

Bilag til Medicinrådets vurdering af trastuzumab deruxtecan til behandling af fremskreden HER2-muteret pulmonalt adenokarcinom efter standard førstelinjebehandling

Vers. 1.0



Bilagsoversigt

1. Ansøgers notat til Rådet vedr. trastuzumab deruxtecan
2. Forhandlingsnotat fra Amgros vedr. trastuzumab deruxtecan
3. Ansøgers endelige ansøgning vedr. trastuzumab deruxtecan

Medicinrådet

Dampfærgevej 21-23, 3. sal
2100 København Ø

28.04.2026

Note on the DMC evaluation report of Enhertu (trastuzumab deruxtecan) for the treatment of adult patients with advanced HER2-mutated non-small cell lung cancer (NSCLC) following treatment with platinum-based chemotherapy with or without immunotherapy.

Daiichi-Sankyo and AstraZeneca would like to thank the DMC secretariat for the collaboration on the evaluation of Enhertu and appreciate the opportunity to provide a comment prior to the final decision.

This application was submitted to the DMC on encouragement from the council and the regional drug committees (Regionale Lægemiddelkomitéer) following an observed increase in applications for individual reimbursement of Enhertu indicating an unmet medical need for a patient population with no efficacious treatment options.

In current Danish practice, NSCLC patients with the HER2-mutation are treated with immunotherapy and platinum-based chemotherapy in combination or sequentially when diagnosed with metastatic disease. If progression occurs, patients will be offered docetaxel as the next line of treatment as per clinical practice or a protocolised experimental treatment if available. In the second line and beyond, docetaxel is associated with limited outcomes, with median overall survival generally expected to be between 9-12 months.

The DESTINY-Lung02 trial demonstrates the efficacy of Enhertu in patients with HER2-mutated NSCLC. The DMCs evaluation report notes that Enhertu is likely a substantially better treatment than the current standard treatment with docetaxel. However, the evaluation report also notes that the magnitude of the benefit cannot be firmly established with the current evidence. Based on the indirect treatment comparison and the DMC's health economic base case, it is however evident that the benefits would most likely be of clinical relevance and Enhertu could extend the patients' overall survival by an additional 12 months incremental to current standard of care.

The prevalence of HER2-mutation is low. In NSCLC, it is estimated that approx. 1-3% harbour the mutation. The HER2-mutation is identified through the routine NGS testing of NSCLC patients in current clinical practice. In Denmark, approx. 10-30 Danish NSCLC patients annually are estimated to harbour the mutation in 1L.

Given the very small size of the eligible population, the budget impact should be reasonable. The DMC estimates that 5-10 patients would be eligible for Enhertu in 2L+ annually. At public list price (AIP), the year 5 budget impact is calculated to be 5.2m DKK, corresponding to the cost of treating 7 patients annually with Enhertu while prolonging the survival of the patients.

To conclude, DESTINY-Lung02 demonstrates that Enhertu provides a clinically relevant treatment option for the high unmet-need population of patients with HER2-mutated NSCLC. Given the rarity of the HER2-mutation in NSCLC, the introduction of Enhertu is expected to come with a reasonable budget impact, while improving the outcomes for patients.

Kind regards,

Martin Phuc Tran
HTA Manager
AstraZeneca A/S

Cecilie Astrup
Market Access Manager
AstraZeneca A/S

Mie Yoon
Head of Market Access Denmark
Daiichi Sankyo Nordics Aps

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

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LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.10.2026
Leverandør	AstraZeneca
Lægemiddel	Enhertu (trastuzumab deruxtecan)
Ansøgt indikation	Behandling af voksne patienter med fremskreden ikke småcellet lungekræft (NSCLC), hvis tumorer har en aktiverende HER2 (ERBB2)-mutation, og som har behov for systemisk behandling efter platinbaseret kemoterapi med eller uden immunterapi. + Behandling af voksne patienter med fremskredent HER2- positivt adenokarcinom i ventriklen eller den gastroøsofageale overgang (GEJ), som tidligere har fået et trastuzumab-baseret regime
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har følgende aftalepris på Enhertu (trastuzumab deruxtecan):

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Enhertu	100 mg (1 stk.)	10.628,99	████████	████████

Aftaleforhold

Amgros har en eksisterende aftale på Enhertu som gælder til den 31.03.2027. Ved anbefaling af disse to indikationer, vil der blive indgået en ny aftale med start [REDACTED].

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Konkurrencesituationen – lungekræft

Førstelinjebehandling af patienter med ikke-planocellulær NSCLC er enten en PD-(L)1-hæmmer som monoterapi eller i kombination med platinbaseret kemoterapi. Efterfølgende tilbydes platinbaseret kemoterapi og/eller docetaxel afhængigt af førstelinjebehandlingen. På nuværende tidspunkt er der ingen godkendt standardbehandling målrettet patienter med HER2-muteret NSCLC.

Enhertu er anbefalet af Medicinrådet til andenlinjebehandling af metastatisk HER2+ brystkræft.

Tabel 2 viser lægemiddeludgifter til behandling med Enhertu for et gennemsnitlig behandlingsforløb på ca. 47 uger svarende til 0,9 år, jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af fremskreden HER2-muteret NSCLC efter platinbaseret kemoterapi med eller uden immunterapi.

Tabel 2: Lægemiddeludgifter pr. patient – lungekræft

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 47 uger (SAIP, DKK)
Enhertu	100 mg (1 stk.)	5,4 mg/kg* hver 3. uge, i.v.	████████	████████

*Kropsvægt for gennemsnitspatient er 74,2 kg jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af fremskreden HER2-muteret NSCLC efter platinbaseret kemoterapi med eller uden immunterapi.

Konkurrencesituationen – kræft i mavesæk eller mavemund

Den nuværende behandling er kemoterapi – enten et taxan (paclitaxel eller docetaxel) eller irinotecan. Enhertu er tidligere anbefalet til flere indikationer indenfor brystkræft.

Tabel 3 viser lægemiddeludgiften ved behandling med Enhertu for et gennemsnitligt behandlingsforløb på ██████████. Lægemiddeludgifter til kemoterapi er ikke medtaget i beregningen nedenfor, da den udgør mindre end 10.000 DKK for et års behandling.

Tabel 3: Lægemiddeludgifter pr. patient – kræft i mavesæk eller mavemund

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Enhertu	100 mg (1 stk.)	6,4 mg/kg* hver 3. uge, i.v.	████████	████████

*Patientvægt 67,7 kg. Jf. Medicinrådets vurdering af trastuzumab deruxtecan til behandling af HER2-positiv adenokarcinom i mavesæk eller mavemund

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

Status fra andre lande – lungekræft

Tabel 5: Status fra andre lande

Land	Status	Link
Norge	Ikke anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Anbefalet	Link til vurdering

Status fra andre lande – kræft i mavesæk og mavemund

Tabel 6: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Anbefalet	Link til vurdering
England	Under vurdering	Link til status

Opsummering

Amgros har en eksisterende aftale på Enhertu. Anbefales Enhertu til lungekræft på baggrund af den foreslåede alternative aftale, kan aftalen tidligst starte den [REDACTED]

[REDACTED]



Application for the assessment of
Enhertu (trastuzumab deruxtecan)
for adult patients with advanced
NSCLC whose tumours have an
activating HER2 (ERBB2)
mutation and who require systemic
therapy following platinum-based
chemotherapy with or without
immunotherapy

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]



Contact information

Contact information	
Name	Martin Phuc Tran / AstraZeneca
Title	HTA Manager
Phone number	+45 2647 4513
E-mail	martinphuc.tran@astrazeneca.com
Name	Cecilie Astrup / AstraZeneca
Title	Market Access Manager
Phone number	+45 3165 6949
E-mail	cecilie.astrup@astrazeneca.com
Name	Mie Yoon / Daiichi-Sankyo Nordics ApS
Title	Head of Market Access Denmark
Phone number	+45 2857 9858
E-mail	mie.yoon@daiichisankyo.com



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Abbreviations

Abbreviation	Definiton
1L	1st line
2L	2nd line
AE	Adverse event
AIC	Akaike Information Criterion
AIP	Apotekernes indkøbspris
BIC	Bayesian Information Criterion
BICR	Blinded independent central review
CEAC	Cost-Effectiveness Acceptability Curve
CI	Confidence interval
CNS	Central nervous system
cORR	Confirmed objective response rate
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut off
DK	Denmark
DKK	Danish Kroner
DMC	Danish Medicine Council
DOR	Duration of response
DRG	Diagnosis related group
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESS	Effect sample size
FAS	Full analysis set
HER2m	HER2 mutation
HR	Hazard ratio
HRQoL	Health-related Quality of Life
HSUV	Health state utility value
ICER	Incremental Cost-Effectiveness Ratio
IPD	Individual patient data
ITC	Indirect treatment comparison
IV	Intervenous
KM	Kaplan-Meier



MAIC	Matching adjusted indirect comparison
N/A	Not available
NC	Not calculatable
NGS	Next-generation sequencing
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressed disease
PF	Progression-free
PFS	Progression-free survival
PHA	Proportional hazard assumption
PR	Partial response
PSM	Partitioned survival model
Q3W	Every 3 weeks
QALY	Quality-adjusted Life Year
QOL	Quality of life
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumours
SCLC	Small cell lung cancer
SLR	Systematic literature review
SoC	Standard of care
T-DXd	trastuzumab deruxtecan
TEM	Treatment effect modifier
TTD	Time to treatment discontinuation



1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Enhertu
Generic name	Trastuzumab deruxtecan
Therapeutic indication as defined by EMA	Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.
Marketing authorization holder in Denmark	Daiichi Sankyo Europe GmbH Zielstattstrasse 48 81379 München Tyskland
ATC code	L01FD04
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	Approved, 18 Oct 2023.
Has the medicine received a conditional marketing authorization?	EMA/H/C/005124/II/0027
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	<u>Breast cancer</u> • <i>HER2-positive breast cancer:</i> Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received one or more prior anti-HER2-based regimens. • <i>HER2-low breast cancer:</i> Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy. • <i>HER2-low or HER2-ultralow breast cancer:</i> Enhertu as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone



Overview of the medicine

receptor (HR)-positive (HR+), HER2-low or HER2-ultralow breast cancer who have received at least one endocrine therapy in the metastatic setting and who are not considered suitable for endocrine therapy as the next line of treatment

Gastric cancer

- Enhertu as monotherapy is indicated for the treatment of adult patients with advanced HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma who have received a prior trastuzumab-based regimen.

Other indications that have been evaluated by the DMC (yes/no)

Yes, HER2-positive breast cancer and HER2-low breast cancer.

Joint Nordic assessment (JNHB)

Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No, Enhertu is included in clinical practice in Finland and Sweden for NSCLC.

Is the product suitable for a joint Nordic assessment? No

If no, why not? Enhertu for NSCLC is already reimbursed in Finland and Sweden.

Dispensing group

BEGR

Packaging – types, sizes/number of units and concentrations

1 unit powder conc. for infusion solution, 100 mg



2. Summary table

Summary	
Indication relevant for the assessment	Enhertu as monotherapy is indicated for the treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.
Dosage regimen and administration	The recommended dose of Enhertu is 5.4 mg/kg body weight given as an intravenous infusion once every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity.
Choice of comparator	Docetaxel
Prognosis with current treatment (comparator)	According to current Danish clinical practice guidelines, docetaxel is recommended for patients with metastatic NSCLC when both platinum-based chemotherapy and IO have been exhausted (1). The CheckMate 057 study assessed the efficacy and safety of nivolumab vs. docetaxel(2). This study enrolled patients with metastatic NSCLC who needed additional systemic treatment after receiving platinum-based chemotherapy. In CheckMate 057, patients treated with docetaxel had a median overall survival of 9.4 months (N=290, 95% CI: 8.1–10.7), highlighting the limited effectiveness and poor prognosis associated with current standard treatment options(2).
Type of evidence for the clinical evaluation	As the study on Enhertu is a phase II single arm study, an unanchored matching-adjusted indirect comparison (MAIC) has been conducted to allow for a comparative analysis with the current standard of care, docetaxel, on OS and PFS.
Most important efficacy endpoints (Difference/gain compared to comparator)	Objective response rate (ORR), duration of response (DOR) Progression Free Survival (PFS) and Overall Survival (OS)
Most important serious adverse events for the intervention and comparator	In DESTINY-Lung02, the most frequent serious adverse event was pleural effusion, observed in 4.0% of the patients in the T-DXd 5.4 mg/kg-arm. In CheckMate 057, the most frequent serious adverse event was febrile neutropenia, observed in 9.0% of the patients treated with docetaxel.
Impact on health-related quality of life	Clinical documentation: T-DXd 5.4 mg/kg, HRQoL was assessed using EORTC QLQ-C30 and EQ-VAS in DESTINY-Lung02. On both instruments, no clinically significant difference was observed in patients, administered with T-DXd 5.4 mg/kg throughout the study period.



Summary	
	For docetaxel in CheckMate 057, only EQ-VAS data was identified. Over the duration of the study, a change from baseline that exceeded a minimally important difference of 10 points, was not observed. Health economic model: Quality of life is assumed to be equal between the two arms, hence, EQ-5D-5L data from DESTINY-Lung02 was mapped to the progression-free and progressed-disease health state and applied in the health economic model.
Type of economic analysis that is submitted	Type of analysis: Cost-utility analysis Type of model: Partitioned survival model
Data sources used to model the clinical effects	DESTINY-Lung02 MAIC vs. docetaxel in CheckMate057
Data sources used to model the health-related quality of life	EQ-5D-5L data from DESTINY-Lung02 mapped to Danish preference weights
Life years gained	1.5 years
QALYs gained	1.22 QALY
Incremental costs	788,641 DKK
ICER (DKK/QALY)	643,887 DKK/QALY
Uncertainty associated with the ICER estimate	The deterministic sensitivity analysis identified, the HSUV for the progression-free health state, average body weight and HSUV for the post-progression health state to be the three parameters with the most impact on the ICER estimate.
Number of eligible patients in Denmark	Annually, 5-10 patients with HER2m NSCLC are estimated to be eligible for 2L+ treatment with T-DXd 5.4 mg/kg following prior treatment with platinum-based chemotherapy and immunotherapy.
Budget impact (in year 5)	5.2m DKK



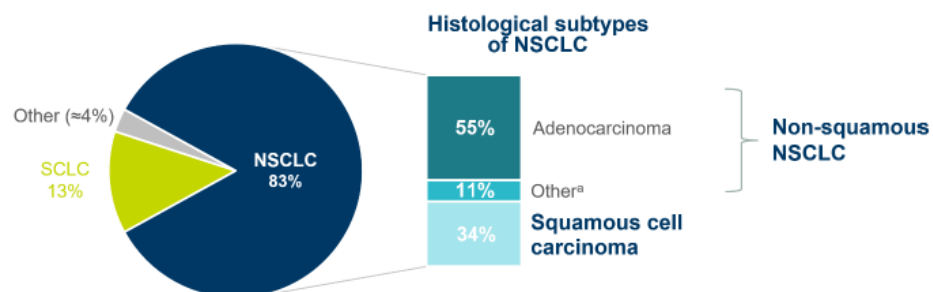
3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Non-small cell lung cancer (NSCLC) is a disease in which malignant cells form in the tissues of the lung (3-5). Epithelial cells are the most common lung cell – they line the airways and make mucus, which lubricates and protects the lung (6). NSCLC encompasses any type of epithelial lung cancer other than small cell lung cancer (SCLC), and is the most common type of lung cancer, accounting for 80–85% of all lung cancers (5).

NSCLC is a histologically diverse cancer (7-9), with the histological subtypes correlating with site of origin within the respiratory tract (7). NSCLC is divided into two groups based on histology: non-squamous cell carcinoma and squamous cell carcinoma (Figure 2) (7, 9). NSCLC adenocarcinoma is the most common histological subtype of lung cancer (8, 9).

Figure 1. Lung cancer classification



a) Includes large cell carcinoma and NSCLC not otherwise specified. NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Sources: (7, 9)

Patients with metastatic NSCLC experience a wide range of symptoms, many of which are non-specific and include fatigue, loss of appetite and weight loss (10, 11). These are often ignored by patients leading to delays in diagnosis and treatment (12). Evidence shows that nearly 50% of patients with NSCLC are diagnosed with metastatic disease, and patients with early-stage lung cancers at diagnosis often relapse into the metastatic stage (13, 14). Late-stage diagnosis leads to very poor survival – estimated between 4% and 7% at five years (15). While recent advancements in first-line treatments for metastatic disease have improved patient outcomes, however, in the second-line setting, patients continue to face poor overall survival with reported medians between seven and nine months and few efficacious treatment options (16).



Survival can also be affected by various other factors, including the presence of oncogenic drivers such as HER2 mutations (17, 18). Evidence suggests that the presence of a HER2 mutation may worsen prognosis compared to patients with HER2 negative/wild type disease as well as those with other oncogenic mutations (19). However, the full impact of HER2-mutations on survival outcomes in patients with metastatic NSCLC remains an area of research (20-30). In a European cohort, patients identified with a tumour that harboured HER2 mutations tended to be female (2/3 of patients), non-smokers and younger (median age 61 years)(31).

In addition to poor survival, patients with NSCLC suffer significant morbidity, which increases as the disease symptoms intensify over time. This leads to patients with more advanced disease experiencing progressively worsening quality of life (QoL) and reduced ability to perform daily tasks (32). While there are no studies investigating the disease burden specific to patients with HER2m NSCLC, it is highly likely that such patients would suffer the same consequences as other patients with NSCLC. Outcomes related to health utility, work productivity and daily activity impairment worsen, especially in those with unresectable or metastatic disease (32-34). Increased activity impairment has been shown to reduce QoL (as measured by EQ-5D-3L) nearly threefold (33).

3.2 Patient population

Lung cancer is one of the most common types of cancer in Denmark. Approximately 5,000 patients are diagnosed with lung cancer pr. year in Denmark, the majority of the incidences are NSCLC, approx. 82% of the total incidence rate(35).

Table 1 Incidence and prevalence in the past 5 years(35)

Year	2020	2021	2022	2023	2024
Incidence in Denmark	4942	5135	5127	5132	4979
Prevalence in Denmark	NA	NA	NA	NA	NA
Incidence NSCLC	4061	4209	4173	4194	4115
Global prevalence *	NA	NA	NA	NA	NA

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

The patient population eligible for trastuzumab deruxtecan (T-DXd) in line with DESTINY-Lung02 consists of patients with metastatic or locally advanced non-small cell lung cancer who have received platinum-based chemotherapy, which in most cases is administered together with an immunotherapy or after an immunotherapy in Denmark. The patients must have a tumour harbouring a mutation in the HER2-gene and must be fit enough to receive further treatment after progression on platinum-based chemotherapy with or without immunotherapy.



The incidence of HER2-mutation (HER2m) frequency is uncertain. Currently no data reports frequency of this mutation in Danish patients, and we therefore must rely on international sources and assumptions.

Patients with HER2m NSCLC are typically younger, more likely to be women, and more likely never to have smoked tobacco compared to the typical patient with NSCLC. This indicates that patients are somewhat younger than the general patient population, in line with what is seen in other therapeutic areas, like breast cancer (36-38). The impact on the survival of HER2m in NSCLC is unknown.

A French study, sequencing 17 644 patients found that less than 1 % of the patients tested carried this mutation, while another study including 3 800 patients (39), found a frequency of 1.7 % (40). The Danish clinical guidelines state the HER2-mutation frequency to be between 1-3%(1).

Clinicians consulted in a Nordic ad-board indicated that HER2m are rare findings and estimated that the frequency of HER2m in NSCLC patients to be around 1% in the Nordics (41). Based on this estimate of 1%, of the 1,470 patients estimated by the DMC, who have non-squamous NSCLC and are candidates for PD-L1 treatment in Denmark, approx. 15 patients have non-squamous NSCLC with a HER2m (41, 42). Accounting for the proportion of patients who are not fit for treatment beyond the PD-L1 and platinum-based treatment, the estimated number of NSCLC patients in 2L+ with HER2m and eligible for T-DXd would be between 5-10 patients annually.

Table 2 Estimated number of patients eligible for T-DXd

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	5-10	5-10	5-10	5-10	5-10

3.3 Current treatment options

The indication for DESTINY-Lung02 is for NSCLC patients, who have an activating HER2 mutations and who have been treated with platinum-based chemotherapy with or without immunotherapy(43).

Upon diagnosis of NSCLC, patients are screened for actionable genomic alterations with a next-generation sequencing (NGS) panel in which HER2 (ERBB2) mutation can be detected and identified. Currently, HER2 mutations are tested within most NGS panels, however, reporting of HER2m may vary across centres.

The treatment options for HER2 mutated patients, that have been treated with platinum-based chemotherapy with or without immunotherapy, in combination or in sequence, is currently very limited and patients have a poor prognosis. No treatment has been recommended specifically for NSCLC patients harbouring HER2 mutations, hence



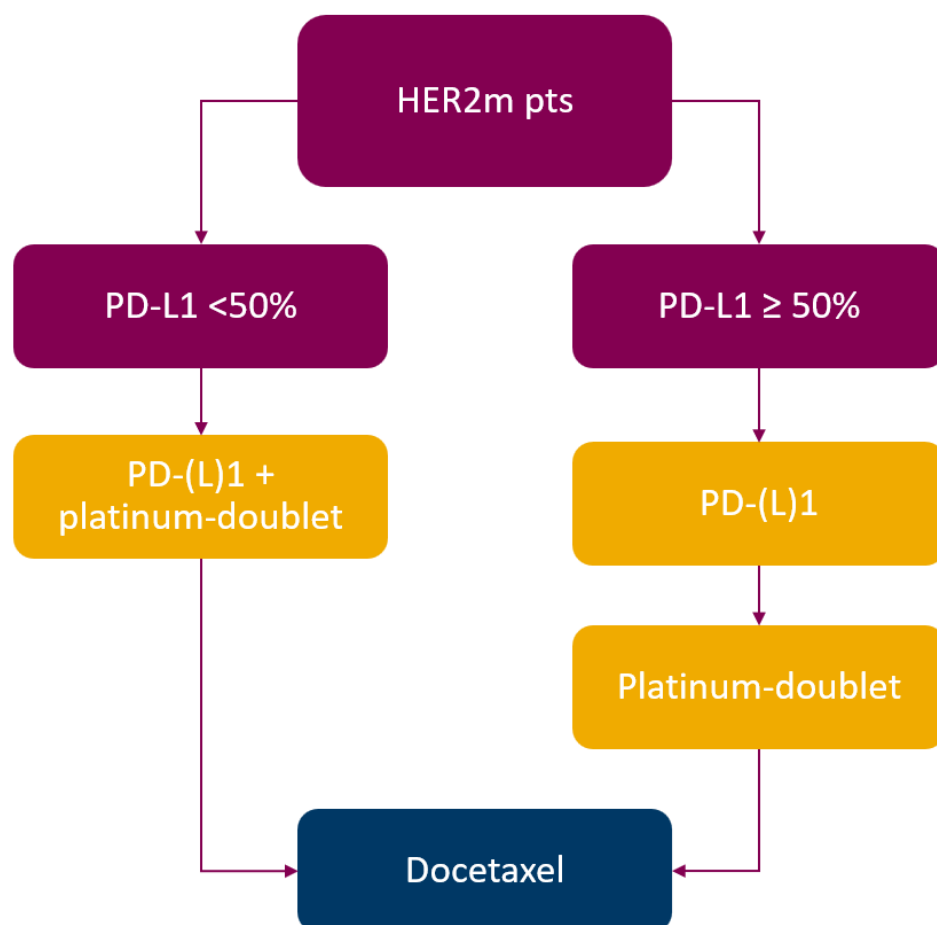
these patients will be treated with non-targeted therapies according to the treatment algorithm for NSCLC patients without any actionable genomic alterations.

For all non-squamous NSCLC patients without any actionable genomic alterations, the standard first-line regimen will be a PD-1/L1 inhibitor, either in combination with platinum-based chemotherapy (PD-L1 < 50% or as monotherapy (PD-L1 ≥ 50%))(44). For patients that receive PD-1/L1 inhibitor as monotherapy, the second-line treatment is platinum-based chemotherapy(44). Therefore, by the time patients become platinum-experienced, most will have received platinum-based chemotherapy either alongside immunotherapy or afterward.

Following platinum-based chemotherapy and immunotherapy, the next systemic therapy according to clinical guidelines is docetaxel, 75 mg/m³ every third week until progression or unacceptable toxicity(1).

The prognosis with docetaxel is generally perceived to be poor in 2L+ NSCLC following platinum-based chemotherapy, with an observed overall survival of approx. 10 months(45).

Figure 2. Current treatment algorithm for HER2m NSCLC patients(46).





3.4 The intervention

T-DXd is an IV administered HER2-directed antibody drug conjugate. The dose is 5.4 mg/kg administered as an IV infusion once every 3 weeks. Treatment with T-DXd can be continued until disease progression, unless there is evidence of unacceptable toxicity.

Overview of intervention	
Indication relevant for the assessment	Treatment of adult patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy.
ATMP	N/A, not ATMP.
Method of administration	Intravenous infusion
Dosing	5.4 mg/kg every 3 rd week
Dosing in the health economic model (including relative dose intensity)	5.4 mg/kg every 3 rd week (RDI = 93.48%)
Should the medicine be administered with other medicines?	No
Treatment duration / criteria for end of treatment	Treat 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?	Currently, not all departments test for ERBB2 (HER2) as routine in their NGS reflex testing of NSCLC patients, as no HER2-targeted therapy has been recommended for metastatic NSCLC. In the model, ERBB2 testing is assumed to be included in the current NGS panel if recommended, hence no additional cost has been included in the model.
Package size(s)	One vial of powder for concentrate for solution for infusion contains 100 mg of trastuzumab deruxtecan

3.4.1 Description of ATMP

N/A.



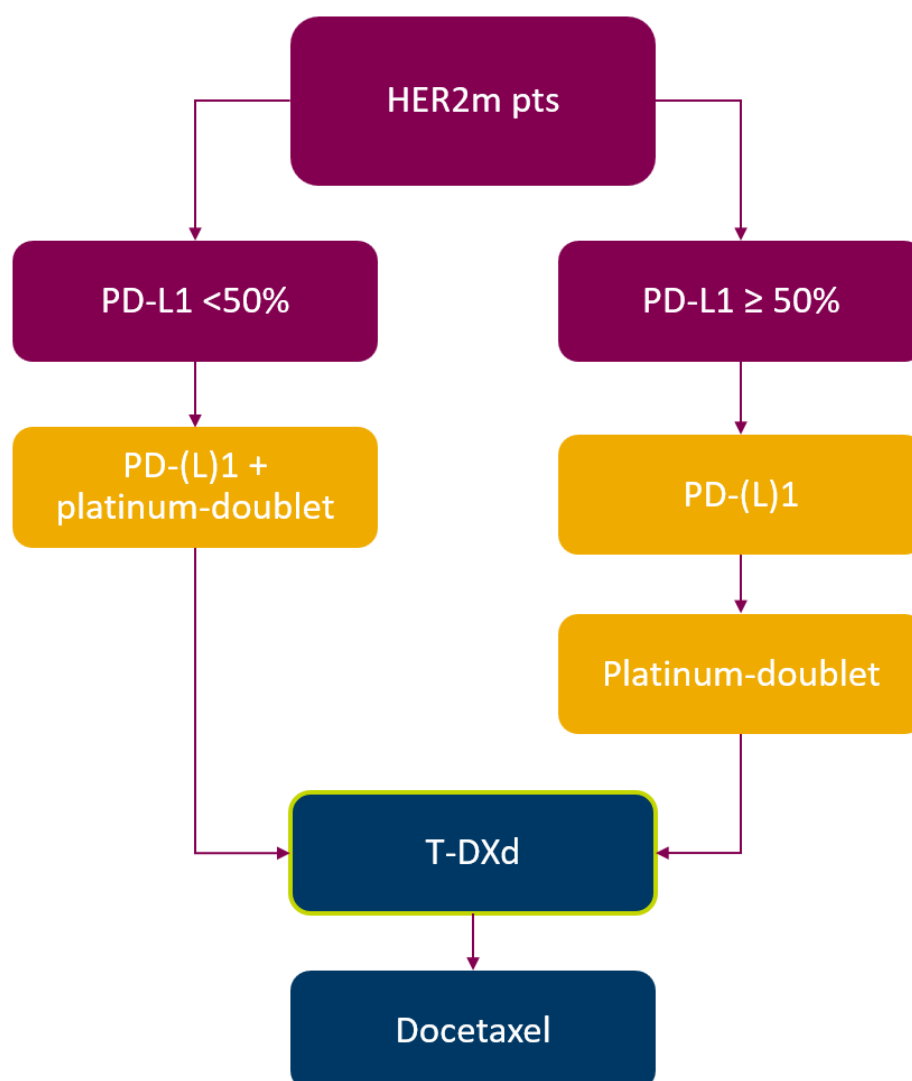
3.4.2 The intervention in relation to Danish clinical practice

Based on the approved indication, patients eligible for T-DXd should have been treated with platinum-based chemotherapy with or without immunotherapy before being treated with T-DXd(43).

Currently, metastatic NSCLC patients with HER2 mutations cannot be offered any targeted therapy in routine care and are instead treated with docetaxel following treatment with platinum-based chemotherapy. T-DXd would displace docetaxel in the treatment algorithm following both immunotherapy and platinum-based chemotherapy for patients whose tumours have a HER2 mutation, if recommended as standard treatment.



Figure 3. Adapted treatment algorithm for HER2m NSCLC, based on Danish guidelines(47).



3.5 Choice of comparator(s)

As described in section 3.3, patients would most likely go on to receive docetaxel in Danish clinical practice following platinum-based chemotherapy and immunotherapy. Therefore, docetaxel has been deemed a relevant comparator for this application.

Overview of comparator	
Generic name	Docetaxel
ATC code	L01CD02



Overview of comparator

Mechanism of action	Docetaxel is an antineoplastic agent which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments. Docetaxel has been shown in vitro to disrupt the microtubular network in cells which is essential for vital mitotic and interphase cellular functions.
Method of administration	Intravenous infusion
Dosing	75 mg/m ² every 3rd week
Dosing in the health economic model (including relative dose intensity)	75 mg/m ² every 3rd week, RDI 100%
Should the medicine be administered with other medicines?	No
Treatment duration/ criteria for end of treatment	Treat until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	1 ml, 20 mg/ml 4 ml, 20 mg/ml 8 ml, 20 mg/ml

3.6 Cost-effectiveness of the comparator(s)

The comparator, docetaxel, used for the cost-utility analysis in this submission is in line with standard of care (SoC) for 2L+ treatment of patients with NSCLC following treatment with platinum-based chemotherapy in Denmark. Docetaxel is off patent with multiple generic suppliers in the Danish market, hence why it is reasonable to assume that docetaxel is a cost-effective treatment.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Outcomes deemed relevant for comparison and included in this application are described in Table 3. To establish a relative efficacy between T-DXd and docetaxel, a



naïve comparison has been conducted for ORR and DOR and an unanchored matching-adjusted indirect comparison (MAIC) has been conducted on PFS and OS

Table 3 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Objective response rate (ORR) DESTINY-Lung02 Checkmate 057	Destiny Lung: Q6W (± 7 d) CheckMate057: Q6W (± 5 days)	ORR is defined as the proportion of patients who achieve either a complete response (CR) or partial response (PR) to treatment	According to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1).
Duration of response (DoR) DESTINY-Lung02 Checkmate 057		DoR is defined as time from initial response (CR or PR) until documented tumour progression or death from any cause	According to RECIST v1.1
Progression-free survival (PFS) DESTINY-Lung02 Checkmate 057		PFS is defined as the time from the date of random assignment to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause. Patients not known to have progressed or died are censored at the date of last adequate assessment.	According to RECIST v1.1
Overall survival (OS) DESTINY-Lung02 Checkmate 057		OS is defined as the time from the date of random assignment to the date of death due to any cause.	Time to event

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

Validity of outcomes

The purpose of medical treatment of NSCLC in the metastatic setting is to extend the patient's life and stabilize the disease for as long as possible. OS and PFS are therefore endpoints of particularly high relevance which is why they also provide the foundation for establishing cost-effectiveness in the health economic analysis. Additionally, ORR and DoR are relevant indicators of anti-tumour activity which is associated with a higher degree of disease stabilization.



4. Health economic analysis

4.1 Model structure

For the health economic analysis, a partitioned survival model (PSM) was chosen. The model consists of three mutually exclusive health states, illustrated in Figure 4:

- Progression-free (PF): Defined as the period before the patient has experienced disease progression
- Progressed disease (PD): Defined as the period where the patient remains alive following disease progression, and they may receive treatment with subsequent anticancer therapy and supportive care
- Dead: An absorbing state into which patients transition upon their death from any cause

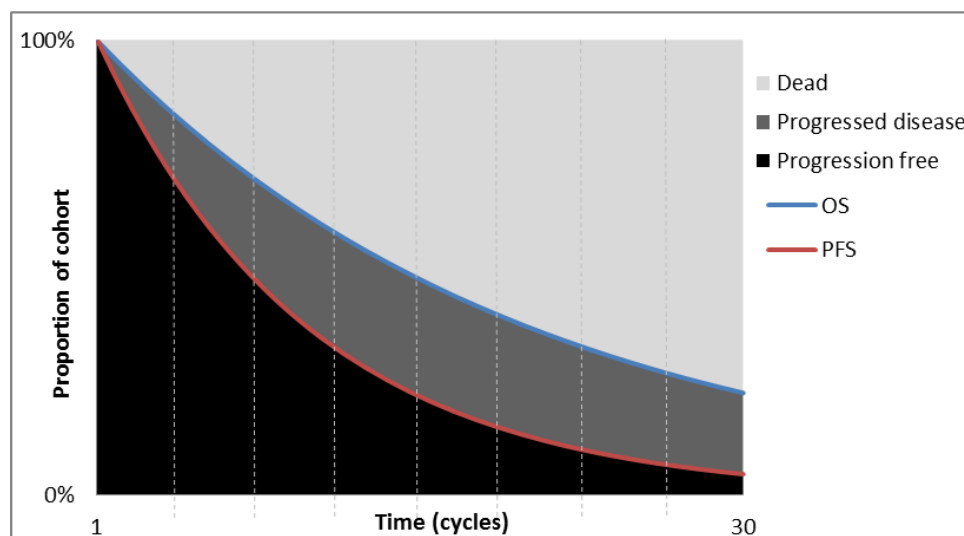
The health state membership over time in the PSM is informed by the PFS and OS curves. The proportion of patients alive over time is estimated directly from the OS curve. OS is then partitioned into the PF and PD states using the PFS curve. The proportion of patients occupying the PF state is derived directly from the PFS cumulative survival probability over time, whilst the proportion occupying the PD state over time is calculated from OS minus PFS. The proportion occupying the death state over time is estimated from one minus OS.

As the DESTINY-Lung02 trial data did not extend to the modelled time horizon, extrapolation of the OS and PFS Kaplan-Meier (KM) data was necessary to inform health state memberships for the duration of the modelled time horizon. In absence of a direct trial comparison to docetaxel in the DESTINY-Lung02, an indirect treatment comparison (ITC) has been conducted between T-DXd versus docetaxel. The hazard ratios (HR) derived from the ITC was applied on the T-DXd PFS and OS curve to the extrapolate PFS and OS for the docetaxel arm.

Time to treatment discontinuation (TTD) is used to estimate the acquisition and administration costs for T-DXd. In absence of TTD for docetaxel, the PFS HR of T-DXd versus docetaxel was applied on the T-DXd TTD to derive the duration of treatment.



Figure 4. PSM structure (illustrative)



4.2 Model features

Table 4 Features of the economic model

Model features	Description	Justification
Patient population	Patients with HER2m NSCLC, who has previously been treated with platinum-based chemotherapy	Trial population relevant for clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Lifetime (30 years)	To capture all health benefits and costs in line with DMC guidelines. Given the mean age of 59.8 years in the 5.4mg/kg arm of DESTINY-Lung02 and the estimated long-term survival of these patients, the lifetime horizon was considered to be 30 years.
Cycle length	7 days	To best reflect the rapid progression of the disease and to account for different treatment schedules.
Half-cycle correction	Yes	
Discount rate	3.5 %	The DMC applies a discount rate of 3.5 % for all years



Model features	Description	Justification
Intervention	Trastuzumab deruxtecan 5.4 mg/kg (T-DXd)	Intervention in scope for application
Comparator(s)	Docetaxel	According to national treatment guideline.
Outcomes	PFS, OS & TTD QALY and costs	

5. Overview of literature

As DESTINY-Lung02 did not include a control arm with docetaxel, a systematic literature search (SLR) has been conducted to identify literature on docetaxel to establish relative efficacy.

5.1 Literature used for the clinical assessment

A global SLR from May 2024 was adapted to identify literature for the clinical assessment between T-DXd and docetaxel in HER2m NSCLC patients following platinum-based chemotherapy. The adapted SLR identified published literature on DESTINY-Lung02 for T-DXd and CheckMate 057 for docetaxel.

In addition to the identified literature in peer-reviewed journals from the SLR, a hand-searched was conducted November 2025 to identify one additional publication on DESTINY-Lung02 was identified beyond the SLR, as this publication was published after the global SLR was conducted.

Additionally, two data-on-file clinical study reports from DESTINY-Lung02 and the published EPAR based on CheckMate 057 have been included as additional literature.

All literature used in this application has been summarised in Table 5.



Table 5 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*
Jänne PA, Goto Y, Kubo T, et al. Final Analysis Results and Patient-Reported Outcomes From DESTINY-Lung02-A Dose-Blinded, Randomized, Phase 2 Study of Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic NSCLC. <i>J Thorac Oncol</i> . Published online July 30, 2025. doi:10.1016/j.jtho.2025.07.129(48)	DESTINY-Lung02	NCT04644237	Start: 19-03-2021 Primary analysis DCO: 23-12-2022 Final OS DCO: 25-08-2023	T-DXd vs. docetaxel
Goto K, Goto Y, Kubo T, et al. Trastuzumab Deruxtecan in Patients With <i>HER2</i> -Mutant Metastatic Non-Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial. <i>J Clin Oncol</i> . 2023;41(31):4852-4863. doi:10.1200/JCO.23.01361(49)				
Data on file – DESTINY-Lung02 primary analysis – clinical study report(50)				



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*
Data on file – DESTINY-Lung02 final OS analysis – clinical study report(51)				
Borghaei H, Gettinger S, Vokes EE, et al. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. <i>J Clin Oncol</i> . 2021;39(7):723-733. doi:10.1200/JCO.20.01605(45)	CheckMate 057	NCT01673867	Start: 02-11-2012 Primary analysis DCO: 02-07-2015 Five-year outcomes study DCO: 16-05-2019	T-DXd vs. docetaxel
Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. <i>N Engl J Med</i> . 2015;373(17):1627-1639. doi:10.1056/NEJMoa1507643(2)				
EPAR, CheckMate 057(52)				

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



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

Table 6 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
Data on file. DESTINY-Lung02 final OS analysis clinical study report(51)	- EORTC QLQ-C30 - EQ-VAS - EQ-5D-5L based HSUV for pre-progressed and post-progressed health state derived from linear mixed model based on clinical trial data.	10.1, 10.2, 10.2.3.2
Jänne PA, Goto Y, Kubo T, et al. Final Analysis Results and Patient-Reported Outcomes From DESTINY-Lung02-A Dose-Blinded, Randomized, Phase 2 Study of Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic NSCLC. <i>J Thorac Oncol</i> . Published online July 30, 2025. doi:10.1016/j.jtho.2025.07.129(48)		
Reck M, Brahmer J, Bennett B, et al. Evaluation of health-related quality of life and symptoms in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. <i>Eur J Cancer</i> . 2018;102:23-30. doi:10.1016/j.ejca.2018.05.005(53)	- EQ-VAS data for docetaxel from CheckMate 057	10.2
Bristol-Myers Squibb GmbH & Co. KGaA, Dossier zur Nutzenbewertung nach § 35a SGB V, Nutzenbewertungsverfahren zum Wirkstoff Nivolumab (neues Anwendungsgebiet: nicht-kleinzelliges Lungenkarzinom, Nicht-Plattenepithelhistologie, nach vorheriger Chemotherapie), Modul 4C, 2016(54)		



5.3 Literature used for inputs for the health economic model

Table 7 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
N/A	N/A	N/A	N/A



6. Efficacy

6.1 Efficacy of T-DXd compared to docetaxel for patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy

6.1.1 Relevant studies

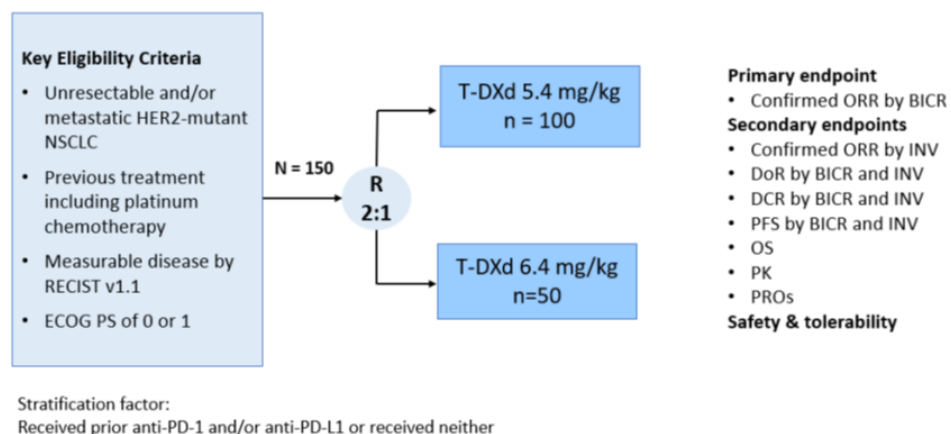
In addition to DESTINY-Lung02, a relevant docetaxel comparator was identified in CheckMate 057. The literature search found no studies of docetaxel after platinum-based chemotherapy specifically in advanced HER2-mutated NSCLC. Therefore, data for docetaxel following platinum-based chemotherapy were identified in CheckMate 057, which enrolled a broader non-squamous NSCLC population with unknown HER2 status. While not HER2-mutated, this cohort provides an alternative data source to support a relative efficacy comparison of T-DXd versus docetaxel.

6.1.1.1 DESTINY-Lung02

DESTINY-Lung02 is a randomized, multicentre, blinded, 2-cohort, phase II study conducted at 47 sites across North America, Asia, Europe, and Australia evaluating the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with previously treated HER2m metastatic or locally advanced NSCLC(49).

A summary of the trial design is shown in Figure 5.

Figure 5. Summary of trial design of DESTINY-Lung02(49)



6.1.1.2 Checkmate 057

CheckMate 057 is an open-label trial that included 582 adults with non-squamous NSCLC, whose disease had progressed after previous platinum-based chemotherapy and who



had not previously had a PD-1 or PD-L1 inhibitor(2). Patients were randomised to have either nivolumab (3 mg per kg) or docetaxel 75 mg/m² every 3 weeks(2).

A summary of the trial design is shown in Figure 6.

Figure 6. Summary of trial design of CheckMate 057(2)

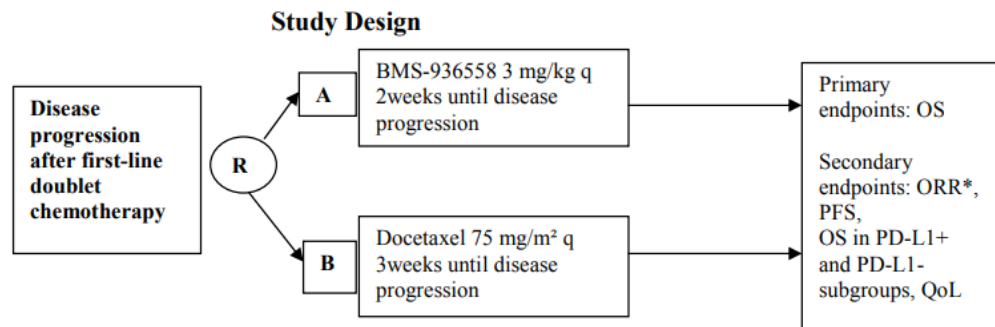




Table 8 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
DESTINY-Lung02, NCT04644237(48, 49)	Randomized, blinded two-cohort, phase II study	Median follow-up: 15.8 months in T-DXd 5.4 mg/kg arm	Patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC) participants who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (second line or later) that must have contained a platinum-based chemotherapy drug	Trastuzumab deruxtecan (T-DXd) 5.4 mg/kg or 6.4 mg/kg every third week until disease progression or unacceptable toxicity	None	Primary: Confirmed ORR by BICR Secondary: Duration of response by BICR (DoR), disease control rate, progression-free survival by BICR, overall survival Median follow-up (Q1–Q3): 15.8 (8.2–20.7) months in T-DXd 5.4 mg/kg arm
CheckMate 057, NCT01673867(2, 45)	Randomized, open-label, phase III study.	The median follow-up for this OS data cut was 69.4 months(45)	PD-(L)1naive NSCLC patients with active disease and incomplete response to conventional treatment.	Nivolumab	Docetaxel 75 mg/m ² Q3W	Primary: OS Secondary: PFS by BICR, Confirmed ORR by BICR, duration of response by BICR, HRQoL Median follow-up on OS: 69.4 months (minimum follow-up was 64.5 months) Median follow-up on PFS: Not reported (primary analysis)



6.1.2 Comparability of studies

Both studies are conducted on metastatic non-squamous NSCLC patients following prior treatment on platinum-based chemotherapy. A major difference is the lack of identified HER2-mutation status of the patient population in CheckMate 057, hence why the population would be less representative of the efficacy of docetaxel in a HER2 mutated NSCLC population. HER2-mutations may result in a reduced overall survival and an increased risk of developing brain metastases, hence survival prognosis might be worse in a HER2 mutated patient population compared to patients without HER2-mutated NSCLC(55).

In place of lacking efficacy evidence for docetaxel in HER2-mutated NSCLC patients, the docetaxel arm of CheckMate 057 was assumed as a valid alternative for the efficacy and safety comparison.

6.1.2.1 Comparability of patients across studies

The two included patient populations appear to be fairly similar in terms of baseline characteristics, apart from the fact that the patients in CheckMate 057 not being HER2-mutation positive.

The two key differences in patient characteristics observed between the DESTINY-Lung02 T-DXd 5.4 mg/kg arm and CheckMate 057 were in terms of the number of prior lines of therapy and disease stage. DESTINY-Lung02 required at least one prior line whereas CheckMate 057 required one or two prior lines. DESTINY-Lung02 included only metastatic patients whereas CheckMate 057 included both stage IIIB and stage IV patients. This was adjusted in the MAIC in the DESTINY-Lung02 population.

Additionally, a larger proportion of female subjects was included in DESTINY-Lung02 than in CheckMate057. This is in line with the expectation that the HER2-mutation is more frequent in female as described in section 3.2. In DESTINY-Lung02, more patients with brain metastases was enrolled than in CheckMate057, hence it is possible to assume that the tumor burden of patients DESTINY-Lung02 was higher than in CheckMate057 at enrolment. In CheckMate057, a larger proportion of patients were current or former smokers than in DESTINY-Lung02. These factors were also adjusted in the MAIC in the DESTINY-Lung02 population. Please refer to Table 15 for the list of adjustments conducted in the MAIC and to Table 16 for the adjusted baseline characteristics of DESTINY-Lung02 in the MAIC.



Table 9 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (2, 43, 45, 48, 52, 56)

		Destiny- Lung02	CheckMate 057
		T-DXd 5.4 mg/kg arm (N = 102)	Docetaxel (N = 290)
Age – mean		59.8	62.3
Gender	Female n (%)	65 (63.7)	122 (42.1)
Race	Asian, n (%)	65 (63.7)	8 (2.8)
	Black or African American, n (%)	0	9 (3.1)
	White, n (%)	23 (22.5)	266 (91.7)
	Other, n (%)	14 (13.7)	7 (2.4)
Weight at Baseline (kg)	Mean	63.6	NA
	Standard deviation	15.12	NA
ECOG PS	0, n (%)	29 (28.4)	95 (32.8)
	1, n (%)	73 (71.6)	194 (66.9)
	Other, n (%)	0	1 (<1)
Type of HER2 mutation (n [%])	Kinase domain, n (%)	99 (97.1)	NA
	Extracellular domain, n (%)	3 (2.9)	NA
Disease stage (n [%])	IIIB	0	24 (8.3)
	IV	102	266 (91.7)
Histology (n [%])	Adenocarcinoma, n (%)	100 (98.0)	273 (94.1)
	Squamous, n (%)	1 (1.0)	0
	Other, n (%)	1 (1.0)	17 (5.9)
Brain metastases %	n (%)	35 (34.3)	34 (11.7))
	≤2, n (%)	69 (67.6)	290 (100)



		Destiny- Lung02	CheckMate 057
		T-DXd 5.4 mg/kg arm (N = 102)	Docetaxel (N = 290)
Number of lines or prior systemic therapy for advanced/metastatic disease	>2, n (%)	33 (32.4)	0
	Patients who received prior anti-PD-1 and/or anti-PD-L1 treatment, n (%)	74 (72.5)	NA
	Patients who received prior platinum-based therapy, n (%)	102 (100.0)	290 (100.0)
Smoking status	Never, n (%)	55 (53.9)	60 (20.7)
	Current or former smokers, n (%)	47 (46.1)	227 (78.3)
	Unknown, n (%)	0	3 (1.0)

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

The Danish patient population eligible for treatment with T-DXd is expected to be aligned with the EMA-indication for DESTINY-Lung02.

A look-up in the Danish Cancer registry was conducted to characterise HER2-mutated metastatic NSCLC patients in Denmark. Only 33 patients were diagnosed between 2017 and 2022 with an identified known HER2 mutation in a total cohort of 12,446. The low HER2 mutation rate could likely be attributed to the reporting of HER2 status from the NGS testing not being fully implemented at all centres in the period between 2017 and 2022.

The mean age of these 33 patients were 70.9 years and 66.7% of the patients were female in the registry look-up. Aligning with the feedback from an ad-board on HER2 mutated NSCLC patients, where patients were expected to be older in clinical practice than the patients included in DESTINY-Lung02(41). However, as the hazard of the parametric extrapolation far exceeds the background mortality risk observed in Denmark, this is not expected to have a significant impact in the health economic analysis. Therefore, the mean age of patients in DESTINY-Lung02 has been used in the health economic model. A scenario analysis on the health economic analysis has been conducted to illustrate the impact of adjusting the mean age, which in the model would be adjusting the applied lower bound of background mortality. This scenario analysis is not expected to alter the cost-effectiveness estimate significantly. In clinical practice,



older patients may be frailer, which potentially could adjust the treatment duration observed in clinical practice downwards when compared to the clinical trial. This derivative effect on treatment duration of age has not been adjusted for in the scenario analysis conducted.

The proportion of females in Danish clinical practice matched the patient distribution in DESTINY-Lung02 with a 2/3 of the patients being female, and with the expectation by the clinicians in the advisory board on HER2 mutated NSCLC patients(41).

In DESTINY-Lung02, the mean weight was 63.6 kg, however, with a mean height of 164 cm, patients in the trial might be slightly shorter and have a lower body weight. In the Danish Medicines Council's treatment guideline for lung cancer 1st line treatment, the weight is 72 kg. Therefore, to better reflect the treatment cost in clinical practice, a body weight estimate based on the one derived from the treatment guideline has been used in the health economic analysis, with an adjustment to reflect the weight distribution applied in the health economic model.

Table 10 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model
Age	70.9 years (57)	59.8 years(50)
Gender (%- female)	66.7% (57)	67.7% (50)
Patient weight	72 kg (46)	72.4 kg*(46)

Note: *, adjusted from the Danish population estimate to reflect the weight distribution in the health economic model.

6.1.4 Efficacy – results per DESTINY-Lung02

6.1.4.1 ORR and DOR

For patients in the FAS randomised to the T-DXd 5.4 mg/kg dose group, the median follow-up was 15.8 months (range, 1.1-28.6) (48, 51). As of the DCO (25 Aug 2023), confirmed ORR based on blinded independent central review (BICR) was 50.0% (95% CI: 39.9, 60.1), with 31 (2.9%) patient achieving confirmed CR and 48 (47.1%) patients achieving confirmed PR.

Detailed results for T-DXd 5.4 mg/kg are presented in Table 11.

Table 11. Objective response and disease control rate at the final data cut for DESTINY-Lung02, DCO 25 Aug 2023(48, 51).

Parameter	Trastuzumab deruxtecan 5.4 mg/kg (N = 102)
Best overall response (confirmed) (n [%])	
CR	3 (2.9 %)



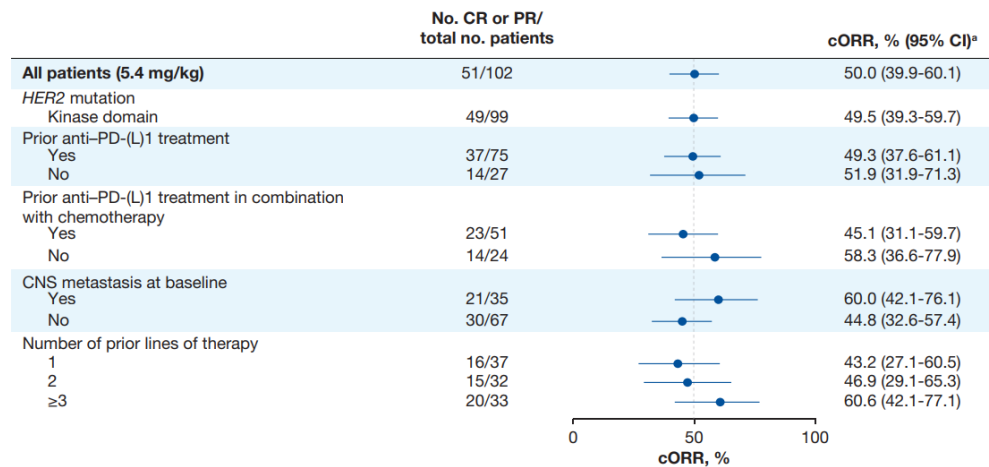
PR	48 (47.1 %)
SD	44 (43.1 %)
PD	4 (3.9 %)
Non-evaluable	3 (2.9 %)
Confirmed ORR	
n (%)	51 (50.0 %)
95% CI	39.9 % - 60.1 %
Duration of response	
Median (95% CI), months	12.6 (6.4; NE)

Abbreviation: CR: complete response; PR: partial response; SD: stable disease; PD: progressed disease; CI: confidence interval; NE: non evaluable.

Exploratory subgroup analyses were performed on the FAS where sufficient events for analysis were available (≥ 10 patients in each group). Stratification factors included type of HER2 mutation, prior PD-(L)1 therapy, prior combination PD-(L)1 therapy and chemotherapy, prior lines of therapy, and CNS metastasis status at baseline (48, 51). At the final analysis, responses were observed regardless of the number of lines of prior therapy received and the presence or absence of baseline CNS metastases in the T-DXd 5.4 mg/kg arm (Figure 7)



Figure 7. Subgroup analysis of ORR by BICR, 5.4mg/kg Q3W cohort (FAS, DCO: 25 Aug 2023) (48, 51)



Abbreviations: BICR: blinded independent central review; CI: confidence interval; CNS: central nervous system; cORR: confirmed objective response rate; CR: complete response; DCO: data cut-off; FAS: Full Analysis Set; *HER2*: human epidermal growth factor receptor 2; ORR: objective response rate; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; PR: partial response; Q3W: every 3 weeks; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1.

^a ORR by BICR per RECIST v1.1. The 2-sided 95% CIs were based on the exact (Clopper-Pearson) method for binomial distribution.

DCO: 25 Aug 2023

Source: (48, 51)

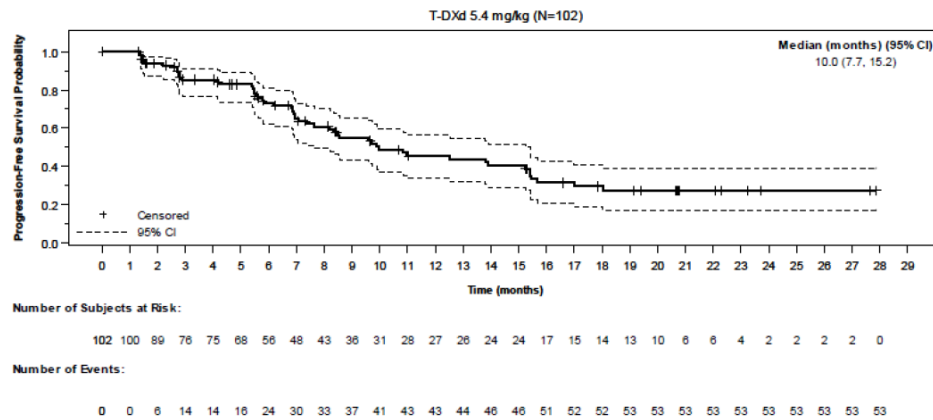
6.1.4.2 Progression-free survival

Median PFS based on BICR was 10.0 months (95% CI: 7.7, 15.2) in the T-DXd 5.4 mg/kg arm, 53 events were observed (of which 42 events were progressive disease and 11 events were deaths). The Kaplan-Meier plot of PFS by BICR for both dose groups is shown in Figure 8; data for 49/102 (48.0%) patients in the T-DXd 5.4 mg/kg dose group were censored as indicated by cross marks in Figure 8(48, 51).

In the T-DXd 5.4 mg/kg dose group, the estimated PFS rates at 6, 12, and 18 months were 0.73 (95% CI: 0.62, 0.81), 0.45 (95% CI: 0.34, 0.56), and 0.29 (95% CI: 0.19, 0.41), respectively. Of 102 patients in this group, 42 had progressive disease (41.2%) and 11 had died (10.8%) as of the DCO (25 Aug 2023) (48, 51).



Figure 8. Kaplan-Meier analysis of PFS by BICR (FAS; DCO: 25 Aug 2023) (51)



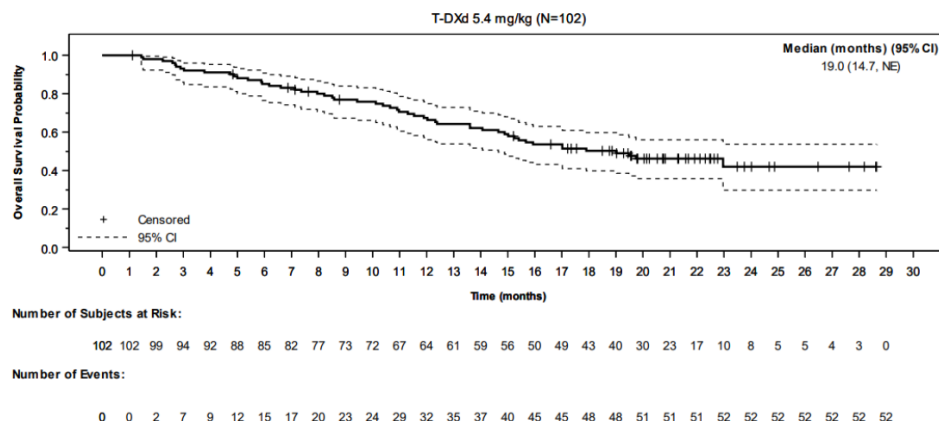
Abbreviations: CI: confidence interval; DCO: data cut-off;; T-DXd: trastuzumab deruxtecan.
PD was assessed by BICR using RECIST v1.1.
DCO: 25 Aug 2023

6.1.4.3 Overall survival

Median OS was 19.0 months (95% CI: 14.7, NE) in the T-DXd 5.4 mg/kg arm, where 52 events were observed at the data cut off. The Kaplan-Meier plot of OS is shown in Figure 9; data for 50/102 (49.0%) patients in the T-DXd 5.4 mg/kg dose group were censored as indicated by cross marks in Figure 9(48, 51).

In the T-DXd 5.4 mg/kg dose group, the estimated OS rates at 6, 12, and 18 months were 0.85 (95% CI: 0.76, 0.91), 0.67 (95% CI: 0.56, 0.76), and 0.50 (95% CI: 0.40, 0.60), respectively(48, 51).

Figure 9. Kaplan-Meier Analysis of OS (FAS; DCO: 25 Aug 2023)(51) (51)



Abbreviations: CI: confidence interval; DCO: data cut-off;; T-DXd: trastuzumab deruxtecan.
PD was assessed by BICR using RECIST v1.1.
DCO: 25 Aug 2023



6.1.5 Efficacy – results per CheckMate 057

6.1.5.1 ORR and DOR

In patients treated with docetaxel in CheckMate 057, the confirmed ORR based on BICR was 12.4% (95% CI: 9%, 12.4%), with 1 (0.3%) patient achieving confirmed CR and 35 (12.0%) patients achieving confirmed PR(2).

Detailed results on patients treated with docetaxel in CheckMate 057 are presented in Table 12.

Table 12 Objective response and disease control rate for CheckMate 057, DCO 18 March 2015(2).

Parameter	Docetaxel (N = 290)
Best overall response (confirmed) (n [%])	
CR	1 (0.3 %)
PR	35 (12.0 %)
SD	122 (41.8 %)
PD	85 (29.1 %)
Non-evaluable	47 (16.1 %)
Confirmed ORR	
n (%)	36 (12.4 %)
95% CI	9 % - 17 %
Duration of response	
Median (95% CI), months	5.6 (4.4 - 6.9)

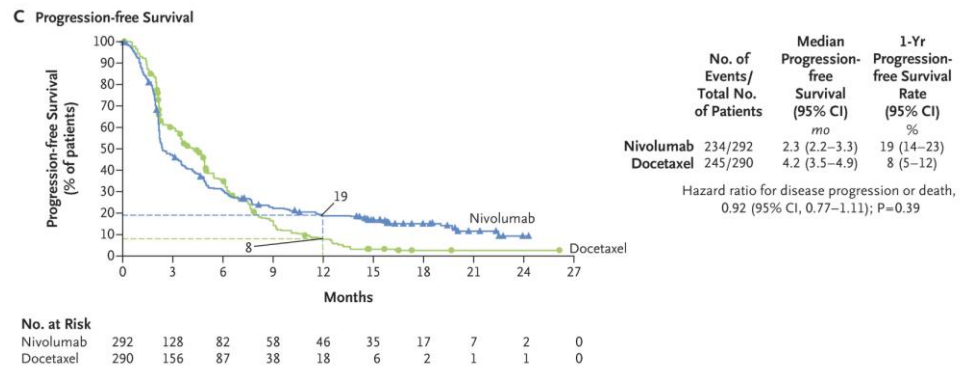
6.1.5.2 Progression-free survival

In CheckMate 057, the median PFS based on BICR was 4.2 months (95% CI: 3.5;4.9 months) in the docetaxel arm with 245 events having been observed at the data cut off(2). The 1-year PFS rate of the docetaxel arm was observed to be 8% (95% CI: 5;12%)(2).

The Kaplan-Meier plot of PFS by BICR from the CheckMate057 trial is shown in Figure 10.



Figure 10. KM Curve for PFS in CheckMate 057 for docetaxel and nivolumab. DCO 18 March 2015(2)

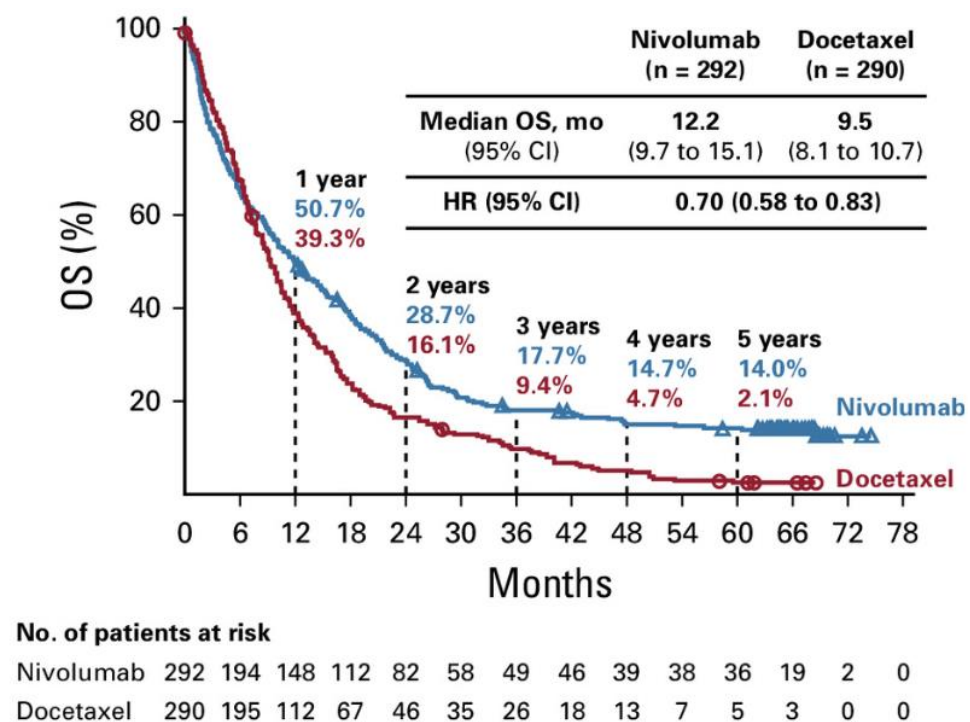


6.1.5.3 Overall survival

In CheckMate 057, the median OS was 9.5 months (95% CI: 8.1; 10.7 months) in the docetaxel arm, the number of events has not been reported for DCO 16 May 2019(45). The 1-year OS rate of the docetaxel arm was observed to be 39.3%. The median follow-up for this OS data cut was 69.4 months(45).

The Kaplan-Meier plot of OS from the CheckMate057 trial is shown in Figure 10.

Figure 11. KM Curve for OS in CheckMate 057 for docetaxel and nivolumab. DCO 16 May 2019(45)





7. Comparative analyses of efficacy

Given the lack of comparator arm in DESTINY-Lung02 for the T-DXd 5.4 mg/kg arm, a traditional indirect treatment comparison could not be conducted. Instead, a naïve comparison and an unanchored matching-adjusted indirect comparison (MAIC) has been conducted versus the docetaxel arm in CheckMate 057 to evaluate the relative efficacy of T-DXd 5.4 mg/kg versus docetaxel for treatment metastatic NSCLC with HER2 mutations following prior treatment with platinum-based chemotherapy.

As HER2-mutated NSCLC may be associated with a worse prognosis, the relative efficacy of T-DXd established in the MAIC to docetaxel in CheckMate 057 could potentially be underestimated, as outcomes of docetaxel patients in CheckMate 057 may be better than if investigated in a HER2-mutated patient population.

7.1.1 Differences in definitions of outcomes between studies

All outcomes deemed relevant for the comparison between T-DXd and docetaxel was included in both DESTINY-Lung02 and CheckMate 057, hence have therefore been included for the comparative analyses in the submission.

In both trial, response (ORR and DOR) and PFS was assessed with RECIST v1.1, however, a difference was observed in the reported outcomes. Results reported from DESTINY-Lung02 for response and progression was assessed by BICR, while in CheckMate 057, the results reported for response and progressions was assessed by investigator.

Table 13. Comparison of outcome definitions

Outcome	DESTINY-Lung02	CheckMate057
ORR	RECIST 1.1 by BICR	RECIST 1.1 by investigator
Duration of response	Time from initial response (CR or PR) based on BICR assessment until documented tumour progression or death from any cause	Time from initial recorded CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented)
PFS	RECIST 1.1 by BICR	RECIST 1.1 by investigator
OS	Time from randomization until death from any cause	Time from randomization until death from any cause



7.1.2 Method of synthesis

7.1.2.1 Naïve comparison

A naïve, cross-trial comparison of ORR and duration of response was conducted between T-DXd (5.4 mg/kg) from DESTINY-Lung02 and docetaxel from CheckMate 057.

7.1.2.2 MAIC

A MAIC was conducted between T-DXd and docetaxel on the endpoints, OS and PFS. The MAIC was a comparison based on the T-DXd 5.4 mg/kg arm from DESTINY-Lung02 and the docetaxel arm from CheckMate 057.

The eligibility criteria of CheckMate 057 are summarized in Table 14 below.

The two key differences observed between the DESTINY-Lung02 T-DXd 5.4 mg/kg arm and CheckMate 057 were in terms of the number of prior lines of therapy and disease stage. DESTINY-Lung02 required at least one prior line whereas CheckMate 057 required one or two prior lines. DESTINY-Lung02 included only metastatic patients whereas CheckMate 057 included both stage IIIB and stage IV patients. Therefore, DESTINY-Lung02 was restricted to patients being treated at 2nd or 3rd line only and out of 102 patients, 69 were included from the T-DXd 5.4 mg/kg arm of DESTINY-Lung02.

Table 14. Eligibility criteria for CheckMate-057 trial

Eligibility	Criteria
Inclusion	≥18 years old men and women
	Stage IIIB or IV non-squamous NSCLC
	Two prior multimodal lines maximum (radiation therapy, surgical resection, chemoradiation therapy), with one prior platinum doublet-based chemotherapy regimen for advanced metastatic disease
	Measurable disease by computerized tomography / magnetic resonance imaging per RECIST 1.1
	ECOG PS of 0 to 1
	Treatment washout period before enrolment:
	Treatment with any investigational agent within 14 days of first administration of study treatment
	Systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomization
	CNS metastases asymptomatic or treated and subjects are neurologically returned to baseline for at least 2 weeks prior to enrolment



Exclusion	Previously treated with docetaxel, anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 anti-CTLA-4
	Exclusion of subjects with:
	Central nervous system (CNS) metastases (unless asymptomatic or treated with return to baseline for at least two weeks prior enrolment)
	Carcinomatous meningitis
	Active or history of known or suspected autoimmune disease
	Subjects on corticosteroids (stable/decreasing dose ≤ 10 mg daily prednisone)

Abbreviations: CNS: central nervous system; CTLA-4: cytotoxic T-lymphocyte antigen-4; ECOG: Eastern Cooperative Oncology Group; NSCLC: non-small cell lung cancer; PD-1: programmed death protein 1; PD-L1: programmed death-ligand 1; PD-L2: programmed death-ligand 2; PS: performance status; RECIST: Response Evaluation Criteria In Solid Tumours

The PFS and OS KM curves from CheckMate 057 reported in the primary publications are presented in Figure 10 and Figure 11.

Table 15 reports the complete list of factors to be adjusted for based on the list of prognostic factors and treatment effect modifiers (TEM) identified. However, adjustment was feasible only for six of them (reported in **bold** in Table 15).

Table 15. Prognostic factors and TEMs used for the adjustment vs CheckMate 057

Variable listed in protocol	Adjustment made on
Age*	% <65 years
Sex*	% males
Smoking status*	% non-smokers
Disease stage [^]	No restriction as DL-02 only included stage IV patients
Mutations (EGFR, ALK, KRAS) [§]	Not adjusted, as majority of patients in selected studies do not carry any driver mutations
Histology [§]	Analysis focusing on populations with non-squamous NSCLC
ECOG/WHO performance status*	% ECOG 0
Number of metastatic sites*	% liver metastases present at baseline % brain metastases
Previous treatment received*	% with one prior line of systemic therapy
Gross tumour volume [^]	Not available
Tumour diameter [^]	Not available
Nodal volume [^]	Not available

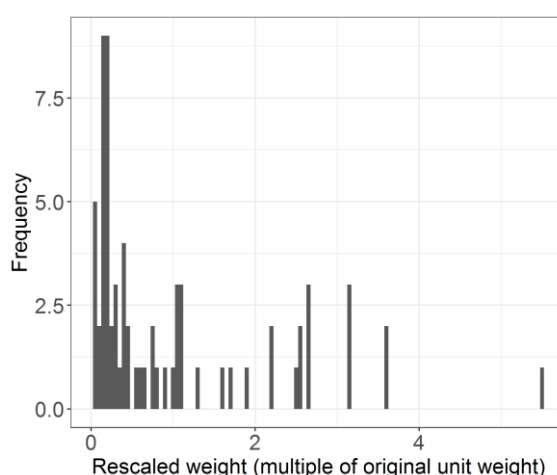
Note: *Used for the adjustment without specific limitation associated, [^]Not accounted for given lack of data available, [§]Not needed given project assumptions, **Bold**, indicates variables used for adjusted



Abbreviations: ALK: anaplastic lymphoma kinase; CNS: central nervous system; ECOG: Eastern Cooperative Oncology Group; EGFR: epidermal growth factor receptor; KRAS: Kirsten rat sarcoma virus; WHO: World Health Organisation

One individual from the DESTINY-Lung02 T-DXd 5.4 mg/kg arm had an extreme weight (above greater than 5) (Figure 12), but the effective sample size (ESS) was low (N=29.7) corresponding to 29.1% of the initial sample size. Therefore, all patients with a rescaled weight above 3 could still drive the results from the MAIC.

Figure 12. Plot of rescaled weights obtained for the MAIC of T-DXd vs docetaxel based on CheckMate 057



Abbreviations: MAIC: matching-adjusted indirect comparison; T-DXd: trastuzumab deruxtecan

Baseline characteristics were compared between the docetaxel arm in CheckMate 057, the original DESTINY-Lung02 T-DXd 5.4 mg/kg arm, the DESTINY-Lung02 T-DXd 5.4 mg/kg arm after restriction to 2nd and 3rd line patients and the reweighted arm (Table 16).

Post-weighting, baseline characteristics between the docetaxel arm in CheckMate 057 and the reweighted DESTINY-Lung02 T-DXd 5.4 mg/kg arm were well matched.

Table 16. Comparison of baseline characteristics between DESTINY-Lung02 T-DXd 5.4 mg/kg arm (pre and post-weighting) (DCO Aug 2023) and docetaxel based on CheckMate 057

	Docetaxel in CheckMate 057	DESTINY-Lung02 T-DXd 5.4 mg/kg arm	DESTINY-Lung02 T-DXd 5.4 mg/kg arm restricted to 2 nd and 3 rd lines	DESTINY-Lung02 T-DXd 5.4 mg/kg reweighted arm
N or ESS	290	102 [^]	69 [^]	29.7 [^]
Age*, mean or median**	62.3	59.8	59.2	60.0
Age, % patients <65 years	53.4%	60.8%	62.3%	53.4%
% ECOG 0	32.8%	28.4%	27.5%	32.8%
Sex, % males	57.9%	36.3 % [^]	36.2% [^]	57.9% [^]
Smoking status, % never smokers	20.7%	53.9% [^]	53.6% [^]	20.7% [^]



% liver metastases	20.7%	23.5%	20.3%	20.7%
% brain metastases	11.7%	34.3% [^]	33.3% [^]	11.7% [^]
% prior platinum-based therapy	100.0%	100.0%	100.0%	100.0%
Prior lines of systemic therapy, % 1 prior line	89.3%	36.3% [^]	53.6% [^]	89.3% [^]

Note: *age was included as categorical variable in adjustment, **mean age reported for DESTINY-Lung02, median reported for CheckMate 057, [^]No major difference between reweighted T-DXd arm and comparator, however difference from the original DL-02 population are observed.

Abbreviations: ECOG: Eastern Cooperative Oncology Group; ESS: effective sample size; NA: not applicable; T-DXd: trastuzumab deruxtecan

7.1.3 Results from the comparative analysis

The results from the comparative efficacy analyses between T-DXd 5.4 mg/kg and docetaxel are summarized in Table 17. Results from the comparative analyses are reported in depth in the following sections.

Table 17 Results from the comparative analysis of T-DXd 5.4 mg/kg vs. docetaxel for patients with advanced NSCLC whose tumours have an activating HER2 (ERBB2) mutation and who require systemic therapy following platinum-based chemotherapy with or without immunotherapy

Outcome measure	T-DXd 5.4 mg/kg (N = 102)	Docetaxel (N = 290)	Result
Confirmed ORR – naïve comparison	n = 51 (50.0%)	n = 36 (12.4%)	Absolute diff: 37.6%
Duration of response - naïve comparison	12.6 month (95% CI: 6.4, NE)	5.6 month (95% CI: 4.4, 6.9)	Absolute diff: 7.0 months
Progression-free survival (PFS) - unadjusted	10.0 months (95% CI: 95% CI: 7.7; 15.2)	4.6 months (95% CI: 3.6; 5.0)*	HR: 0.32 (95% CI: 0.23; 0.42)
Progression-free survival (PFS) – MAIC base case (ESS=29.7)	13.8 months (95% CI: 6.2; 15.7)	4.6 months (95% CI: 3.6; 5.0)*	HR: 0.29 (95% CI: 0.17; 0.51)
Overall survival (OS) – Unadjusted	19.0 months (95% CI: 14.7; NE)	9.5 months (95% CI: 8.2,11.2)*	HR: 0.44 (95% CI: 0.33; 0.60)
Overall survival (OS) – MAIC base case (ESS=29.7)	NE (95% CI: 11.3, NE)	9.5 months (95% CI: 8.2,11.2)*	HR: 0.43 (95% CI: 0.24; 0.78)

Note: *, based on digitized curve of CheckMate 057 (N=290)



7.1.4 Efficacy – results per ORR and duration of response (Naïve comparison)

A naïve side-by-side comparisons of the response rates is presented in Table 18.

A greater proportion of patients had confirmed response when treated with T-DXd, compared to docetaxel. In DESTINY-Lung02, 50% of patients treated with T-DXd 5.4 mg/kg achieved complete response or partial response. In CheckMate 057, 12.4% of patients treated with docetaxel achieved complete response or partial response. The duration of response was observed to be 12.6 months in DESTINY-Lung02 in the T-DXd 5.4 mg/kg, while in CheckMate 057, a DoR of 5.6 months was observed in patients treated with docetaxel.

The naïve comparison indicates that, in NSCLC patients previously treated with platinum-based chemotherapy, T-DXd offers a greater likelihood of achieving a clinically meaningful tumor response than docetaxel, with responses that are more durable.

Table 18. Naïve side-by-side comparison of objective response rate and duration of response between T-DXd 5.4 mg/kg in DESTINY-Lung02 and docetaxel in CheckMate 057

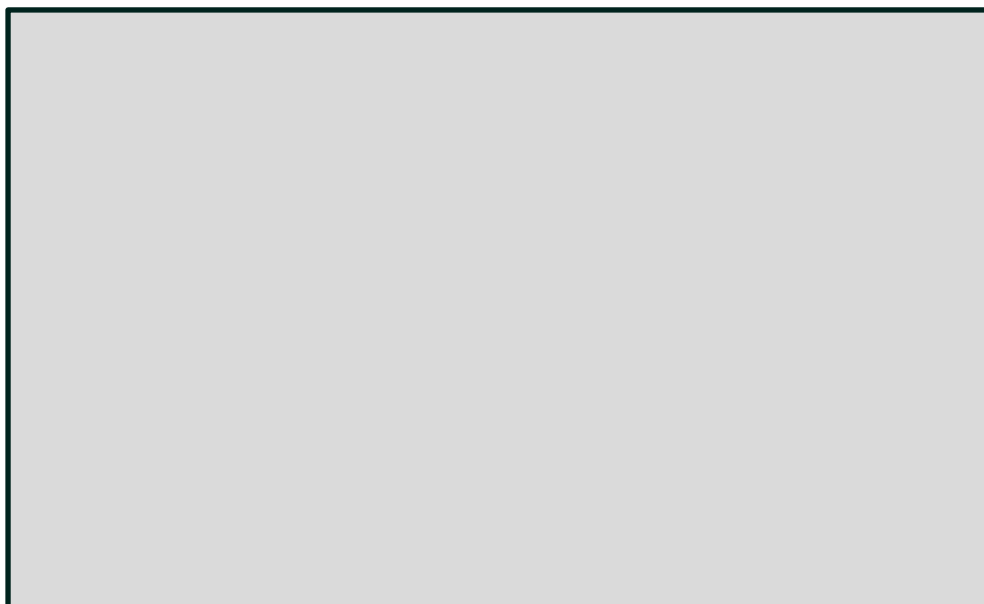
Parameter	Trastuzumab deruxtecan 5.4 mg/kg (N = 102)	Docetaxel (N = 290)
Best overall response (confirmed) (n [%])		
CR	3 (2.9 %)	1 (0.3 %)
PR	48 (47.1 %)	35 (12.0 %)
SD	44 (43.1 %)	122 (41.8 %)
PD	4 (3.9 %)	85 (29.1 %)
Non-evaluable	3 (2.9 %)	47 (16.1 %)
Confirmed ORR		
n (%)	51 (50.0 %)	36 (12.4 %)
95% CI	39.9 % - 60.1 %	9 % - 17 %
Duration of response		
Median (95% CI), months	12.6 (6.4; NE)	5.6 (4.4; 6.9)

7.1.5 Efficacy – results per PFS (MAIC)

The PFS curves for the docetaxel arm in CheckMate 057, the DESTINY-Lung02 T-DXd 5.4 mg/kg arm both FAS and after restriction of patients to 2nd and 3rd lines, and the DESTINY-Lung02 T-DXd 5.4 mg/kg arm after restriction and reweighting of patients are presented in Figure 13.



Figure 13. PFS curves for T-DXd (after restriction and after reweighting) and docetaxel based on reconstructed pseudo IPD from CheckMate 057 (DCO Aug 2023)



Abbreviations: DCO: data cut-off; FAS: full-analysis set; IPD: individual patient data; PFS: progression-free survival; T-DXd: trastuzumab deruxtecan

The proportional hazards assumption (PHA) was visually assessed in the KM curves (Figure 13), the log-cumulative hazards plot (Figure 35), and the Schoenfeld residuals plot; p-value for the Grambsch-Therneau test was 0.72 (Figure 36). The PHA was not rejected.

The median PFS obtained for docetaxel and T-DXd 5.4 mg/kg before and after restriction and reweighting of patients are reported in Table 19.

Table 19. Median PFS for T-DXd 5.4 mg/kg and docetaxel based on CheckMate 057 (DCO Aug 2023)

Treatment arm	Analyses stage	Median PFS in months
		[95% CI]
T-DXd	Original T-DXd 5.4 mg/kg arm (N=102)	10.0 [7.7, 15.2]
	Restricted T-DXd 5.4 mg/kg arm to 2 nd or 3 rd line (N=69)	9.7 [7.1, 15.4]
	Restricted and reweighted T-DXd 5.4 mg/kg arm, after MAIC (ESS=29.7)	13.8 [6.2, 15.7]
Docetaxel	CheckMate 057 – published results (N=290)	4.2 [3.5, 4.9]
	Digitized curve (N=290)	4.6 [3.6, 5.0]



Abbreviations: CI: confidence interval; DCO: data cut-off; ESS: effective sample size; MAIC: matching-adjusted indirect comparison; NE: not evaluable; PFS: progression-free survival; T-DXd: trastuzumab deruxtecan

The PFS HR [95% CI] obtained for T-DXd versus docetaxel from the MAIC was 0.29 [0.17, 0.51], showing a significant benefit for T-DXd (Table 20). The PFS HR [95% CI] from the sensitivity analysis conducted on the FAS was 0.29 [0.17, 0.49] with an ESS of 31.4. Unadjusted HR and HRs obtained through the base case and FAS MAICs are reported in Table 20.

Table 20. MAIC PFS HRs for T-DXd 5.4 mg/kg versus docetaxel based on CheckMate 057 (DCO Aug 2023)

Analysis	Comparison	PFS HR [95% CI]
		T-DXd vs docetaxel
Unadjusted	Original T-DXd 5.4 mg/kg arm (N=102) vs docetaxel from digitized curve	0.32 [0.23, 0.43]
Base case MAIC	Restricted and reweighted T-DXd 5.4 mg/kg arm (ESS=29.7) vs docetaxel from digitized curve	0.29 [0.17, 0.51]
Sensitivity MAIC (FAS)	Rewighted T-DXd 5.4 mg/kg arm (ESS=31.4) vs docetaxel from digitized curve	0.29 [0.17, 0.49]

Note: MAIC CIs were computed using the robust sandwich variance estimation

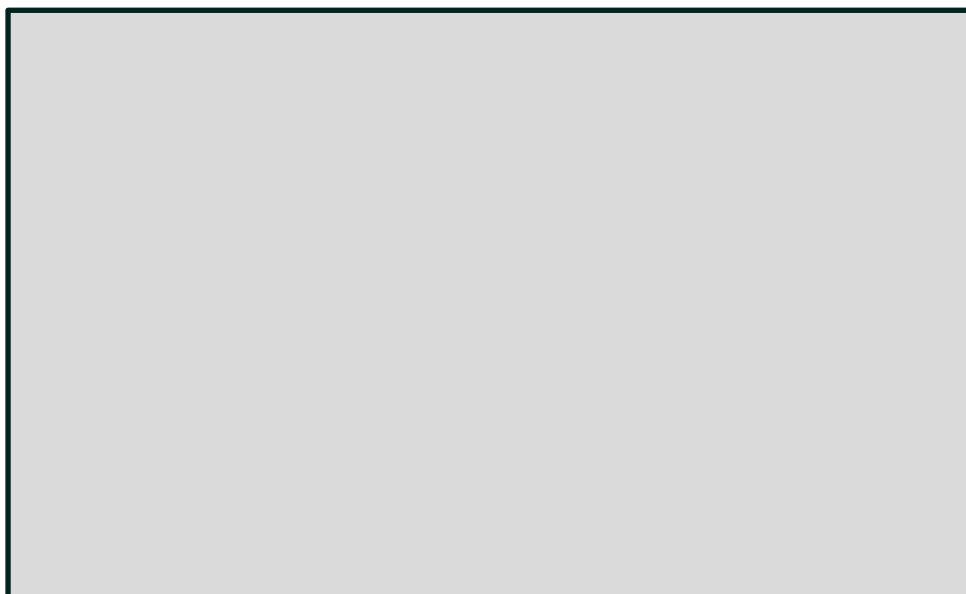
Abbreviations: CI: confidence interval; DCO: data cut-off; ESS: effective sample size; FAS: full-analysis set; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; PFS: progression-free survival; T-DXd: trastuzumab deruxtecan

7.1.6 Efficacy – results per OS (MAIC)

The OS curves for the docetaxel arm in CheckMate 057, the DESTINY-Lung02 T-DXd 5.4 mg/kg arm both FAS and after restriction of patients to 2nd and 3rd lines, and the DESTINY-Lung02 T-DXd 5.4 mg/kg arm after restriction and reweighting of patients are presented in Figure 14.



Figure 14. OS curves for T-DXd (after restriction and after reweighting) and docetaxel based on reconstructed pseudo IPD from CheckMate 057 (DCO Aug 2023)



Abbreviations: DCO: data cut-off; FAS: full-analysis set; IPD: individual patient data; OS: overall survival; T-DXd: trastuzumab deruxtecan

Similar to PFS, PHA was visually assessed with the KM curves (T-DXd weighted and docetaxel) which crossed with a drop in the T-DXd arm at 3 months, following which, the curves appear proportional (Figure 14). The log-cumulative hazards plot shows slight crossing of curves (Figure 37) but the Schoenfeld residuals plot did not show a specific trend with a p-value for the Grambsch-Therneau test of 0.18 (Figure 38). Validity of the PHA was considered uncertain. However, given the potential violation appears to happen in the first few months, it was still considered reasonable enough to conduct a standard Cox model to estimate the average HR over the follow-up period.

The median OS obtained for docetaxel and T-DXd before and after restriction and reweighting of patients are reported in Table 21.

Table 21. Median OS for T-DXd 5.4 mg/kg and docetaxel based on CheckMate 057 (DCO Aug 2023)

Treatment arm	Analyses stage	Median OS in months [95% CI]
T-DXd	Original T-DXd 5.4 mg/kg arm (N=102)	19.0 [14.7, NE]
	Restricted T-DXd 5.4 mg/kg arm to 2 nd or 3 rd line (N=69)	19.5 [12.3, NE]
	Restricted and reweighted T-DXd 5.4 mg/kg arm, after MAIC (ESS=29.7)	NE [11.3, NE]



Docetaxel	CheckMate 057 – published results (N=290)	9.4 [8.1, 10.7]
	Digitized curve (N=290)	9.5 [8.2, 11.2]

Abbreviations: CI: confidence interval; DCO: data cut-off; ESS: effective sample size; MAIC: matching-adjusted indirect comparison; NE: not evaluable; OS: overall survival; T-DXd: trastuzumab deruxtecan

The OS HR [95% CI] obtained for T-DXd versus docetaxel via the MAIC was 0.43 [0.24, 0.78], showing a significant benefit for T-DXd (see Table 22). The OS HR [95% CI] from the sensitivity analysis conducted on the FAS was 0.42 [0.23, 0.75] of an ESS of 31.4. The unadjusted HR as well as HRs obtained through the base case and FAS MAICs for OS are reported in Table 22.

Table 22. MAIC OS HRs for T-DXd 5.4 mg/kg versus docetaxel based on CheckMate 057 (DCO Aug 2023)

Analysis	Comparison	OS HR [95% CI] T-DXd vs docetaxel
Unadjusted	Original T-DXd 5.4 mg/kg arm (N=102) vs docetaxel from digitized curve	0.44 [0.33, 0.60]
Base case MAIC	Restricted and reweighted T-DXd 5.4 mg/kg arm (ESS=29.7) vs docetaxel from digitized curve	0.43 [0.24, 0.78]
Sensitivity MAIC (FAS)	Rewighted T-DXd 5.4 mg/kg arm (ESS=31.4) vs docetaxel from digitized curve	0.42 [0.23, 0.75]

Note: MAIC CIs were computed using the robust sandwich variance estimation
Abbreviations: CI: confidence interval; DCO: data cut-off; ESS: effective sample size; FAS: full-analysis set; HR: hazard ratio; MAIC: matching-adjusted indirect comparison; OS: overall survival; T-DXd: trastuzumab deruxtecan

8. Modelling of efficacy in the health economic analysis

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

In order to model long-term survival for PFS, OS and TTD of T-DXd 5.4 mg/kg, individual patient time-to-event data from DESTINY-Lung02 were used to generate KM plots for each outcome. The level of maturity of the data meant that extrapolation of the KM to the model time horizon was necessary. The general principles underlining the survival analysis of PFS, OS and TTD followed the approach outlined in the Technical Support Document 14 for survival analysis published by NICE DSU(58).



8.1.1 Extrapolation of efficacy data

8.1.1.1 Extrapolation of progression-free survival (PFS)

A summary of the assumptions applied in the extrapolation of PFS is provided in Table 23 for the T-DXd 5.4 mg/kg-arm in the health economic analysis. The base case extrapolation of PFS on T-DXd and the HR-derived PFS curve of docetaxel are visualized in Figure 15. Please consult appendix D.1 for further information on the extrapolation of PFS.

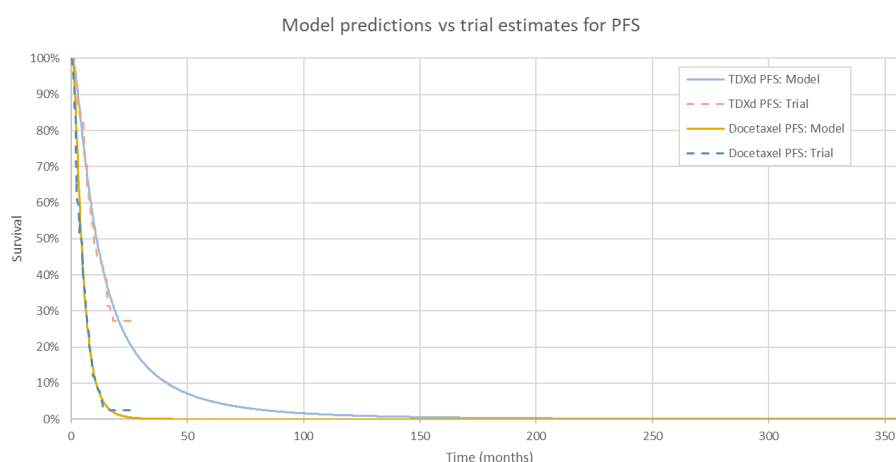
Table 23 Summary of assumptions associated with extrapolation of PFS T-DXd 5.4 mg/kg and Docetaxel

Method/approach	Description/assumption
Data input	DESTINY-Lung02 MAIC vs. docetaxel in CheckMate577
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best BIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best visual fit	T-DXd 5.4 mg/kg: lognormal or gen gamma
Function with best fit according to evaluation of smoothed hazard assumptions	T-DXd 5.4 mg/kg: gen gamma or log normal
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	T-DXd 5.4 mg/kg: lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes, indirect through OS extrapolation.
Adjustment for treatment switching/cross-over	Not applicable, no comparator arm in study.
Assumptions of waning effect	No



Method/approach	Description/assumption
Assumptions of cure point	No

Figure 15. Base case extrapolations of PFS with observed data from DESTINY-Lung2 for T-DXd across entire time horizon. Docetaxel PFS curve derived using HR rate from MAIC.



8.1.2 Extrapolation of overall survival

A summary of the assumptions applied in the extrapolation of OS is provided in Table 24 for the T-DXd 5.4 mg/kg-arm in the health economic analysis. The base case extrapolation of OS on T-DXd and the HR-derived OS curve of docetaxel are visualized in Figure 16. Please consult appendix D.2 for further information on the extrapolation of OS.

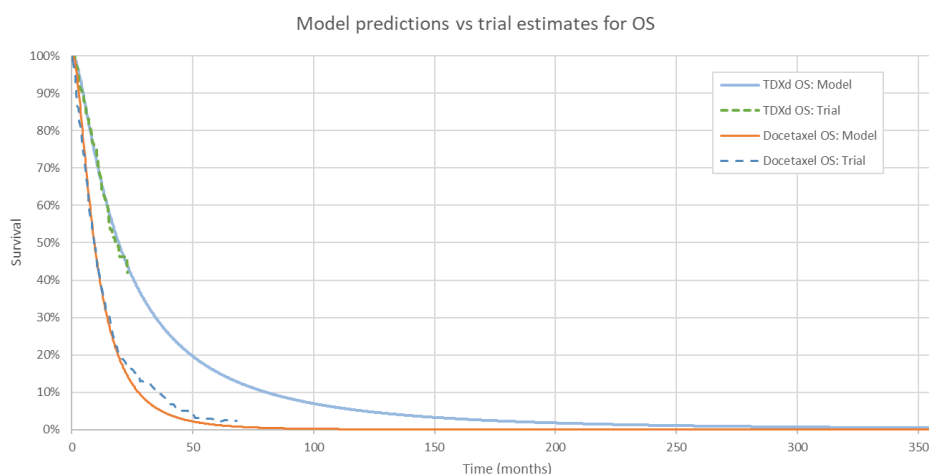
Table 24 Summary of assumptions associated with extrapolation of OS T-DXd 5.4 mg/kg and Docetaxel

Method/approach	Description/assumption
Data input	DESTINY-Lung02 MAIC vs. docetaxel in CheckMate577
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	No
Function with best AIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best BIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best visual fit	T-DXd 5.4 mg/kg: lognormal



Method/approach	Description/assumption
Function with best fit according to evaluation of smoothed hazard assumptions	T-DXd 5.4 mg/kg: lognormal or loglogistic
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	T-DXd 5.4 mg/kg: lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable, no comparator arm in study.
Assumptions of waning effect	No
Assumptions of cure point	No

Figure 16. Base case extrapolations of OS with observed data from DESTINY-Lung2 for T-DXd across entire time horizon. Docetaxel OS curve derived using HR rate from MAIC.



8.1.2.1 Extrapolation of time to treatment discontinuation

A summary of the assumptions applied in the extrapolation of TTD is provided in Table 25 for the T-DXd 5.4 mg/kg-arm in the health economic analysis. The base case extrapolation of TTD on T-DXd and the TTD curve of docetaxel (assumed to be equal to



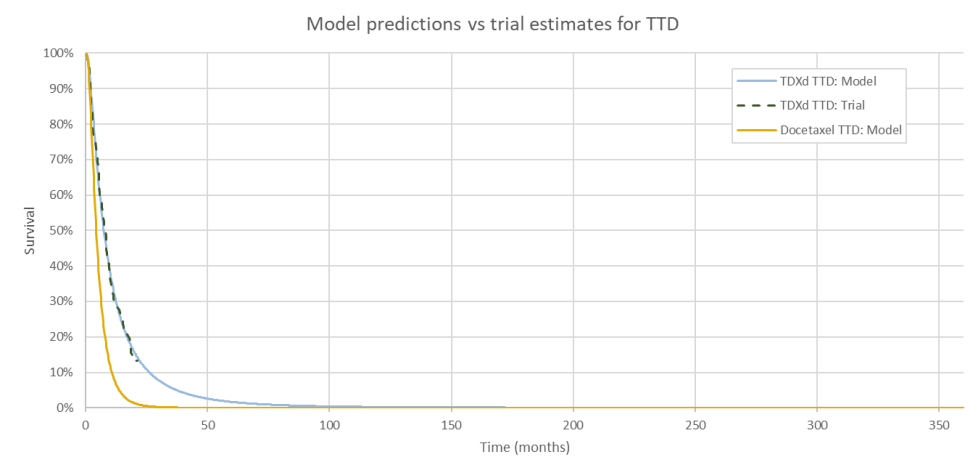
PFS) are visualized in Figure 17. Please consult appendix D.3 for further information on the extrapolation of OS.

Table 25 Summary of assumptions associated with extrapolation of TTD T-DXd 5.4 mg/kg

Method/approach	Description/assumption
Data input	DESTINY-Lung02 MAIC vs. docetaxel in CheckMate577
Model	Standard parametric models
Assumption of proportional hazards between intervention and comparator	Not applicable
Function with best AIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best BIC fit	T-DXd 5.4 mg/kg: lognormal
Function with best visual fit	T-DXd 5.4 mg/kg: lognormal
Function with best fit according to evaluation of smoothed hazard assumptions	T-DXd 5.4 mg/kg: lognormal or loglogistic
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	T-DXd 5.4 mg/kg: lognormal
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	Not applicable, no comparator arm in study.
Assumptions of waning effect	No
Assumptions of cure point	No



Figure 17. Base case extrapolations of TTD with observed data from DESTINY-Lung2 for T-DXd across entire time horizon. Docetaxel TTD curve is assumed to be equal to PFS curve of docetaxel.



8.1.3 Calculation of transition probabilities

Not applicable for the chosen model approach.

Table 26 Transitions in the health economic model

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

8.2 Presentation of efficacy data from [additional documentation]

N/A.

8.3 Modelling effects of subsequent treatments

N/A.

8.4 Other assumptions regarding efficacy in the model

As described in section 4, DESTINY-Lung02 did not include a direct trial comparison to docetaxel. Therefore, the extrapolation of the docetaxel arm in the health economic analysis is based on the HR derived from the ITC vs. CheckMate 057 on PFS and OS.



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

An overview of modelled average treatment length and time in model health states is shown in Table 27. Estimates that are undiscounted and not adjusted for half cycle correction are shown in Table 28.

Table 27 Estimates in the model (undiscounted, no half-cycle correction, OS adjusted for background mortality)

	Modelled average	Modelled median	Observed median from relevant study
PFS			
T-DXd 5.4 mg/kg	18.75 months ='T-DXd'!O20	10.81 months ='T-DXd'!O21	10.0 months DESTINY-Lung02 DCO 25 Aug 2023
Docetaxel	5.60 months ='Mono ChT'!O20	4.14 months ='Mono ChT'!O21	4.6 months CheckMate 057 DCO 18 March 2015
OS			
T-DXd 5.4 mg/kg	35.21 months ='T-DXd'!M20	19.32 months ='T-DXd'!M21	19.0 months DESTINY-Lung02 DCO 25 Aug 2023
Docetaxel	13.28 months ='Mono ChT'!M20	9.20 months ='Mono ChT'!M21	9.5 months CheckMate 057 DCO 16 May 2019

Table 28 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [months]	Progression-free [months]	Post-progression [months]
T-DXd 5.4 mg/kg	12.15	18.75	16.46
Docetaxel	5.60	5.60	7.68



9. Safety

9.1 Safety data from the clinical documentation

The AEs profiles for T-DXd 5.4 mg/kg in DESTINY-Lung02 and for docetaxel in CheckMate 057 are presented in Table 29. The data in the table includes population dosed with T-DXd 5.4 mg/kg or docetaxel, hence excluding subjects that have been randomized, but not received the assigned treatment. Overall, the safety profiles for T-DXd 5.4 mg/kg and docetaxel were consistent with the known safety profiles of the medicines.

When comparing data from DESTINY-Lung02 and CheckMate057, a markedly longer median treatment duration was observed with T-DXd (7.66 months) than with docetaxel in CheckMate057 (median duration of study therapy: 2.3 months)(52). This aligns with the PFS benefit observed with T-DXd in DESTINY-Lung02, and the better disease control would lead to a longer treatment duration than with docetaxel, as observed in CheckMate057.

In both trials, nearly all patients experienced an adverse event (AE). This is expected with an ADC, as T-DXd, and with a taxane, as docetaxel. Similar rates of serious adverse events were observed in both trials, where 39.6% of T-DXd patients experienced a serious AE (SAE) in DESTINY-Lung02 and 41.4% of docetaxel patients experienced a SAE in CheckMate057.

For CTCAE grade ≥ 3 AEs, a lower proportion of events were observed with T-DXd in DESTINY-Lung02 (56.4%) than with docetaxel in CheckMate057 (72.4%), despite the large difference in treatment exposure between the treatment. This could indicate that T-DXd could potential be more tolerable for patients, reducing the number of hospitalisations required due to adverse events.

For T-DXd, interstitial lung disease (ILD) has been identified as an adverse event of special interest (AESI) at the start of the clinical program for T-DXd. Additional data for ILD has been included in this application from the Aug 2023 data in Appendix M.

Table 29 Overview of safety events. Table presents treatment-emergent adverse events from DESTINY-Lung02(51) and CheckMate 057(52).

	T-DXd 5.4 mg/kg (N= 101) (51) Median duration of treatment: 7.66 months	Docetaxel (N=268) (52) Median duration of treatment: 2.3 months (95% CI: 2.10, 2.83)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NC
Number and proportion of patients with ≥ 1	101/101 (100.0%)	265/268 (98.9%)	1.1% (-0.1%; 2.4%)



	T-DXd 5.4 mg/kg (N= 101) (51) Median duration of treatment: 7.66 months	Docetaxel (N=268) (52) Median duration of treatment: 2.3 months (95% CI: 2.10, 2.83)	Difference, % (95 % CI)
adverse events, n (%)			
Number of serious adverse events*, n	NR	NR	NC
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	40/101 (39.6%)	111/268 (41.4%)	-1.8% (-13.0%; 9.4%)
Number of CTCAE grade ≥ 3 events, n	NR	NR	NC
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events [§] , n (%)	57/101 (56.4%)	194/268 (72.4%)	-16.0% (-27.0%; - 4.9%)
Number of adverse reactions, n	NR	NR	NC
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NC
Number and proportion of patients who had a dose reduction, n (%)	22/101 (21.8%)	69/268 (25.7%)	-4.0% (-13.6%; 5.6%)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	60/101 (59.4%)	65/268 (24.3%)	35.2% (24.3%; 46.0%)



	T-DXd 5.4 mg/kg (N= 101) (51) Median duration of treatment: 7.66 months	Docetaxel (N=268) (52) Median duration of treatment: 2.3 months (95% CI: 2.10, 2.83)	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	17/101 (16.8%)	58/268 (21.6%)	-4.8% (-13.6%; 4.0%)
Number and proportion of patients who died due to adverse events, n (%)	6/101 (5.9%)	14/268 (5.2%)	0.7% (-4.6%; 6.0%)

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the [ICH's complete definition](#)).

§ CTCAE v. 5.0 must be used if available.

In DESTINY-Lung02, no serious adverse was reported in more than 5% of the patients.
The full overview of serious adverse events has been reported in Appendix E.

Table 30 Serious adverse events <5%, DESTINY-Lung02(50)

Adverse events	T-DXd 5.4 mg/kg (N=101)		T-DXd 6.4 mg/kg (N=50)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
N/A	N/A	N/A	N/A	N/A

In CheckMate057, febrile neutropenia was observed as an serious adverse event in 9% of patients receiving docetaxel. A more exhaustive list has been reported in Appendix E.



Table 31 Serious adverse events <5%, CheckMate 057(52)

Adverse events		
Docetaxel (N=268) (52) Median duration of treatment: 2.3 months (95% CI: 2.10, 2.83)		
	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)		
Febrile neutropenia	24 (9.0%)	N/A

AEs were included in the health economic analysis to reflect the health care costs associated. The selection criteria of AEs were those that were treatment-emergent, grade 3 or higher, and occurred in $\geq 5\%$ of the population in DESTINY-Lung02 trial or CheckMate 057, with the addition of interstitial lung disease (ILD) as adverse event of special interest for T-DXd.

Table 32 Adverse events used in the health economic model

Adverse events				
Adverse event, n (%)	T-DXd	Docetaxel		Justification
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	
Anaemia	11.88%	4.85%	T-DXd 5.4 mg/kg: Sourced from DESTINY-Lung02(51)	Treatment-emergent, grade 3 or higher adverse event, and occurring in $\geq 5\%$ of the population in the T-DXd 5.4 mg/kg arm in DESTINY-Lung02 trial or the docetaxel arm of CheckMate 057
Febrile neutropenia	0.00%	10.82%		
ILD	1.98%	0.00%		
Neutrophil count decreased	13.86%	5.97%	Docetaxel: Sourced from CheckMate057, EPAR (Table 33, p55) (52)	
Pneumonia/pneumonitis	0.00%	5.60%		
Fatigue	7.92%	6.72%		
Leukopenia	5.94%	8.58%		
Thrombocytopenia	5.94%	0.00%		



Adverse events	T-DXd	Docetaxel
Hypokalaemia	7.92%	0.00%

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

N/A.



Table 33 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								



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

An assessment of HRQoL data has been conducted to analyse the impact on QoL on patients when treated with T-DXd 5.4 mg/kg and docetaxel.

Data on EORTC QLQ-C30, EQ-VAS and EQ-5D-5L is presented in the subsequent sections. Data from DESTINY-Lung02 has been presented for all instruments, while only EQ-VAS data was identified in the published literature for CheckMate057. EQ-5D-5L data from FLAURA2 has been mapped to HSUVs with the Danish tariff set for the health economic model.

Table 34 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	DESTINY-Lung02	HRQoL impact of T-DXd
EQ-5D-5L + EQ-VAS	DESTINY-Lung02 CheckMate 057 (Only EQ-VAS)	Naïve comparison of HRQoL between T-DXd and docetaxel Health state utility values

10.1 Presentation of the health-related quality of life EORTC QLQ-C30

EORTC QLQ-C30 was reported in DESTINY-Lung02, however, the instrument was not used in Checkmate057, therefore in the following section, only results from DESTINY-Lung02 for T-DXd 5.4 mg/kg has been reported.

10.1.1 Study design and measuring instrument

In DESTINY-Lung02, patient reported outcomes were assessed as secondary endpoints using the EORTC QLQ-C30 questionnaire. PRO data was collected for all patients from randomization every 3-week cycle until 40 days (plus 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first.(48)

Changes in score compared to baseline were evaluated. A clinically meaningful change was defined as change ≥ 10 points from baseline. Patients with no baseline data or no post-baseline PRO assessment will be excluded from the change from baseline analysis. A paper instrument or electronic patient-reported outcome (ePRO) data collection modality was employed for the collection of data. The PRO questionnaires was completed by the subjects at the investigational site prior to the completion of other study assessments and the administration of trastuzumab deruxtecan.(48)



10.1.2 Data collection

The overall compliance rates for completion of the EORTC QLQ-C30 questionnaire was high at baseline (100%) and remained high ($\geq 90\%$) to cycle 20, where the expected number to complete dropped to 14 subjects.

Table 35 Pattern of missing data and completion, DCO Aug 2023(48). Cycles are 3 weeks long.

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)
Baseline	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 4 (3.9%)	T-DXd 5.4 mg/kg N = 98	T-DXd 5.4 mg/kg N = 98 (100.0%)
Cycle 2 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 10 (9.8%)	T-DXd 5.4 mg/kg N = 100	T-DXd 5.4 mg/kg N = 92 (92.0%)
Cycle 3 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 17 (16.7%)	T-DXd 5.4 mg/kg N = 91	T-DXd 5.4 mg/kg N = 85 (93.4%)
Cycle 4 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 22 (21.6%)	T-DXd 5.4 mg/kg N = 84	T-DXd 5.4 mg/kg N = 80 (95.2%)
Cycle 5 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 26 (25.5%)	T-DXd 5.4 mg/kg N = 79	T-DXd 5.4 mg/kg N = 76 (96.2%)
Cycle 6 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 31 (30.4%)	T-DXd 5.4 mg/kg N = 76	T-DXd 5.4 mg/kg N = 71 (93.4%)
Cycle 7 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 35 (34.3%)	T-DXd 5.4 mg/kg N = 70	T-DXd 5.4 mg/kg N = 67 (95.7%)
Cycle 8 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 41 (40.2%)	T-DXd 5.4 mg/kg N = 65	T-DXd 5.4 mg/kg N = 61 (93.8%)
Cycle 9 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 46 (45.1%)	T-DXd 5.4 mg/kg N = 60	T-DXd 5.4 mg/kg N = 56 (93.3%)
Cycle 10 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 49 (48.0%)	T-DXd 5.4 mg/kg N = 56	T-DXd 5.4 mg/kg N = 53 (94.6%)
Cycle 11 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 54 (52.9%)	T-DXd 5.4 mg/kg N = 51	T-DXd 5.4 mg/kg N = 48 (94.1%)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 12 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 58 (56.9%)	T-DXd 5.4 mg/kg N = 46	T-DXd 5.4 mg/kg N = 44 (95.7%)
Cycle 13 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 59 (57.8%)	T-DXd 5.4 mg/kg N = 44	T-DXd 5.4 mg/kg N = 43 (97.7%)
Cycle 14 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 65 (63.7%)	T-DXd 5.4 mg/kg N = 41	T-DXd 5.4 mg/kg N = 37 (90.2%)
Cycle 15 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 68 (66.7%)	T-DXd 5.4 mg/kg N = 35	T-DXd 5.4 mg/kg N = 34 (97.1%)
Cycle 16 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 74 (72.5%)	T-DXd 5.4 mg/kg N = 29	T-DXd 5.4 mg/kg N = 28 (96.6%)
Cycle 17 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 78 (76.5%)	T-DXd 5.4 mg/kg N = 26	T-DXd 5.4 mg/kg N = 24 (92.3%)
Cycle 18 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 81 (79.4%)	T-DXd 5.4 mg/kg N = 22	T-DXd 5.4 mg/kg N = 21 (95.5%)
Cycle 19 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 84 (82.4%)	T-DXd 5.4 mg/kg N = 18	T-DXd 5.4 mg/kg N = 18 (100.0%)
Cycle 20 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 89 (87.3%)	T-DXd 5.4 mg/kg N = 14	T-DXd 5.4 mg/kg N = 13 (92.9%)
Cycle 21 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 94 (92.2%)	T-DXd 5.4 mg/kg N = 12	T-DXd 5.4 mg/kg N = 8 (66.7%)
Cycle 22 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 6	T-DXd 5.4 mg/kg N = 2 (33.3%)
Cycle 23 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 5	T-DXd 5.4 mg/kg N = 2 (40.0%)
Cycle 24 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 25 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 26 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 27 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 101 (99.0%)	T-DXd 5.4 mg/kg N = 2	T-DXd 5.4 mg/kg N = 1 (50.0%)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 28 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 101 (99.0%)	T-DXd 5.4 mg/kg N = 2	T-DXd 5.4 mg/kg N = 1 (50.0%)
Cycle 29 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 102 (100.0%)	T-DXd 5.4 mg/kg N = 1	T-DXd 5.4 mg/kg N = 0 (0.0%)
Cycle 30 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 102 (100.0%)	T-DXd 5.4 mg/kg N = 1	T-DXd 5.4 mg/kg N = 0 (0.0%)

10.1.3 HRQoL results

In the T-DXd 5.4-mg/kg arm, HRQoL was sustained while on treatment. The EORTC QLQ-C30 global health status score maintained stable until cycle 26, after which the number of patients remaining on treatment decreased to <10%, and the results were no longer considered informative after this data point.

Figure 18. Change from baseline in EORTC QLQ-C30 global health status in DESTINY-Lung02, DCO Aug 2023.(48)

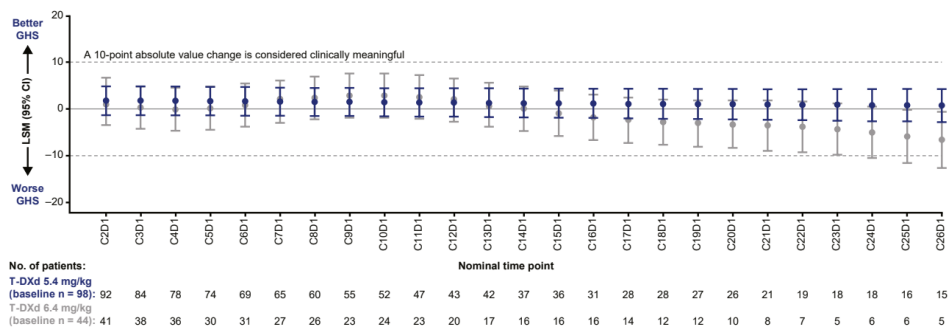


Table 36 HRQoL - EORTC QLQ-C30 in DESTINY-Lung02 change from baseline summary statistics (DCO Aug 2023), not available. Data from an earlier data cut is included appendix N.

	T-DXd 5.4 mg/kg		T-DXd 6.4 mg/kg	
	N	Mean (SE)	N	Mean (SE)
Baseline	NA	NA	NA	NA



10.2 Presentation of the health-related quality of life EQ-5D & EQ-VAS

10.2.1 Study design and measuring instrument

10.2.1.1 DESTINY-Lung02

In DESTINY-Lung02, patient reported outcomes were assessed as secondary endpoints using the EQ-5D-5L and EQ-VAS questionnaire. PRO data was collected for all patients from randomization every 3-week cycle until 40 days (plus 7 days) after the last study drug administration or before starting new anticancer treatment, whichever comes first(48).

Changes in score compared to baseline were evaluated. A clinically meaningful change was defined as change ≥ 10 points from baseline. Patients with no baseline data or no post-baseline PRO assessment will be excluded from the change from baseline analysis. A paper instrument or ePRO data collection modality was employed for the collection of data. The PRO questionnaires were completed by the subjects at the investigational site prior to the completion of other study assessments and the administration of trastuzumab deruxtecan.(48)

10.2.1.2 CheckMate 057

In CheckMate 057, overall health status was assessed with EQ-5D VAS. PRO data was collected for all patients at baseline and every 3 weeks for the first 6 month on treatment and subsequently, every 6 weeks while on treatment, and at two follow-up visits after treatment discontinuation. Data was collected using a touch screen electronic PC tablet for the subject's completion of the PRO questionnaires. Subjects entered the data directly onto the electronic PC tablet at the time of the scheduled visits, prior to any study procedures and study drug infusion.(53)

10.2.2 Data collection

10.2.2.1 DESTINY-Lung02

The overall compliance rates for completion of the EQ-5D-5L and EQ-VAS questionnaire was high at baseline (100%) and remained high ($\geq 90\%$) to cycle 20, where the expected number to complete dropped to 14 subjects.

Table 37 Pattern of missing data and completion, DCO Aug 2023(48). Cycles are 3 weeks long.

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	Number of patients "at	Number of patients who completed (% of



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
		missing (% of patients at randomization)	risk" at time point X	patients expected to complete)
Baseline	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 7 (6.9%)	T-DXd 5.4 mg/kg N = 95	T-DXd 5.4 mg/kg N = 95 (100.0%)
Cycle 2 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 14 (13.7%)	T-DXd 5.4 mg/kg N = 100	T-DXd 5.4 mg/kg N = 88 (88.0%)
Cycle 3 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 19 (18.6%)	T-DXd 5.4 mg/kg N = 91	T-DXd 5.4 mg/kg N = 83 (91.2%)
Cycle 4 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 23 (22.5%)	T-DXd 5.4 mg/kg N = 84	T-DXd 5.4 mg/kg N = 79 (94.0%)
Cycle 5 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 27 (26.5%)	T-DXd 5.4 mg/kg N = 79	T-DXd 5.4 mg/kg N = 75 (94.9%)
Cycle 6 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 32 (31.4%)	T-DXd 5.4 mg/kg N = 76	T-DXd 5.4 mg/kg N = 70 (92.1%)
Cycle 7 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 37 (36.3%)	T-DXd 5.4 mg/kg N = 70	T-DXd 5.4 mg/kg N = 65 (92.9%)
Cycle 8 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 42 (41.2%)	T-DXd 5.4 mg/kg N = 65	T-DXd 5.4 mg/kg N = 60 (92.3%)
Cycle 9 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 47 (46.1%)	T-DXd 5.4 mg/kg N = 60	T-DXd 5.4 mg/kg N = 55 (91.7%)
Cycle 10 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 49 (48.0%)	T-DXd 5.4 mg/kg N = 56	T-DXd 5.4 mg/kg N = 53 (94.6%)
Cycle 11 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 54 (52.9%)	T-DXd 5.4 mg/kg N = 51	T-DXd 5.4 mg/kg N = 48 (94.1%)
Cycle 12 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 58 (56.9%)	T-DXd 5.4 mg/kg N = 46	T-DXd 5.4 mg/kg N = 44 (95.7%)
Cycle 13 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 59 (57.8%)	T-DXd 5.4 mg/kg N = 44	T-DXd 5.4 mg/kg N = 43 (97.7%)
Cycle 14 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 66 (64.7%)	T-DXd 5.4 mg/kg N = 41	T-DXd 5.4 mg/kg N = 36 (87.8%)
Cycle 15 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 68 (66.7%)	T-DXd 5.4 mg/kg N = 35	T-DXd 5.4 mg/kg N = 34 (97.1%)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Cycle 16 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 75 (73.5%)	T-DXd 5.4 mg/kg N = 29	T-DXd 5.4 mg/kg N = 27 (93.1%)
Cycle 17 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 78 (76.5%)	T-DXd 5.4 mg/kg N = 26	T-DXd 5.4 mg/kg N = 24 (92.3%)
Cycle 18 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 81 (79.4%)	T-DXd 5.4 mg/kg N = 22	T-DXd 5.4 mg/kg N = 21 (95.5%)
Cycle 19 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 84 (82.4%)	T-DXd 5.4 mg/kg N = 18	T-DXd 5.4 mg/kg N = 18 (100.0%)
Cycle 20 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 89 (87.3%)	T-DXd 5.4 mg/kg N = 14	T-DXd 5.4 mg/kg N = 13 (92.9%)
Cycle 21 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 94 (92.2%)	T-DXd 5.4 mg/kg N = 12	T-DXd 5.4 mg/kg N = 8 (66.7%)
Cycle 22 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 6	T-DXd 5.4 mg/kg N = 2 (33.3%)
Cycle 23 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 5	T-DXd 5.4 mg/kg N = 2 (40.0%)
Cycle 24 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 25 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 26 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 100 (98.0%)	T-DXd 5.4 mg/kg N = 4	T-DXd 5.4 mg/kg N = 2 (50.0%)
Cycle 27 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 101 (99.0%)	T-DXd 5.4 mg/kg N = 2	T-DXd 5.4 mg/kg N = 1 (50.0%)
Cycle 28 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 101 (99.0%)	T-DXd 5.4 mg/kg N = 2	T-DXd 5.4 mg/kg N = 1 (50.0%)
Cycle 29 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 102 (100.0%)	T-DXd 5.4 mg/kg N = 1	T-DXd 5.4 mg/kg N = 0 (0.0%)
Cycle 30 Day 1	T-DXd 5.4 mg/kg N = 102	T-DXd 5.4 mg/kg = 102 (100.0%)	T-DXd 5.4 mg/kg N = 1	T-DXd 5.4 mg/kg N = 0 (0.0%)



10.2.2.2 CheckMate 057

The overall compliance rates for completion of the EQ-VAS questionnaire were quite fluctuating in the first observation points, ranging between 66.5% and 80.0% completion rate. The number of completions appeared to follow the time to progression in the docetaxel arm fairly well, where the observed median PFS was 4.6 months.

Table 38 Pattern of missing data and completion, DCO 18 March 2015(53)

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)
Baseline	Docetaxel N = 290	58 (20.0%)	NR	232 (80.0%)
Baseline and ≥1 post-baseline assessment	Docetaxel N = 290	78 (26.9%)	NR	212 (73.1%)
Week 3	Docetaxel N = 290	129 (44.5%)	NR	161 (66.5%)
Week 6	Docetaxel N = 290	124 (42.8%)	NR	166 (79.4%)
Week 9	Docetaxel N = 290	175 (60.3%)	NR	115 (75.2%)
Week 12	Docetaxel N = 290	185 (63.8%)	NR	105 (79.5%)
Week 15	Docetaxel N = 290	213 (73.4%)	NR	77 (72.6%)
Week 18	Docetaxel N = 290	219 (75.5%)	NR	71 (78.0%)
Week 21	Docetaxel N = 290	246 (84.8%)	NR	44 (72.1%)
Week 24	Docetaxel N = 290	248 (85.5%)	NR	42 (84.0%)



Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
Week 30	Docetaxel N = 290	259 (89.3%)	NR	31 (86.1%)
Week 36	Docetaxel N = 290	268 (92.4%)	NR	22 (91.7%)
Week 42	Docetaxel N = 290	278 (95.9%)	NR	12 (80.0%)
Week 48	Docetaxel N = 290	279 (96.2%)	NR	11 (91.7%)
Week 54	Docetaxel N = 290	283 (97.6%)	NR	7 (87.5%)
Week 60	Docetaxel N = 290	287 (99.0%)	NR	3 (100%)
Week 66	Docetaxel N = 290	289 (99.7%)	NR	1 (100%)
Week 72	Docetaxel N = 290	290 (100.0%)	NR	0
Week 78	Docetaxel N = 290	290 (100.0%)	NR	0
Week 84	Docetaxel N = 290	290 (100.0%)	NR	0
Week 90	Docetaxel N = 290	290 (100.0%)	NR	0
Week 96	Docetaxel N = 290	290 (100.0%)	NR	0
Week 102	Docetaxel N = 290	290 (100.0%)	NR	0
Week 108	Docetaxel N = 290	290 (100.0%)	NR	0
Follow-up 1	Docetaxel N = 290	193 (66.6%)	NR	97 (39.8%)
Follow-up 2	Docetaxel N = 290	212 (73.1%)	NR	78 (42.9%)



Time point	HRQoL population	Missing N (%)	Expected to complete	Completion N (%)
	N		N	

Note: NR, not reported.

10.2.3 HRQoL results

10.2.3.1 DESTINY-Lung02

In the T-DXd 5.4-mg/kg arm, EQ-VAS score maintained stable, and scores did not indicate a change in HRQoL that was considered clinically meaningful.

Figure 19. Change from baseline in EQ-VAS scale, DCO Aug 2023(48)

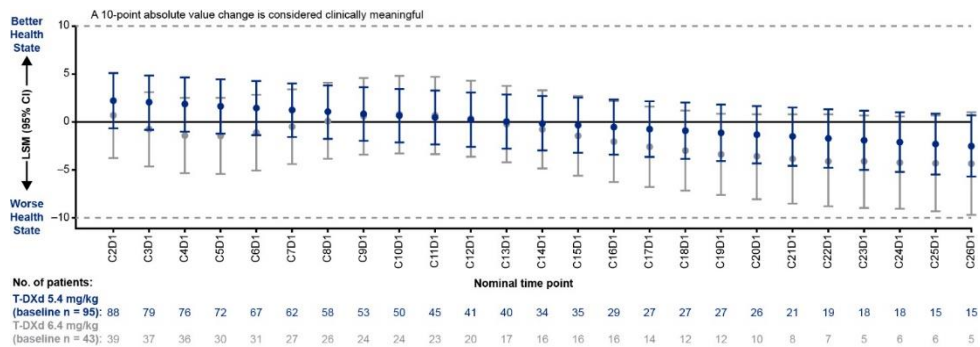


Table 39 HRQoL – EQ-VAS in DESTINY-Lung02 change from baseline summary statistics (DCO Aug 2023), not available. Data from an earlier data cut is included appendix N.

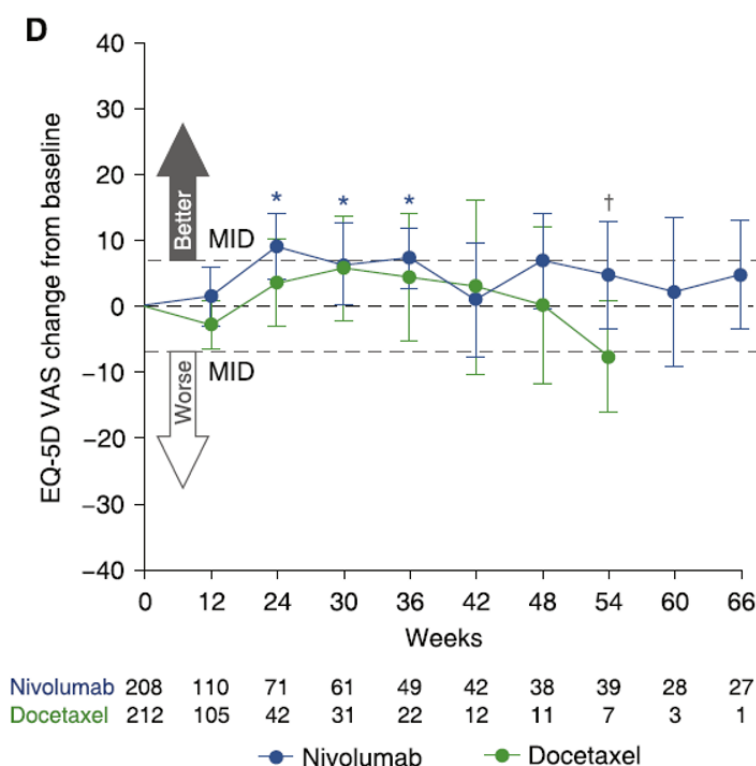
	T-DXd 5.4 mg/kg		T-DXd 6.4 mg/kg	
	N	Mean (SE)	N	Mean (SE)
Baseline	NA	NA	NA	NA

10.2.3.2 CheckMate 057

In the docetaxel arm, EQ-5D-5L VAS score maintained stable within the limits of minimally important difference until the number of respondents dropped to single-digit at week 54.



Figure 20. Change from baseline in EQ-VAS scale in CheckMate 057, DCO 18 March 2015 (53)



Note: MID, minimally important difference (defined as 7 points)

Table 40 HRQoL EQ-VAS scale in CheckMate 057 summary statistics, not available in published literature.

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	NA	NA	NA	NA	NA

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

10.3.1 HSUV calculation

10.3.1.1 Mapping

Utility values used in the base case analysis were based on progression status (i.e., progression-free survival and post-progression survival) and obtained from the DESTINY-



Lung02 trial, DCO 25 Aug 2023. The EQ-5D-5L values was mapped mapped using the Danish preference weight set(59).

Utility scores based on progression-free and progression health states were derived using linear mixed model, which takes into account the within-individual correlation between the repeated measurement of EQ-5D-5L data in DESTINY-Lung02.

Two linear mixed models were constructed to assess the impact on utility by progression status (progressed, progression-free)[referred to as model 1] and progression status and treatment status (progressed, progression-free, on treatment, off treatment)[referred to as model 2], results of both models are presented in Table 41. The analysis results show that there was not a significant association between treatment status and utility value, given few observations available for utilities off-treatment. Therefore, the mixed model with a single covariate of disease/progression status was selected, which is consistent with the health states defined in the economic model.

Table 41. DESTINY-Lung02, Utilities based on progression status and treatment status using the Danish preference weight set - Results of linear mixed models - Full Analysis Set(51)

	Model 1 * 2 Regression coefficients (95% CI) p-value	Model 2 * 2 Regression coefficients (95% CI) p-value
Intercept	0.830 (0.786, 0.873)	0.817 (0.761, 0.873)
	<0.0001	<0.0001
Progression status (progression vs progression-free)	-0.059 (-0.088, -0.030)	-0.058 (-0.087, -0.029)
	<0.0001	0.0001
Treatment status (on treatment vs off treatment)	N/A	0.013 (-0.025, 0.051)
	N/A	0.4926
AIC	-1668.05	-1662.46
BIC	-1657.67	-1652.08

Table 42. DESTINY-Lung02 progression-based utility values mapped using the Danish preference weight set(59).

Health state	# observations	Value (95% CI)
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Progression-free	1145	0.8298 (0.7864 - 0.8733)
Post-progression	157	0.7710 (0.7197 - 0.8222)

10.3.2 Disutility calculation

Disutilities associated with adverse events has been assumed to be captured within the EQ-5D-5L instrument, and inclusions of additional disutilities could lead to potential double counting of the impact of adverse events on the patients' HRQoL. Therefore, disutilities associated with adverse events has been excluded.

10.3.3 HSUV results

Table 43 Overview of health state utility values applied in the health economic model.

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free	0.8298 (0.77864 – 0.8733)	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate. Based on 1145 observation from 101 subjects.
Post-progression	0.7710 (0.7197 – 0.8222)	EQ-5D-5L	DK	MMRM analysis with progression- status as covariate. Based on 157 observation from 101 subjects.

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

N/A.

10.4.1 Study design

N/A.

10.4.2 Data collection

N/A.

10.4.3 HRQoL Results

N/A.



10.4.4 HSUV and disutility results

N/A.

Table 44 Overview of health state utility values [and disutilities]

Results [95% CI]	Instrument	Tariff (value set) used	Comments
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N/A.

Table 45 Overview of literature-based health state utility values

Results [95% CI]	Instrument	Tariff (value set) used	Comments
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N/A.



11. Resource use and associated costs

The sum of costs for managing patients with metastatic NSCLC patients are described below. Included costs are reported in 2025 Danish kroner (DKK). The model includes the following costs, which are discussed in detail below:

- Pharmaceutical costs
- Administration costs
- Disease management costs
- Adverse events related costs
- Subsequent treatments costs
- Patient costs

11.1 Medicines - intervention and comparator

The medicine cost for intervention and comparator is outlined in Table 46, and they were based on the pharmacy purchase prices (AIP) from medicinpriser.dk. Perfect vial sharing is assumed for both therapies. Both docetaxel and T-DXd is used for other tumour types, ensuring adequate turnover at the hospitals to enable vial sharing. We do acknowledge that it might not be possible to completely eliminate wastage, however, we are not aware of an adequate estimate to adjust for imperfect vial sharing. Therefore for the base case, the analysis has not been adjusted for the imperfect vial sharing in clinical practice. This is expected to provide a slightly more optimistic cost-effectiveness estimate for T-DXd.

Relative dose intensity (RDI) observed in DESTINY-Lung02 for T-DXd includes the impact of dose reduction and interruptions observed in the trial and has been included in the analysis to capture expected dose-reductions and interruptions that would occur in Danish clinical practice. For docetaxel, an RDI of 100% was assumed in absence of a relevant source. Data was not available to quantify the impact of the actual drug cost of docetaxel from CheckMate057 based on pack size distribution, dose reductions and interruptions. However, the expected impact of a lower RDI or complete data to estimate the drug costs of docetaxel is predicted to be miniscule due to the low unit cost of generic docetaxel in the Danish market, hence an assumption of 100% RDI is not expected to alter the cost-effectiveness estimate significantly.

Drug acquisition costs are applied in line with the dosing schedules, as detailed in Table 47.



Table 46. Unit cost of all medicines used in the model. Updated 22/12/2025

Medicine	ATC code	Strength	Packaging size	Price DKK (AIP)	Type of administration
T-DXd	L01FD04	100 mg vial	1 pc	10,856.99	IV
			1 ml	35.00	IV
Docetaxel	L01CD02	20 mg/ml	4 ml	150.00	IV
			8 ml	309.00	IV

Table 47. Dosing of medicines used in the model for primary therapy

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
<i>Intervention</i>				
T-DXd	5.4 mg/kg	93.48%	Every 3rd week	Yes
<i>Comparator</i>				
Docetaxel	75 mg/m ²	100%	Every 3rd week	Yes

11.2 Medicines– co-administration

N/A.

11.3 Administration costs

The cost of administration was included for both T-DXd and docetaxel, as both are administered via an IV infusion (in primary and subsequent treatment). The unit cost has been sourced from the Danish DRG list for 2025 (60).

Table 48 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV infusion	T-DXd and docetaxel: Every 3rd week	1,330	DRG 04MA98: MDC04 1-dagsgruppe, patienter på mindst 7 år	DRG 2025 (60)



11.4 Disease management costs

Costs related to disease management were modelled using a health-state approach. Assumptions surrounding health care resource use frequency was based on prior appraisals within metastatic NSCLC at the DMC(61, 62).

Unit costs of the disease management was sourced from the Danish DRG list for 2025(60).

Table 49 Disease management costs used in the model regardless of disease health state

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient visit	Every 3 rd week	1,330	04MA98	DRG 2025
CT scan (chest)	Every 3 rd month	2,701	30PR06	DRG 2025

11.5 Costs associated with management of adverse events

Adverse event costs were applied as a one-off cost at treatment initiation (i.e. the first cycle of the model). Unit costs for managing grade 3 or higher AEs sourced from the Danish DRG list for 2025(60). Table 50 displays the unit costs used in the model.

Table 50 Cost associated with management of adverse events

Adverse event	DRG code	Unit cost/DRG tariff
Anaemia	16MA98	DKK 2,208
Febrile neutropenia	16MA98	DKK 2,208
ILD	04MA17	DKK 48,957
Neutrophil count decreased	16MA98	DKK 0
Pneumonia/pneumonitis	04MA13	DKK 44,614
Fatigue	No cost assumed associated with fatigue	DKK 0
Leukopenia	16MA98	DKK 2,208
Thrombocytopenia	16MA98	DKK 2,208
Hypokalaemia	Assumed to be resolved during outpatient visit	DKK 0



11.6 Subsequent treatment costs

The analysis will include the costs associated with subsequent treatment, hereunder the associated drug and administration costs. The total cost of subsequent treatments is applied as a one-off cost to patients entering the progressed-disease state.

Treatment options are limited once the disease has progressed to 2nd line and beyond.

Following treatment with docetaxel in the 2nd/3rd line setting, no treatments are listed in the clinical treatment guideline, therefore it has been assumed that patients in the docetaxel arm either receive best supportive care or is enrolled in an experimental trial. Hence, no cost associated with subsequent treatment will be accrued for patients in the docetaxel arm after docetaxel.

Following treatment with T-DXd in the 2nd/3rd line setting, treatment with docetaxel has not been attempted, therefore it has been assumed that patients who progress on T-DXd will go on to receive docetaxel as a subsequent therapy. In DESTINY-Lung02, █ patients treated with T-DXd received a subsequent systemic anti-cancer therapy. Relative to the 53 patients who had a PFS event, it is therefore assumed that ███% (██/53) of patients who have a PFS event would receive subsequent docetaxel.

Please refer to Table 52 for assumed distribution of subsequent treatment applied in the health economic model.

Table 51 Medicines of subsequent treatments

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Docetaxel	75 mg/m2	100%	Every 3 rd week	Yes, perfect vial sharing assumed (i.e. no wastage assumed).

Table 52 Modelled proportion and distribution of subsequent treatments following T-DXd and docetaxel in 2L+.

Medicine	T-DXd arm	Docetaxel arm
Proportion of patients receiving subsequent treatment	████%	100%
- Docetaxel	100%	0%
- Best supportive care/experimental therapy	0%	100%



Table 53 Treatment duration of subsequent treatment included in the model

Medicine	Treatment duration	Source
Docetaxel	13.04 weeks	Median number of doxetaxel cycles converted to weeks(63)

11.7 Patient costs

Patient costs were included in the analysis stratified by disease health state in the model. Based on the administration frequency of the primary treatment (every 3 weeks) and the frequency of resource use (i.e., outpatient visits every 3 weeks), a time consumption of approx. 120 minutes every 3rd week was assumed for all patients in the model, assuming that some alignment between dosing and monitoring is plausible. The assumed patient costs were applied regardless of health state.

The unit costs have been sourced from the unit cost list by the DMC(64), see Table 55.

Table 54 Patient costs used in the model

Activity	Time spent [minutes, hours, days]
Pre-progression health state	120 min every 3 rd week
Post-progression health state	120 min every 3 rd week

Table 55. Unit costs used in the model for patient cost (64)

Activity	Cost [DKK]
Cost per patient hour	DKK 188.00
Cost per transport	DKK 140.00

11.8 Other costs

N/A.



12. Results

12.1 Base case overview

Table 56 Base case overview

Feature	Description
Comparator	Docetaxel
Type of model	Partitioned survival model
Time horizon	Lifetime (30 years)
Treatment line	2 nd /3 rd line treatment. Subsequent treatments are included.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in DESTINY-Lung02. Danish population weights were used to estimate health-state utility values. Age-adjusted according to DMC method guideline.
Costs included	• Pharmaceutical costs • Administration costs • Disease management costs • Adverse events related costs • Subsequent treatments costs • Patient costs
Dosage of medicine	T-DXd: 5.4 mg/kg (RDI: 93.48%) Docetaxel: 75 mg/m ² (RDI: 100%)
Average time on treatment	T-DXd: 12.15 months Docetaxel: 5.6 months
Parametric function for PFS	T-DXd: lognormal Docetaxel: Derived from T-DXd PFS extrapolation
Parametric function for OS	T-DXd: lognormal Docetaxel: Derived from T-DXd OS extrapolation
Inclusion of waste	Vial sharing assumed.
Average time in pre-progression health state	T-DXd: 18.75 months



Feature	Description
	Docetaxel: 5.60 months
Average time in post-progression health state	T-DXd: 16.46 months Docetaxel: 7.68 months

12.1.1 Base case results

The base case results are presented in Table 57. Over the life horizon, the total discounted cost associated with T-DXd 5.4 mg/kg was estimated to 849,104 DKK, while the total discounted LYs and QALYs was estimated to 2.6 LYs and 2.07 QALYs.

The total discounted cost associated with docetaxel was estimated to 60,462 DKK, while the total discounted LYs and QALYs was estimated to 1.1 LYs and 0.84 QALYs.

The majority of the incremental costs is comprised of the additional drug acquisition costs of T-DXd in the T-DXd arm when compared to the docetaxel arm. The incremental cost per QALY gained for T-DXd 5.4 mg/kg vs. docetaxel was estimate to 643,887 DKK per QALY.

Table 57 Base case results, discounted estimates

	T-DXd 5.4 mg/kg [DKK]	Docetaxel [DKK]	Difference
Drug acquisition costs	695,078	669	694,409
Drug administration costs	23,189	11,207	11,982
Adverse event costs	1,494	3,033	-1,538
Monitoring costs	88,211	36,009	52,203
Subsequent treatment	15,404	0	15,404
Patient time and transport costs	23,383	9,545	13,838
Total costs	846,759	60,462	786,297
Life years gained (pre-progression)	1.48	0.47	1.01
Life years gained (post-progression)	1.14	0.62	0.53
Total life years	2.62	1.08	1.54



	T-DXd 5.4 mg/kg [DKK]	Docetaxel [DKK]	Difference
QALYs (pre-progression)	1.22	0.38	0.83
QALYs (post-progression)	0.86	0.47	0.39
QALYs (adverse reactions)	0	0	0
Total QALYs	2.08	0.86	1.22
Incremental costs per life year gained			509,972 DKK per LY
Incremental cost per QALY gained (ICER)			641,973 DKK per QALY

12.2 Sensitivity analyses

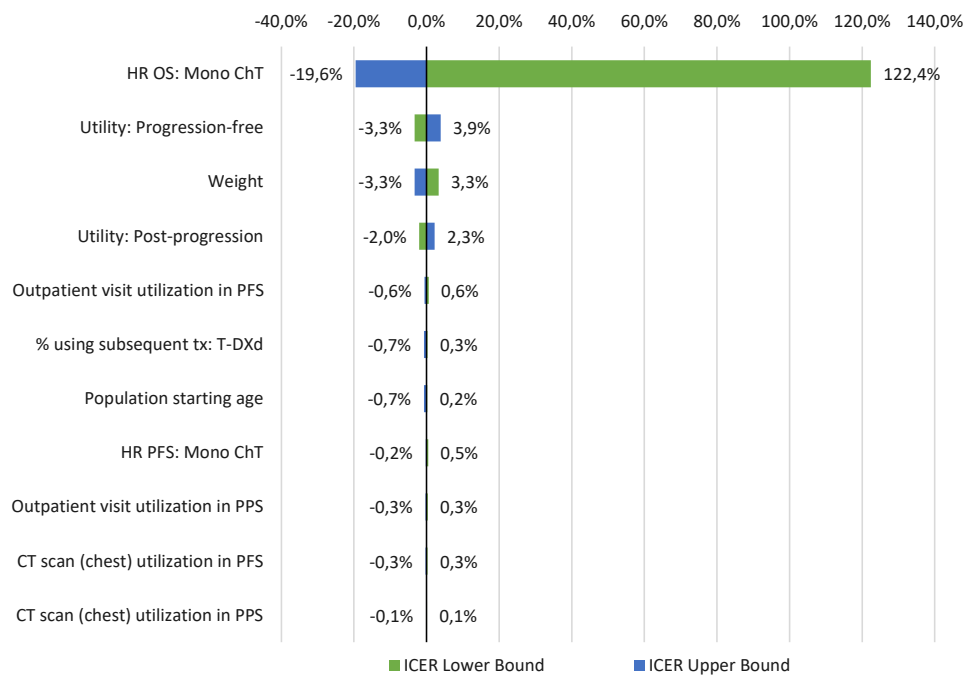
12.2.1 Deterministic sensitivity analyses

The deterministic sensitivity analysis (DSA) produces tornado plots for T-DXd compared with docetaxel, showing the inputs that impacts the ICER the most; **default variation is the lower and upper bounds of the confidence intervals**, in absence of confidence intervals 10% +/- variation is assumed. The ICER tornado plot is shown in Figure 21.

The ICER tornado plot shows that the ICER is most sensitive to the HR on OS between docetaxel and T-DXd, which the highest impact on the ICER (between -19.6 and 122.4%). Varying other input values leads to no more than a 3.3% change in ICER compared with the base case, suggesting that the ICER is less sensitive to these inputs.



Figure 21. ICER Tornado plot for DSA



Note: IV, refers to the unit cost of IV administration



Table 58 One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	NA	NA	786,297	1.22	641,973
HR OS: Mono ChT	Upper bound	Upper bound	746,761	0.523	1,427,861
HR OS: Mono ChT	Lower bound	Lower bound	804,966	1.559	516,434
Weight	Upper bound	Upper bound	812,349	1.22	663,243
Weight	Lower bound	Lower bound	760,631	1.22	621,018
Outpatient visit utilization in PFS	Upper bound	Upper bound	788,792	1.22	644,010
Outpatient visit utilization in PFS	Lower bound	Lower bound	784,029	1.22	640,121
Population starting age	Upper bound	Upper bound	786,274	1.22	643,221
Population starting age	Lower bound	Lower bound	786,303	1.23	637,440
HR PFS: Mono ChT	Upper bound	Upper bound	779,560	1.209	644,931
HR PFS: Mono ChT	Lower bound	Lower bound	789,971	1.234	640,391

12.2.2 Probabilistic sensitivity analyses

The mean results of the probabilistic sensitivity analysis are presented in Table 59 for T-DXd and docetaxel using 1000 Monte Carlo simulations. Over the lifetime time horizon, the total discounted costs and QALYs associated with T-DXd were 853,196 DKK and 2.12 QALY, respectively. For docetaxel, total costs were 64,090 DKK and total QALYs were 0.92. Consistent with the deterministic base case, T-DXd had higher total costs and QALYs than docetaxel.



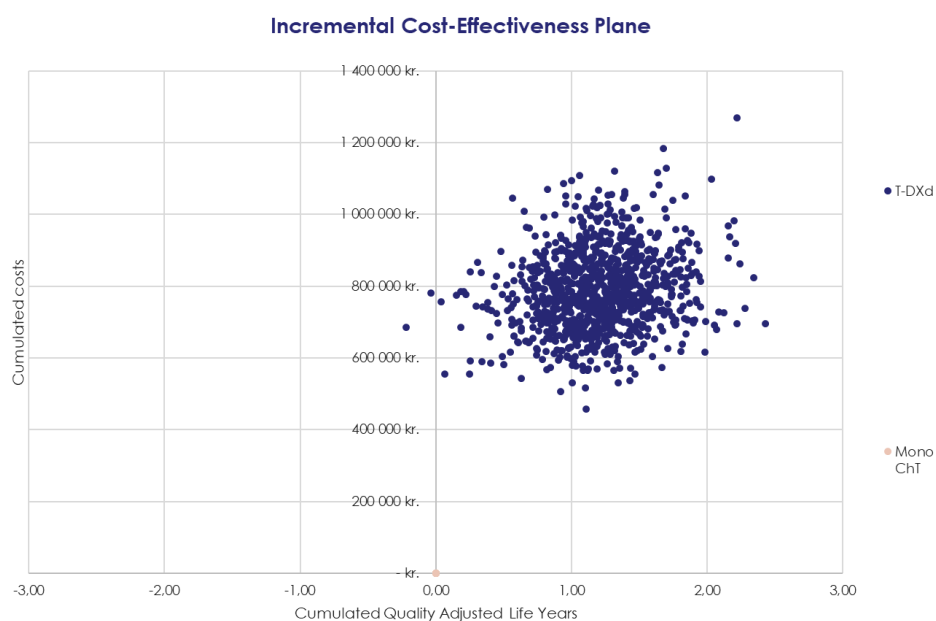
Table 59. Discounted results of the probabilistic analysis

Regimen	Mean Total Costs (DKK)	Mean Total QALYs	Δ Costs (DKK)	Δ QALYs	Incremental cost per QALY (DKK per QALY)
T-DXd	853,196	2.12	789,106	1.20	655,128
Docetaxel	64,090	0.92			

Abbreviations: QALY: quality adjusted life year; ICER: incremental cost-effectiveness ratio.

The cost-effectiveness plane for T-DXd and docetaxel is shown in Figure 22. It shows the distribution of all the simulations from the PSA.

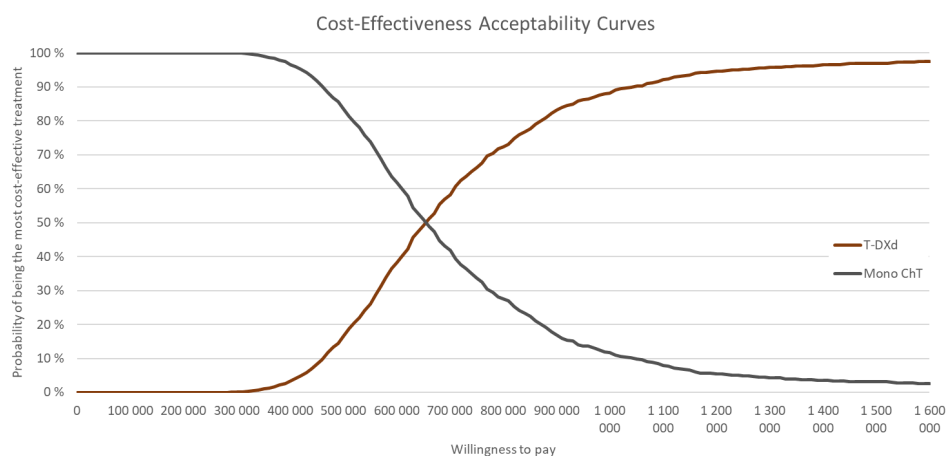
Figure 22. The cost-effectiveness plane



The cost-effectiveness acceptability curve (CEAC) for T-DXd vs. docetaxel is shown in Figure 23. The CEAC shows the probability that the treatment is acceptable based on various acceptability thresholds. T-DXd had a higher probability of being cost-effective vs docetaxel at willingness to pay thresholds greater than 650,000 DKK per QALY.

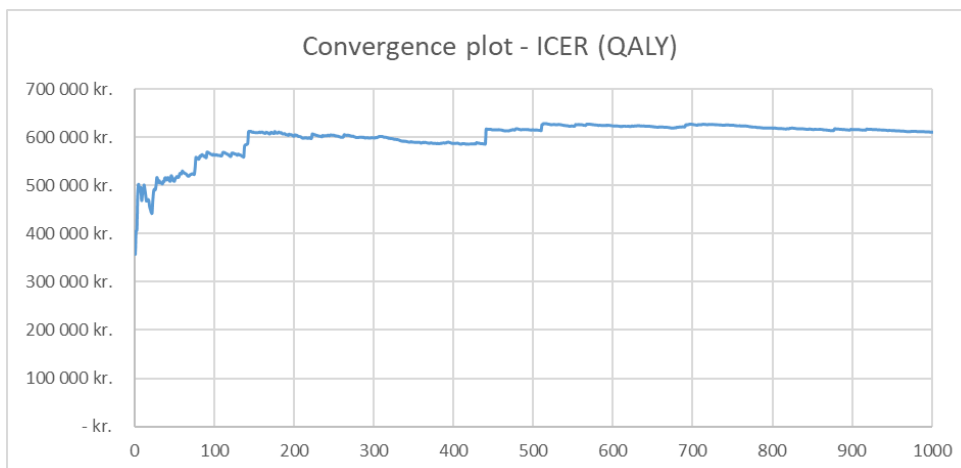


Figure 23. The cost-effectiveness acceptability curve



Convergence plots show the variation in the ICERs generated by the probabilistic simulations against the number of iterations or samples. The plot, Figure 24, demonstrate that probabilistic results were stable after just over 500 iterations, suggesting that 1000 iterations is a sufficient number of iterations to reach a stable result.

Figure 24. ICER Convergence plot



12.2.3 Scenario analysis

Results for the scenario analyses are presented in Table 60. In the majority of the scenario analyses, the ICER for T-DXd versus docetaxel varied by less than 12% except one scenario.

The scenarios with the largest impact on the ICER was observed using the Gamma curve for the OS, PFS and TTD of T-DXd (40.99%) and using the Generalized Gamma curve for OS, PFS and TTD of T-DXd (-10.04%).

Table 60. Scenario analyses explored in the model



Category	Scenario	ICER (DKK per QALY)	Diff-%
Base case	Base case	641,973	-
Patient characteristics	Average age in register look-up population, 70.9 years	634,031	-1.24%
	Mean weight observed in DESTINY-Lung02, 63.6 kg	584,522	-8.95%
Extrapolation scenarios	Use Gamma curve for OS, PFS and TTD on T-DXd	904,700	+40.92%
	Use Generalized gamma for OS, PFS and TTD on T-DXd	577,533	-10.04%
HR scenarios	Apply unadjusted HR for the docetaxel arm	655,494	+2.11%

13. Budget impact analysis

Number of patients (including assumptions of market share)

As stated in section 3.2, the frequency of HER2 mutations in NSCLC is rather low, and the number expected to be eligible for 2L+ treatment with T-DXd is estimated to be between 5-10 patients annually. As this estimate is uncertain to a number of factors, such as progression to 2L and variances in incidence of HER2-mutation, the patient estimate eligible for treatment with T-DXd in 2nd line or later has been assumed to 7 patients annually for the budget impact analysis.

Table 61 Number of new patients expected to be treated over the next five-year period if the T-DXd is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
T-DXd	7	7	7	7	7
Docetaxel	0	0	0	0	0
Non-recommendation					
T-DXd	0	0	0	0	0
Docetaxel	7	7	7	7	7

Budget impact

The budget impact is obtained by multiplying the patient numbers in Table 61 with the cost per patient. The budget impact increase from around DKK 3.3m in year 1 to a budget impact of DKK 5.2m in year 5 (Table 62).



Table 62 Expected budget impact of recommending the T-DXd for the indication, [million DKK]

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	3.6m	4.7m	5.2m	5.4m	5.6m
The medicine under consideration is NOT recommended	0.3m	0.3m	0.3m	0.4m	0.4m
Budget impact of the recommendation	3.3m	4.4m	4.8m	5.1m	5.2m



14. List of experts

N/A.



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Appendix A. Main characteristics of studies included

Table 63 Main characteristic of studies included

Trial name: DESTINY-Lung02		NCT number: NCT04644237	
Objective	Evaluate the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg once every 3 weeks in patients with previously treated HER2m metastatic or locally advanced NSCLC.		
Publications – title, author, journal, year	Jänne PA, Goto Y, Kubo T, et al. Final Analysis Results and Patient-Reported Outcomes From DESTINY-Lung02-A Dose-Blinded, Randomized, Phase 2 Study of Trastuzumab Deruxtecan in Patients With HER2-Mutant Metastatic NSCLC. <i>J Thorac Oncol</i>. Published online July 30, 2025. doi:10.1016/j.jtho.2025.07.129(48) Goto K, Goto Y, Kubo T, et al. Trastuzumab Deruxtecan in Patients With <i>HER2</i>-Mutant Metastatic Non-Small-Cell Lung Cancer: Primary Results From the Randomized, Phase II DESTINY-Lung02 Trial. <i>J Clin Oncol</i>. 2023;41(31):4852-4863. doi:10.1200/JCO.23.01361(49)		
Study type and design	Randomized, multicentre, blinded, 2-cohort, phase II study		
Sample size (n)	<i>n</i>=152 <i>T-DXd</i> 5.4 mg/kg <i>n</i>=102 <i>T-DXd</i> 6.4 mg/kg <i>n</i>=50		
Main inclusion criteria	Subjects had to meet all of the following criteria to be eligible for randomization into the study: 1. Must have provided informed consent for study participation (see Section 10.1.2) before performance of any study-specific procedure or test. 2. Men or women ≥18 years old, unless local regulation requires a higher age for consent. 3. Pathologically documented metastatic NSCLC with a known activating HER2 mutation. The HER2 mutation must be documented from an archival or fresh tumour tissue sample analysed by Clinical Laboratory Improvement Amendments (CLIA) certified laboratory or equivalent laboratory performing testing to Good Laboratory Practice (GLP) standard. Note: HER2 mutation documented only from a liquid biopsy sample cannot be used for enrolment. 4. Subjects who had previous treatment including platinum therapy in the metastatic/locally advanced setting and not amenable to curative surgery or radiation. The subject must have progressed during or after the last treatment regimen or discontinued because of unacceptable toxicity. 5. Presence of at least 1 measurable lesion confirmed by BICR based on RECIST version 1.1.		



Trial name: DESTINY-Lung02

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6. Is willing and able to provide an adequate archival tumour tissue sample. A fresh biopsy is required if an archival tumour tissue sample cannot be supplied. Resection and core needle biopsy are acceptable. Other tissue samples, e.g., fine needle aspirates or cell block are not acceptable. For detailed instruction on tissue submission, please refer to the laboratory manual.
7. Had ECOG PS of 0 to 1.
8. Had LVEF $\geq$ 50% within 28 days before randomization.
9. Had adequate organ function within 14 days before randomization, including adequate bone marrow, renal, hepatic, and blood clotting functions.
10. Had adequate wash out periods for previous treatments before randomization.
11. Male and female subjects of reproductive/childbearing potential had to agree to use a highly effective form of contraception or avoid intercourse during and upon completion of the study and for at least 7 months for females and for 4 months for males after the last dose of study drug.
12. Male subjects could not freeze or donate sperm starting at randomization and throughout the study period, and at least 4 months after the final study drug administration. Preservation of sperm should have been considered prior to randomization in this study.
13. Female subjects could not donate, or retrieve for their own use, ova from the time of randomization and throughout the study treatment period, and for at least 7 months after the final study drug administration. Female subjects had to refrain from breastfeeding throughout this time. Preservation of ova might have been considered prior to randomization in this study.
14. Life expectancy of 3 months or more

**Main exclusion
criteria**

1. Had a known driver mutation in the EGFR, BRAF, or MET exon 14 gene or a known ALK, ROS1, RET, or NTRK fusion.
 2. Had a medical history of myocardial infarction within 6 months before randomization, symptomatic congestive heart failure (CHF) (New York Heart Association Class II to IV). Subjects with troponin levels above ULN at screening (as defined by the manufacturer), and without any MI related symptoms should have had a cardiologic consultation before randomization to rule out MI.
 3. Had a corrected QT interval (QTcF) prolongation $>$ 470 msec (females) or $>$ 450 msec (males) based on average of the triplicate 12-lead ECG at screening.
 4. Had a history of (non-infectious) ILD/pneumonitis that required steroids, had current ILD/pneumonitis, or where suspected ILD/pneumonitis could not be ruled out by imaging at screening.
 5. Had spinal cord compression or clinically active CNS metastases, defined as untreated and symptomatic, or requiring therapy with corticosteroids or anticonvulsants to control associated symptoms at time of inclusion. Subjects with clinically inactive brain metastases could be included in
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Trial name: DESTINY-Lung02

**NCT number:
NCT04644237**

- the study. Subjects with treated brain metastases that were no longer symptomatic and who required no treatment with corticosteroids or anticonvulsants could be included in the study if they had recovered from the acute toxic effect of radiotherapy. A minimum of 2 weeks must have elapsed between the end of brain radiotherapy and study randomization.
6. Has had multiple primary malignancies within 3 years, except adequately resected non-melanoma skin cancer, curatively treated in-situ disease, or other solid tumours curatively treated.
 7. Had a history of severe hypersensitivity reactions to either the drug substances or inactive ingredients in the drug product.
 8. Had a history of severe hypersensitivity reactions to other monoclonal antibodies.
 9. Had an uncontrolled infection requiring IV antibiotics, antivirals, or antifungals.
 10. Had substance abuse or any other medical conditions such as clinically significant cardiac or psychological conditions, that might, in the opinion of the investigator, interfere with the subject's participation in the clinical study or evaluation of the clinical study results.
 11. Had a known human immunodeficiency virus (HIV) infection. Subjects should be tested for HIV prior to randomization if required by local regulations or institutional review board (IRB)/independent ethics committee (IEC).
 12. Known active clinically relevant liver disease (e.g., active hepatitis B, or active hepatitis C), such as those with serologic evidence of viral infection within 28 days of Cycle 1, Day 1. Subjects with past or resolved hepatitis B virus (HBV) infection were eligible, if negative for hepatitis B surface antigen (HBsAg[-]) and positive for hepatitis B core antibody (anti-HBc[+]). Subjects positive for hepatitis C (HCV) antibody are eligible only if the polymerase chain reaction is negative for HCV RNA.
 13. Unresolved toxicities from previous anticancer therapy, defined as toxicities (other than alopecia) not yet resolved to Grade ≤ 1 or baseline. Note: Subjects may be enrolled with chronic Grade 2 toxicities (defined as no worsening to $>$ Grade 2 for at least 3 months prior to randomization and managed with standard of care treatment) which the investigator deems related to previous anticancer therapy, such as:
 - a. Chemotherapy-induced neuropathy
 - b. Fatigue
 - c. Residual toxicities from prior IO treatment: Grade 1 or Grade 2 endocrinopathies which may include:
 - Hypothyroidism/ hyperthyroidism
 - Type I diabetes
 - Hyperglycaemia
 - Adrenal insufficiency
 - Adrenalitis
 - Skin hypopigmentation (vitiligo)
 14. Was pregnant, breastfeeding, or planning to become pregnant.
 15. Otherwise considered inappropriate for the study by the investigator.



Trial name: DESTINY-Lung02		NCT number: NCT04644237		
		16. Had lung-specific intercurrent clinically significant illnesses including, but not limited to, any underlying pulmonary disorder (e.g., pulmonary emboli within three months of the study randomization, severe asthma, severe COPD, restrictive lung disease, pleural effusion etc.). 17. Had any autoimmune, connective tissue or inflammatory disorders (e.g., Rheumatoid arthritis, Sjögren's, sarcoidosis etc.) where there was documented, or a suspicion of pulmonary involvement at the time of screening.		
Intervention	Eligible patients were randomly assigned 2:1 to T-DXd 5.4 mg/kg once every 3 weeks or 6.4 mg/kg once every 3 weeks, respectively			
Comparator(s)	No comparator			
Follow-up time	Median follow-up (Q1–Q3): 15.8 (8.2–20.7) months in T-DXd 5.4 mg/kg arm			
Is the study used in the health economic model?	Yes.			
Primary, secondary and exploratory endpoints	Tumour assessment based on the RECIST 1.1 criteria was performed at screening, and every 6 weeks (+/- 1 week) until disease progression or start of the next treatment. The primary efficacy endpoint was confirmed objective response rate (ORR), defined as the sum of complete and partial response rates, based on RECIST version 1.1, assessed by blinded, independent central review (BICR). Secondary endpoints include: - Duration of response (DoR), defined as time from the initial response (CR or PR) until documented tumour progression or death from any cause. DoR was only defined for subjects who achieved confirmed CR or PR. - Disease control rate (DCR), defined as the proportion of subjects who achieve CR, PR, or SD during study treatment. - Progression free survival (PFS), defined as the time from date of randomization until first objective radiographic tumour progression or death from any cause, based on BICR and investigator assessment. - Objective response rate (ORR), defined above, based on investigator assessment. - Overall survival (OS), defined as the time from date of randomization until death from any cause. Subjects last known to be alive are censored at the date of last contact. A sample size of 150 patients was originally planned for this study on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeded and excluded the ORR benchmark of 26.4%. This benchmark			



Trial name: DESTINY-Lung02		NCT number: NCT04644237	
		was the upper limit of the 95% CI (ORR, 22.9%; 95% CI, 19.7 to 26.4%) in the ramucirumab plus docetaxel arm of the REVEL trial, which was investigated as a second-line treatment for patients with advanced NSCLC after platinum-based therapy (65). Efficacy end points and biomarkers were assessed in all patients randomly assigned to receive study treatment (including those who were randomly assigned but not treated). Safety was assessed in all randomly assigned patients who received at least one dose of study treatment. This study was not powered to statistically compare treatment arms. Endpoints included in this application: PFS, OS, ORR, DOR, EORTC-QLQ C30, EQ-5D-5L	
Method of analysis		A sample size of 150 patients was originally planned for this study on the basis of the probability evaluation that the 95% Clopper-Pearson CI exceeded and excluded the ORR benchmark of 26.4%. Efficacy end points and biomarkers were assessed in all patients randomly assigned to receive study treatment (including those who were randomly assigned but not treated). Safety was assessed in all randomly assigned patients who received at least one dose of study treatment. ORR by BICR and investigator assessment was estimated using 2-sided Clopper-Pearson 95% CIs. DoR, PFS, and OS were analyzed using the Kaplan-Meier method, with 2-sided 95% CIs calculated using the Brookmeyer-Crowley method. This study was not powered to statistically compare treatment arms. All statistical analyses were performed using SAS version 9.3 or higher.	
Subgroup analyses		Efficacy (ORR) planned subgroups: • Prior therapy: ○ Received anti-PD-1 and/or anti-PD-L1 ○ Received neither • CNS metastasis: Yes, No • HER2 status (mutation type): Kinase domain, Extracellular domain, Transmembrane domain • Geography (Japan vs RoW): Japan, Rest of World (non-Japan) • Age: <65, ≥65 years; <75, ≥75 years • Sex: Female, Male • Smoking status: Current, Previous, Never • Race: White, Asian, Others • Region: Asia, North America and Australia, Europe	



Trial name: DESTINY-Lung02	NCT number: NCT04644237
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Other relevant
information

Table 64 Main characteristic of studies included

Trial name: CheckMate 057	NCT number: NCT01673867
Objective	Study to compare the overall survival of nivolumab vs. docetaxel in subjects with NSCLC after failure of prior platinum-based chemotherapy
Publications – title, author, journal, year	Borghaei H, Gettinger S, Vokes EE, et al. Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non-Small-Cell Lung Cancer. <i>J Clin Oncol</i>. 2021;39(7):723-733. doi:10.1200/JCO.20.01605(45) Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. <i>N Engl J Med</i>. 2015;373(17):1627-1639. doi:10.1056/NEJMoa1507643(2) Reck M, Brahmer J, Bennett B, et al. Evaluation of health-related quality of life and symptoms in patients with advanced non-squamous non-small cell lung cancer treated with nivolumab or docetaxel in CheckMate 057. <i>Eur J Cancer</i>. 2018;102:23-30. doi:10.1016/j.ejca.2018.05.005(53)
Study type and design	Randomized, open-label, phase 3 study with two 1:1 arms.
Sample size (n)	Total n=582 Nivolumab, n=292 Docetaxel, n=290
Main inclusion criteria	• Men & women ≥18 years of age • Subjects with histologically or cytologically-documented non-squamous cell NSCLC who present with Stage IIIB/IV disease or recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy for locally advanced disease) and who will receive study therapy as second or third line of treatment for advanced disease • Disease recurrence or progression during/after one prior platinum doublet-based chemotherapy regimen for advanced or metastatic disease • Measurable disease by Computed tomography (CT)/Magnetic resonance imaging (MRI) per RECIST 1.1 criteria



Trial name: CheckMate 057		NCT number: NCT01673867	
		• Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 • A formalin fixed, paraffin-embedded (FFPE) tumor tissue block or unstained slides of tumor sample (archival or recent) must be available for biomarker evaluation. Specimens must be received by the central lab prior to randomization. Biopsy should be excisional, incisional or core needle. Fine needle aspiration is insufficient	
Main exclusion criteria		• Subjects with untreated central nervous system (CNS) metastases are excluded. Subjects are eligible if CNS metastases are asymptomatic or treated and subjects are neurologically returned to baseline for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10mg daily prednisone (or equivalent) • Subjects with carcinomatous meningitis • Subjects with active or recent history of known or suspected autoimmune disease. Subjects with Type 1 diabetes mellitus, hypothyroidism only requiring hormone replacement, or skin disorders (vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll • Subjects with a condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of randomization • Prior therapy with anti-programmed death-1 (anti-PD-1), anti-programmed cell death ligand 1 (anti-PD-L1), anti-programmed cell death ligand 2 (anti-PD-L2), anti-cluster of differentiation 137 (anti-CD137), or anti-Cytotoxic T lymphocyte-associated antigen 4 (anti-CTLA-4) antibody (including Ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways) • Prior treatment with Docetaxel • Treatment with any investigational agent within 14 days of first administration of study treatment	
Intervention		Nivolumab, 3 mg/kg every 2 nd week, n=292	
Comparator(s)		Docetaxel, 75 mg/m ² every 3 rd week, n=290	
Follow-up time		Median follow-up on OS: 69.4 months (minimum follow-up was 64.5 months)	
Is the study used in the health economic model?		Yes, indirectly used through the MAIC.	



Trial name: CheckMate 057		NCT number: NCT01673867	
Primary, secondary and exploratory endpoints	Primary: OS (defined as the time between the date of randomisation and the date of death). For patients without documentation of death, OS was censored on the last date the patient was known to be alive.		
	Secondary:		
	•Investigator-assessed ORR (defined as the number of patients whose best confirmed objective response was either a confirmed complete or partial response, as determined by the investigator, divided by the number of randomised patients)*		
	Duration of response (defined as the time between the date of first confirmed response to the date of the first documented tumour progression [per RECIST 1.1] or death due to any cause, whichever occurs first)†		
	Time to response (defined as the time from randomisation to the date of the first confirmed response. Time to response will be evaluated for responders only).		
	Investigator-assessed PFS (defined as the time from randomisation to the date of the first documented tumour progression as determined by the investigator using RECIST 1.1 criteria or death due to any cause)‡		
	HRQoL as measured by: o Disease-related symptom improvement rate by week 12 as measured by the Lung Cancer Symptom Scale (defined as the proportion of randomised patients who had 10 points or more decrease from baseline in Average Symptom Burden Index score at any time between randomisation and week 12) o Overall health status using the EQ-5D Index and Visual Analogue Scale (exploratory outcome)**		
	Safety and tolerability (exploratory outcome), based on frequency of deaths, AEs, serious AEs, AEs leading to discontinuation of study drug, AEs leading to dose delay, Select AEs and specific clinical laboratory assessments.		
	Immunogenicity of nivolumab (exploratory outcome), based on serum ADA and neutralising ADA response to nivolumab‡‡		
	Endpoints included in this application:		
OS, PFS by investigator, ORR, DoR and HRQoL			
Method of analysis	OS and PFS were analysed with the use of a two-sided log-rank test stratified according to prior maintenance treatment and line of therapy. HR and CI were estimated with the use of a stratified Cox proportional hazards model.		
	Survival curves and rates were estimated with the use of the Kaplan-Meier method. The rates of ORR were compared with the use of a stratified, two-sided Cochran-Mantel-Haenszel test. Non-conventional benefit (i.e. a reduction in the size or number [or both] of target lesions with simultaneous appearance of new lesions or initial progression		



Trial name: CheckMate 057

**NCT number:
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followed by either tumour reduction or no further progression for at least two tumour assessments) in patients treated beyond initial progression was not included in response-based analyses (ORR or PFS).

Median survival time along with 95% CI were constructed based on log-log transformed CI for the survivor function $S(t)$. Rates at fixed time points (e.g. OS at 6 months) were derived from the Kaplan-Meier estimate, and the formula for corresponding CI was derived based on Greenwood variance derivation and on log-log transformation applied on the survivor function $S(t)$.

Unless otherwise specified, a stratified log-rank test was performed to test the comparison between time to event distributions (e.g. PFS and OS).

P values from sensitivity analyses were for descriptive purpose only, and there were no multiplicity adjustments for these analyses. Investigator-assessed BOR was summarised by response category for each treatment group. ORR was computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI was calculated using Cochran-Mantel-Haenszel methodology and adjusted by the same stratification factors as in primary analysis of OS. A by-patient listing of BOR and tumour measurements was provided. The stratified odds ratios (Mantel-Haenszel estimator) between the treatments was provided along with the 95% CI. The difference was tested via the Cochran-Mantel-Haenszel test using a two-sided, 5% α level.

Subgroup analyses

Efficacy (OS, ORR and PFS) planned subgroups:

- Age
 - Sex
 - Race
 - Region
 - Baseline ECOG PS
 - Smoking status
 - Presence of CNS metastases
 - Prior neoadjuvant vs. adjuvant treatment
 - Prior use of maintenance therapy
 - Line of therapy
 - EGFR mutation status
 - ALK translocation status
-



Trial name: CheckMate 057

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- KRAS mutation status
- Mesenchymal Epithelial Transition receptor status
- Cell type
- Time from diagnosis to randomization
- Time from completion of most recent regimen to randomisation

**Other relevant
information**



Appendix B. Efficacy results per study

Results per study

Table 65 Results per study

Results of DESTINY-Lung02 (NCT04644237)											
				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		
Confirmed Objective response rate	T-DXd 5.4 mg/kg	102	50.0% (39.9 - 60.1%)	NA	NA	NA	NA	NA	NA	According to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). No relative effect estimated between the two arms.	(51)
Duration of response	T-DXd 5.4 mg/kg	102	12.6 months (6.4 - NE)	NA	NA	NA	NA	NA	NA	According to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). No relative effect estimated between the two arms.	(51)



Results of DESTINY-Lung02 (NCT04644237)											
				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		
Progression-free survival	T-DXd 5.4 mg/kg	102	10.0 months (7.7 – 15.2)	NA	NA	NA	NA	NA	NA	According to the Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v1.1). No relative effect estimated between the two arms.	(51)
Overall survival	T-DXd 5.4 mg/kg	102	19.0 months (14.7 – NE)	NA	NA	NA	NA	NA	NA	Overall survival is defined as the time interval between the date of enrollment and the date of death due to any cause.	(51)



Table 66 Results per study

Results of CheckMate057 (NCT01673867)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	References
Confirmed Objective response rate	Nivolumab	292	19.2% (15 - 24%)	NA	NA	NA	OR: 1.7	1.1 – 2.6	P=0.02	(2) ORR will be computed in each treatment group along with the exact 95% CI using Clopper-Pearson method. An estimate of the difference in ORRs and corresponding 95% CI will be calculated using CMH methodology and adjusted by the same stratification factors as for primary analysis of OS. In addition, the stratified odds ratios (Mantel-Haenszel estimator) between the treatments will be provided along with the 95% CI. The difference will be tested via the Cochran Mantel-Haenszel (CMH) test using a two-sided, 5% alpha level.
	Docetaxel	290	12.4% (9 – 17%)							



Results of CheckMate057 (NCT01673867)											
Outcome	Study arm	N	Result (CI)	Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
				Difference	95% CI	P value	Difference	95% CI	P value		
Duration of response	Nivolumab	292	17.2 months (10.8 – 30.8)	NA	NA	NA	HR: 0.26	0.15 – 0.43	NA	Duration of response in each treatment group will be estimated using KM product-limit method for subjects who achieve PR or CR. Duration of stable disease will also be estimated in each treatment groups using KM product-limit method for subjects with SD as best response. Median values along with two-sided 95% CI will be calculated.	(2)
	Docetaxel	290	5.6 months (4.4 – 6.9)								
Progression-free survival	Nivolumab	292	2.3 months (2.2 – 3.3)	NA	NA	NA	HR: 0.92	0.77 – 1.11	P=0.39	The survival rates are based on the Kaplan–Meier estimator. Two-sided 95% CIs for median PFS will be computed by Brookmeyer and Crowley method. The HR and the corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazard model using	(2)
	Docetaxel	290	4.2 months (3.5 – 4.9)								



Results of CheckMate057 (NCT01673867)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	
Overall survival	Nivolumab	292	12.2 months (9.8 – 15.1)	NA	NA	NA	HR: 0.70	0.58 – 0.83	NA	The survival rates are based on the Kaplan–Meier estimator. Two-sided 95% CIs for median OS will be computed by Brookmeyer and Crowley method. The HR and the corresponding two-sided 95% CI will be estimated in a stratified Cox proportional hazard model using randomized arm as a single covariate
	Docetaxel	290	9.5 months (8.1 – 10.7)							



Appendix C. Comparative analysis of efficacy

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 67 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effectNA			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	P value	Difference	CI	P value		
Naïve comparison Objective response rate	DESTINY-Lung02, T-DXd 5.4 mg/kg: 50.0% CheckMate 057, docetaxel: 12.4%	37.6%	NA	NA	NA	NA	NA	Naïve comparison	No
Naïve comparison Duration of response	DESTINY-Lung02, T-DXd 5.4 mg/kg: 12.6 months CheckMate 057, docetaxel: 5.6 months	7.0 months	NA	NA	NA	NA	NA	Naïve comparison	No
Progression-free survival (PFS) - unadjusted	DESTINY-Lung02, T-DXd 5.4 mg/kg: 10.0 months CheckMate 057, docetaxel: 4.6 months	5.4 months	NA	NA	HR: 0.32	0.23 – 0.42	NA	Unadjusted ITC based on digitized curves	Yes, scenario
Progression-free survival (PFS) – MAIC base case (ESS=29.7)	DESTINY-Lung02, T-DXd 5.4 mg/kg: 13.8 months	9.2 months	NA	NA	HR: 0.29	0.17 – 0.51	NA	Unanchored MAIC	Yes, base case



Outcome	Absolute difference in effect			Relative difference in effectNA			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
	CheckMate 057, docetaxel: 4.6 months							
Overall survival (OS) – Unadjusted	DESTINY-Lung02, T-DXd 5.4 mg/kg: 19.0 months CheckMate 057, docetaxel: 9.5 months	9.5 months	NA	NA	HR: 0.44	0.33 – 0.60	NA	Unadjusted ITC based on digitized curves Yes, scenario
Overall survival (OS) – MAIC base case (ESS=29.7)	DESTINY-Lung02, T-DXd 5.4 mg/kg: not estimable CheckMate 057, docetaxel: 9.5 months	NA	NA	NA	HR: 0.43	0.24 – 0.78	NA	Unanchored MAIC Yes, base case



Appendix D. Extrapolation

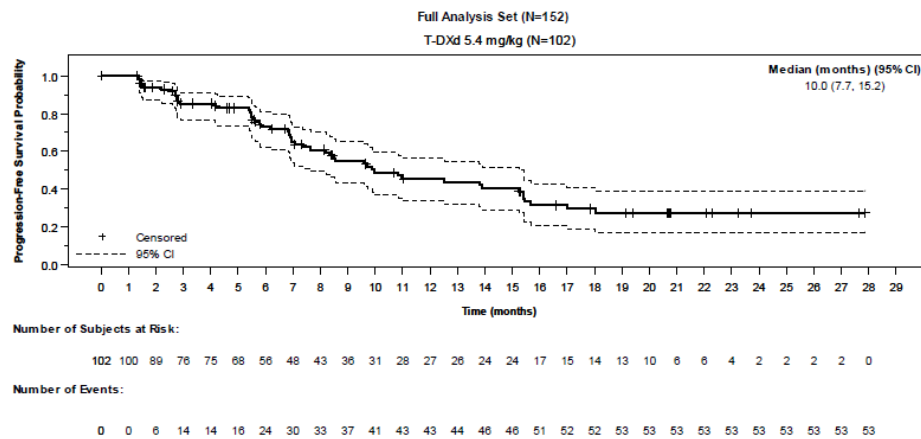
D.1 Extrapolation of progression-free survival

D.1.1 Data input

At the time of the final analysis (DCO 25 Aug 2023) of the DESTINY-Lung02 trial, 53/102 (52.0%) patients had events, and 49/102 (48.0%) patients were censored in the T-DXd 5.4 mg/kg arm. Follow-up extended to 27.9 months, at which point the KM estimate of PFS was 27.2%. The median PFS based on BICR in the T-DXd 5.4 mg/kg arm was 10.0 months (95% CI: 7.7, 15.2).

The KM curve of PFS for T-DXd from DESTINY-Lung02 (5.4kg/mg) is shown in Figure 25.

Figure 25. KM Curve for PFS in DESTINY-LUNG02 T-DXd 5.4 mg/kg arm (DCO 25 Aug 2023)



D.1.2 Model

The data were analysed using the same approach. Seven parametric survival functions were fitted, including exponential, Weibull, Gompertz, lognormal, loglogistic, gamma and generalized gamma.

D.1.3 Proportional hazards

N/A, single arm extrapolation.

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

Model fit statistics for each of the models are shown in Table 70. The lognormal model was the model of best fit according to AIC and BIC.



Table 68. Measurement of AIC and BIC of the Different Distributions Used to Model PFS (DCO 25 Aug 2023)

Distribution	AIC	BIC
Exponential	408.03	410.65
Weibull	406.08	411.33
Gompertz	409.77	415.02
Log-logistic	400.80	406.05
Log-normal	399.41	404.66
Gamma	404.44	409.69
Generalized Gamma	400.93	408.81

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; PFS, progression-free survival.

D.1.5 Evaluation of visual fit

The PFS estimates of T-DXd from each of the available distributions over 5 years are shown in Figure 26. Landmark survival predictions and the observed KM estimates are shown in Table 69. The lognormal model modestly underestimated PFS at 2 years compared with the observed data. All the models underestimated PFS at 2 years, with the generalized gamma predicting the closest value. At 5 and 10 years, the lognormal predicts the lowest survival with a declining longer-term hazard, amongst the group of more optimistic models (lognormal, loglogistic, generalized gamma).

Figure 26. 5-year extrapolation and KM of PFS for T-DXd (DCO 25 Aug 2023)

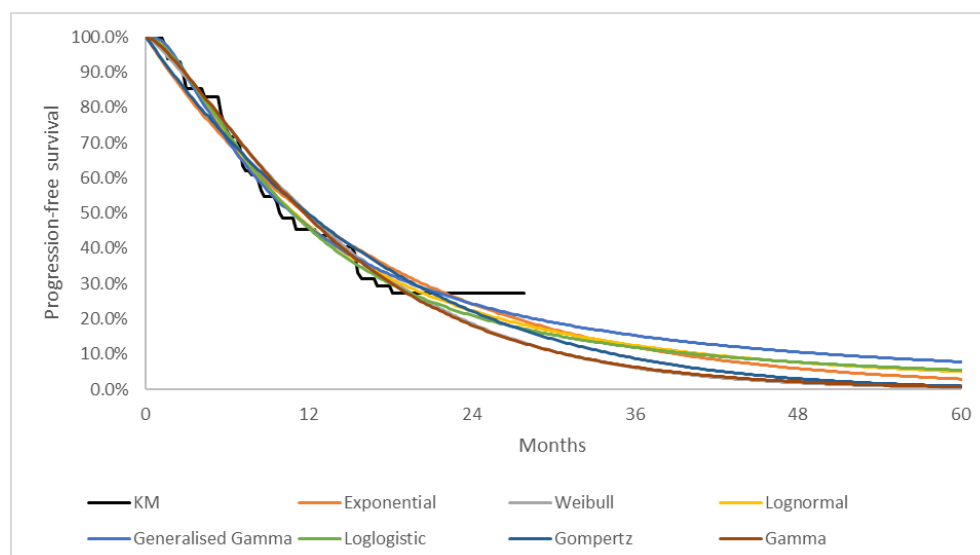


Table 69. Extrapolation and KM Estimates of PFS for T-DXd (DCO 25 Aug 2023)

Curve	1 year	2 years	3 years	5 years	10 years
T-DXd PFS KM	45.34%	27.22%	-	-	-



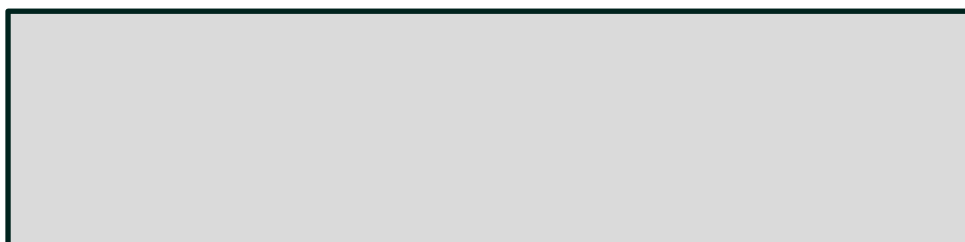
Exponential	49.39%	24.39%	11.89%	2.90%	0.08%
Weibull	49.68%	18.79%	6.05%	0.49%	0.00%
Log-normal	46.57%	22.46%	12.40%	4.98%	1.02%
Generalized gamma	46.17%	24.43%	15.23%	7.78%	2.71%
Log-logistic	45.88%	21.04%	11.81%	5.42%	1.77%
Gompertz	49.87%	22.37%	8.71%	0.88%	0.00%
Gamma	48.89%	18.36%	6.27%	0.69%	0.00%

Abbreviations: DCO, data cut-off; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan.

D.1.6 Evaluation of hazard functions

The modelled hazard curve based on lognormal function is compared with a smoothed non-parametric curve in Figure 27. The inverted U-shape shown in the smoothed empirical hazard curve was captured by the fitted lognormal function, despite its slightly slower decline in the hazard over time. Please refer to Appendix K for smoothed hazard curves for all extrapolations.

Figure 27. Comparison of the hazard for OS estimated using the lognormal distribution with the smoothed hazard curve from DESTINY-Lung02



D.1.7 Validation and discussion of extrapolated curves

Based on goodness-of-fit statistics and visual fit, for the base case the **log-normal** distribution was chosen. It provides a good fit to the data (best AIC/BIC) and a reasonable tail.

Alternatives to the choice of this curve will be tested in scenario analyses using the generalized gamma (very optimistic) and gamma (pessimistic) extrapolation models.

D.1.8 Adjustment of background mortality

PFS is capped by OS, and therefore indirectly adjusted to background mortality.

D.1.9 Adjustment for treatment switching/cross-over

N/A.

D.1.10 Waning effect



N/A.

D.1.11 Cure-point

N/A.

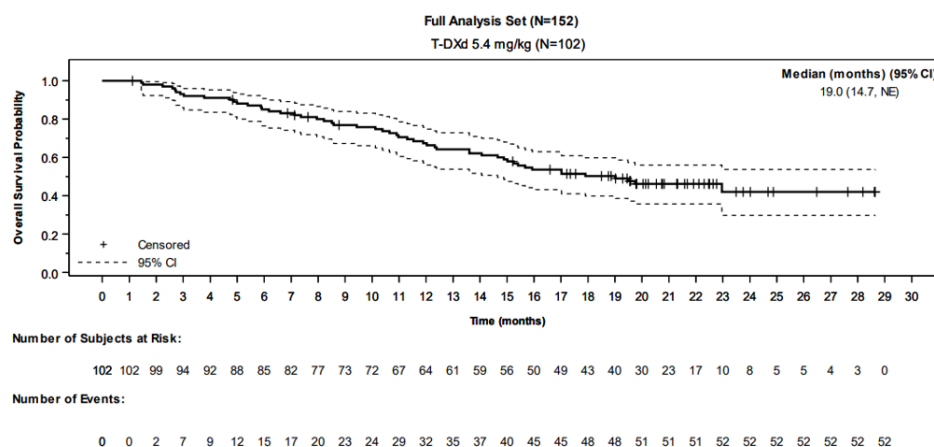
D.2 Extrapolation of overall survival (OS)

D.2.1 Data input

At the time of the final analysis (DCO 25 Aug 2023) of the DESTINY-Lung02 trial, 52/102 (51.0%) patients died, and 50/102 (49.0%) patients were censored in the T-DXd 5.4 mg/kg arm. Follow-up extended to 28.7 months, at which point the KM estimate of survival was 42.0%. The median OS estimate in the T-DXd 5.4 mg/kg arm was 19.0 months (95% CI: 14.7, NE).

The KM curve of OS for T-DXd from DESTINY-Lung02 (5.4kg/mg) is shown in Figure 28.

Figure 28. KM Curve for OS in DESTINY-LUNG02 T-DXd 5.4 mg/kg arm (DCO 25 Aug 2023)



Abbreviations: CI, confidence interval; DESTINY-LUNG02, DESTINY-Lung02; KM, Kaplan-Meier; OS: overall survival; T-DXd, trastuzumab deruxtecan

D.2.2 Model

The data were analysed using the same approach. Seven parametric survival functions were fitted, including exponential, Weibull, Gompertz, lognormal, loglogistic, gamma and generalized gamma.

D.2.3 Proportional hazards

N/A, single arm extrapolation.

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



Model fit statistics for each of the models are shown in Table 70. The lognormal model was the model of best fit according to AIC and BIC.

Table 70. Measurement of AIC and BIC of the Different Distributions Used to Model OS (DCO 25 Aug 2023)

Distribution	AIC	BIC
Exponential	456.43	459.05
Weibull	454.23	459.48
Gompertz	457.27	462.52
Log-logistic	452.08	457.33
Log-normal	451.03	456.28
Gamma	453.36	458.61
Generalized Gamma	452.99	460.86

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; PFS, progression-free survival.

D.2.5 Evaluation of visual fit

The OS estimates of T-DXd from each of the available distributions over 5 years are shown in Figure 29. Landmark survival predictions and the observed KM estimates are provided in Table 71. The lognormal model provided the closest prediction to the observed data at 2 years. At 5 and 10 years, the lognormal predicts the lowest survival with a declining longer-term hazard, amongst the group of more optimistic models (lognormal, loglogistic, generalized gamma).

Figure 29. 5-year extrapolation and KM of OS for T-DXd (DCO 25 Aug 2023)

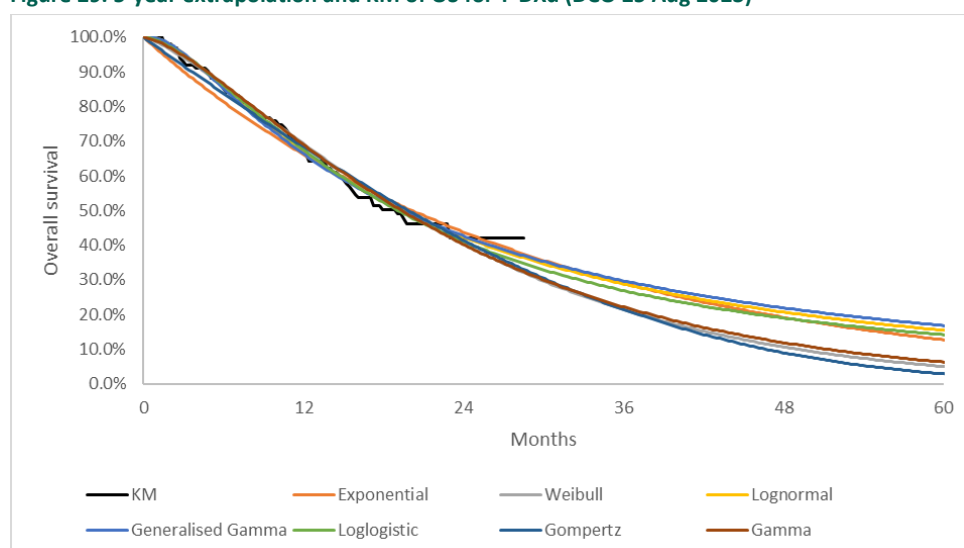




Table 71. Extrapolation and KM Estimates of OS for T-DXd (DCO 25 Aug 2023)

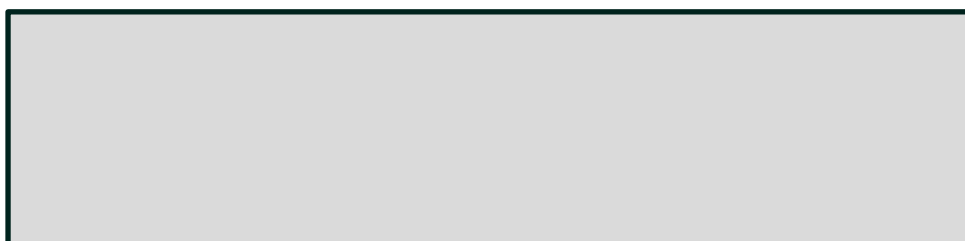
Curve	1 year	2 years	3 years	5 years	10 years
T-DXd OS KM	67.42%	42.02%	-	-	-
Exponential	66.27%	43.91%	28.87%	12.68%	1.61%
Weibull	69.36%	40.50%	21.28%	4.96%	0.06%
Log-normal	66.78%	42.45%	28.73%	15.41%	5.01%
Generalized gamma	66.47%	42.79%	29.64%	16.77%	6.24%
Log-logistic	67.67%	41.22%	26.81%	14.11%	5.22%
Gompertz	68.47%	41.58%	21.25%	2.83%	0.00%
Gamma	69.13%	40.40%	22.07%	6.22%	0.21%

Abbreviations: DCO, data cut-off; OS, overall survival; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan.

D.2.6 Evaluation of hazard functions

The modelled hazard curve based on lognormal function is compared with a smoothed non-parametric curve in Figure 30. The fitted curve for the lognormal function is a reasonable match to the observed data. Please refer to Appendix K for smoothed hazard curves for all extrapolations.

Figure 30. Comparison of the hazard for OS estimated using a lognormal distribution with the smoothed hazard curve from DESTINY-Lung02



D.2.7 Validation and discussion of extrapolated curves

Based on goodness-of-fit statistics and visual fit, for the base case the log-normal distribution was chosen. It provides a good fit to the data (best AIC/BIC) and is reflective of the tail of the KM data.

As the log-normal distribution projects a rather optimistic results compared to other standard parametric distributions, the gamma distribution (i.e., more pessimistic estimates) was also explored in a scenario analysis. No further exploratory analyses were conducted with Gompertz distribution (i.e., very pessimistic estimates), as the long-term results obtained with this curve were not aligned with the observed survival in clinical practice and the expected clinical profile of T-DXd.

D.2.8 Adjustment of background mortality



OS has been adjusted to background mortality as per DMC guidance. The hazard of the overall survival has been capped as such that the modelled hazard cannot become lower than the hazard observed in the general population in Denmark.

D.2.9 Adjustment for treatment switching/cross-over

N/A.

D.2.10 Waning effect

N/A.

D.2.11 Cure-point

N/A.

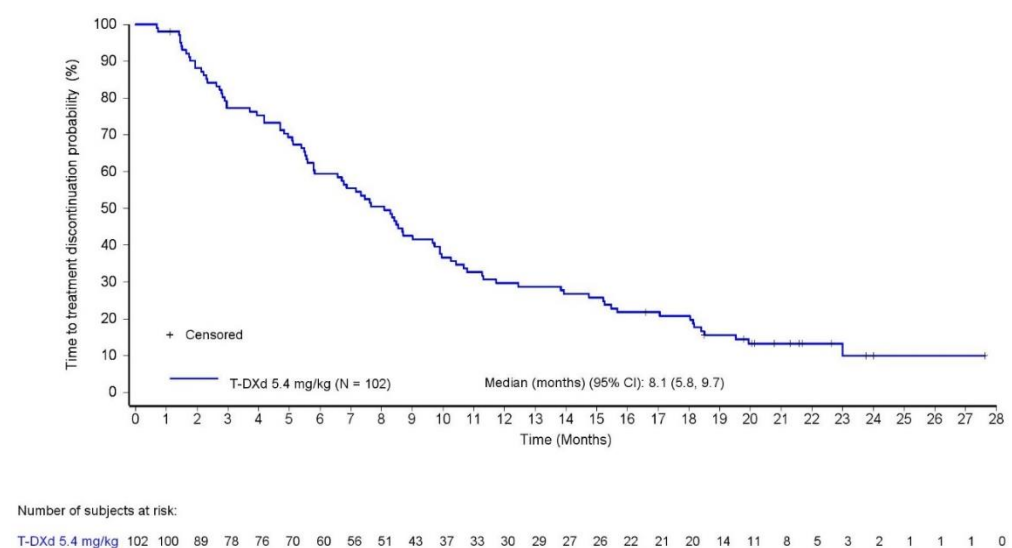
D.3 Extrapolation of time-to-treatment discontinuation (TTD)

D.3.1 Data input

At the time of the final analysis (DCO 25 Aug 2023) of the DESTINY-Lung02 trial, 88/102 (86.3%) patients had events, and 14/102 (13.7%) patients were censored in the T-DXd 5.4 mg/kg arm. Follow-up extended to 27.6 months, at which point the KM estimate of PFS was 9.9%. The median TTD estimate in the T-DXd 5.4 mg/kg arm was 8.1 months (95% CI: 5.8, 9.7).

The KM curve of TTD for T-DXd from DESTINY-Lung02 (5.4kg/mg) is shown in Figure 31.

Figure 31. KM Curve for TTD in DESTINY-LUNG02 T-DXd 5.4 mg/kg arm (DCO 25 Aug 2023)



Abbreviations: CI, confidence interval; DESTINY-LUNG02, DESTINY-Lung02; KM, Kaplan-Meier; OS: overall survival; T-DXd, trastuzumab deruxtecan



D.3.2 Model

The data were analysed using the same approach. Seven parametric survival functions were fitted, including exponential, Weibull, Gompertz, lognormal, loglogistic, gamma and generalized gamma.

D.3.3 Proportional hazards

N/A, single arm extrapolation.

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

Model fit statistics for each of the models are shown in Table 72. The lognormal model was the model of best fit according to AIC and BIC.

Table 72. Measurement of AIC and BIC of the Different Distributions Used to Model TTD (DCO 25 Aug 2023)

Distribution	AIC	BIC
Exponential	600.36	602.99
Weibull	597.47	602.72
Gompertz	601.36	606.61
Log-logistic	593.55	598.80
Log-normal	591.81	597.06
Gamma	595.68	600.93
Generalized Gamma	593.71	601.59

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; DCO, data cut-off; PFS, progression-free survival.

D.3.5 Evaluation of visual fit

The TTD estimates of T-DXd from each of the available distributions over 5 years are shown in Figure 32Figure 29. Landmark survival predictions and the observed KM estimates are shown in Table 73. The lognormal model overestimated TTD at two years compared to the observed data. The closest prediction at two years is provided by the Gompertz function. At 5 and 10 years, the lognormal model predicts the second highest survival across all of the models fitted.



Figure 32. 5-year extrapolation and KM of TTD for T-DXd (DCO 25 Aug 2023)

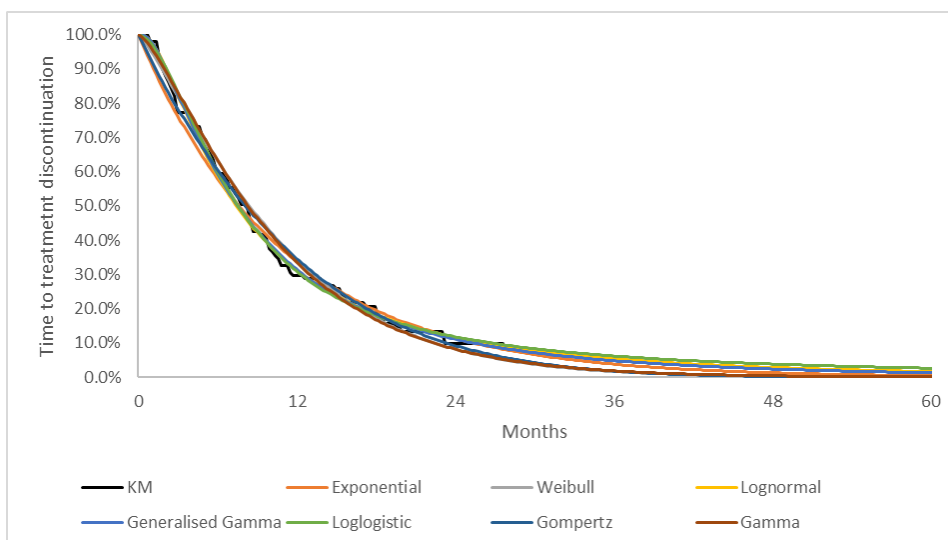


Table 73. Extrapolation and KM Estimates TTD for T-DXd (DCO 25 Aug 2023)

Curve	1 year	2 years	3 years	5 years	10 years
T-DXd TTD KM	29.71%	9.93%	-	-	-
Exponential	33.79%	11.41%	3.78%	0.43%	0.00%
Weibull	34.39%	8.28%	1.62%	0.05%	0.00%
Log-normal	31.42%	11.67%	5.35%	1.65%	0.23%
Generalized gamma	31.58%	11.17%	4.79%	1.29%	0.13%
Log-logistic	31.06%	11.85%	6.15%	2.63%	0.80%
Gompertz	34.75%	9.35%	1.77%	0.02%	0.00%
Gamma	33.70%	8.29%	1.83%	0.09%	0.00%

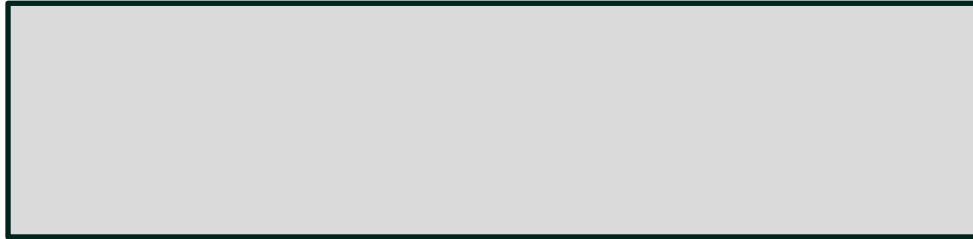
Abbreviations: DCO, data cut-off; OS, overall survival; KM, Kaplan-Meier; T-DXd, trastuzumab deruxtecan.

D.3.6 Evaluation of hazard functions

The modelled hazard curve based on lognormal function is compared with a smoothed non-parametric curve in Figure 33. The smoothed non-parametric curve suggests a rising hazard over time which the lognormal function does not capture. The increasing hazard in the latter portion of the smoothed non-parametric curve may not be a completely reliable predictor of the longer-term discontinuation trend. Please refer to Appendix K for smoothed hazard curves for all extrapolations.



Figure 33. Comparison of the hazard for TTD estimated using a log-normal distribution with the smoothed non-parametric hazard curve



D.3.7 Validation and discussion of extrapolated curves

Based on goodness-of-fit statistics and visual fit, for the base case the **log-normal** distribution was chosen, however with this being slightly conservative, an scenario analyses with gamma were tested as an alternative with a shorter TTD.

D.3.8 Adjustment of background mortality

D.3.9 Adjustment for treatment switching/cross-over

N/A.

D.3.10 Waning effect

N/A.

D.3.11 Cure-point

N/A.



Appendix E. Serious adverse events

Table 74. Serious adverse events observed in DESTINY-Lung02, DCO Aug 2023(51)

Grouped Term / MedDRA Preferred Term	T-DXd 5.4 mg/kg (N=101)	T-DXd 6.4 mg/kg (N=50)	Overall (N=151)
Subjects with Any Serious TEAE	40 (39.6%)	24 (48.0%)	64 (42.4%)
Fatigue [a]	1 (1.0%)	4 (8.0%)	5 (3.3%)
Pleural effusion	4 (4.0%)	1 (2.0%)	5 (3.3%)
Pneumonia	2 (2.0%)	3 (6.0%)	5 (3.3%)
Thrombocytopenia [a]	3 (3.0%)	2 (4.0%)	5 (3.3%)
Interstitial lung disease	2 (2.0%)	2 (4.0%)	4 (2.6%)
Pneumonitis	2 (2.0%)	2 (4.0%)	4 (2.6%)
Neutropenia [a]	1 (1.0%)	2 (4.0%)	3 (2.0%)
Vomiting	2 (2.0%)	1 (2.0%)	3 (2.0%)
Anaemia [a]	0	2 (4.0%)	2 (1.3%)
Dehydration	0	2 (4.0%)	2 (1.3%)
Diarrhoea	1 (1.0%)	1 (2.0%)	2 (1.3%)
Dyspnoea	2 (2.0%)	0	2 (1.3%)
General physical health deterioration	1 (1.0%)	1 (2.0%)	2 (1.3%)
Lung neoplasm malignant	2 (2.0%)	0	2 (1.3%)
Malignant neoplasm progression	2 (2.0%)	0	2 (1.3%)
Myocarditis	2 (2.0%)	0	2 (1.3%)
Nausea	2 (2.0%)	0	2 (1.3%)
Neurological symptom	1 (1.0%)	1 (2.0%)	2 (1.3%)
Pericardial effusion	1 (1.0%)	1 (2.0%)	2 (1.3%)
Pulmonary embolism	2 (2.0%)	0	2 (1.3%)
Respiratory failure	2 (2.0%)	0	2 (1.3%)
Troponin I increased	2 (2.0%)	0	2 (1.3%)
Urinary tract infection	1 (1.0%)	1 (2.0%)	2 (1.3%)
Acute kidney injury	0	1 (2.0%)	1 (0.7%)
Acute myocardial infarction	1 (1.0%)	0	1 (0.7%)



Anxiety	0	1 (2.0%)	1 (0.7%)
COVID-19	1 (1.0%)	0	1 (0.7%)
COVID-19 pneumonia	1 (1.0%)	0	1 (0.7%)
Cancer pain	1 (1.0%)	0	1 (0.7%)
Cerebrovascular accident	1 (1.0%)	0	1 (0.7%)
Cholecystitis	1 (1.0%)	0	1 (0.7%)
Colitis	0	1 (2.0%)	1 (0.7%)
Disorientation	0	1 (2.0%)	1 (0.7%)
Duodenal ulcer	1 (1.0%)	0	1 (0.7%)
Enterocolitis	0	1 (2.0%)	1 (0.7%)
General physical condition abnormal	0	1 (2.0%)	1 (0.7%)
Hydrocephalus	0	1 (2.0%)	1 (0.7%)
Hypothyroidism	1 (1.0%)	0	1 (0.7%)
Ileus	1 (1.0%)	0	1 (0.7%)
Intestinal perforation	1 (1.0%)	0	1 (0.7%)
Intracranial pressure increased	1 (1.0%)	0	1 (0.7%)
Intracranial tumour haemorrhage	1 (1.0%)	0	1 (0.7%)
Large intestinal obstruction	1 (1.0%)	0	1 (0.7%)
Meningitis	0	1 (2.0%)	1 (0.7%)
Metastases to meninges	1 (1.0%)	0	1 (0.7%)
Musculoskeletal pain [a]	1 (1.0%)	0	1 (0.7%)
Odynophagia	0	1 (2.0%)	1 (0.7%)
Optic nerve disorder	1 (1.0%)	0	1 (0.7%)
Pneumococcal sepsis	1 (1.0%)	0	1 (0.7%)
Pneumonia haemophilus	0	1 (2.0%)	1 (0.7%)
Pneumothorax	1 (1.0%)	0	1 (0.7%)
Post procedural infection	0	1 (2.0%)	1 (0.7%)
Pyrexia	1 (1.0%)	0	1 (0.7%)
Spinal compression fracture	1 (1.0%)	0	1 (0.7%)
Subdural haemorrhage	1 (1.0%)	0	1 (0.7%)
Tracheal haemorrhage	1 (1.0%)	0	1 (0.7%)
Ureteric obstruction	1 (1.0%)	0	1 (0.7%)



Note: [a] Grouped terms are abdominal pain (abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, Gastrointestinal pain), anaemia (haemoglobin decreased, red blood cell count decreased, anaemia, Haematocrit decreased), Lymphopenia (Lymphocyte count decreased, Lymphopenia), Neutropenia (Neutrophil count decreased, Neutropenia), Thrombocytopenia (Platelet count decreased, Thrombocytopenia), stomatitis (stomatitis, Aphthous ulcerous ulceration, oral mucosa erosion, oral mucosal blistering, oral mucosal eruption), Leukopenia (white blood cell count decrease, Leukopenia), Upper respiratory tract infection (Influenza, Influenza like illness, Upper respiratory tract infection, nasopharyngitis, pharyngitis, sinusitis, rhinitis, laryngitis), Headache (Migraine, Headache, Sinus headache), Rash (Rash, Rash pustular, Rash maculopapular, Rash papular, Rash macular, Rash pruritic), Fatigue (Fatigue, Asthenia, Malaise, Lethargy), Transaminases increased (Transaminases increased, Aspartate aminotransferase increased, Alanine aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic function abnormal, Liver function test increased, Hypertransaminasaemia), Hypokalaemia (Hypokalaemia, Blood potassium decreased), Musculoskeletal pain (Back pain, Myalgia, pain in extremity, Musculoskeletal pain, muscle spasms, bone pain, neck pain, musculoskeletal chest pain, limb discomfort) Skin hyperpigmentation (Skin hyperpigmentation, skin discolouration, pigmentation disorder), Blood bilirubin increased (Blood bilirubin increased, Hyperbilirubinaemia, Bilirubin conjugated increased, Blood bilirubin unconjugated increased) and Vision blurred (Vision blurred, Visual impairment).



Table 75. Serious adverse events observed >1% of treated subjects in CheckMate057, DCO 16 April 2015

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	134 (46.7)	95 (33.1)	23 (8.0)	111 (41.4)	91 (34.0)	14 (5.2)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	41 (14.3)	28 (9.8)	4 (1.4)	22 (8.2)	18 (6.7)	2 (0.7)
PULMONARY EMBOLISM	11 (3.8)	8 (2.8)	2 (0.7)	3 (1.1)	3 (1.1)	0
DYSNOEA	9 (3.1)	5 (1.7)	1 (0.3)	5 (1.9)	4 (1.5)	0
PLEURAL EFFUSION	8 (2.8)	4 (1.4)	0	3 (1.1)	2 (0.7)	0
RESPIRATORY FAILURE	6 (2.1)	5 (1.7)	1 (0.3)	4 (1.5)	2 (0.7)	2 (0.7)
PNEUMONITIS	4 (1.4)	3 (1.0)	0	0	0	0
HAEMOPTYSIS	2 (0.7)	0	0	3 (1.1)	2 (0.7)	0
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	38 (13.2)	20 (7.0)	13 (4.5)	11 (4.1)	4 (1.5)	7 (2.6)
MALIGNANT NEOPLASM PROGRESSION	23 (8.0)	12 (4.2)	11 (3.8)	7 (2.6)	1 (0.4)	6 (2.2)
METASTASES TO CENTRAL NERVOUS SYSTEM	3 (1.0)	1 (0.3)	0	1 (0.4)	1 (0.4)	0
INFECTIONS AND INFESTATIONS	24 (8.4)	19 (6.6)	1 (0.3)	28 (10.4)	24 (9.0)	2 (0.7)
PNEUMONIA	12 (4.2)	9 (3.1)	1 (0.3)	13 (4.9)	11 (4.1)	1 (0.4)
BRONCHITIS	3 (1.0)	2 (0.7)	0	3 (1.1)	2 (0.7)	1 (0.4)
RESPIRATORY TRACT INFECTION	1 (0.3)	1 (0.3)	0	3 (1.1)	3 (1.1)	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	23 (8.0)	14 (4.9)	3 (1.0)	16 (6.0)	9 (3.4)	3 (1.1)
PAIN	5 (1.7)	4 (1.4)	0	3 (1.1)	3 (1.1)	0
GENERAL PHYSICAL HEALTH DETERIORATION	4 (1.4)	3 (1.0)	1 (0.3)	3 (1.1)	3 (1.1)	0
FATIGUE	4 (1.4)	1 (0.3)	0	4 (1.5)	0	0
ASTHENIA	3 (1.0)	1 (0.3)	0	3 (1.1)	2 (0.7)	0
GASTROINTESTINAL DISORDERS	18 (6.3)	13 (4.5)	0	11 (4.1)	8 (3.0)	0
NAUSEA	4 (1.4)	3 (1.0)	0	2 (0.7)	1 (0.4)	0
DIARRHOEA	3 (1.0)	2 (0.7)	0	1 (0.4)	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	11 (3.8)	11 (3.8)	0	5 (1.9)	4 (1.5)	0
BACK PAIN	2 (0.7)	2 (0.7)	0	3 (1.1)	2 (0.7)	0
NERVOUS SYSTEM DISORDERS	10 (3.5)	8 (2.8)	0	2 (0.7)	2 (0.7)	0
HEADACHE	4 (1.4)	2 (0.7)	0	0	0	0
CARDIAC DISORDERS	9 (3.1)	8 (2.8)	1 (0.3)	6 (2.2)	5 (1.9)	0
PERICARDIAL EFFUSION	2 (0.7)	2 (0.7)	0	3 (1.1)	3 (1.1)	0
PSYCHIATRIC DISORDERS	4 (1.4)	2 (0.7)	0	5 (1.9)	5 (1.9)	0
MENTAL STATUS CHANGES	0	0	0	3 (1.1)	3 (1.1)	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (0.7)	1 (0.3)	0	37 (13.8)	35 (13.1)	1 (0.4)
ANAEMIA	2 (0.7)	1 (0.3)	0	4 (1.5)	2 (0.7)	1 (0.4)
FEBRILE NEUTROPENIA	0	0	0	24 (9.0)	24 (9.0)	0
NEUTROPENIA	0	0	0	8 (3.0)	8 (3.0)	0
METABOLISM AND NUTRITION DISORDERS	2 (0.7)	2 (0.7)	0	5 (1.9)	4 (1.5)	0
DEHYDRATION	0	0	0	4 (1.5)	4 (1.5)	0

MedDRA Version: 17.1

CTC Version 4.0

Includes events reported between first dose and 30 days after last dose of study therapy.

Source: Refer to Table 8.3.1-1 of CA209057 Final CSR

Source: Procedure No. EMEA/H/C/003985/II/0002, Table 44 (p65) (52)



Appendix F. Health-related quality of life

N/A, no domain specific data presented.



Appendix G. Probabilistic sensitivity analyses

Table 76. Overview of parameters in the PSA

Category	Sub-category	Description	Base case	Lower bound	Upper bound	Distribution
Population		Population starting age	59.8	NA	NA	Normal
		Proportion of male	0.36	NA	NA	Beta
		Weight	72.0	NA	NA	Normal
		Height	1.64	NA	NA	Normal
		Creatinine clearance	83.3	NA	NA	Normal
Survival curves DL-02	T-DXd PFS	PFS distribution T-DXd - Parameter 1	2.39 2495	NA	NA	Cholesky decomposition
		PFS distribution T-DXd - Parameter 2	0.03 3162	NA	NA	Cholesky decomposition
Survival curves DL-02	T-DXd OS DL-02	OS distribution T-DXd - Parameter 1	2.96 3145	NA	NA	Cholesky decomposition
		OS distribution T-DXd - Parameter 2	0.10 467	NA	NA	Cholesky decomposition
Survival curves DL-02	T-DXd TTD DL-02	TTD distribution T-DXd - Parameter 1	2.00 7485	NA	NA	Cholesky decomposition
		TTD distribution T-DXd - Parameter 2	- 0.02 085	NA	NA	Cholesky decomposition
Relative efficacy	PFS	HR PFS: Mono ChT	0.29 43	NA	NA	Lognormal
Relative efficacy	OS	HR OS: Mono ChT	0.42 51	NA	NA	Lognormal
Safety	T-DXd	T-DXd: Anaemia	0.11 8812	NA	NA	Beta
		T-DXd: Febrile neutropenia	0	NA	NA	Beta



		T-DXd: ILD	0.01 9802	NA	NA	Beta
		T-DXd: Lymphocyte count decreased	0	NA	NA	Beta
		T-DXd: Nausea/vom iting	0	NA	NA	Beta
		T-DXd: Neutrophil count decreased	0.13 8614	NA	NA	Beta
		T-DXd: Pneumonia/ pneumonitis	0	NA	NA	Beta
		T-DXd: Fatigue	0.07 9208	NA	NA	Beta
		T-DXd: Leukopenia	0.05 9406	NA	NA	Beta
		T-DXd: Thrombocyt openia	0.05 9406	NA	NA	Beta
		T-DXd: Hypokalaemi a	0.07 9208	NA	NA	Beta
Safety	Mono ChT	Mono ChT: Anaemia	0.04 8507	NA	NA	Beta
		Mono ChT: Febrile neutropenia	0.10 8209	NA	NA	Beta
		Mono ChT: ILD	0	NA	NA	Beta
		Mono ChT: Lymphocyte count decreased	0	NA	NA	Beta
		Mono ChT: Nausea/vom iting	0	NA	NA	Beta
		Mono ChT: Neutrophil count decreased	0.05 9701	NA	NA	Beta
		Mono ChT: Pneumonia/ pneumonitis	0.05 597	NA	NA	Beta
		Mono ChT: Fatigue	0.06 7164	NA	NA	Beta



		Mono ChT: Leukopenia	0.085821	NA	NA	Beta
		Mono ChT: Thrombocytopenia	0	NA	NA	Beta
		Mono ChT: Hypokalaemia	0	NA	NA	Beta
Unit costs	Drug administration	IV	1330	NA	NA	Gamma
		Peroral	0	NA	NA	Gamma
	Disease management costs	Chest X-ray unit cost	0	NA	NA	Gamma
		CT scan (chest) unit cost	2701	NA	NA	Gamma
		CT scan (other) unit cost	2701	NA	NA	Gamma
		ECG unit cost	0	NA	NA	Gamma
		Outpatient visit unit cost	1330	NA	NA	Gamma
		Community nurse visit unit cost	0	NA	NA	Gamma
		Clinical nurse specialist unit cost	0	NA	NA	Gamma
		GP surgery unit cost	0	NA	NA	Gamma
		GP home visit unit cost	0	NA	NA	Gamma
		Therapist visit unit cost	0	NA	NA	Gamma
	Adverse events	Anaemia management cost	2208	NA	NA	Gamma
		Febrile neutropenia	2208	NA	NA	Gamma



		management cost				
		ILD management cost	48957	NA	NA	Gamma
		Lymphocyte count decreased management cost	0	NA	NA	Gamma
		Nausea/vomiting management cost	0	NA	NA	Gamma
		Neutrophil count decreased management cost	0	NA	NA	Gamma
		Pneumonia/pneumonitis management cost	44614	NA	NA	Gamma
		Fatigue management cost	0	NA	NA	Gamma
		Leukopenia management cost	2208	NA	NA	Gamma
		Thrombocytopenia management cost	2208	NA	NA	Gamma
		Hypokalaemia management cost	0	NA	NA	Gamma
	Terminal care	Terminal care cost	0	NA	NA	Gamma
Healthcare resource use	PFS	Chest X-ray utilization in PFS	0	NA	NA	Gamma
		CT scan (chest) utilization in PFS	4	NA	NA	Gamma
		CT scan (other) utilization in PFS	0	NA	NA	Gamma



		ECG utilization in PFS	0	NA	NA	Gamma
		Outpatient visit utilization in PFS	17.3 3333	NA	NA	Gamma
		Community nurse visit utilization in PFS	0	NA	NA	Gamma
		Clinical nurse specialist utilization in PFS	0	NA	NA	Gamma
		GP surgery utilization in PFS	0	NA	NA	Gamma
		GP home visit utilization in PFS	0	NA	NA	Gamma
		Therapist visit utilization in PFS	0	NA	NA	Gamma
Healthcare resource use	PPS	Chest X-ray utilization in PPS	0	NA	NA	Gamma
		CT scan (chest) utilization in PPS	4	NA	NA	Gamma
		CT scan (other) utilization in PPS	0	NA	NA	Gamma
		ECG utilization in PPS	0	NA	NA	Gamma
		Outpatient visit utilization in PPS	17.3 3333	NA	NA	Gamma
		Community nurse visit utilization in PPS	0	NA	NA	Gamma
		Clinical nurse	0	NA	NA	Gamma



	specialist utilization in PPS				
	GP surgery utilization in PPS	0	NA	NA	Gamma
	GP home visit utilization in PPS	0	NA	NA	Gamma
	Therapist visit utilization in PPS	0	NA	NA	Gamma
Subsequent therapy	ToT Subs Tx Immunotherapy: T-DXd	13.0 4464	NA	NA	Normal
	ToT Subs Tx HER2: T-DXd	15.8 571	NA	NA	Normal
	ToT Subs Tx Immunotherapy: Mono ChT	13.0 4464	NA	NA	Normal
	ToT Subs Tx HER2: Mono ChT	0	NA	NA	Normal



Appendix H. Literature searches for the clinical assessment

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

The DESTINY-Lung02 trial was conducted in adult patients with metastatic NSCLC who have a *HER2* mutation. Currently, there are no approved therapies for the treatment of NSCLC with *HER2* mutations other than Enhertu. This means that the treatment paradigm for patients with *HER2*-mutated NSCLC is reflective of the management of patients without, or with undetermined or mixed, actionable oncogenic drivers, hence why a search for a literature search has been conducted for a wider patient population.

A wider global SLR has been conducted and has been adapted to be suitable for this DMC application for Enhertu in Denmark. As docetaxel has been identified as the relevant comparator, the adaption of the SLR involved exclusion of irrelevant comparators.

The study types of interest included randomised, non-randomised and single-arm clinical trials. Systematic reviews of clinical trials were included for cross-referencing and identifying relevant studies. Observational studies, reviews, letters and editorials were excluded.

Search terms were developed, and the following databases were searched:

- **EMBASE** (via www.embase.com)
- **MEDLINE** (via <https://pubmed.ncbi.nlm.nih.gov/>)
- **MEDLINE In-Process** (<https://pubmed.ncbi.nlm.nih.gov/>)
- **The Cochrane Library** (via <https://cochranelibrary.com/>, including the Cochrane Central Register of Controlled Trials [CENTRAL] database)
- **Database of Abstracts of Reviews of Effects (DARE)** (via <https://www.crd.york.ac.uk/CRDWeb/>)

Table 77 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	Original search: inception until 1 September 2020 Search update: 1 September 2020 to 16 May 2024	Original search: 1 September 2020 1 st full Search update: 16 May 2024 <i>Hand search for newer publication</i>



Database	Platform/source	Relevant period for the search	Date of search completion
Medline and MEDLINE In Process	via PubMed.gov	Original search: inception until 1 September 2020 Search update: 1 September 2020 to 16 May 2024	<i>on identified studies from the global SLR:</i> 11 Nov 2025
The Cochrane library and CINAHL	via cochranelibrary.com	Original search: inception until 1 September 2020 Search update: 1 September 2020 to 16 May 2024	
DARE	via https://www.crd.york.ac.uk/CRDWeb/	Original search: inception until 1 September 2020 Search update: 1 September 2020 to 16 May 2024	

Table 78 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Table 79 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

H.1.1 Search strategies

Date of the searches (Table 80, Table 81, Table 82): 1 September 2020

Table 80: Search terms of EMBASE and MEDLINE (via www.embase.com)

Search terms	No.	Query	Results
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Population (Combination of indexed and free-text search terms for NSCLC, including proximity operators to combine non-small cell type with lung and tumour search terms)	#1	'non small cell lung cancer'/syn OR 'non small cell lung cancer'/exp OR 'non small cell lung cancer' OR nslc OR ((('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR 'pancoast') AND ((lung NEAR/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR *squamous OR adenocarcinoma*)):ab,ti))	174,293
	#2	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND ('lung'/exp OR 'lung') AND ('neoplasm'/exp OR 'neoplasm' OR 'cancer'/exp OR 'cancer' OR 'carcinoma'/exp OR 'carcinoma' OR 'malignancy'/exp OR 'malignancy' OR 'tumour'/exp OR 'tumour')	139,391
	#3	#1 OR #2	174,892
Intervention and comparators (Exploding indexed search terms for intervention and comparators, including generic and brand names)	#4	'cisplatin'/exp OR cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis-dichlorodiammineplatinum' OR 'platino' OR 'platidiam' OR 'platino' OR biocisplatinum	193,170
	#5	'carboplatin'/exp OR carboplatin OR (1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplattine	71,928
	#6	durvalumab OR imfinzi OR 'medi 4736' OR medi4736	3953
	#7	'nivolumab'/exp OR 'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'nivolumab' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	18,913
	#8	'pembrolizumab'/exp OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475' OR 'sch900475'	16,548
	#9	'ipilimumab'/exp OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	14,797
	#10	'atezolizumab'/exp OR 'atezolizumab' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq' OR 'tecntriq'	5873
	#11	'paclitaxel'/exp OR paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR	117,384



'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622
OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301
OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR
hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR
mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR
'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR
'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100'
OR oaspac100 OR oncogel OR onxol OR pacitaxel OR
'paclitaxel nab' OR pacxel OR padexol OR parexel OR
paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb
05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR
yewtaxan

#12	'pemetrexed'/exp OR pemetrexed OR alimta OR armisarte OR ciambra OR elimta OR 'ly 231514' OR ly231514 OR 'pemetrexed disodium' OR 'pemetrexed disodium hemipentahydrate' OR 'pemetrexed ditromethamine' OR 'pemetrexed sodium' OR 'pemetrexed tromethamine' OR pemfexy OR pemta	14,780
#13	'tyrosine kinase inhibitor'/exp OR 'protein tyrosine kinase inhibitor'/exp OR 'protein kinase inhibitor'/exp OR 'epidermal growth factor receptor kinase inhibitor'/exp OR 'protein serine threonine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor'/syn OR 'tyrosine kinase inhibitor' OR tki:ab,ti OR tkis:ab,ti OR 'afatinib'/syn OR 'afatinib'/exp OR afatinib OR gilotrif OR 'bibw 2992 ma2' OR 'erlotinib'/syn OR 'erlotinib'/exp OR erlotinib OR tarceva OR 'cp-358774' OR 'osi774' OR 'gefitinib'/syn OR 'gefitinib'/exp OR gefitinib OR iressa OR 'zd 1839' OR 'imatinib'/syn OR 'imatinib'/exp OR 'imatinib' OR gleeevec OR 'sti-571' OR 'sti 571' OR 'dacomitinib'/syn OR 'dacomitinib'/exp OR 'dacomitinib' OR 'pf-00299804' OR 'pf 00299804' OR 'dasatinib'/syn OR 'dasatinib'/exp OR 'dasatinib' OR sprycel OR 'bms-354825' OR 'bms 354825' OR 'naquotinib'/syn OR 'naquotinib'/exp OR 'naquotinib' OR 'asp8273' OR 'asp-8273' OR 'osimertinib'/syn OR 'osimertinib'/exp OR osimertinib OR mereletinib OR tagrisso OR 'azd9291' OR 'anaplastic lymphoma kinase inhibitor'/exp OR 'alk inhibitor' OR 'mitogen activated protein kinase kinase inhibitor'/exp OR 'map inhibitor' OR 'mek inhibitor' OR 'b raf kinase inhibitor'/exp OR 'braf kinase inhibitor' OR 'antineoplastic monoclonal antibody'/exp OR nintedanib/exp OR vargatef	683,672
#14	'vinorelbine':ti,ab,tn OR 'eunades':ti,ab,tn OR 'exelbine':ti,ab,tn OR 'navelbin':ti,ab,tn OR 'navelbine':ti,ab,tn OR 'navirel':ti,ab,tn OR 'vinbine':ti,ab,tn OR 'vinelbine':ti,ab,tn OR 'vinorelbine ditartrate':ti,ab,tn OR 'vinorelbine tartrate':ti,ab,tn	6692
#15	'gemcitabine':ti,ab,tn OR 'gemcitabine hydrochloride':ti,ab,tn OR 'gemcite':ti,ab,tn OR 'gemzar':ti,ab,tn	29,524



#16	'everolimus':ti,ab,tn OR 'affinitor':ti,ab,tn OR 'afinitor':ti,ab,tn OR 'afinitor disperz':ti,ab,tn OR 'certican':ti,ab,tn OR 'votubia':ti,ab,tn OR 'zortress':ti,ab,tn	15,660
#17	'docetaxel'/exp OR 'dxl' OR 'dtx'	60,086
#18	'doxorubicin' OR 'adriamycin' OR 'caelyx' OR 'myocet' OR 'dxr' OR 'doxorubicin hydrochloride'	199,508
#19	'alectinib'/exp OR 'alecensa'	1751
#20	'bevacizumab'/exp OR 'avastin' OR 'anti-vegf monoclonal antibody' OR 'rhumb-vegf'	58,614
#21	'carmatinib' OR 'tabrecta' OR 'inc280'	68
#22	'certinib' OR 'ldk378' OR 'zykadia'	237
#23	'crizotinib'/exp OR 'xalkori' OR 'pf-02341066' OR 'crizonix'	8147
#24	'dabrafenib'/exp OR 'tafinlar' OR 'gsk-2118436'	4372
#25	'entrectinib'/exp OR 'rxdx-101' OR 'rozlytrek'	485
#26	'lorlatinib'/exp OR 'lorviqua' OR 'pf-6463922'	617
#27	'mechlorethamine hydrochloride'/exp OR 'chlormethine' OR 'mustargen' OR 'mustine' OR 'embikhin'	17,141
#28	'trametinib'/exp OR 'mekinist' OR 'gsk1120212'	5204
#29	'methotrexate'/exp OR 'mtx' OR 'amethopterin' OR 'trexall' OR 'rheumatrex' OR 'otrexup'	183,768
#30	'necitumumab'/exp OR 'portrazza'	441
#31	'ramucirumab'/exp OR cyramza OR 'ly3009806' OR 'imc- 1121b'	2840
#32	'selpercatinib'/exp OR 'retevmo' OR 'loxo-292'	94
#33	'ceritinib'/exp OR 'ceritinib' OR 'zykadia' OR 'ldk378'	1922
#34	'brigatinib'/exp OR brigatinib OR alunbrig OR ap26113	862
#35	'capmatinib'/exp OR capmatinib OR tabrecta OR inc280	352
#36	'trastuzumab emtansine'/exp OR 'trastuzumab emtansine' OR 'trastuzumab' OR 'kadcyla' OR 'trastuzumab-dm1' OR 'ado-trastuzumab emtansine'	41,084



	#37	'poziotinib'/exp OR poziotinib OR 'nov120101' OR 'hm781-36b'	152
	#38	'pyrotinib'/exp OR pyrotinib	77
	#39	'tak-788' OR 'ap32788'	29
	#40	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39	1,216,959
Adapted Cochrane Highly Sensitive Search Strategy for identifying randomised trials in EMBASE	#41	'randomized controlled trial'/exp	617,622
	#42	'controlled clinical trial'/exp	789,050
	#43	random*:ti,ab	1,561,411
	#44	randomization/exp	87,573
	#45	'intermethod comparison'/exp	264,607
	#46	placebo:ti,ab	309,776
	#47	compare:ti OR compared:ti OR comparison:ti	537,425
	#48	(evaluated:ab OR evaluate:ab OR evaluating:ab OR assessed:ab OR assess:ab) AND (compare:ab OR compared:ab OR comparing:ab OR comparison:ab)	2,146,965
	#49	(open NEXT/1 label):ti,ab	80,424
	#50	(double:ti,ab OR single:ti,ab OR doubly:ti,ab OR singly:ti,ab) NEXT/1 (blind:ti,ab OR blinded:ti,ab OR blindly:ti,ab)	236,142
	#51	'double blind procedure'/exp	175,387
	#52	parallel AND group*:ti,ab	77,258
	#53	(crossover:ti,ab OR (cross:ti,ab AND over:ti,ab))	211,259
	#54	((assign* OR match OR matched OR allocation) NEXT/5 (alternate OR group*1 OR intervention*1 OR patient*1 OR subject*1 OR participant*1)):ti,ab	207
	#55	assigned:ti,ab OR allocated:ti,ab	393,530
	#56	(controlled NEXT/7 (study OR design OR trial)):ti,ab	337,093
	#57	volunteer:ti,ab OR volunteers:ti,ab	249,918



#58	'human experiment'/exp	511,457
#59	trial:ti	312,207
#60	'phase 2 clinical trial'/exp	81,983
#61	'phase 3 clinical trial'/exp	47,872
#62	'phase 4 clinical trial'/exp	3964
#63	#41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62	5,129,332
#64	(random* NEXT/1 sampl* NEXT/7 ('cross section*' OR questionnaire*1 OR survey* OR database*1)):ti,ab	1658
#65	'comparative study'/exp OR 'controlled study'/exp OR 'randomi?ed controlled:ti,ab or randomly assigned:ti,ab'	8,712,000
#66	#64 NOT #65	1219
#67	'cross-sectional study'/exp	361,977
#68	'randomized controlled trial'/exp OR 'controlled clinical trial'/exp OR 'controlled study'/exp OR 'randomi?ed controlled:ti,ab' OR 'control group*1:ti,ab'	7,797,350
#69	#67 NOT #68	241,870
#70	(case NEXT/1 control) AND random*	25,450
#71	randomi?ed:ti,ab AND controlled:ti,ab	419,730
#72	#70 NOT #71	21,740
#73	systematic:ti AND review:ti NOT (trial:ti OR study:ti)	156,802
#74	review:ab AND review:it NOT trial:ti	808,562
#75	'we searched':ab AND (review:ti OR review:pt)	17,488
#76	'update review':ab	109
#77	(databases NEXT/4 searched):ab	25,779
#78	rat:ti OR rats:ti OR mouse:ti OR mice:ti OR swine:ti OR porcine:ti OR murine:ti OR sheep:ti OR lambs:ti OR pigs:ti OR piglets:ti OR rabbit:ti OR rabbits:ti OR cat:ti OR cats:ti OR dog:ti OR dogs:ti OR cattle:ti OR bovine:ti OR monkey:ti OR monkeys:ti OR trout:ti OR marmoset*1:ti	2,363,034



	#79	'animal experiment'/exp	2,590,032
	#80	#78 AND #79	1,076,156
	#81	'animal experiment'/exp NOT ('human experiment'/exp OR 'human'/exp)	2,265,379
	#82	#66 OR #69 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #80 OR #81	3,488,645
	#83	#63 NOT #82	4,559,636
Combining search terms and exclusions	#84	#3 AND #40 AND #83	21,207
	#85	#3 AND #40 AND #83 AND ([article]/lim OR [article in press]/lim) AND [english]/lim	9177

Abbreviation: NSCLC, non-small cell lung cancer

Table 81: Search terms for MEDLINE and MEDLINE-in-Process (via www.pubmed.gov)

Search terms	No	Query	Results
Population (Combination of indexed and free-text search terms for NSCLC, including proximity operators to combine non-small cell type with lung and tumour search terms)	#1	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND ('lung'[mh] OR 'lung') AND ('neoplasm'[mh] OR 'neoplasm' OR 'cancer'[mh] OR 'cancer' OR 'carcinoma'[mh] OR 'carcinoma' OR 'malignancy'[mh] OR 'malignancy' OR 'tumour'[mh] OR 'tumour')	80,991
	#2	(carcinoma, non small cell lung[mh]) OR 'non small cell lung cancer' OR nsclc	80,759
	#3	('non-small-cell'[tiab] OR 'non-small cell'[tiab] OR 'non small cell'[tiab] OR 'nonsmall cell'[tiab] OR 'pancoast'[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])	68,053
	#4	#1 OR #2 OR #3	83,055
Intervention/ comparators (Exploding indexed search terms for intervention and	#5	'cisplatin'[mh] OR cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis diamminedichloroplatinum' OR 'cis-dichlorodiammineplatinum' OR 'platino' OR 'platidium' OR 'platino' OR biocisplatinum	79,098



comparators, including generic and brand names)	#6	'carboplatin'[mh] OR carboplatin OR (1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplalin OR paraplaline	17,811
	#7	durvalumab OR imfinzi OR 'medi 4736' OR medi4736	587
	#8	'nivolumab'[mh] OR 'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'nivolumab' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	5342
	#9	'pembrolizumab'[mh] OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475'	4313
	#10	'ipilimumab'[mh] OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'yervoy'	3702
	#11	'atezolizumab'[mh] OR 'atezolizumab' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq'	1200
	#12	'paclitaxel'[mh] OR paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan	45,708
	#13	'pemetrexed'[mh] OR pemetrexed OR alimta OR armisarte OR ciambra OR elimta OR 'ly 231514' OR ly231514 OR 'pemetrexed disodium' OR 'pemetrexed disodium hemipentahydrate' OR 'pemetrexed ditromethamine' OR 'pemetrexed sodium' OR 'pemetrexed tromethamine' OR pemfexy OR pemta	3546
	#14	'tyrosine kinase inhibitor'(66) OR 'protein tyrosine kinase inhibitor'(66) OR 'protein kinase inhibitor'(66) OR	235,518



'epidermal growth factor receptor kinase inhibitor'(66) OR
'protein serine threonine kinase inhibitor'(66) OR
'tyrosine kinase inhibitor' OR tki[tiab] OR tkis[tiab] OR
'afatinib' OR 'afatinib'(66) OR afatinib OR gilotrif OR 'bibw
2992 ma2' OR 'erlotinib' OR 'erlotinib'(66) OR erlotinib OR
tarceva OR 'cp-358774' OR 'osi774' OR 'gefitinib' OR
'gefitinib'(66) OR gefitinib OR iressa OR 'zd 1839' OR
'imatinib' OR 'imatinib'(66) OR 'imatinib' OR gleevec OR
'sti-571' OR 'sti 571' OR 'dacomitinib' OR 'dacomitinib'(66)
OR 'dacomitinib' OR 'pf-00299804' OR 'pf 00299804' OR
'dasatinib' OR 'dasatinib'(66) OR 'dasatinib' OR sprycel OR
'bms-354825' OR 'bms 354825' OR 'sunitinib' OR
'sunitinib'(66) OR 'sunitinib' OR sutent OR 'su11248' OR
'su-11248' OR 'naquotinib' OR 'naquotinib'(66) OR
'naquotinib' OR 'asp8273' OR 'asp-8273' OR 'osimertinib'
OR 'osimertinib'(66) OR osimertinib OR mereletinib OR
tagrisso OR 'azd9291' OR 'anaplastic lymphoma kinase
inhibitor'(66) OR 'alk inhibitor' OR 'mitogen activated
protein kinase kinase inhibitor'(66) OR 'map inhibitor' OR
'mek inhibitor' OR 'b raf kinase inhibitor'(66) OR 'braf
kinase inhibitor' OR 'antineoplastic monoclonal
antibody'(66) OR nintedanib[mh] OR nintedanib OR
vargatef

#15	"vinorelbine"[TW] OR "eunades"[TW] OR "exelbine"[TW] OR "navelbin"[TW] OR "navelbine"[TW] OR "navirel"[TW] OR "vinbine"[TW] OR "vinelbine"[TW] OR "vinorelbine ditartrate"[TW] OR "vinorelbine tartrate"[TW]	4167
#16	"gemcitabine"[TW] OR "gemcitabine hydrochloride"[TW] OR "gemcite"[TW] OR "gemzar"[TW]	17,214
#17	"everolimus"[TW] OR "affinitor"[TW] OR "afinitor"[TW] OR "afinitor disperz"[TW] OR "certican"[TW] OR "votubia"[TW] OR "zortress"[TW]	7450
#18	'docetaxel'[mh] OR 'docetaxel' OR 'dxl' OR 'dtx'	17,434
#19	'doxorubicin'[mh] OR 'doxorubicin' OR 'adriamycin' OR 'caelyx' OR 'myocet' OR 'dxr' OR 'doxorubicin hydrochloride'	78,818
#20	'alectinib'[mh] OR 'alectinib' OR 'alecensa'	537
#21	'bevacizumab'[mh] OR 'bevacizumab' OR 'avastin' OR 'anti-vegf monoclonal antibody' OR 'rhumab-vegf'	19,103
#22	'carmatinib'[mh] OR 'carmatinib' OR 'tabrecta' OR 'inc280'	61
#23	'certinib'[mh] OR 'certinib' OR 'ldk378' OR 'zykadia'	493
#24	'crizotinib'[mh] OR 'crizotinib' OR 'xalkori' OR 'pf- 02341066' OR 'crizonix'	2417



#25	'dabrafenib'[mh] OR 'dabrafenib' OR 'tafinlar' OR 'gsk-2118436'	1169
#26	'entrectinib'[mh] OR 'entrectinib' OR 'rxdx-101' OR 'rozlytrek'	121
#27	'lorlatinib'[mh] OR 'lorlatinib' OR 'lorviqua' OR 'pf-6463922'	180
#28	'mechlorethamine hydrochloride'[mh] OR 'mechlorethamine hydrochloride' OR 'chlormethine' OR 'mustargen' OR 'mustine' OR 'embikhin'	5898
#29	'trametinib'[mh] OR 'trametinib' OR 'mekinist' OR 'gsk1120212'	1277
#30	'methotrexate'[mh] OR 'mtx' OR 'amethopterin' OR 'trexall' OR 'rheumatrex' OR 'otrexup'	56,106
#31	'necitumumab'[mh] OR 'necitumumab' OR 'portazza'	88
#32	'ramucirumab'[mh] OR 'ramucirumab' OR 'cyramza' OR 'ly3009806' OR 'imc-1121b'	794
#33	'selpercatinib'[mh] OR 'selpercatinib' OR 'retevmo' OR 'loxo-292'	30
#34	'ceritinib'[mh] OR ceritinib OR zykadia OR ldk378	493
#35	'brigatinib'[mh] OR brigatinib OR alunbrig OR ap26113	183
#36	'capmatinib'[mh] OR capmatinib OR tabrecta OR inc280	61
#37	'trastuzumab emtansine'[mh] OR 'trastuzumab emtansine' OR 'trastuzumab' OR 'kadcyla' OR 'trastuzumab-dm1' OR 'ado-trastuzumab emtansine'	11,501
#38	'poziotinib'[mh] OR poziotinib OR 'nov120101' OR 'hm781-36b'	39
#39	'pyrotinib'[mh] OR pyrotinib	38
#40	'tak-788' OR 'ap32788'	4
#41	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40	495,821
#42	'randomized controlled trial'[mh:noexp]	135,759



Adapted Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision- maximising version	#43	'controlled clinical trial'[mh:noexp]	47,804
	#44	'random'[tiab]	276,686
	#45	'randomization'[mh:noexp]	103,487
	#46	'intermethod comparison'[mh:noexp]	0
	#47	'placebo'[tiab]	216,189
	#48	'compare'[ti] OR 'compared'[ti] OR 'comparison'[ti]	407,928
	#49	('evaluated'[tiab] OR 'evaluate'[tiab] OR 'evaluating'[tiab] OR 'assessed'[tiab] OR 'assess'[tiab]) AND ('compare'[tiab] OR 'compared'[tiab] OR 'comparing'[tiab] OR 'comparison'[tiab])	1,451,152
	#50	'open'[tiab] AND 'label'[tiab]	44,355
	#51	(double[tiab] OR single[tiab] OR doubly[tiab] OR singly[tiab]) AND (blind[tiab] OR blinded[tiab] OR blindly[tiab])	180,267
	#52	'double blind procedure'[mh:noexp]	167
	#53	'parallel group'[tiab]	16,589
	#54	'crossover'[tiab] OR 'cross over'[tiab]	86,026
	#55	('assign'[tiab] OR match[tiab] OR matched[tiab] OR allocation[tiab]) AND (alternate[tiab] OR group[tiab] OR intervention[tiab] OR patient[tiab] OR subject[tiab] OR participant[tiab])	188,514
	#56	assigned[tiab] OR allocated[tiab]	307,759
	#57	controlled[tiab] AND (study[tiab] OR design[tiab] OR trial[tiab])	471,327
	#58	volunteer[tiab] OR volunteers[tiab]	185,651
	#59	'human experiment'[mh:noexp]	0
	#60	trial[ti]	223,546
	#61	'phase 2'[mh] OR 'phase II'[mh]	7837
	#62	'phase 3'[mh] OR 'phase III'[mh]	9551
	#63	'phase 4'[mh] OR 'phase IV'[mh]	305



#64	#42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63	3,147,196
#65	random[tiab] AND sampl[tiab] AND ('cross section'[tiab] OR questionnaire[tiab] OR survey[tiab] OR database[tiab]) NOT ('comparative study'[mh:noexp] OR 'randomized controlled'[tiab] OR 'randomised controlled'[tiab] OR 'randomly assigned'[tiab])	1
#66	'cross-sectional study'[mh:noexp] NOT ('randomized controlled trial'[mh:noexp] OR 'controlled clinical study'[mh:noexp] OR 'controlled study'[mh:noexp] OR 'randomized controlled trial'[tiab] OR 'randomised controlled trial'[tiab] OR 'control group'[tiab])	326,626
#67	((case[tiab] AND control[tiab]) AND random[tiab]) NOT ('randomized controlled'[tiab] OR 'randomised controlled'[tiab])	424
#68	'systematic review'[tiab] NOT (trial[tiab] OR study[tiab])	83,315
#69	('review'[tiab] AND 'review'[pt]) NOT trial[ti]	1,009,757
#70	'we searched'[tiab] AND (review[ti] OR review[pt])	28,891
#71	'update review'[tiab]	217
#72	'database'[tiab] AND 'searched'[tiab]	19,600
#73	(rat[ti] OR rats[ti] OR mouse[ti] OR mice[ti] OR swine[ti] OR porcine[ti] OR murine[ti] OR sheep[ti] OR lambs[ti] OR pigs[ti] OR piglets[ti] OR rabbit[ti] OR rabbits[ti] OR cat[ti] OR cats[ti] OR dog[ti] OR dogs[ti] OR cattle[ti] OR bovine[ti] OR monkey[ti] OR monkeys[ti] OR trout[ti] OR marmoset[ti]) AND 'animal experiment'[mh:noexp]	312
#74	'animal experiment'[mh:noexp] NOT ('human experiment'[mh:noexp] OR human[mh:noexp])	2289
#75	#65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74	1,386,636
#76	#64 NOT #75	2,953,122
Combining search terms	#77 #4 AND #41 AND #76	6506

Abbreviation: NSCLC, non-small cell lung cancer



Table 82: Search terms for Cochrane (via <https://www.cochranelibrary.com/>)

Search terms	No.	Query	Results
Population	#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	4264
	#2	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND 'lung' AND ('neoplasm' OR 'cancer' OR 'carcinoma' OR 'malignancy' OR 'tumour')	13,898
	#3	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR 'pancoast') AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)	15,781
	#4	#1 OR #2 OR #3	15,788
Intervention/ comparators	#5	MeSH descriptor: [Cisplatin] explode all trees	4977
	#6	cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis diamminedichloroplatinum' OR 'cis-dichlorodiammineplatinum' OR 'platino' OR 'platidiam' OR 'platino' OR biocisplatinum	14,579
	#7	MeSH descriptor: [Carboplatin] explode all trees	1549
	#8	carboplatin OR (1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplatine	7045
	#9	MeSH descriptor: [Paclitaxel] explode all trees	3435
	#10	paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan	12,975



#11	MeSH descriptor: [Pemetrexed] explode all trees	630
#12	pemetrexed OR alimta OR armisarte OR ciambra OR elimta OR 'ly 231514' OR ly231514 OR 'pemetrexed disodium' OR 'pemetrexed disodium hemipentahydrate' OR 'pemetrexed ditromethamine' OR 'pemetrexed sodium' OR 'pemetrexed tromethamine' OR pemfexy OR pemta	1986
#13	durvalumab OR imfinzi OR 'medi 4736' OR medi4736	578
#14	MeSH descriptor: [Nivolumab] explode all trees	422
#15	'bms 936558' OR 'bms936558' OR 'cmab 819' OR 'cmab819' OR 'mdx 1106' OR 'mdx1106' OR 'nivolumab' OR 'ono 4538' OR 'ono4538' OR 'opdivo'	1693
#16	'pembrolizumab' OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475' OR 'sch900475'	1462
#17	'ipilimumab' OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	1174
#18	'atezolizumab' OR 'atezolizumab' OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR 'mpdl3280a' OR 'rg 7446' OR 'rg7446' OR 'tecentriq' OR 'tecntriq'	723
#19	'tyrosine kinase inhibitor' OR 'protein tyrosine kinase inhibitor' OR 'protein kinase inhibitor' OR 'epidermal growth factor receptor kinase inhibitor' OR 'protein serine threonine kinase inhibitor' OR tki:ab,ti OR tkis:ab,ti OR 'afatinib' OR gilotrif OR 'bibw 2992 ma2' OR 'erlotinib' OR tarceva OR 'cp-358774' OR 'osi774' OR 'gefitinib' OR iressa OR 'zd 1839' OR 'imatinib' OR gleevec OR 'sti-571' OR 'sti 571' OR 'dacomitinib' OR 'pf-00299804' OR 'pf 00299804' OR 'dasatinib' OR sprycel OR 'bms-354825' OR 'bms 354825' OR 'naquotinib' OR 'asp8273' OR 'asp-8273' OR 'osimertinib' OR mereletinib OR tagrisso OR 'azd9291' OR 'anaplastic lymphoma kinase inhibitor' OR 'alk inhibitor' OR 'mitogen activated protein kinase kinase inhibitor' OR 'map inhibitor' OR 'mek inhibitor' OR 'b raf kinase inhibitor' OR 'braf kinase inhibitor' OR 'antineoplastic monoclonal antibody' OR nintedanib OR vargatef	9429
#20	'vinorelbine':ti,ab,tn OR 'eunades':ti,ab,tn OR 'exelbine':ti,ab,tn OR 'navelbin':ti,ab,tn OR 'navelbine':ti,ab,tn OR 'navirel':ti,ab,tn OR 'vinbine':ti,ab,tn OR 'vinelbine':ti,ab,tn OR 'vinorelbine ditartrate':ti,ab,tn OR 'vinorelbine tartrate':ti,ab,tn	1623
#21	'gemcitabine':ti,ab,tn OR 'gemcitabine hydrochloride':ti,ab,tn OR 'gemcite':ti,ab,tn OR 'gemzar':ti,ab,tn	5380



#22	'everolimus':ti,ab,tn OR 'affinitor':ti,ab,tn OR 'afinitor':ti,ab,tn OR 'afinitor disperz':ti,ab,tn OR 'certican':ti,ab,tn OR 'votubia':ti,ab,tn OR 'zortress':ti,ab,tn	3529
#23	'docetaxel' OR 'dxl' OR 'dtx'	7191
#24	'doxorubicin' OR 'adriamycin' OR 'caelyx' OR 'myocet' OR 'dxr' OR 'doxorubicin hydrochloride'	8713
#25	'alectinib' OR 'alecensa'	111
#26	'bevacizumab' OR 'avastin' OR 'anti-vegf monoclonal antibody' OR 'rhumab-vegf'	6901
#27	'carmatinib' OR 'tabrecta' OR 'inc280'	15
#28	'certinib' OR 'ldk378' OR 'zykadia'	8
#29	'crizotinib' OR 'xalkori' OR 'pf-02341066' OR 'crizonix'	322
#30	'dabrafenib' OR 'tafinlar' OR 'gsk-2118436'	214
#31	'entrectinib' OR 'rxdx-101' OR 'rozlytrek'	11
#32	'lorlatinib' OR 'lorviqua' OR 'pf-6463922'	24
#33	'mechlorethamine hydrochloride' OR 'chlormethine' OR 'mustargen' OR 'mustine' OR 'embikhin'	75
#34	'trametinib' OR 'mekinist' OR 'gsk1120212'	262
#35	'methotrexate' OR 'mtx' OR 'amethopterin' OR 'trexall' OR 'rheumatrex' OR 'otrexup'	12,192
#36	'necitumumab' OR 'portrazza'	57
#37	'ramucirumab' OR cyramza OR 'ly3009806' OR 'imc-1121b'	491
#38	'selpercatinib' OR 'retevmo' OR 'loxo-292'	2
#39	'ceritinib' OR 'zykadia' OR 'ldk378'	67
#40	brigatinib OR alunbrig OR ap26113	78
#41	capmatinib OR tabrecta OR inc280	23
#42	'trastuzumab emtansine' OR 'trastuzumab' OR 'kadcyla' OR 'trastuzumab-dm1' OR 'ado-trastuzumab emtansine'	2692
#43	'poziotinib' OR 'nov120101'	3



	#44	pyrotinib	27
	#45	'tak-788' OR 'ap32788'	3
	#46	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45	69,716
Combining search terms for population, comparators and applying the trials filter	#47	#46 and #4	9714
	#48	#4 AND #47 Limits: Trials (TOTAL)	9179
		ICTRP	1353
		CINAHL	26
		Cochrane Library	6892
		ClinicalTrials.gov	1326

Abbreviations: CINAHL, Cumulative Index to Nursing and Allied Health Literature; ICTRP, International Clinical Trials Registry Platform; MeSH, medical subject headings

Search terms for MEDLINE (searched via pubmed.com). Primary research objective. September 2024.

Search terms	No	Query
Population	#1	(non-small-cell OR “non-small cell” OR “non small cell” OR “nonsmall cell”) AND (lung[mh] OR lung) AND (neoplasm[mh] OR neoplasm OR cancer[mh] OR cancer OR carcinoma[mh] OR carcinoma OR malignancy[mh] OR malignancy OR tumour[mh] OR tumour)
	#2	carcinoma, non small cell lung[mh] OR “non small cell lung cancer” OR nsccl
	#3	(non-small-cell[tiab] OR “non-small cell”[tiab] OR “non small cell”[tiab] OR “nonsmall cell”[tiab] OR pancoast[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])
	#4	#1 OR #2 OR #3
	#5	unresect*[tiab] OR non-resect*[tiab] OR nonresect*[tiab] OR inoper*[tiab] OR unremovable[tiab] OR metast*[tiab] OR advanc*[tiab] OR “stage III”[tiab] OR “stage 3”[tiab] OR “stage IV”[tiab] OR “stage 4”[tiab] OR “late stage”[tiab] OR late-stage[tiab]
	#6	#4 AND #5



	#7	HER2 OR HER2m OR HER2 mutant* OR HER2 mutat* OR HER2+ OR HER2-positive OR "HER2 positive" OR HER-2 OR HER-2m OR HER-2 mutant* OR HER-2 mutat* OR HER-2+ OR HER-2-positive OR "HER-2 positive" OR HER2 exon20 mutat* OR HER-2 exon20 mutat* OR HER2 exon 20 mutat* OR HER-2 exon 20 mutat* OR HER2 exon 20 insertion OR HER2 exon20 insertion OR HER-2 exon 20 insertion OR HER-2 exon20 insertion OR HER2 tyrosine kinase domain mutat* OR HER-2 tyrosine kinase domain mutat* OR HER2 TKD mutat* OR HER-2 TKD mutat* OR HER2 alteration OR HER-2 alteration OR HER2 aberration OR HER-2 aberration OR gene, her2[mh] OR genes, her2[mh] OR her2 gene[mh] OR her2 genes[mh] OR "human epidermal growth factor receptor 2" OR "human epidermal growth factor receptor-2" OR "human epidermal growth factor receptor2" OR "erbB 2" OR erbB-2 OR genes, erbB-2[mh] OR gene, erbB-2[mh] OR receptor, ErbB-2[mh] OR "erythroblastic oncogene B 2" OR "erythroblastic oncogene B-2" OR "erythroblastic oncogene B2" OR "erythroblastic oncogeneB2" OR "erythroblastic oncogeneB 2"
	#8	#6 AND #7
Removing Phase I trials	#9	"phase 2" OR "phase II" OR "phase 3" OR "phase III" OR "phase 4" OR "phase IV"
	#10	Clinical Trial, phase II[mh] OR Clinical Trials, Phase II as Topic[mh]
	#11	Clinical Trial, phase III[mh] OR Clinical Trials, Phase III as Topic[mh]
	#12	Clinical Trial, phase IV[mh] OR Clinical Trials, Phase IV as Topic[mh]
	#13	#9 OR #10 OR #11 OR #12
	#14	#8 AND #13
Remove animal studies	#15	(animals[mh] NOT humans[mh])
	#16	#14 NOT #15
Year filter	#17	#16 AND ("2020/09/01"[Date - Publication] : "3000"[Date - Publication])

Search terms for MEDLINE (searched via pubmed.com). Secondary research objective. September 2024.

Search terms	No	Query
Population	#1	(non-small-cell OR "non-small cell" OR "non small cell" OR "nonsmall cell") AND (lung[mh] OR lung) AND (neoplasm[mh] OR neoplasm OR cancer[mh] OR cancer OR carcinoma[mh] OR carcinoma OR malignancy[mh] OR malignancy OR tumour[mh] OR tumour)
	#2	carcinoma, non small cell lung[mh] OR "non small cell lung cancer" OR nsclc



	#3	(non-small-cell[tiab] OR “non-small cell”[tiab] OR “non small cell”[tiab] OR “nonsmall cell”[tiab] OR pancoast[tiab]) AND (cancer*[tiab] OR carcin*[tiab] OR neoplasm*[tiab] OR tumour*[tiab] OR tumor*[tiab] OR squamous[tiab] OR adenocarcinoma*[tiab])
	#4	#1 OR #2 OR #3
Specific population terms	#5	unresect*[tiab] OR non-resect*[tiab] OR nonresect*[tiab] OR inoper*[tiab] OR unremovable[tiab] OR metast*[tiab] OR advanc*[tiab] OR “stage III”[tiab] OR “stage 3”[tiab] OR “stage IV”[tiab] OR “stage 4”[tiab] OR “late stage”[tiab] OR late-stage[tiab]
	#6	#4 AND #5
Treatments of interest	#7	carboplatin[mh] OR carboplatin OR (1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplantine
	#8	cisplatin[mh] OR cisplatin OR “platinum diamminodichloride” OR cis-platinum OR “cis platinum” OR cisplatinum OR dichlorodiammineplatinum OR cis-diamminedichloroplatinum OR “cis diamminedichloroplatinum” OR cis-dichlorodiammineplatinum OR platinol OR platidiam OR platino OR biocisplatinum
	#9	durvalumab OR imfinzi OR “medi 4736” OR medi4736
	#10	bevacizumab[mh] OR bevacizumab OR avastin OR “anti-vegf monoclonal antibody” OR rhumab-vegf
	#11	nivolumab[mh] OR “bms 936558” OR bms936558 OR “cmab 819” OR cmab819 OR “mdx 1106” OR mdx1106 OR nivolumab OR “ono 4538” OR ono4538 OR opdivo
	#12	pembrolizumab[mh] OR Keytruda OR lambrolizumab OR “mk 3475” OR mk3475 OR pembrolizumab OR “sch 900475”
	#13	ipilimumab[mh] OR “bms 734016” OR bms734016 OR ipilimumab OR “mdx 010” OR “mdx 101” OR mdx010 OR mdx101 OR strentarga OR yervoy
	#14	atezolizumab[mh] OR atezolizumab OR “monoclonal antibody mpdl 3280a” OR “monoclonal antibody mpdl3280a” OR “mpdl 3280a” OR mpdl3280a OR “rg 7446” OR rg7446 OR tecentriq
	#15	paclitaxel[mh] OR paclitaxel OR “abi 007” OR abi007 OR abraxane OR “albumin bound paclitaxel” OR “albumin-bound paclitaxel” OR anzatax OR apealea OR asotax OR biotax OR “bms 181339” OR bms181339 OR “bmy 45622” OR bmy45622 OR bristaxol OR britaxol OR coroxane OR “dts 301” OR dts301 OR “endotag 1” OR formoxol OR genexol OR “genexol pm” OR hunxol OR ifaxol OR infinnium OR intaxel OR “mbt 0206” OR mbt0206 OR medixel OR mitotax OR “nab paclitaxel” OR “nanoparticle albumin bound paclitaxel” OR “nsc 125973” OR “nsc 673089” OR nsc125973 OR nsc673089 OR “oas pac



100" OR oaspac100 OR oncogel OR onxol OR pacitaxel OR "paclitaxel nab"
OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR
pazenir OR praxel OR "sb 05" OR sb05 OR taxocris OR taxol OR taxus OR
taycovit OR yewtaxan

-
- #16 pemetrexed[mh] OR pemetrexed OR alimta OR armisarte OR ciambra OR
elimta OR "ly 231514" OR ly231514 OR "pemetrexed disodium" OR
"pemetrexed disodium hemipentahydrate" OR "pemetrexed
ditromethamine" OR "pemetrexed sodium" OR "pemetrexed
tromethamine" OR pemfexy OR pemta
-
- #17 "tyrosine kinase inhibitor" OR "protein tyrosine kinase inhibitor" OR "protein
kinase inhibitor" OR "epidermal growth factor receptor kinase inhibitor" OR
"protein serine threonine kinase inhibitor" OR "tyrosine kinase inhibitor" OR
tki[tiab] OR tkis[tiab] OR afatinib OR gilotrif OR "bibw 2992 ma2" OR
erlotinib OR tarceva OR cp-358774 OR osi774 OR gefitinib OR iressa OR "zd
1839" OR imatinib OR gleevec OR sti-571 OR "sti 571" OR dacomitinib OR pf-
00299804 OR "pf 00299804" OR dasatinib OR sprycel OR bms-354825 OR
"bms 354825" OR sunitinib OR sutent OR su11248 OR su-11248 OR
naquotinib OR asp8273 OR asp-8273 OR osimertinib OR mereletinib OR
tagrisso OR azd9291 OR "anaplastic lymphoma kinase inhibitor" OR "alk
inhibitor" OR "mitogen activated protein kinase kinase inhibitor" OR "map
inhibitor" OR "mek inhibitor" OR "b raf kinase inhibitor" OR "braf kinase
inhibitor" OR "antineoplastic monoclonal antibody" OR nintedanib[mh] OR
nintedanib OR vargatef OR Ofev
-
- #18 vinorelbine[TW] OR eunades[TW] OR exelbine[TW] OR navelbin[TW] OR
navelbine[TW] OR navirel[TW] OR vinbine[TW] OR vinelbine[TW] OR
"vinorelbine ditartrate"[TW] OR "vinorelbine tartrate"[TW]
-
- #19 gemcitabine[TW] OR "gemcitabine hydrochloride"[TW] OR gemcite[TW] OR
gemzar[TW]
-
- #20 everolimus[TW] OR affinitor[TW] OR afinitor[TW] OR "afinitor disperz"[TW]
OR certican[TW] OR votubia[TW] OR zortress[TW]
-
- #21 docetaxel[mh] OR docetaxel OR dxi OR dtx
-
- #22 doxorubicin[mh] OR doxorubicin OR adriamycin OR caelyx OR myocet OR dxr
OR "doxorubicin hydrochloride"
-
- #23 alectinib[mh] OR alectinib OR alecensa
-
- #24 carmatinib[mh] OR carmatinib OR tabrecta OR inc280
-
- #25 certinib[mh] OR certinib OR ldk378 OR zykadia
-
- #26 crizotinib[mh] OR crizotinib OR xalkori OR pf-02341066 OR crizonix
-
- #27 dabrafenib[mh] OR dabrafenib OR tafinlar OR gsk-2118436
-
- #28 entrectinib[mh] OR entrectinib OR rxdx-101 OR rozlytrek
-



- #29 lorlatinib[mh] OR lorlatinib OR lorviqua OR pf-6463922
-
- #30 mechlorethamine hydrochloride[mh] OR mechlorethamine hydrochloride OR chlormethine OR mustargen OR mustine OR embikhin
-
- #31 trametinib[mh] OR trametinib OR mekinist OR gsk1120212
-
- #32 methotrexate[mh] OR mtx OR amethopterin OR trexall OR rheumatrex OR otrexup
-
- #33 necitumumab[mh] OR necitumumab OR portazza
-
- #34 ramucirumab[mh] OR ramucirumab OR cyramza OR ly3009806 OR imc-1121b
-
- #35 selpercatinib[mh] OR selpercatinib OR retevmo OR loxo-292
-
- #36 ceritinib[mh] OR ceritinib OR zykadia OR ldk378
-
- #37 brigatinib[mh] OR brigatinib OR alunbrig OR ap26113
-
- #38 capmatinib[mh] OR capmatinib OR tabrecta OR inc280
-
- #39 trastuzumab emtansine[mh] OR "trastuzumab emtansine" OR trastuzumab OR kadcyra OR trastuzumab-dm1 OR "ado-trastuzumab emtansine"
-
- #40 poziotinib[mh] OR poziotinib OR nov120101 OR hm781-36b
-
- #41 pyrotinib[mh] OR pyrotinib
-
- #42 mobocertanib OR tak-788 OR ap32788
-
- #43 oxaliplatin[mh] OR oxaliplatin OR oxalatoplatin OR oxalatoplatinum OR oxaliplatine OR 1-OHP OR L-OHP OR PR-54780 OR eloxatin OR "1,2-Diaminocyclohexane Platinum Oxalate" OR "1,2-Diaminocyclohexane(trans-1)oxalatoplatinum(II)" OR "ACT 078" OR ACT-078 OR ACT078 OR "Cis-oxalato-(trans-1)-1,2-diaminocyclohexane-platinum(II)" OR Eloxatin OR Eloxatine OR "L-OHP Cpd" OR "Oxalato-(1,2-cyclohexanediamine)platinum II" OR "Oxaliplatin, (SP-4-2-(1R-trans))-isomer" OR "Oxaliplatin, (SP-4-2-(1S-trans))-isomer" OR "Oxaliplatin, (SP-4-3-(cis))-isomer" OR Oxaliplatine OR "Platinum(2+) ethanedioate (1R,2R)-1,2-cyclohexanediamine (1:1:1)" OR "Platinum(II)-1,2-cyclohexanediamine Oxalate"
-
- #44 Enhertu OR "Trastuzumab deruxtecan" OR "Fam-trastuzumab deruxtecan-nxki" OR T-DXd OR DS-8201a
-
- #45 Etoposide[mh] OR etoposide OR Celltop OR "Demethyl Epipodophyllotoxin Ethylidene Glucoside" OR eposide OR eposin OR Eto-GRY OR "Eto GRY" OR Etomedac OR Etopos OR "Etoposide Pierre Fabre" OR "Etoposide Teva" OR "Etoposide, (5S)-Isomer" OR "Etoposide, (5a alpha)-Isomer" OR "Etoposide, (5a alpha,9 alpha)-Isomer" OR "Etoposide, alpha D Glucopyranosyl Isomer"
-



OR "Etoposide, alpha-D-Glucopyranosyl Isomer" OR "Etoposido Ferrer Farma" OR Exitop OR Lastet OR "NSC 141540" OR NSC141540 OR NSC-141540 OR Onkoposid OR Riboposid OR Toposar OR "VP 16 213" OR "VP 16-213" OR VP-16 OR "VP 16" OR VP16 OR Vepesid OR Vépéside-Sandoz OR "Vépéside Sandoz"

#46 Irinotecan[mh] OR irinotecan OR 7-Ethyl-10-hydroxycamptothecin OR "7 Ethyl 10 hydroxycamptothecin" OR "CPT 11" OR CPT-11 OR CTP11 OR Camptosar OR Camptothecin-11 OR "Camptothecin 11" OR "Irinotecan Hydrochloride" OR Irrinotecan OR "NK012 Compound" OR "SN 38" OR "SN 38 11" OR SN-38 OR SN-38-11 OR SN3811

#47 Topotecan[mh] OR topotecan OR 9-Dimethylaminomethyl-10-hydroxycamptothecin OR "9 Dimethylaminomethyl 10 hydroxycamptothecin" OR Hycamtamine OR Hycamtin OR NSC-609699 OR "NSC 609699" OR NSC609699 OR "Nogitecan Hydrochloride" OR SK&F-104864-A OR SKF-104864-A OR "SKF 104864 A" OR SK&F104864A OR SKF104864A OR "SK&F 104864 A" OR "Topotecan Hydrochloride" OR "Topotecan Monohydrochloride, (S)-Isomer"

#48 Apatinib OR "apatinib mesylate" OR Rivoceranib OR "Rivoceranib mesylate" OR YN968D1 OR YN-968D1 OR "YN 968D1" OR TK02X14ASJ

#49 Fruquintinib OR Fruzaqla OR HMPL-013 OR HMPL013 OR 49DXG3M5ZW OR fruquintinibum OR Elunate

#50 Pazopanib OR Votrient OR pazopanibum OR GW786034 OR "GW 786034" OR "indazolympyrimidine 13"

#51 Pralsetinib OR Gavreto OR BLU-667 OR BLU667 OR 1WPE73O1WV OR BLU-123244 OR BLU123244 OR pralsetinibum

#52 Bavixumab OR PGN401 OR "PGN 401" OR PGN-401

#53 Tremelimumab OR Imjudo OR tremelimumab-actl OR ticilimumab OR CP-675 OR "CP 675" OR "CP-675,206" OR "CP675 cpd" OR QEN1X95CIX OR tremelimumabum

#54 Sotorasib OR Lumakras OR Lumykras OR "AMG 510" OR AMG-510 OR AMG510 OR "Kras G12C inhibitor 9" OR sotorasibum

#55 Tepotinib OR Tepmetko OR EMD-1214063 OR "EMD 1214063" OR EMD1214063 OR MSC2156119 OR MSC-2156119 OR 1IJV77EI07 OR tepotinibum

#56 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

#57 randomized controlled trial[pt]



Cochrane 2008 highly sensitive RCT search filter (pubMed format)	#58	controlled clinical trial[pt]
	#59	randomized[tiab]
	#60	placebo[tiab]
	#61	clinical trials as topic[mh]
	#62	randomly[tiab]
	#63	trial[tiab]
	#64	#57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
Irrelevant study types	#65	systematic review*[tiab] OR review*[tiab] OR review[pt] OR “we searched”[tiab] OR database[tiab] OR searched[tiab] OR survey*[tiab] OR questionnaire*[tiab] OR meta analysis[mh] OR meta analysis as topic[mh] OR meta analysis[pt] OR ((indirect[tiab] OR "indirect treatment"[tiab] OR "mixed treatment"[tiab] OR bayesian[tiab]) AND (comparison*[tiab])) OR NMA[tiab] OR review, systematic[mh] OR systematic review[pt] OR registr*[tiab] OR “real world”[tiab] OR real-world*[tiab] OR observational stud*[tiab] OR prospective*[tiab] OR retrospective*[tiab] OR observational study[pt] OR epidemiologic methods[mh] OR epidemiologic studies[mh] OR case reports[mh] OR case reports[pt] OR validation study[pt] OR longitudinal*[tiab] OR (natural[tiab] AND experiment[tiab]) OR “non experiment”[tiab] OR nonexperiment*[tiab] OR surveys and questionnaires[mh] OR health care surveys[mh] OR self report[mh] OR self reports[mh] OR "self report"[tiab] OR "self reporting"[tiab] OR selfreport*[tiab] OR "self reported"[tiab] OR letters as topic[mh] OR letters as topics[mh]
	#66	#64 NOT #65
Remove animal studies and letters	#67	(animals[mh] NOT humans[mh])
	#68	#66 NOT #67
	#69	#6 AND #56 AND #68
Year filter	#70	#69 AND ("2020/09/01"[Date - Publication] : "3000"[Date - Publication])



Search terms for Embase (searched via embase.com). Primary research objective May 2024

Search terms	No	Query
Population	#1	(non-small-cell OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND ('lung'/exp OR lung) AND ('neoplasm'/exp OR neoplasm OR 'malignant neoplasm'/exp OR cancer OR 'carcinoma'/exp OR carcinoma OR malignancy OR tumour)
	#2	('non small cell lung cancer'/exp) OR 'non small cell lung cancer' OR nsclc
	#3	((non-small-cell OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR pancoast) NEXT/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)) :ti,ab,kw
	#4	#1 OR #2 OR #3
	#5	(unresect* OR non-resect* OR nonresect* OR inoper* OR unremovable OR metast* OR advanc* OR 'stage III' OR 'stage 3' OR 'stage IV' OR 'stage 4' OR 'late stage' OR late-stage):ti,ab,kw
	#6	#4 AND #5
	#7	HER2 OR HER2m OR 'HER2 mutant*' OR 'HER2 mutat*' OR HER2+ OR HER2-positive OR 'HER2 positive' OR HER-2 OR HER-2m OR 'HER-2 mutant*' OR 'HER-2 mutat*' OR HER-2+ OR HER-2-positive OR 'HER-2 positive' OR 'HER2 exon 20 mutat*' OR 'HER-2 exon 20 mutat*' OR 'HER2 exon 20 insertion' OR 'HER2 exon20 insertion' OR 'HER-2 exon 20 insertion' OR 'HER-2 exon20 insertion' OR 'HER2 tyrosine kinase domain mutat*' OR 'HER-2 tyrosine kinase domain mutat*' OR 'HER2 TKD mutat*' OR 'HER-2 TKD mutat*' OR 'HER2 alteration' OR 'HER-2 alteration' OR 'HER2 aberration' OR 'HER-2 aberration' OR 'human epidermal growth factor receptor 2' OR 'human epidermal growth factor receptor-2' OR 'human epidermal growth factor receptor2' OR 'erbB 2' OR erbB-2 OR 'erythroblastic oncogene B 2' OR 'erythroblastic oncogene B-2' OR 'erythroblastic oncogene B2' OR 'erythroblastic oncogeneB2' OR 'erythroblastic oncogeneB 2'
	#8	'epidermal growth factor receptor 2'/exp
	#9	#7 OR #8
	#10	#6 AND #9
Removing Phase I trials	#11	('phase 2' OR 'phase II' OR 'phase 3' OR 'phase III' OR 'phase 4' OR 'phase IV')
	#12	'phase 2 clinical trial'/exp OR 'phase 2 clinical trial (topic)'/exp
	#13	'phase 3 clinical trial'/exp OR 'phase 3 clinical trial (topic)'/exp
	#14	'phase 4 clinical trial'/exp OR 'phase 4 clinical trial (topic)'/exp



	#15	#11 OR #12 OR #13 OR #14
	#16	#10 AND #15
Remove animal studies	#17	('animal experiment'/de NOT ('human experiment'/de OR 'human'/de))
	#18	#16 NOT #17
Year filter	#19	#18 AND from date 2020/09/01 to present

Search terms for Embase (searched via embase.com). Secondary research objective May 2024

Search terms	No	Query
Population	#1	(non-small-cell OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND ('lung'/exp OR lung) AND ('neoplasm'/exp OR neoplasm OR 'malignant neoplasm'/exp OR cancer OR 'carcinoma'/exp OR carcinoma OR malignancy OR tumour)
	#2	('non small cell lung cancer'/exp) OR 'non small cell lung cancer' OR nscld
	#3	((('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR pancoast) NEXT/3 (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)):ti,ab,kw
	#4	#1 OR #2 OR #3
Specific population terms	#5	(unresect* OR non-resect* OR nonresect* OR inoper* OR unremovable OR metast* OR advanc* OR 'stage III' OR 'stage 3' OR 'stage IV' OR 'stage 4' OR 'late stage' OR late-stage):ti,ab,kw
	#6	#4 AND #5
Treatments of interest	#7	'carboplatin'/exp OR carboplatin OR (1, AND 1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplattine
	#8	'cisplatin'/exp OR cisplatin OR 'platinum diamminodichloride' OR cis-platinum OR 'cis platinum' OR cisplatinum OR dichlorodiammineplatinum OR cis-diamminedichloroplatinum OR 'cis diamminedichloroplatinum' OR cis-dichlorodiammineplatinum OR platinol OR platidiam OR platino OR biocisplatinum
	#9	'durvalumab'/exp OR durvalumab OR imfinzi OR 'medi 4736' OR medi4736



- #10 'bevacizumab'/exp OR avastin OR 'anti-vegf monoclonal antibody' OR rhumab-vegf
-
- #11 'nivolumab'/exp OR 'bms 936558' OR bms936558 OR 'cmab 819' OR cmab819 OR 'mdx 1106' OR mdx1106 OR nivolumab OR 'ono 4538' OR ono4538 OR opdivo
-
- #12 'pembrolizumab'/exp OR keytruda OR lambrolizumab OR 'mk 3475' OR mk3475 OR 'pembrolizumab' OR 'sch 900475' OR sch900475
-
- #13 'ipilimumab'/exp OR 'bms 734016' OR bms734016 OR ipilimumab OR 'mdx 010' OR 'mdx 101' OR mdx010 OR mdx101 OR strentarga OR yervoy
-
- #14 'atezolizumab'/exp OR atezolizumab OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR mpdl3280a OR 'rg 7446' OR rg7446 OR tecentriq OR tecntriq
-
- #15 'paclitaxel'/exp OR paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR paxcel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan
-
- #16 'pemetrexed'/exp OR pemetrexed OR alimta OR armisarte OR ciambra OR elimta OR 'ly 231514' OR ly231514 OR 'pemetrexed disodium' OR 'pemetrexed disodium hemipentahydrate' OR 'pemetrexed ditromethamine' OR 'pemetrexed sodium' OR 'pemetrexed tromethamine' OR pemfexy OR pemta
-
- #17 'protein tyrosine kinase inhibitor'/exp OR 'protein kinase inhibitor'/exp OR 'epidermal growth factor receptor kinase inhibitor'/exp OR 'protein serine threonine kinase inhibitor'/exp OR 'tyrosine kinase inhibitor'/syn OR 'tyrosine kinase inhibitor' OR tki:ab,ti OR tkis:ab,ti OR afatinib/syn OR 'afatinib'/exp OR afatinib OR gilotrif OR 'bibw 2992 ma2' OR erlotinib/syn OR 'erlotinib'/exp OR erlotinib OR tarceva OR cp-358774 OR osi774 OR gefitinib/syn OR 'gefitinib'/exp OR gefitinib OR iressa OR 'zd 1839' OR imatinib/syn OR 'imatinib'/exp OR imatinib OR gleevec OR sti-571 OR 'sti 571' OR dacomitinib/syn OR 'dacomitinib'/exp OR dacomitinib OR pf-00299804 OR 'pf 00299804' OR dasatinib/syn OR 'dasatinib'/exp OR dasatinib OR sprycel OR bms-354825 OR 'bms 354825' OR naquotinib/syn OR 'naquotinib'/exp OR naquotinib OR asp8273 OR asp-8273 OR osimertinib/syn OR 'osimertinib'/exp OR osimertinib OR mereletinib OR tagrisso OR azd9291 OR 'anaplastic lymphoma kinase inhibitor'/exp OR 'alk inhibitor' OR 'mitogen activated protein kinase inhibitor'/exp OR 'map inhibitor' OR 'mek inhibitor' OR 'b raf kinase inhibitor'/exp OR 'braf kinase



inhibitor' OR 'antineoplastic monoclonal antibody'/exp OR 'nintedanib'/exp
OR vargatef OR Ofev

#18 'vinorelbine tartrate'/exp OR vinorelbine:ti,ab,tn OR eunades:ti,ab,tn OR
exelbine:ti,ab,tn OR navelbin:ti,ab,tn OR navelbine:ti,ab,tn OR
navirel:ti,ab,tn OR vinbine:ti,ab,tn OR vinelbine:ti,ab,tn OR 'vinorelbine
ditartrate':ti,ab,tn OR 'vinorelbine tartrate':ti,ab,tn

#19 'gemcitabine'/exp OR gemcitabine:ti,ab,tn OR 'gemcitabine
hydrochloride':ti,ab,tn OR gemcite:ti,ab,tn OR gemzar:ti,ab,tn

#20 'everolimus'/exp OR everolimus:ti,ab,tn OR affinitor:ti,ab,tn OR
afinitor:ti,ab,tn OR 'afinitor disperz':ti,ab,tn OR certican:ti,ab,tn OR
votubia:ti,ab,tn OR zortress:ti,ab,tn

#21 'docetaxel'/exp OR dxi OR dtx

#22 'doxorubicin'/exp OR doxorubicin OR adriamycin OR caelyx OR myocet OR
dxr OR 'doxorubicin hydrochloride'

#23 'alectinib'/exp OR alecensa

#24 carmatinib OR tabrecta OR inc280

#25 Certinib OR ldk378 OR zykadia

#26 'crizotinib'/exp OR xalkori OR pf-02341066 OR crizonix

#27 'dabrafenib'/exp OR tafinlar OR gsk-2118436

#28 'entrectinib'/exp OR rxdx-101 OR rozlytrek

#29 'Lorlatinib'/exp OR lorviqua OR pf-6463922

#30 'chlormethine'/exp OR chlormethine OR 'mechlorethamine hydrochloride'
OR mustargen OR mustine OR embikhin

#31 'trametinib'/exp OR mekinist OR gsk1120212

#32 'methotrexate'/exp OR mtx OR amethopterin OR trexall OR rheumatrex OR
otrexup

#33 'necitumumab'/exp OR portrazza

#34 'ramucirumab'/exp OR cyramza OR ly3009806 OR imc-1121b

#35 'selpercatinib'/exp OR retevmo OR loxo-292

#36 'ceritinib'/exp OR ceritinib OR zykadia OR ldk378

#37 'brigatinib'/exp OR brigatinib OR alunbrig OR ap26113



- #38 'capmatinib'/exp OR capmatinib OR tabrecta OR inc280
-
- #39 'trastuzumab emtansine'/exp OR 'trastuzumab emtansine' OR trastuzumab OR kadcyca OR trastuzumab-dm1 OR 'ado-trastuzumab emtansine'
-
- #40 'poziotinib'/exp OR poziotinib OR nov120101 OR hm781-36b
-
- #41 pyrotinib
-
- #42 'mobocertinib'/exp OR mobocertanib OR tak-788 OR ap32788
-
- #43 'Oxaliplatin'/exp OR oxaliplatin OR oxalatoplatin OR oxalatoplatinum OR oxaliplatine OR 1-OHP OR L-OHP OR PR-54780 OR eloxatin OR '1,2-Diaminocyclohexane Platinum Oxalate' OR '1,2-Diamminocyclohexane(trans-1)oxolatoplatinum(II)' OR 'ACT 078' OR ACT-078 OR ACT078 OR 'Cis-oxalato-(trans-I)-1,2-diaminocyclohexane-platinum(II)' OR Eloxatin OR Eloxatine OR 'L-OHP Cpd' OR 'Oxalato-(1,2-cyclohexanediamine)platinum II' OR 'Oxaliplatin, (SP-4-2-(1R-trans))-isomer' OR 'Oxaliplatin, (SP-4-2-(1S-trans))-isomer' OR 'Oxaliplatin, (SP-4-3-(cis))-isomer' OR Oxaliplatine OR 'Platinum(2+) ethanedioate (1R,2R)-1,2-cyclohexanediamine (1:1:1)' OR 'Platinum(II)-1,2-cyclohexanediamine Oxalate'
-
- #44 'trastuzumab deruxtecan'/exp OR Enhertu OR 'Trastuzumab deruxtecan' OR 'Fam-trastuzumab deruxtecan-nxki' OR T-DXd OR DS-8201a
-
- #45 'Etoposide'/exp OR etoposide OR Celltop OR 'Demethyl Epipodophyllotoxin Ethylidene Glucoside' OR eposide OR eposin OR Eto-GRY OR 'Eto GRY' OR Etomedac OR Etopos OR 'Etoposide Pierre Fabre' OR 'Etoposide Teva' OR 'Etoposide, (5S)-Isomer' OR 'Etoposide, (5a alpha)-Isomer' OR 'Etoposide, (5a alpha,9 alpha)-Isomer' OR 'Etoposide, alpha D Glucopyranosyl Isomer' OR 'Etoposide, alpha-D-Glucopyranosyl Isomer' OR 'Etoposido Ferrer Farma' OR Exitop OR Lastet OR 'NSC 141540' OR NSC141540 OR NSC-141540 OR Onkoposid OR Riboposid OR Toposar OR 'VP 16 213' OR 'VP 16-213' OR VP-16 OR 'VP 16' OR VP16 OR Vepesid OR Vépéside-Sandoz OR 'Vépéside Sandoz'
-
- #46 'Irinotecan'/exp OR irinotecan OR 7-Ethyl-10-hydroxycamptothecin OR '7 Ethyl 10 hydroxycamptothecin' OR 'CPT 11' OR CPT-11 OR CTP11 OR Camptosar OR Camptothecin-11 OR 'Camptothecin 11' OR 'Irinotecan Hydrochloride' OR Irrinotecan OR 'NK012 Compound' OR 'SN 38' OR 'SN 38 11' OR SN-38 OR SN-38-11 OR SN3811
-
- #47 'Topotecan'/exp OR topotecan OR 9-Dimethylaminomethyl-10-hydroxycamptothecin OR '9 Dimethylaminomethyl 10 hydroxycamptothecin' OR Hycamtamine OR Hycamtin OR NSC-609699 OR 'NSC 609699' OR NSC609699 OR 'Nogitecan Hydrochloride' OR SK&F-104864-A OR SKF-104864-A OR 'SKF 104864 A' OR SK&F104864A OR SKF104864A OR 'SK&F 104864 A' OR 'Topotecan Hydrochloride' OR 'Topotecan Monohydrochloride, (S)-Isomer'
-



	#48	'Rivoceranib'/exp OR apatinib OR 'apatinib mesylate' OR rivoceranib OR 'rivoceranib mesylate' OR YN968D1 OR YN-968D1 OR 'YN 968D1' OR TK02X14ASJ
	#49	'Fruquintinib'/exp OR fruquintinib OR fruzaqla OR HMPL-013 OR HMPL013 OR 49DXG3M5ZW OR fruquintinibum OR elunate
	#50	'Pazopanib'/exp OR pazopanib OR votrient OR pazopanibum OR GW786034 OR 'GW 786034' OR 'indazolympyrimidine 13'
	#51	'Pralsetinib'/exp OR pralsetinib OR gavreto OR BLU-667 OR BLU667 OR 1WPE73O1WV OR BLU-123244 OR BLU123244 OR pralsetinibum
	#52	'Bavituximab'/exp OR bavituximab OR PGN401 OR 'PGN 401' OR PGN-401
	#53	'Ticlimumab'/exp OR tremelimumab OR Imjudo OR tremelimumab-actl OR ticilimumab OR CP-675 OR 'CP 675' OR 'CP-675,206' OR 'CP675 cpd' OR QEN1X95CIX OR tremelimumabum
	#54	'Sotorasib'/exp OR sotorasib OR Lumakras OR Lumykras OR 'AMG 510' OR AMG-510 OR AMG510 OR 'Kras G12C inhibitor 9' OR sotorasibum
	#55	Tepotinib/exp OR tepotinib OR Tepmetko OR EMD-1214063 OR 'EMD 1214063' OR EMD1214063 OR MSC2156119 OR MSC-2156119 OR 1IJV77EI07 OR tepotinibum
	#56	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
Cochrane 2008 highly sensitive RCT search filter (PubMed format translated to Embase)	#57	'randomized controlled trial'/exp
	#58	'controlled clinical trial'/exp
	#59	Randomized:ti,ab
	#60	placebo:ti,ab
	#61	'clinical trial (topic)'/exp
	#62	Randomly:ti,ab
	#63	Trial:ti,ab
	#64	#57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63
	#65	('systematic review*' OR review* OR 'we searched' OR database OR searched OR survey* OR questionnai* OR ((indirect OR 'indirect treatment' OR 'mixed treatment' OR Bayesian) AND (comparison*)) OR NMA OR



	registr* OR 'real world' OR 'real-world*' OR 'observational stud*' OR prospective* OR retrospective* OR longitudinal* OR (natural AND experiment) OR 'non experiment' OR nonexperiment* OR 'self report' OR 'self reporting' OR selfreport* OR 'self reported'):ti,ab,kw
	#66 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic review'/exp OR 'medical literature'/exp OR 'questionnaire'/exp OR 'health care survey'/exp OR 'self report'/exp OR 'review'/exp OR 'observational study'/exp OR 'validation study'/exp
	#67 #65 OR #66
	#68 #64 NOT #67
	#69 ('animal'/exp NOT 'human'/exp)
	#70 #68 NOT #69
	#71 #6 AND #56 AND #70
Year filter	#72 #71 AND ('article'/it OR 'article in press'/it) AND [english]/lim AND [01-09-2020]/sd NOT [16-05-2024]/sd



**Search terms for Cochrane (searched via cochrane.com). Primary research objective
September 2024.**

Search terms	No	Query
Population	#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
	#2	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND 'lung' AND ('neoplasm' OR 'cancer' OR 'carcinoma' OR 'malignancy' OR 'tumour')
	#3	('non-small-cell' OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR 'pancoast') AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)
	#4	#1 OR #2 OR #3
	#5	((unresect* OR non-resect* OR nonresect* OR inoper* OR metast* OR advanc*) NEAR ('stage III' OR 'stage 3' OR 'stage IV' OR 'stage 4' OR 'late stage' OR 'late-stage')):ti,ab,kw
	#6	#4 AND #5
	#7	('HER2m' OR 'HER-2' OR 'HER2' OR 'HER-2m' OR 'HER2 positive' OR 'HER-2 positive' OR 'HER2 exon 20 insertion' OR 'HER2 exon20 insertion' OR 'HER-2 exon 20 insertion' OR 'HER-2 exon20 insertion' OR 'HER2 alteration' OR 'HER-2 alteration' OR 'HER2 aberration' OR 'HER-2 aberration' OR 'human epidermal growth factor receptor 2' OR 'human epidermal growth factor receptor-2' OR 'human epidermal growth factor receptor2' OR 'erbB 2' OR 'erbB-2' OR 'erythroblastic oncogene B 2' OR 'erythroblastic oncogene B-2' OR 'erythroblastic oncogene B2' OR 'erythroblastic oncogeneB2' OR 'erythroblastic oncogeneB 2' OR 'erythroblastic oncogeneB 2' OR HER2 mutant* OR HER2 mutat* OR HER-2 mutant* OR HER-2 mutat* OR HER2 exon 20 mutat* OR HER-2 exon 20 mutat* OR HER2 tyrosine kinase domain mutat* OR HER-2 tyrosine kinase domain mutat* OR HER2 TKD mutat* OR HER-2 TKD mutat*)
	#8	MeSH descriptor: [Genes, erbB-2] explode all trees
	#9	#7 OR #8
	#10	#6 AND #9
Removing Phase I trials	#11	('phase 2' OR 'phase II' OR 'phase 3' OR 'phase III' OR 'phase 4' OR 'phase IV')
	#12	MeSH descriptor: [Clinical Trials, Phase II as Topic] explode all trees
	#13	MeSH descriptor: [Clinical Trials, Phase III as Topic] explode all trees
	#14	MeSH descriptor: [Clinical Trials, Phase IV as Topic] explode all trees



	#15	#11 OR #12 OR #13 OR #14
	#16	#10 AND #15
Remove animal studies	#17	('animals' NOT 'humans'):ti,ab,kw
	#18	#16 NOT #17
Year filter	#19	#18 AND from date 2020/09/01 to present (with Cochrane Library publication date from Sep 2020 to May 2024)

Search terms for Cochrane (searched via cochrane.com). Secondary research objective September 2024.

Search terms	No	Query
Population	#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees
	#2	(non-small-cell OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell') AND lung AND (neoplasm OR cancer OR carcinoma OR malignancy OR tumour)
	#3	(non-small-cell OR 'non-small cell' OR 'non small cell' OR 'nonsmall cell' OR pancoast) AND (cancer* OR carcin* OR neoplasm* OR tumour* OR tumor* OR squamous OR adenocarcinoma*)
	#4	#1 OR #2 OR #3
Specific population terms	#5	((unresect* OR non-resect* OR nonresect* OR inoper* OR metast* OR advanc*) NEAR ('stage III' OR 'stage 3' OR 'stage IV' OR 'stage 4' OR 'late stage' OR late-stage)):ti,ab,kw
	#6	#4 AND #5
Treatments of interest	#7	MeSH descriptor: [Carboplatin] explode all trees
	#8	carboplatin OR (1 AND cyclobutanedicarboxylato AND diammineplatinum) OR blastocarb OR boplatex OR carboplat OR carboplatino OR carbosin OR carbotec OR carplan OR cycloplatin OR diamminecyclobutanedicarboxylatoplatinum OR erbakar OR ercar OR ifacap OR kemocarb OR oncocarbin OR paraplatin OR paraplatine
	#9	MeSH descriptor: [Cisplatin] explode all trees
	#10	cisplatin OR 'platinum diamminodichloride' OR cis-platinum OR 'cis platinum' OR cisplatinum OR dichlorodiammineplatinum OR cis-diamminedichloroplatinum OR 'cis diamminedichloroplatinum' OR cis-dichlorodiammineplatinum OR platinol OR platidiam OR platino OR biocisplatinum
	#11	durvalumab OR imfinzi OR 'medi 4736' OR medi4736



- #12 MeSH descriptor: [Bevacizumab] explode all trees
-
- #13 bevacizumab OR avastin OR 'anti-vegf monoclonal antibody' OR rhumab-vegf
-
- #14 MeSH descriptor: [Nivolumab] explode all trees
-
- #15 'bms 936558' OR bms936558 OR 'cmab 819' OR cmab819 OR 'mdx 1106' OR mdx1106 OR nivolumab OR 'ono 4538' OR ono4538 OR opdivo
-
- #16 pembrolizumab OR keytruda OR lambrolizumab OR 'mk 3475' OR mk3475 OR 'sch 900475' OR sch900475
-
- #17 MeSH descriptor: [ipilimumab] explode all trees
-
- #18 ipilimumab OR 'bms 734016' OR bms734016 OR 'mdx 010' OR 'mdx 101' OR mdx010 OR mdx101 OR strentarga OR yervoy
-
- #19 atezolizumab OR 'monoclonal antibody mpdl 3280a' OR 'monoclonal antibody mpdl3280a' OR 'mpdl 3280a' OR mpdl3280a OR 'rg 7446' OR rg7446 OR tecentriq OR tecntriq
-
- #20 MeSH descriptor: [Paclitaxel] explode all trees
-
- #21 paclitaxel OR 'abi 007' OR abi007 OR abraxane OR 'albumin bound paclitaxel' OR 'albumin-bound paclitaxel' OR anzatax OR apealea OR asotax OR biotax OR 'bms 181339' OR bms181339 OR 'bmy 45622' OR bmy45622 OR bristaxol OR britaxol OR coroxane OR 'dts 301' OR dts301 OR 'endotag 1' OR formoxol OR genexol OR 'genexol pm' OR hunxol OR ifaxol OR infinnium OR intaxel OR 'mbt 0206' OR mbt0206 OR medixel OR mitotax OR 'nab paclitaxel' OR 'nanoparticle albumin bound paclitaxel' OR 'nsc 125973' OR 'nsc 673089' OR nsc125973 OR nsc673089 OR 'oas pac 100' OR oaspac100 OR oncogel OR onxol OR pacitaxel OR 'paclitaxel nab' OR pacxel OR padexol OR parexel OR paxceed OR paxene OR paxus OR pazenir OR praxel OR 'sb 05' OR sb05 OR taxocris OR taxol OR taxus OR taycovit OR yewtaxan
-
- #22 MeSH descriptor: [Pemetrexed] explode all trees
-
- #23 pemetrexed OR alimta OR armisarte OR ciambra OR elimta OR 'ly 231514' OR ly231514 OR 'pemetrexed disodium' OR 'pemetrexed disodium hemipentahydrate' OR 'pemetrexed ditromethamine' OR 'pemetrexed sodium' OR 'pemetrexed tromethamine' OR pemfexy OR pemta
-
- #24 MeSH descriptor: [Tyrosine Kinase Inhibitors] explode all trees
-
- #25 MeSH descriptor: [Protein Kinase Inhibitors] explode all trees
-
- #26 MeSH descriptor: [Afatinib] explode all trees
-
- #27 MeSH descriptor: [Dasatinib] explode all trees
-
- #28 MeSH descriptor: [Antineoplastic Agents, Immunological] explode all trees
-



- #29 'tyrosine kinase inhibitor' OR 'protein tyrosine kinase inhibitor' OR 'protein kinase inhibitor' OR 'epidermal growth factor receptor kinase inhibitor' OR 'protein serine threonine kinase inhibitor' OR tki:ab,ti OR tkis:ab,ti OR 'afatinib' OR gilotrif OR 'bibw 2992 ma2' OR erlotinib OR tarceva OR cp-358774 OR osi774 OR gefitinib OR iressa OR 'zd 1839' OR imatinib OR gleevec OR sti-571 OR 'sti 571' OR dacomitinib OR pf-00299804 OR 'pf 00299804' OR dasatinib OR sprycel OR bms-354825 OR 'bms 354825' OR naquotinib OR asp8273 OR asp-8273 OR osimertinib OR mereletinib OR tagrisso OR azd9291 OR 'anaplastic lymphoma kinase inhibitor' OR 'alk inhibitor' OR 'mitogen activated protein kinase kinase inhibitor' OR 'map inhibitor' OR 'mek inhibitor' OR 'b raf kinase inhibitor' OR 'braf kinase inhibitor' OR 'antineoplastic monoclonal antibody' OR nintedanib OR vargatef OR Ofev
-
- #30 vinorelbine:ti,ab,tn OR eunades:ti,ab,tn OR exelbine:ti,ab,tn OR navelbin:ti,ab,tn OR navelbine:ti,ab,tn OR navirel:ti,ab,tn OR vinbine:ti,ab,tn OR vinelbine:ti,ab,tn OR vinorelbine ditartrate:ti,ab,tn OR 'vinorelbine tartrate':ti,ab,tn
-
- #31 gemcitabine:ti,ab,tn OR 'gemcitabine hydrochloride':ti,ab,tn OR gemcite:ti,ab,tn OR gemzar:ti,ab,tn
-
- #32 everolimus:ti,ab,tn OR affinitor:ti,ab,tn OR afinitor:ti,ab,tn OR 'afinitor disperz':ti,ab,tn OR certican:ti,ab,tn OR votubia:ti,ab,tn OR zortress:ti,ab,tn
-
- #33 MeSH descriptor: [Docetaxel] explode all trees
-
- #34 docetaxel OR dxi OR dtx
-
- #35 doxorubicin OR adriamycin OR caelyx OR myocet OR dxr OR 'doxorubicin hydrochloride'
-
- #36 alectinib OR alecensa
-
- #37 carmatinib OR tabrecta OR 'inc280'
-
- #38 certinib OR ldk378 OR zykadia
-
- #39 MeSH descriptor: [Crizotinib] explode all trees
-
- #40 crizotinib OR xalkori OR pf-02341066 OR crizonix
-
- #41 dabrafenib OR tafinlar OR gsk-2118436
-
- #42 entrectinib OR rxdx-101 OR rozlytrek
-
- #43 lorlatinib OR lorviqua OR pf-6463922
-
- #44 MeSH descriptor: [Mechlorethamine] explode all trees
-
- #45 'mechlorethamine hydrochloride' OR chlormethine OR mustargen OR mustine OR embikhin
-



#46	trametinib OR mekinist OR gsk1120212
#47	MeSH descriptor: [Methotrexate] explode all trees
#48	methotrexate OR mtx OR amethopterin OR trexall OR rheumatrex OR otrexup
#49	necitumumab OR portrazza
#50	MeSH descriptor: [Ramucirumab] explode all trees
#51	ramucirumab OR cyramza OR ly3009806 OR imc-1121b
#52	selpercatinib OR retevmo OR loxo-292
#53	ceritinib OR zykadia OR ldk378
#54	brigatinib OR alunbrig OR ap26113
#55	capmatinib OR tabrecta OR inc280
#56	MeSH descriptor: [Ado-Trastuzumab Emtansine] explode all trees
#57	'trastuzumab emtansine' OR trastuzumab OR kadcyla OR trastuzumab-dm1 OR 'ado-trastuzumab emtansine'
#58	poziotinib OR nov120101
#59	pyrotinib
#60	mobocertanib OR tak-788 OR ap32788
#61	MeSH descriptor: [Oxaliplatin] explode all trees
#62	Oxaliplatin OR oxalatoplatin OR oxalatoplatinum OR L-OHP OR PR-54780 OR eloxatin OR 'ACT 078' OR ACT-078 OR ACT078 OR Eloxatine OR 'L-OHP Cpd' OR Oxaliplatine
#63	Enhertu OR 'Trastuzumab deruxtecan' OR 'Fam-trastuzumab deruxtecan-nxki' OR T-DXd OR DS-8201a
#64	MeSH descriptor: [Etoposide] explode all trees
#65	etoposide OR Celltop OR 'Demethyl Epipodophyllotoxin Ethylidine Glucoside' OR eposide OR eposin OR Eto-GRY OR 'Eto GRY' OR Etomedac OR Etopos OR 'Etoposide Pierre Fabre' OR 'Etoposide Teva' OR 'Etoposide, alpha D Glucopyranosyl Isomer' OR 'Etoposide, alpha-D-Glucopyranosyl Isomer' OR 'Etoposido Ferrer Farma' OR Exitop OR Lastet OR 'NSC 141540' OR NSC141540 OR NSC-141540 OR Onkoposid OR Riboposid OR Toposar OR 'VP 16 213' OR VP-16 OR 'VP 16' OR VP16 OR Vepesid OR Vépéside-Sandoz OR 'Vépéside Sandoz'



	#66	MeSH descriptor: [Irinotecan] explode all trees
	#67	irinotecan OR '7 Ethyl 10 hydroxycamptothecin' OR 'CPT 11' OR CPT-11 OR CTP11 OR Camptosar OR Camptothecin-11 OR 'Camptothecin 11' OR 'Irinotecan Hydrochloride' OR Irrinotecan OR 'NK012 Compound' OR 'SN 38' OR 'SN 38 11' OR SN-38 OR SN3811
	#68	MeSH descriptor: [Topotecan] explode all trees
	#69	topotecan OR '9 Dimethylaminomethyl 10 hydroxycamptothecin' OR Hycamtamine OR Hycamtin OR NSC-609699 OR 'NSC 609699' OR NSC609699 OR 'Nogitecan Hydrochloride' OR 'SKF 104864 A' OR SK&F104864A OR SKF104864A OR 'SK&F 104864 A' OR 'Topotecan Hydrochloride'
	#70	Apatinib OR 'apatinib mesylate' OR Rivoceranib OR 'Rivoceranib mesylate' OR YN968D1 OR YN-968D1 OR 'YN 968D1' OR TK02X14ASJ
	#71	Fruquintinib OR Fruzaqla OR HMPL-013 OR HMPL013 OR 49DXG3M5ZW OR fruquintinibum OR Elunate
	#72	Pazopanib OR Votrient OR pazopanibum OR GW786034 OR 'GW 786034' OR 'indazolylpyrimidine 13'
	#73	Pralsetinib OR Gavreto OR BLU-667 OR BLU667 OR 1WPE73O1WV OR BLU-123244 OR BLU123244 OR pralsetinibum
	#74	Bavituximab OR PGN401 OR 'PGN 401' OR PGN-401
	#75	Tremelimumab OR Imjudo OR tremelimumab-actl OR ticilimumab OR CP-675 OR 'CP 675' OR 'CP-675,206' OR 'CP675 cpd' OR QEN1X95CIX OR tremelimumabum
	#76	Sotorasib OR Lumakras OR Lumykras OR 'AMG 510' OR AMG-510 OR AMG510 OR 'Kras G12C inhibitor 9' OR sotorasibum
	#77	Tepotinib OR Tepmetko OR EMD-1214063 OR 'EMD 1214063' OR EMD1214063 OR MSC2156119 OR MSC-2156119 OR 1IJV77EI07 OR tepotinibum
	#78	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77
RCT filter	#79	MeSH descriptor: [Randomized Controlled Trial] explode all trees
	#80	MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees



	#81	('randomized clinical trial' OR 'randomized control trial' OR 'randomized controlled clinical trial' OR randomized controlled stud* OR 'randomized controlled trial' OR randomized-control trial* OR randomised control trial* OR randomised controlled clinical trial* OR randomised control stud* OR randomised control trial* OR randomised-controlled trial*):ti,ab,kw
	#82	#79 OR #80 OR #81
Remove animal studies and letters	#83	(animals NOT humans):ti,ab,kw
	#84	#82 NOT #83
	#85	#6 AND #78 AND #84
Year filter	#86	#85 AND from date 2020/09/01 to present (with Cochrane Library publication date from Sep 2020 to May 2024), in trials

H.1.2 Systematic selection of studies

Title and abstracts of studies identified from the search strategy were reviewed by two independent researchers in parallel according to predefined selection criteria. Articles that were identified as potentially relevant on the basis of titles and abstracts (where available), were reviewed in full by two independent screeners in parallel based on the same inclusion and exclusion criteria. Any discrepancy was resolved by discussion. A third reviewer assessed any remaining disagreements and provided the final decision

Table 83 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Primary research objective: Adult (≥18 years) patients with unresectable or metastatic non-squamous NSCLC harbouring any HER2 gene alteration Secondary research objective: Adult (≥18 years) patients with unresectable or metastatic non-squamous NSCLC with a HER2 gene alteration or with wild-type, undetermined or with a mixed mutation status for other actionable genetic mutations (eg EGFR, ALK, ROS1, MET or KRAS)	Patients with SCLC; studies that do not separately report results for patients with stage IIb and IV NSCLC; studies pooling results for earlier stages (stage I, II and IIIa) of NSCLC; studies reporting results for patients with mixed histology NSCLC, without stratified results	No changes



Intervention	Second or later-line treatments approved for the treatment of NSCLC or best supportive care	Studies including chemotherapy regimens and/or targeted therapies not approved by the EMA or US FDA for the treatment of NSCLC	Docetaxel was identified as the relevant comparator for this application. Studies without docetaxel was excluded.
Comparators	■ Overall survival (OS), including (hazard ratio, median, landmark survival rates) ■ Progression free survival (PFS), (hazard ratio, median, landmark survival rates, time to progression based on criteria reported in relevant publication) ■ Objective report rate (ORR), disease control rate (DCR), duration of response (DoR) based on criteria reported in the relevant publication ■ Time to response, time to subsequent treatment, post-progression survival ■ Recurrence-free survival ■ Disease-free survival ■ Mortality, all-cause/ cancer-related ■ Life expectancy ■ Relative survival/ mortality ■ Grade 3/ 4/ 5 AEs ■ Key AEs of interest (ILD, GI AEs, etc.) Time to treatment discontinuation	Studies that do not report on any of the outcomes listed under the inclusion criteria	No changes
Outcomes	Primary research objective: RCTs, non-randomized trials or single-arm trials (Phase 2, 3 and 4) Secondary research objective: RCTs	Phase 1 trials, case studies/reports, observational studies (including prospective, retrospective,	No changes



cross-sectional),
reviews

Study design/publication type	Peer-reviewed publications in journals or retrieved via hand searches	Letters and editorials	No changes
	Conference abstracts (published after 2020)	Conference abstracts (published 2020 or earlier)	
Language restrictions	Full text version available in English	Not available in English	No changes

Abbreviations: *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; *EMA*, European Medicines Agency; *FDA*, Food and Drug Administration; *HER2*, human epidermal growth factor receptor 2; *HRQoL*, health-related quality of life; *KRAS*, Kirsten rat sarcoma viral oncogene homolog; *MET*, MET proto-oncogene, receptor tyrosine kinase; *NSCLC*, non-small cell lung cancer; *RCT*, randomised controlled trial; *ROS1*, C-ros oncogene; *SCLC*, small cell lung cancer



Figure 34. PRISMA diagram, part above the dotted line illustrates the global SLR

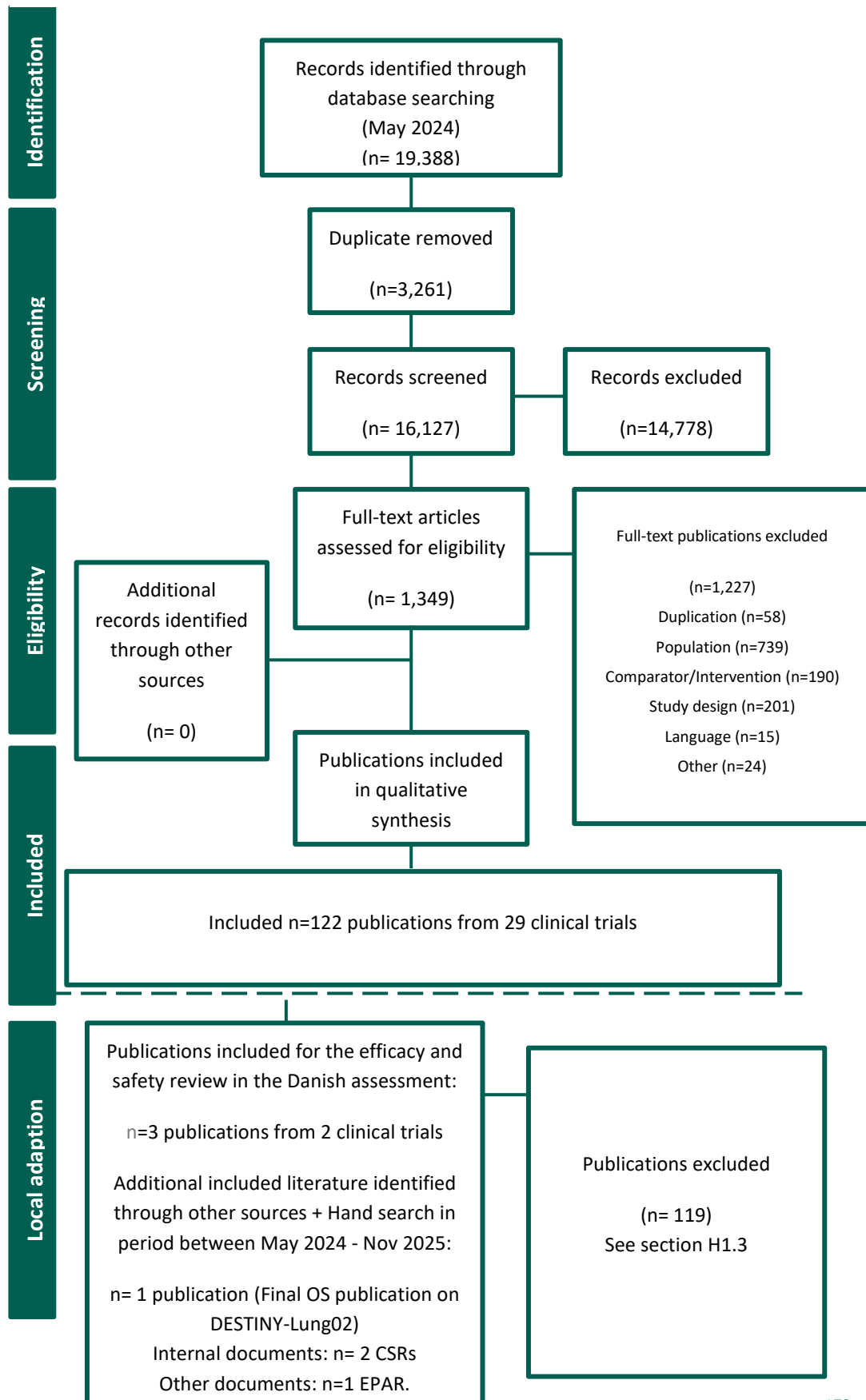




Table 84 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Destiny-Lung 02	To evaluate the safety and efficacy of trastuzumab deruxtecan in HER2-mutated metastatic non-small cell lung cancer (NSCLC) participants who had disease recurrence or progression during/after at least one regimen of prior anticancer therapy (second line or later) that must have contained a platinum-based chemotherapy drug.	Randomized, two-arm, phase 2 study	HER2-mutated metastatic NSCLC with prior treatment on platinum-based chemotherapy	T-DXd 5.4 mg/kg T-DXd 6.4 mg/kg	Objective response rate	Duration of response Progression-free survival Overall survival
CheckMate 057	To compare the overall survival of BMS-936558 (Nivolumab) as compared with Docetaxel in subjects with non-squamous cell non-small cell lung cancer (NSCLC) after failure of prior platinum-based chemotherapy	Open-label randomized phase 3 trial	Non-squamous cell NSCLC after failure of prior platinum-based chemotherapy	Nivolumab 3 mg/kg (N = 292) Docetaxel 75 mg/m2 (N = 290)	Overall survival	Objective response rate Duration of response Progression-free survival



H.1.3 Excluded fulltext references

Table 85. Original SLR September 2020, excluded full-text references in local adaption

#	Author, title of publication and year	Reason for exclusion
1	Arrieta O.; Cruz-Rico G.; Soto E.; Ramirez-Tirado L-A.; Caballe-Perez E.; et al. Reduction in hepatocyte growth factor serum levels is associated with improved prognosis in advanced lung adenocarcinoma patients treated with afatinib: a phase II trial 2016	Not intervention/comparator of interest
2	Arrieta O.G.; Barron F.; Carmona A.; Ramirez-Tirado L.; Barron Z.I.Z.; Cardona A.F.; Bautista Y.; Aldaco F.; Lazaro M.; Baez R.; Gerson R.; Blanco C. Efficacy and Safety of Pembrolizumab Plus Docetaxel vs Docetaxel Alone in Patients With Previously Treated Advanced Non-Small Cell Lung Cancer 2020	Not intervention/comparator of interest
3	Chen Y-M.; Fan W-C.; Tsai C-M.; Liu S-H.; Shih J-F.; Chou T-Y.; Wu C-H.; Chou K-T.; Lee Y-C.; Perng R-P.; Whang-Peng J. A phase II randomized trial of gefitinib alone or with tegafur/uracil treatment in patients with pulmonary adenocarcinoma who had failed previous chemotherapy 2011	Not intervention/comparator of interest
4	Felip E.; Hellmann MD.; Hui R.; Carcereny E.; Leighl NB.; Ahn M-J.; et al. 4-year overall survival for patients with advanced NSCLC treated with pembrolizumab: results from KEYNOTE-001 2018	Not intervention/comparator of interest, study design not of interest
5	Chen Y-M.; Liu J.M.; Chou T-Y.; Perng R-P.; Tsai C-M.; Whang-Peng J. Phase II randomized study of daily gefitinib treatment alone or with vinorelbine every 2 weeks in patients with adenocarcinoma of the lung who failed at least 2 regimens of chemotherapy 2007	Not intervention/comparator of interest
6	Cortot A.B.; Valette C.A.; Molinier O.; Le Moulec S.; Barlesi F.; Zalcman G.; et al. Weekly paclitaxel plus bevacizumab versus docetaxel as second or third-line treatment in advanced non-squamous non-small cell lung cancer (NSCLC): results from the phase III study IFCT-1103 ULTIMATE 2020	Study design not of interest.
7	Cufer T.; Vrdoljak E.; Gaafar R.; Erensoy I.; Pemberton K. Phase II, open-label, randomized study (SIGN) of single-agent gefitinib (IRESSA) or docetaxel as second-line therapy in patients with advanced (stage IIIB or IV) non-small-cell lung cancer 2006	Not intervention/comparator of interest
8	De Greve J.; Moran T.; Graas M-P.; Galdermans D.; Vuylsteke P.; Canon J-L.; Schallier D.; Decoste L.; Teugels E.; Massey D.; chand V.K.; Vansteenkiste J. Phase II study of afatinib, an irreversible ErbB family blocker, in demographically and genotypically defined lung adenocarcinoma 2015	Not intervention/comparator of interest
9	de Langen A.J.; Jebbink M.; Hashemi S.M.S.; Kuiper J.L.; de Bruin-Visser J.; Monkhorst K.; Thunnissen E.; Smit E.F. Trastuzumab and paclitaxel in patients with EGFR mutated NSCLC that express HER2 after progression on EGFR TKI treatment 2018	Not intervention/comparator of interest
10	Du N.; Li X.; Fan Z. Intrapleural combination therapy with bevacizumab and cisplatin for non-small cell lung cancer-mediated malignant pleural effusion 2013	Not intervention/comparator of interest
11	Ellis P.M.; Liu G.; Millward M.; Perrone F.; Shepherd F.A.; Sun S.; et al. NCIC CTG BR.26: A phase III randomized, double-blind, placebo controlled trial of dacotinib	Not intervention/



	versus placebo in patients with advanced/metastatic non-small cell lung cancer (NSCLC) who receive prior chemotherapy and an EGFR TKI 2014	comparator of interest
12	Fan Y.; Chen J.; Zhou C.; Wang H.; Shu Y.; Zhang J.; Hua H.; Huang D.C-L.; Zhou C. Afatinib in patients with advanced non-small cell lung cancer harboring HER2 mutations, previously treated with chemotherapy: a phase II trial 2020	Not intervention/comparator of interest
13	Gerber D.E.; Horn L.; Boyer M.; Sanborn R.; Natale R.; Ralmero R.; et al. Randomized phase 3 study of docetaxel plus bavituximab in previously treated non-squamous non-small-cell lung cancer 2018	Not intervention/comparator of interest
14	Gerber D.E.; Spigel D.R.; Giorgazde D.; Shtivelband M.; Ponomarova O.V.; et al. Docetaxel plus bavituximab in previously treated, advanced nonsquamous non-small-cell lung cancer 2016	Study design not of interest.
15	Jiang Q.; Zhang N-L.; Ma D-Y.; Tan B-X.; et al. Efficacy and safety of apatinib plus docetaxel as the second or above line treatment in advanced nonsquamous NSCLC 2019	Study design not of interest.
16	Hannah N.H.; Kaiser R.; Sullivan R.N.; Aren O.R.; Ahn M-J.; et al. Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): A randomized, double-blind, phase III trial 2016	Not intervention/comparator of interest
17	Hattori Y.; Satouchi M.; Katakami N.; Fujita S.; Kaji R.; Hata A.; et al. A phase II study of pemetrexed in patients with previously heavily treated non-squamous non-small cell lung cancer (HANSHIN Oncology Group 001) 2014	Not intervention/comparator of interest
18	Heist R.S.; Fidias P.; Huberman M.; Ardman B.; Sequist L.V.; Temel J.S.; Lynch T.J. A phase II study of oxaliplatin, pemetrexed, and bevacizumab in previously treated advanced non-small cell lung cancer 2008	Not intervention/comparator of interest
19	Herbst R.S.; Johnson D.H.; Miniberg E.; Carbone D.P.; et al. Phase I/II trial evaluating the anti-vascular endothelial growth factor monoclonal antibody bevacizumab in combination with the HER-1/epidermal growth factor receptor tyrosine kinase inhibitor erlotinib for patients with recurrent non-small-cell lung cancer 2005	Not intervention/comparator of interest
20	Ahn M-J.; Kim S-W.; Cho B-C.; Ahn J.S.; et al. Phase II study of afatinib as third-line treatment for patients in Korea with stage IIIB/IV non-small cell lung cancer harboring wild-type EGFR 2014	Not intervention/comparator of interest
21	Daniel Morgensztern, MD1; Manuel Cobo, MD, PhD2; Santiago Ponce Aix, MD3; Pieter E. Postmus, MD, PhD4; Conrad R. Lewanski, MD5; Jaafar Bennouna, MD, PhD6; Jürgen R. Fischer, MD7; Oscar Juan-Vidal, MD8; David J. Stewart, MD9; Gianpiero Fasola, MD10; Andrea Ardizzoni, MD11; Rafia Bhole, MD12; Marianne Wolfsteiner, MD13; Denis C. Talbot, MD14; Teng Jin Ong, MD12; and Ramaswamy Govindan, MD1; on behalf of the ABOUND.2L+ Investigators ABOUND.2L+: A Randomized Phase 2 Study of Nanoparticle Albumin-Bound Paclitaxel With or Without CC-486 as Second-Line Treatment for Advanced Nonsquamous Non-Small Cell Lung Cancer (NSCLC) 2018	Not intervention/comparator of interest
22	R. Palmero, P. Bidoli, I.M. Bondarenko, M. Boyer, P. Germonpre, D. Ghizdavescu, A. Kotsakis, H. Lena, G. Losonczy, K. Park, M. Reck, W. Su, N. Kallinteris, M. Tang, J. Lai, J. Shan, D.R. Spigel Final Clinical Results from SUNRISE: A Phase III, Randomized,	Not intervention/



	Double-Blind, Placebo-Controlled Multicenter Trial of Bavituximab Plus Docetaxel in Patients with Previously Treated Stage IIb/IV Nonsquamous Non Small Cell Lung Cancer 2017	comparator of interest
23	Steven F. Powell, Amer Beitinjaneh, Mathewos Tessema, Robin L. Bliss, Robert A. Kratzke, Joseph Leach, and Arkadiusz Z. Dudek Phase II Study of Topotecan and Bevacizumab in Advanced, Refractory Non—Small-Cell Lung Cancer 2013	Not intervention/comparator of interest
24	Yong Song, Liyun Miao, Zhaoxia Wang, Meiqi Shi Combination of apatinib and docetaxel in treating advanced non-squamous non-small cell lung cancer patients with wild-type EGFR: a multi-center, phase II trial 2020	Not intervention/comparator of interest
25	Hirsh, V., Latreille, J., Kreisman, H., Desjardins, P., Ofiara, L., Whittom, R., ... & Pintos, J. Sequential therapy with Vinorelbine followed by Gemcitabine in patients with metastatic non small cell lung cancer (NSCLC), performance status (PS) 2, or elderly with comorbidities—a multicenter phase II trial 2005	Not intervention/comparator of interest
26	Hotta K, Aoe K, Kozuki T, Ohashi K, Ninomiya K, Ichihara E, Kubo T, Ninomiya T, Chikamori K, Harada D, Nogami N. A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non—Small Cell Lung Cancer 2018	Not intervention/comparator of interest
27	Takeda et al. Bevacizumab beyond disease progression after first-line treatment with bevacizumab plus chemotherapy in advanced nonsquamous non-small cell lung cancer (WJOG 5910L): an open-label, randomized, phase II trial 2015	Not intervention/comparator of interest
28	Urata et al. Randomized Phase III Study Comparing Gefitinib With Erlotinib in Patients With Previously Treated Advanced Lung Adenocarcinoma: WJOG 5108L 2016	Not intervention/comparator of interest
29	Weiss et al. A single-arm phase II trial of pazopanib in patients with advanced non-small cell lung cancer with non-squamous histology with disease progression on bevacizumab containing therapy 2014	Not intervention/comparator of interest
30	Wu et al. A Phase II Clinical Trial of Apatinib in Pretreated Advanced Non-squamous Non—small-cell Lung Cancer 2018	Not intervention/comparator of interest
31	Yamaguchi et al. Bevacizumab with single-agent chemotherapy in previously treated non-squamous non-small-cell lung cancer: Phase II study 2018	Not intervention/comparator of interest
32	Zhou et al. Pyrotinib in HER2-Mutant Advanced Lung Adenocarcinoma After Platinum-Based Chemotherapy: A Multicenter, Open-Label, Single-Arm, Phase II Study 2020	Not intervention/comparator of interest
33	Zhou et al. Pemetrexed versus gefitinib as a second-line treatment in advanced nonsquamous nonsmall-cell lung cancer patients harboring wild-type EGFR (CTONG0806): a multicenter randomized trial 2014	Not intervention/comparator of interest



34	Katakami N.; Atagi S.; Goto K.; Hida T.; Horai T.; et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both 2013	Not population of interest, nor intervention/comparator of interest.
35	Kim Y.H.; Nishimura T.; Ozasa H.; Nagai H.; Sakamori Y.; Iwata T.; Sunadome H.; Nishimura T.; Mishima M. Phase II study of pemetrexed and erlotinib in pretreated nonsquamous, non-small-cell lung cancer patients without an EGFR mutation 2013	Not intervention/comparator of interest
36	Lee D.H.; Lee J.S.; Kim S-W.; Rodrigues-Pereira J.; et al. Three-arm randomised controlled phase 2 study comparing pemetrexed and erlotinib to either pemetrexed or erlotinib alone as second-line treatment for never-smokers with non-squamous non-small cell lung cancer 2013	Not intervention/comparator of interest
37	Lee J.S.; Lee K.H.; Cho E.K.; et al. Nivolumab in advanced non-small-cell lung cancer patients who failed prior platinum-based chemotherapy 2018	Not intervention/comparator of interest
38	Lu S.; Chang J.; Liu X.; et al. Randomized, double-blind, placebo-controlled, multicenter phase II study of fruquintinib after two prior chemotherapy regimens in Chinese patients with advanced nonsquamous non-small-cell lung cancer 2018	Not intervention/comparator of interest
39	Minami S.; Kijima T.; Hamaguchi M.; et al. Phase II study of pemetrexed plus intermittent erlotinib combination therapy for pretreated advance non-squamous non-small cell lung cancer with documentation of epidermal growth factor receptor mutation status 2013	Not intervention/comparator of interest
40	Gottfried M.; Bennouna J.; Bondarenko I.; et al. Efficacy and safety of nintedanib plus docetaxel in patients with advanced lung adenocarcinoma: complementary and exploratory analyses of the phase III LUME-Lung 1 study 2017	Not intervention/comparator of interest
41	Smit E.F.; Nakagawa K.; Nagasaka M.; Felip E.; Goto Y.; et al. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-mutated metastatic non-small cell lung cancer (NSCLC): Interim results of DESTINY-Lung-01 2020	Study design not of interest.
42	Millan S.; Trukhin D.; Kolesnik O.; Poddubskaya E.; et al. Bevacizumab biosimilar and reference bevacizumab in subjects with stage IIIB/IV no squamous non-small cell lung cancer (NSCLC) (STELLA study): Results for the primary endpoint in a confirmatory, double-blind, randomized, controlled study 2020	Not intervention/comparator of interest
43	Grohe C.; Gleiber W.; Haas S.; Kruger S.; Schulze M.; Atz J.; Kaiser R. Efficacy and safety of nintedanib + docetaxel in lung adenocarcinoma patients (pts) following treatment with immune checkpoint inhibitors (ICIs): Updated results of the ongoing non-interventional study (NIC) VARGADO (NCT02392455) 2019	Not intervention/comparator of interest
44	Reckamp K.L.; Giaccone G.; Camidge D.R.; et al. A phase 2 trial of dacotinib (PF-00299804), an oral, irreversible pan-HER (human epidermal growth factor receptor) inhibitor, in patients with advanced non-small cell lung cancer after failure of prior chemotherapy and erlotinib 2014	Not intervention/comparator of interest
45	Shimizu T.; Nakagawa Y.; Asai Y.; Tsujino I.; Takahashi N.; Gon Y. A phase II study of the combination of docetaxel and bevacizumab for previously treated non-small cell lung cancer 2019	Not intervention/



		comparator of interest
46	Fehrenbacher L. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. 2016. Lancet 2016	Study design not of interest.
47	Fehrenbacher L. Updated Efficacy Analysis Including Secondary Population Results for OAK: A Randomized Phase III Study of Atezolizumab versus Docetaxel in Patients with Previously Treated Advanced Non–Small Cell Lung Cancer. 201 2018	Study design not of interest.
48	Rittmeyer A. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. 2017. Lancet 2017	Study design not of interest.
49	Smith D.A. Updated survival and biomarker analyses of a randomized phase II study of atezolizumab vs docetaxel in 2L/3L NSCLC (POPLAR). 2016. Journal of Clinical Oncology 2016	Study design not of interest.
50	Garon E.B. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, 2014	Study design not of interest.
51	Leighl, N. B., Hellmann, M. D., Hui, R., Carcereny, E., Felip, E., Ahn, M.-J Pembrolizumab in patients with advanced non-small-cell lung cancer (KEYNOTE-001): 3-year results from an open-label, phase 1 study. 2019	Study design not of interest.
52	Garon E.B. Five-Year Overall Survival for Patients With Advanced Non–Small-Cell Lung Cancer Treated With Pembrolizumab: Results From the Phase I KEYNOTE-001 Study. 2019. J Clin oncol 2019	Study design not of interest.
53	Herbst R.S. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. 2016. Lancet 2016	Study design not of interest.
54	Herbst R.S. Long-Term Outcomes and Retreatment Among Patients With Previously Treated, Programmed Death-Ligand 1–Positive, Advanced Non–Small-Cell Lung Cancer in the KEYNOTE-010 Study. 2020. J Clin Oncol 2020	Study design not of interest.
55	Wu Y.L. Nivolumab Versus Docetaxel in a Predominantly Chinese Patient Population With Previously Treated Advanced NSCLC: CheckMate 078 Randomized Phase III Clinical Trial. 2019. J Thorac Oncol 2019	Patient population not of interest.
56	Aerts J.G. A randomized phase II study comparing erlotinib versus erlotinib with alternating chemotherapy in relapsed non-small-cell lung cancer patients: The NVALT-10 study. 2013. Ann Oncol 2013	Patient population not of interest.
57	Planchard D. ARCTIC: durvalumab with or without tremelimumab as third-line or later treatment of metastatic non-small-cell lung cancer. 2020. Ann Oncol 2020	Not intervention/ comparator of interest.
58	Choi M.K. A phase II trial of gefitinib monotherapy in pretreated patients with advanced non-small cell lung cancer not harboring activating EGFR mutations: implications of sensitive EGFR mutation test. 2015. Cancer Chemot 2015	Not intervention/ comparator of interest.



59	Garon E.B. Exploratory analysis of front-line therapies in REVEL: a randomised phase 3 study of ramucirumab plus docetaxel versus docetaxel for the treatment of stage IV non-small-cell lung cancer after disease progression 2020	Study design not of interest.
60	Maruyama R. Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. 2008. J Clin Oncol 2008	Patient population not of interest.
61	Thatcher N. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation 2005	Not intervention/ comparator of interest.
62	Chang A. Gefitinib (IRESSA) in patients of Asian origin with refractory advanced non-small cell lung cancer: subset analysis from the ISEL study. 2006. J Thorac Oncol 2006	Patient population not of interest.
63	Heigener D.F. Second-line erlotinib in patients with advanced non-small-cell lung cancer: subgroup analyses from the TRUST study. 2011. Lung cancer 2011	Not intervention/ comparator of interest.
64	Kawaguchi T. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). 2014. J Clin Onco 2014	Patient population not of interest.
65	Garassino M.C. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. 2013. Lancet Oncol 2013	Study design not of interest.
66	Juan O. 2015 Intercalated Dosing Schedule of Erlotinib and Docetaxel as a Therapeutic Strategy to Avoid Antagonism and Optimize Its Benefits in Advanced Non-Small-Cell Lung Cancer. A Randomized Phase II Clinical Trial. 2015. 2015	Patient population not of interest.
67	Perng R-P. High efficacy of erlotinib in Taiwanese NSCLC patients in an expanded access program study previously treated with chemotherapy. 2008. Lung cancer 2008	Patient population not of interest.
68	Smit E.F. A randomized, double-blind, phase III study comparing two doses of erlotinib for second-line treatment of current smokers with advanced non-small-cell lung cancer (CurrentS). 2016. Lung cancer 2016	Patient population not of interest.
69	Spigel D.R. Final survival and safety results from a multicenter, open-label, phase 3b trial of erlotinib in patients with advanced nonsmall cell lung cancer. 2008. Cancer 2008	Not intervention/ comparator of interest.
70	Yoshioka H. A phase II trial of erlotinib monotherapy in pretreated patients with advanced non-small cell lung cancer who do not possess active EGFR mutations: Okayama Lung Cancer Study Group trial 0705. 2010. J Thorac Oncol 2010	Patient population not of interest.



71	Ramalingam S.S. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. 2014. <i>Lancet Oncol</i> 2014	Not intervention/comparator of interest.
72	Chang G-C. Second-line pemetrexed treatment in Taiwanese patients with advanced nonsmall cell lung cancer: An open-label single-arm study. 2013. <i>Journal of the Formosan Medical Association</i> 2013	Patient population not of interest.
73	Karampeazis A. Pemetrexed versus erlotinib in pretreated patients with advanced non-small cell lung cancer: a Hellenic Oncology Research Group (HORG) randomized phase 3 study. 2013. <i>Cancer</i> 2013	Not intervention/comparator of interest.
74	Kim H.S. A phase II study of pemetrexed and carboplatin as a salvage therapy for platinum-pretreated patients with non-small cell lung cancer. 2010. <i>Lung Cancer</i> 2010	Not intervention/comparator of interest.
75	Smit E.F. Randomized phase II and pharmacogenetic study of pemetrexed compared with pemetrexed plus carboplatin in pretreated patients with advanced non-small-cell lung cancer. 2009. <i>J Clin Oncol</i> 2009	Not intervention/comparator of interest.
76	Kim H.T. A phase II study of irinotecan plus cisplatin for patients with advanced stage IIIB or IV NSCLC previously treated with nonplatinum-based chemotherapy. 2006. <i>Cancer</i> 2006	Not intervention/comparator of interest.
77	Sakata S. Phase II trial of weekly nab-paclitaxel for previously treated advanced non-small cell lung cancer: Kumamoto thoracic oncology study group (KTOSG) trial 1301. 2016. <i>Lung cancer</i> 2016	Not intervention/comparator of interest.
78	Anzai M. Efficacy and safety of nanoparticle albumin-bound paclitaxel monotherapy as second-line therapy of cytotoxic anticancer drugs in patients with advanced non-small cell lung cancer. 2017. <i>Medicine (Baltimore)</i> 2017	Not intervention/comparator of interest.
79	Kim H.T. A phase II study of irinotecan plus cisplatin for patients with advanced stage IIIB or IV NSCLC previously treated with nonplatinum-based chemotherapy. 2006. <i>Cancer</i> 2006	Not intervention/comparator of interest.
80	Sakata S. Phase II trial of weekly nab-paclitaxel for previously treated advanced non-small cell lung cancer: Kumamoto thoracic oncology study group (KTOSG) trial 1301. 2016. <i>Lung cancer</i> 2016	Not intervention/comparator of interest.
81	Anzai M. Efficacy and safety of nanoparticle albumin-bound paclitaxel monotherapy as second-line therapy of cytotoxic anticancer drugs in patients with advanced non-small cell lung cancer. 2017. <i>Medicine (Baltimore)</i> 2017	Not intervention/comparator of interest.

Table 86. Updated SLR September 2024, excluded full-text references in local adaption

#	Author, title of publication and year	Reason for exclusion
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1	Li B. T. et al., Trastuzumab deruxtecan in HER2-mutant non-small-cell lung cancer, 2022	Patient population not of interest.
2	Smit E.F. et al., Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial, 2024	Patient population not of interest.
3	Li B. T. et al., LBA45: Primary data from DESTINY-Lung01: A phase II trial of trastuzumab deruxtecan (T-DXd) in patients (Pts) with HER2-mutated (HER2m) metastatic non-small cell lung cancer (NSCLC), 2021	Patient population not of interest.
4	Nakagawa K. et al., OA04.05: Trastuzumab deruxtecan in HER2-overexpressing metastatic non-small cell lung cancer: interim Results of DESTINY-Lung01, 2021	Patient population not of interest.
5	Smit E.F. et al., MA11.03: Trastuzumab deruxtecan in HER2-mutated metastatic non-small cell lung cancer (NSCLC): interim results of DESTINY-Lung01, 2021	Patient population not of interest.
6	Li B. T. et al., 976P: Phase II trial of trastuzumab deruxtecan (T-DXd) in patients (Pts) with HER2-mutated (HER2m) metastatic non-small cell lung cancer (NSCLC): Registrational data from DESTINY Lung01, 2022	Patient population not of interest.
7	Smit E.F. et al., 976P: Trastuzumab deruxtecan in patients (pts) with HER2-overexpressing (HER2-OE) metastatic non-small cell lung cancer (NSCLC): Results from the DESTINY-Lung01 trial, 2022	Patient population not of interest.
8	Cheema P. et al., Efficacy and safety of trastuzumab deruxtecan (T-DXd) with durvalumab in patients with non-small cell lung cancer (HER2 altered NSCLC) who progressed on anti-PD1/PD-L1 therapy (HUDSON) , 2023	Patient population not of interest.
9	Yang G. et al., Pyrotinib combined with apatinib for targeting metastatic non-small cell lung cancer with HER2 alterations: a prospective, open-label, single-arm phase 2 study (PATHER2), 2022	Not intervention/comparat or of interest.
10	Yang G. et al., P86.02 Pyrotinib combined with apatinib for HER2-mutant non-small cell lung cancer: interim analysis from a phase II clinical study , 2021	Not intervention/comparat or of interest.
11	Yang G. et al., Efficacy and safety of pan-ErbB inhibitor pyrotinib combined with antiangiogenic agent apatinib for HER2-mutant or amplified metastatic NSCLC: a phase II clinical study, 2021	Not intervention/comparat or of interest.
12	Mazieres J. et al., Combination of trastuzumab, pertuzumab, and docetaxel in patients with advanced non-small-cell lung cancer harboring HER2 mutations: results from the IFCT-1703 R2D2 trial, 2022	Not intervention/comparat or of interest.
13	Mazieres J. et al., Combination of trastuzumab, pertuzumab, and docetaxel in patients with advanced non-small-cell lung cancer (NSCLC) harboring HER2 mutation: final results from the IFCT-1703 R2D2 trial, 2021	Not intervention/comparat or of interest.
14	Elamin Y.Y. et al., Pozotinib for Patients With HER2 Exon 20 Mutant Non-Small-Cell Lung Cancer: Results From a Phase II Trial, 2022	Not intervention/comparat or of interest.
15	Le X. et al., Pozotinib in non-small-cell lung cancer harboring HER2 exon 20 insertion mutations after prior therapies: ZENITH20-2 trial, 2022	Not intervention/comparat or of interest.



16	Salawu A. et al., A phase 2 trial of afatinib in patients with solid tumors that harbor genomic aberrations in the HER family: the MOBILITY3 basket study, 2022	Not intervention/comparat or of interest.
17	Song Z. et al., Efficacy and safety of pyrotinib in advanced lung adenocarcinoma with HER2 mutations: a multicenter, single-arm, phase II trial, 2022	Not intervention/comparat or of interest.
18	Borghaei H. et al., Five-Year Outcomes From the Randomized, Phase III Trials CheckMate 017 and 057: Nivolumab Versus Docetaxel in Previously Treated Non–Small-Cell Lung Cancer, 2021	Included
19	Lu S. et al., Nivolumab versus docetaxel in a predominantly Chinese patient population with previously treated advanced non-small cell lung cancer: 2-year follow-up from a randomized, open-label, phase 3 study (CheckMate 078), 2021	Patient population not of interest.
20	Mazieres J. et al., Atezolizumab versus docetaxel in pretreated patients with NSCLC: final results from the randomized phase 2 POPLAR and phase 3 OAK clinical trials, 2021	Not intervention/comparat or of interest.
21	Mazieres J. et al., 4-Year Survival in Randomised Phase II (POPLAR) and Phase III (OAK) Studies of Atezolizumab vs. Docetaxel in 2L+ NSCLC, 2021	Not intervention/comparat or of interest.
22	Herbst R.S. et al., Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1–Positive Advanced NSCLC, 2021	Study design not of interest.
23	Waterhouse D.M. et al., Continuous Versus 1-Year Fixed-Duration Nivolumab in Previously Treated Advanced Non–Small-Cell Lung Cancer: CheckMate 153, 2020	Not intervention/comparat or of interest.
24	Yoneshima Y. et al., Phase 3 Trial Comparing Nanoparticle Albumin-Bound Paclitaxel With Docetaxel for Previously Treated Advanced NSCLC, 2021	Not intervention/comparat or of interest.
25	Kim E.J. et al., A Phase I/IIa Randomized Trial Evaluating the Safety and Efficacy of SNK01 Plus Pembrolizumab in Patients with Stage IV Non–Small Cell Lung Cancer, 2022	Not intervention/comparat or of interest.
26	Steendam C.M.J. et al., Randomized phase III study of docetaxel versus docetaxel plus intercalated erlotinib in patients with relapsed non-squamous non-small cell lung carcinoma, 2021	Not intervention/comparat or of interest.
27	Taniguchi Y. et al., A Randomized Comparison of Nivolumab versus NivolumabpDocetaxel for Previously Treated Advanced or Recurrent ICI-Naïve Non–Small Cell Lung Cancer: TORG1630, 2022	Not intervention/comparat or of interest.
28	Takeuchi S. et al., Standard versus low-dose nab-paclitaxel in previously treated patients with advanced non-small cell lung cancer: a randomized phase II trial (JMT0 LC14-01), 2023	Not intervention/comparat or of interest.
29	Chen F. et al., 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., 2022	Not intervention/comparat or of interest.
30	Borghaei H. et al., SAPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, 2024	Patient population not of interest.
31	Borghaei H. et al., SAPHIRE: phase III study of sitravatinib plus nivolumab versus docetaxel in patients with previously treated advanced non-squamous non-small cell lung cancer (NSCLC), 2023	Patient population not of interest.



32	Reckamp K.L. et al., Phase II randomized study of ramucirumab and pembrolizumab versus standard of care in advanced non–small-cell lung cancer previously treated with immunotherapy—Lung-MAP S1800A, 2022	Not intervention/comparat or of interest.
33	Ghiringhelli F. et al., Atezolizumab and bevacizumab (atezo + bev) ± radiotherapy (RT) vs docetaxel (doc) in checkpoint inhibitor (CPI) experienced metastatic NSCLC (mNSCLC): Results from the phase Ib/II MORPHEUS-lung study, 2023	Patient population not of interest.
34	Peled N. et al., MK-7684A (vibostolimab [vibo] plus pembrolizumab [pembro] coformulation) with/without docetaxel in metastatic NSCLC after platinum-chemotherapy (chemo) and immunotherapy, 2023	Not intervention/comparat or of interest.
35	Neal J. et al., CONTACT-01: a randomized phase III trial of atezolizumab + cabozantinib versus docetaxel for metastatic non–small cell lung cancer after a checkpoint inhibitor and chemotherapy, 2024	Not intervention/comparat or of interest.
36	Han B. et al., Subgroup analysis in patients (pts) with non-squamous (N-Sq), EGFR-wild type (wt), second/third-line NSCLC from the global phase (Ph) 3 trial DUBLIN-3 (BPI-2358-103) with the plinabulin/docetaxel (Plin/Doc) combination versus Doc alone., 2022	Not intervention/comparat or of interest.
37	Park K. et al., Avelumab Versus Docetaxel in Patients With Platinum-Treated Advanced NSCLC: 2-Year Follow-Up From the JAVELIN Lung 200 Phase 3 Trial, 2021	Not intervention/comparat or of interest.
38	Herbst R. S. et al., COAST: an open-label, phase II, multidrug platform study of durvalumab alone or in combination with oleclumab or monalizumab in patients with unresectable, stage III non–small-cell lung cancer, 2022	Not intervention/comparat or of interest.

H.1.4 Quality assessment

The quality of studies included in the SLR were assessed according to the criteria outlined in the NICE single technology appraisal template. The full list of questions is provided and the quality assessment of the studies is presented in Table 87.

Table 87. Quality assessment results for parallel-group RCTs

Trial number (acronym)	Trial 1	Trial 2	[Add more columns as needed]
Q1: Was randomisation carried out appropriately?	(yes/no/not clear/NA)	(yes/no/not clear/NA)	
Q2: Was the concealment of treatment allocation adequate?	(yes/no/not clear/NA)	(yes/no/not clear/NA)	
Q3: Were the groups similar at the outset of the study in terms of prognostic factors?	(yes/no/not clear/NA)	(yes/no/not clear/NA)	
Q4: Were the care providers, participants and outcome assessors blind to treatment allocation?	(yes/no/not clear/NA)	(yes/no/not clear/NA)	
Q5: Were there any unexpected imbalances in drop-outs between groups?	(yes/no/not clear/NA)	(yes/no/not clear/NA)	



Q6: Is there any evidence to suggest that the authors measured more outcomes than they reported? (yes/no/not clear/NA) (yes/no/not clear/NA)

Q7: Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data? (yes/no/not clear/NA) (yes/no/not clear/NA)

Source: Single technology appraisal: user guide for company evidence submission template (1 April 2017), Section 2.5.

Adapted from Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care (University of York Centre for Reviews and Dissemination)

Abbreviations: CRD, Centre for Reviews and Dissemination; NA, not applicable; RCT, randomised controlled trial

Table 88: Quality assessment of the included clinical trials

Trial name, identifier	Q1*	Q2*	Q3*	Q4*	Q5*	Q6*	Q7*
DESTINY-Lung 02, NCT04644237	U	U	U	Y	N	N	Y
CHECKMATE057, NCT01673867	U	NA	Y	N	N	N	Y

Abbreviations: N, no; NA, not applicable; Q, question; U, unclear; Y, yes

H.1.5 Unpublished data

CSR for primary analysis and final analysis for DESTINY-Lung02 included as unpublished data.



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

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

NA

Table 89 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Abbreviations:

Table 90 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
NA	NA	NA	NA

Table 91 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
NA	NA	NA	NA	NA

I.1.1 Search strategies

NA

Table 92 Search strategy for [name of database]

No.	Query	Results
NA	NA	NA

I.1.2 Quality assessment and generalizability of estimates

NA

I.1.3 Unpublished data

NA



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

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

NA

J.1.1 Example: Systematic search for [...]

NA

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
NA	NA	NA	NA

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

NA

Table 52 Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NA	NA	NA	NA

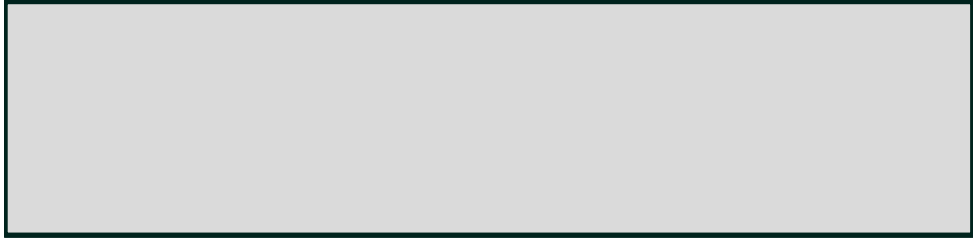
Abbreviations:



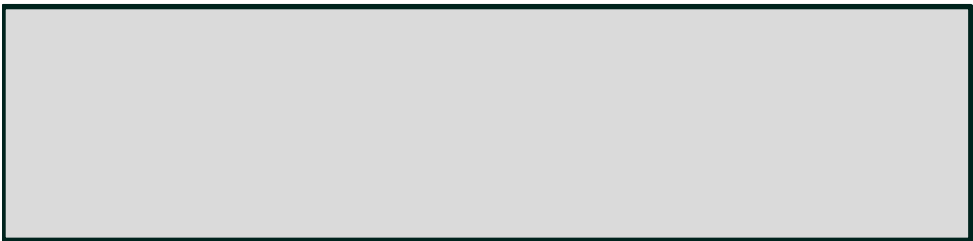
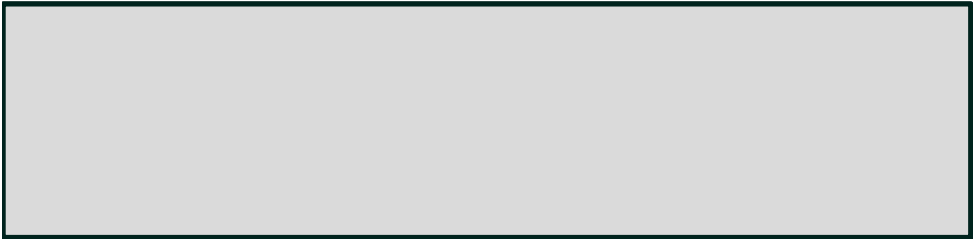
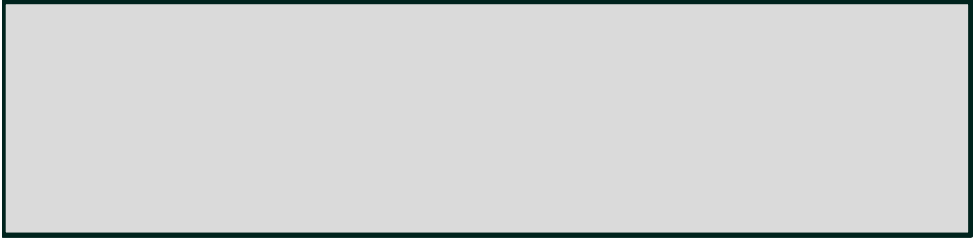
Appendix K. Hazard plots of extrapolations compared with smoothed hazard plots from DESTINY-Lung02

K.1 PFS





K.2 OS





K.3 TTD

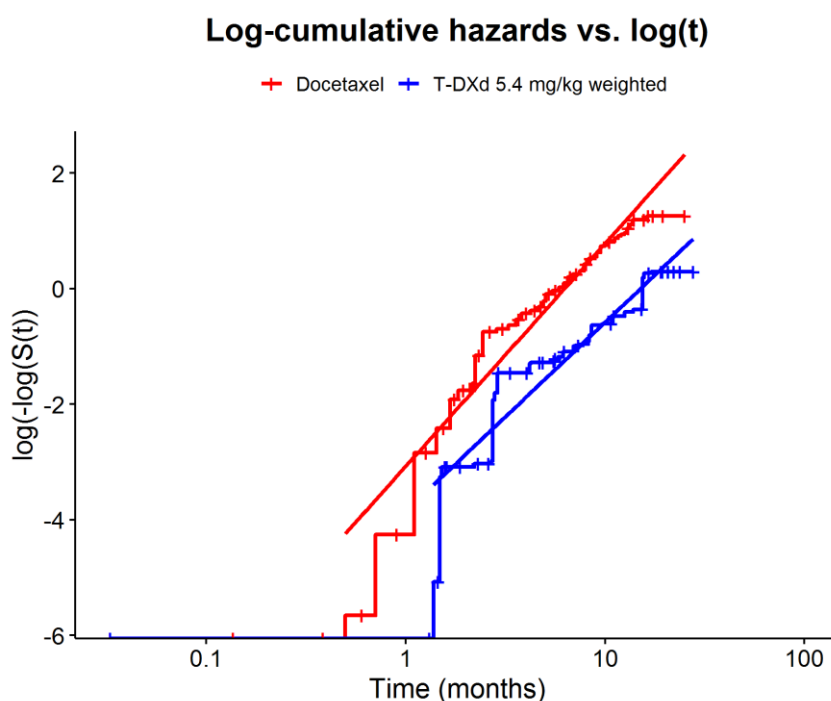




Appendix L. Diagnostic plots MAIC vs. docetaxel from CheckMate 057

L.1 MAIC vs docetaxel from CheckMate 057: PFS

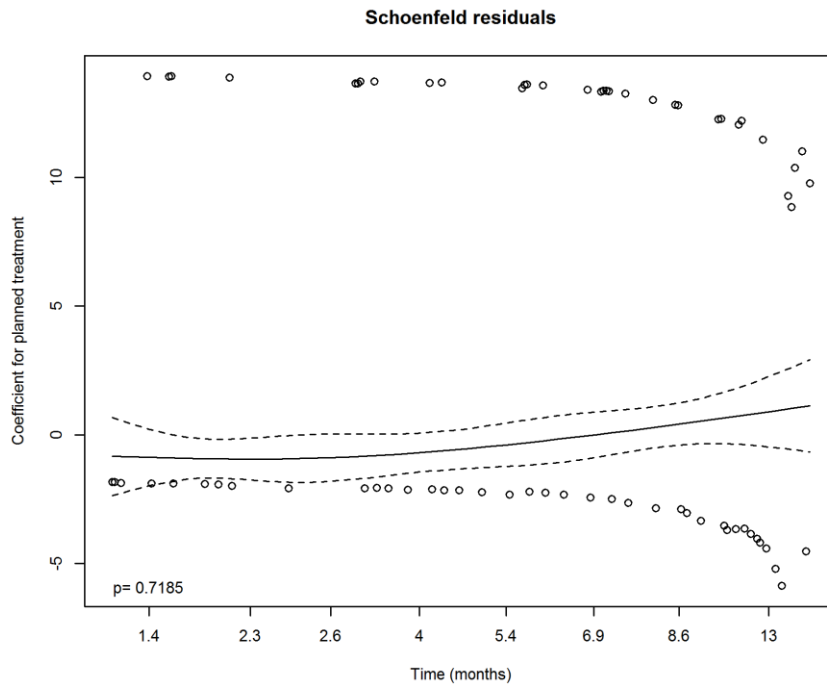
Figure 35. Log-cumulative hazards plot for PFS of T-DXd and docetaxel based on CheckMate 057 (DCO Aug 2023)



Abbreviations: DCO: data cut-off; PFS: progression-free survival; T-DXd: trastuzumab deruxtecan



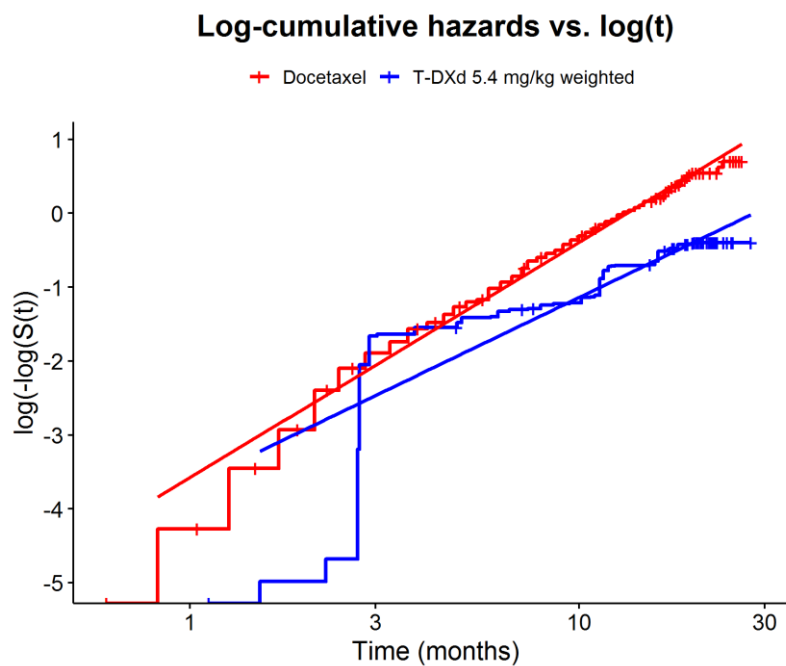
Figure 36. Schoenfeld residuals plot for PFS (T-DXd vs docetaxel based on CheckMate 057) (DCO Aug 2023)



Abbreviations: DCO: data cut-off; PFS: progression-free survival; T-DXd: trastuzumab deruxtecan

L.2 MAIC vs docetaxel from CheckMate 057: OS

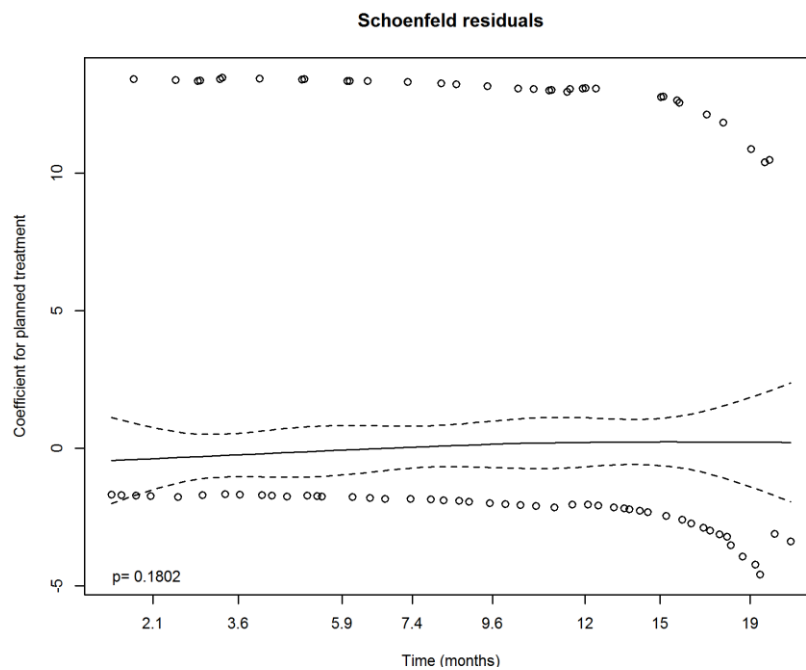
Figure 37. Log-cumulative hazards plot for OS of T-DXd and docetaxel based on CheckMate 057 (DCO Aug 2023)





Abbreviations: DCO: data cut-off; OS: overall survival; T-DXd: trastuzumab deruxtecan

Figure 38. Schoenfeld residuals plot for OS (T-DXd vs docetaxel based on CheckMate 057 (DCO Aug 2023))



Abbreviations: DCO: data cut-off; OS: overall survival; T-DXd: trastuzumab deruxtecan



Appendix M. HRQoL data from DESTINY-Lung02, DCO 23-12-2022

Table 93 HRQoL - EORTC QLC-C30 in DESTINY-Lung02 change from baseline summary statistics (DCO 2022-12-23)I(50)

	T-DXd 5.4 mg/kg		T-DXd 6.4 mg/kg	
	N	Mean (SE)	N	Mean (SE)
Baseline	98	61.65 (25.235)	44	63.45 (24.260)
Cycle 2 Day 1	92	2.90 (19.783)	41	2.64 (23.603)
Cycle 3 Day 1	83	2.71 (20.167)	38	2.63 (21.584)
Cycle 7 Day 1	65	4.23 (19.439)	27	0.93 (26.487)
Cycle 8 Day 1	60	7.92 (18.502)	26	4.81 (26.995)
Cycle 9 Day 1	55	5.45 (22.235)	22	6.44 (27.570)
Cycle 10 Day 1	52	3.53 (20.766)	24	9.03 (25.763)
Cycle 11 Day 1	47	3.19 (22.957)	22	9.47 (24.840)
Cycle 12 Day 1	43	2.13 (21.292)	20	5.00 (23.632)
Cycle 13 Day 1	42	5.56 (19.965)	17	2.45 (22.586)
Cycle 14 Day 1	36	3.94 (18.201)	16	-0.52 (21.617)
Cycle 15 Day 1	35	-0.24 (19.437)	16	1.56 (24.574)
Cycle 16 Day 1	28	1.79 (16.875)	14	-0.60 (24.561)
Cycle 17 Day 1	24	-1.74 (20.848)	10	5.00 (24.595)
Cycle 18 Day 1	21	-2.38 (20.606)	9	-0.93 (28.089)
Cycle 19 Day 1	18	-0.46 (18.628)	8	3.13 (17.783)
Cycle 20 Day 1	13	-3.85 (20.303)	3	-2.78 (24.056)
Cycle 21 Day 1	8	-6.25 (13.176)	2	16.67 (23.570)
Cycle 22 Day 1	2	8.33 (11.785)	0	NE



T-DXd 5.4 mg/kg			T-DXd 6.4 mg/kg	
Cycle 23 Day 1	2	25.00 (35.355)	0	—
Cycle 24 Day 1	2	-4.17 (5.893)	0	—
Cycle 25 Day 1	2	-12.50 (17.678)	0	—
Cycle 26 Day 1	2	-12.50 (17.678)	0	—
Cycle 27 Day 1	1	0.00 (NE)	0	—
Cycle 28 Day 1	1	0.00 (NE)	0	—
End of Treatment	41	-4.27 (21.820)	19	2.19 (30.154)
40-Day Follow-up	15	-1.11 (17.780)	8	15.63 (31.947)

Table 94 HRQoL – EQ-VAS in DESTINY-Lung02 change from baseline summary statistics (DCO 2022-12-23)(50)

	T-DXd 5.4 mg/kg		T-DXd 6.4 mg/kg	
	N	Mean (SE)	N	Mean (SE)
Baseline	95	65.92 (24.037)	43	70.21 (17.484)
Change from Baseline Cycle 2 Day 1	88	2.61 (15.333)	39	2.85 (17.676)
Change from Baseline Cycle 3 Day 1	79	3.35 (17.046)	37	-1.41 (20.344)
Change from Baseline Cycle 4 Day 1	76	4.91 (19.872)	36	-0.03 (14.673)
Change from Baseline Cycle 5 Day 1	72	3.65 (18.429)	30	0.57 (15.950)
Change from Baseline Cycle 6 Day 1	67	3.12 (18.113)	31	-0.61 (17.185)
Change from Baseline Cycle 7 Day 1	62	4.56 (15.031)	27	-5.26 (17.463)
Change from Baseline Cycle 8 Day 1	58	4.88 (15.974)	26	1.69 (16.470)
Change from Baseline Cycle 9 Day 1	53	2.62 (17.961)	23	0.39 (16.359)
Change from Baseline Cycle 10 Day 1	50	2.40 (19.204)	24	1.08 (18.692)
Change from Baseline Cycle 11 Day 1	45	1.91 (16.017)	22	1.64 (14.981)
Change from Baseline Cycle 12 Day 1	41	0.22 (15.457)	20	1.15 (16.011)



Change from Baseline Cycle 13 Day 1	40	1.15 (13.089)	17	1.00 (14.616)
Change from Baseline Cycle 14 Day 1	33	0.94 (12.730)	16	-2.81 (13.288)
Change from Baseline Cycle 15 Day 1	33	-0.64 (14.624)	16	-2.06 (15.238)
Change from Baseline Cycle 16 Day 1	26	-2.00 (16.042)	14	-2.64 (17.973)
Change from Baseline Cycle 17 Day 1	23	-1.17 (13.533)	10	-3.20 (17.364)
Change from Baseline Cycle 18 Day 1	21	-0.81 (10.405)	9	-10.00 (22.666)
Change from Baseline Cycle 19 Day 1	18	-0.61 (8.147)	8	-8.13 (13.943)
Change from Baseline Cycle 20 Day 1	13	-3.00 (8.052)	3	-6.00 (18.735)
Change from Baseline Cycle 21 Day 1	8	-2.63 (6.070)	2	4.00 (7.071)
Change from Baseline Cycle 22 Day 1	2	0.00 (15.556)	0	—
Change from Baseline Cycle 23 Day 1	2	1.50 (7.778)	0	—
Change from Baseline Cycle 24 Day 1	2	4.50 (2.121)	0	—
Change from Baseline Cycle 25 Day 1	2	-1.00 (5.657)	0	—



Appendix N. Grade ≥ 3 CTCAE adverse events

Table 95. Overview of all grade 3+ treatment emergent adverse events observed in Destiny-Lung02, DCO 25 Aug 2023(51).

Grouped Term / MedDRA Preferred Term	T-DXd 5.4 mg/kg (N=101)
Neutropenia	19 (18.8)
Anaemia	12 (11.9)
Leukopenia	6 (5.9)
Fatigue	8 (7.9)
Thrombocytopenia	6 (5.9)
Hypokalaemia	8 (7.9)
Nausea	4 (4.0)
Lymphopenia	4 (4.0)
Decreased appetite	2 (2.0)
Pleural effusion	3 (3.0)
Pneumonia	1 (1.0)
Transaminases increased	3 (3.0)
Vomiting	3 (3.0)
Acute kidney injury	1 (1.0)
Blood bilirubin increased	1 (1.0)
Diarrhoea	1 (1.0)
Pneumonitis	2 (2.0)
Weight decreased	3 (3.0)
Dyspnoea	2 (2.0)
Hyperglycaemia	1 (1.0)
Interstitial lung disease	1 (1.0)
Lung neoplasm malignant	2 (2.0)
Malignant neoplasm progression	2 (2.0)
Neurological symptom	1 (1.0)
Pericardial effusion	1 (1.0)
Pulmonary embolism	2 (2.0)
Respiratory failure	2 (2.0)
Urinary tract infection	1 (1.0)
Acute coronary syndrome	1 (1.0)



Acute myocardial infarction	1 (1.0)
Arrhythmia	1 (1.0)
COVID-19 pneumonia	1 (1.0)
Cancer pain	1 (1.0)
Cerebrovascular accident	1 (1.0)
Cholecystitis	1 (1.0)
Chronic kidney disease	1 (1.0)
Constipation	1 (1.0)
Cough	1 (1.0)
Diabetes mellitus	1 (1.0)
Duodenal ulcer	1 (1.0)
Hypoacusis	1 (1.0)
Hypothyroidism	1 (1.0)
Ileus	1 (1.0)
Intestinal perforation	1 (1.0)
Intracranial pressure increased	1 (1.0)
Intracranial tumour haemorrhage	1 (1.0)
Large intestinal obstruction	1 (1.0)
Metastases to meninges	1 (1.0)
Musculoskeletal pain [a]	1 (1.0)
Myocarditis	1 (1.0)
Optic nerve disorder	1 (1.0)
Pneumococcal sepsis	1 (1.0)
Sepsis	1 (1.0)
Spinal compression fracture	1 (1.0)
Subdural haemorrhage	1 (1.0)
Syncope	1 (1.0)
Tracheal haemorrhage	1 (1.0)
Troponin I increased	1 (1.0)
Troponin increased	1 (1.0)
Visual acuity reduced	1 (1.0)



Table 96. Summary of AEs (All Causality) reported within 30 Days of last dose in ≥5% of All Treated Subjects in CheckMate057(52).

System Organ Class (%) Preferred Term (%)	Nivolumab 3 mg/kg N = 287			Docetaxel N = 268		
	Any Grade	Grade 3-4	Grade 5	Any Grade	Grade 3-4	Grade 5
TOTAL SUBJECTS WITH AN EVENT	280 (97.6)	132 (46.0)	23 (8.0)	265 (98.9)	180 (67.2)	14 (5.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	196 (68.3)	35 (12.2)	3 (1.0)	202 (75.4)	46 (17.2)	3 (1.1)
FATIGUE	91 (31.7)	9 (3.1)	0	102 (38.1)	18 (6.7)	0
ASTHENIA	59 (20.6)	10 (3.5)	0	62 (23.1)	11 (4.1)	0
PIREXIA	35 (12.2)	1 (0.3)	0	42 (15.7)	0	0
CEPHALIC PERIPHERAL PAIN	23 (8.0)	2 (0.7)	0	16 (5.9)	0 (0.7)	0
NON-CARDIAC CHEST PAIN	16 (5.6)	2 (0.7)	0	15 (5.6)	5 (1.1)	0
MUCOSAL INFLAMMATION	6 (2.1)	1 (0.3)	0	21 (7.8)	5 (1.9)	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	165 (57.5)	41 (14.3)	4 (1.4)	151 (56.3)	29 (10.8)	2 (0.7)
COUGH	76 (26.5)	1 (0.3)	0	82 (30.1)	0	0
DYSPIKNEA	65 (22.6)	14 (4.9)	1 (0.3)	63 (23.5)	10 (3.7)	0
HAEMOPTYSIS	16 (5.6)	0	0	16 (6.0)	0 (0.7)	0
PLEURAL EFFUSION	16 (5.6)	7 (2.4)	0	10 (3.8)	0 (0.7)	0
PRODUCTIVE COUGH	17 (5.9)	0	0	15 (5.6)	0	0
GROGGEREAL PAIN	17 (5.9)	0	0	15 (5.6)	0	0
DYSPIKNEA EXERCUTIONAL	8 (2.8)	0	0	16 (6.0)	3 (1.1)	0
GASTROINTESTINAL DISORDERS	161 (56.1)	17 (5.9)	0	161 (60.1)	17 (6.3)	0
CONSTIPATION	66 (23.0)	2 (0.7)	0	45 (16.9)	0 (0.7)	0
NUSEA	63 (21.9)	1 (0.3)	0	80 (30.0)	0 (0.7)	0
DIARRHOEA	45 (15.7)	3 (1.0)	0	73 (27.2)	0 (1.1)	0
VOMITING	36 (12.5)	1 (0.3)	0	30 (11.2)	0	0
ABDOMINAL PAIN	15 (5.2)	0	0	17 (6.3)	0 (1.1)	0
STOMATITIS	6 (2.1)	1 (0.3)	0	24 (9.0)	2 (0.7)	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	131 (45.6)	20 (7.0)	0	117 (43.7)	13 (4.9)	0
ARTHRALGIA	46 (16.0)	1 (0.3)	0	32 (11.9)	0 (0.7)	0
MUSCULOSKELETAL PAIN	39 (13.6)	0 (0.3)	0	12 (4.5)	0	0
BACK PAIN	36 (12.5)	1 (0.3)	0	37 (13.8)	0 (0.7)	0
PAIN IN EXTREMITY	36 (12.5)	1 (0.3)	0	37 (13.8)	0 (1.1)	0
MYALGIA	18 (6.3)	1 (0.3)	0	35 (13.1)	0	0
MUSCULOSKELETAL CHEST PAIN	15 (5.2)	1 (0.3)	0	13 (4.8)	0 (0.4)	0
METABOLISM AND NUTRITION DISORDERS	123 (42.9)	25 (8.7)	0	91 (34.0)	23 (8.2)	0
DECREASED APPETITE	63 (21.9)	1 (0.3)	0	58 (21.6)	1 (0.4)	0
HYPERSILICAEMIA	13 (4.5)	1 (0.3)	0	15 (5.6)	0 (1.9)	0
NERVOUS SYSTEM DISORDERS	100 (34.8)	9 (3.1)	0	124 (46.3)	7 (2.6)	0
HEADACHE	28 (9.7)	3 (1.0)	0	32 (11.9)	0	0
DIZZINESS	25 (8.7)	0 (0.3)	0	24 (9.0)	0 (0.4)	0
PARAESTHESIA	12 (4.2)	0	0	14 (5.2)	0	0
NEUROPATHY PERIPHERAL	8 (2.8)	0	0	26 (9.7)	0 (1.1)	0
DYSGEUSIA	7 (2.4)	0	0	27 (10.1)	0	0
INFECTIONS AND INFESTATIONS	98 (34.1)	26 (9.1)	1 (0.3)	112 (41.8)	30 (11.2)	2 (0.7)
HEMATOPIA	17 (5.9)	0 (0.3)	0	13 (4.8)	14 (5.2)	1 (0.4)
UPPER RESPIRATORY TRACT INFECTION	17 (5.9)	0	0	12 (4.5)	1 (0.4)	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	97 (33.8)	3 (1.0)	0	117 (43.7)	22 (8.2)	0
RASH	36 (12.5)	1 (0.3)	0	13 (4.8)	0	0
PRURITUS	33 (11.5)	0	0	13 (4.8)	0	0
ITCHY SKIN	20 (7.0)	0	0	16 (5.9)	0	0
ERYTHEMA	6 (2.1)	0	0	16 (5.9)	0 (0.4)	0
ALOPECIA	4 (1.4)	0	0	70 (26.1)	0	0
INVESTIGATIONS	88 (30.7)	15 (5.2)	0	79 (29.1)	29 (10.8)	0
WEIGHT DECREASED	22 (7.7)	0	0	16 (5.9)	0	0
ALANINE AMINOTRANSFERASE INCREASED	16 (5.6)	1 (0.3)	0	16 (5.9)	0 (0.4)	0
NEUTROPHIL COUNT DECREASED	1 (0.3)	1 (0.3)	0	16 (5.9)	16 (6.0)	0
WHITE BLOOD CELL COUNT DECREASED	0	0	0	22 (8.2)	12 (4.5)	0
PSYCHIATRIC DISORDERS	56 (19.5)	5 (1.7)	0	42 (15.7)	5 (1.9)	0
DEPRESSION	20 (7.0)	0 (0.3)	0	22 (8.2)	0	0
ANXIETY	16 (5.6)	0	0	5 (1.9)	0	0
EOPLASM BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	47 (16.4)	24 (8.4)	13 (4.5)	15 (5.6)	5 (1.9)	7 (2.6)
MALIGNANT NEOPLASM PROGRESSION	25 (8.7)	14 (4.9)	11 (3.8)	8 (3.0)	1 (0.4)	6 (2.2)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	44 (15.3)	7 (2.4)	0	157 (58.6)	110 (41.0)	1 (0.4)
ANAEMIA	34 (11.8)	5 (1.7)	0	65 (24.2)	13 (4.8)	1 (0.4)
NEUTROPENIA	2 (0.7)	1 (0.3)	0	97 (36.2)	75 (28.0)	0
FEVERILE NEUTROPENIA	0	0	0	30 (11.2)	23 (8.6)	0
LEUKOPENIA	0	0	0	29 (10.8)	23 (8.6)	0
EYE DISORDERS	33 (11.5)	0	0	39 (14.2)	0	0
LACRIMATION INCREASED	3 (1.0)	0	0	22 (8.2)	0	0
ENDOCRINE DISORDERS	25 (8.7)	1 (0.3)	0	0 (0.4)	0	0
HYPOTHYROIDISM	13 (4.5)	0	0	0	0	0



Appendix O. Adjudicated ILD events associated with T-DXd

Table 97. Adjudicated Drug-Related ILD in Destiny-Lung02, DCO Aug 2023(48)

Adjudicated Drug-Related ILD Variable	T-DXd 5.4 mg/kg (n = 101)	T-DXd 6.4 mg/kg (n = 50)
Any grade, n (%)	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0) ^c	1 (2.0) ^c
Grade ≥3	2 (2.0)	2 (4.0)
Outcome of ILD events, ^{d,e}, n/N (%)		
Fatal	1/15 (6.7)	1/16 (6.3)
Not recovered/not resolved	3/15 (20.0)	6/16 (37.5)
Recovering/resolving	1/15 (6.7)	0
Recovered/resolved with sequelae	0	1/16 (6.3)
Recovered/resolved	10/15 (66.7)	8/16 (50.0)
Treatment of ILD, ^{e,f}		
Steroids ^g	12/15 (80.0)	13/16 (81.3)
Antibiotics	7/15 (46.7)	5/16 (31.8)
Steroids and antibiotics	6/15 (40.0)	4/16 (25.0)
Anti-PD-(L)1 as prior immediate treatment, n/N (%)		
Yes	6/15 (40.0)	5/16 (31.3)
No	5/15 (33.3)	8/16 (50.0)



Missing	4/15 (26.7)	3/16 (18.8)
Time since completion of prior anti-PD-(L)1 therapy, ^h, n/N (%)		
3 mo	5/44 (11.4)	10/28 (35.7)
≤3 mo	6/30 (20.0)	3/11 (27.3)
No prior therapy	4/27 (14.8)	3/11 (27.3)
Prior IO therapy, ⁱ, n/N (%)		
Yes	10/15 (66.7)	12/16 (75.0)
No	5/15 (33.3)	4/16 (25.0)
Time from IO therapies, n/N (%)		
<3 mo	6/15 (40.0)	3/16 (18.8)
≥3 to ≤6 mo	0	3/16 (18.8)
>6 mo,	4/15 (26.7)	6/16 (37.5)
Tobacco users, n/N (%)		
Never	7/15 (46.7)	9/16 (56.3)
Former	8/15 (53.3)	7/16 (43.8)

a At data cutoff (August 25, 2023), all potential cases of ILD were adjudicated by the adjudication committee, with no pending cases. b Randomly assigned patients who received ≥1 T-DXd dose. c At the 5.4-mg/kg dose, the fatal case involved a 73-year-old (age at screening) female patient who had received two earlier anticancer regimens, including carboplatin, pemetrexed, anti-PD-(L)1 therapy, and an EGFR TKI; her most recent anti-PD-(L)1 treatment occurred 2 years before study enrollment. At the 6.4-mg/kg dose, the fatal case involved an 85-year-old female patient with no history of prior IO therapy. She had received two prior systemic anticancer treatments, which included carboplatin, pemetrexed, and a taxane. Both patients developed respiratory symptoms after several treatment cycles. Initial management did not include corticosteroids for the patient in the T-DXd 6.4-mg/kg arm, but the patient in the T-DXd 5.4-mg/kg arm received IV methylprednisolone 1000 mg once daily starting on 8 March 2022, following the onset of grade 3 respiratory failure (later determined to be pneumonitis). Pneumonitis was not suspected until later stages and progressed quickly, resulting in death. d The outcome of the worst ILD event denominator is based on the adjudicated drug-related ILD. e Percentages are calculated using the total number of patients with adjudicated drug-related ILD as the denominator. f Treatment of ILD includes the antibiotics and/or steroids used and reported by investigators for patients with adjudicated drug-related ILD. g Steroid medication included betamethasone, dexchlorpheniramine maleate, dexamethasone, dexamethasone sodium phosphate, hydrocortisone, methylprednisolone, methylprednisolone sodium succinate, prednisolone, and prednisone. h A 3-month cutoff was used as a balance between the reduced blood concentrations of immunotherapies (half-life) and the ability to withhold treatment. i Prior IO therapies included atezolizumab, durvalumab, ipilimumab, nivolumab, pembrolizumab, and tremelimumab. EGFR, epidermal growth factor receptor; ILD, interstitial lung disease; IV, intravenous; IO, immuno-oncology; PD-(L)1, programmed death-(ligand) 1; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor.



Appendix P. Prior cancer treatments

Table 98. Type of prior cancer treatments in CheckMate057(2)

Docetaxel (n=290)		
Prior surgery, n (%)		218 (75%)
Prior radiotherapy, n (%)		138 (48%)
Type of prior systemic therapy, n (%)	Platinum-based therapy	290 (100%)
	ALK inhibitor	2 (1%)
	EGFR tyrosine kinase inhibitor	24 (8%)
	Other – experimental therapy	18 (6%)
Best response to most recent prior systemic regimen according to the investigator, n (%)	Complete or partial response	68 (23%)
	Stable disease	96 (33%)
	Progressive disease	116 (40%)
	Unknown/not reported	10 (3%)
Time from completion of most recent prior systemic regimen, n (%)	<3 months	183 (63%)
	3-6 months	56 (19%)
	>6 months	51 (18%)



Table 99. Prior cancer treatments in Destiny-Lung02(50).

	T-DXd 5.4 mg/kg (N=102)
Any Prior Systemic Cancer Therapy (n [%])	
Yes	102 (100)
Platinum-based Therapy	102 (100)
Docetaxel Treatment	30 (29.4)
Anti PD-1 Treatment	59 (57.8)
Anti PD-L1 Treatment	23 (22.5)
Anti PD-(L)1 Treatment	75 (73.5)
Platinum and Anti PD-(L)1 Therapy	24 (23.5)
But Not in Combination	
Platinum Therapy in Combination with	51 (50.0)
Anti PD-(L)1 Therapy	
No	0
Intended for [a] (n [%])	
Neo-Adjuvant	3 (2.9)
Adjuvant	12 (11.8)
Locally Advanced/Metastatic	45 (44.1)
Metastatic	66 (64.7)
Preventative	0
Maintenance	22 (21.6)
Other	1 (1.0)
If Locally Advanced or Metastatic, Line of Therapy [b] (n [%])	
1st Line	102 (100)
2nd Line	58 (56.9)
3rd Line	30 (29.4)
4th+ Line	21 (20.6)
Number of Prior Therapy Regimens (n [%])	
0	0
1	31 (30.4)
2	34 (33.3)
3	11 (10.8)
4	9 (8.8)
5	8 (7.8)
>5	9 (8.8)
Number of Prior Therapy Regimens	
n	102
Mean	2.7
Standard Deviation	2.12
Median	2.0
Min, Max	1, 12
Prior Systemic Cancer Therapy and Intended for [a] Group (n [%])	
Platinum-based Therapy	
Locally Advanced/Metastatic	43 (42.2)
Metastatic	61 (59.8)
Best Response to Most Recent Prior Therapy [c] (n [%])	
Complete Response (CR)	1 (1.0)
Partial Response (PR)	24 (23.5)
Stable Disease (SD)	38 (37.3)
Progressive Disease (PD)	25 (24.5)
Unknown (UNK)	12 (11.8)
Not Applicable (NA)	2 (2.0)
Reason for Discontinuation of Most Recent Prior Therapy [c] (n [%])	
Disease Progression	76 (74.5)
Adverse Event	7 (6.9)
Completed Therapy	6 (5.9)
Investigator Decision	5 (4.9)
Cost	0
Patient Choice	3 (2.9)
Regimen Availability	1 (1.0)
Unknown	3 (2.9)
Other	1 (1.0)
Prior Radiation Therapy (n [%])	
Yes	58 (56.9)
No	44 (43.1)
Prior Cancer Surgery (n [%])	
Yes	25 (24.5)
No	77 (75.5)





Appendix Q. Subsequent anti-cancer treatment

Table 100. Subsequent cancer therapy received in CheckMate 057, DCO 18 March 2015(2).

Category	Docetaxel (N=290)
Patients with any subsequent therapy, n (%)	175 (60)
Subsequent radiotherapy, n (%)	87 (30)
Subsequent systemic therapy, n (%)	144 (50)
Chemotherapy, n (%)	100 (35)
- Taxane	78 (27)
- Antimetabolite	22 (8)
- Platinum agents	29 (10)
- Vinca alkaloids	1 (<1)
- Alkylating agents	3 (1)
- Topoisomerase inhibitor	1 (<1)
EGFR/ALK inhibitors, n (%)	64 (22)
- Erlotinib	50 (17)
- Afatinib	7 (2)
- Crizotinib	4 (1)
- Gefitinib	5 (2)
- Other	3 (1)
VEGF(R) inhibitors, n (%)	7 (3)
Immunotherapy, n (%)	6 (2)
- Anti-CA6	0
- MEDI4736	1 (<1)
- MPDL3280A	2 (1)
- Nivolumab	1 (<1)
- Pembrolizumab	1 (<1)
- Other	1 (<1)
Experimental therapy, n (%)†	12 (4)

Data are based on a March 18, 2015 database lock.

Abbreviations: ALK = Anaplastic Lymphoma Kinase; EGFR = Epidermal Growth Factor Receptor; VEGF(R) = Vascular Endothelial Growth Factor (Receptor)

Note: Subsequent therapy was defined as therapy started on or after first dosing date (randomisation date if patient was never treated).

* Patients may have received more than one type of subsequent therapy. † Non-immunotherapy experimental agents.





Table 101. Subsequent cancer therapy received in DESTINY Lung02, DCO 25 August 2023(67)

	T-DXd 5.4 mg/kg (N=102) n (%)
Subjects with any post anti-cancer systemic therapy	46 (45.1)
DOCETAXEL	13 (12.7)
CARBOPLATIN	10 (9.8)
GEMCITABINE	8 (7.8)
PACLITAXEL	8 (7.8)
INVESTIGATIONAL ANTINEOPLASTIC DRUGS	7 (6.9)
RAMUCIRUMAB	6 (5.9)
ATEZOLIZUMAB	5 (4.9)
GIMERACIL;OTERACIL POTASSIUM;TEGAFUR	5 (4.9)
BEVACIZUMAB	4 (3.9)
VINORELBINE	4 (3.9)
PEMETREXED	3 (2.9)
AFATINIB	2 (2.0)
NIVOLUMAB	2 (2.0)
PEMBROLIZUMAB	2 (2.0)
TRASTUZUMAB	2 (2.0)
TRASTUZUMAB DERUXTECAN	2 (2.0)
TRASTUZUMAB EMTANSINE	2 (2.0)
CAPMATINIB	1 (1.0)
CISPLATIN	1 (1.0)
EGFR (EPIDERMAL GROWTH FACTOR RECEPTOR) INHIBITORS	1 (1.0)
ETOPOSIDE	1 (1.0)
GIMERACIL	1 (1.0)
HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) TYROSINE KINASE INHIBITORS	1 (1.0)
INVESTIGATIONAL DRUG	1 (1.0)
IPILIMUMAB	1 (1.0)
IRINOTECAN	1 (1.0)
MOBOCERTINIB	1 (1.0)
OTERACIL POTASSIUM	1 (1.0)
PEMETREXED DISODIUM HEPTAHYDRATE	1 (1.0)
TEGAFUR	1 (1.0)

Danish Medicines Council

Secretariat

Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk