexed monotherapy after induction therapy with carboplatin, pemetrexed, and bevacizumab in patients with advanced non-squamous non small cell lung cancer.[#]	
37	KEYNOTE-021	Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. The lancet oncology. 2016 Nov 1;17(11):1497-508.[#]	Borghaei H, Langer C, Gadgeel S, Papadimitrakopoulou V, Patnaik A, Powell S, Gentzler R, Martins R, Stevenson J, Jalal S, Panwalkar A. OA 17.01 Pemetrexed-Carboplatin Plus Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC: KEYNOTE-021 Cohort G Update. Journal of Thoracic Oncology. 2017 Nov 1;12(11):S1791.[#]
			Gentzler RD, Langer CJ, Borghaei H, Gadgeel SM, Papadimitrakopoulou V, Patnaik A, Powell SF, Martins RG, Stevenson J, Jalal SI, Panwalkar AW. 24-

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			month overall survival from KEYNOTE-021 cohort G: Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC.[#]
			Borghaei H, Langer CJ, Gadgeel S, Papadimitrakopoulou VA, Patnaik A, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Jalal SI, Panwalkar A. 24-month overall survival from KEYNOTE-021 cohort G: Pemetrexed and carboplatin with or without Pembrolizumab as first-line therapy for advanced nonsquamous non–small cell lung Cancer. Journal of Thoracic Oncology. 2019 Jan 1;14(1):124-9.[@]
			Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI. Long-term overall survival from KEYNOTE-021 cohort G: pemetrexed and carboplatin with or without pembrolizumab as first-line therapy for advanced nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Jan 1;16(1):162-8.[$]
			Awad MM, Gadgeel SM, Borghaei H, Patnaik A, Yang JC, Powell SF, Gentzler RD, Martins RG, Stevenson JP, Altan M, Jalal SI. OFP01. 02 KEYNOTE-021 Cohort G Long-Term Follow-up: First-Line (1L) Pemetrexed and Carboplatin (PC) with or without Pembrolizumab for Advanced Nonsquamous NSCLC. Journal of Thoracic Oncology. 2021 Jan 1;16(1):S8.[$]
			Gadgeel SM, Stevenson JP, Langer CJ, Gandhi L, Borghaei H, Patnaik A, Villaruz LC, Gubens M, Hauke R, Yang JC, Sequist LV, Bachman R, Saraf S, Raftopoulos H, Papadimitrakopoulou V. Pembrolizumab and platinum-based chemotherapy as first-line therapy for advanced non-small-cell lung cancer: Phase 1 cohorts from the KEYNOTE-021 study. Lung Cancer. 2018 Nov;125:273-281. doi: 10.1016/j.lungcan.2018.08.019. Epub 2018 Aug 25. PMID: 30429032; PMCID: PMC6886233.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
38	KEYNOTE-024	Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. N engl J med. 2016 Nov 10;375:1823-33.[#]	Brahmer JR, Rodriguez-Abreu D, Robinson AG, Hui R, Csõszi T, Fülöp A, et al. Progression after the next line of therapy (PFS2) and updated OS among patients (pts) with advanced NSCLC and PD-L1 tumour proportion score (TPS) ≥50% enrolled in KEYNOTE-024. 2017;35(15_suppl):9000[#]
			Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Updated Analysis of KEYNOTE-024: Pembrolizumab Versus Platinum-Based Chemotherapy for Advanced Non-Small-Cell Lung Cancer With PD-L1 Tumour Proportion Score of 50% or Greater. J Clin Oncol. 2019;37(7):537-46.[@]
			Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T,'Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M. Five-year outcomes with pembrolizumab versus chemotherapy for metastatic non–small-cell lung cancer with PD-L1 tumour proportion score≥ 50%. Journal of Clinical Oncology. 2021 Apr:JCO-21.[$]
			J.R. Brahmer , D. Rodriguez-Abreu , A.G. Robinson , R. Hui , T. Csoszi }, A. Fülöp , M. Gottfried , N. Peled , A. Tafreshi , S. Cuffe , M. O'Brien, S. Rao, K. Hotta, T.A. Leal, J.W. Riess, E. Jensen, B. Zhao, M.C. Pietanza, M. Reck. KEYNOTE-024 5-year OS update: First-line (1L) pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) in patients (pts) with metastatic NSCLC and PD-L1 tumour proportion score (TPS) ‡50%. Annals of Oncology. 2020 Volume 21 S1181-S1182.
39	65Plus	Schuette W, Schneider CP, Engel-Riedel W, Schumann C, Kohlhaeufl M, Serke MH, Hoeffken G, Kortsik C, Reck M. 65Plus: open-label study of bevacizumab in combination with pemetrexed or pemetrexed/carboplatin as first-line treatment of patients with advanced or recurrent	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		nonsquamous non-small-cell lung cancer. Lung Cancer: Targets and Therapy. 2017;8:217.[#]	
40	Spigel 2018	Spigel DR, Hainsworth JD, Joseph MJ, Shipley DL, Hagan MK, Thompson DS, Burris III HA, Greco FA. Randomised phase 2 trial of pemetrexed, pemetrexed/bevacizumab, and pemetrexed/carboplatin/bevacizumab in patients with stage IIIB/IV non–small cell lung cancer and an Eastern Cooperative Oncology Group performance status of 2. Cancer. 2018 May 1;124(9):1982-91.[#]	
41	Lee ASCO 2016	Lee DH, Cho EK, Ahn JS, Kim D-W, Cho BC, Lee KH, et al. Open-label, multicenter, randomised phase III trial of pemetrexed/carboplatin doublet vs pemetrexed singlet in chemotherapy-naive elderly patients aged 70 or more with advanced non-squamous non-small cell lung cancer and good performance status. 2016;34(15_suppl):9081.[#]	
42	KEYNOTE 042	Lopes G, Wu Y-L, Kudaba I, Kowalski D, Cho BC, Castro G, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumour proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. 2018;36(18_suppl):LBA4-LBA.[#]	Mok TS, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, Castro Jr G, Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. The Lancet. 2019 May 4;393(10183):1819-30.[@] Lopes G, Wu Y-L, Kudaba I, Kowalski D, Cho BC, Castro G, et al. Pembrolizumab (pembro) versus platinum-based chemotherapy (chemo) as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumour proportion score (TPS) ≥ 1%: Open-label, phase 3 KEYNOTE-042 study. 2018;36(18_suppl):LBA4-LBA.[@]

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Mok TS, Wu YL, Kudaba I, Kowalski DM, Cho BC, Turna HZ, de Castro G, Srimuninnimit V, Laktionov KK, Bondarenko I, Kubota K. Final analysis of the phase III KEYNOTE-042 study: Pembrolizumab (Pembro) versus platinum-based chemotherapy (Chemo) as first-line therapy for patients (Pts) with PD-L1–positive locally advanced/metastatic NSCLC. Annals of Oncology. 2019 Apr 1;30:i38.[@]
			Cho BC, Wu Y, Lopes G, Kudaba I, Kowalski DM, Turna HZ, De Castro G, Caglevic C, Zhang L, Karaszewska B, Laktionov KK. FP13. 04 KEYNOTE-042 3-Year Survival Update: 1L Pembrolizumab vs Platinum-Based Chemotherapy for PD-L1+Locally Advanced/Metastatic NSCLC. Journal of Thoracic Oncology. 2021 Mar 1;16(3):S225-6.[$]
			Castro GD, Kudaba I, Wu Y, et al. 363 KEYNOTE-042 5-year survival update: pembrolizumab versus chemotherapy in patients with previously untreated, PD-L1–positive, locally advanced or metastatic non–small-cell lung cancer. Journal for ImmunoTherapy of Cancer 2021;9:doi: 10.1136/jitc-2021-SITC2021.363
			Gilberto de Castro Jr, Iveta Kudaba, Yi-Long Wu, Gilberto Lopes, Dariusz M. Kowalski, Hande Z. Turna, Christian Caglevic, Li Zhang, Boguslawa Karaszewska, Konstantin K. Laktionov, Vichien Srimuninnimit, Igor Bondarenko, Kaoru Kubota, Rinee Mukherjee, Jianxin Lin, Fabricio Souza, Tony S.K. Mok, and Byoung Chul Cho. Journal of Clinical Oncology 2023 41:11, 1986-1991
			Kaoru Kubota , Byoung Chul Cho , Vichien Srimuninnimit , Yu Fan , Jianying Zhou , Li Zhang , Qing Zhou , Yukio Hosomi , Hiroaki Takeoka, Rinee Mukherjee, Wei Fu, Fabricio Souza, Tony S.K. Mok, Li Zhang. O8-4 KEYNOTE-042: 5-year

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			update of first-line pembrolizumab in Asian patients with locally advanced/metastatic PD-L1-positive NSCLC.
			Y. Wu, L. Zhang, Y. Fan, J. Zhou, L. Zhang, Q. Zhou, W. Li, C. Hu, G. Chen, X. Zhang, C. Zhou, T. Dang, J. Penrod, D. Kush, Y. Qin, B. Li, T. Mok. KEYNOTE-042 China Study: First-Line Pembrolizumab vs Chemotherapy in Chinese Patients with Advanced NSCLC with PD-L1 TPS 1%. Journal of Thoracic Oncology Vol. 14, S290-S291.
43	KEYNOTE-042 - China	Wu YL, Zhang L, Fan Y, Zhou J, Zhang L, Zhou Q, et al. Randomised clinical trial of pembrolizumab vs chemotherapy for previously untreated Chinese patients with PD-L1-positive locally advanced or metastatic non-small-cell lung cancer: KEYNOTE-042 China Study. International journal of cancer. 2021;148(9):2313-20.[$]	
44	JCOG1210/WJOG7813L	Okamoto I, Nokihara H, Nomura S, Niho S, Sugawara S, Horinouchi H, Azuma K, Yoneshima Y, Murakami H, Hosomi Y, Atagi S. Comparison of Carboplatin Plus Pemetrexed Followed by Maintenance Pemetrexed With Docetaxel Monotherapy in Elderly Patients With Advanced Nonsquamous Non–Small Cell Lung Cancer: A Phase 3 Randomised Clinical Trial. JAMA oncology. 2020 May 1;6(5):e196828.[@]	Okamoto I, Nokihara H, Yoh K, Sugawara S, Horinouchi H, Azuma K, et al. Randomised phase III study comparing carboplatin plus pemetrexed followed by pemetrexed versus docetaxel in elderly patients with advanced non-squamous non-small-cell lung cancer (JCOG1210/WJOG7813L). 2019;37(15_suppl):9031.[@]
45	IMPower130	West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, McCune S, Mekhail T, Zer A. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-	West HL, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Abstract CT200: IMpower130: Progression-free survival (PFS) and safety analysis from a randomised phase 3 study of carboplatin+nab-paclitaxel (CnP) with or without atezolizumab as first-line (1L) therapy in advanced non-squamous NSCLC. 2019;79(13 Supplement):CT200-CT.[@]

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		small-cell lung cancer (IMpower130): a multicenter, randomised, open-label, phase 3 trial. The Lancet Oncology. 2019 Jul 1;20(7):924-37.[@]	Cappuzzo F, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, Kopp HG, Daniel D, Mccune S, Mekhail T, Zer A. IMpower130: Progression-free survival (PFS) and safety analysis from a randomised phase III study of carboplatin+nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. Annals of Oncology. 2018 Oct 1;29:viii742-3.[@]
			A randomised phase 3 study of Carboplatin+NAB-paclitaxel with or without atezolizumab as first-line therapy in advanced non-squamous NSCLC: Impower130. Tumori J. Vol 105, Issue 6_suppl, 2019.[$]
46	IMPOWER132	Nishio M, Barlesi F, West H, Ball S, Bordoni R, Cobo M, Longeras PD, Goldschmidt Jr J, Novello S, Orlandi F, Sanborn RE. Atezolizumab Plus Chemotherapy for First-Line Treatment of Nonsquamous NSCLC: Results From the Randomised Phase 3 IMpower132 Trial. Journal of Thoracic Oncology. 2021 Apr 1;16(4):653-64.[$]	Barlesi F, Nishio M, Cobo M, Steele N, Paramonov V, Parente B, Dear R, Berard H, Peled N, Seneviratne LC, Baldini E. IMpower132: efficacy of atezolizumab (atezo)+carboplatin (carbo)/cisplatin (cis)+pemetrexed (pem) as 1L treatment in key subgroups with stage IV non-squamous non-small cell lung cancer (NSCLC). Annals of Oncology. 2018 Oct 1;29:viii743-4.[@]
			Papadimitrakopoulou V, Cobo M, Bordoni R, dubray-Longeras P, Szalai Z, Ursol G, et al. OA05.07 IMpower132: PFS and Safety Results with 1L Atezolizumab+Carboplatin/Cisplatin+Pemetrexed in Stage IV Non-Squamous NSCLC. Journal of Thoracic Oncology. 2018;13:S332-S3.[@]
47	IMPOWER132 - China	Lu S, Fang J, Wang Z, Fan Y, Liu Y, He J, Cao B, Zhou J, Hu J, Xia J, liu W. 102P Primary results from the China cohort of IMpower132: Atezolizumab (atezo)+carboplatin (carbo) or cisplatin (cis)+pemetrexed (pem) as first-line therapy in advanced NSCLC. Journal of Thoracic Oncology. 2021 Apr 1;16(4):S753.[$]	Lu S, Fang J, Wang Z, Fan Y, Liu Y, He J, Zhou J, Hu J, Xia J, Liu W, Shi J, Yi J, Cao L. Results from the IMpower132 China cohort: Atezolizumab plus platinum-based chemotherapy in advanced non-small cell lung cancer. Cancer Med. 2023 Feb;12(3):2666-2676. doi: 10.1002/cam4.5144. Epub 2022 Sep 2. PMID: 36052772; PMCID: PMC9939192.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
48	IMPOWER132 - Japan	Nishio M, Saito H, Goto K, Watanabe S, Sueoka-Aragane N, Okuma Y, Kasahara K, Chikamori K, Nakagawa Y, Kawakami T. IMpower132: Atezolizumab plus platinum-based chemotherapy vs chemotherapy for advanced NSCLC in Japanese patients. Cancer science. 2021 Apr;112(4):1534.[$]	
49	ORIENT-11	Yang Y, Wang Z, Fang J, Yu Q, Han B, Cang S, Chen G, Mei X, Yang Z, Ma R, Bi M. Efficacy and safety of sintilimab plus pemetrexed and platinum as first-line treatment for locally advanced or metastatic nonsquamous NSCLC: a randomised, double-blind, phase 3 study (Oncology pRogram by InnovENT anti-PD-1-11). Journal of Thoracic Oncology. 2020 Oct 1;15(10):1636-46.[$]	Yang, Y., Sun, J., Wang, Z., Fang, J., Yu, Q., Han, B., Cang, S., Chen, G., Mei, X., Yang, Z., Ma, R., Bi, M., Ren, X., Zhou, J., Li, B., Song, Y., Feng, J., Li, J., He, Z., Zhou, R., … Zhang, L. (2021). Updated Overall Survival Data and Predictive Biomarkers of Sintilimab Plus Pemetrexed and Platinum as First-Line Treatment for Locally Advanced or Metastatic Nonsquamous NSCLC in the Phase 3 ORIENT-11 Study. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 16(12), 2109–2120. https://doi.org/10.1016/j.jtho.2021.07.015 Zhang L, Wang Z, Fang J, Yu Q, Han B, Cang S, Chen G, Mei X, Yang Z, Stefaniak V, Lin Y. Final overall survival data of sintilimab plus pemetrexed and platinum as First-Line treatment for locally advanced or metastatic nonsquamous NSCLC in the Phase 3 ORIENT-11 study. Lung Cancer. 2022 Sep 1;171:56-60. Yunpeng Yang, Zhehai Wang, Jian Fang, Qitao Yu, Baohui Han, Shundong Cang, Gongyan Chen, Xiaodong Mei, Zhixiong Yang, Victoria Jennifer Stefaniak, David Raymond Ferry, Yumin Zhao, Shuyan Wang, Yan Wang, Luyao Sun, and Li Zhang Journal of Clinical Oncology 2022 40:16_suppl, e21157-e21157
50	Hensing 2019	Hensing TA, Wang XF, Gao J, Stinchcombe T, Knopp MV, Dudek AZ, et al. Randomised multicenter phase II trial	https://clinicaltrials.gov/study/NCT02591615?tab=results

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		evaluating the sequencing of PD-1 inhibition with pembrolizumab (P) and standard platinum-based chemotherapy (C) in patients (pts) with metastatic non-small cell lung cancer (NSCLC) (AFT-09). 2019;37(15_suppl):9088[@]	
51	CLEAR	Koyama R, Udagawa H, Sugiyama E, Komuta K, Mori M, Yokoyama T, Sasaki T, Saito H, Ishida H, Nakagawa H, Sekine A. Randomised phase II study comparing cisplatin+pemetrexed+bevacizumab with carboplatin+paclitaxel+bevacizumab in treatment-naïve advanced non-squamous non-small cell lung cancer (CLEAR study). Annals of Oncology. 2018 Oct 1;29:viii518.[@]	Harada T, Udagawa H, Sugiyama E, Atagi S, Koyama R, Watanabe S, Nakamura Y, Harada D, Hataji O, Tanaka F, Niimi A. P1. 01-33 Randomised Phase 2 Study Comparing CBDCA+PTX+BEV and CDDP+PEM+BEV in Treatment-Naïve Advanced Non-Sq NSCLC (CLEAR study). Journal of Thoracic Oncology. 2018 Oct 1;13(10):S472-3.[@]
			Udagawa H, Sugiyama E, Harada T, Atagi S, Koyama R, Watanabe S, Nakamura Y, Harada D, Hataji O, Tanaka F, Kida H, Satouchi M, Maeno K, Inoue A, Yoh K, Yamane Y, Urata Y, Yoshioka H, Yamanaka T, Goto K. Bevacizumab plus platinum-based chemotherapy in advanced non-squamous non-small-cell lung cancer: a randomized, open-label phase 2 study (CLEAR). Transl Lung Cancer Res. 2021 Jul;10(7):3059-3070. doi: 10.21037/tlcr-21-240. PMID: 34430347; PMCID: PMC8350093.
52	Chu (2021)	Chu T, Lu J, Bi M, Zhang H, Zhuang W, Yu Y, Shi J, Chen Z, Zhang X, Guo Q, Liu Q. Equivalent efficacy study of QL1101 and bevacizumab on untreated advanced non-squamous non-small cell lung cancer patients: a phase 3 randomised, double-blind clinical trial. Cancer Biology & Medicine. 2021 Jul 15;18(3):816.[$]	
53	CameL	Zhou C, Chen G, Huang Y, Zhou J, Lin L, Feng J, Wang Z, Shu Y, Shi J, Hu Y, Wang Q. Camrelizumab plus carboplatin and pemetrexed versus chemotherapy alone in chemotherapy-	Zhou, C., Chen, G., Huang, Y., Zhou, J., Lin, L., Feng, J., Wang, Z., Shu, Y., Shi, J., Hu, Y., Wang, Q., Cheng, Y., Wu, F., Chen, J., Lin, X., Wang, Y., Huang, J., Cui, J., Cao, L., Liu, Y., … CameL Study Group (2023). Camrelizumab Plus Carboplatin

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		naive patients with advanced non-squamous non-small-cell lung cancer (CameL): a randomised, open-label, multicenter, phase 3 trial. The Lancet Respiratory Medicine. 2021 Mar 1;9(3):305-14.[$]	and Pemetrexed as First-Line Treatment for Advanced Nonsquamous NSCLC: Extended Follow-Up of CameL Phase 3 Trial. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 18(5), 628–639. https://doi.org/10.1016/j.jtho.2022.12.017
54	Yadav 2021	Yadav A, Malik PS, Khurana S, Jain D, Vishnubhatla S, Yadav M, Pathy S, Mohan A, Kumar L. An Open-Label Randomised Controlled Trial Comparing the Efficacy and Safety of Pemetrexed-Carboplatin versus (Weekly) Paclitaxel-Carboplatin as First-Line Chemotherapy in Advanced Non-Squamous Non-Small Cell Lung Cancer. Oncology. 2021;99(6):389-96.[$]	
55	TASUKI-52	Sugawara S, Lee JS, Kang JH, Kim HR, Inui N, Hida T, Lee KH, Yoshida T, Tanaka H, Yang CT, Nishio M. Nivolumab with carboplatin, paclitaxel, and bevacizumab for first-line treatment of advanced non-squamous non-small cell lung cancer. Annals of Oncology. 2021 Jun 15.[$]	Lee JS, Sugawara S, Kang JH, Kim HR, Inui N, Hida T, Lee KH, Yoshida T, Tanaka H, Yang CT, Nishio M. LBA54 Randomised phase III trial of nivolumab in combination with carboplatin, paclitaxel, and bevacizumab as first-line treatment for patients with advanced or recurrent non-squamous NSCLC. Annals of Oncology. 2020 Sep 1;31:S1184-5.[$]
56	Shi (2021)	Shi Y, Lei K, Jia Y, Ni B, He Z, Bi M, Wang X, Shi J, Zhou M, Sun Q, Wang G. Bevacizumab biosimilar LY01008 compared with bevacizumab (Avastin) as first-line treatment for Chinese patients with unresectable, metastatic, or recurrent non-squamous non–small-cell lung cancer: A multicenter, randomised, double-blinded, phase III trial. Cancer Communications. 2021 Sep;41(9):889-903.[$]	
57	LOGIK1201	Fukuda M, Kitazaki T, Ogawara D, Ichiki M, Mukae H, Maruyama R, Nakagaki N, Shimada M, Ikeda T, Kishimoto J,	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		Harada T. Randomised phase II study of pemetrexed or pemetrexed plus bevacizumab for elderly patients with previously untreated non-squamous non-small cell lung cancer: results of the Lung oncology group in Kyushu (LOGIK1201). Lung Cancer. 2019 Jun 1;132:1-8.[@]	
58	TORG1323	Kozuki T, Nogami N, Hataji O, Tsunezuka Y, Seki N, Harada T, Fujimoto N, Bessho A, Takamura K, Takahashi K, Satouchi M. Open-label, multicenter, randomised phase II study on docetaxel plus bevacizumab or pemetrexed plus bevacizumab for treatment of elderly (aged≥ 75 years) patients with previously untreated advanced non-squamous non-small cell lung cancer: TORG1323. Translational Lung Cancer Research. 2020 Jun;9(3):459.[@]	
59	ABOUND.70+	Langer CJ, Kim ES, Anderson EC, Jotte RM, Modiano M, Haggstrom DE, Socoteanu MP, Smith DA, Dakhil C, Konduri K, Berry T. nab-Paclitaxel-based therapy in underserved patient populations: the ABOUND. 70+study in elderly patients with advanced NSCLC. Frontiers in oncology. 2018 Jul 24;8:262.[@]	
60	LIBRETTO-001	Drilon A, Oxnard GR, Tan DS, Loong HH, Johnson M, Gainor J, McCoach CE, Gautschi O, Besse B, Cho BC, Peled N. Efficacy of selpercatinib in RET fusion–positive non–small-cell lung cancer. New England Journal of Medicine. 2020 Aug 27;383(9):813-24.[@]	Besse B, Drilon AE, Solomon BJ, Subbiah V, Tan DS, Park K, De Braud FG, Alonso G, Wolf J, Soldatenkova V, Lin AK. Updated overall efficacy and safety of selpercatinib in patients (pts) with RET fusion+non-small cell lung cancer (NSCLC).[$]
			Drilon A, Subbiah V, Gautschi O, Tomasini P, De Braud FG, Solomon B, Tan DS, Alonso G, Wolf J, Park K, Goto K. 27P Durability of efficacy and safety with

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			selpercatinib in patients (pts) with RET fusion+ non-small cell lung cancer (NSCLC). Annals of Oncology. 2022 Apr 1;33:S43.
61	ARROW	Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier PA, Lopes G, Tan DS, Garralda E. Pralsetinib for RET fusion-positive non-small-cell lung cancer (ARROW): a multi-cohort, open-label, phase 1/2 study. The Lancet Oncology. 2021 Jun 9.[$]	Thomas M, Griesinger F, Schuler M, Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier P. Registrational dataset from the phase 1/2 ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion plus non-small-cell lung cancer (NSCLC). InONCOLOGY RESEARCH AND TREATMENT 2020 Oct 1 (Vol. 43, No. SUPPL 4, pp. 141-142). ALLSCHWILERSTRASSE 10, CH-4009 BASEL, SWITZERLAND: KARGER.[$]
			Gainor JF, Curigliano G, Kim DW, Lee DH, Besse B, Baik CS, Doebele RC, Cassier P, Lopes G, Tan DW, Garralda E. MO01. 38 Registrational Dataset from the Phase 1/2 ARROW Trial of Pralsetinib (BLU-667) in Patients with Advanced RET Fusion+Non-Small-Cell Lung Cancer (NSCLC). Journal of thoracic oncology. 2021 Jan 1;16(1):S31-2.[$]
			Curigliano G, Gainor JF, Griesinger F, Thomas M, Subbiah V, Baik CS, Tan DS, Lee DH, Misch D, Garralda E, Kim DW. Safety and efficacy of pralsetinib in patients with advanced RET fusion–positive non-small cell lung cancer: update from the ARROW trial.[$]
			Gainor JF, Curigliano G, Kim D-W, Lee DH, Besse B, Baik CS, et al. Registrational dataset from the phase I/II ARROW trial of pralsetinib (BLU-667) in patients (pts) with advanced RET fusion+non-small cell lung cancer (NSCLC). 2020;38(15_suppl):9515.[@]
			Zhou Q, Wu Y, Chang J, Wang H, Fan Y, Zhao J, Wu G, Sun Y, Sun M, Wang X, Shi H. MA02. 02 Efficacy and Safety of Pralsetinib in Chinese Patients with Advanced RET Fusion+ Non-Small Cell Lung Cancer. Journal of Thoracic Oncology. 2021 Oct 1;16(10):S889-90.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Gadgeel SM, Gainor J, Cappuzzo F, Garralda E, Lee DH, Mazieres J, Kim DW, Zhu V, Lopes G, Miller S, Nowicka M. 984P Relationship between RET fusion partner and treatment outcomes in patients (pts) with non-small cell lung cancer (NSCLC) from the phase I/II ARROW study and real-world data (RWD). Annals of Oncology. 2022 Sep 1;33:S1001-2.
			Besse B, Griesinger F, Curigliano G, Thomas M, Subbiah V, Baik CS, Tan DS, Lee DH, Garralda E, Kim DW, Van Der Wekken AJ. 1170P Updated efficacy and safety data from the phase I/II ARROW study of pralsetinib in patients (pts) with advanced RET fusion+ non-small cell lung cancer (NSCLC). Annals of Oncology. 2022 Sep 1;33:S1083-4.
62	IMPOWER110	Herbst RS, Giaccone G, de Marinis F, Reinmuth N, Vergnenegre A, Barrios CH, Morise M, Felip E, Andric Z, Geater S, Özgüroğlu M. Atezolizumab for first-line treatment of PD-L1–selected patients with NSCLC. New England Journal of Medicine. 2020 Oct 1;383(14):1328-39.[$]	Jassem J, de Marinis F, Giaccone G, Vergnenegre A, Barrios CH, Morise M, Felip E, Oprean C, Kim Yc, Andric Z, Mocci S. Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naïve Programmed Death-Ligand 1–Selected NSCLC. Journal of Thoracic Oncology. 2021 Jul 12.[$]
			https://classic.clinicaltrials.gov/ct2/show/NCT02409342
			Herbst RS, De Marinis F, Giaccone G, Reinmuth N, Vergnenegre A, Barrios CH, Morise M, Felip E, Andric Z, Geater S, Ozguroglu M. LBA1 Clinical efficacy of atezolizumab (atezo) in biomarker subgroups by SP142, SP263 and 22C3 PD-L1 immunohistochemistry (IHC) assays and by blood tumour mutational burden (bTMB): Results from the IMpower110 study. Annals of Oncology. 2019 Dec 1;30:xi62-3.
63	CheckMate 9LA	Paz-Ares L, Ciuleanu TE, Cobo M, Schenker M, Zurawski B, Menezes J, Richardet E, Bennouna J, Felip E, Juan-Vidal O,	John T, Sakai H, Ikeda S, Cheng Y, Kasahara K, Sato Y, Nakahara Y, Takeda M, Kaneda H, Zhang H, Maemondo M. First-line nivolumab plus ipilimumab

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		Alexandru A. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. The Lancet Oncology. 2021 Feb 1;22(2):198-211.[$]	combined with two cycles of chemotherapy in advanced non-small cell lung cancer: a subanalysis of Asian patients in CheckMate 9LA. International journal of clinical oncology. 2022 Apr;27(4):695-706.
			Carbone DP, Paz-Ares LG, Ciuleanu TE, Cobo-Dols M, Bennouna J, Cheng Y, Mizutani H, Lingua A, Reyes F, Reinmuth N, Menezes J. OA01. 04 First-Line Nivolumab+ Ipilimumab+ Chemotherapy in Metastatic NSCLC: CheckMate 9LA 3-Year Update. Journal of Thoracic Oncology. 2023 Mar 1;18(3):e2.
			Paz-Ares LG, Ciuleanu TE, Cobo M, Bennouna J, Schenker M, Cheng Y, Juan-Vidal O, Mizutani H, Lingua A, Reyes-Cosmelli F, Reinmuth N. First-line nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone for metastatic NSCLC in CheckMate 9LA: 3-year clinical update and outcomes in patients with brain metastases or select somatic mutations. Journal of Thoracic Oncology. 2023 Feb 1;18(2):204-22.
			Paz-Ares LG, Ciuleanu TE, Cobo-Dols M, Bennouna J, Cheng Y, Mizutani H, Lingua A, Reyes F, Reinmuth N, Janoski De Menezes J, Jassem J. First-line (1L) nivolumab (NIVO)+ ipilimumab (IPI)+ 2 cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients (pts) with metastatic non–small cell lung cancer (NSCLC): 3-year update from CheckMate 9LA.
			Reck M, Ciuleanu TE, Dols MC, Schenker M, Zurawski B, Menezes J, Richardet E, Bennouna J, Felip E, Juan-Vidal O, Alexandru A. Nivolumab (NIVO)+ ipilimumab (IPI)+ 2 cycles of platinum-doublet chemotherapy (chemo) vs 4 cycles chemo as first-line (1L) treatment (tx) for stage IV/recurrent non-small cell lung cancer (NSCLC): CheckMate 9LA.
			Niels Reinmuth ; Luis Paz-Ares ; Tudor-Eliade Ciuleanu ; Manuel Cobo-Dols ; Jaafar Bennouna ; Ying Cheng ; Hideaki Mizutani ; Alejo Lingua ; Felipe Reyes ;

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
			Juliana Menezes; Jacek Jassem; Svetlana Protsenko; Kynan Feeney; Emmanuel de la Mora Jimenez; Shun Lu; Thomas John; David Paul Carbone; Xiaoqing Zhang; Nan Hu; Martin Reck. First-line (1L) nivolumab (NIVO) + ipilimumab (IPI) + 2 cycles of chemotherapy (chemo) vs chemo alone (4 cycles) in patients (pts) with metastatic non-small cell lung cancer (mNSCLC): 3-year update from CheckMate 9LA. Oncol Res Treat 2022;45(suppl 1):5 DOI: 10.1159/000521004
64	STELLA	Trukhin D, Poddubskaya E, Andric Z, Makharadze T, Bellala RS, Charoentum C, Ruiz EP, Fulop A, Ali IA, Syrigos K, Katgi N. Efficacy, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar) versus Reference Bevacizumab in Advanced Non-Small Cell Lung Cancer: A Randomised, Double-Blind, Phase III Study (STELLA). BioDrugs. 2021 Apr 29:1-6.[$]	Trukhin D, Poddubskaya E, Zoran A, Bondarenko I, Shevnia S, Zaric B, Bellala R, Charoentum C, Perez L, Bullo F, Garcia F. Bevacizumab biosimilar (MB02) and reference bevacizumab in patients with stage IIIB/IV non-squamous non-small cell lung cancer (NSCLC)(STELLA study): Multiple Imputation analysis.[$]
65	KEYNOTE-598	Boyer M, Şendur MA, Rodríguez-Abreu D, Park K, Lee DH, Çiçin I, Yumuk PF, Orlandi FJ, Leal TA, Molinier O, Soparattanapaisarn N. Pembrolizumab plus ipilimumab or placebo for metastatic non–small-cell lung cancer with PD-L1 tumour proportion score≥ 50%: Randomised, double-blind phase III KEYNOTE-598 study. Journal of Clinical Oncology. 2021 Jan:JCO-20.[$]	Abreu DR, Reck M, Şendur N, Park K, Lee DH, Cicin I, Yumuk PF, Orlandi FJ, Leal TA, Soparattanapaisarn N, Langleben A. 6MO Pembrolizumab plus ipilimumab or placebo in previously untreated metastatic NSCLC with PD-L1 tumor proportion score≥ 50%: KEYNOTE-598 3-year follow-up. Annals of Oncology. 2022 Apr 1;33:S30-1.
66	CITYSCAPE	Rodriguez-Abreu D, Johnson ML, Hussein M, Scherz A, Cobo M, Patel AJ, Secen N, Lee KH, Massuti B, Hiret S, Yang J. Randomised, double-blind, phase II study of tiragolumab plus atezolizumab versus placebo plus atezolizumab as first-line treatment for PD-L1-selected NSCLC (CITYSCAPE). InSWISS	Cho BC, Abreu DR, Hussein M, Cobo M, Patel AJ, Secen N, Lee KH, Massuti B, Hiret S, Yang JC, Barlesi F. Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): Primary and follow-up analyses of a randomised, double-blind, phase 2 study. The Lancet Oncology. 2022 Jun 1;23(6):781-92.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		MEDICAL WEEKLY 2020 Nov 18 (pp. 31S-31S). FARNSBURGERSTR 8, CH-4132 MUTTENZ, SWITZERLAND: EMH SWISS MEDICAL PUBLISHERS LTD.[$]	Cho BC, Rodriguez-Abreu D, Hussein M, Cobo M, Patel A, Secen N, Gerstner G, Kim DW, Lee YG, Su WC, Huang E. LBA2 Updated analysis and patient-reported outcomes (PROs) from CITYSCAPE: A randomised, double-blind, phase II study of the anti-TIGIT antibody tiragolumab+ atezolizumab (TA) versus placebo+ atezolizumab (PA) as first-line treatment for PD-L1+ NSCLC. Annals of Oncology. 2021 Dec 1;32:S1428.
67	Socinski (2020)	Socinski MA, Waller C, Idris T, Bondarenko I, Luft A, Beckmann K, Vishweswaramurthy A, Loganathan S, Ranganna G, Barve A. 1391P Phase III confirmatory efficacy and safety study of proposed bevacizumab biosimilar (MYL-1402O) compared with avastin, in the first-line treatment of patients with stage IV non-squamous non-small cell lung cancer (nsNSCLC). Annals of Oncology. 2020 Sep 1;31:S883-4.[$]	Socinski MA, Waller CF, Idris T, Bondarenko I, Luft A, Beckmann K, Vishweswaramurthy A, Loganathan S, Donnelly C, Hummel MA, Shapiro R. Phase III double-blind study comparing the efficacy and safety of proposed biosimilar MYL-1402O and reference bevacizumab in stage IV non-small-cell lung cancer. Therapeutic Advances in Medical Oncology. 2021 Nov;13:17588359211045845.
68	RATIONALE 304	Lu S, Wang J, Yu Y, Yu X, Hu Y, Ai X, Ma Z, Li X, Zhuang W, Liu Y, Li W. Tislelizumab Plus Chemotherapy as First-line Treatment for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer (RATIONALE 304): A Randomised Phase 3 Trial. Journal of Thoracic Oncology. 2021 May 23.[$]	Lu S, Wang J, Yu Y, Yu X, Hu Y, Ma Z, Li X, Zhuang W, Liu Y, Li W, Cui J. RATIONALE 304: Tislelizumab (TIS) plus chemotherapy versus chemotherapy alone as first line (1L) treatment for non-squamous (non-sq) NSCLC in patients (pts) aged 65–75 years. InCANCER RESEARCH 2022 Jun 15 (Vol. 82, No. 12). 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA: AMER ASSOC CANCER RESEARCH.
69	EMPOWER-Lung 1	Sezer A, Kilickap S, Gümüş M, Bondarenko I, Özgüroğlu M, Gogishvili M, Turk HM, Cicin I, Bentsion D, Gladkov O, Clingan P. Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicenter, open-label, global, phase 3, randomised,	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		controlled trial. The Lancet. 2021 Feb 13;397(10274):592-604.[$]	
70	MYSTIC	Rizvi NA, Cho BC, Reinmuth N, Lee KH, Luft A, Ahn MJ, van den Heuvel MM, Cobo M, Vicente D, Smolin A, Moiseyenko V. Durvalumab with or without tremelimumab vs standard chemotherapy in first-line treatment of metastatic non–small cell lung cancer: the MYSTIC phase 3 randomised clinical trial. JAMA oncology. 2020 May 1;6(5):661-74.[$]	
71	GEMSTONE-302	Zhou C, Wang Z, Sun Y, Cao L, Ma Z, Wu R, Yu Y, Yao W, Chang J, Chen J, Zhuang W, Cui J, Chen X, Lu Y, Shen H, Wang J, Li P, Qin M, Lu D, Yang J. Sugemalimab versus placebo, in combination with platinum-based chemotherapy, as first-line treatment of metastatic non-small-cell lung cancer (GEMSTONE-302): interim and final analyses of a double-blind, randomised, phase 3 clinical trial. Lancet Oncol. 2022 Feb;23(2):220-233.	
72	LEAP-007	Wang, Jiabing & Luft, A. & Jiménez, E. & Lee, J.S. & Koralewski, P. & Karadurmus, N. & Sugawara, Shunichi & Livi, L. & Basappa, N.S. & Quantin, X. & Dudnik, J. & Ortiz, D. & Mekhail, T. & Okpara, C.E. & Zimmer, Z. & Samkari, A. & Bhagwati, N. & Csőszi, T.. (2021). 120O Pembrolizumab (Pembro) with or without lenvatinib (Lenva) in first-line metastatic NSCLC with PD-L1 TPS ≥1% (LEAP-007): A phase III, randomized, double-blind study. Annals of Oncology. 32. S1429-S1430.	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
73	CCTG BR34	Leighl NB, Laurie SA, Goss GD, Hughes BG, Stockler M, Tsao MS, Hwang DM, Joubert P, Kulkarni S, Blais N, Joy AA. CCTG BR34: A randomized phase 2 trial of durvalumab and tremelimumab with or without platinum-based chemotherapy in patients with metastatic NSCLC. Journal of Thoracic Oncology. 2022 Mar 1;17(3):434-45.	
74	LIBRETTO-321	Lu S, Cheng Y, Huang D, Sun Y, Wu L, Zhou C, Zhou J, Guo Y, Chen L, Shao J. MA02. 01 efficacy and safety of selpercatinib in Chinese patients with ret fusion-positive non-small cell lung cancer: a phase 2 trial. Journal of Thoracic Oncology. 2021 Oct 1;16(10):S888-9.	https://ClinicalTrials.gov/show/NCT04280081
75	Ohe (2022)	Ohe Y, Bondarenko I, Andric Z, Ostapenko Y, Ciuleanu T, Moiseenko F, Makharadze T, Shevnya S, Oleksiienko A, Ruiz EY, Kim S. Abstract CT551: Randomized phase III study comparing the efficacy and safety of CT-P16, a new biosimilar, to reference bevacizumab (Avastin®) in patients with metastatic or recurrent non-small cell lung cancer (NSCLC). Cancer Research. 2022 Jun 15;82(12_Supplement):CT551-.	Verschraegen C, Andric ZG, Ciuleanu TE, Moiseenko FV, Makharadze T, Shevnia S, Oleksiienko A, Riuz EY, Kim SH, Ahn KY, Park TH. 1027P 1-year follow-up of a phase III study to compare efficacy and safety of a bevacizumab biosimilar, CT-P16, and reference bevacizumab as first-line treatment for metastatic or recurrent non-squamous non-small cell lung cancer. Annals of Oncology. 2022 Sep 1;33:S1024-5.
76	Fadeeva (2021)	Fadeeva N, Roy B, Nagarkar R, Adamchuk H, Matrosova M, Tjulandin S, Stroyakovskiy D, Zhuravleva D, Voevodin G, Shustova M, Kryukov KA. 1338P A phase III study comparing BCD-021, a bevacizumab biosimilar, and reference bevacizumab in patients with stage IIIB or IV non-squamous NSCLC. Annals of Oncology. 2021 Sep 1;32:S1022.	Filon O, Orlov S, Burdaeva O, Kopp MV, Kotiv B, Alekseev S, Pecheniy A, Stroyakovskiy D, Gladkov O, Khorinko A, Matrosova M. Efficacy and safety of BCD-021, bevacizumab biosimilar candidate, compared to Avastin: Results of international multicenter randomized double blind phase III study in patients with advanced non-squamous NSCLC.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
77	Chen (2022)	Chen L, Trukhin D, Kolesnik O, Gomez Rangel JD, Cil T, Li X, Cicin I, Kobziev O, Shen Y, Liu Z, Oleksandr I. Clinical efficacy and safety of the BAT1706 (proposed bevacizumab biosimilar) compared with reference bevacizumab in patients with advanced nonsquamous NSCLC: A randomized, double-blind, phase III study.	
78	Wan (2021)	Wan R, Dong X, Chen Q, Yu Y, Yang S, Zhang X, Zhang G, Pan Y, Sun S, Zhou C, Hong W. Efficacy and safety of MIL60 compared with bevacizumab in advanced or recurrent non-squamous non-small cell lung cancer: a phase 3 randomized, double-blind study. EClinicalMedicine. 2021 Dec 1;42.	Wang J, Wang R, Dong X, Chen Q, Yu Y, Yang S, Zhang X, Zhang G, Pan Y, Sun S, Zhou C. 1339P Efficacy and safety of MIL60, a bevacizumab biosimilar, in combination with paclitaxel/carboplatin in patients with advanced or recurrent non-squamous non-small cell lung cancer: A randomized, double-blind, multicenter phase III study. Annals of Oncology. 2021 Sep 1;32:S1023.
79	Metzenmacher (2021)	Metzenmacher M, Kopp HG, Griesinger F, Reinmuth N, Sebastian M, Serke M, Waller CF, Thomas M, Eggert J, Schmid-Bindert G, Hoiczyk M. A randomized, multicenter phase II study comparing efficacy, safety and tolerability of two dosing regimens of cisplatin and pemetrexed in patients with advanced or metastatic non-small-cell lung cancer. Therapeutic Advances in Medical Oncology. 2021 Mar;13:1758835921996506.	
80	Souquet (2022)	Souquet PJ, Audigier-Valette C, Molinier O, Cortot A, Margery J, Moreau L, Gervais R, Barlesi F, Pichon E, Zalcman G, Dumont P. Tailoring maintenance chemotherapy upon response to induction chemotherapy as compared with pemetrexed continuation maintenance in advanced non-squamous NSCLC patients: Results of the IFCT-GFPC-1101 multicenter	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		randomized phase III trial. Lung Cancer. 2022 Feb 1;164:84-90.	
81	Lena (2022)	Lena H, Monnet I, Bylicki O, Audigier-Valette C, Falchero L, Vergnenegre A, Demontrond P, Greillier L, Geier M, Guisier F, Decroisette C. Randomized phase III study of nivolumab and ipilimumab versus carboplatin-based doublet in first-line treatment of PS 2 or elderly (≥ 70 years) patients with advanced non–small cell lung cancer (Energy-GFPC 06-2015 study).	
82	CTONG1901	Liu SY, Zhou Q, Yan HH, Bin G, Yang MY, Deng JY, Tu HY, Zhang X, Su J, Yang J, Wu YL. Sintilimab versus pembrolizumab in monotherapy or combination with chemotherapy as first-line therapy for advanced non–small cell lung cancer: Results from phase 2, randomized clinical trial (CTONG1901).	Liu SY, Zhou Q, Yan HH, Gan B, Yang MY, Deng JY, Tu HY, Zhang XC, Su J, Yang JJ, Wu YL. EP08. 01-085 Sintilimab versus Pembrolizumab as Monotherapy or in Combination with Chemotherapy for Treatment Naïve Metastatic Non-small Cell Lung Cancer. Journal of Thoracic Oncology. 2022 Sep 1;17(9):S381-2.
83	Govindan (2022)	Govindan R, Lind M, Insa A, Khan SA, Uskov D, Tafreshi A, Guclu S, Bar J, Kato T, Lee KH, Nakagawa K. Veliparib Plus Carboplatin and Paclitaxel Versus Investigator's Choice of Standard Chemotherapy in Patients With Advanced Non–Squamous Non–Small Cell Lung Cancer. Clinical Lung Cancer. 2022 May 1;23(3):214-25.	
84	CHOICE-01	Wang Z, Wu L, Li B, Cheng Y, Li X, Wang X, Han L, Wu X, Fan Y, Yu Y, Lv D. Toripalimab Plus Chemotherapy for Patients With Treatment-Naive Advanced Non–Small-Cell Lung Cancer: A Multicenter Randomized Phase III Trial (CHOICE-01). Journal of Clinical Oncology. 2023 Jan 1;41(3):651.	Wang J, Wang Z, Wu L, Li B, Cheng Y, Li X, Wang X, Han L, Wu X, Fan Y, Yu Y. MA13. 08 CHOICE-01: A phase 3 study of toripalimab versus placebo in combination with first-line chemotherapy for advanced NSCLC. Journal of Thoracic Oncology. 2021 Oct 1;16(10):S927-8.

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
85	PERLA	Peters S, Lim SM, Granados AO, Pinto GD, Fuentes CS, Russo GL, Schenker M, Ahn JS, Reck M, Szijgyarto Z, Huseinovic N. 57O Randomized double-blind phase II trial (PERLA) of dostarlimab (dostar)+ chemotherapy (CT) vs pembrolizumab (pembro)+ CT in metastatic non-squamous NSCLC: Primary results. Immuno-Oncology and Technology. 2022 Dec 1;16.	
86	Ahn (2022)	Ahn MJ, Kim SW, Costa EC, Rodríguez LM, Oliveira J, Molla MI, Majem M, Costa L, Su WC, Lee KH, Yang JH. LBA56 MEDI5752 or pembrolizumab (P) plus carboplatin/pemetrexed (CP) in treatment-naïve (1L) non-small cell lung cancer (NSCLC): A phase Ib/II trial. Annals of Oncology. 2022 Sep 1;33:S1423.	
87	POSEIDON	Garon EB, Cho BC, Luft A, Alatorre-Alexander J, Geater SL, Kim SW, Ursol G, Hussein M, Lim FL, Yang CT, Araujo LH. EP08. 01-027 Durvalumab (D)±Tremelimumab (T)+ Chemotherapy (CT) in 1L Metastatic NSCLC: Outcomes by Tumour PD-L1 Expression in POSEIDON. Journal of Thoracic Oncology. 2022 Sep 1;17(9):S349-50.	
88	SUNRISE	Han B, Chu T, Yu Z, Wang J, Zhao Y, Mu X, Yu X, Shi X, Shi Q, Guan M, Ding C. LBA57 Sintilimab plus anlotinib versus platinum-based chemotherapy as first-line therapy in metastatic NSCLC (SUNRISE): An open label, multi-center, randomized, phase II study. Annals of Oncology. 2022 Sep 1;33:S1423-4.	
89	EMPOWER-Lung 3	Gogishvili M, Melkadze T, Makharadze T, Giorgadze D, Dvorkin M, Penkov K, Laktionov K, Nemsadze G, Nechaeva M,	Baramidze A, Gogishvili M, Melkadze T, Giorgadze D, Penkov KD, Makharadze T, Kalinka E, Nechaeva M, Laktionov K, Gessner C, Jaime BM. 122MO

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		Rozhkova I, Kalinka E. Cemiplimab plus chemotherapy versus chemotherapy alone in non-small cell lung cancer: a randomized, controlled, double-blind phase 3 trial. Nature Medicine. 2022 Nov;28(11):2374-80.	Cemiplimab (cemi)+ platinum doublet chemotherapy (chemo)+ ipilimumab (ipi) for first-line treatment of advanced non-small cell lung cancer (NSCLC): EMPOWER-Lung 3 part I. Immuno-Oncology and Technology. 2022 Dec 1;16.
90	NEPTUNE	Cheng Y, Zhou Q, Han B, Fan Y, Shan L, Chang J, Sun S, Fang J, Chen Y, Sun J, Wu G. NEPTUNE China cohort: First-line durvalumab plus tremelimumab in Chinese patients with metastatic non-small-cell lung cancer. Lung Cancer. 2023 Apr 1;178:87-95.	
91	BFAST	Peters S, Dziadziuszko R, Morabito A, Felip E, Gadgeel SM, Cheema P, Cobo M, Andric Z, Barrios CH, Yamaguchi M, Dansin E. Atezolizumab versus chemotherapy in advanced or metastatic NSCLC with high blood-based tumor mutational burden: primary analysis of BFAST cohort C randomized phase 3 trial. Nature medicine. 2022 Sep;28(9):1831-9.	
92	TORG 1321	Kasai T, Mori K, Nakamura Y, Seki N, Ichikawa Y, Saito H, Kondo T, Nishikawa K, Otsu S, Bessho A, Tanaka H. Randomized, Phase II study of pemetrexed plus bevacizumab versus pemetrexed alone after treatment with cisplatin, pemetrexed, and bevacizumab in advanced non-squamous, non-small cell lung cancer: TORG (thoracic oncology research group) 1321. Cancer Medicine. 2023 May 24.	
93	CANOPY-1	Tan DS, Felip E, Castro G, Solomon BJ, Greystoke A, Cho B, Cobo M, Kim TM, Ganguly S, Carcereny E, Paz-Ares L. Canakinumab in combination with first-line (1L)	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
		pembrolizumab plus chemotherapy for advanced non-small cell lung cancer (aNSCLC): Results from the CANOPY-1 phase 3 trial. InCancer Research 2022. AMER ASSOC CANCER RESEARCH.	
94	NACA	Hou X, Feng W, Long H, Bu Q, Zhou C, Liu H, Cheng C, Wang L, Wu G, Wen S, Zhou T. Nedaplatin plus pemetrexed or cisplatin plus pemetrexed as first-line chemotherapy for EGFR/ALK-negative advanced lung adenocarcinoma (NACA): A multicenter, open-label, non-inferiority, randomized, phase III trial.	
95	AVANA	Syrigos K, Abert I, Andric Z, Bondarenko IN, Dvorkin M, Galic K, Galiulin R, Kuchava V, Sriuranpong V, Trukhin D, Zhavrid E. Efficacy and safety of bevacizumab biosimilar FKB238 versus originator bevacizumab: results from AVANA, a phase III trial in patients with non-squamous non-small-cell lung cancer (non-sq-NSCLC). BioDrugs. 2021 Jul;35:417-28.	
96	Reck 2020	Reck M, Luft A, Bondarenko I, Shevnia S, Trukhin D, Kovalenko NV, Vacharadze K, Andrea F, Hontsa A, Choi J, Shin D. A phase III, randomized, double-blind, multicenter study to compare the efficacy, safety, pharmacokinetics, and immunogenicity between SB8 (proposed bevacizumab biosimilar) and reference bevacizumab in patients with metastatic or recurrent nonsquamous non-small cell lung cancer. Lung Cancer. 2020 Aug 1;146:12-8.	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
97	Checkmate -026	Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, Felip E, van den Heuvel MM, Ciuleanu TE, Badin F, Ready N. First-line nivolumab in stage IV or recurrent non–small-cell lung cancer. New England Journal of Medicine. 2017 Jun 22;376(25):2415-26.	
98	Reinmuth 2019	Reinmuth N, Bryl M, Bondarenko I, Syrigos K, Vladimirov V, Zereu M, Bair AH, Hilton F, Liau K, Kasahara K. PF-06439535 (a bevacizumab biosimilar) compared with reference bevacizumab (Avastin®), both plus paclitaxel and carboplatin, as first-line treatment for advanced non-squamous non-small-cell lung cancer: a randomized, double-blind study. BioDrugs. 2019 Oct;33:555-70.	
99	Wozniak 1998	Wozniak AJ, Crowley JJ, Balcerzak SP, Weiss GR, Spiridonidis CH, Baker LH, Albain KS, Kelly K, Taylor SA, Gandara DR, Livingston RB. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. Journal of Clinical Oncology. 1998 Jul;16(7):2459-65.	
100	Tan 2009	Tan EH, Rolski J, Grodzki T, Schneider CP, Gatzemeier U, Zatloukal P, Aitini E, Carteni G, Riska H, Tsai YH, Abratt R. Global Lung Oncology Branch trial 3 (GLOB3): final results of a randomised multinational phase III study alternating oral and iv vinorelbine plus cisplatin versus docetaxel plus cisplatin as first-line treatment of advanced non-small-cell lung cancer. Annals of oncology. 2009 Jul 1;20(7):1249-56.	

No.	Trial name/NCT number/trial registration number/ author (year)	Primary reference	Secondary reference
101	NAVoTrial 01	Bennouna J, Havel L, Krzakowski M, Kollmeier J, Gervais R, Dansin E, Serke M, Favaretto A, Szczesna A, Cobo M, Ciuffreda L. Oral Vinorelbine plus Cisplatin as first-line chemotherapy in nonsquamous non–small-cell lung cancer: Final results of an international randomized phase II study (NAVotrial 01). Clinical Lung Cancer. 2014 Jul 1;15(4):258-65.	
102	FAST	Boni C, Tiseo M, Boni L, Baldini E, Recchia F, Barone C, Grossi F, Germano D, Matano E, Marini G, Labianca R. Triplets versus doublets, with or without cisplatin, in the first-line treatment of stage IIIB–IV non-small cell lung cancer (NSCLC) patients: a multicenter randomised factorial trial (FAST). British journal of cancer. 2012 Feb;106(4):658-65.	

* Original SLR.
# First update.
@ Second update.

H.1.3 Excluded full text references

The excluded full text references for the clinical SLR are reported below.

Table 104 List of studies excluded from the clinical SLR

First author, year	Title	Reason for exclusion
N/A	N/A	N/A

Table 105 List of studies excluded from the clinical SLR2

First author, year	Title	Reason for exclusion
N/A	N/A	N/A

H.1.4 Local adaptation clinical SLR

To support this submission for retsevmo monotherapy in adults with advanced RET fusion–positive NSCLC not previously treated with a RET inhibitor, the global SLR was adapted by excluding studies not relevant to the Danish setting. Only the publication by Garassino et al. (46) from the KEYNOTE-189 trial was considered eligible for inclusion in the local adaptation, in addition to LIBRETTO-001. Both KEYNOTE-189 and LIBRETTO-001 were also identified through the TLR conducted specifically for this submission (see below). All other sources from the global SLR were excluded as not relevant for the present assessment. The local adaptation is illustrated in Figure 34.

Targeted literature review – clinical studies

In addition to the SLR, a targeted literature review (TLR) was undertaken to identify and extract inputs for the clinical assessment that were not covered by the global SLR (Table 103). The search was conducted on September 6, 2025 (Table 106). Twelve literature inputs were included to inform clinical efficacy.

Table 106 Sources included in the targeted literature search

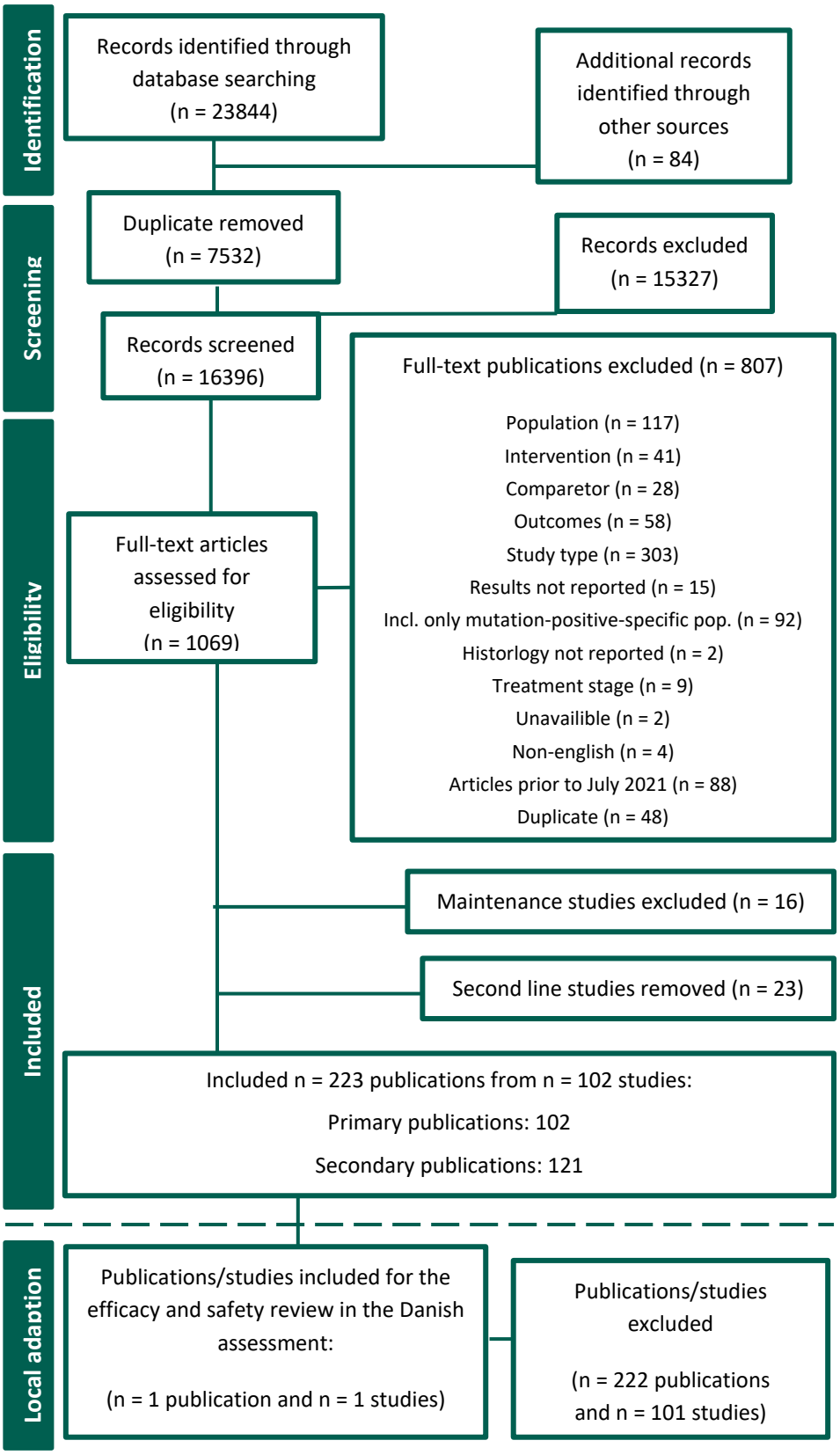
Trial	Reference	Search strategy	Date of search
LIBRETTO-431	Eli Lilly, data on file (LIBRETTO-431), data cutoff 1 May 2023 (clinical study report) (38)	Hand search	09.09.2025
LIBRETTO-431	Zhou, Caicun, Benjamin Solomon, Herbert H. Loong, Keunchil Park, Maurice Pérol, Edurne Arriola, Silvia Novello et al. "First-line selpercatinib or chemotherapy and pembrolizumab in	Hand search	09.09.2025

Trial	Reference	Search strategy	Date of search
	RET fusion–positive NSCLC." New England Journal of Medicine 389, no. 20 (2023): 1839-1850. (4)		
LIBRETTO-431	Analysis Plan to Estimate the Relative Treatment Effect in Overall Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431: Treatment Switching and Extrapolation. Data on file (Eli Lilly) February 2024 (47)	Hand search	09.09.2025
LIBRETTO-431	Analysis Plan to Estimate the Relative Treatment Effect in Progression-Free Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431. Data on file (Eli Lilly) 29 January 2024 (48)	Hand search	09.09.2025
LIBRETTO-001	Eli Lilly, data on file (LIBRETTO-001), data cutoff 13 January 2023 (clinical study report) (39)	Hand search	09.09.2025
LIBRETTO-001	35P Final data from phase I/II LIBRETTO-001 trial of selpercatinib in RET fusion-positive non-small cell lung cancer Gautschi, O. et al. ESMO Open, Volume 9, 102614 (40)	Hand search	09.09.2025
LIBRETTO-001	Wirth, L. J., Sherman, E., Robinson, B., Solomon, B., Kang, H., Lorch, J., Worden, F., Brose, M., Patel, J., Leboulleux, S.,	Hand search	09.09.2025

Trial	Reference	Search strategy	Date of search
	Godbert, Y., Barlesi, F., Morris, J. C., Owonikoko, T. K., Tan, D. S. W., Gautschi, O., Weiss, J., de la Fouchardiere, C., Burkard, M. E., . . . Cabanillas, M. E. (2020). Efficacy of selpercatinib in RET-altered thyroid cancers. N Engl J Med, 383(9), 825-835.(41)		
LIBRETTO-001	Wirth, L. J., Subbiah, V., Worden, F., Solomon, B., Robinson, A. G., Hadoux, J., Tomasini, P., Weiler, D., Deschler-Baier, B., Tan, D., Lin, Y., Bayt, T., Maeda, P., Drilon, A., & Cassier, P. (2023). Updated safety and efficacy of selpercatinib in patients with RET-activated thyroid cancer: data from LIBRETTO-001. Ann Oncol. (42)	Hand search	09.09.2025
LIBRETTO-001	Drilon, A. (2022, 30 March-2 April). Durability of efficacy and safety with selpercatinib in patients (pts) with RET fusion+ non-small-cell lung cancer (NSCLC): LIBRETTO-001 [poster] European Lung Cancer Conference, Prague, Czech Republic (43)	Hand search	09.09.2025
LIBRETTO-001	Drilon, A., Oxnard, G., Wirth, L., Besse, B., Gautschi, O., Tan, D. S. W., & al., e. (2019, 7-10 September). Registrational results of LIBRETTO-001: a	Hand search	09.09.2025

Trial	Reference	Search strategy	Date of search
	phase 1/2 trial of selpercatinib (LOXO-292) in patients with RET fusion-positive lung cancers World Conference on Lung Cancer, Barcelona, Spain. (44)		
LIBRETTO-001	Drilon, A., Oxnard, G. R., Tan, D. S. W., Loong, H. H. F., Johnson, M., Gainor, J., McCoach, C. E., Gautschi, O., Besse, B., Cho, B. C., Peled, N., Weiss, J., Kim, Y. J., Ohe, Y., Nishio, M., Park, K., Patel, J., Seto, T., Sakamoto, T., . . . Subbiah, V. (2020). Efficacy of selpercatinib in RET fusion-positive non-small-cell lung cancer. N Engl J Med, 383(9), 813-824. (45)	Hand search	09.09.2025
LIBRETTO-001	Data on file Unpublished data 2024, Comparative efficacy of Selpercatinib vs Pembrolizumab + Platinum doublet chemotherapy in 1L NSCLC. A matching-adjusted indirect comparison (MAIC) of LIBRETTO-001 and KEYNOTE-189 2024 (49)	Hand search	09.09.2025

Figure 46 PRISMA diagram including local adaptation (clinical SLR)



H.1.5 Quality assessment

A formal risk of bias assessment was conducted in accordance with the guidelines provided by the Centre for Reviews and Dissemination (CRD). In addition, as the data identified by this SLR were used in a network meta-analysis, any statistical issues around studies were minimised.

SLR1 and SLR2: The risk of bias assessment was conducted according to the Cochrane risk of bias tool described in the Cochrane Handbook. The following seven components were assessed:

- random sequence generation
- allocation concealment
- blinding of participants and personnel
- blinding of outcome assessment
- incomplete outcome data
    - Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
        - Did the analysis include an intention-to-treat analysis? If so, was this appropriate, and were appropriate methods used to account for missing data?
- selective reporting
- other sources of bias

The seven components can be allocated either of the three statuses: high, low, or unclear risk of bias. Often, where an unclear risk of bias status was assigned, this was thought to reflect poor reporting rather than underlying methodological weaknesses. The Cochrane risk of bias tool used for this review was slightly modified to incorporate additional criteria for incomplete data based on recommendations from CRD. Important aspects of risk of bias in clinical trials are not normally reported in conference abstracts owing to text restrictions and hence we were unable to conduct this assessment of trials reported only in conference abstracts.

SLR3, SLR4, SLR5, and SLR6: RCTs were assessed to the standards recommended by the National Institute for Health and Care Excellence (NICE) (published in 2013, last updated in 2016).

The following four components can be allocated based on either of the three statuses: low, high, or unclear/unknown risk of bias:

- selection bias (systematic differences between the comparison groups)
- performance bias (systematic differences between groups in the care provided apart from the intervention under investigation)
- attrition bias (systematic differences between the comparison groups with respect to loss of participants)
- detection bias (bias in how outcomes are ascertained, diagnosed, or verified)

Single-arm trials were assessed by the Critical Appraisal Skills Programme (CASP) cohort study checklist. The checklist have the following questionnaire:

1. Did the study address a clearly focused issue?
2. Was the cohort recruited in an acceptable way?
3. Was the exposure accurately measured to minimise bias?
4. Was the outcome accurately measured to minimise bias?
5A. Have the authors identified all important confounding factors?
List the ones you think might be important, that the author missed.
5B. Have they taken into account the confounding factors in the design and/or analysis?
6A. Was the follow-up of subjects complete enough?
6B. Was the follow-up of subjects long enough?
7. What are the results of this study?
8. How precise are the results?
9. Do you believe the results?
10. Can the results be applied to the local population?
11. Do the results of this study fit with other available evidence?
12. What are the implications of this study for practice?

H.1.6 Unpublished data

N/A

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

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

An economic global targeted literature review (TLR) was conducted to identify resource use, cost, and utility data that are relevant to economic analyses in NSCLC and TC. The economic TLR is reported below.

Objective

The objective of the global TLR is to identify resource use, cost, and utility data that are relevant to economic analyses in NSCLC and TC. The original TLR was conducted by an external vendor in year 2019 (covering 2L NSCLC: January 2015 to August 2019; TC: January 2017 to August 2019). An update to the original work was conducted in year 2022 (search timeframe: Second-line NSCLC & TC: 2019 to September 2022, First-line NSCLC: 2015 to September 2022). The scope for the update was amended to include 1L NSCLC. This protocol describes an update to the most recent literature review, including 1L NSCLC, 2L NSCLC, and TC, and conducted in year 2024 (search timeframe: September 2022 to March 2024).

I.1.1 Search strategies

I.1.1.1 Information sources

The following medical literature databases will be searched to identify relevant publications for inclusion in the TLR using the OVID® platform:

- Medical Literature Analysis and Retrieval System Online (MEDLINE®) ALL and MEDLINE® In-Process
- Excerpta Medica Database (EMBASE®)
- Cochrane Library, including the following:
    - Cochrane Central Register of Controlled Trials (CENTRAL)
    - Cochrane Database of Systemic Reviews
- EconLit

Details of the full search strategies employed are provided in Section I.1.1.2.

Table 107 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Medline	Ovid	September 2022 - March 2024	March 2024
Embase	Ovid	September 2022 - March 2024	March 2024
Cochrane Library	Ovid	September 2022 - March 2024	March 2024

Database	Platform	Relevant period for the search	Date of search completion
EconLit	Ovid	September 2022 - March 2024	March 2024

Abbreviations: CEA = Tufts Medical Center Cost-Effectiveness Analysis; ICER = Institute for Clinical and Economic Review.

To complement the search of published studies identified from the electronic databases described above, conference proceedings from the scientific congresses listed in Table 108 will be searched for relevant abstracts submitted and/or presented over the last years (September 2022-March 2024). This is because it is expected that all studies of a reasonable quality reported in abstract form prior to this date will have been published in a peer-reviewed journal. We will use the same eligibility criteria as described in Appendix I.1.2 to review conference abstracts (Table 116).

Table 108 Conference material included in the literature search

Conference	Source of abstracts	Relevant period for the search	Date of search
International Society for Pharmacoeconomics and Outcomes Research	N/A	September 2022-March 2024	March 2024
American Society of Clinical Oncology	N/A	September 2022-March 2024	March 2024
European Society for Medical Oncology	N/A	September 2022-March 2024	March 2024
International Association for the Study of Lung Cancer	N/A	September 2022-March 2024	March 2024

HTA websites and registries in Table 109 was be searched.

Table 109 Other sources included in the literature search

Source name	Location/source	Relevant period for the search	Date of search
NICE	https://www.nice.org.uk/	September 2022-March 2024	March 2024
Scottish Medical Consortium	https://www.scottishmedicines.org.uk/	September 2022-March 2024	March 2024

Source name	Location/source	Relevant period for the search	Date of search
Canadian Agency for Drugs and Technologies in Health	https://www.cadth.ca/	September 2022-March 2024	March 2024

Reference lists of pertinent systematic reviews and meta-analyses published were searched for additional studies of interest. These reference lists were typically good sources of additional material that supplemented the articles identified in the medical literature databases.

I.1.1.2 Search strings

The electronic database searching was performed on March 2024 using the OVID® platform. The search stings are provided in Table **110** and the same search strategy is used for all databases.

Table 110 Search strategy First-line NSCLC (14 March 2024)

No.	Query
#1	exp lung neoplasms/
#2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.
#3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.
#4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.
#5	1 or 2 or 3 or 4
#6	(first line therapy or first-line or first line or 1st line or untreated or treatment naive or previously untreated or first-line to progression or first line to progression).tw,kw.
#7	5 and 6
#8	exp cost of illness/ or drug costs.mp. or health care costs.mp. or health care utili$.mp. or resource utili$.mp. or resource us$.mp. or cost$.mp. or direct cost$.mp. or indirect cost$.mp. or societ$ cost$.mp. or productivity.mp. or price$.mp. or health resource$.mp. or unit cost$.mp. or medical cost$.mp. or laboratory cost$.mp or diagnostic cost$.mp or physician cost$.mp or exp drug costs/ or exp health care costs/ or exp health care utilization/ or exp absenteeism/ or exp productivity/
#9	exp healthcare utilization/ or exp hospitalization/ or exp length of stay/ or exp drug utilization/ or exp cost/ or exp economics/ or exp health economics/ or exp pharmacoeconomics/ or ((Quality adj Life) or quality of life or qol or hrql or HrQoL or health related quality of life or QALY or EuroQoL or EQ5D or EQ-5D-3L or EQ-5D-5L or Health Utilities Index or HUI or SF-6D or patient reported outcome* or PRO or well?being or unmet need* or daily life activities or unemploy* or employ* or productivity).ab,ti.
#10	8 or 9

No.	Query
#11	7 and 10
#12	(editorial or letter or note or book or book series or chapter or "review" or case reports or comment or lectures or news or newspaper article or Practice Guideline).pt. or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or primate or primates or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).ti,ab,mp.
#13	11 not 12
#14	(202209* or 202210* or 202211* or 202212* or 2023* or 2024*).dt.
#15	13 and 14

Table 111 Search strategy for Second-line NSCLC (14 March 2024)

No.	Query
#1	exp lung neoplasms/
#2	(non-small cell lung cancer or nonsmall cell lung cancer or NSCLC or nonsmall-cell lung cancer or non-small-cell lung cancer).tw,kw.
#3	((Lung or bronchial or pulmonary) and (non-small-cell or nonsmall-cell or non-small cell)).tw,kw.
#4	((lung$ or bronch* or pulmonary) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).tw,kw.
#5	1 or 2 or 3 or 4
#6	(second line therapy or second-line or second line or 2nd line or relapse or relapsed or refractory or recurrent or resistant or failed or rescue or pretreated or pre-treated or previously treated or retreated or progressive).tw,kw.
#7	5 and 6
#8	exp cost of illness/ or drug costs.mp. or health care costs.mp. or health care utili$.mp. or resource utili$.mp. or resource us$.mp. or cost$.mp. or direct cost$.mp. or indirect cost$.mp. or societ$ cost$.mp. or productivity.mp. or price$.mp. or health resource$.mp. or unit cost$.mp. or medical cost$.mp. or laboratory cost$.mp or diagnostic cost$.mp or physician cost$.mp or exp drug costs/ or exp health care costs/ or exp health care utilization/ or exp absenteeism/ or exp productivity/
#9	exp healthcare utilization/ or exp hospitalization/ or exp length of stay/ or exp drug utilization/ or exp cost/ or exp economics/ or exp health economics/ or exp pharmacoeconomics/ or ((Quality adj Life) or quality of life or qol or hrql or HrQoL or health related quality of life or QALY or EuroQoL or EQ5D or EQ-5D-3L or EQ-5D-5L or Health Utilities Index or HUI or SF-6D or patient reported outcome* or PRO or well?being or unmet need* or daily life activities or unemploy* or employ* or productivity).ab,ti.
#10	8 or 9
#11	7 and 10
#12	(editorial or letter or note or book or book series or chapter or "review" or case reports or comment or lectures or news or newspaper article or Practice Guideline).pt. or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or primate or primates or nonhuman or animal

No.	Query
	experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).ti,ab,mp.
#13	11 not 12
#14	(202209* or 202210* or 202211* or 202212* or 2023* or 2024*).dt.
#15	13 and 14

Table 112 Search strategy for Thyroid Cancer (14 March 2024)

No.	Query
#1	exp thyroid neoplasms/
#2	((papillary thyroid or thyroid papillary or thyroid papilla) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or microcarcinoma)).mp.
#3	((medullary thyroid or thyroid medullary) and (cancer* or carcinoma* or neoplasm* or tumour* or tumor* or adenoma*)).mp.
#4	((Differentiated thyroid or well differentiated thyroid or thyroid follicular or thyroid gland follicular or thyroid follicle or thyroid gland follicle or thyroideal follicle or thyroideal follicular or thyroideal gland follicular) adj3 (adenocarcinoma* or cancer* or carcinoma* or neoplasm* or tumour* or tumor*)).mp.
#5	1 or 2 or 3 or 4
#6	exp cost of illness/ or drug costs.mp. or health care costs.mp. or health care utili$.mp. or resource utili$.mp. or resource us$.mp. or cost$.mp. or direct cost$.mp. or indirect cost$.mp. or societ$ cost$.mp. or productivity.mp. or price$.mp. or health resource$.mp. or unit cost$.mp. or medical cost$.mp. or laboratory cost$.mp or diagnostic cost$.mp or physician cost$.mp or exp drug costs/ or exp health care costs/ or exp health care utilization/ or exp absenteeism/ or exp productivity/
#7	exp healthcare utilization/ or exp hospitalization/ or exp length of stay/ or exp drug utilization/ or exp cost/ or exp economics/ or exp health economics/ or exp pharmacoeconomics/ or ((Quality adj Life) or quality of life or qol or hrql or HrQoL or health related quality of life or QALY or EuroQoL or EQ5D or EQ-5D-3L or EQ-5D-5L or Health Utilities Index or HUI or SF-6D or patient reported outcome* or PRO or well?being or unmet need* or daily life activities or unemploy* or employ* or productivity).ab,ti.
#8	6 or 7
#9	5 and 8
#10	(editorial or letter or note or book or book series or chapter or "review" or case reports or comment or lectures or news or newspaper article or Practice Guideline).pt. or (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep or primate or primates or nonhuman or animal experiment or animal tissue or animal cell or animal model or in vitro study or in vitro or in vitro studies or in vitro technique or in vitro techniques).ti,ab,mp.
#11	9 not 10
#12	(202209* or 202210* or 202211* or 202212* or 2023* or 2024*).dt.
#13	11 and 12

I.1.1.2.1 Summary of Preliminary Database Search

A summary of the preliminary database search across all included databases is provided in Table 113 to Table 115.

Table 113 Summary of search results for first-line NSCLC

Database	Date(s) Searched	First-line NSCLC
MEDLINE	September 2022 - March 2024	205
EMBASE	September 2022 - March 2024	325
Cochrane	September 2022 - March 2024	63
EconLit	September 2022 - March 2024	1
EMBASE – Conference abstracts	September 2022 - March 2024	334
Total (after deduplication)		**928**

Abbreviations: CEA = cost-effectiveness analysis; ICER = Institute for Clinical and Economic Review.

Table 114 Summary of search results for second-line NSCLC

Database	Date(s) Searched	First-line NSCLC
MEDLINE	September 2022 - March 2024	196
EMBASE	September 2022 - March 2024	495
Cochrane	September 2022 - March 2024	53
EconLit	September 2022 - March 2024	1
EMBASE – Conference abstracts	September 2022 - March 2024	313
Total (after deduplication)		**1058**

Abbreviations: CEA = cost-effectiveness analysis; ICER = Institute for Clinical and Economic Review.

Table 115 Summary of search results for thyroid cancer

Database	Date(s) Searched	First-line NSCLC
MEDLINE	September 2022 - March 2024	317
EMBASE	September 2022 - March 2024	744
Cochrane	September 2022 - March 2024	30
EconLit	September 2022 - March 2024	0
EMBASE – Conference abstracts	September 2022 - March 2024	31
Total (after deduplication)		**1122**

Abbreviations: CEA = cost-effectiveness analysis; ICER = Institute for Clinical and Economic Review.

I.1.2 Systematic selection of studies

DistillerSR (DistillerSR Inc, 2024) was used for the study selection process. The study selection consisted of the following 2 steps:

Level 1: Title-abstract screening: Titles and abstracts identified in the literature searches were downloaded and deduplicated in EndNote before being imported into DistillerSR for screening against the predefined eligibility criteria. DistillerAI, a natural language processing tool within DistillerSR, applies a naïve Bayesian approach to abstract screening after being trained on human/manual decisions.For this review, DistillerAI was trained and tested as follows:

- The references screened by reviewers were divided into a training set (used to train DistillerAI) and a test set (used to compare DistillerAI's decisions with those of human reviewers).
- Reviewers employed DistillerSR software to screen all titles and abstracts manually. Their inclusion/exclusion decisions were saved within the system (training set).
- DistillerAI was subsequently trained on this subset of manually screened references and then applied to assess inclusion/exclusion of the remaining references.
- The decisions of DistillerAI were compared against those of the reviewers to evaluate performance.
- An additional audit step (DistillerAI Audit) was undertaken to identify any potential erroneous exclusions and to ensure no relevant records were missed.

All final inclusion and exclusion decisions were made by professional reviewers. DistillerAI was used only as an aid in prioritising records and verifying consistency, not as a substitute for reviewer judgement.

Level 2: Full-text screening: The full-text of all citations included following Level 1 screening was retrieved for detailed eligibility assessment. Screening was performed by a single reviewer according to the pre-specified inclusion criteria (Table 116). A quality check was undertaken on at least 10% of the citations by a second reviewer to ensure consistency and accuracy in study selection. In cases of disagreement regarding study relevance, consensus was reached through consultation with a third reviewer.

The inclusion and exclusion process at both levels of screening was fully documented and presented using PRISMA flow diagrams (Figure 47 to Figure 49), which detail the number of articles included and excluded at each stage of screening.

Table 116 Inclusion and exclusion criteria for economic TLR

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	• Patients with NSCLC treated with first-line or second-line therapy • Patients with TC (medullary, papillary or differentiated; any line of therapy or none)	Patients with other type of cancers
Intervention and comparator	Any intervention (or none)	None

Outcomes	At least one of the following outcomes:
	• Direct costs of interest may include the following:
	  ○ Medication costs
	  ○ Outpatient visit costs
		Studies that do not report at least one of the outcomes of interest

	○ Hospitalization costs (ED or hospital/inpatient visits) ○ Laboratory costs ○ Diagnostic costs ○ Physician costs ○ Cost per treatment success or per response or per QALY gained • Indirect or other costs of interest, including the following: ○ Productivity loss of patients and caregivers (wages lost because of travel or because of absence from work due to outpatient visits) ○ Out-of-pocket expenses ○ Travel costs for patient and caregiver ○ Absenteeism: Days lost from work for caregiver • Resource-use estimates (e.g., number of hospitalisations and length of stay, drug utilization, physician visits, other) • Utility estimates, including but not limited to ○ EQ-5D ○ SF-6D ○ HUI ○ Vignette valuation ○ Utility of the caregiver	
Study design	• Economic analyses (cost-effectiveness, cost-utility, and cost-minimisation analyses)[a] • Utility studies (including studies where utility weights were mapped from other instruments, e.g., disease-specific patient-reported outcome measures) • Prospective studies reporting costs or resource utilization (e.g., observational studies, clinical trials, cross-sectional studies) • Retrospective studies reporting costs or resource utilization (e.g., cost-of-illness, database studies) • Systematic reviews of economic analyses, utility, resource use, or cost studies[a]	• Consensus reports • News articles • Non-systematic reviews and narrative reviews • Articles reporting cost estimates without any supporting data (e.g., commentaries making general reference to cost burden) • Guidelines, commentaries, letters, editorials • Animal or in vitro studies • Pharmacokinetic or pharmacodynamic studies

Time frame	• Database searches: September 2022 to March 2024 • Conference abstract searches: September 2022 to March 2024	None
Language	No restrictions	None

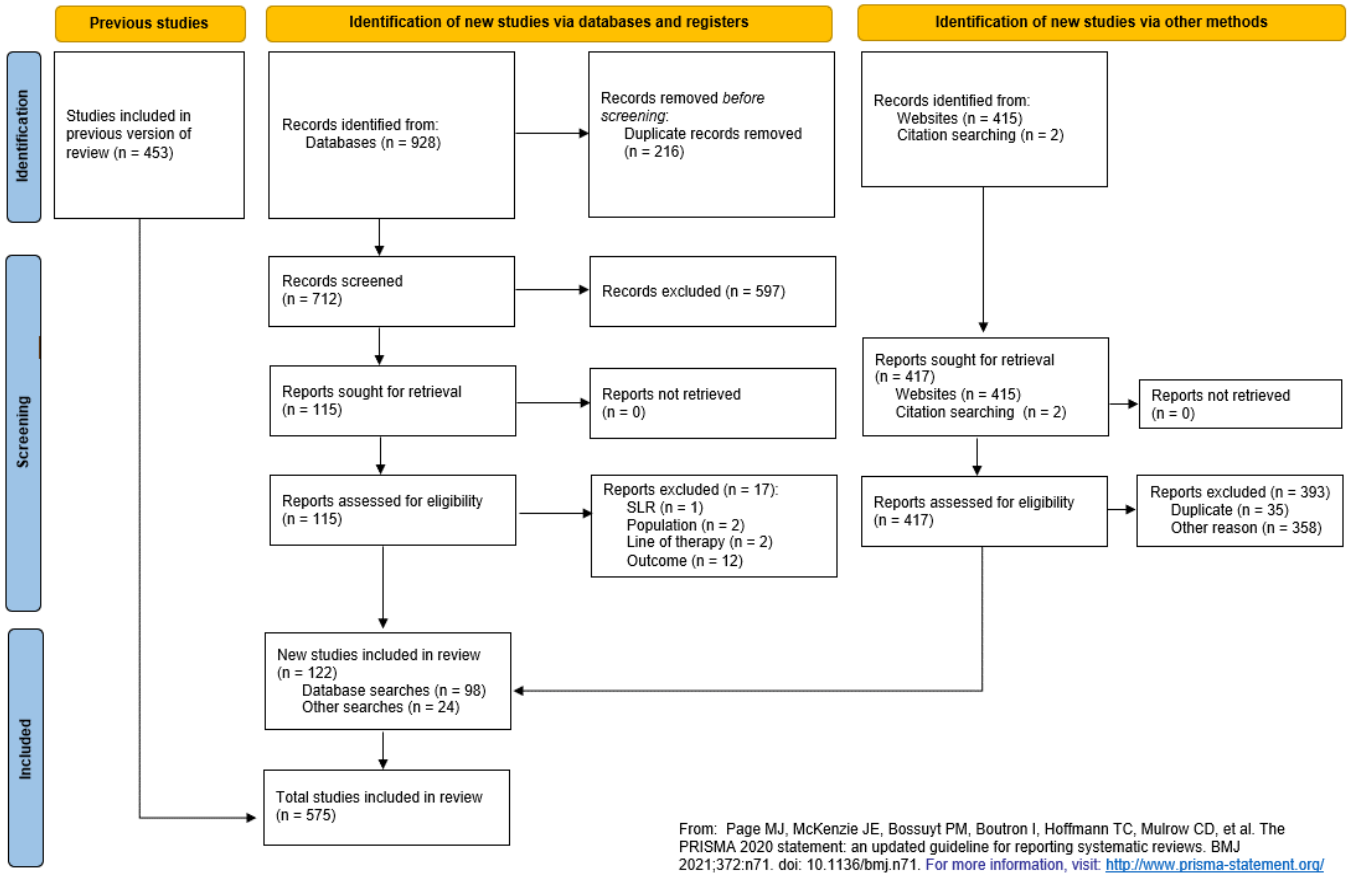
Abbreviations: ED = emergency department; HUI = Health Utilities Index; NSCLC = non-small cell lung cancer; QALY = quality-adjusted life-year; SF-6D = Short-Form 6-Dimension Health Survey; TC = thyroid cancer.
[a] Economic analyses and systematic reviews will be included at level 1 screening, used for identification of primary studies, and then excluded at level 2 screening

.

I.1.2.1 Data extraction

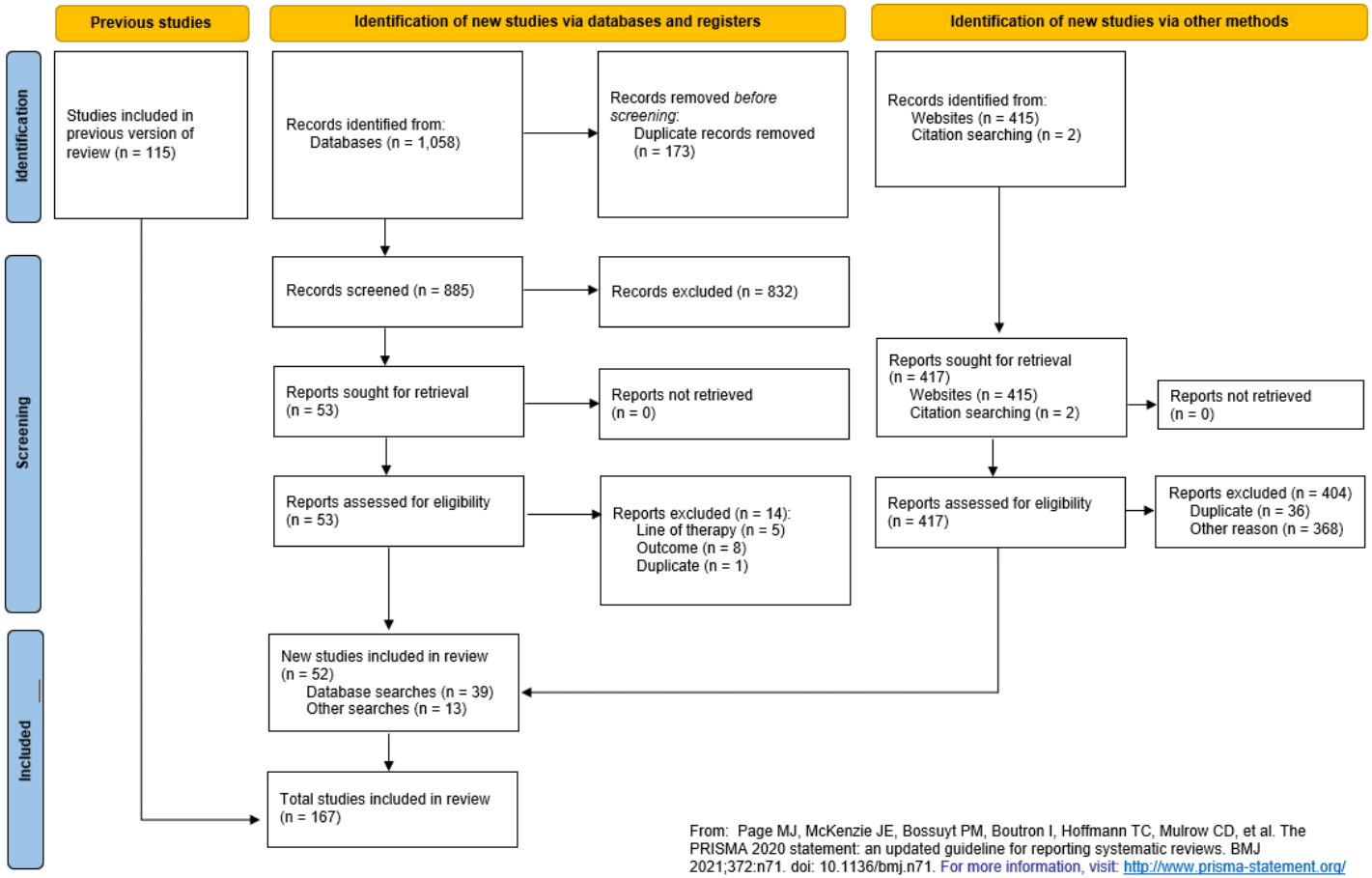
Data in the TLR was extracted using a tailored extraction sheet in Microsoft Excel® by a single reviewer. Quality-control procedures included verification of all extracted data with original sources by a researcher who did not perform the primary data extraction. No quality assessment was undertaken for this TLR.

Figure 47 PRISMA flow diagram for first-line NSCLC



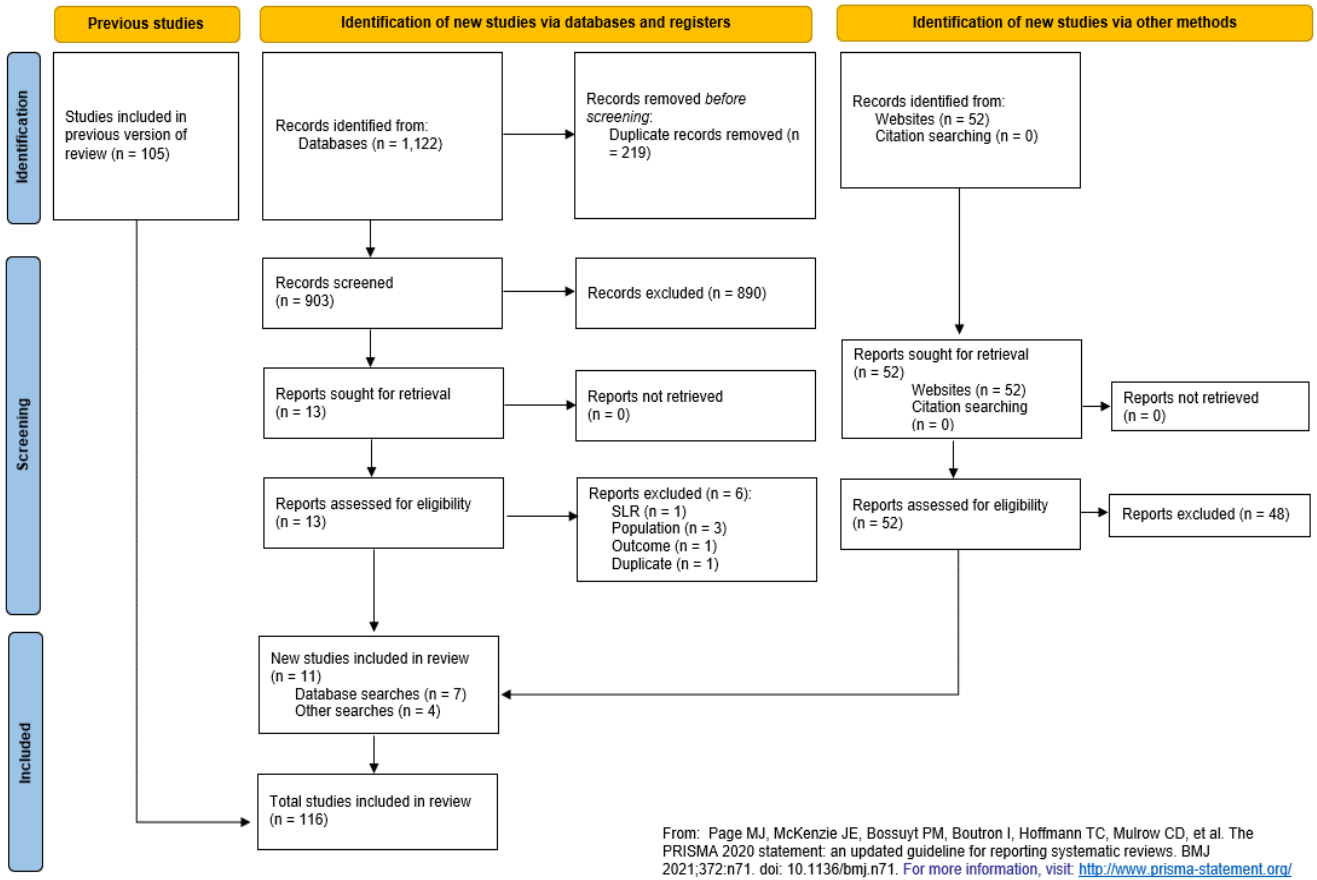
From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 48 PRISMA flow diagram for second-line NSCLC



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Figure 49 PRISMA flow diagram for thyroid cancer



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

I.1.3 Included full text references

All studies newly identified in the 2024 update of the global TLR, which supersedes previous versions to ensure use of the most recent evidence for the health economic model, are summarised in Table 117, Table 118 and Table 119.

Table 117 Overview of study design for studies included for first-line NSCLC (September 2022-March 2024)

No.	Author	Title	Year	Study design
1	Barco, V.,Guiot, V.,Acosta, A.,de Lacey, T.,Maervoet, J.,Lee, A.	EE512 Comparing Costs of Immune Checkpoint Inhibitors for Treatment of 1L NSCLC in Colombia“ A Cost Minimisation Analysis	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
2	Benyounes, K.,Delzard, M.,Le Lay, K.,Bianic, F.,Bougeard, C.	EE426 Budget Impact Analysis of Atezolizumab in 1ST Line Treatment for Patients With PD-L1 High Metastatic NSCLC From a French Payor Perspective	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
3	Berling, M.,Chaudhary, M. A.,Yuan, Y.,Varol, N.,Dale, P.,Testa, E.,Klint, J.,Lee, A.,Lubinga, S. J.,Penrod, J. R.	Cost-effectiveness analysis of nivolumab plus ipilimumab versus platinum-doublet chemotherapy for first-line treatment of stage IV or recurrent non-small cell lung cancer in the United States	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
4	Bestvina, C. M.,Waters, D.,Morrison, L.,Emond, B.,Lafeuille, M. H.,Hilts, A.,Lefebvre, P.,He, A.,Vanderpoel, J.	Cost of genetic testing, delayed care, and suboptimal treatment associated with polymerase chain reaction versus next-generation sequencing biomarker testing for genomic alterations in metastatic non-small cell lung cancer	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
5	Calamia, M.,Geller, R.,Walden, P.,MacDonald, K.,Abraham, I.	PP01.52 Budget Impact Analysis of Toripalimab Versus Pembrolizumab in Previously Untreated Advanced Squamous NSCLC	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
6	Canadian Agency for Drugs and Technologies in Health	Nivolumab: Reimbursement review	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
7	Canadian Agency for Drugs and Technologies in Health	Pralsetinib: Reimbursement review	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
8	Canadian Agency for Drugs and Technologies in Health	Tepotinib: Reimbursement review	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
9	Chen, P., Li, Y., Jing, X., Chen, J., Chen, S., & Yang, Q.	Cost-effectiveness analysis of sugemalimab in combination with chemotherapy as first-line treatment in Chinese patients with metastatic NSCLC	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
10	Chen, P.,Li, Y.,Jing, X.,Chen, J.,Chen, S.,Yang, Q.	Cost-effectiveness analysis of sugemalimab in combination with chemotherapy as first-line treatment in Chinese patients with metastatic NSCLC	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
11	Chen, P.,Wang, X.,Zhu, S.,Li, H.,Rui, M.,Wang, Y.,Sun, H.,Ma, A.	Economic evaluation of sintilimab plus chemotherapy vs. pembrolizumab plus chemotherapy for the treatment of first-line advanced or metastatic squamous NSCLC	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
12	Chen, T.,Xie, R.,Zhao, Q.,Cai, H.,Yang, L.	Cost-Utility Analysis of Camrelizumab Plus Chemotherapy Versus Chemotherapy Alone as a First-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
13	Chen, X.,Zhao, M.,Tian, L.	Economic evaluation of five first-line PD-(L)1 inhibitors for treating non-squamous non-small cell lung cancer in China: A cost-effectiveness analysis based on network meta-analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
14	Cheng, R., Zhou, Z., & Liu, Q.	Cost-effectiveness of first-line versus second-line use of domestic anti-PD-1 antibody sintilimab in Chinese patients with advanced or metastatic squamous non-small cell lung cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
15	Cheng, R.,Zhou, Z.,Liu, Q.	The Cost-Effectiveness of Sugemalimab Plus Chemotherapy as First-Line Treatment for Metastatic Squamous and Non-squamous NSCLC in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
16	Cheng, R.,Zhou, Z.,Liu, Q.	Cost-effectiveness of first-line versus second-line use of domestic anti-PD-1 antibody sintilimab in Chinese patients with advanced or metastatic squamous non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
17	Chisaki, Y.,Nakano, H.,Minamide, J.,Yano, Y.	Cost-Effectiveness Analysis of Atezolizumab versus Platinum-Based Chemotherapy as First-Line Treatment for Patients with Unresectable Advanced Non-small Cell Lung Cancer with PD-L1 Expression Status in Japan	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
18	Cho, S. M.,Lee, H. S.,Jeon, S.,Kim, Y.,Kong, S. Y.,Lee, J. K.,Lee, K. A.	Cost-Effectiveness Analysis of Three Diagnostic Strategies for the Detection of EGFR Mutation in Advanced Non-Small Cell Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
19	Chu, R. W., Vegas García, A., Hickey, C., Power, D. G., & Gorry, C.	Cost-Effectiveness of First-Line Pembrolizumab Monotherapy Versus Chemotherapy in High Programmed Death-Ligand 1 Advanced Non-Small Cell Lung Cancer in the Irish Healthcare Setting	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
20	Chu, R. W.,Vegas Garcia, A.,Hickey, C.,Power, D. G.,Gorry, C.	Cost-Effectiveness of First-Line Pembrolizumab Monotherapy Versus Chemotherapy in High Programmed Death-Ligand 1 Advanced Non-Small Cell Lung Cancer in the Irish Healthcare Setting	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
21	Chu, R.,Tudor, R.,Choi, D. S.,Wong, O.,Chan, K. K. W.,Leighl, N. B.,Chan, B. C. F.,Coyte, P. C.,Rebecca, H. H.	HTA4 Pembrolizumab Vs. Standard of Care Chemotherapy As First-Line Treatment for Advanced Non-Small Cell Lung Cancer with High Pd-L1 Expression Levels: A Cost-Utility Analysis from the Ontario, Canada Public Payer Perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
22	Corrao, G.,Franchi, M.,Zaffaroni, M.,Vincini, M. G.,de Marinis, F.,Spaggiari, L.,Orecchia, R.,Marvaso, G.,Jereczek-Fossa, B. A.	Upfront Advanced Radiotherapy and New Drugs for NSCLC Patients with Synchronous Brain Metastases: Is the Juice Worth the Squeeze? A Real-World Analysis from Lombardy, Italy	2023	Real world analysis
23	Cranmer, H., Kearns, I., Young, M., Humphries, M. J., & Trueman, D.	The cost-effectiveness of brigatinib in adult patients with ALK inhibitor-naive ALK-positive non-small cell lung cancer from a US perspective	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
24	Dai, H.,Wang, W.,Fan, X.,Chen, Y.	Cost-effectiveness of camrelizumab plus chemotherapy vs. chemotherapy in the first-line treatment of non-squamous NSCLC: Evidence from China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
25	De Castro, J.,Insa, A.,Collado-Borrell, R.,Escudero-Vilaplana, V.,Martinez, A.,Fernandez, E.,Sullivan, I.,Arrabal, N.,Carcedo, D.,Manzaneque, A.	Economic burden of locoregional and metastatic relapses in resectable early-stage non-small cell lung cancer in Spain	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
26	Ferreira, P.,Senna, T.,SebastiÃ£o, M.,Alexandre, R. F.,Almeida, P.	Cost-Effectiveness Analysis of Crizotinib Versus Chemoterapy for First Line Treatment of Non-Small Cell Lung Cancer Alk+, from the Brazilian Public Healthcare System Perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
27	Gentili, N.,Balzi, W.,Foca, F.,Danesi, V.,Altini, M.,Delmonte, A.,Bronte, G.,Crino, L.,De Luigi, N.,Mariotti, M.,Verlicchi, A.,Burgio, M. A.,Roncadori, A.,Burke, T.,Massa, I.	Healthcare Costs and Resource Utilisation of Italian Metastatic Non-Small Cell Lung Cancer Patients	2024	Retrospective observational study
28	Goto, Y.,Kawamura, K.,Fukuhara, T.,Namba, Y.,Aoe, K.,Shukuya, T.,Tsuda, T.,Santorelli, M. L.,Taniguchi, K.,Kamitani, T.,Irisawa, M.,Kanda, K.,Abe, M.,Burke, T.,Nokihara, H.	Health Care Resource Use Among Patients with Advanced Non-Small Cell Lung Cancer in Japan, 2017-2019	2023	Observational study
29	Gourzoulidis, G.,Zisimopoulou, O.,Liavas, A.,Tzanetakos, C.	Lorlatinib as a first-line treatment of adult patients with anaplastic lymphoma kinase-positive advanced non-small cell lung cancer: Alpha cost-effectiveness analysis in Greece	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
30	Gourzoulidis, G.,Zisimopoulou, O.,Liavas, A.,Tzanetakos, C.	EE219 Lorlatinib as a First-Line Treatment of Adult Patients with Anaplastic Lymphoma Kinase-Positive Advanced Non-Small Cell Lung Cancer: A Cost-Effectiveness Analysis in Greece	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
31	Griffiths, A.,Young, R.,Yuan, Y.,Chaudhary, M.,Lee, A.,Gordon, J.,McEwan, P.	EE513 Health Economic Evaluation Incorporating Mixture Cure Survival Analysis of Nivolumab Plus Ipilimumab for Previously Untreated Metastatic NSCLC	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
32	He, X.,Fu, S.	Cost-Utility Analysis of Lorlatinib for First-Line Treatment for ALK Positive Advanced Non-Small Cell Lung Cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
33	Hui, W.,Song, R.,Tao, H.,Gao, Z.,Zhu, M.,Zhang, M.,Wu, H.,Gong, D.,Zhang, X.,Cai, Y.	Cost-effectiveness of first-line immunotherapy combinations with or without chemotherapy for advanced non-small cell lung cancer: a modelling approach	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
34	Huo, G.,Liu, W.,Kang, S.,Chen, P.	Toripalimab plus chemotherapy vs. chemotherapy in patients with advanced non-small-cell lung cancer: A cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
35	Isla, D.,Lopez-Brea, M.,Espinosa, M.,Arrabal, N.,Perez-Parente, D.,Carcedo, D.,Bernabe-Caro, R.	Cost-effectiveness of atezolizumab versus pembrolizumab as first-line treatment in PD-L1-positive advanced non-small-cell lung cancer in Spain	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
36	Jansen, J. P.,Ragavan, M. V.,Chen, C.,Douglas, M. P.,Phillips, K. A.	The Health Inequality Impact of Liquid Biopsy to Inform First-Line Treatment of Advanced Non-Small Cell Lung Cancer: A Distributional Cost-Effectiveness Analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
37	Kish, J.,Liassou, D.,Hartman, J.,Lubinga, S. J.,Chopra, D.,Feinberg, B.	Better together? costs of first-line chemoimmunotherapy for advanced non-small cell lung cancer	2023	NA
38	Kittrongsiri, K.,Abogunrin, S.,Celik, H.,Sangroongruangsri, S.	Cost-effectiveness analysis of first-line atezolizumab for patients with stage IV non-small cell lung cancer whose	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
		tumours have a high-programmed death ligand 1 expression in Thailand		
39	Le, H.,Ladino Montero, D.,Lowry, C.,Lawless, H.,Baijal, S.	P2.10-05 Cost of Managing Brain Metastases in Patients with ALK+ aNSCLC with First-Line Tyrosine Kinase Inhibitors (TKIs) in the UK	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
40	Li, F.,Chen, Y.,Xiao, D.,Jiang, S.,Yang, Y.	Cost-Effectiveness Analysis of Sintilimab Plus Chemotherapy in Advanced Non-Squamous Non-Small Cell Lung Cancer: A Societal Perspective	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
41	Li, W., & Wan, L.	Cost-effectiveness analysis of sugemalimab vs. placebo, in combination with chemotherapy, for treatment of first-line metastatic NSCLC in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
42	Li, W.,Wan, L.	Cost-effectiveness analysis of sugemalimab vs. placebo, in combination with chemotherapy, for treatment of first-line metastatic NSCLC in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
43	Li, Y., Liang, X., Yang, T., Guo, S., & Chen, X	Pembrolizumab vs cemiplimab for the treatment of advanced non-small cell lung cancer with PD-L1 expression levels of at least 50%: A network meta-analysis and cost-effectiveness analysis	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
44	Liang, X., Chen, X., Li, H., & Li, Y.	Tislelizumab plus chemotherapy is more cost-effective than chemotherapy alone as first-line therapy for advanced non-squamous non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
45	Liang, X.,Chen, X.,Li, H.,Li, Y.	Cost-effectiveness of camrelizumab plus chemotherapy in advanced squamous non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
46	Liang, X.,Chen, X.,Li, H.,Li, Y.	Tislelizumab plus chemotherapy is more cost-effective than chemotherapy alone as first-line therapy for advanced non-squamous non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
47	Liang, X.,Chen, X.,Li, H.,Liu, X.,Li, Y.	Sugemalimab plus chemotherapy vs. chemotherapy for metastatic non-small-cell lung cancer: A cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
48	Libanore, A.,Lee, A.,Baginska, B.,Chaudhary, M. A.,Maervoet, J.,Ray, S.,Yuan, Y.	EE203 Cost-Effectiveness Analysis of Nivolumab Plus Ipilimumab Versus Other First-Line Therapies for Patients With Stage IV or Recurrent Non-Small Cell Lung Cancer in the United States	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
49	Liu, H., Wang, Y., & He, Q.	Cost-effectiveness analysis of sintilimab plus pemetrexed and platinum versus chemotherapy alone as first-line treatment in metastatic non-squamous non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
50	Liu, H.,Wang, Y.,He, Q.	Cost-effectiveness analysis of sintilimab plus pemetrexed and platinum versus chemotherapy alone as first-line treatment in metastatic non-squamous non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
51	Liu, W.,Huo, G.,Chen, P.	First-line tremelimumab plus durvalumab and chemotherapy versus chemotherapy alone for metastatic non-small cell lung cancer: a cost-effectiveness analysis in the United States	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
52	Liu, W.,Huo, G.,Chen, P.	Cost-effectiveness of first-line versus second-line use of brigatinib followed by lorlatinib in patients with ALK-positive non-small cell lung cancer	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
53	Liu, W.,Huo, G.,Li, M.,Chen, P.	First-line versus second-line use of pralsetinib in treatment of rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer: a cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
54	Low, J. L.,Huang, Y.,Sooi, K.,Chan, Z. Y.,Yong, W. P.,Lee, S. C.,Goh, B. C.	Real-world assessment of attenuated dosing anti-PD1 therapy as an alternative dosing strategy in a high-income country (as defined by World Bank)	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
55	Lu, T.,Huang, Y.,Cai, Z.,Lin, W.,Chen, X.,Chen, R.,Hu, Y.	The cost-effectiveness of cemiplimab plus chemotherapy as the first-line treatment for advanced non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
56	Luo, X., Zhou, Z., Zeng, X., Peng, L., & Liu, Q	Cost-effectiveness of ensartinib, crizotinib, ceritinib, alectinib, brigatinib and lorlatinib in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
57	Luo, X.,Liu, Q.,Zhou, Z.,Yi, L.,Peng, L.,Wan, X.,Zeng, X.,Tan, C.,Li, S.	Cost-Effectiveness of Bevacizumab Biosimilar LY01008 Combined With Chemotherapy as First-Line Treatment for Chinese Patients With Advanced or Recurrent Nonsquamous Non-Small Cell Lung Cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
58	Luo, X.,Zhou, Z.,Zeng, X.,Liu, Q.	The Cost-Effectiveness of Tislelizumab Plus Chemotherapy for Locally Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
59	Luo, X.,Zhou, Z.,Zeng, X.,Peng, L.,Liu, Q.	Cost-effectiveness of ensartinib, crizotinib, ceritinib, alectinib, brigatinib and lorlatinib in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
60	MacDonald, K.,Walden, P.,Geller, R.,Abraham, I.	PP01.51 Cost-Efficiency and Budget-Neutral Expanded Access Modeling of Toripalimab over Pembrolizumab in Advanced NSCLC	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
61	Marin Pozo, J. F.,Cao ViÃ±a, V.,Marin Caba, E.,Plaza Arbeo, A.,Gutierrez Lucena, L.,Contreras Collado, R.	CO137 Health Outcomes of ALK-Inhibitors in Non-Small Cell Lung Cancer in Real Clinical Practice	2023	Retrospective observational study

No.	Author	Title	Year	Study design
62	Mfumbilwa, Z. A.,Simons, Mjhg,Ramaekers, B.,Retel, V. P.,Mankor, J. M.,Groen, H. J. M.,Aerts, Jgjv,Joore, M.,Wilschut, J. A.,Coupe, V. M. H.	Exploring the Cost Effectiveness of a Whole-Genome Sequencing-Based Biomarker for Treatment Selection in Patients with Advanced Lung Cancer Ineligible for Targeted Therapy	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
63	Minhinnick, A. M.,Dunn, A. H.,Arabnejad, V.,Paddison, J. S.,Jackson, C. G. C. A.,Pointer, S. M.,Gurney, J. K.,Cameron, L. B.	Use of Novel National Data Sets to Monitor Chemotherapy Use and Outcomes: A Retrospective Cohort Study of Non-Small-Cell Lung Cancer in Aotearoa New Zealand	2024	Retrospective observational study
64	Naik, J.,Beavers, N.,Nilsson, F. O. L.,Iadeluca, L.,Lowry, C.	Cost-Effectiveness of Lorlatinib in First-Line Treatment of Adult Patients with Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small-Cell Lung Cancer in Sweden	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
65	National Institute for Health and Care Excellence	Selpercatinib for untreated RET fusion-positive advanced non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
66	National Institute for Health and Care Excellence	Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
67	National Institute for Health and Care Excellence	Dabrafenib plus trametinib for treating BRAF V600 mutation-positive advanced non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
68	National Institute for Health and Care Excellence	Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
69	Orsini, I.,Venkatachalam, M.,Yuan, Y.,Lee, A.,Penrod, J. R.	HTA14 Expanding the HTA Cost-Effectiveness Analyses for CheckMate 9LA: Nivolumab Plus Ipilimumab Plus Chemotherapy As First-Line Strategy for Non-Small Cell Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
70	Orsini, I.,Venkatachalam, M.,Yuan, Y.,Lee, A.,Penrod, J. R.	P2.30-02 Assessing the Impact of Using Disease-Specific Novel Value Elements on Cost-Effectiveness Results in Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
71	Orsini, I.,Venkatachalam, M.,Yuan, Y.,Lee, A.,Penrod, J. R.	Identifying and Quantifying Elements of Value for Nivolumab and Ipilimumab in First-Line Non-Small Cell Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
72	Powell, A. C.,Yay Donderici, E.,Zhang, N. J.,Forbes, S. P.,Wiedower, J.,McNeal, A. C.,Hiatt, M. D.	Associations Among Optimal Lung Cancer Treatment, Clinical Outcomes, and Health Care Utilization in Patients Who Underwent Comprehensive Genomic Profiling	2024	Retrospective observational study
73	Presa, M.,Vicente, D.,Calles, A.,Salinas-Ortega, L.,Naik, J.,GarcÃ-a, L. F.,Soto, J.	EE193 Lorlatinib as a First-Line Treatment for ALK+ Advanced Non-Small Cell Lung Cancer: A Cost-Effectiveness Analysis in Spain	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
74	Quek, R. G. W.,Theriou, C.,Smare, C.,Keeping, S.,Xu, Y.,Konidaris, G.,LaFontaine, P. R.,Harnett, J.	EE280 Budget Impact (BI) of First-Line (1L) Cemiplimab Monotherapy for Advanced Non-Small Cell Lung Cancer (aNSCLC) with Programmed Cell Death-Ligand 1 (PD-L1) â‰¥50% in a Large US Health Plan: An Updated Analysis	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
75	Reck, M.,Ciuleanu, T. E.,Cobo, M.,Schenker, M.,Zurawski, B.,Menezes, J.,Richardet, E.,Bennouna, J.,Felip, E.,Juan-Vidal, O.,Alexandru, A.,Cheng, Y.,Sakai, H.,Paz-Ares, L.,Lu, S.,John, T.,Sun, X.,Moisei, A.,Taylor, F.,Lawrance, R.,Zhang, X.,Sylvester, J.,Yuan, Y.,Blum, S. I.,Penrod, J. R.,Carbone, D. P.	First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: CheckMate 9LA 2-year patient-reported outcomes	2023	RCT
76	Reguart Aransay, N.,SÃ¡nchez, J.,Juan Vidal, O. J.,Aguilo Domingo, M.,Arriola, E.,LÃ³pez, C.,Botella, X.,Cots, F.,Montironi, C.,Palanca, S.,BorrÃ s, E.,Masfarre Pinto, L.,Planellas, L.,Lloansi Vila, A.	1410P Characterization of patients with advanced non-small-cell lung cancer (NSCLC) harboring KRASG12C mutation and their associated direct healthcare costs in Spanish routine clinical practice (SILK study)	2023	Observational, retrospective, multicenter

No.	Author	Title	Year	Study design
77	Rumi, F.,Xoxi, E.,Cicchetti, A.	EE466 Budget Impact Analysis of Cemiplimab for First-Line (1L) Advanced Non-Small Cell Lung Cancer (NSCLC) With Programmed Cell Death-Ligand 1 (PD-L1)â‰¥ 50% in Italy	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
78	Rungtivasuwan, C.,Eiamprapaporn, P.	Survival outcome and cost-effectiveness of tyrosine kinase inhibitor in EGFR sensitive mutation advanced-stage NSCLC in Thammasat university hospital	2022	Retrospective study including model based analysis (CE, CU, CM, BIM and other cost analysis)
79	SÃ¡nchez-MartÃ-n, J.,LeÃ³n, L.,SÃ¡nchez-HernÃ¡ndez, A.,Uria, E.,Nieves, D.	EE327 Cost-Effectiveness Analysis of Cemiplimab for Patients With Advanced Non-Small Cell Lung Carcinoma in Spain	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
80	Schwartzberg, L.,Wu, A.,Hartman, J.,Wang, T.,Yin, X.,Chen, J.,Betts, K. A.,Lubinga, S. J.	1135P Adverse event (AE) burden of nivolumab-based immuno-oncology (IO) therapy with/without chemotherapy (chemo) for first-line (1L) advanced non-small cell lung cancer (aNSCLC)	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
81	Scottish Medicines Consortium	Nivolumab (Opdivo) - SMC261 full submission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
82	Scottish Medicines Consortium	Selpercatinib (Retsevmo) - SMC2573 full submission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
83	Scottish Medicines Consortium	Pralsetinib (Gavreto) - SMC2496 full submission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
84	Scottish Medicines Consortium	Tepotinib (Tepmetko) - SMC2535 resubmission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
85	Senna, T.,Alexandre, R. F.,Almeida, P.,SebastiÃ£o, M.,Ferreira, P.	EE151 Cost-Minimization of Lorlatinib Versus Alectinib for First Line Treatment for Treatment of Alk-Positive Nonâ€“Small-Cell Lung Cancer from the Brazilian Private Healthcare System Perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
86	Shang, F.,Zhang, B.,Kang, S.	Cost-effectiveness analysis of atezolizumab plus chemotherapy as first-line treatment for patients with advanced nonsquamous non-small-cell lung cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
87	Shi, Y.,Qian, D.,Li, Y.,Chen, W.,Bo, M.,Zhang, M.,Shi, J.,Jia, B.,Dai, Y.,Li, G.	Comparing the cost-effectiveness of sintilimab + pemetrexed plus platinum and pemetrexed plus platinum alone as a first-line therapy for Chinese patients with nonsquamous non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
88	Shimamoto, T.,Tateyama, Y.,Kobayashi, D.,Yamamoto, K.,Takahashi, Y.,Ueshima, H.,Sasaki, K.,Nakayama, T.,Iwami, T.	Survival and medical costs of non-small cell lung cancer patients according to the first-line treatment: An observational study using the Kyoto City Integrated Database	2023	Observational study
89	Shu, Y., Ding, Y., He, X., Liu, Y., Wu, P., & Zhang, Q	Cost-effectiveness of osimertinib versus standard EGFR-TKI as first-line treatment for EGFR-mutated advanced non-small-cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
90	Shu, Y.,Ding, Y.,He, X.,Liu, Y.,Wu, P.,Zhang, Q.	Cost-effectiveness of osimertinib versus standard EGFR-TKI as first-line treatment for EGFR-mutated advanced non-small-cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
91	Shu, Y.,Ding, Y.,Li, F.,Zhang, Q.	Cost-effectiveness of nivolumab plus ipilimumab versus chemotherapy as first-line therapy in advanced non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
92	Simmons, D.,Welch, E.,Pyrih, N.,Jiang, Z.,Xiao, Y.,Jassim, R.	EE270 The Economic Burden of Metastatic Non-Small Cell Lung Cancer in US Patients without an EGFR or ALK Mutation	2023	Retrospective observational cohort

No.	Author	Title	Year	Study design
93	Spira, A. I.,Knoll, S.,Smith, T. W.,Scotchmer, A.,Bauer, M.	Health Care Resource Utilization (HCRU) and Costs of First-Line Systemic Therapy (1LT) for Locally Advanced or Metastatic Non-Small Cell Lung Cancer (a/mNSCLC) - A Secondary Analysis of Claims Data from the United States (US)	2023	Real-world, retrospective cohort
94	Stenehjem, D.,Lubinga, S. J.,Wu, A.,Betts, K. A.	Adverse event costs associated with first-line therapy for advanced non-small cell lung cancer in the United States: An analysis of clinical trials of immune checkpoint inhibitors	2023	Observational study
95	Taminato, A.,Barbosa, A.,Bento de Lima, C.,CorÃ¡, G.,Antonini Ribeiro, R.,Magro, F. J. B.	EE574 Cemiplimab and Pembrolizumab for Advanced Non-Small Cell Lung Cancer With PD-L1 â‰¥ 50%: Number Needed to Treat and Cost of Preventing an Event in the Brazilian Private Healthcare System Perspective	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
96	Toler, A.,Geddes, J.,Parratt, A.,Davis, S.	EE279 Real-World Evidence Relating Cytopenia Diagnosis to Hospitalization and Cost of Care in the Treatment of Non-Small Cell Lung Cancer Patients	2023	Retrospective observational
97	Tsai, Y. L.,Chang, C. J.	Budget Impact Analysis of Comprehensive Genomic Profiling in Advanced Non-Small Cell Lung Cancer in Taiwan	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
98	Vanderpoel, J.,Emond, B.,Ghelerter, I.,Milbers, K.,Lafeuille, M. H.,Lefebvre, P.,Ellis, L. A.	Healthcare Resource Utilization and Costs in Patients with EGFR-Mutated Advanced Non-Small Cell Lung Cancer Receiving First-Line Treatment in the United States: An Insurance Claims-Based Descriptive Analysis	2023	Observational study
99	Verbeek, F.,van Gils, C.,Heine, R.,Uyl-De Groot, C.	One Size Does Not Fit All: Calculating the Cost-Effectiveness of Multiple Indications of Pembrolizumab in the Netherlands	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
100	Wang, H., Liao, L., Xu, Y., Long, Y., Wang, Y., & Zhou, Y	Economic evaluation of first-line sugemalimab plus chemotherapy for metastatic non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
101	Wang, H.,Liao, L.,Xu, Y.,Long, Y.,Wang, Y.,Zhou, Y.	Economic evaluation of first-line sugemalimab plus chemotherapy for metastatic non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
102	Wang, H.,Long, Y.,Xu, Y.,Liao, L.,Zhou, Y.	Economic evaluation of toripalimab combined with chemotherapy in the treatment of non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
103	Wu, Y.,Ren, K.,Wan, Y.,Lin, H. M.	Economic burden in patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC), with or without brain metastases, receiving first-line ALK inhibitors	2023	Retrospective observational study
104	Wu, Y.,Tao, L.,Chang, L.,Wang, F.,Sun, S.,Sam, H.	EE303 Cost-Effectiveness Analysis of Pd-L1 Testing Associated with Pembrolizumab for First-Line Treatment of Advanced NSCLC in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
105	Yang, M., Vioix, H., Sachdev, R., Stargardter, M., Tosh, J., Pfeiffer, B. M., & Paik, P. K.	Cost-Effectiveness of Tepotinib versus Capmatinib for the Treatment of Adult Patients with Metastatic Non-Small Cell Lung Cancer Harboring Mesenchymal-epithelial Transition Exon 14 (METex14) Skipping	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
106	Yang, S. C.,Ou, H. T.,Su, W. C.,Wang, S. Y.	Cost-effectiveness of first-line immunotherapies for advanced non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
107	Yip, C. Y.,Greystoke, A.,Abogunrin, S.,Belleli, R.,Di Maio, D.,Rouse, P.,Jovanoski, N.	Cost-effectiveness analysis of adjuvant atezolizumab in stage II-IIIA non-small cell lung cancer expressing >=50% PD-L1: A United Kingdom health care perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
108	Yoshioka, S.,Chen, W.,Maeda, T.,Morimoto, K.,Moriwaki, K.,Shimozuma, K.	EE380 Cost-Effectiveness Analysis of Erlotinib Plus Bevacizumab As First-Line Therapy for Advanced EGFR Mutation-Positive Non-Squamous Non-Small Cell Lung Cancer in Japan	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
109	Zhang, C.,Liu, Y.,Tan, J.,Tian, P.,Li, W.	Cost-effectiveness evaluation based on two models of first-line atezolizumab monotherapy and chemotherapy for advanced non-small cell lung cancer with high-PDL1 expression	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
110	Zhang, H.,Li, L.,Feng, L.,Zhou, Z.,Zhang, X.,Feng, J.,Liu, Q.	Biomarkers-Based Cost-Effectiveness of Toripalimab Plus Chemotherapy for Patients with Treatment-Naive Advanced Non-Small Cell Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
111	Zhang, M.,Liu, X.,Wen, F.,Wu, Q.,Zhou, K.,Bai, L.,Li, Q.	First-line Cemiplimab versus Standard Chemotherapy in Advanced Non-small Cell Lung Cancer Patients with at Least 50% Programmed Cell Death Receptor Ligand-1 Positivity: Analysis of Cost-effectiveness	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
112	Zhang, M.,Xu, K.,Lin, Y.,Zhou, C.,Bao, Y.,Zhang, L.,Li, X.	Cost-effectiveness analysis of toripalimab plus chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
113	Zhang, Q.,Tian, P.,Li, W.	Cost-utility analysis of first-generation EGFR-TKIs as the first-line treatment for advanced non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
114	Zhang, X.,Zhang, H.,Li, L. F.,Feng, L.,Liu, Q.	Cost-Effectiveness Analysis of Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
115	Zhao, M.,Shao, T.,Chi, Z.,Tang, W.	Effectiveness and cost-effectiveness analysis of 11 treatment paths, seven first-line and three second-line	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
		treatments for Chinese patients with advanced wild-type squamous non-small cell lung cancer: A sequential model		
116	Zheng, Z., Zhu, H., Fang, L., & Cai, H.	Cost-effectiveness analysis of sugemalimab vs. chemotherapy as first-line treatment of metastatic nonsquamous non-small cell lung cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
117	Zheng, Z.,Fang, L.,Cai, H.	First-line treatment with durvalumab plus chemotherapy versus chemotherapy alone for metastatic non-small-cell lung cancer in the USA: a cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
118	Zheng, Z.,Zhu, G.,Cao, X.,Cai, H.,Zhu, H.	A cost-effectiveness analysis of first-line toripalimab plus chemotherapy in advanced nonsquamous non-small cell lung cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
119	Zheng, Z.,Zhu, H.,Fang, L.,Cai, H.	Cost-effectiveness analysis of sugemalimab vs. chemotherapy as first-line treatment of metastatic nonsquamous non-small cell lung cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
120	Zhou, K.,Shu, P.,Zheng, H.,Li, Q.	Cost-effectiveness analysis of toripalimab plus chemotherapy as the first-line treatment in patients with advanced non-small cell lung cancer (NSCLC) without EGFR or ALK driver mutations from the Chinese perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
121	Zhu, G.,Cai, H.,Zheng, Z.	Cemiplimab combined with chemotherapy versus chemotherapy in advanced non-small cell lung cancer: an updated EMPOWER-Lung 3 trial-based cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
122	Zou, D.,Ye, W.,Hess, L. M.,Bhandari, N. R.,Ale-Ali, A.,Foster, J.,Quon, P.,Harris, M.	Diagnostic Value and Cost-Effectiveness of Next-Generation Sequencingâ€“Based Testing for Treatment of Patients with Advanced/Metastatic Non-Squamous Nonâ€“Small-Cell Lung Cancer in the United States	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

Table 118 Overview of study design for studies included for second-line NSCLC (September 2022-March 2024)

No.	Author	Title	Year	Study design
1	Arrieta, O.,Ramos-Ramirez, M.,Garces-Flores, H.,Cabrera-Miranda, L. A.,Valencia-Velarde, A.,Frias-Gasga, A.,Soto-Molina, H.	WS08.07 Evaluation of a Risk-sharing Agreement for Atezolizumab Treatment in NSCLC Patients: A Strategy to Improve Access in Low Income Countries	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
2	Arriola, E.,Batteson, R.,Hook, E.,Wheat, H.,Vioix, H.,Morros, M.,Ãguila, M.,de los Santos Real, H.,Fernandez Soberon, S.,Brines, M.,VÃ¡zquez, S.	EE146 Cost-effectiveness of Tepotinib for Patients With Previously Treated Advanced Non-Small Cell Lung Cancer Harboring Metex14 Skipping Alterations in Spain	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
3	Benyounes, K.,Delzard, M.,Le Lay, K.,Bianic, F.,Bougeard, C.	EE426 Budget Impact Analysis of Atezolizumab in 1ST Line Treatment for Patients With PD-L1 High Metastatic NSCLC From a French Payor Perspective	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
4	Berardi, A.,Laurie, M.,Theriou, C.,Orsini, I.,Bouwmeester, W.,Gao, S.,Korytowsky, B.	EE357 Cost per Responder Analysis Comparing Adagrasib and Sotorasib in Patients With KRAS G12C-Mutated Previously Treated Non-Small Cell Lung Cancer (NSCLC)	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
5	Byun, J. Y.,Lee, J. E.,Shim, Y. B.,Kim, J.,Lee, S. Y.,Shin, B. R.,Yoon, N. R.,Park, M. H.,Lee, E. K.	Economic Burden of Recurrence in Completely Resected Stage IB-IIIA Non-Small Cell Lung Cancer: A Retrospective Study Using Nationwide Claims Data of South Korea	2023	Retrospective cohort
6	Canadian Agency for Drugs and Technologies in Health	Sotorasib: Reimbursement recommendation	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
7	Canadian Agency for Drugs and Technologies in Health	Amivantamab: Reimbursement review	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
8	Canadian Agency for Drugs and Technologies in Health	Pralsetinib: Reimbursement review	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
9	Canadian Agency for Drugs and Technologies in Health	Atezolizumab: Reimbursement review	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
10	Canadian Agency for Drugs and Technologies in Health	Tepotinib: Reimbursement review	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
11	Chen, P., Yang, Q., Li, Y., Jing, X., & Chen, J.	Cost-effectiveness analysis of adjuvant therapy with atezolizumab in Chinese patients with stage IB-IIIA resectable NSCLC after adjuvant chemotherapy	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
12	Cheng, R., Zhou, Z., & Liu, Q.	Cost-effectiveness of first-line versus second-line use of domestic anti-PD-1 antibody sintilimab in Chinese patients with advanced or metastatic squamous non-small cell lung cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
13	Cheng, R.,Zhou, Z.,Liu, Q.	Cost-effectiveness of first-line versus second-line use of domestic anti-PD-1 antibody sintilimab in Chinese patients with advanced or metastatic squamous non-small cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
14	Cho, S. M.,Lee, H. S.,Jeon, S.,Kim, Y.,Kong, S. Y.,Lee, J. K.,Lee, K. A.	Cost-Effectiveness Analysis of Three Diagnostic Strategies for the Detection of EGFR Mutation in Advanced Non-Small Cell Lung Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
15	Das, M.,Ogale, S.,Jovanoski, N.,Johnson, A.,Nguyen, C.,Bhagwakar, J.,Lee, J. S.	Cost-effectiveness of adjuvant atezolizumab for patients with stage II-IIIA PD-L1+ non-small-cell lung cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
16	De Castro, J.,Insa, A.,Collado-Borrell, R.,Escudero-Vilaplana, V.,Martinez, A.,Fernandez, E.,Sullivan, I.,Arrabal, N.,Carcedo, D.,Manzaneque, A.	Economic burden of locoregional and metastatic relapses in resectable early-stage non-small cell lung cancer in Spain	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
17	Donington, J.,Hu, X.,Zhang, S.,Song, Y.,Arunachalam, A.,Chirovsky, D.,Gao, C.,Lerner, A.,Jiang, A.,Signorovitch, J.,Samkari, A.	Event-free survival as a predictor of overall survival and recurrence burden of patients with nonâ€“small cell lung cancer receiving neoadjuvant therapy	2024	Retrospective observational
18	Fukui, Y.,Chen, W.,Maeda, T.,Morimoto, K.,Moriwaki, K.,Shimozuma, K.	EE498 Economic Evaluation of Nanoparticle Albumin-Bound paclitaxel for Previously Treated Advanced NSCLC in Japan	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
19	Gong, J.,Su, D.,Shang, J.,Xu, S.,Tang, L.,Sun, Z.,Liu, G.	Cost-Effectiveness of Tislelizumab Versus Docetaxel for Previously Treated Advanced Non-Small-Cell Lung Cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
20	Goto, Y.,Kawamura, K.,Fukuhara, T.,Namba, Y.,Aoe, K.,Shukuya, T.,Tsuda, T.,Santorelli, M. L.,Taniguchi, K.,Kamitani, T.,Irisawa, M.,Kanda, K.,Abe, M.,Burke, T.,Nokihara, H.	Health Care Resource Use Among Patients with Advanced Non-Small Cell Lung Cancer in Japan, 2017-2019	2023	Observational study

No.	Author	Title	Year	Study design
21	Gupta, D.,Gupta, N.,Singh, N.,Prinja, S.	Economic Evaluation of Targeted Therapies for Anaplastic Lymphoma Kinase- and ROS1 Fusion-Positive Non-Small Cell Lung Cancer in India	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
22	Hernandez, L. G.,Young, M.	EE153 Budget Impact Analysis of Introducing Mobocertinib for Locally Advanced or Metastatic Epidermal Growth Factor Receptor Exon 20 Insertion-Positive Non-Small-Cell Lung Cancer in the United States from the Payer Perspective	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
23	Hernandez, L.,Young, M.	The budget impact of introducing mobocertinib for the postplatinum treatment of advanced non-small cell lung cancer harboring epidermal growth factor receptor exon 20 insertion mutations	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
24	Jiang, Y., Zhao, M., Liu, R., & Zheng, X.	Sotorasib versus Docetaxel for treatment of US and Chinese patients with advanced non-small-cell lung cancer with KRAS p.G12C-mutated: A cost-effectiveness analysis to inform drug pricing	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
25	Jo, A. R.,Oh, B. C.,Kwon, S. H.,Nam, J. H.,Yang, S. Y.,Kim, M. J.,Lee, E. K.	Healthcare Resource Utilization and Costs Associated With Previously Treated Advanced Non-Small Cell Lung Cancer Patients Without EGFR Mutations or ALK Rearrangements in Korea	2022	Retrospective cohort
26	Kessler, J. E.,Park, K. N.,Grizzle, A. J.,Hurwitz, J. T.	Cost of illness of stage IV non-small cell lung cancer (NSCLC) positive for programmed cell death ligand 1 (PD-L1) in the US	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
27	Lemmon, C. A.,Zabor, E. C.,Pennell, N. A.	Modeling the Cost-Effectiveness of Adjuvant Osimertinib for Patients with Resected EGFR-mutant Non-Small Cell Lung Cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
28	Leung, J. H.,Chang, C. W.,Chan, A. L. F.,Lang, H. C.	Cost-effectiveness of immune checkpoint inhibitors in the treatment of non-small-cell lung cancer as a second line in Taiwan	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
29	Liao, M.,Kang, S.	Economic evaluation of sintilimab versus docetaxel as second-line treatment for patients with advanced or metastatic squamous non-small-cell lung cancer in China: a model-based cost-effectiveness analysis	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
30	Liu, K.,Zhu, Y.,Zhu, H.,Zeng, M.	Combination tumor-treating fields treatment for patients with metastatic non-small cell lung cancer: A cost-effectiveness analysis	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
31	Liu, W.,Huo, G.,Chen, P.	Cost-effectiveness of first-line versus second-line use of brigatinib followed by lorlatinib in patients with ALK-positive non-small cell lung cancer	2024	Model based analysis (CE, CU, CM, BIM and other cost analysis)
32	Liu, W.,Huo, G.,Li, M.,Chen, P.	First-line versus second-line use of pralsetinib in treatment of rearranged during transfection (RET) fusion-positive advanced non-small cell lung cancer: a cost-effectiveness analysis	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
33	MÃ¤nnik, T.,Jovanoski, N.,Vuojolainen, M.,Knuuttila, A.,Jekunen, A.,Laine, J.	EE209 Cost-Effectiveness Analysis of Atezolizumab as Adjuvant Treatment in Adult Patients Following Complete Resection and Platinum-Based Chemotherapy with Non-Small Cell Lung Cancer (NSCLC) in Finland	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
34	Marcellusi, A.,Belfiore, M.,Tempre, R.,Russo, A.	EE508 Cost Estimation Model of Prevented Recurrences with Atezolizumab in Early Non-Small Cell Lung Cancer in Italy	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
35	Muthusamy, B.,Zabor, E. C.,Pennell, N. A.	Clinical and financial implications of ADUARA trial on a real-world population	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
36	National Institute for Health and Care Excellence	Amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy.	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
37	National Institute for Health and Care Excellence	Atezolizumab for adjuvant treatment of resected non-small-cell lung cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
38	Plessala, I.,Cawston, H.,Cortes, J.,Ajjouri, R.,Le Lay, K.,Souquet, P. J.,Chouaid, C.	Cost-effectiveness analysis of atezolizumab as adjuvant treatment of patients with stage II-IIIA non-small cell lung cancer, PD-L1+>=50% of tumor cells in France: A modeling study	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
39	Plessala, I.,Chouaid, C.,Souquet, P. J.,Cawston, H.,Cortes, J.,Le Lay, K.,Roula, A.	EE324 Cost-Effectiveness analysis of Atezolizumab as Adjuvant Treatment of Patients With Stage II-IIIA Non-Small Cell Lung Cancer, With Pd-L1â‰¥50% of Tumor Cells, in France	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
40	Rungtivasuwan, C.,Eiamprapaporn, P.	Survival outcome and cost-effectiveness of tyrosine kinase inhibitor in EGFR sensitive mutation advanced-stage NSCLC in Thammasat university hospital	2022	Retrospective study including model based analysis (CE, CU, CM, BIM and other cost analysis)
41	Scottish Medicines Consortium	Pralsetinib (Gavreto) - SMC2496 full submission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
42	Scottish Medicines Consortium	Tepotinib (Tepmetko) - SMC2535 resubmission	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
43	Shi, S.,Jiang, Y.	Cost-Effectiveness of Lorlatinib in Second-Line Treatment of ALK-Positive Advanced Non-Small Cell Lung Cancer in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
44	Shi, Y.,Pei, R.,Liu, S.	Osimertinib versus platinum-pemetrexed in patients with previously treated EGFR T790M advanced non-small cell lung cancer: An updated AURA3 trial-based cost-effectiveness analysis	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
45	Silva Miguel, L.,Pinheiro, B.,Carvalho, P.,Jovanoski, N.,Belleli, R.,Abogunrin, S.,Alves, P.,AraÃºjo, A.,Barata, F.,Hespanhol, V.,da Luz, R.,Borges, M.	A Cost-Effectiveness Analysis of Atezolizumab as Adjuvant Treatment Following Complete Resection and Platinum-Based Chemotherapy in Adult Patients With Early-Stage Non-Small Cell Lung Cancer With a High Risk of Recurrence	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
46	Yang, M., Vioix, H., Sachdev, R., Stargardter, M., Tosh, J., Pfeiffer, B. M., & Paik, P. K.	Cost-Effectiveness of Tepotinib versus Capmatinib for the Treatment of Adult Patients with Metastatic Non-Small Cell Lung Cancer Harboring Mesenchymal-epithelial Transition Exon 14 (METex14) Skipping	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
47	Yang, Y. H.,Tan, E. C. H.,Chiang, C. L.,Huang, S. Y.	CO173 Outcomes, Treatment Pattern, and Related Cost of Late-Stage Non-Small Cell Lung (NSCLC) Cancer in Taiwan	2023	Comprehensive analysis
48	Yip, C. Y.,Greystoke, A.,Abogunrin, S.,Belleli, R.,Di Maio, D.,Rouse, P.,Jovanoski, N.	Cost-effectiveness analysis of adjuvant atezolizumab in stage II-IIIA non-small cell lung cancer expressing >=50% PD-L1: A United Kingdom health care perspective	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
49	Zhang, X.,Fang, P.,Su, G.,Gui, S.,Shen, A.	Cost-effectiveness of ensartinib for patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
50	Zhao, M.,Shao, T.,Chi, Z.,Tang, W.	Effectiveness and cost-effectiveness analysis of 11 treatment paths, seven first-line and three second-line treatments for Chinese patients with advanced wild-type squamous non-small cell lung cancer: A sequential model	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
51	Zhou, D.,Luo, X.,Zhou, Z.,Zeng, X.,Wan, X.,Tan, C.,Liu, Q.	Cost-effectiveness analysis of tislelizumab, nivolumab and docetaxel as second- and third-line for advanced or metastatic non-small cell lung cancer in China	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
52	Zuo, G. Y.,Wang, Y.,Gao, Y.,Zhang, Y. J.,Zhu, F. F.	CO214 Model Predictions for Lifetime Health Benefits of Mobocertinib and Current Treatment Options in Post-Platinum Patients with Locally Advanced or Metastatic NSCLC Harboring Egfr Exon 20 Insertion Mutation in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

Table 119 Overview of study design for studies included for thyroid cancer (September 2022-March 2024)

No.	Author	Title	Year	Study design
	Thyroid Cancer			
1	Baek, H. S.,Ha, J.,Kim, K.,Bae, J.,Kim, J. S.,Kim, S.,Lim, D. J.,Kim, C.	Cost-Effectiveness of Active Surveillance Compared to Early Surgery of Small Papillary Thyroid Cancer: A Retrospective Study on a Korean Population	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
2	Canadian Agency for Drugs and Technologies in Health	Cabozantinib: Reimbursement review	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
3	Canadian Agency for Drugs and Technologies in Health	Selpercatinib: Reimbursement review (December 2022)	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
4	Canadian Agency for Drugs and Technologies in Health	Selpercatinib: Reimbursement review (September 2022)	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)
5	Hao, Q.,Vanness, D.,Boltz, M. M.,Hollenbeak, C. S.	EE384 Cost-Effectiveness of Hemithyroidectomy Versus Total Thyroidectomy for Patients with Low Risk Differentiated Thyroid Cancer	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)

No.	Author	Title	Year	Study design
6	Huang, D.,Peng, J.,Chen, N.,Yang, Q.,Jiang, L.	Mapping study of papillary thyroid carcinoma in China: Predicting EQ-5D-5L utility values from FACT-H&N	2023	Mapping model
7	Huang, D.,Zeng, D.,Tang, Y.,Jiang, L.,Yang, Q.	Mapping the EORTC QLQ-C30 and QLQ H&N35 to the EQ-5D-5L and SF-6D for papillary thyroid carcinoma	2024	Mapping model
8	Kang, I. K.,Bae, J. S.,Kim, J. S.,Kim, K.	Cost-effectiveness of intraoperative neural monitoring of recurrent laryngeal nerves in thyroid lobectomy for papillary thyroid carcinoma	2024	NA
9	Lai, M.,Zhang, M. M.,Qin, Q. Q.,An, Y.,Li, Y. T.,Yuan, W. Z.	Cost-effectiveness of active surveillance versus early surgery for thyroid micropapillary carcinoma based on diagnostic and treatment norms in China	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
10	National Institute for Health and Care Excellence	"Cabozantinib for previously treated advanced differentiated thyroid cancer unsuitable for or refractory to radioactive iodine.	2023	Model based analysis (CE, CU, CM, BIM and other cost analysis)
11	Shi, B.,Ma, W.,Pan, H.,Shi, Y.,Zhang, H.,Xing, S.	Cost-Effectiveness of Apatinib and Cabozantinib for the Treatment of Radioiodine-Refractory Differentiated Thyroid Cancer	2022	Model based analysis (CE, CU, CM, BIM and other cost analysis)

I.1.4 Excluded full text references

Table 120 List of studies excluded from the TLR

First author, year	Title	Journal	Exclusion reason	Exclusion subreason
N/A	N/A	N/A	N/A	N/A

I.1.5 Local adaptation economic SLR

To support this submission for retsevmo monotherapy in the treatment of adults with advanced RET fusion–positive NSCLC not previously treated with a RET inhibitor in Denmark, the global TLR was adapted by excluding all studies not relevant to a Danish setting. The objective of the global TLR was to identify resource use, cost, and utility data that are relevant to economic analyses in NSCLC and TC. As no sources were identified that aligned with the Danish setting, all sources from the global TLR were excluded as inputs for the health economic model. The local adaptation is illustrated in Figure 50.

Targeted literature review – economic studies

In addition to the global TLR, a new targeted literature review was undertaken to identify resource use, cost, and utility data specific to the Danish setting. Sixteen sources were identified and used in the health economic model (Table 121).

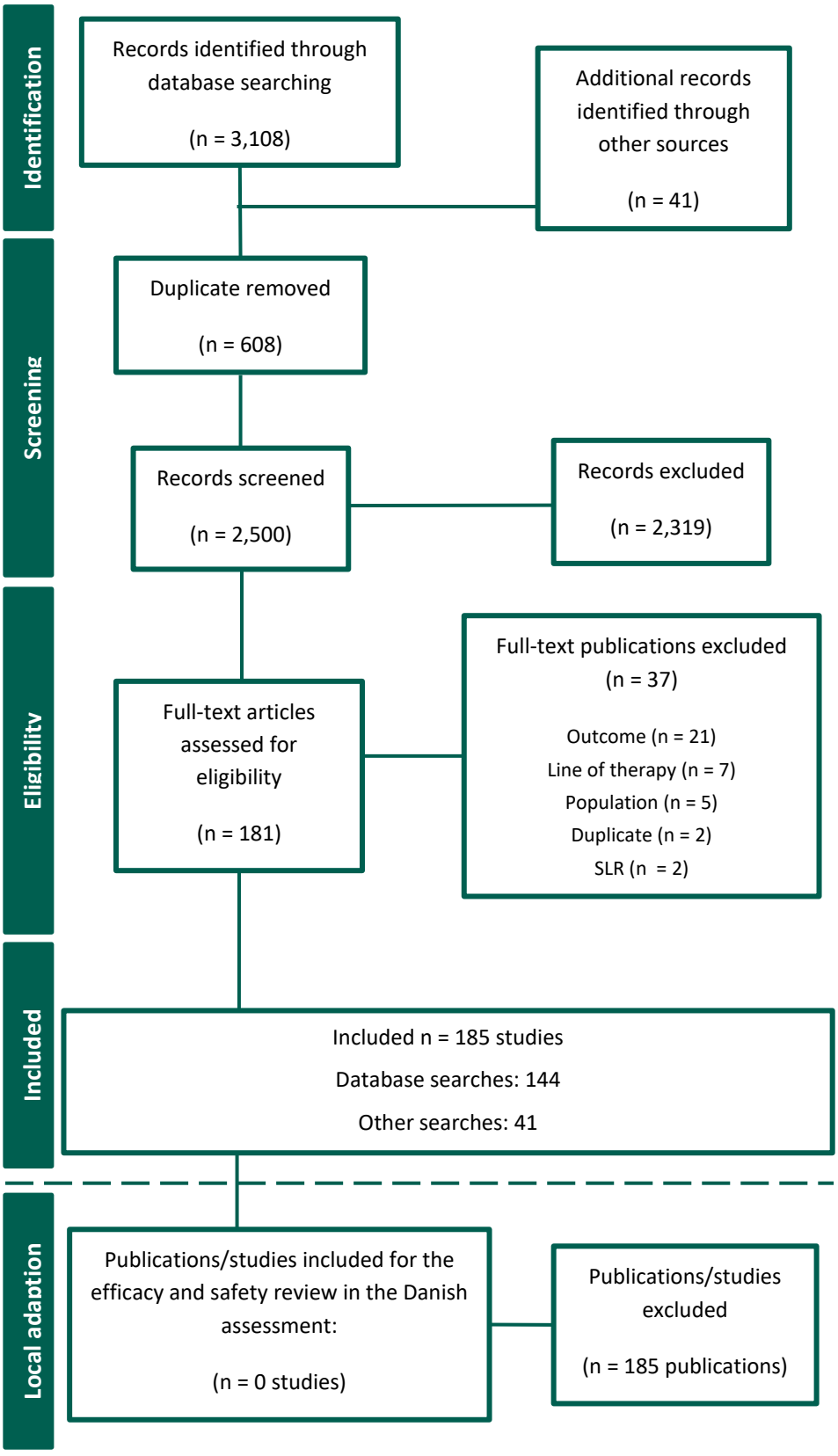
Table 121 Sources included in the targeted literature search

Source	Search strategy	Date of search
Eli Lilly, data on file (LIBRETTO-431), PRO SAP report 2023 (50)	Hand search	10.09.2025
Eli Lilly, data on file (LIBRETTO-431), PRO analysis report 2023 (51)	Hand search	10.09.2025
Eli Lilly, data on file (LIBRETTO-431), EQ-5D-5L Denmark analysis 2023 (DCO 2024) (52)	Hand search	10.09.2025
Eli Lilly, data on file (LIBRETTO-001), PRO analysis (DCO January 2023) (39)	Hand search	10.09.2025
Nafees, B., Stafford, M., Gavriel, S., Bhalla, S., & Watkins, J. (2008). Health state utilities for non-small cell lung cancer. Health and quality of life outcomes, 6, 1-15. (53)	Hand search	10.09.2025
National Institute for Health and Care Excellence, Pembrolizumab for treating PD-L1-positive non-small-cell lung cancer after chemotherapy (TA428) 2017 (54)	Hand search	10.09.2025

Martí, S. G., Colantonio, L., Bardach, A., Galante, J., Lopez, A., Caporale, J., ... & Pichon-Riviere, A. (2013). A cost-effectiveness analysis of a 10-valent pneumococcal conjugate vaccine in children in six Latin American countries. Cost effectiveness and resource allocation, 11, 1-17. (55)	Hand search	10.09.2025
Doyle, S., Lloyd, A., & Walker, M. (2008). Health state utility scores in advanced non-small cell lung cancer. Lung Cancer, 62(3), 374-380. (56)	Hand search	10.09.2025
National Institute for Health and Care Excellence, Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer (TA347) 2015 (57)	Hand search	10.09.2025
Eli Lilly, data on file (LIBRETTO-431), data cutoff 1 May 2023 (Clinical study report) (38)	Hand search	10.09.2025
Sireci, A., Morosini, D., & Rothenberg, S. (2019). P1. 01-101 efficacy of immune checkpoint inhibition in RET fusion positive non-small cell lung cancer patients. Journal of Thoracic Oncology, 14(10), S401. (58)	Hand search	10.09.2025
National Institute for Health and Care Excellence. Atezolizumab for treating locally advanced or metastatic non-small-cell lung cancer after chemotherapy. Technology Appraisal. NICE; 2018. (32)	Hand search	10.09.2025
The Danish Medicines Council, assessment report of Retsevmo®, Bilag til Medicinrådets anbefaling vedrørende selpercatinib til behandling af RET-forandret kræft i skjoldbruskkirtlen eller	Hand search	10.09.2025

ikke småcellet lungekræft – Revurdering (2022) (1)		
National Institute for Health and Care Excellence. Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer. Technology Appraisal NICE; 2019 (TA584) (34)	Hand search	10.09.2025
National Institute for Health and Care Excellence. Pembrolizumab for untreated PD-L1-positive metastatic non-small-cell lung cancer. NICE; 2018 (TA531) (59)	Hand search	10.09.2025
National Institute for Health and Care Excellence. Nivolumab for advanced non-squamous non-small-cell lung cancer after chemotherapy. NICE; 2021 (TA713 previously TA484) (60)	Hand search	10.09.2025

Figure 50 PRISMA diagram including local adaptation (economic SLR)



I.1.6 Quality assessment and generalizability of estimates

N/A

I.1.7 Unpublished data

N/A

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

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

An economic TLR was conducted to identify and summarize resource use, cost, and utility data that are relevant to economic analyses in NSCLC and TC. To avoid repetition the economic TLR as a whole (targeting both HRQoL and inputs for the health economic model) is in Appendix I.

Appendix K. Estimate the Treatment Effect of Selpercatinib in RET Fusion-Positive NSCLC LIBRETTO-431

K.1 Progression-free survival

Based on the analysis plan: *Analysis Plan to Estimate the Relative Treatment Effect in Progression-Free Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431*

The LIBRETTO-431 trial included randomisation to the following 2 treatment arms (refer to Figure 19):

- Selpercatinib (n = 159)
- Standard of care: pemetrexed + carboplatin or cisplatin ± pembrolizumab (n = 102)

The choice of whether to prescribe pembrolizumab was made before the physician knew to which treatment arm a patient belonged. Therefore, the LIBRETTO-431 can be split according to ITT with pembrolizumab without breaking the randomisation of the study.

The analysis uses data from the overall populations with a covariate for ITT with pembrolizumab. We have 3 options for the analyses:

1. Fit models to the subgroup of patients that were not intended to receive pembrolizumab (n = 49)
    a. The sample size may be too small to show a treatment effect and the results may be prone to sampling error.
1. Assume there is no difference between the patient populations and use the ITT overall population (n = 261)
    a. May be problematic if the relative treatment effect for selpercatinib versus the control differs between the patient populations for ITT with pembrolizumab. For this option we need to assume that pembrolizumab has no benefit in this patient population. Leone et al. (2020) reviewed the evidence for the response to immune-checkpoint inhibitors in patients with *RET* fusion-positive NSCLC. Currently all the evidence comes from small samples from observational studies. Offin et al. (2019) reported on the results from 13 patients with *RET* fusion-positive NSCLC who received programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) inhibitors at some point during their treatment history. No objective response was observed. Mazieries et al. (2019) reported similar results from the IMMUNOTARGET registry, where only

1 of 16 evaluated patients achieved a partial response. Guisier et al. (2020) reported that 3 out of 9 patients with *RET* fusion-positive NSCLC who received pembrolizumab or nivolumab achieved partial response. Lu et al. (2020) reported that 2 out 10 patients with *RET* fusion-positive NSCLC who received immune-checkpoint inhibitors had an evaluable response. It may therefore be reasonable to assume that pembrolizumab had little or no effect in LIBRETTO-431, which would make the ITT population appropriate for the submission to NICE and other country submissions.

2. Assume that there is no treatment-effect interaction for intention to receive pembrolizumab but allow the survival in the patient populations to differ by ITT with pembrolizumab (overall population, n = 261)
    a. Could be used if there is a difference in survival between the patient populations for ITT with and without pembrolizumab but with no evidence of a treatment effect interaction.

Survival appears to be better in the patient population that was intended to receive pembrolizumab. It is possible that patients benefited from this treatment and/or the physicians selected healthier patients to receive this treatment (see table below).

Table 122 Median survival (months) for PFS by review type, treatment, and patient population (with and without pembrolizumab)

Population	Intended to receive pembrolizumab	Not intended to receive pembrolizumab
Selpercatinib		
BICR	24.84	19.12
Investigator assessment	24.84	20.27
Control		
BICR	11.17	NR
Investigator assessment	14.03	9.43

Source: Eli Lilly, data on file, 2024

From the BICR data presented in Table 86 (Appendix D.2.1), there appears to be little indication of a treatment-effect interaction with intent to prescribe pembrolizumab. Lilly has assessed the following 13 patient characteristics for treatment-effect interactions: age (< 65, ≥ 65), Eastern Cooperative Oncology Group (ECOG) (0, 1, 2), disease stage (III, IVA, IVB), brain metastases, liver metastases, sex, race (Asian vs. non-Asian), region (East Asian vs. non-East Asian), smoker (former/current vs. never), RET specimen type (blood, tissue), RET fusion result (CCDC9, KIF5B, Positive). No significant treatment-effect interactions were found in the ITT with pembrolizumab population. The treatment-effect interactions for race and gender were the closest to being significant with *P* values of 0.3792 and 0.3970, respectively. Therefore, if the BICR data are used there may be justification for using the third approach (i.e., include a covariate for intent to prescribe pembrolizumab and use the ITT population).

The results from investigator assessment are not consistent with those from BICR. They appear to show a treatment-effect interaction with patient population (ITT pembrolizumab) (HR of 0.520, 0.573, and 0.261 (for ITT, intent to prescribe pembrolizumab, and intent to not prescribe pembrolizumab, respectively). Using the BICR

data, it is considered reasonable to claim that there is no treatment-effect interaction with whether patients were intended to receive pembrolizumab or not, hence fitting a Cox model stratified by treatment with a covariate for whether patients were intended to receive pembrolizumab.

Figure 51 An example showing survival predictions from a cox model stratified by treatment with intent to prescribe pembrolizumab as a covariate

source: Eli Lilly, data on file, 2024 (48)

This approach will mean that confidence intervals are larger in the patient population that was considered not suitable for pembrolizumab, but the actual shape of the curve will reflect that in the ITT population and so is less susceptible to difference caused by sampling error.

K.2 Overall survival

Based on the analysis plan: *Analysis Plan to Estimate the Relative Treatment Effect in Overall Survival for Selpercatinib in RET Fusion-Positive Non–Small Cell Lung Cancer Using Data From LIBRETTO-431: Treatment Switching and Extrapolation*

The primary objectives of this analysis are as follows:

- Perform treatment-switching adjustments for OS data from LIBRETTO-431.
- Perform extrapolation of the predicted survival from the treatment-switching methods.

Similar for PFS, the LIBRETTO-431 trial is demonstrated in Figure 19 (selpercatinib (n=159) and control (pemetrexed + carboplatin or cisplatin ± pembrolizumab (n = 102)).

At progression, in the control arm, patients could switch to selpercatinib. If control group patients switch treatments and benefit from the new treatment, then the treatment effect of selpercatinib will be underestimated. Various statistical methods are available to adjust survival estimates in the presence of treatment switching, but each method makes important assumptions and is subject to limitations.

Simple adjustment methods include the following:

- Censoring switchers at the point of switch
- Excluding switches

These approaches are highly prone to selection bias because switching is likely to be associated with prognosis. These methods are not recommended by Latimer and Abrams (2014) (77). Methods included in the NICE DSU 16 guidelines include:

- Rank preserving structural failure time models (RPSFTMs) (non-parametric, semiparametric, and parametric method) represent randomisation-based methods for estimating counterfactual survival times (i.e., survival times that would have been observed in the absence of switching). A method referred to as g-estimation is used to estimate a time acceleration factor that can be applied to survival times in the control to create the counterfactual data.
- Two-stage method: when switching is permitted only after disease progression, this timepoint can be used as a secondary "baseline." An accelerated failure time model (such as a Weibull model) that includes covariates measured at the time of progression, and including a covariate indicating treatment switch, can be fitted to the post-progression control group data to produce an estimate of the treatment effect received by patients who switched compared with control group patients who did not switch. The resulting acceleration factor can then be used to "shrink" the survival times of switching patients to derive a counterfactual data set unaffected by switching.
- The inverse probability of censoring weighting (IPCW) method represents an observational-based approach, whereby data for switchers are censored at the point of switch and remaining observations are weighted with the aim of removing any censoring-related selection bias.

Not further information is provided as LIBRETTO-431 OS data will not be used for OS extrapolation in this submission.

Appendix L. Summary of post discontinuation therapy

Of the [redacted] patients (including 3 patients who were randomized but did not receive treatment) that have discontinued the control arm treatment, [redacted] patients (Figure 52) [redacted] crossed over and received selpercatinib on study.

Off study, in the ITT-Pembrolizumab Population, [redacted] of patients in the selpercatinib arm and [redacted] of patients in the control arm received any poststudy discontinuation systemic therapy. In the first subsequent line, the most commonly received postdiscontinuation systemic therapies (≥5% in either treatment arm) were for selpercatinib versus control, respectively:

[redacted]

In the ITT-Pembrolizumab Population, selective RET inhibitors were received in any line of poststudy discontinuation systemic therapy by patients in both treatment arms (selpercatinib versus control, respectively):

[redacted]

Table 123 and Table 124 summaries the poststudy discontinuation therapy and surgery for the ITT-Pembrolizumab Population and ITT Population, respectively.

Figure 52 Study patient disposition figure for ITT-Pembrolizumab Population

Abbreviations: ITT , intent-to-treat; ITT-Pembrolizumab, patients included in the ITT Population who were stratified with the intent to receive pembrolizumab in the event of the control-arm assignment *RET*-altered other cancers; N, number of patients in analysis population; RET, REarranged during Transfection.
Data cutoff date: 01 May 2023.

Table 123 Summary of post discontinuation therapy and surgery ITT-pembrolizumab population

	Selpercatinib (n=129) (%)	Pemetrexed + platinum + pembrolizumab (n = 83) (%)	Total (n = 212) (%)
Surgical procedure	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Systemic therapy			
Overall	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
PACLITAXEL	[redacted]	[redacted]	[redacted]
CISPLATIN	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB	[redacted]	[redacted]	[redacted]

DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]
RELATLIMAB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
TRAMETINIB	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
1st subsequent line			
Overall	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
PACLITAXEL	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]

UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
RELATLIMAB	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
2nd or later subsequent line			
Overall	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
CISPLATIN	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]

ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
TRAMETINIB	[redacted]	[redacted]	[redacted]
Systemic Therapies: Regimen			
Overall	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PACLITAXEL, ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]

ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB, BEVACIZUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN, CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CISPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN, GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CISPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
DABRAFENIB, PRALSETINIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL, RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
IPILIMUMAB, NIVOLUMAB, RELATLIMAB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]

PACLITAXEL, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
PEMETREXED, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID, ATEZOLIZUMAB, CARBOPLATIN, GEMCITABINE	[redacted]	[redacted]	[redacted]
Systemic Therapies: 1st line regimen			
Overall	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PACLITAXEL, ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]

UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB, BEVACIZUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN, CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
IPILIMUMAB, NIVOLUMAB, RELATLIMAB	[redacted]	[redacted]	[redacted]
PACLITAXEL, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
PEMETREXED, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID, ATEZOLIZUMAB, CARBOPLATIN, GEMCITABINE	[redacted]	[redacted]	[redacted]
Systemic Therapies: 2nd or later line regimen			
Overall	[redacted]	[redacted]	[redacted]

SELPERCATINIB	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CISPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN, GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CISPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
DABRAFENIB, PRALSETINIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL, RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]

Table 124 Summary of post discontinuation therapy and surgery overall ITT population

	Selpercatinib (n=159) (%)	Pemetrexed + platinum + pembrolizumab (n = 102) (%)	Total (n = 261) (%)
Surgical procedure	[redacted]	[redacted]	[redacted]
Radiotherapy	[redacted]	[redacted]	[redacted]
Systemic therapy			
Overall	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
PACLITAXEL	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
CISPLATIN	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
CAMRELIZUMAB	[redacted]	[redacted]	[redacted]

CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CRIZOTINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]
NINTEDANIB	[redacted]	[redacted]	[redacted]
RELATLIMAB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
TRAMETINIB	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
1st subsequent line			
Overall	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PACLITAXEL	[redacted]	[redacted]	[redacted]

ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
IPILIMUMAB	[redacted]	[redacted]	[redacted]
NINTEDANIB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
RELATLIMAB	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID	[redacted]	[redacted]	[redacted]
2nd or later subsequent line			
Overall	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]

CISPLATIN	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CRIZOTINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
TRAMETINIB	[redacted]	[redacted]	[redacted]
Systemic Therapies: Regimen			
Overall	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
DOCETAXEL	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]

BEVACIZUMAB, CARBOPLATIN, PACLITAXEL, ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB, BEVACIZUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN, CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CISPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN, GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CISPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
CRIZOTINIB, SELPERCATINIB	[redacted]	[redacted]	[redacted]

DABRAFENIB, PRALSETINIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL, RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
IPILIMUMAB, NIVOLUMAB, RELATLIMAB	[redacted]	[redacted]	[redacted]
NINTEDANIB	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
PACLITAXEL, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
PEMETREXED, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
Systemic Therapies: 1st line regimen			
Overall	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]

PRALSETINIB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PEMBROLIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PACLITAXEL, ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
INVESTIGATIONAL DRUG	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
UNSPECIFIED HERBAL AND TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB, BEVACIZUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PACLITAXEL	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN, CAMRELIZUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL;NINTEDANIB	[redacted]	[redacted]	[redacted]
GEMCITABINE	[redacted]	[redacted]	[redacted]
IPILIMUMAB, NIVOLUMAB, RELATLIMAB	[redacted]	[redacted]	[redacted]
NINTEDANIB	[redacted]	[redacted]	[redacted]
PACLITAXEL, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]

PEMBROLIZUMAB, CARBOPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]
PEMETREXED, CARBOPLATIN, PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
TEMOZOLOMIDE	[redacted]	[redacted]	[redacted]
TISLELIZUMAB	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]
UNSPECIFIED TRADITIONAL MEDICINE	[redacted]	[redacted]	[redacted]
ZOLEDRONIC ACID, ATEZOLIZUMAB, CARBOPLATIN, GEMCITABINE	[redacted]	[redacted]	[redacted]
Systemic Therapies: 2nd or later line regimen			
Overall	[redacted]	[redacted]	[redacted]
SELPERCATINIB	[redacted]	[redacted]	[redacted]
RAMUCIRUMAB, DOCETAXEL	[redacted]	[redacted]	[redacted]
ALL OTHER THERAPEUTIC PRODUCTS	[redacted]	[redacted]	[redacted]
ATEZOLIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CARBOPLATIN	[redacted]	[redacted]	[redacted]
BEVACIZUMAB, PEMETREXED, CISPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN	[redacted]	[redacted]	[redacted]
CARBOPLATIN, GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
CATEQUENTINIB	[redacted]	[redacted]	[redacted]
CISPLATIN, PEMETREXED	[redacted]	[redacted]	[redacted]

CRIZOTINIB, SELPERCATINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB, PRALSETINIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DABRAFENIB, TRAMETINIB	[redacted]	[redacted]	[redacted]
DENOSUMAB	[redacted]	[redacted]	[redacted]
DOCETAXEL, RAMUCIRUMAB	[redacted]	[redacted]	[redacted]
GIMERACIL;OTERACIL;TEGAFUR	[redacted]	[redacted]	[redacted]
NIVOLUMAB	[redacted]	[redacted]	[redacted]
PEMBROLIZUMAB	[redacted]	[redacted]	[redacted]
PEMETREXED	[redacted]	[redacted]	[redacted]
PRALSETINIB	[redacted]	[redacted]	[redacted]
SACITUZUMAB GOVITECAN	[redacted]	[redacted]	[redacted]
TEGAFUR;URACIL	[redacted]	[redacted]	[redacted]
TRADITIONAL CHINESE MEDICINE (TCM) DECOCTION	[redacted]	[redacted]	[redacted]

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk