Medicinrådet

Bilag til direkte indplacering af durvalumab i kombination med begrænset behandling med tremelimumab og platinbaseret kemoterapi i Medicinrådets evidensgennemgang vedr. lægemidler til førstelinjebehandling af uhelbredelig lungekræft

Vers. 1.0

Bilagsoversigt

1. Amgros' forhandlingsnotat vedr. durvalumab i komb. med begrænset behandling med tremelimumab og platinbaseret kemoterapi
2. Ansøgning vedr. durvalumab i komb. med begrænset behandling med tremelimumab og platinbaseret kemoterapi

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02.10.2026

LSC/DBS

Forhandlingsnotat

Dato for vurdering i Medicinrådet	28.10.2026
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab) + Imjudo (tremelimumab)
Ansøgt indikation	Durvalumab i kombination med tremelimumab og platinbaseret kemoterapi til førstelinjebehandling af voksne med metastatisk ikke småcellet lungekræft (NSCLC) uden sensibiliserende EGFR-mutationer eller ALK-positive mutationer
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse – direkte indplacering

Prisinformation

Amgros har følgende priser på Imfinzi og Imjudo:

Tabel 1: Aftalepris

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP
Imfinzi	50 mg/ml (2,4 ml)	4.005,90	[redacted]	[redacted]
Imfinzi	50 mg/ml (10 ml)	16.588,06	[redacted]	[redacted]
Imjudo	20 mg/ml (15 ml)	155.726,82	[redacted]	[redacted]

Aftaleforhold

Imfinzi og Imjudo indgår begge i udbuddet for immunterapi. Amgros har en eksisterende aftale for begge lægemidler. Aftalen gælder til den 31.12.2027. Der er inkluderet mulighed for prisregulering i aftalen.
[redacted]

Konkurrencesituationen

Medicinrådet har vurderet, hvorvidt Imfinzi + Imjudo + kemoterapi (D+T+CT) og Keytruda (pembrolizumab) + kemoterapi (P+CT) er klinisk ligeværdige som førstelinjebehandling til behandlingsnaive patienter med metastatisk NSCLC uden sensibiliserende EGFR- eller ALK-positive mutationer med ikke-planocellulær histologi, samt om D+T+CT og Opdivo (nivolumab) + Yervoy (ipilimumab) + kemoterapi (N+I+CT) er klinisk ligeværdige som førstelinjebehandling til behandlingsnaive patienter med metastatisk NSCLC uden sensibiliserende EGFR eller ALK-positive mutationer med planocellulær histologi.

Overordnet vurderer Medicinrådet, at det nuværende datagrundlag er for usikkert til, at D+T+CT kan betragtes som et klinisk ligeværdigt behandlingsalternativ til henholdsvis P+CT ved ikke-planocellulær NSCLC og N+I+CT ved planocellulær NSCLC hos patienter med PD-L1-ekspression < 1 %, jf. Tillæg til Medicinrådets evidensgennemgang vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft.

Tabel 2 viser lægemiddeludgiften til hhv. Imfinzi og Imjudo, Opdivo og Yervoy, og Keytruda for et behandlingsforløb på 48 uger, jf. Medicinrådets tværgående omkostningsanalyse vedr. PD-(L)1-hæmmere. Der er ikke medregnet lægemiddeludgifter til kemoterapi, da disse udgør en mindre del af den samlede lægemiddeludgift.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 48 uger (SAIP, DKK)
Imfinzi	50 mg/ml (10 ml)	Under platinbaseret kemoterapi: 1.500 mg hver 3. uge i 4 cyklusser, i.v. Post-platinbaseret kemoterapi: 1.500 mg hver 4. uge, i.v.	[redacted]	[redacted]
Imjudo	20 mg/ml (15 ml)	Under platinbaseret kemoterapi: 75 mg hver 3. uge i 4 cyklusser, i.v. En 5. dosis på 75 mg bør gives i uge 16, i.v.	[redacted]	[redacted]
Imfinzi i kombination med Imjudo				[redacted]

Opdivo	240 mg (1 stk.)	Under platinbaseret kemoterapi: 360 mg hver 3. uge i 2 cyklusser, i.v. Post-platinbaseret kemoterapi: 360 mg hver 3. uge, i.v.	[redacted]	[redacted]
Yervoy	5 mg/ml (10 ml)	Under platinbaseret kemoterapi: 1 mg/kg* hver 6. uge i 1 cyklus, i.v. Post-platinbaseret kemoterapi: 1 mg/kg* hver 6. uge, i.v.	[redacted]	[redacted]
Opdivo i kombination med Yervoy				[redacted]
Keytruda	395 mg (1 stk.)	Under platinbaseret kemoterapi: 395 mg hver 3. uge i 4 cyklusser, s.c. Post-platinbaseret kemoterapi: 395 mg hver 3. uge, s.c.	[redacted]	[redacted]

*Benyttet gennemsnitsvægt på 72 kg, Opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering
England	Ikke vurderet	

Opsummering

Imfinzi indgår i udbuddet for immunterapier der gælder indtil den 31.12.2027. Leverandøren har derfor kun mulighed for at sænke deres pris ved en aktivering af prisreguleringsmekanismen.

[redacted]

Medicinrådet

Instructions for pharmaceutical companies

This is the dossier for submitting documentation to the Danish Medicines Council as part of the assessment process for a new drug or an indication extension.

Please note the following requirements:

The Danish Medicines Council's secretariat carries out a technical validation of all missions. This means that the application must comply with all requirements specified in *the checklist for formal requirements* on the Danish Medicines Council's website before the assessment process can begin (day 0).

Companies must always use the current version of the checklist, dossier, standard Excel sheets and method guidelines.

All applications must comply with data protection regulations. Find out more about the Danish Medical Council's data policy here .

Text in gray and [in brackets] is provided for illustrative purposes only and must be deleted.

All sections in the dossier must be completed. If a section or appendix is not applicable, indicate "N/A" and a brief explanation of the reason.

If a joint European assessment has been prepared under the EU HTA Regulation (JCA), the company should not submit the same information that is already included in the dossier to the JCA. Instead, the company should refer to the specific section of the JCA report where the information is presented. Please note that it may be relevant to submit data from the same studies or updates of analyses that are included in the JCA report, e.g. if data have become available from a later data cut-off than the one used in the JCA report, or if new data for comparators change the results of a relevant comparative analysis from the JCA report. The assessment process will not begin until all requirements have been met.
The application can be submitted in both Danish and English.

Documentation to be submitted

The following documentation must be sent to the Danish Medicines Council's e-mail address: ansogning@medicinraadet.dk.

Submission dossier in Word format

Submission dossier in PDF format

One Excel file containing both a health economic analysis and a budget impact analysis. The analyses must be linked to the standard Excel sheets from the Danish Medicine Council's Excel template "Standard sheets".

The European Public Assessment Report (EPAR) must be attached. Please include a draft if the final version has not been published at the time of application and submit the final version as soon as possible thereafter.

Companies are encouraged to submit an importable reference list as a RIS file.

DENNE SIDE ER IKKE SLETTES

Medicinrådet

Confidential information in the application and any attachments and notes

The Danish Medicines Council publishes the application (including any annexes and notes) on its website together with the assessment report and recommendation.

The Danish Medicines Council must ensure the highest possible degree of transparency in the assessment of new drugs, in accordance with the Council´s terms of reference and the general principles of administrative law. The application must therefore be as transparent as possible (including any annexes and notes). The Danish Medicines Council may redact (black out) specific information if it is considered confidential and of significant importance to the company. Any redactions must always be limited to individual words/values and shall not cover entire sentences or sections of text.

Confidential information must be marked in the first version of the application. If the application, annexes or any subsequent notes contain confidential information, the companies must submit two versions:

- one version for the Danish Medicines Council's case processing, in which the confidential information is marked with turquoise marking (Hex: #00FFFF).
- one version for publication on the Danish Medicines Council's website, in which the confidential information is redacted using black masking. The Danish Medicines Council will publish this version.

It is the company's responsibility to ensure that the redactions is sufficient so that the confidential information cannot be read when published on the Danish Medicines Council's website. This can be done, for example, by covering the information to be redacted with black markings and simultaneously replacing the underlying text with placeholder characters (e.g., "XXX"), ensuring that the original text/information cannot be read when editing the document. Further information about confidential information and redaction is available on the Danish Medicines Council's website.

When redacting specific information, the company must provide concrete and specific justifications explaining why each redacted element is of significant importance to the company and why it should not be disclosed to the public. The justifications must be stated in Appendix K. If the application contains confidential information, completion of Appendix K is a requirement in the technical validation.

Please note that the company's redaction of information on the grounds of confidentiality does not necessarily result in corresponding 1:1-redactions in the context of request for access to documents. The Danish Medicines Council may only withhold information or documents from disclosure to the extent permitted by the provisions of the Danish Access to Public Administration Files Act. When processing a request for access to documents, the Danish Medicines Council therefore conducts an independent and specific assessment in accordance with the provisions of the Act. As a general rule, the Council will initially obtain a statement from the company for the purposes of the specific assessment.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be signed with a certificate by the company before submission to the Danish Medicines Council. Find out more here.

DENNE SIDE ER UKLASSIFICERET

Version log

Version	Date	Revision
2.0	February 20, 2026	New English version approved and published.
1.0	September 1, 2023	The application form in is posted on the Danish Medicines Council's website.

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Application for the assessment of Imfinzi (durvalumab) in combination with a limited course of Imjudo (tremelimumab) and four cycles of SoC platinum-based chemotherapy for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations*

*Application is only concerning the specific subgroups with:

- Squamous NSCLC with PD-L1 < 1 %
- Non-squamous NSCLC with PD-L1 < 1 %

Submitted May 4th, 2026

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Updated version September 9th, 2026

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Abbreviations

BTC	Biliary Tract Cancer	LS-SCLC	limited-stage Small Cell Lung Cancer
CADTH	Canadian Agency for Drugs and Technologies in Health	MAIC	Matching Adjusted Indirect Comparison
CD80	Cluster of differentiation 80	MEDLINE	Medical Literature Analysis and Retrieval System Online

CDSR	Cochrane Database of Systematic Reviews	MIBC	Muscle Invasive Bladder Cancer
CENTRAL	Cochrane Central Register of Controlled Trials	mNSCLC	metastatic non-small cell lung cancer
CI	confidence interval	N+I+CT	nivolumab + ipilimumab + platinum-based chemotherapy
CNS	central nervous system	NA	not available
CSR	Clinical Study Report	NICE	National Institute for Health and Care Excellence
CT	platinum-based chemotherapy	NIHR	National Institute for Health and Care Research
CTLA-4	cytotoxic T-lymphocyte-associated protein 4	NSCLC	non-small cell lung cancer
D+CT	durvalumab plus chemotherapy	OR	odds ratio
D+T+CT	durvalumab + tremelimumab + platinum-based chemotherapy	ORR	objective response rate
DCO	data cut-off	OS	overall survival
DMC	Danish Medicines Council	P+CT	pembrolizumab + platinum-based chemotherapy
dMMR	mismatch repair deficient	PBAC	Pharmaceutical Benefits Advisory Committee
DoR	duration of response	PD-L1	programmed death ligand
DRG	Diagnosis Related Group	PFS	progression-free survival
DSU	Decision Support Unit	pMMR	mismatch repair proficient
ECOG	Eastern Cooperative Oncology Group	PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
EGFR	epidermal growth factor receptor	PRO	patient-reported outcome
ELCC	European Lung Cancer Conferences	PSA	probabilistic sensitivity analyses
EMA	European Medicines Agency	QALY	Quality-Adjusted Life Year
EMBASE	Excerpta Medica Database	QoL	Quality of life

EPAR	European Public Assessment Report	Q3W / Q4W / Q6W	once every 3 weeks / 4 weeks / 6 weeks
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30	RCT	randomised controlled trial
EQ-5D-3L	EuroQol 5-Dimension 3-Level	RECIST	Response Evaluation Criteria in Solid Tumours
EQ-5D-5L	EuroQol 5-Dimension 5-Level	RIS	Research Information Systems
EQ-VAS	EuroQol Visual Analogue Scale	RR	risk ratio
ES-SCLC	extensive-stage Small Cell Lung Cancer	SAE	serious adverse event
ESMO	European Society for Medical Oncology	SCLC	Small Cell Lung Cancer
ESS	effective sample size	SLR	systematic literature review
EUCTR	EU Clinical Trials Register	SMD	standardized mean differences
HCC	Hepatocellular Carcinoma	SoC	standard of care
HR	hazard ratio	STK11	serine/threonine kinase 11
HRQoL	health-related quality of life	T+D+CT	tremelimumab + durvalumab + platinum-based chemotherapy
HTA	Health Technology Assessment	TEM	treatment effect modifier
ICI	immune checkpoint inhibitor	TFST	Time to first subsequent treatment
ICER	incremental cost-effectiveness ratio	TMB	tumor mutational burden
IO	immuno-oncology	TNM	tumour, lymph node, metastasis
IPD	individual patient-level data	TPS	Tumor Proportion Score
ITC	indirect treatment comparison	TSST	Time to second subsequent treatment
ITT	intention to treat	TTF	Time to treatment failure
JCA	joint European assessment	TTD	time to deterioration

JNHB	Joint Nordic Assessment	TTP	Time to progression
KEAP1	Kelch-like ECH-associated protein 1	VAS	visual analogue scale
KRAS	Kirsten rat sarcoma virus	WCLC	World Conference on Lung Cancer

1. Information about the drug

Drug information	
Trade name	Imfinzi
Generic name	Durvalumab
Indication as formulated by the European Medicines Agency (EMA)	IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.
Marketing Authorization Holder in Denmark	**Imfinzi**: AstraZeneca AB SE-151 85 Södertälje Sweden **Imjudo**: AstraZeneca AB SE-151 85 Södertälje Sweden
ATC code	**Imfinzi**: L01FF03, **Imjudo**: L01FX20
Combination therapy and/or concurrent treatment	Imfinzi (durvalumab) in combination with Imjudo (tremelimumab) and platinum-based chemotherapy
Expected date of EU approval (marketing authorisation)	Approved February 21st, 2023 Procedure IMJUDO: EMEA/H/C/004650/0000. Procedure IMFINZI: EMEA/H/C/004771/II/0041.
Has the drug received a conditional marketing authorisation?	No
Has the drug been in 'accelerated' assessment' at EMA?	No
Does the drug have orphan drug designation?	No
Other indications approved by the EMA	**Imfinzi:** **Non-Small Cell Lung Cancer (NSCLC)**

- IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements.
- IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements
- IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

Small Cell Lung Cancer (SCLC)

- IMFINZI as monotherapy is indicated for the treatment of adults with limited-stage SCLC (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.
- IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage SCLC (ES-SCLC).

Biliary Tract Cancer (BTC)

- IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC.

Hepatocellular Carcinoma (HCC)

- IMFINZI as monotherapy is indicated for the first line treatment of adults with advanced or unresectable HCC.
- IMFINZI in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC.

Endometrial Cancer

- IMFINZI in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:
- IMFINZI as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)

	• IMFINZI in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR). **Muscle Invasive Bladder Cancer (MIBC)** • IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable MIBC. **Gastric or Gastro-oesophageal Junction Adenocarcinoma (GC/GEJC)** • IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma. **IMJUDO:** • in combination with durvalumab is indicated for the first line treatment of adults with advanced or unresectable HCC. • in combination with durvalumab and platinum-based chemotherapy is indicated for the first line treatment of adults with metastatic NSCLC (mNSCLC) with no sensitising EGFR mutations or ALK positive mutations.
Other indications that have been evaluated by the Danish Medicines Council	• IMFINZI as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥ 1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy (see section 5.1). **Outcome**: approved • IMFINZI in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by IMFINZI as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements. **Outcome**: rejected • IMFINZI in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with ES-SCLC. **Outcome**: approved • IMFINZI as monotherapy is indicated for the treatment of adults with LS-SCLC whose disease has not progressed following platinum-based chemoradiation therapy. **Outcome:** approved

	• IMFINZI in combination with gemcitabine and cisplatin is indicated for the first-line treatment of adults with unresectable or metastatic BTC. **Outcome**: approved • **IMFINZI** in combination with **tremelimumab** is indicated for the first line treatment of adults with advanced or unresectable HCC. **Outcome**: approved • IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable MIBC. **Outcome**: rejected • IMFINZI in combination with FLOT chemotherapy as neoadjuvant and adjuvant treatment, followed by adjuvant IMFINZI monotherapy, is indicated for the treatment of adults with resectable gastric or gastro-oesophageal junction adenocarcinoma. **Outcome**: approved
Joint Nordic Assessment (JNHB): **Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?**	In Denmark a similar study (CheckMate 9LA) with nivolumab + ipilimumab was assessed by DMC in 2022 and again in 2025 and outcome was a partial recommendation. The nivolumab/ipilimumab combination is not recommended in all Nordic countries.
Joint Nordic Assessment (JNHB): Is the drug suitable for a joint Nordic assessment?	No, different processes/systems and we have applied later in Denmark than some of the other countries.
Has a joint European assessment (JCA) been carried out via the EU HTA Regulation?	No
Delivery	BEGR
Packaging – types, sizes/number of units and concentrations	**Imfinzi**: • 2.4 ml (a total of 120 mg durvalumab) of concentrate in a vial. • 10 ml (a total of 500 mg durvalumab) of concentrate in a vial. **Imjudo**: • 1.25 ml (a total of 25 mg tremelimumab) concentrate in a vial. Pack size of 1 single-dose vial. Was launched in Medicinpriser.dk March 30th, 2026. • 15 ml (a total of 300 mg tremelimumab) concentrate in a vial. Pack size of 1 single-

	dose vial. (available in Medicinpriser.dk). This pack is not approved for the POSEIDON indication.

2. Summary table

Overview	
Indication relevant to the assessment	IMFINZI in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with mNSCLC with no sensitising EGFR mutations or ALK positive mutations. Application is only concerning the specific subgroups: • Squamous NSCLC with PD-L1 < 1 % • Non-squamous NSCLC with PD-L1 < 1 %
Dosage regimen and administration route	**Tremelimumab** 75 mg IV plus **durvalumab** IV 1,500 mg and **platinum-based chemotherapy** IV **(D+T+CT)** for up to four 21-day cycles, followed by durvalumab IV once every 4 weeks until progression and one additional tremelimumab dose or chemotherapy for up to six 21-day cycles (with or without maintenance pemetrexed; all arms)
Comparator selection	The treatment goal for mNSCLC is symptom relief and prolongation of life. Patients with mNSCLC can receive different types of treatment depending on the characteristics of the tumor. If the tumor has mutations that can be targeted by treatment (in Danish clinical practice, these are activating EGFR mutations and ALK translocations), a targeted treatment is the first choice. Otherwise, the treatment is selected based on whether the tumor is squamous or non-squamous, and the amount of PD-L1 expression. In the POSEIDON study the comparator is platinum-based chemotherapy (CT). The comparator arm does not correspond to current standard treatment in most of the populations that the current guidelines are divided into. For patients with **squamous** cell histology and **PD-L1 expression < 1%,** CT was golden standard, however **nivolumab + ipilimumab + CT (N+I+CT)** has replaced CT in this group in late 2022. This combination treatment is given as an intravenous infusion, and the recommended dose is 360 mg of nivolumab every 3 weeks in combination with 1 mg/kg of ipilimumab every 6 weeks and CT every 3 weeks. After two cycles of CT, treatment is continued with 360 mg of nivolumab every 3 weeks in combination with 1 mg/kg of ipilimumab every 6

	weeks. Treatment is continued until disease progression, unacceptable toxicity or a maximum of 24 months in patients without disease progression. In the **non-squamous** subgroup with **PD-L1 expression < 1%**, **pembrolizumab + CT (P+CT)** is currently recommended. In the KEYNOTE-189 study patients received 200 mg pembrolizumab or saline placebo every 3 weeks for up to 35 cycles. All patients received pemetrexed and investigators' choice of cisplatin or carboplatin every 3 weeks for 4 cycles followed by pemetrexed maintenance therapy every 3 weeks. In Denmark pembrolizumab is administered weight-based (off-label). Further four treatment groups are defined by DMC and here the recommendation is immune checkpoint inhibitor (ICI) monotherapy for squamous and non-squamous and PD-L1 expression ≥ 50 % and ICI plus CT for non- squamous and squamous NSCLC and PD-L1 expression 1 – 49 %. In summery AstraZeneca is applying for "direkte indplacering" of D+T+CT in the above 2 mentioned subgroups (with bold). The reason for choosing these subgroups out of six is mainly due to the fact that PD-L1 + CTLA-4 combinations show greater efficacy for squamous mNSCLC with PD-L1 < 1% (as N+I+CT is already recommended) and for non-squamous mNSCLC with PD-L1 < 1% where PD-L1+CTLA-4 may be particularly effective in mutation-defined subgroups (i.e., STK11, KRAS, KEAP1) that are predominantly seen in non-squamous disease.
Prognosis with current standard treatment (comparator(s))	In 2023, the one-year survival rate for Danish patients with locally advanced lung cancer (diagnosed in 2022) was between 45.5% and 66.4%, while the five-year survival rate for the same patient group (diagnosed in 2018) was between 9.4% and 26.2% [1]. For patients with advanced/metastatic lung cancer, the 1-year survival rate in 2023 (diagnosed in 2022) was between 26.4% and 46.3%, while the 5-year survival rate (diagnosed in 2018) varied from 5.6% to 9.8% [1].
Type of documentation for the clinical evaluation	Matching adjusted indirect comparison (MAIC) for efficacy and Bucher indirect treatment comparison (ITC) for safety
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared to comparator(s))	In the **mixed histology** with **PD-L1 < 1%** D+T+CT vs. N+I+CT: • Hazard ratio (HR) for overall survival (OS): 0.93 (95% CI: 0.62, 1.39) • HR for progression free survival (PFS): 0.86 (95% CI: 0.57, 1.31) **Non-squamous** D+T+CT vs. P+CT and with **PD-L1 < 1 %:** • HR for OS: 1.11 (95% CI: 0.66, 1.88) • HR for PFS: 0.90 (95% CI: 0.54, 1.49) In a subgroup of **non-squamous** histology:

	• HR for OS, D+T+CT vs. P+CT: 0.91 (95% CI: 0.66, 1.26) • HR for PFS, D+T+CT vs. P+CT: 1.22 (95% CI: 0.86, 1.73) In ITT population (mixed histology): • HR for OS , D+T+CT vs. N+I+CT : 0.83 (0.65, 1.06) • HR for PFS, D+T+CT vs. N+I+CT : 0.91 (0.70, 1.20) In a subgroup of **squamous** histology: • HR for OS, D+T+CT vs. N+I+CT: 1.21 (95% CI: 0.81, 1.79) • HR for PFS, D+T+CT vs. N+I+CT: 1.25 (95% CI: 0.82, 1.90) Since an indirect comparison was not conducted on outcomes for health-related quality of life (HRQoL), it is not included in this report.
Serious adverse events for the intervention and comparator	In a subgroup of **non-squamous** histology: • Odds ratio (OR) for adverse events (AEs) leading to discontinuation (any cause), D+T+CT vs. P+CT: 0.70 (95%: 0.37, 1.34) An indirect comparison in safety between D+T+CT vs. N+I+CT in a subgroup of squamous histology and PD-L1 < 1% is not available at this moment. However, a comparison in the intend-to-treat (ITT) population, i.e., mixed histology, between these studies is available; • OR for AEs leading to discontinuation (any cause), D+T+CT vs. N+I+CT: 0.53 (95%: 0.28, 1.02) POSEIDON study reports that the most frequent serious AEs (SAEs) in D+T+CT arm (N=330) were anaemia (4.5%), followed by pneumonia (3.6%), thrombocytopenia (2.4%), and febrile neutropenia (2.1%) [2]. The most frequent AEs (grade 3-5) were anaemia (18.5%), neutropenia (16.3%), thrombocytopenia (8.4%), and fatigue (7.7%) in P+CT arm (N=405) [3] while the most frequent AEs (grade 3-4) were neutropenia (7.0%), anaemia (5.9%), and diarrhea (4.2%) [4]
Type of health economic analysis	Not applicable
Health economic model	Not applicable
Outcomes and sources for extrapolating patient transitions	Not applicable

Instrument and sources for health-related quality of life	Not applicable
Life years gained (discounted, corrected for half-cycle and background mortality)	Not applicable
QALYs gained (discounted, corrected for half-cycle and background mortality)	Not applicable
ICER (DKK/QALY) (discounted, corrected for half-cycle and background mortality)	Not applicable
Company's assessment of uncertainty	The comparators of interest for this assessment are pembrolizumab in combination with platinum-based chemotherapy (P+CT) and nivolumab in combination with ipilimumab and platinum-based chemotherapy (N+I+CT). The latter is the only currently DMC recommended IO+IO+CT regimen, which, as D+T+CT, also includes the combination of an anti-PD-(L)1 inhibitor and anti-CTLA-4 inhibitor. A comparison of baseline characteristics shows large differences between the relevant trials in the proportion of patients with race ('Asian' versus 'non-Asian') and smoking status ('never' versus 'current or former'), which, along with histology ('non-squamous' versus 'squamous'), were characteristics identified as treatment effect modifiers (TEMs) in POSEIDON. The impact of these imbalances in TEMs between studies on the relative efficacy of D+T+CT versus P+CT and N+I+CT can be seen through comparison of HRs from ITCs before and after weighting in the MAIC. In each case, after adjusting for these differences in the MAIC the HRs for D+T+CT vs. P+CT and N+I+CT are lower than the HRs from the ITC before weighting. Conclusions on the relative efficacy of D+T+CT versus P+CT and N+I+CT should therefore consider the impact of these imbalances, with the ITCs after weighting in the MAIC providing less biased estimates of relative efficacy. The MAIC suggests D+T+CT is numerically more effective than N+I+CT for OS and PFS in the mixed histology with PD-L1 < 1%. An ITC in the subgroup of squamous with PD-L1 < 1% was not feasible due to an insufficient number of matchable patients to derive meaningful interpretation. In the non-squamous with PD-L1 < 1%, D+T+CT is numerically more effective than P+CT for PFS but not OS. Across all comparisons (before and after weighting), the 95% confidence intervals for the estimated HRs include 1, indicating no nominally statistically significant differences in outcomes. Nonetheless, these analyses support the recommendation of D+T+CT in the requested populations, as a new first-line treatment option

for adult patients with metastatic NSCLC with tumours that lack activating EGFR mutations and ALK fusions and with signs of low probability to respond to current standard-of-care chemoimmunotherapy.

3. Patient population, intervention, choice of comparator(s) and outcome(s)

3.1 Patient population

3.1.1 The disease

NSCLC is the most common type of lung cancer, accounting for between 80% to 90% of cases in Denmark [5]. Lung cancer is categorised according to the American Joint Committee on Cancer (AJCC) staging criteria, which utilise the tumour, lymph node, metastasis (TNM) system [6, 7]. About half of NSCLC patients are diagnosed with advanced, metastatic disease and have a poor prognosis [5]. mNSCLC (stage IV disease) is characterized by the spread of cancer beyond the lungs to distant organs such as the brain, bones, liver, or adrenal glands.

Adenocarcinoma is the most common type of NSCLC, representing about half of all lung cancers while squamous cell carcinomas comprise roughly one quarter. A proportion of adenocarcinomas is characterized by so called “driver mutations”, which have consequences for treatment allocation. Treating lung cancer patients for their targetable mutations, including EGFR- or ALK mutations, has shown to benefit patients in terms of survival and remains the standard of care (SoC) according to international guidelines [8, 9]. Nevertheless, not all patients with lung adenocarcinoma have known driver mutations present. Targetable molecular alterations are identified in approximately 60% of lung adenocarcinoma patients in Western populations and 80% among Asian populations [10]. For eligible patients with mNSCLC lacking targetable driver mutations, ICIs have reshaped first-line therapy by significantly improving OS and delivering more durable responses compared with CT alone. For squamous mNSCLC, dual ICI regimens combined with limited CT (e.g., nivolumab plus ipilimumab) have demonstrated a greater magnitude of benefit in squamous histology than in non-squamous [11], offering a critical option for this historically poor-prognosis group [12-15]. For non-squamous mNSCLC, the standard treatment involves ICI combinations with pemetrexed and platinum-based chemotherapy, which provide durable survival and have maintained benefit across 5-year and 6-year landmark analyses [3, 16].

The PD-L1 <1% subgroup of mNSCLC has historically been more difficult to treat because these tumours often exhibit primary resistance to anti–PD-(L)1 monotherapy [17]. This resistance is frequently linked to an immunologically "cold" tumor microenvironment,

which lacks the significant T-cell infiltration required for single-agent immune checkpoint inhibitors (ICIs) to be effective [18, 19]. This subgroup became more treatable through the strategic combination of dual ICIs and limited chemotherapy, which addresses these biological challenges. The approach leverages complementary mechanisms where anti–PD-1 therapy reactivates pre-existing anti-tumor T cells, while anti–CTLA-4 therapy primes de novo T-cell responses and broadens the T-cell repertoire. Together, these effects "heat up" immunologically cold tumours by enhancing T-cell proliferation, diversification, and tumour infiltration, thereby amplifying anti-tumour activity [20, 21].

Patients with STK11, KEAP1, and KRAS (co-) mutations represent subgroups in mNSCLC (mainly in non-squamous histology) with higher unmet medical need due to relatively poor outcomes on standard therapies, including immunotherapy [22-26]. Emerging evidence from clinical trials and molecular studies suggests combination immunotherapy (PD-(L)1 inhibitor + CTLA-4 inhibitor) may provide better response in these harder-to-treat molecular subtypes [2, 27-29].

KRAS mutations are found in approximately 30% of NSCLC patients in Denmark [30, 31]. The KRAS oncogene is often co-mutated with STK11 and KEAP1 [22], which have immunomodulatory effects and are linked to poor prognosis and limited response to standard therapies such as immunotherapy [22, 32]. These genes normally act to inhibit cell proliferation and tumour development, so their loss or inactivation removes this inhibition of cell proliferation and contributes to abnormal proliferation of the tumour cells. KEAP1 mutations have also been shown to confer resistance to radiotherapy [33]. STK11 mutations are found in approximately 10–20% of non-squamous NSCLC cases and KEAP1 in approximately 10-15% [34, 35]. The TRITON study is currently going to evaluate the effectiveness of dual immune checkpoint inhibition (PD-1/PD-L1 inhibitor plus CTLA-4 inhibitor) in advanced NSCLC, including molecularly defined subgroups such as KRAS, STK11, and KEAP1 mutated tumours [36]. The dual inhibition approach aims to overcome intrinsic resistance mechanisms associated with STK11 and KEAP1 mutations, which have historically been linked to poorer prognosis and limited benefit from standard immunotherapy [22].

In Denmark, diagnosis of mNSCLC involves [37]:

- Initial imaging with CT thorax and upper abdomen with intravenous contrast
- PET/CT for patients considered for potentially curative treatment
- Tissue biopsy for histological confirmation and molecular testing
- Molecular testing (gene panels) is routinely performed on non-squamous NSCLC samples to identify targetable mutations such as EGFR, ALK, ROS1, BRAF, KRAS, MET, HER2, NTRK, and RET. This testing is crucial for guiding treatment decisions, particularly for targeted therapies.
- PD-L1 immunohistochemistry is performed on all NSCLC samples, both squamous and non-squamous.

In Denmark, despite improvements in outcomes at earlier cancer stages, survival for metastatic disease remains poor; the 5-year survival rate is under 10% for patients with stage IVA or IVB disease [5].

Quality of life (QoL) is an important consideration for mNSCLC patients. Lung cancer patients experience significant QoL deterioration due to both disease symptoms and treatment side effects, with fatigue, pain, dyspnoea, and psychological distress being particularly burdensome [38].

3.1.2 Selected patient population

The following steps were used to estimate the number of eligible patients for mNSCLC who are eligible for durvalumab in combination with tremelimumab in Denmark. It is currently not entirely clear which patients are optimally suited for D+T+CT versus the current SoC. The estimates presented reflect our best assessment based on recent annual reports from the Danish Lung Cancer Register [5], supplemented by other sources [39] and assumption.

Based on the results from the POSEIDON study, we believe that certain patient subgroups may derive particular benefit from this treatment. Notably, patients with STK11, KEAP1, and/or KRAS (co-) mutations demonstrated especially promising outcomes. STK11 and KEAP1 mutations are present in about 10–20% of patients [34, 35].

- NSCLC cases: ≈ 4,100 patients [5]
- Stage IV (40%): ≈ 1,640 patients (Danish lung cancer registry [39])
- EGFR- and ALK wildtype (78%): ≈ 1,279 patients (Danish lung cancer registry [39])
- IO naïve (85%): ≈ 1,087 patients (Assumption)
- PD-L1 status identified (85%): ≈ 924 patients (Danish lung cancer registry [39])
- PD-L1 < 1% (33%): ≈ 305 patients (Danish lung cancer registry [39])
- Non-squamous (80%): ≈ 244 patients (Danish lung cancer registry [39])
    - STK11 and KEAP1 mutations (10%): ≈ 24 patients (Assumption)
    - Share (20%): ≈ 5 patients (Assumption)
- Squamous histology (20%) ≈ 61 patients
    - Share (20%): ≈ 12 patients (Assumption)
- Non-squamous (5) + squamous (12) = 17

Combining mutation prevalence with assumption for competitive market share, we estimate approximately 17 eligible patients per year (assuming 100% patient uptake). On this basis, Table 2 presents projected numbers of eligible patients over the next five years, assuming the above parameters remain unchanged.

Table 1. Expected number of patients and patient uptake when implementing the intervention

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of patients*	15	15	16	16	17
Patient uptake**	*50%*	*60%*	*70%*	*80%*	90%

*The number of patients in Denmark eligible for the new treatment in accordance with the EMA indication.
**Since dual immune checkpoint inhibition is already established for squamous mNSCLC, patient update is considered only for non-squamous mNSCLC.

3.2 Intervention

Table 2. Overview of the intervention, durvalumab + tremelimumab

Therapeutic indication relevant to the assessment	Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line treatment of adults with mNSCLC with no sensitising EGFR mutations or ALK positive mutations. Application is only concerning the specific subgroups: • Squamous NSCLC with PD-L1 < 1 % • Non-squamous NSCLC with PD-L1 < 1%
Generic name	Durvalumab (Imfinzi), tremelimumab (Imjudo)
ATC code	L01FF03, L01FX20
Mechanism of action	**Durvalumab** is an ICI that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation 80 (CD80). The blockade of PD-L1/PD-1 and PD-L1/CD80 communication prevents the inhibition of immune responses caused by overexpressed PD-L1, allowing the immune system to exert a cytotoxic T cell-driven response against PD-L1-expressing tumour cells. **Tremelimumab** is a human monoclonal antibody that targets the activity of cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). It blocks the activity of CTLA-4, contributing to T-cell activation, priming the immune response to cancer and fostering cancer cell death.
Administration method	Intravenous infusion
Packaging type, pack sizes, shelf life and strengths	**Imfinzi** (durvalumab) concentrate for solution for infusion: 50 mg/mL vial. Single-dose vials. **Imjudo** (tremelimumab) concentrate for solution for infusion: 20 mg/mL vial. Single-dose vials.
Package size(s)	**Imfinzi**: • Pack size of 1 single-dose vial (120 mg/2.4 mL) • Pack size of 1 single-dose vial (500 mg/10 mL). **Imjudo**: • Pack size of 1 single-dose vial (25 mg/1.25 mL, launched in Medicinpriser.dk March 30th, 2026. • Pack size of 1 single-dose vial (300 mg/15 mL, not approved for POSEIDON indication).
If vials: Can these be shared?	No

Pre-medication: Should pre-medication be administered? Which one?	No
Co-administration: Should the drug be administered with other drugs? Which ones?	Durvalumab and tremelimumab are used in combination with platinum-based chemotherapy.
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	No (the relevant biomarkers for ALK, EGFR mutations and PD-L1 expression are standard tests for mNSCLC patients)

Table 3. The intervention in the study and the health economic D + T + CT

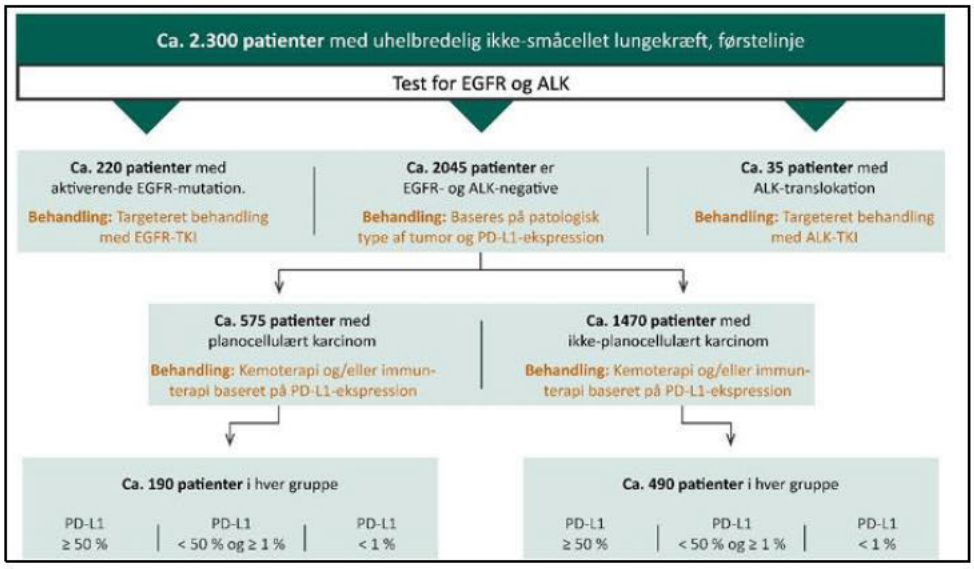
	Study	Health economic model
Dosage and frequency **[if weight-based, please state weight in brackets and any criteria for transition to flat-dose]**	Initial (cycles 1 – 4): durvalumab 1500 mg every 3 weeks; tremelimumab 75 mg every 3 weeks; platinum doublet every 3 weeks (non-squamous, pemetrexed + carboplatin/cisplatin; squamous, paclitaxel/nab-paclitaxel + carboplatin/cisplatin). Maintenance (from cycle 5): durvalumab 1500 mg every 4 weeks; one additional tremelimumab 75 mg dose at week 16 (non-squamous, pemetrexed 500 mg/m^2 every 4 weeks; squamous, no CT). D+T+CT is expected to be used in accordance with SmPC [40, 41], with an exception that it will only be used for patients with PD-L1 < 1% due to the Danish treatment guidelines [37].	Not applicable
Average dose	Fixed dosing, durvalumab 1,500 mg and tremelimumab 75 mg	Not applicable
Criteria for treatment discontinuation	In POSEIDON study, patients continued treatment until disease progression, unacceptable toxicity, or consent withdrawal [29]. In Danish clinical practice, patients are treated with ICIs no more than two years.	Not applicable
Treatment duration	Median total duration of D+T+CT arm (n=330) was 29.8 (range: 1.1 – 317.4) weeks [29]. Median number of cycles per drug was, • Durvalumab: 8 (range: 1 – 80) [29]	Not applicable

Study	Health economic model
• Tremelimumab: 5 (1 – 9) [42] • Pemetrexed + carboplatin: [redacted] [43] • Pemetrexed + cisplatin: [redacted] [43] • Gemcitabine + carboplatin: [redacted] [43] • Gemcitabine + carboplatin: [redacted] [43] • Abraxane + carboplatin: [redacted] [43]	
Dose adjustment: Report if/how dose adjustment is made*	No dose adjustment was permitted for durvalumab or tremelimumab.	Not applicable
Dose pause: Specify if/how pause (treatment interruption) is performed*	No dose pause was permitted for durvalumab or tremelimumab.	Not applicable

3.2.1 The intervention in the context of Danish clinical practice

The current DMC recommendations for first line treatment of mNSCLC are described below. It prioritizes targeted therapy for tumours harbouring sensitizing EGFR mutations or ALK translocation. In the absence of these alterations, treatment selection is guided by histology (squamous versus non-squamous) and PD-L1 expression level. Within this framework, D+T+CT is designated for use in squamous tumours with PD-L1 <1% and in non-squamous tumours with PD-L1 <1%.

Figure 1. The Danish Medical Council's recommendations for first-line treatment of metastatic non-small cell lung cancer



3.2.2 ATMP

Not applicable

3.3 Selection of comparator(s)

Table 4. Comparator overview, pembrolizumab

Therapeutic indication relevant to the assessment	Pembrolizumab in combination with pemetrexed and platinum chemotherapy is indicated for the first-line treatment of adult patients with mNSCLC whose tumours have no EGFR or ALK genomic tumour aberrations. Pembrolizumab + CT is currently recommended for these patients with non-squamous histology and PD-L1 < 1%.
Generic name	Pembrolizumab
ATC code	L01XC18
Mechanism of action	Anti-PD-1 monoclonal antibody; blocks PD-1 interaction with PD-L1/PD-L2 and enhances anti-tumour T-cell responses
Administration method	Intravenous infusion
Packaging type, pack sizes, shelf life and strengths	Keytruda (pembrolizumab) concentrate for solution for infusion: 25 mg/mL vial. Single-dose vials.
Package size(s)	1-single-dose vial 25 mg/ml in 4 ml
If vials: Can these be shared?	No
Pre-medication: Should pre-medication be administered? Which one?	No
Co-administration: Should the drug be administered with other drugs? Which ones?	Pembrolizumab is used in combination with platinum-based chemotherapy.
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	No

Table 5. Comparator in the study and the health economic model, pembrolizumab

	Study	Health economic model
Dosage and frequency **[if weight-based, please state weight in brackets and any criteria for transition to flat-dose]**	Pembrolizumab: 200 mg administered intravenously every 3 weeks (Q3W). Chemotherapy: Initial phase, pemetrexed (500 mg/m²) plus the investigator's choice of either cisplatin (75 mg/m²) or carboplatin (AUC 5 mg/mL/min) administered intravenously every 3 weeks for 4 cycles. Maintenance phase, pemetrexed (500 mg/m²) administered intravenously every 3 weeks.	Not applicable
Average dose	Fixed dosing, pembrolizumab 200 mg	Not applicable
Criteria for treatment discontinuation	P+CT arm in KEYNOTE-189 was discontinued upon radiographic disease progression, unacceptable toxicity, investigator decision, patient withdrawal of consent, or completion of the maximum course of 35 cycles (2 years) of pembrolizumab [16].	Not applicable
Treatment duration	Median number of cycles per drug in pembrolizumab + pemetrexed + carboplatin arm (n=294), • Pembrolizumab: 10 (range: 1 – 30) [16] • Pemetrexed: 9 (range: 1 – 30) [16] • Carboplatin: 4 (range: 1 – 4) [16] Median number of cycles per drug in pembrolizumab + pemetrexed + cisplatin arm (n=111), • Pembrolizumab: 11 (range: 1 – 26) [16] • Pemetrexed: 9 (range: 1 – 26) [16] • Cisplatin: 4 (range: 1 – 4) [16]	Not applicable
Dose adjustment: Report if/how dose adjustment is made*	No dose adjustment was permitted for pembrolizumab.	Not applicable
Dose pause: Specify if/how pause (treatment interruption) is performed*	No dose pause was permitted for pembrolizumab.	Not applicable

Table 6. Comparator overview, nivolumab + ipilimumab

Therapeutic indication relevant to the assessment	Nivolumab in combination with ipilimumab and two cycles of platinum-based CT is indicated for the first-line treatment of adult patients with metastatic or recurrent NSCLC with no sensitising EGFR mutations or ALK translocations, regardless of PD-L1 expression. N+I+CT is the currently recommended therapy for these patients with squamous histology and PD-L1 < 1%.
Generic name	Nivolumab (Opdivo), ipilimumab (Yervoy)
ATC code	L01FF01 and L01FX04
Mechanism of action	Nivolumab is a monoclonal antibody that blocks the PD-1 receptor on T cells, preventing interaction with PD-L1/PD-L2 and thereby restoring anti-tumour immune activity. CTLA-4 checkpoint inhibitor; blocks CTLA-4 inhibitory signalling, increasing T-cell activation/effector response against tumour cells
Administration method	Intravenous infusion
Packaging type, pack sizes, shelf life and strengths	**Opdivo** (nivolumab) concentrate for solution for infusion: 10 mg/mL vial. Single-dose vials. **Yervoy** (ipilimumab) concentrate for solution for infusion: 5 mg/mL vial. Single-dose vials.
Package size(s)	**Opdivo**: • 40 mg/4 ml x 1, 100 mg/10 ml x 1 vial ,120 mg/12 ml x 1 and 240 mg/24 ml x1 vial concentrate for solution for infusion • 600 mg subcutaneous **Ipilimumab:** • 50 mg/10 ml x 1 vial concentrate for solution for infusion • 200 mg/40 ml x 1 vial concentrate for solution for infusion
If vials: Can these be shared?	No
Pre-medication: Should pre-medication be administered? Which one?	No
Co-administration: Should the drug be administered with other drugs? Which ones?	Nivolumab and ipilimumab are used in combination with platinum-based chemotherapy.

Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	No

Table 7. Comparator in the study and the health economic model, nivolumab + ipilimumab

	Study	Health economic model
Dosage and frequency	Nivolumab 360 mg every 3 weeks plus ipilimumab 1 mg/kg (approximately 80mg [44]) every 6 weeks, combined with two cycles of platinum-doublet CT administered every 3 weeks.	Not applicable
Average dose	Fixed dosing, nivolumab 200 mg and ipilimumab 1 mg/kg	Not applicable
Criteria for treatment discontinuation	N+I+CT arm in CheckMate-9LA was discontinued for disease progression, unacceptable toxicity, or completion of the maximum 2-year course of immunotherapy [12].	Not applicable
Treatment duration	Median total duration of N+I+CT arm (n=358) was 6.1 (range: 0 – 24.4) months [12]. Median number of cycles per drug in N+I+CT arm: • Nivolumab: 9 (range: 1 – 36) [12] • Ipilimumab: 4 (range: 1 – 18) [12] • Chemotherapy: not available (7% of the patients received 1 cycle of CT while 93% received 2 cycles) [12]	Not applicable
Dose adjustment: Report if/how dose adjustment is made*	No dose adjustment was permitted for nivolumab or ipilimumab.	Not applicable
Dose pause: Specify if/how pause (treatment interruption) is performed*	No dose pause was permitted for nivolumab or ipilimumab.	Not applicable

3.4 Subsequent treatment

In POSEIDON study, 42.9% of patients in the D+T+CT arm received any subsequent therapy (7.4% received subsequent immunotherapy) [29]. In CheckMate-9LA study, 43.8% of patients in the N+I+CT arm received any subsequent therapy (8.0% receiving subsequent immunotherapy) while in KEYNOTE-189 (P+CT arm), 54.6% received any subsequent therapy (21.5% received subsequent immunotherapy [11, 15]. Subsequent therapies after first-line therapy for mNSCLC without EGFR/ALK alterations are expected to be broadly comparable across the intervention and relevant comparators. Given similar availability and clinical appropriateness of post-progression options across arms, a differential impact on outcomes from subsequent treatment is not expected. The distribution of subsequent treatments per study is presented in Appendix C.

Table 8. Assumptions regarding subsequent treatment in the health economic analysis

Subsequent treatment	[Intervention] %	[Comparator] %	Average treatment duration including source	Dosage (Dose, frequency and form of administration including source)	Any assumptions regarding dose adjustment and pause including source
Not applicable					

3.5 Relevant outcomes

3.5.1 Definition of outcomes

Table 9. Outcomes

Outcome	Follow-up time	Definition
OS in POSEIDON	63.4 months (median, DCO at 24/08/23) [29]	The time from random assignment to death from any cause
PFS in POSEIDON	34.9 months (median, DCO at 24/07/19) [2]	The time from random assignment to objective disease progression (assessed by BICR per RECIST v1.1) or death from any cause
OS in KEYNOTE-189	64.6 month (median, DCO at 08/03/22) [45]	The time from randomization to death from any cause
PFS in KEYNOTE-189	46.3 months (median, DCO at 28/08/20) [46]	The time from randomization to disease progression (assessed by BICR per RECIST v1.1) or death from any cause

Outcome	Follow-up time	Definition
OS in CheckMate-9LA	54.5 months (median, DCO at 13/02/23) [47]	The time from randomization to the date of death from any cause
PFS in CheckMate-9LA	30.7 months (median, DCO at 18/02/21) [4]	The time from randomization to the date of first documented tumour progression (assessed by BICR per RECIST v1.1), death from any cause

Note: The datasets (with the specified DCOs above) are used in the MAIC for PFS and OS, respectively. Additional clarifications and future data updates for these studies will be provided in Table 12.
Source: [2, 4, 29, 45-47]

3.5.2 Relevance of outcomes

No intermediate or surrogate outcomes were considered.

3.5.3 The validity of outcomes

No other outcomes than OS and PFS were considered.

4. Health economic analysis

4.1 Basic assumptions

Table 10. Basic assumptions in the health economic analysis

Assumption regarding	Assumption	Justification
Not applicable		

4.2 Model type and model structure

Table 11. Choice of health economic analysis, model and model structure

Health economic analysis	Model type	Model structure	Assumptions
Not applicable			

5. Literature overview

5.1 Literature used to assess clinical efficacy and safety

Table 12. Relevant literature included in the assessment of efficacy and safety

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Johnson M et al., PL02.01 Durvalumab ± Tremelimumab + Chemotherapy as First-line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study. Journal of Thoracic Oncology 2021;16:S844. [48]	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 24/07/19 Future data cut-offs: None	PFS for D+T+CT vs. P+CT in non-squamous subgroup and D+T+CT vs. N+I+CT in squamous subgroup and ITT population
Johnson M et al., Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: The Phase III POSEIDON Study. J Clin Oncol. 2023 Feb 20;41(6):1213-1227. [2]	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 24/07/19 Future data cut-offs: None	PFS for D+T+CT vs. P+CT in non-squamous subgroup with PD-L1<1%, and D+T+CT vs. N+I+CT in ITT population with PD-L1<1%
Peters S et al., Durvalumab With or Without Tremelimumab in Combination With Chemotherapy in First-Line Metastatic NSCLC: Five-Year Overall Survival Outcomes From the Phase 3 POSEIDON Trial. Journal of Thoracic Oncology Vol. 20 No. 1: 76–93. [29]	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 24/08/23 Future data cut-offs: None	OS for D+T+CT vs. P+CT in non-squamous subgroup, D+T+CT vs. N+I+CT in squamous subgroup and ITT population, D+T+CT vs. P+CT in non-squamous subgroup with PD-L1<1%, and D+T+CT vs. N+I+CT in ITT population with PD-L1<1%
Garon EB et al., A Brief Report of Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: Outcomes	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 12/03/2021 Future data cut-offs: None	PFS for D+T+CT vs. P+CT in non-squamous subgroup and D+T+CT vs. N+I+CT in squamous subgroup and ITT population

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
by Tumor PD-L1 Expression in the Phase 3 POSEIDON Study. Clinical Lung Cancer 2024;25(3):266-273 [49]				
POSEIDON CSR [43]	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 12/03/2021 Future data cut-offs: None	Safety for D+T+CT vs. P+CT in non-squamous subgroup.
Johnson ML et al., Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study, J Clin Oncol 41:1213-1227. [2]	POSEIDON	NCT03164616	Start: 01/06/17 End: Ongoing (active, not recruiting) Data-cut: 12/03/21 Future data cut-offs: None	Safety for D+T+CT vs. N+I+CT in ITT population.
Gray J, et al., FP13.02 Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189. Journal of Thoracic Oncology 2021;16:S224. [46]	KEYNOTE-189	NCT02578680	Start: 15/01/16 End: 22/06/23 Data-cut: 28/08/20 Future data cut-offs: None	PFS for D+T+CT vs. P+CT in non-squamous subgroup.
Garassino MC, et al., Pembrolizumab Plus Pemetrexed and Platinum in Non-squamous Non-Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study. J Clin Oncol 2023 Apr;41(11):1992-1998. [45]	KEYNOTE-189	NCT02578680	Start: 15/01/16 End: 22/06/23 Data-cut: 08/03/22 Future data cut-offs: None	OS for D+T+CT vs. P+CT in non-squamous subgroup, and D+T+CT vs. P+CT in non-squamous subgroup with PD-L1<1% PFS for D+T+CT vs. P+CT in non-squamous subgroup with PD-L1<1%
Rodríguez-Abreu D, et al., Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final	KEYNOTE-189	NCT02578680	Start: 15/01/16 End: 22/06/23 Data-cut: 20/05/19 Future data cut-offs: None	Safety for D+T+CT vs. P+CT for non-squamous histology subgroup.

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
analysis from KEYNOTE-189, Ann Oncol. 2021 Jul;32(7):881-895. [3]				
Reck M et al., First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update, SMO Open. 2021 Oct;6(5):100273. [4]	CheckMate-9LA	NCT03215706	Start: 24/08/17 End: 18/10/24 Data-cut: 18/02/21 Future data cut-offs: None	PFS for D+T+CT vs. N+I+CT in squamous subgroup and ITT population Safety for D+T+CT vs. N+I+CT in ITT population
Paz-Ares LG et al., First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial, Lancet Oncol. 2021 Feb;22(2):198-211. [12]	CheckMate-9LA	NCT03215706	Start: 24/08/17 End: 18/10/24 Data-cut: 09/03/20 Future data cut-offs: None	PFS for D+T+CT vs. N+I+CT in ITT population with PD-L1<1%
Paz-Ares LG et al., First-Line Nivolumab Plus Ipilimumab With Chemotherapy Versus Chemotherapy Alone for Metastatic NSCLC in CheckMate 9LA: 3-Year Clinical Update and Outcomes in Patients With Brain Metastases or Select Somatic Mutations, Journal of Thoracic Oncology 2023 Feb;18(2): p204-222. [50]	CheckMate-9LA	NCT03215706	Start: 24/08/17 End: 18/10/24 Data-cut: 15/02/22 Future data cut-offs: None	OS for D+T+CT vs. N+I+CT in ITT population with PD-L1<1%
Carbone DP et al., First-line (1L) nivolumab (N) + ipilimumab (I) + chemotherapy (C) vs C alone in patients (pts) with metastatic NSCLC (mNSCLC) from CheckMate 9LA: 4-y clinical update and outcomes by tumor histologic subtype (THS).	CheckMate-9LA	NCT03215706	Start: 24/08/17 End: 18/10/24 Data-cut: 13/02/23 Future data cut-offs: None	OS for D+T+CT vs. N+I+CT in squamous subgroup and ITT population

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Journal of Clinical Oncology 2023 41:17_suppl, LBA9023-LBA9023. [47]				

5.2 Literature used to assess health-related quality of life

Table 13. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Garon EB, et al., Patient-reported outcomes with durvalumab, with or without tremelimumab, plus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer (POSEIDON), Lung Cancer. 2023 Dec:186:107422. [51]	EORTC QLQ-C30	Head-to-head study	Section 10.2.1
POSEIDON CSR [43]	EQ-VAS	Head-to-head study	Section 10.2.2
Garassino MC, et al., Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial, Lancet Oncol. 2020 Mar;21(3):387-397. [52]	EORTC QLQ-C30	Systematic literature search (Appendix I)	Section 10.2.3

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
Reck M et al., First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: CheckMate 9LA 2-year patient-reported outcomes, Eur J Cancer. 2023 Apr:183:174-187. [53]	EQ-VAS	Systematic literature search (Appendix I)	Section 10.2.4

5.3 Literature used for input into the health economic model

Table 14. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
Not applicable			

6. Clinical studies

6.1 D+T+CT compared with CT for first line treatment of mNSCLC without EGFR mutations or ALK rearrangements

6.1.1 Relevant studies

POSEIDON is a global, randomized, open-label phase III trial evaluating D+T+CT vs. CT or D+CT vs CT as first line mNSCLC without EGFR mutations or ALK fusions. A total of 1,013 patients were randomized across 18 countries. A prespecified subset of the ITT population included PD-L1 expression, disease stage, and histology according to the study protocol. The trial demonstrated statistically significant improvements in OS and PFS for D+T+CT versus CT, with long-term follow-up showing sustained OS benefit at 5 years [29]. Efficacy reporting in this submission uses the most recent data cuts; PFS from the primary survival analysis (median follow-up: 34.9 months, DCO at 24/07/19) and OS from the long-term follow-up (median follow-up: 63.4 months, DCO at 24/08/23) [2, 29]. To our knowledge, additional planned data cuts have not been announced.

As of the latest OS DCO, treatment discontinuation in the D+T+CT arm occurred in 311 of 338 randomized patients (92.0%). The main reasons for discontinuation were disease progression (64.8%), AEs (20.7%), withdrawal of consent (5.0%), and other reasons (1.5%). A small proportion of randomized patients did not receive study treatment; 2.1% in the D+T+CT arm and 1.8% in the CT arm [29]. Internal validity is considered high, reflecting the randomized, multicentre phase III design and use of BICR for efficacy assessments. The open-label design may introduce bias in investigator-reported outcomes and safety reporting. External validity is also high, given the multiregional enrolment and alignment with routine clinical practice. However, the chemotherapy-only control is no longer SoC due to subsequent therapeutic advances, which should be considered when interpreting comparative relevance. In POSEIDON, patients in the control arm received investigator-chosen platinum-doublet CT administered every 3 weeks for up to 6 cycles. The permitted regimens were carboplatin plus nab-paclitaxel for patients regardless of histology, cisplatin or carboplatin plus gemcitabine for patients with squamous histology, and cisplatin or carboplatin plus pemetrexed for patients with non-squamous histology. In the control arm safety analysis set, the distribution of CT regimens was 61.3% pemetrexed doublet, 33.6% gemcitabine doublet, and 5.1% nab-paclitaxel doublet. The chemotherapy doses were pemetrexed 500 mg/m², gemcitabine 1000 or 1250 mg/m², nab-paclitaxel 100 mg/m², cisplatin 75 mg/m², and carboplatin AUC 5 or 6, according to the selected regimen. Regarding treatment exposure, 74.2% of patients in the control arm received at least 4 cycles, 27.3% received at least 5 cycles, and 23.1% received at least 6 cycles. 131 patients (64.2%) with non-squamous histology who proceeded a pemetrexed doublet to maintenance phase [2, 29].

Table 15. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
POSEIDON, NCT03164616	Global, randomized, multi-centre, open-label phase III trial	Patients in the intervention arm received a 12-week induction, then maintenance until disease progression. Patients in the comparator arm received CT for up to 18 weeks with optional pemetrexed maintenance	Adults with previously untreated mNSCLC, EGFR/ALK wild-type; ITT mixed-histology cohort (N=1,013)	Tremelimumab (75 mg IV) plus durvalumab (1500 mg IV) and CT every 3 weeks for up to 4 cycles, followed by durvalumab 1500 mg every 4 weeks and a fifth tremelimumab dose at week 16	Investigator's choice of systematic CT administered every 3 weeks for up to 6 cycles	Primary Endpoints: PFS and for the comparison of durvalumab plus chemotherapy (D+CT) versus CT. Secondary Endpoints: Key Alpha-Controlled Endpoints: PFS and OS for T+D+CT versus CT, PFS rate at 12 Months, objective response rate (ORR) (unconfirmed response rate assessed by BICR), duration of response (DoR) (time from first documented response to progression or death), safety and tolerability: (AEs and SAEs), patient-reported outcomes (PROs) (health-related quality of life using EORTC QLQ-C30 and QLQ-LC13), subgroup efficacy by PD-L1 expression level and blood tumour mutational burden (bTMB) The current assessment with regards to clinical efficacy include PFS based on the primary survival analysis (median: 34.9 months) and OS based on the long-term follow-up data (median: 63.4 months) [2, 29].

6.1.2 Comparability of studies

The POSEIDON study is broadly comparable to KEYNOTE-189 and CheckMate-9LA in terms of disease setting, eligible patient populations, and overall study design. A key distinction is the treatment strategy; POSEIDON and CheckMate-9LA evaluated dual immune checkpoint inhibition (a PD-1/PD-L1 inhibitor plus a CTLA-4 inhibitor) in combination with CT, whereas KEYNOTE-189 evaluated a PD-1 inhibitor plus CT. Another important difference is histology inclusion; POSEIDON and CheckMate-9LA enrolled both squamous and non-squamous mNSCLC, whereas KEYNOTE-189 focused on non-squamous mNSCLC.

Baseline characteristics were generally similar across studies. However, there were notable differences in factors identified as treatment effect modifiers (TEMs) including race/region, smoking status, and histology. Given these imbalances, MAICs were performed to account for cross-trial differences and to reduce bias in the estimated relative efficacy. See Section 7.1 for details.

6.1.2.1 Comparability of patients across studies

Table 16. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety

	POSEIDON, ITT			POSEIDON, non-squamous			POSEIDON, squamous		
	Overall (n=675)	D+T+CT (n=338)	CT (n=337)	Overall (n=428)	D+T+CT (n=214)	CT (n=214)	Overall (n=246)	D+T+CT (n=124)	CT (n=122)
Age, <65 years %	54.5%	56.5%	52.2%	54.7%	54.2%	55.1%	54.1%	60.5%	47.5%
Sex, Male %	76.6%	79.6%	73.6%	70.1%	73.8%	66.4%	87.8%	89.5%	86.1%
Race, %									
Asian	33.6%	29.3%	38.0%	36.7%	30.8%	42.5%	28.0%	26.6%	29.5%
Non-Asian	66.4%	70.7%	62.0%	63.3%	69.2%	57.5%	72.0%	73.4%	70.5%
Region of enrolment, %									
Asia	32.6%	28.5%	36.8%	36.0%	30.3%	41.6%	26.4%	25.0%	27.9%
Rest of world	67.4%	71.5%	63.2%	64.0%	69.7%	58.4%	73.6%	75.0%	72.1%
ECOG performance status, %									
0	33.9%	32.5%	35.3%	33.2%	30.4%	36.0%	35.4%	36.3%	34.4%
1	65.9%	67.5%	64.4%	66.8%	69.6%	64.0%	64.6%	63.7%	65.6%

	POSEIDON, ITT			POSEIDON, non-squamous			POSEIDON, squamous		
	Overall (n=675)	D+T+CT (n=338)	CT (n=337)	Overall (n=428)	D+T+CT (n=214)	CT (n=214)	Overall (n=246)	D+T+CT (n=124)	CT (n=122)
Smoking status, %									
Never	20.4%	17.5%	23.4%	25.2%	21.5%	29.0%	12.2%	10.5%	13.9%
Current or former	79.4%	82.6%	76.3%	74.8%	78.5%	71.0%	87.8%	89.5%	86.1%
Metastases at baseline, %									
Liver[1]	22.1%	20.4%	23.7%	18.7%	16.8%	20.6%	28.0%	26.6%	29.5%
Brain/CNS	11.6%	9.8%	13.4%	13.3%	11.2%	15.4%	8.5%	7.3%	9.8%
PD-L1 expression, %									
<1%	37.8%	37.0%	38.6%	38.1%	37.9%	38.3%	37.4%	35.5%	39.3%
≥1%	62.2%	63.0%	61.4%	61.9%	62.1%	61.7%	62.6%	64.5%	60.7%
≥50%	29.3%	29.9%	28.8%	30.1%	30.4%	29.9%	27.6%	29.0%	26.2%

[1]In POSEIDON, Liver = 'Hepatic (including gall bladder)' **Note**: Percentages may not sum to 100% due to some patients having missing data (e.g. non-quantifiable PD-L1 expression). **Source**: POSEIDON DCO at 24/07/19 [2], POSEIDON DCO at 24/08/23 [29], POSEIDON CSR DCO at 24/07/19 [43]

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

The study population in POSEIDON is broadly aligned with the intended Danish patients, defined by the approved indication as adults receiving first-line therapy for mNSCLC without sensitising EGFR mutations or ALK rearrangements. Since direct, setting-specific published evidence for Danish patients was not available, characterization of the Danish population was derived primarily on the Danish Lung Cancer Group's annual report, which provides aggregate demographics and disease features for lung cancer nationally [5].

In comparison with POSEIDON, Danish patients are, on average, older and include a higher proportion of women and non-squamous histology. The prevalence of PD-L1 <1% appears broadly similar between the Danish reports and the trial population.

Table 17. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population (source)	POSEIDON, ITT	Health economic model (source)
Age, <65 years	20.3% [5]	54.5% [2]	Not applicable
Sex, male	46.0% [5]	76.6% [2]	Not applicable
Race, Asian	4% [54]	33.6% [2]	Not applicable
Histology, squamous	23.8% [5]	36.4% [2]	
PD-L1 < 1%	31.4% [5]	37.8% [2]	Not applicable

6.1.4 Analysis method

The primary efficacy analyses for the POSEIDON study were conducted using a stratified log-rank test to assess PFS and OS. To estimate the magnitude of the treatment effect, a stratified Cox proportional hazards model was employed to derive hazard ratios (HRs) and 95% confidence intervals (CIs), utilizing the Efron method to account for ties. These analyses were adjusted for the prespecified randomization stratification factors, which included tumour cell PD-L1 expression, disease stage, and tumour histology. HR CIs were calculated using a profile likelihood approach. A sensitivity analysis was performed for both PFS and OS, which additionally adjusted for further prespecified adjustment variables, including age, sex, smoking history, and race. The handling of missing values for baseline characteristics was minimal, with the proportion of missing measurements reported at 0.3% in CT arm (n=1) for ECOG performance status, histology, and smoking history. For the efficacy outcomes, data were analysed on an ITT basis, meaning all randomized patients were included regardless of the treatment actually received. Censoring rules for PFS defined the endpoint as the time from randomization to

objective progression per RECIST v1.1 or death from any cause; patients without these events were censored at the date of their last evaluable tumour assessment. A specific censoring exception was noted for one patient who died one day prior to randomization and was subsequently censored at Day 1. OS was defined as the time from randomization to death from any cause, with surviving patients censored at the date they were last known to be alive. Intercurrent events such as the initiation of subsequent anticancer therapy were recorded, noting that in-study crossover to the immunotherapy arms was not allowed.

Regarding the proportional hazard assumption, the investigators observed a delayed separation of the Kaplan-Meier curves for the immunotherapy arms compared to the CT arm. This qualitative assessment suggests that the HRs should be interpreted as an average estimate of treatment benefit over the study period rather than a constant effect. To manage the risk of Type I error, a hierarchical multiple testing procedure was implemented with a gatekeeping strategy and an alpha-exhaustive recycling strategy. The initial 5% two-sided alpha was split between the primary PFS (1%) and OS (4%) endpoints for T+D+CT vs. CT upon reaching statistical significance. Alpha spending was managed via a Lan-DeMets function approximating the O'Brien-Fleming approach to account for interim assessments.

6.1.5 Effect – results per POSEIDON ITT

For the T+D+CT regimen, the HR for PFS vs. CT was 0.72, representing a 28% reduction in the risk of progression or death. The Kaplan–Meier PFS curves showed early and durable separation favouring the T+D+CT arm, which was also reflected in the estimated PFS rates. The updated OS analysis demonstrated that T+D+CT arm continued to show a durable overall survival benefit versus CT alone. The OS HR was 0.76.

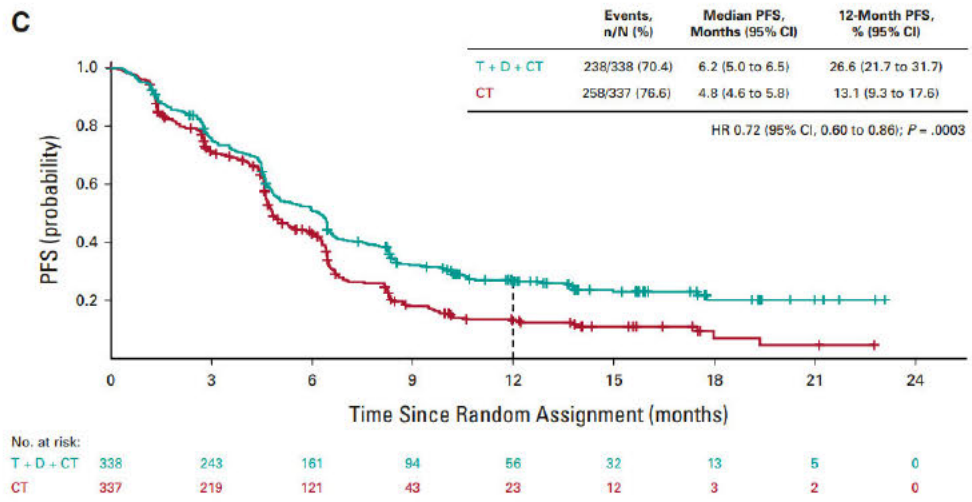
The complementary log-log plot shows evidence of non-proportional hazards for PFS (p-value, 0.049) and OS (p-value, 0.039). Given that the proportional hazards assumption is not met, the reported HRs for OS and PFS should be interpreted as summary measures averaged over the observed follow-up period, rather than as constant treatment effects over time.

Table 18. PFS, POSEIDON ITT population

	D+T+CT (N = 338)	CT (N = 337)
Events, n (%)	238 (70.4%)	258 (76.6%)
Median PFS, months (95% CI)	6.2 (5.0, 6.5)	4.8 (4.6, 5.8)
HR (95% CI)	0.72 (0.60, 0.86)	-

Source: POSEIDON, DCO at 24/07/19 [2]

Figure 2. Kaplan–Meier curves for PFS, POSEIDON ITT population



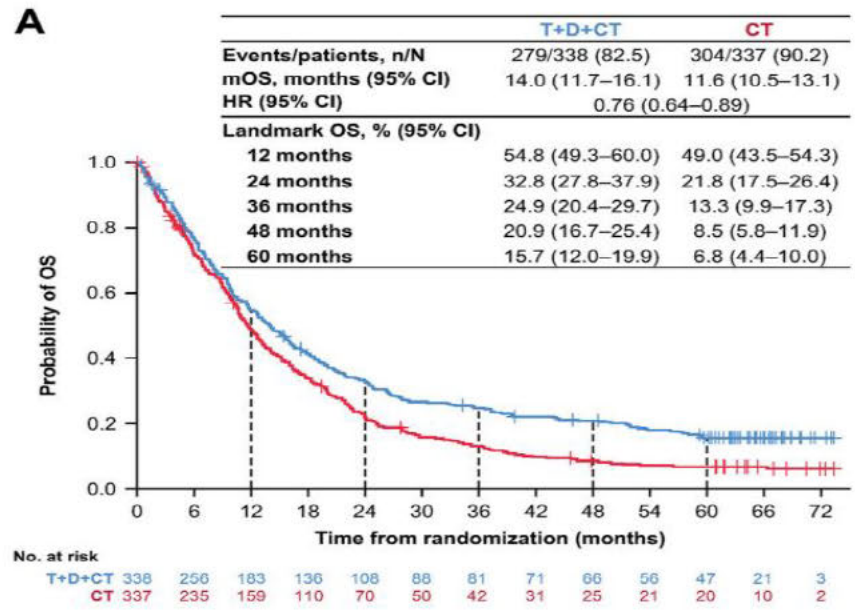
Source: POSEIDON, DCO at 24/07/19 [2]

Table 19. OS, POSEIDON ITT population

	D+T+CT (N = 338)	CT (N = 337)
Deaths, n (%)	279 (82.5%)	304 (90.2%)
Median OS, months (95% CI)	14.0 (11.7, 16.1)	11.6 (10.5, 13.1)
HR (95% CI)	0.76 (0.64, 0.89)	-

Source: POSEIDON, DCO at 24/08/23 [29]

Figure 3. Kaplan-Meier curves for OS, POSEIDON ITT population



Source: POSEIDON, DCO at 24/08/23 [29]

Figure 4. Complementary log-log (event times) vs log (time) plot for PFS, full analysis set



POSEIDON CSR [43]

Figure 5. Complementary log-log (event times) vs log (time) plot for OS, full analysis set



POSEIDON CSR [43]

6.1.6 Effect – results per POSEIDON PD-L1 <1%

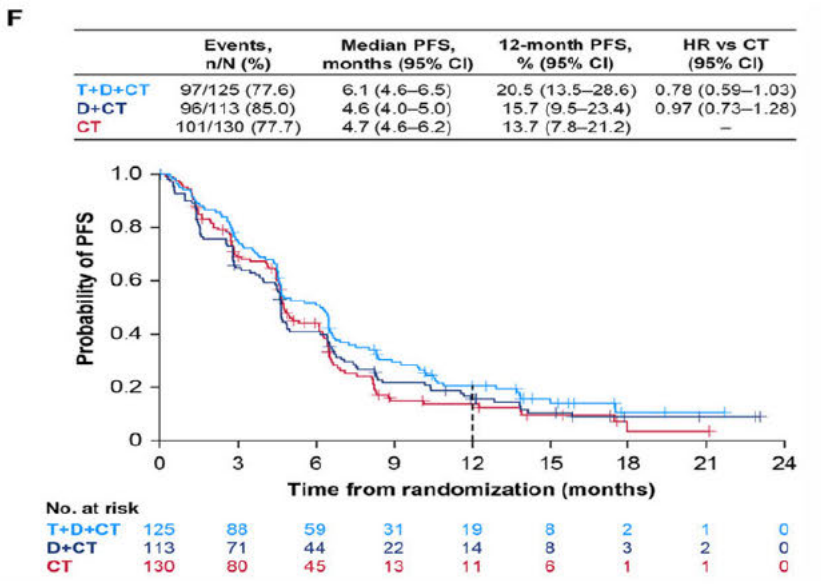
In POSEIDON PD-L1 <1% subgroup, median PFS was 6.1 months (95% CI, 4.6, 6.5) with T+D+CT (n=125) versus 4.7 months (95% CI, 4.6, 6.2) with CT (n=130), with a PFS HR of 0.78 (95% CI, 0.59–1.03) [49]. Median OS was 12.7 months (95% CI, 9.9, 15.5) with T+D+CT versus 11.0 months (95% CI, 8.7, 12.7) with CT, with an OS HR of 0.81 (95% CI, 0.62–1.05) [29]. In the PD-L1 ≥1% subgroup, median PFS was 6.2 months (95% CI, 5.0, 6.8) with T+D+CT (n=213) versus 4.9 months (95% CI, 4.6, 6.0) with CT (n=207), with a PFS HR of 0.68 (95% CI, 0.54, 0.85) [49]. Median OS was 15.6 months (95% CI, 11.6, 18.1) with T+D+CT versus 12.2 months (95% CI, 10.4, 15.2) with CT, with an OS HR of 0.71 (95% CI, 0.58, 0.88) [29]. D+T+CT may remain a rational choice in PD-L1 <1% because effect sizes consistently favour benefit (PFS HR 0.78; OS HR 0.81) with CIs that narrowly cross 1.0, likely reflecting limited sample size and statistical power. Mechanistically, dual checkpoint blockade plus chemotherapy primes and expands T-cell responses in low-immunogenic tumours, offering a clinically meaningful option for a poor-prognosis population with limited alternatives.

Table 20. PFS, POSEIDON PD-L1 <1% subgroup

	D+T+CT (N = 125)	CT (N = 130)
Events, n (%)	97 (77.6%)	101 (77.7%)
Median PFS, months (95% CI)	6.1 (4.6, 6.5)	4.7 (4.6, 6.2)
HR (95% CI)	0.78 (0.59, 1.03)	

Source: POSEIDON, DCO at 24/07/19 [49]

Figure 6. Kaplan–Meier curves for PFS, POSEIDON PD-L1 <1% subgroup



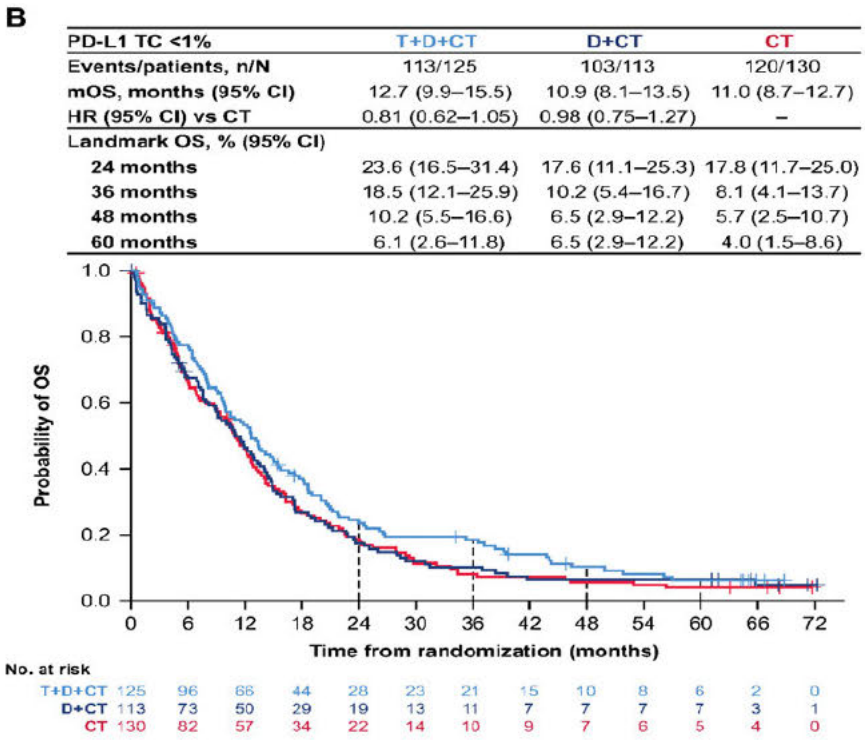
Source: POSEIDON, DCO at 24/07/19 [49]

Table 21. OS, POSEIDON PD-L1 <1% subgroup

	D+T+CT (N = 125)	CT (N = 130)
Deaths, n (%)	113 (90.4%)	120 (92.3%)
Median OS, months (95% CI)	12.7 (9.9, 15.5)	11.0 (8.7, 12.7)
HR (95% CI)	0.81 (0.62, 1.05)	-

Source: POSEIDON, DCO at 24/08/23 [29]

Figure 7. Kaplan-Meier curves for OS, POSEIDON PD-L1 <1% subgroup



Source: POSEIDON, DCO at 24/08/23 [29]

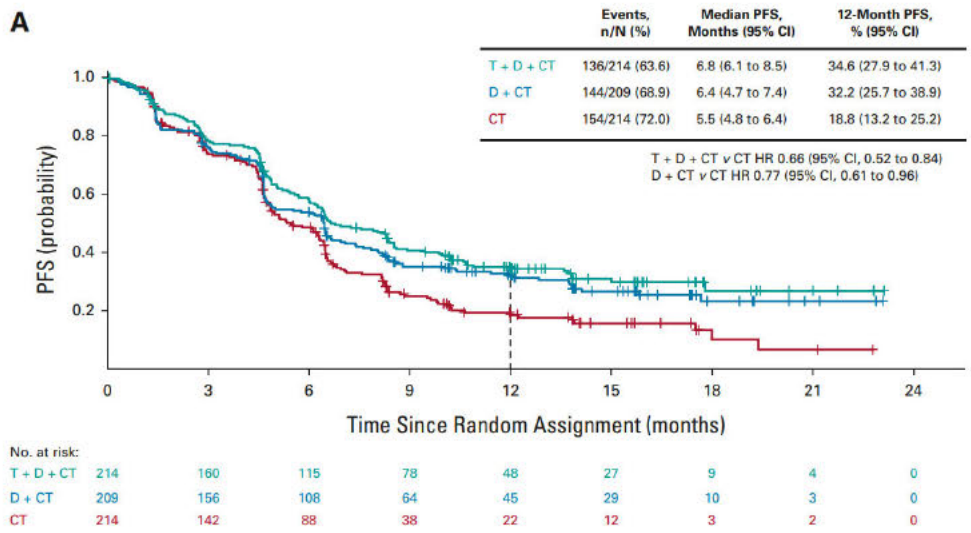
6.1.7 Effect – results per POSEIDON non-squamous

Table 22. PFS, POSEIDON non-squamous subgroup

	D+T+CT (N = 214)	CT (N = 214)
Events, n (%)	136 (63.6%)	154 (72.0%)
Median PFS, months (95% CI)	6.8 (6.1, 8.5)	5.5 (4.8, 6.4)
HR (95% CI)	0.66 (0.52, 0.84)	-

Source: POSEIDON, DCO at 24/07/19 [2]

Figure 8. Kaplan-Meier curves for PFS, POSEIDON non-squamous subgroup



Source: POSEIDON, DCO at 24/07/19 [2]

Table 23. OS, POSEIDON non-squamous subgroup

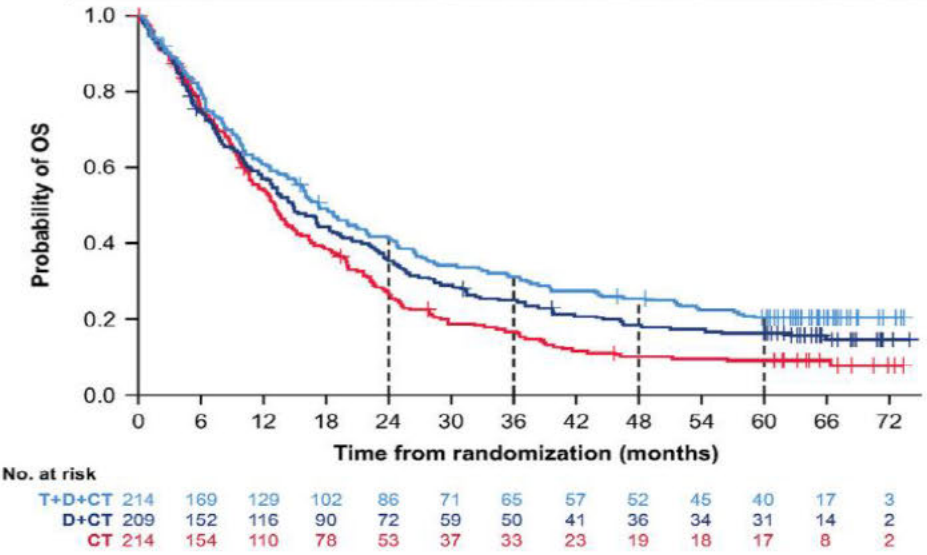
	D+T+CT (N = 214)	CT (N = 214)
Deaths, n (%)	167 (78.0)	186 (86.9)
Median OS, months (95% CI)	17.2 (14.9, 21.8)	13.0 (10.6, 15.1)
HR (95% CI)	0.69 (0.56, 0.85)	-

Source: POSEIDON study, DCO at 24/08/23 [29]

Figure 9. Kaplan-Meier curves for OS, POSEIDON non-squamous subgroup

A

Nonsquamous	T+D+CT	D+CT	CT
Events/patients, n/N	167/214	172/209	186/214
mOS, months (95% CI)	17.2 (14.9–21.8)	14.8 (11.8–18.3)	13.0 (10.6–15.1)
HR (95% CI) vs CT	0.69 (0.56–0.85)	0.81 (0.66–1.00)	–
Landmark OS, % (95% CI)			
24 months	41.3 (34.6–47.9)	35.4 (28.9–42.0)	26.5 (20.6–32.7)
36 months	31.2 (25.1–37.6)	25.0 (19.3–31.1)	16.9 (12.1–22.4)
48 months	25.5 (19.8–31.5)	18.4 (13.4–24.1)	10.2 (6.5–14.9)
60 months	20.5 (15.3–26.2)	16.4 (11.6–21.8)	9.1 (5.6–13.6)



Source: POSEIDON, DCO at 24/08/23 [29]

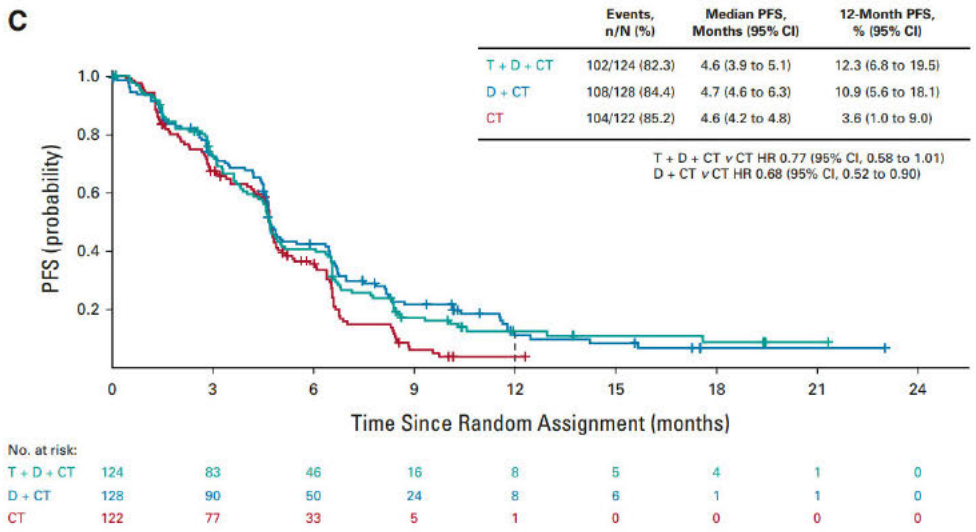
6.1.8 Effect – results per POSEIDON squamous

Table 24. PFS, POSEIDON squamous subgroup

	D+T+CT (N = 124)	CT (N = 122)
Events, n (%)	102 (82.3%)	104 (85.2%)
Median PFS, months (95% CI)	4.6 (3.9, 5.1)	4.6 (4.2, 4.8)
HR (95% CI)	HR 0.77 (0.58, 1.01)	-

Source: POSEIDON, DCO at 24/07/19 [2]

Figure 10. Kaplan-Meier curves for PFS, POSEIDON squamous subgroup



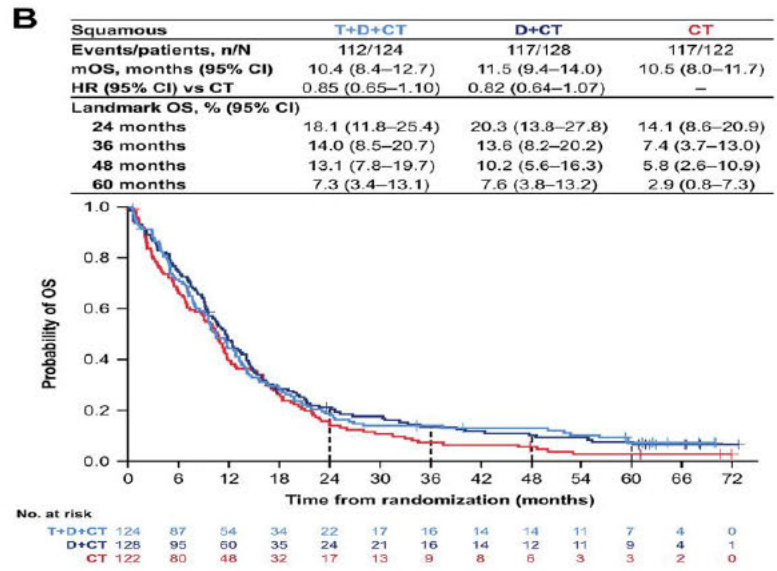
Source: POSEIDON, DCO at 24/07/19 [2]

Table 25. OS, POSEIDON squamous subgroup

	D+T+CT (N = 124)	CT (N = 122)
Deaths, n (%)	112 (90.3)	117 (95.9)
Median OS, months (95% CI)	10.4 (8.4, 12.7)	10.5 (8.0, 11.7)
HR (95% CI) p-value	0.85 (0.65, 1.10)	-

Source: POSEIDON study, DCO at 24/08/23 [29]

Figure 11. Kaplan-Meier curves for OS, POSEIDON squamous



Source: POSEIDON, DCO at 24/08/23 [29]

6.1.9 Effect – results per POSEIDON non-squamous biomarker subgroup

The exploratory analyses were conducted on OS outcomes to evaluate the long-term impact of the D+T+CT regimen in patients with these typically poor-prognosis mutation subgroup, including KRAS, STK11, and KEAP1. These mutations occur predominantly in patients with non-squamous NSCLC. OS was assessed according to STK11 or KRAS mutation status in patients with non-squamous tumour type, and according to KEAP1 mutation status in all patients, regardless of tumour histologic type due to the small number of KEAP1 mutant patients. In the non-squamous mutation-evaluable population overall, 14.2%, 29.7%, and 6.0% had STK11, KRAS, and KEAP1 mutations, and in the overall mutation-evaluable population, 5.2% had KEAP1 mutations [29].

The exploratory analyses were not conducted on PFS.

Table 26. PFS, POSEIDON non-squamous STK11, KRAS and overall KEAP1 mutation subgroup

	Non-squamous STK11 mutant		Non-squamous KRAS mutant		Overall KEAP1 mutant	
	D+T+CT (n = 31)	D+T+CT (n = 60)	D+T+CT (n = 60)	CT (n = 53)	D+T+CT (n = 22)	CT (n = 6)
Events, n (%)	NA	NA	NA	NA	NA	NA
Median PFS, months (95% CI)	NA	NA	NA	NA	NA	NA
HR (95% CI)	NA	NA	NA	NA	NA	NA

Table 27. OS, POSEIDON non-squamous STK11, KRAS and overall KEAP1 mutation subgroup

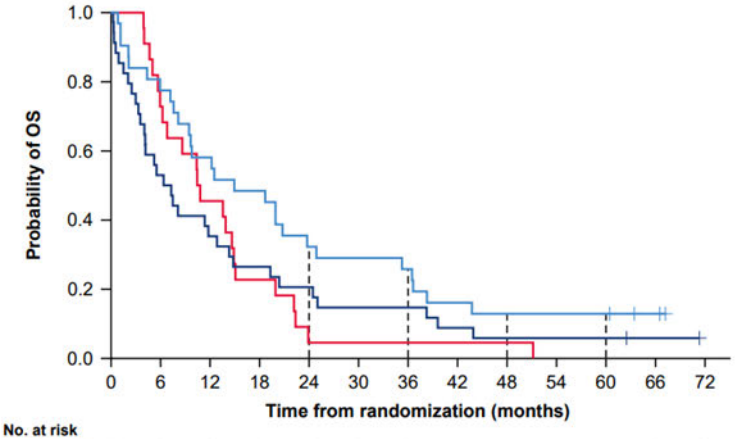
	Non-squamous STK11 mutant		Non-squamous KRAS mutant		Overall KEAP1 mutant	
	D+T+CT (n = 31)	CT (n = 22)	D+T+CT (n = 60)	CT (n = 53)	D+T+CT (n = 22)	CT (n = 6)
Deaths, n (%)	27 (87.1)	22 (100)	47 (78.3)	47 (88.7)	19 (86.4)	6 (100)
Median OS, months (95% CI)	15.0 (8.2, 23.8)	10.7 (6.0, 14.9)	25.7 (9.9, 36.7)	10.4 (7.3, 12.6)	13.7 (7.2, 26.5)	8.7 (5.1, NE)
HR (95% CI)	0.57 (0.32, 1.04)	-	0.55 (0.36, 0.83)		0.43 (0.16, 1.25)	-

Source: POSEIDON, DCO at 24/08/23 [29]

Figure 12. Kaplan–Meier curves for OS, POSEIDON non-squamous STK11 mutant (A), STK11 wild-type (B), KRAS mutant (E), KRAS wild-type (F) and overall KEAP1 mutant (C) and KEAP1 wild-type (D) subgroup.

A

Nonsquamous *STK11* mutant	T+D+CT	D+CT	CT
Events/patients, n/N	27/31	32/34	22/22
mOS, months (95% CI)	15.0 (8.2–23.8)	6.9 (3.6–12.9)	10.7 (6.0–14.9)
HR (95% CI) vs CT	0.57 (0.32–1.04)	1.02 (0.59–1.80)	–
Landmark OS, % (95% CI)			
24 months	32.3 (16.9–48.6)	20.6 (9.1–35.3)	4.5 (0.3–18.9)
36 months	25.8 (12.2–41.8)	14.7 (5.4–28.5)	4.5 (0.3–18.9)
48 months	12.9 (4.1–27.0)	5.9 (1.1–17.2)	4.5 (0.3–18.9)
60 months	12.9 (4.1–27.0)	5.9 (1.1–17.2)	0 (NC)

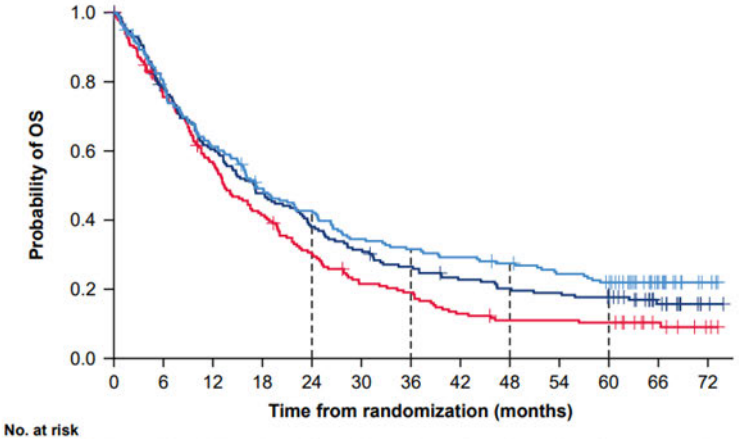


No. at risk

T+D+CT	31	24	18	15	10	9	8	5	4	4	4	2	0
D+CT	34	18	12	9	7	5	5	3	2	2	2	1	0
CT	22	16	10	5	1	1	1	1	1	0	0	0	0

B

Nonsquamous *STK11* wild-type	T+D+CT	D+CT	CT
Events/patients, n/N	135/177	138/169	153/179
mOS, months (95% CI)	17.2 (14.9–22.1)	17.1 (13.3–22.3)	13.4 (11.5–16.8)
HR (95% CI) vs CT	0.71 (0.56–0.90)	0.79 (0.63–1.00)	–
Landmark OS, % (95% CI)			
24 months	42.7 (35.2–49.9)	38.1 (30.7–45.4)	30.1 (23.3–37.0)
36 months	31.6 (24.8–38.5)	26.5 (20.0–33.4)	19.1 (13.5–25.4)
48 months	27.5 (21.0–34.3)	20.2 (14.5–26.7)	11.0 (6.8–16.3)
60 months	22.0 (16.1–28.5)	17.7 (12.3–23.9)	10.4 (6.3–15.6)



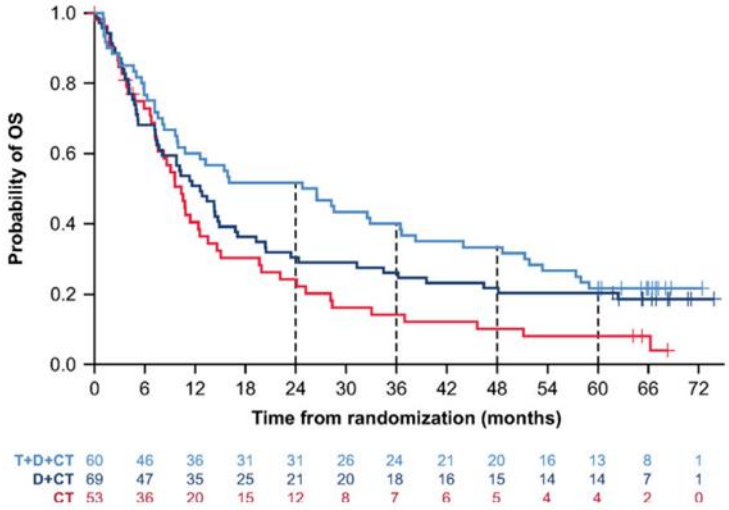
No. at risk

T+D+CT	177	140	107	84	73	59	54	50	46	40	35	15	3
D+CT	169	130	100	79	63	52	43	36	32	30	27	13	2
CT	179	130	96	70	50	35	31	21	17	17	16	8	2

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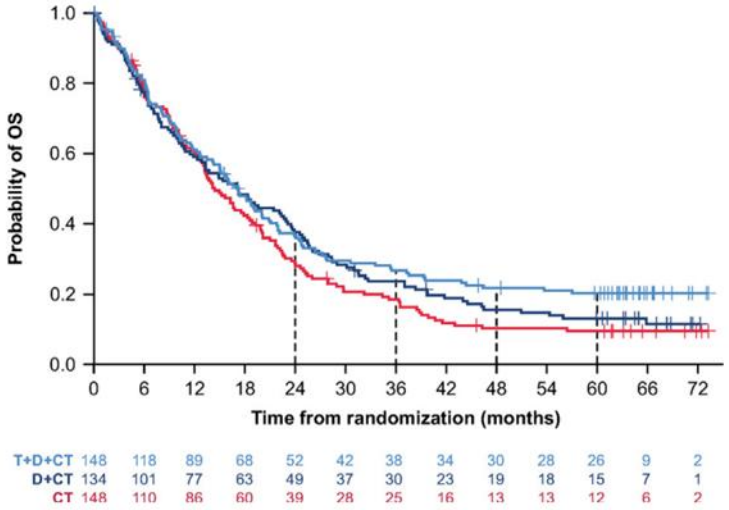
E

Nonsquamous *KRAS* mutant	T+D+CT	D+CT	CT
Events/patients, n/N	47/60	56/69	47/53
mOS, months (95% CI)	25.7 (9.9–36.7)	12.6 (7.5–16.9)	10.4 (7.3–12.6)
HR (95% CI) vs CT	0.55 (0.36–0.83)	0.74 (0.50–1.09)	–
Landmark OS, % (95% CI)			
24 months	51.7 (38.4–63.4)	30.4 (20.1–41.4)	24.3 (13.5–36.7)
36 months	40.0 (27.7–52.0)	26.1 (16.4–36.8)	14.2 (6.2–25.2)
48 months	33.3 (21.8–45.2)	21.7 (12.9–32.0)	10.1 (3.7–20.3)
60 months	21.7 (12.3–32.7)	20.3 (11.8–30.4)	8.1 (2.6–17.7)



F

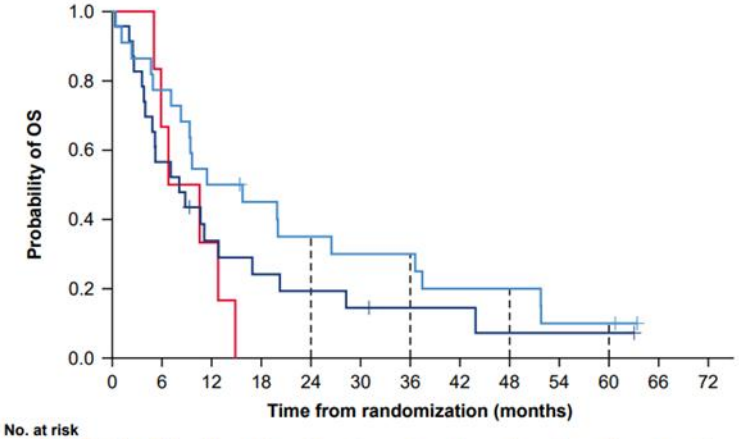
Nonsquamous *KRAS* wild-type	T+D+CT	D+CT	CT
Events/patients, n/N	115/148	114/134	128/148
mOS, months (95% CI)	17.1 (13.4–20.1)	17.1 (12.3–22.6)	14.4 (12.6–18.3)
HR (95% CI) vs CT	0.78 (0.61–1.00)	0.87 (0.68–1.12)	–
Landmark OS, % (95% CI)			
24 months	36.6 (28.8–44.4)	37.6 (29.3–45.8)	28.0 (20.9–35.6)
36 months	26.8 (19.8–34.2)	23.7 (16.8–31.2)	18.5 (12.6–25.4)
48 months	21.8 (15.4–28.9)	15.6 (9.9–22.4)	10.3 (5.9–16.1)
60 months	20.3 (14.1–27.3)	13.1 (7.9–19.6)	9.5 (5.3–15.2)



(Continued)

C

All patients *KEAP1* mutant	T+D+CT	D+CT	CT
Events/patients, n/N	19/22	20/23	6/6
mOS, months (95% CI)	13.7 (7.2–26.5)	8.1 (4.0–12.9)	8.7 (5.1–NE)
HR (95% CI) vs CT	0.43 (0.16–1.25)	0.77 (0.31–2.15)	–
Landmark OS, % (95% CI)			
24 months	35.0 (16.1–54.7)	19.3 (6.2–37.9)	0 (NC)
36 months	30.0 (12.5–49.8)	14.5 (3.7–32.3)	0 (NC)
48 months	20.0 (6.3–39.1)	7.2 (0.6–25.7)	0 (NC)
60 months	10.0 (1.7–27.1)	7.2 (0.6–25.7)	0 (NC)

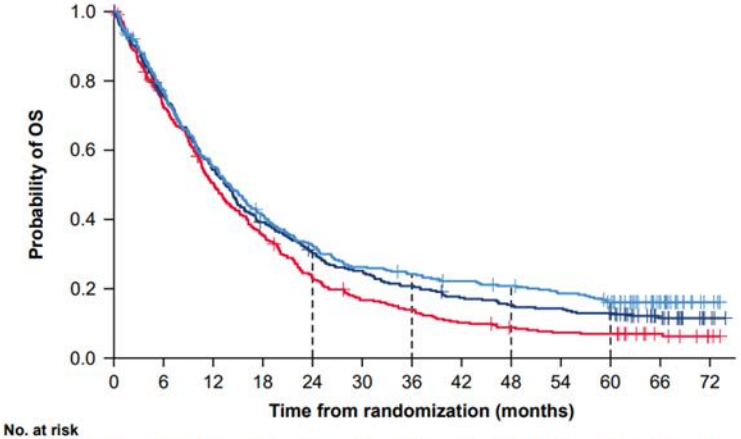


No. at risk

T+D+CT	22	17	11	9	7	6	6	4	4	2	2	0	0
D+CT	23	13	7	5	4	3	2	2	1	1	1	0	0
CT	6	4	2	0	0	0	0	0	0	0	0	0	0

D

All patients *KEAP1* wild-type	T+D+CT	D+CT	CT
Events/patients, n/N	249/303	266/307	281/312
mOS, months (95% CI)	14.0 (11.8–16.1)	13.5 (11.7–14.9)	12.1 (10.6–13.9)
HR (95% CI) vs CT	0.76 (0.64–0.90)	0.83 (0.70–0.98)	–
Landmark OS, % (95% CI)			
24 months	32.4 (27.1–37.7)	30.2 (25.2–35.5)	22.9 (18.3–27.7)
36 months	24.3 (19.6–29.3)	20.8 (16.4–25.6)	14.0 (10.4–18.2)
48 months	20.8 (16.4–25.6)	15.4 (11.6–19.7)	8.9 (6.0–12.4)
60 months	16.2 (12.2–20.6)	13.0 (9.5–17.1)	7.0 (4.4–10.3)



No. at risk

T+D+CT	303	230	165	122	96	78	71	64	59	52	43	21	3
D+CT	307	230	165	118	90	75	62	51	45	42	37	18	3
CT	312	220	152	107	68	49	41	30	24	20	19	10	2

Source: POSEIDON, DCO at 24/08/23 [29]

6.1.10 Effect – results per POSEIDON combined subgroup with PD-L1 <1% and non-squamous or squamous

OS data per histology and PD-L1 <1% is published by Garon et al. in 2024 [49]. Unfortunately, this publication does not include similar PSF data. The data are all from an earlier DCO (March 12th, 2021).

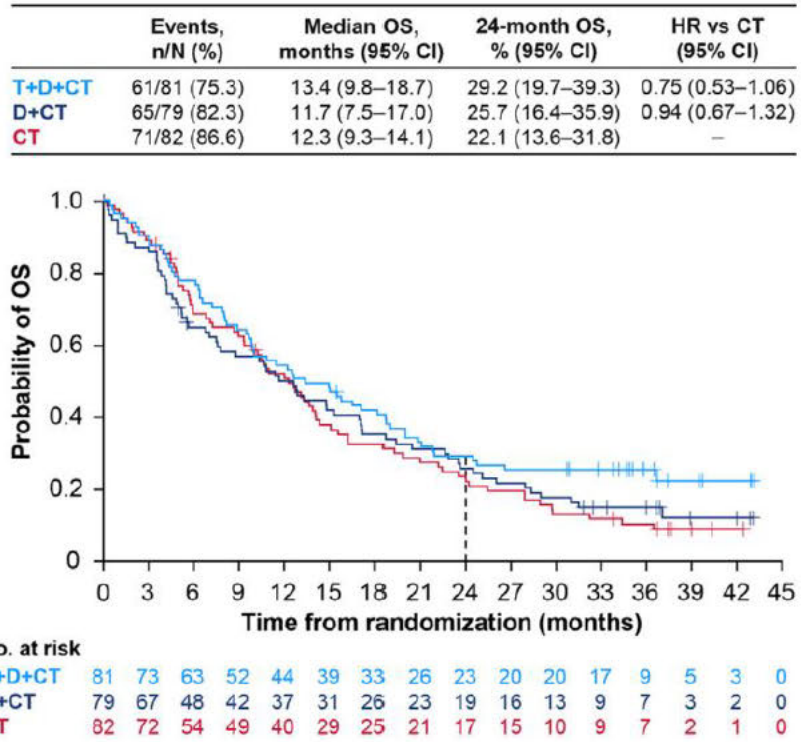
Non-squamous and PD-L1 <1%:

Table 28. OS PD-L1 <1% and non-squamous histology

	D+T+CT (N=81)	CT (N=82)
Deaths, n (%)	61 (75.3)	71 (86.6)
Median OS, months (95% CI)	13.4 (9.8, 18.7)	12.3 (9.3, 14.1)
24-month OS, % (95% CI)	29.2 (19.7, 39.3)	22.1 (13.6, 31.8)
HR (95% CI)	0.75 (0.53, 1.06)	-

Source: POSEIDON, DCO 12/03/2021 [49]

Figure 13. KM OS, PD-L1 <1% and non-squamous histology



Source: POSEIDON, DCO 12/03/2021 [49]

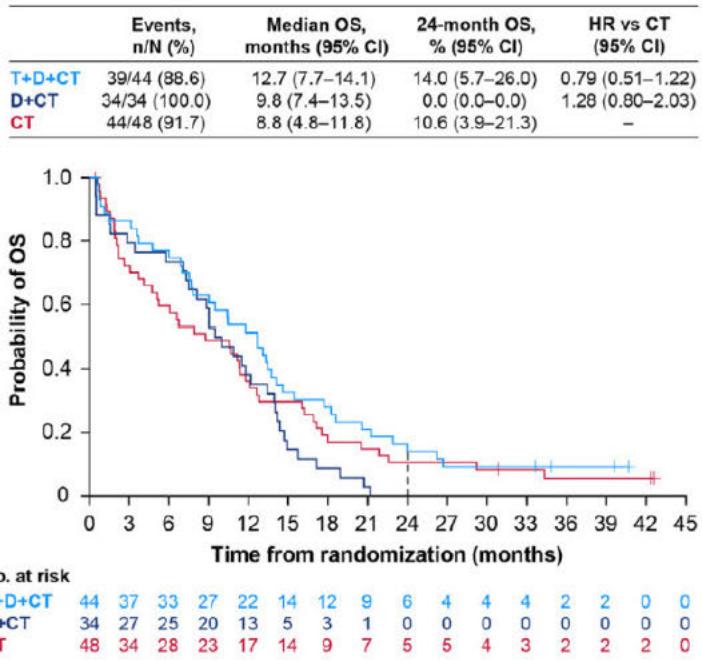
Squamous and PD-L1 <1%:

Table 29. OS, PD-L1 <1% and squamous histology

	D+T+CT (N=44)	CT (N=48)
Deaths, n (%)	39 (88.6)	44 (91.7)
Median OS, months (95% CI)	12.7 (7.7, 14.1)	8.8 (4.8, 11.8)
24-month OS, % (95% CI)	14.0 (5.7, 26.0)	10.6 (3.9, 21.3)
HR (95% CI)	0.79 (0.51, 1.22)	-

Source: POSEIDON, DCO 12/03/2021 [49]

Figure 14. KM OS, PD-L1 <1% and squamous histology



Source: POSEIDON, DCO 12/03/2021 [49]

The POSEIDON 5-year update (DCO at 24/08/23 [29]) showed that OS HRs favoured D+T+CT versus CT in subgroups defined by tumour histology and PD-L1 <1%. However, as with the other PD-L1 subgroup analyses, the numbers of patients remaining at risk at later time points were very low, which limits the interpretability of these subgroup results. Among patients with PD-L1 <1% and non-squamous histology, the OS HRs for D+T+CT versus CT were 0.81 (95% CI: 0.59–1.13). Among patients with PD-L1 <1% and squamous histology, the OS HRs were 0.80 (95% CI: 0.53–1.23) for PD-L1 TC <1%. KM-plots and landmark rates are not available for this DCO.

6.2 P+CT compared with CT for first line treatment of metastatic non-squamous NSCLC without EGFR mutations or ALK rearrangements

6.2.1 Relevant studies

KEYNOTE-189 is a randomized, double-blind phase III trial enrolling adults with previously untreated metastatic non-squamous NSCLC without EGFR or ALK alterations. The PD-L1 subgroup was prespecified as a randomization stratification factor, and patients had no squamous histology per the inclusion criteria [16].

Efficacy results are reported from data cut-off at 28/08/20 (median follow-up: 46.3 months) for PFS and data cut-off at 08/03/22 (median follow-up: 64.6 months) for OS [45, 46], and no further data cuts are planned as the study is complete. At the primary analysis, 65.4% of patients in P+CT arm (268/410) had discontinued treatment. The main reasons were radiographic progression (36.6%), AEs (19.0%), withdrawal of consent (3.9%), clinical progression (2.7%), investigator decision (2.2%), and initiation of new anticancer therapy (1.0%). A small proportion of randomized patients did not start study treatment; 1.2% in P+CT arm and 1.9% in CT arm [16].

Internal validity is considered high, reflecting the randomized, double-blind, placebo-controlled design with BICR for key endpoints. External validity is high, with enrolment across 126 sites in 16 countries, supporting generalizability to the metastatic non-squamous NSCLC population. As similar with POSEIDON, interpretation should consider that the CT alone was used as the comparator.

In KEYNOTE-189, patients in the control arm received pemetrexed 500 mg/m² plus the investigator's choice of cisplatin 75 mg/m² or carboplatin AUC 5 mg/mL/min, administered intravenously every 3 weeks for 4 cycles. 74.3% of patients received all 4 planned doses of cisplatin or carboplatin. In the placebo-pemetrexed-carboplatin group, the mean number of carboplatin administrations was 3.6 (SD, 0.8) with a median of 4.0 (range 1–4), while in the placebo-pemetrexed-cisplatin group, the mean number of cisplatin administrations was 3.6 (SD, 0.9) with a median of 4.0 (range 1–4). After induction therapy, patients continued with pemetrexed 500 mg/m² maintenance therapy every 3 weeks until radiographic progression, unacceptable toxicity, investigator decision, or withdrawal of consent. 66.8% of patients received 5 or more doses of pemetrexed; the mean number of pemetrexed administrations was 7.4 (SD, 5.4) with a median of 6.0 (range 1–24) in the carboplatin subgroup and 8.0 (SD 5.1) with a median of 7.0 (range 1–19) in the cisplatin subgroup [3, 11, 16].

Table 30. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
KEYNOTE-189, NCT02578680	Randomized, controlled, double-blind phase III trial	Patients in the intervention arm received a 12-week induction followed by maintenance therapy until disease progression or a maximum of 35 cycles. Patients in the comparator arm received CT for 12 weeks followed by pemetrexed maintenance	Adults with previously untreated metastatic non-squamous NSCLC, EGFR/ALK wild-type (N=616)	Pembrolizumab (200 mg IV) plus pemetrexed (500 mg/m^2) and investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) every 3 weeks for 4 cycles, followed by pembrolizumab 200 mg every 3 weeks (up to 35 cycles total) and pemetrexed maintenance	Saline placebo (IV) plus pemetrexed (500 mg/m^2) and investigator's choice of cisplatin (75 mg/m^2) or carboplatin (AUC 5 mg/mL/min) every 3 weeks for 4 cycles, followed by saline placebo and pemetrexed maintenance	Primary Endpoints: PFS (BICR per RECIST v1.1), OS Secondary Endpoints: ORR (Confirmed complete or partial response rate assessed by BICR), DoR (time from first documented response to progression or death assessed by BICR). safety and tolerability (assessment of AEs and laboratory abnormalities) The current assessment with regards to clinical efficacy includes PFS based on the updated exploratory analysis (median follow-up: 46.3 months), and OS based on the long-term 5-year follow-up data (median: 64.6 months) [45, 46].

6.2.2 Comparability of studies

See Section 6.1.2 and Section 7.1 for details.

6.2.2.1 Comparability of patients across studies

Table 31. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety

	KEYNOTE-189		
	Overall (n=616)	P+CT (n=410)	CT (n=206)
Age, <65 years %	50.6%	48.0%	55.8%
Sex, Male %	58.9%	62.0%	52.9%
Race, %			
Asian	1.6%	1.0%	2.9%
Non-Asian	98.4%	99%	97.1%
ECOG performance status, %			
0	43.2%	45.4%	38.8%
1	56.2%	53.9%	60.7%
Smoking status, %			
Never	11.9%	11.7%	12.1%
Current or former	88.1%	88.3%	87.9%
Metastases at baseline, %			
Liver	-	NA	NA
Brain/CNS	17.5%	17.8%	17.0%
PD-L1 expression, %			
<1%	30.8%	31.0%	30.6%
≥1%	63.0%	63.4%	62.1%
≥50%	32.8%	32.2%	34.0%

Note: Percentages may not sum to 100% due to some patients having missing data (e.g. non-quantifiable PD-L1 expression). **Source**: KEYNOTE-189 DCO at 08/11/17 [16]

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

Table 32. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population (source)	KEYNOTE-189, ITT	Health economic model (source)
Age, <65 years	20.3% [5]	50.6% [16]	Not applicable
Sex, male	46.0% [5]	58.9% [16]	Not applicable
Race, Asian	4% [54]	1.6% [16]	Not applicable
Histology, non-squamous	76.2% [5]	100% [16]	
PD-L1 < 1%	31.4% [5]	30.8% [16]	Not applicable

6.2.4 Analysis method

The primary efficacy analyses for the KEYNOTE-189 study were conducted in the ITT population, which included all patients who underwent randomization. The evaluation of the primary endpoints, OS and PFS, utilized the Kaplan-Meier method to estimate survival rates over time. Statistical significance for between-group differences was assessed using the stratified log-rank test, while the magnitude of the treatment effect was estimated through a stratified Cox proportional-hazards model. This model utilized Efron's method to handle tied events and was used to derive HRs and their associated 95% confidence intervals. The analyses were strictly adjusted according to the prespecified randomization stratification factors, which included PD-L1 expression, the investigator's choice of platinum-based drug (cisplatin vs. carboplatin), and smoking history. The handling of missing values was documented for both baseline characteristics and efficacy assessments. For baseline ECOG performance status, data were missing for 0.5% of patients in the pembrolizumab-combination group and 0.5% in the placebo-combination group. Regarding PD-L1 expression, specimens could not be evaluated for 5.6% of patients in the pembrolizumab arm and 7.3% in the placebo arm due to inadequate tumour cell counts. For stratification purposes, these non-evaluable patients were assigned to the <1% TPS subgroup, though they were excluded from specific efficacy analyses categorized by PD-L1 score. In terms of censoring rules, OS data for patients who were alive or lost to follow-up were censored at the date the patient was last known to be alive. Notably, data for patients in the placebo arm who crossed over to pembrolizumab monotherapy were not censored at the time of crossover for the OS analysis. For PFS, which was assessed by BICR per RECIST v1.1, patients who were alive without disease progression or who were lost to follow-up were censored at the time of their last imaging assessment. The study addressed intercurrent events by permitting patients in the placebo-combination group to cross over to receive pembrolizumab monotherapy upon verified radiographic disease progression. The effective crossover rate was reported at 55.8% by the time of the final analysis. To manage the risk of Type I

error across multiple analyses, the trial employed the graphical method of Maurer and Bretz and a Lan-DeMets O'Brien-Fleming spending function to update actual boundaries based on the number of events observed at interim points. Regarding the proportional hazard assumption, the long-term updates noted that survival curves appeared to reach a plateau, and investigators observed that median OS estimates could fluctuate with longer follow-up due to substantial censoring occurring around the time medians were reached.

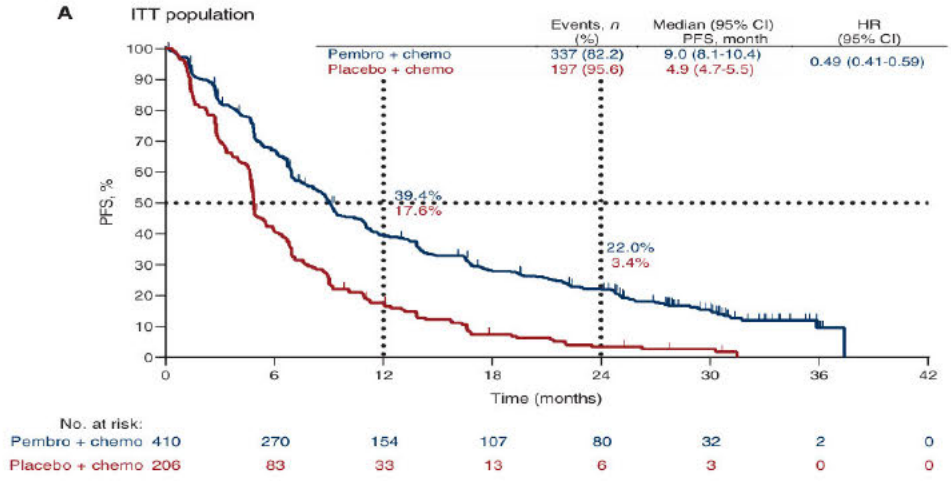
6.2.5 Effect – results per KEYNOTE-189 ITT (non-squamous)

Table 33. PFS, KEYNOTE-189 ITT (non-squamous)

	P+CT (N = 410)	CT (N = 206)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	9.0 (8.1, 10.4)	4.9 (4.7, 5.5)
HR (95% CI)	0.50 (0.41, 0.59)	-

Source: KEYNOTE-189, DCO at 28/08/20 [46]

Figure 15. Kaplan-Meier curves for PFS, KEYNOTE-189 ITT population



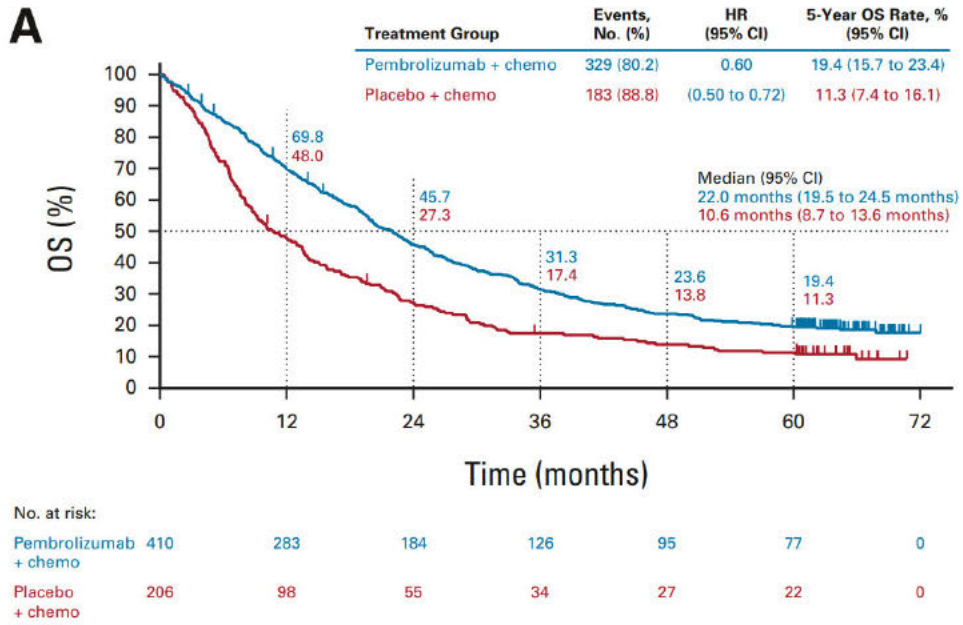
Note: DCO at 28/08/20, which was used for MAIC PFS in this report, did not present KM curves for PFS. **Source:** KEYNOTE-189, DCO at 20/05/19 [3]

Table 34. OS, KEYNOTE-189 ITT (non-squamous)

	P+CT (N = 410)	CT (N = 206)
Deaths, n (%)	329 (80.2%)	183 (88.8%)
Median OS, months (95% CI)	22.0 (19.5, 24.5)	10.6 (8.7, 13.6)
HR (95% CI)	0.60 (0.50, 0.72)	-

Source: KEYNOTE-189, DCO at 08/03/22 [45]

Figure 16. Kaplan-Meier curves for OS, KEYNOTE-189 ITT population



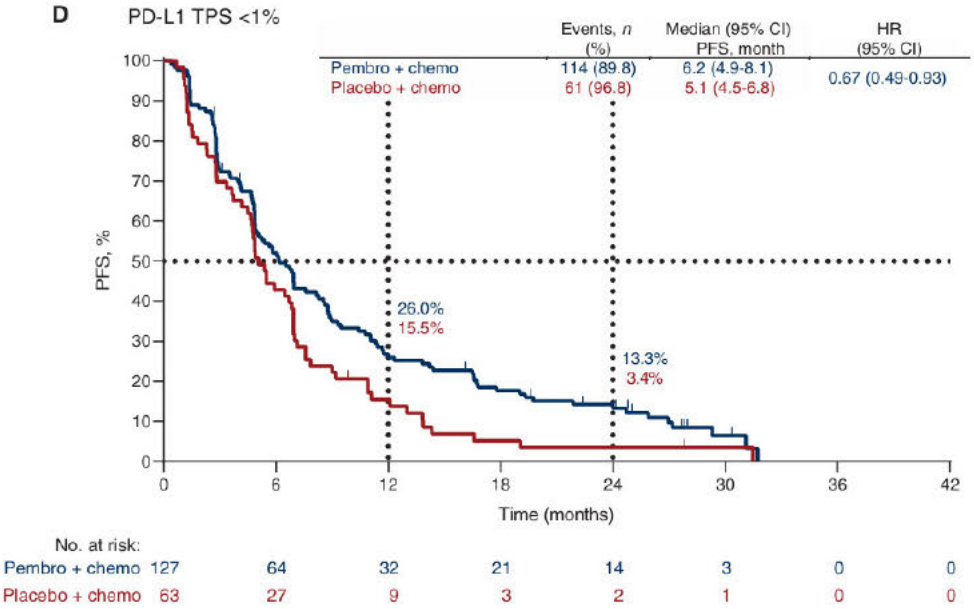
Source: KEYNOTE-189, DCO at 08/03/22 [45]

6.2.6 Effect – results per KEYNOTE-189 PD-L1 <1%

Table 35. PFS, KEYNOTE-189 PD-L1 <1% subgroup

	P+CT (N = 127)	CT (N = 63)
KEYNOTE-189, DCO at 28/08/20 [46]		
Events, n (%)	NA	NA
Median PFS, months (95% CI)	NA	NA
HR (95% CI)	0.68 (0.49, 0.93)	-
KEYNOTE-189, DCO at 20/05/19 [3]		
Events, n (%)	114 (89.8%)	61 (96.8%)
Median PFS, months (95% CI)	6.2 (4.9, 8.1)	5.1 (4.5, 6.8)
HR (95% CI)	0.67 (0.49, 0.93)	-

Table 36. PFS, KEYNOTE-189 PD-L1 <1% subgroup



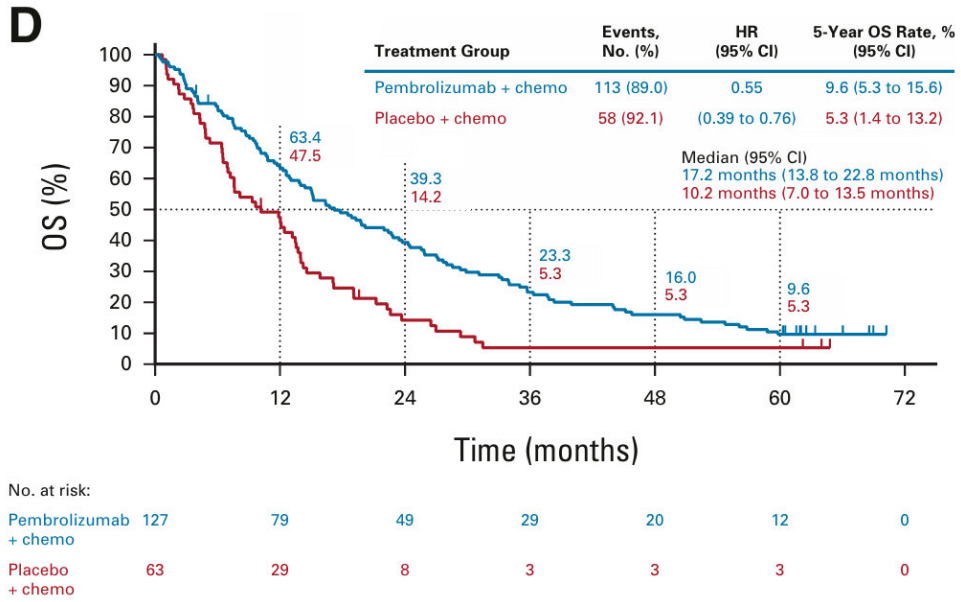
Note: Kaplan-Meier curves for PFS based on DCO at 28/08/20 is not available. **Source**: KEYNOTE-189, DCO at 20/05/19 [3]

Table 37. OS, KEYNOTE-189 PD-L1 <1% subgroup

	P+CT (N = 127)	CT (N = 63)
Deaths, n (%)	113 (89.0%)	58 (92.1%)
Median OS, months (95% CI)	17.2 (13.8, 22.8)	10.2 (7.0, 13.5)
HR (95% CI)	0.55 (0.39, 0.76)	-

Source: KEYNOTE-189, DCO at 08/03/22 [45]

Figure 17. Kaplan-Meier curves for OS, KEYNOTE-189 PD-L1 <1% subgroup



Source: KEYNOTE-189, DCO at 08/03/22 [45]

6.2.7 Effect – results per KEYNOTE-189 non-squamous biomarker subgroup

There is no report of PFS or OS outcomes specifically for the STK11m, KEAP1m, or KRASm biomarker subgroups in KEYNOTE-189 study.

6.3 N+I+CT compared to CT for first line treatment of mNSCLC without EGFR mutations or ALK rearrangements

6.3.1 Relevant studies

CheckMate-9LA is an international, randomized, open-label phase III trial evaluating nivolumab + ipilimumab combined with two cycles of platinum-based CT versus four cycles of CT alone as first line treatment for mNSCLC. The study enrolled mixed histology (squamous and non-squamous) patients, making it the key comparator for the POSEIDON ITT population. A total of 719 patients were randomized across 103 hospitals in 19 countries, stratified by tumour histology, sex, and tumour PD-L1 expression [12].

Efficacy reporting in this submission uses the 2-year update for PFS (median follow-up: 30.7, DCO at 18/02/21) and 4-year update for OS (median follow-up: 54.5 months, DCO at 13/02/23), respectively [4, 47]. In addition, we presented the most recent data from final 6-year update (median follow-up: 75.8 months, DCO at 22/11/24) [15]. To our knowledge, additional planned data cuts have not been announced.

Treatment discontinuation in the N+I+C arm occurred in 86% of treated patients (309/358). The main reasons for not completing the treatment period were disease

progression (51%), study drug toxicity (20%), AEs unrelated to study drug (9%), and death (2%). In the chemotherapy arm, 71% (249/349) of patients discontinued treatment, primarily due to disease progression (50%), AEs unrelated to study drug (8%), study drug toxicity (7%), and patient request (3%). A small proportion of randomized patients did not receive study treatment: 0.8% in the N+I+C arm and 2.5% in CT arm [12, 15]

Internal validity is considered high, reflecting the randomized, multicentre phase III design and use of BICR for primary efficacy assessments. However, the open-label design may introduce bias in investigator-reported outcomes and safety reporting. External validity is also high, given the multiregional enrolment and global population representing routine clinical practice; however, the CT alone control arm is no longer the SoC in many settings due to subsequent therapeutic advances [12].

In CheckMate-9LA, patients in the control arm received histology-based platinum-doublet CT administered intravenously every 3 weeks for 4 cycles. For patients with squamous histology, the regimen was carboplatin AUC 6 plus paclitaxel 200 mg/m². For patients with non-squamous histology, the regimen was either carboplatin AUC 5 or 6 plus pemetrexed 500 mg/m² or cisplatin 75 mg/m² plus pemetrexed 500 mg/m², with the investigator determining before randomisation whether a cisplatin-eligible patient would receive cisplatin. 261 patients (75%) received at least 4 cycles of CT; for the squamous regimen, the mean number of doses received for both carboplatin and paclitaxel was 3.4 (SD, 1.0) and the median was 4.0 (IQR, 3.0–4.0). For patients with non-squamous histology who achieved stable disease or response after induction therapy, optional maintenance pemetrexed 500 mg/m² every 3 weeks was permitted until disease progression or unacceptable toxicity; 159 of 238 patients (67%) with non-squamous histology received maintenance pemetrexed. The mean number of pemetrexed administrations was 9.2 (SD 7.9), with a median of 6.0 (IQR 4.0–12.0), and the median duration of treatment was 2.5 months [4, 12, 15].

Table 38. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
CheckMate-9LA, NCT03215706	Global, randomized, open-label phase III trial	Patients in the intervention arm received a 6-week induction alongside dual immunotherapy, then maintenance until disease progression, unacceptable toxicity, or for a maximum of 2 years. Patients in the comparator arm received CT for up to 12 weeks with optional pemetrexed maintenance	Adults with previously untreated mNSCLC (mixed histology), EGFR/ALK wild-type (N=719)	Nivolumab (360 mg IV) every 3 weeks plus ipilimumab (1 mg/kg IV) every 6 weeks and histology-based CT every 3 weeks for two cycles, followed by nivolumab and ipilimumab for up to 2 years	Investigator's choice of histology-based platinum-doublet CT (IV) administered every 3 weeks for four cycles, with optional pemetrexed maintenance for patients with non-squamous histology	Primary Endpoints: OS Secondary Endpoints: PFS (BICR per RECIST v1.1), ORR (confirmed complete or partial response rate assessed by BICR), DoR (time from first documented response to progression or death assessed by BICR), safety and tolerability (assessment of AEs and laboratory abnormalities) The current assessment with regards to clinical efficacy includes PFS based on the 2-year update data (median follow-up: 30.7 months, DCO at 18/02/21), and OS based on the 4-year update data (median follow-up: 54.5 months, DCO at 13/02/23) [4, 47]

6.3.2 Comparability of studies

See Section 6.1.2 and Section 7.1 for details.

6.3.2.1 Comparability of patients across studies

Table 39. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety

	CheckMate-9LA, ITT		
	Overall (n=719)	N+I+CT (n=361)	CT (n=358)
Age, <65 years %	49.2%	48.8%	49.7%
Sex, Male %	70.1%	69.8%	70.4%
Race, %			
Asian	8.1%	8.3%	8.4%
Non-Asian	91.9%	91.7%	91.6%
ECOG performance status, %			
0	31.3%	31.3%	31.3%
1	68.4%	68.4%	68.4%
Smoking status, %			
Never	13.6%	12.7%	14.5%
Current or former	86.4%	87.3%	85.5%
Metastases at baseline, %			
Liver	21.4%	18.8%	24.0%
Brain/CNS	17.0%	44.6%	46.9%
PD-L1 expression, %			
<1%	36.7%	37.4%	36.0%
≥1%	56.6%	56.2%	57.0%
≥50%	24.2%	21.1%	27.4%

Note: Percentages may not sum to 100% due to some patients having missing data (e.g. non-quantifiable PD-L1 expression). Baseline characteristics including TEMs identified in this report were not available by histology from CheckMate-9LA study. Consequently, we conducted histology-specific MAICs (squamous) for POSEIDON versus CheckMate-9LA by deriving weights to align POSEIDON squamous subgroups with the CheckMate-9LA ITT population. **Source**: CheckMate-9LA DCO at 09/03/20 [12]

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

Table 40. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population (source)	CheckMate-9LA, ITT	Health economic model (source)
Age, <65 years	20.3% [5]	49.2% [12]	Not applicable
Sex, male	46.0% [5]	70.1% [12]	Not applicable
Race, Asian	4% [54]	8.1% [12]	Not applicable
Histology, squamous	23.8% [5]	31.2% [12]	
PD-L1 < 1%	31.4% [5]	36.7% [12]	Not applicable

6.3.4 Analysis method

The primary efficacy assessment in CheckMate-9LA was conducted in the ITT population, which included all patients who underwent randomization. Survival curves and rates for the primary endpoint of OS and the secondary endpoint of PFS were estimated using the Kaplan-Meier method. To estimate the treatment effect, HRs and their associated 95% CIs were derived from a stratified Cox proportional-hazards model using treatment as a single covariate. These analyses were adjusted for the prespecified randomization stratification factors, which included tumour histology, sex, and tumour PD-L1 expression level. Additional sensitivity analyses for OS included the use of an unstratified Cox model and a multivariate analysis adjusted for baseline ECOG performance status, histology, sex, and PD-L1 expression.

The management of missing values was predefined, particularly for PD-L1 expression; patients whose tumour specimens were non-evaluable for PD-L1 were included in the ITT analysis of all randomized patients while they were excluded from the subgroup analyses with PD-L1 expression level. At the time of the primary analysis, the proportion of missing measurements for PD-L1 (non-quantifiable specimens) was 6% in N+I+CT arm and 7% in CT arm. Additionally, baseline ECOG performance status was not reported for one patient in each treatment group, representing less than 1% of the population. For efficacy outcomes, time-to-event data were analysed based on all randomized patients, with no transformations of outcomes or adjustment variables reported for the primary survival models.

Regarding censoring rules and exceptions, OS was defined as the time from randomization to death from any cause, and patients who were alive or lost to follow-up were censored at the last date they were known to be alive. PFS was assessed by BICR per RECIST v1.1 and was defined as the time from randomization to the first documented tumour progression or death from any cause. Under the primary PFS definition, patients were censored at their last evaluable tumour assessment on or before the initiation of any subsequent therapy. A secondary PFS definition that did not censor for the initiation of subsequent therapy was utilized as a sensitivity analysis. Intercurrent events were addressed by the study protocol's prohibition of in-study crossover; however, patients were permitted to receive subsequent systemic therapy upon treatment discontinuation at the investigator's discretion.

The proportional hazards assumption for the OS analysis was evaluated using a Cox model with a time-dependent treatment interaction, which resulted in a non-significant p-value of 0.9197, confirming that the assumption was met. While the study utilized BICR for radiographic assessments to mitigate bias, the trial was open label, which is a factor considered in the assessment of internal validity. No specific weighting, repeated measures correlation structures, or competing risk adjustments like the Aalen-Johansen estimator were reported for the primary survival analyses in the provided documentation. As of the final 6-year update, 38% of the N+I+CT arm and 50% of the CT arm had received at least one subsequent systemic therapy [15].

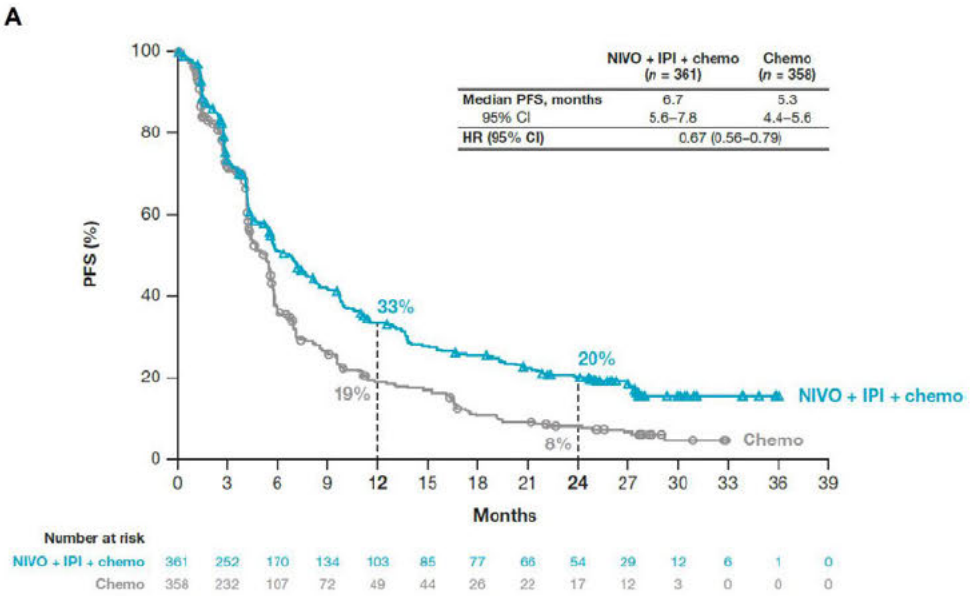
6.3.5 Effect – results per CheckMate-9LA ITT

Table 41. PFS, CheckMate-9LA ITT population

	N+I+CT (N = 361)	CT (N = 358)
Events, n (%)	307 (85.0%)	334 (93.3%)
Median PFS, months (95% CI)	6.7 (5.6, 7.8)	5.3 (4.4, 5.6)
HR (95% CI)	0.67 (0.56, 0.79)	

Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Figure 18. Kaplan–Meier curves for PFS, CheckMate-9LA ITT population



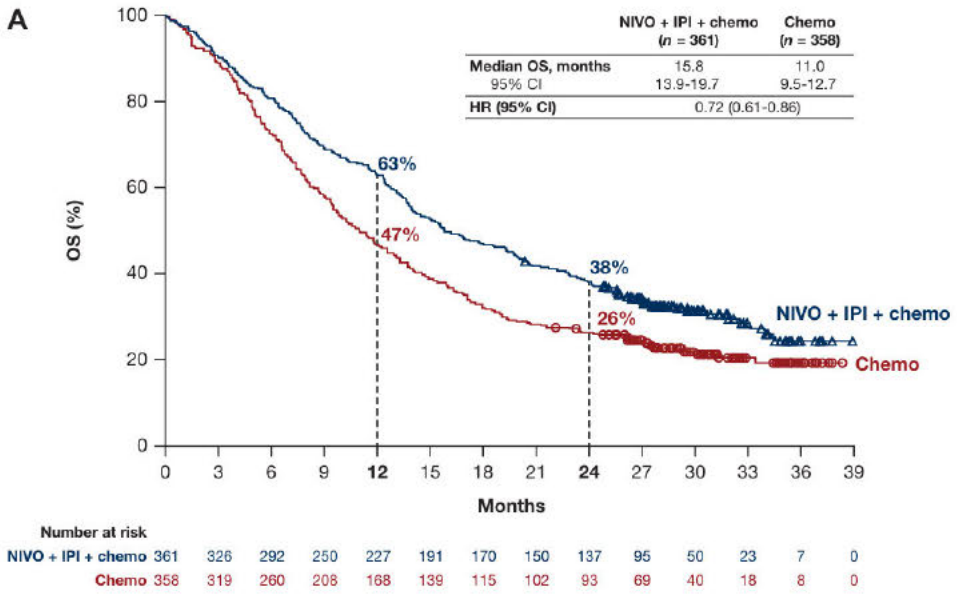
Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Table 42. OS, CheckMate-9LA ITT population

	N+I+CT (N = 361)	CT (N = 358)
CheckMate-9LA study, DCO at 13/02/23 [47]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	15.8 (NA)	11.0 (NA)
HR (95% CI)	0.74 (0.63, 0.87)	
CheckMate-9LA study, DCO at 22/11/24 [15]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	15.8 (13.9, 19.7)	11.0 (9.5, 12.7)
HR (95% CI)	0.74 (0.63, 0.87)	

Note: At the time the MAIC was conducted, the most recent overall survival data available were from DCT at 13/02/23, reported in ASCO abstract.

Figure 19. Kaplan–Meier curves for OS, CheckMate-9LA ITT population



Note: CheckMate-9LA DCO at 13/02/23 did not present Kaplan-Meier curves for OS. **Source:** CheckMate-9LA study, DCO at 22/11/24 [15]

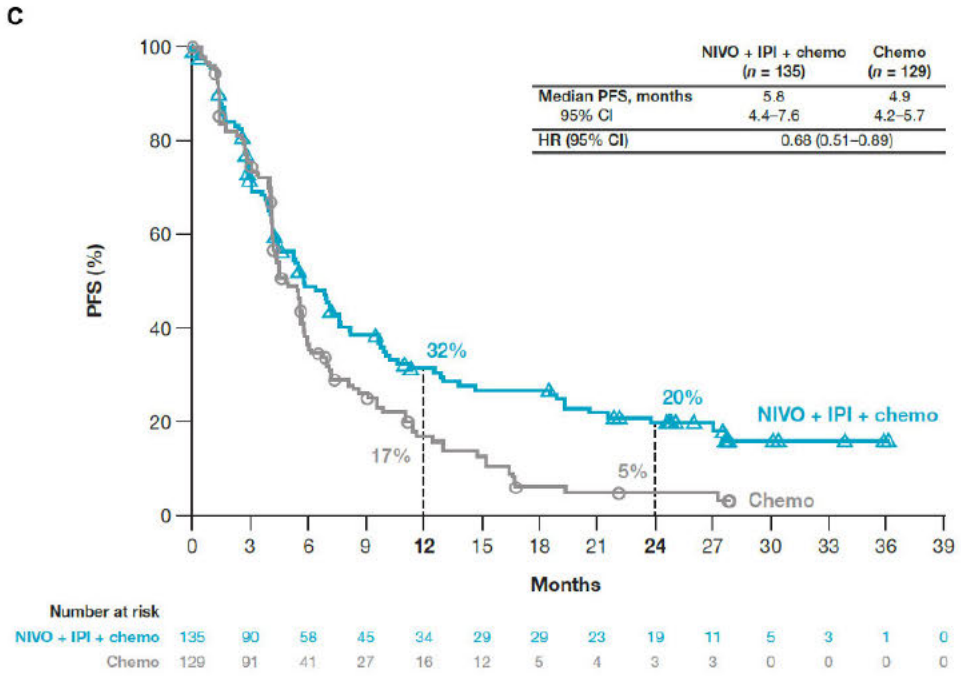
6.3.6 Effect – results per CheckMate-9LA PD-L1 <1%

Table 43. PFS, CheckMate-9LA ITT PD-L1 <1% subgroup

	N+I+CT (N = 135)	CT (N = 129)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	5.8 (4.4, 7.6)	4.9 (4.2, 5.7)
HR (95% CI)	0.68 (0.51, 0.89)	

Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Figure 20. Kaplan–Meier curves for PFS, CheckMate-9LA PD-L1 <1% subgroup

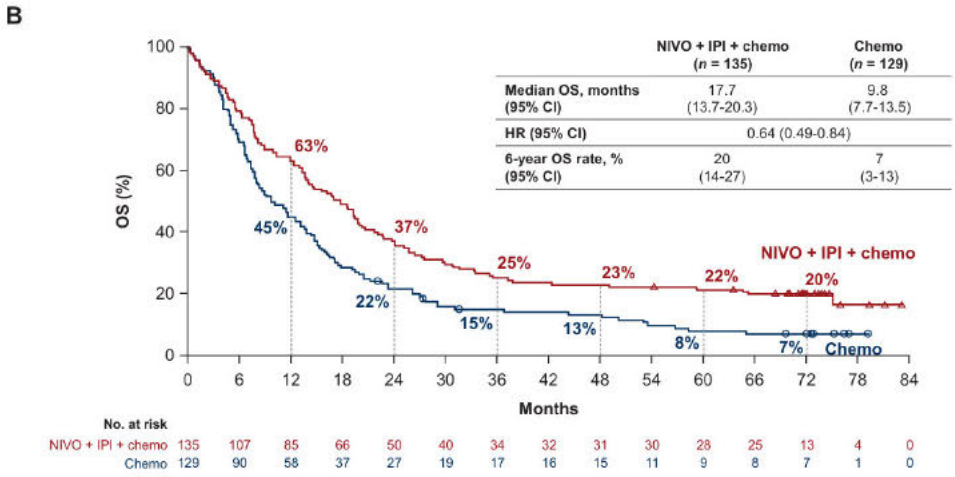


Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Table 44. OS, CheckMate-9LA PD-L1 <1% subgroup

	N+I+CT (N = 135)	CT (N = 129)
CheckMate-9LA study, DCO at 13/02/23 [47]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	17.7 (NA)	9.8 (NA)
HR (95% CI)	0.66 (0.50, 0.86)	
CheckMate-9LA study, DCO at 22/11/24 [15]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	17.7 (13.7, 20.3)	9.8 (7.7, 13.5)
HR (95% CI)	0.64 (0.49, 0.84)	

Figure 21. Kaplan–Meier curves for OS, CheckMate-9LA PD-L1 <1% subgroup



Note: CheckMate-9LA DCO at 13/02/23 did not present Kaplan-Meier curves for OS. **Source**: CheckMate-9LA study, DCO at 22/11/24 [15]

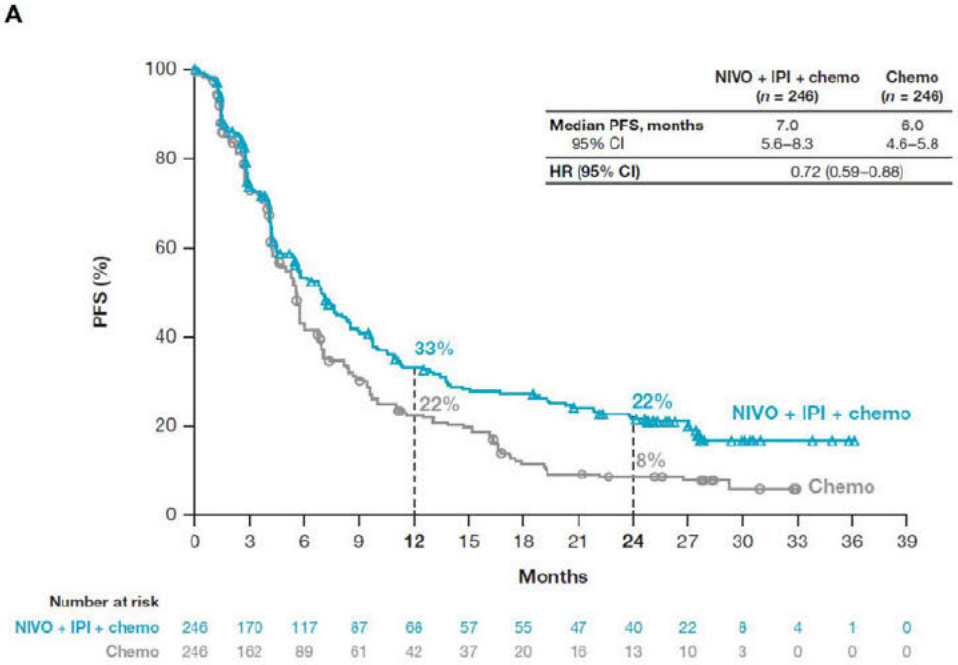
6.3.7 Effect – results per CheckMate-9LA non-squamous

Table 45. PFS, CheckMate-9LA non-squamous subgroup

	N+I+CT (N = 246)	CT (N = 246)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	7.0 (5.6, 8.3)	6.0 (4.6, 5.8)
HR (95% CI)	0.72 (0.59, 0.88)	

Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Figure 22. Kaplan-Meier curves for PFS, CheckMate-9LA non-squamous subgroup



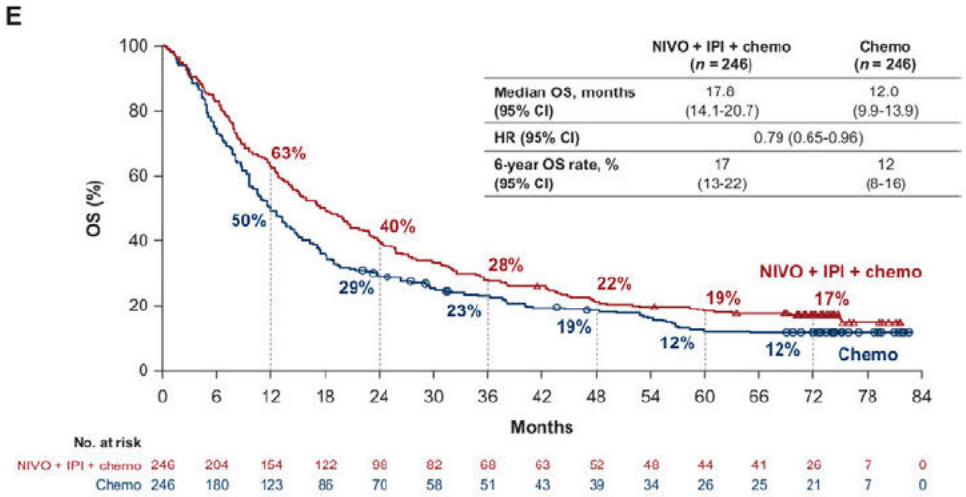
Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Table 46. OS, CheckMate-9LA non-squamous subgroup

	D+T+CT (N = 246)	CT (N = 246)
CheckMate-9LA study, DCO at 13/02/23 [47]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	17.8 (NA)	12.0 (NA)
HR (95% CI)	0.80 (0.66, 0.97)	
CheckMate-9LA study, DCO at 22/11/24 [15]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	17.8 (14.1, 20.7)	12.0 (9.9, 13.9)
HR (95% CI)	0.79 (0.65, 0.96)	

Note: At the time the MAIC was conducted, the most recent overall survival data available were from DCT at 13/02/23, reported in ASCO abstract.

Figure 23. Kaplan-Meier curves for OS, CheckMate-9LA non-squamous subgroup



Note: CheckMate-9LA DCO at 13/02/23 did not present Kaplan-Meier curves for OS. **Source:** CheckMate-9LA study, DCO at 22/11/24 [47]

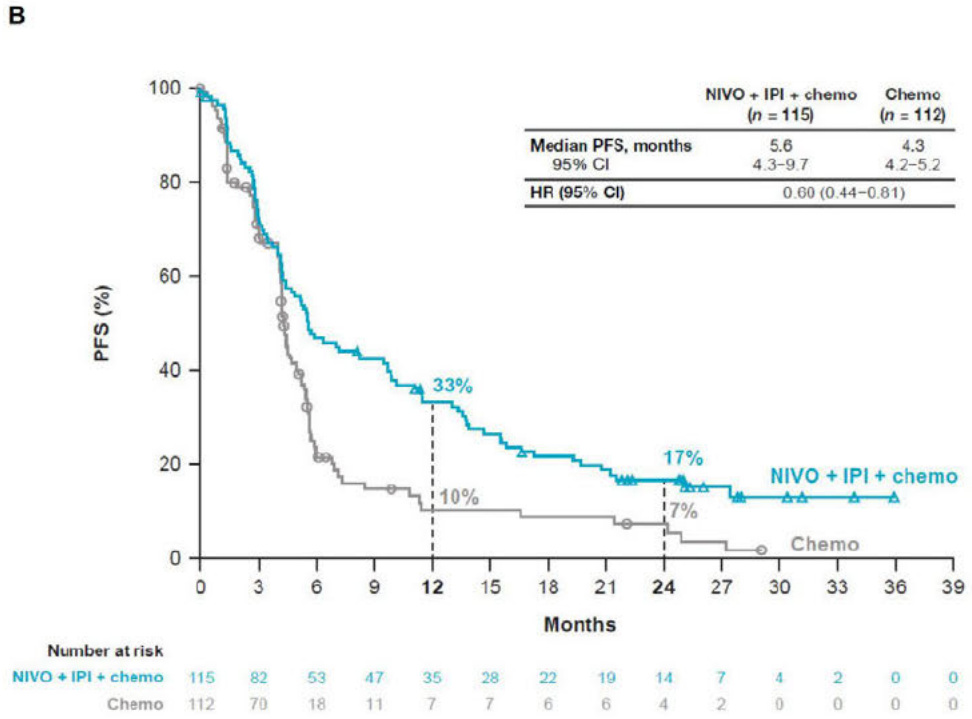
6.3.8 Effect – results per CheckMate-9LA squamous

Table 47. PFS, CheckMate-9LA squamous subgroup

	N+I+CT (N = 115)	CT (N = 112)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	5.6 (4.3, 9.7)	4.3 (4.2, 5.2)
HR (95% CI)	0.60 (0.44, 0.81)	

Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Figure 24. Kaplan-Meier curves for PFS, CheckMate-9LA squamous subgroup



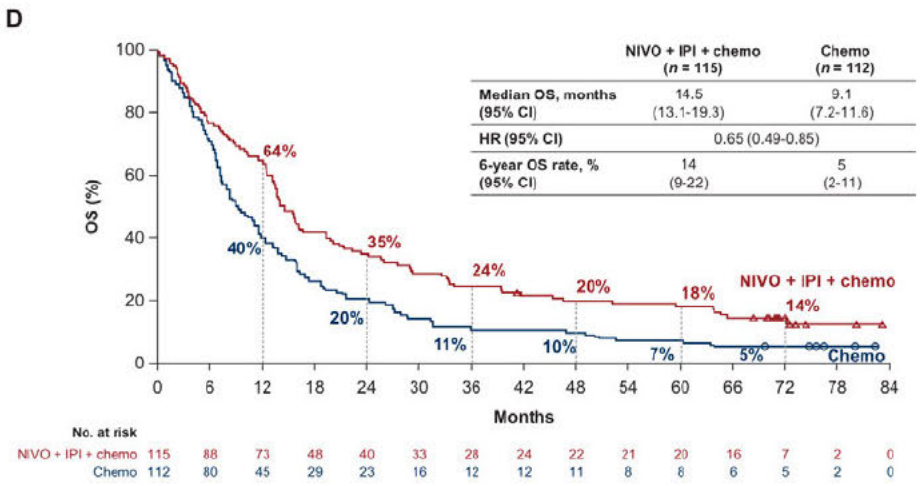
Source: CheckMate-9LA study, DCO at 18/02/21 [4]

Table 48. OS, CheckMate-9LA squamous subgroup

	D+T+CT (N = 115)	CT (N = 122)
CheckMate-9LA study, DCO at 13/02/23 [47]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	14.5 (NA)	9.1 (NA)
HR (95% CI)	0.64 (0.48, 0.84)	
CheckMate-9LA study, DCO at 22/11/24 [15]		
Deaths, n (%)	NA	NA
Median OS, months (95% CI)	14.5 (13.1, 19.3)	9.1 (7.2, 11.6)
HR (95% CI)	0.65 (0.49, 0.85)	

Note: At the time the MAIC was conducted, the most recent overall survival data available were from DCO at 13/02/23, reported in ASCO abstract.

Figure 25. Kaplan-Meier curves for OS, CheckMate-9LA squamous subgroup



Note: CheckMate-9LA DCO at 13/02/23 did not present Kaplan-Meier curves for OS. **Source:** CheckMate-9LA study, DCO at 22/11/24 [47]

6.3.9 Effect – results per CheckMate-9LA non-squamous biomarker subgroup

Table 49. PFS, CheckMate-9LA non-squamous STK11, KRAS and overall KEAP1 mutation subgroup

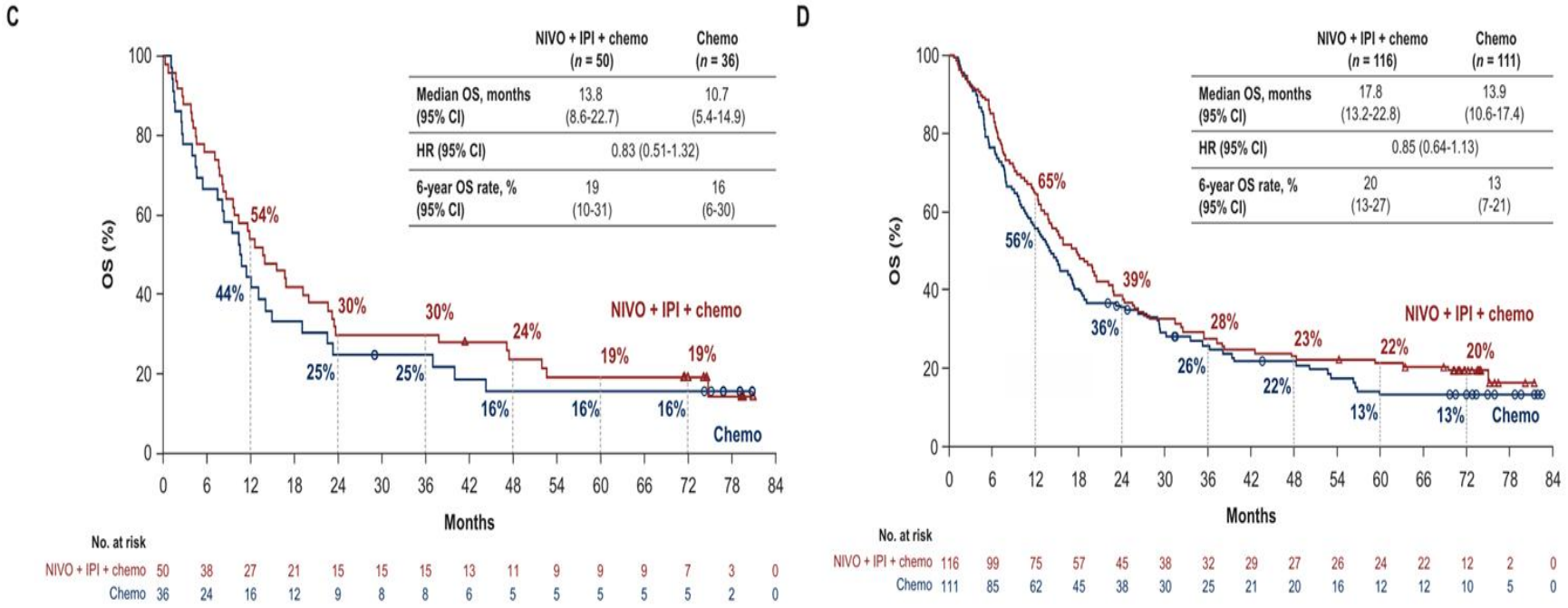
	Non-squamous STK11 mutant		Non-squamous KRAS mutant		Overall KEAP1 mutant	
	N+I+CT (n = 50)	CT (n = 36)	N+I+CT (n = 61)	CT (n = 61)	N+I+CT (n = 18)	CT (n = 20)
Events, n (%)	NA	NA	NA	NA	NA	NA
Median PFS, months	NA	NA	NA	NA	NA	NA
HR (95% CI)	NA	NA	NA	NA	NA	NA

Table 50. OS, CheckMate-9LA non-squamous STK11, KRAS and overall KEAP1 mutation subgroup

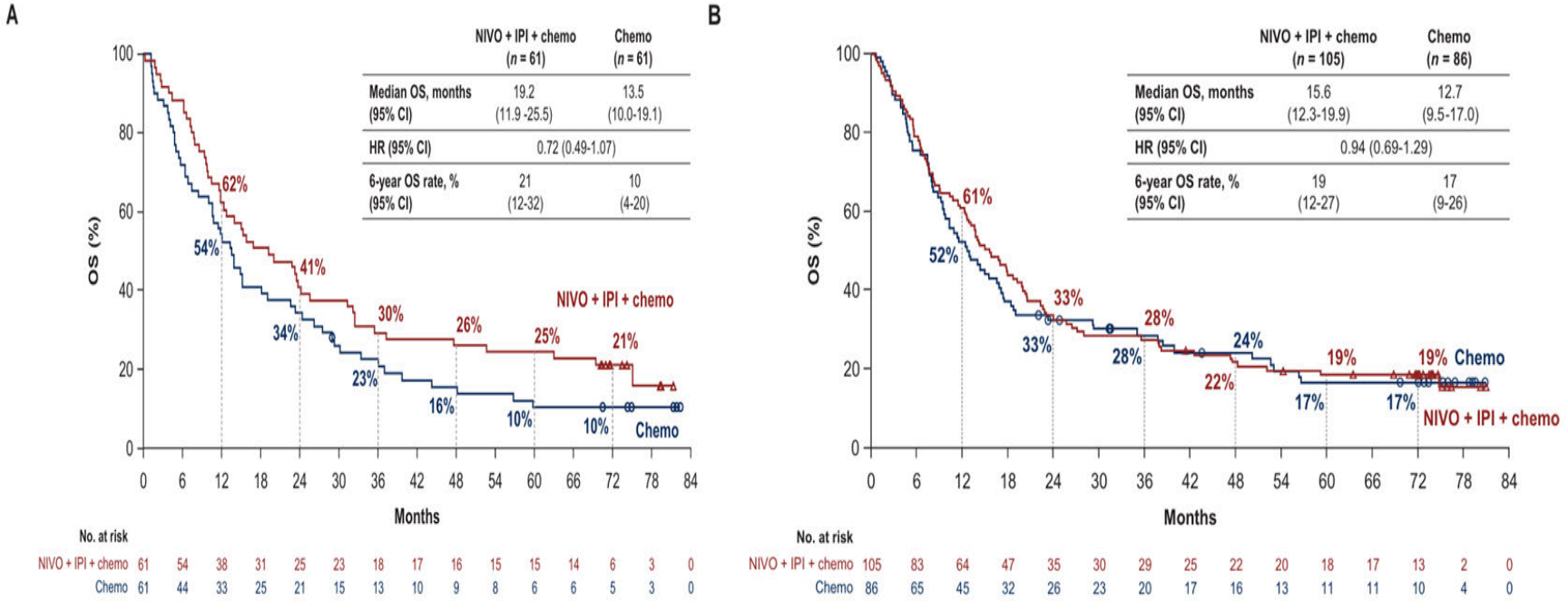
	Non-squamous STK11 mutant		Non-squamous KRAS mutant		Overall KEAP1 mutant	
	N+I+CT (n = 50)	CT (n = 36)	N+I+CT (n = 61)	CT (n = 61)	N+I+CT (n = 18)	CT (n = 20)
Deaths, n (%)	NA	NA	NA	NA	NA	NA
Median OS, months (95% CI)	13.8 (8.6, 22.7)	10.7 (5.4, 14.9)	19.2 (11.9, 25.5)	13.5 (10.0, 19.1)	13.2 (6.6, 22.7)	6.9 (2.8, 11.9)
HR (95% CI)	0.83 (0.51, 1.32)	-	0.72 (0.49, 1.07)	-	0.63 (0.32, 1.24)	-

Source: CheckMate-9LA, DCO at 22/11/24 [15]

Figure 26. Kaplan–Meier curves for OS, CheckMate-9LA non-squamous STK11 mutant (C) and wild-type (D), non-squamous KRAS mutant (A) and wild-type (B) subgroups



(Continued)

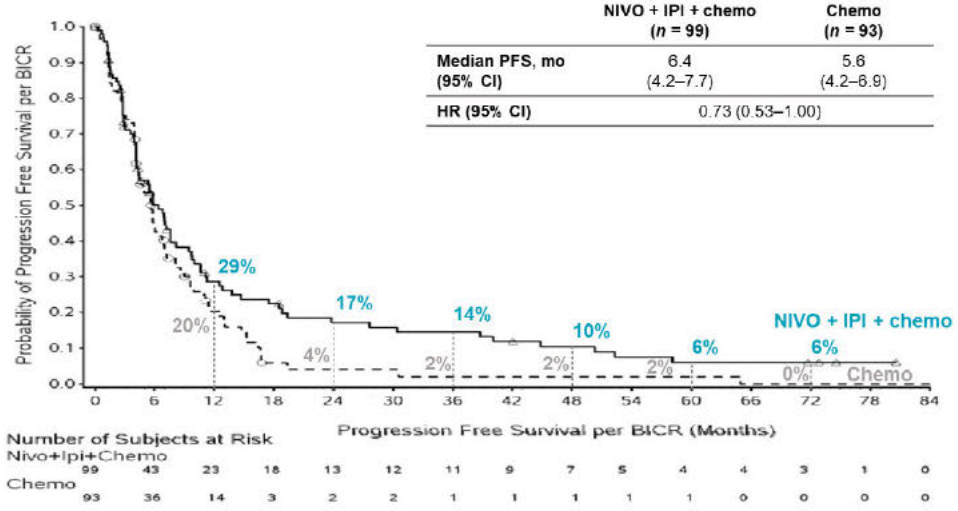


Note: CheckMate-9LA DCO at 22/11/24 did not present Kaplan–Meier curves for overall survival in KEAP1 subgroup. **Source**: CheckMate-9LA, DCO at 22/11/24 [15]

6.3.10 Effect – results per CheckMate-9LA combined subgroup with PD-L1 <1% and non-squamous or squamous

Table 51. PFS. Kaplan–Meier curves for progression-free survival, CheckMate-9LA PD-L1 <1% and non-squamous subgroup

B



Source: CheckMate-9LA study, DCO at 22/11/24 [15]

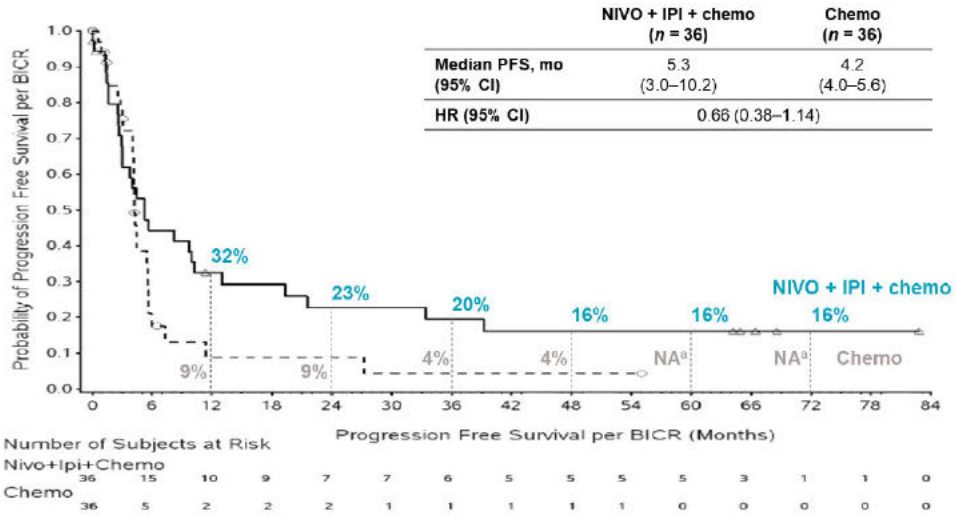
Table 52. PFS, CheckMate-9LA ITT PD-L1 <1% and squamous subgroup

	N+I+CT (N = 36)	CT (N = 36)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	5.3 (3.0, 10.2)	4.2 (4.0, 5.6)
HR (95% CI)	0.68 (0.38, 1.14)	

Source: CheckMate-9LA study, DCO at 22/11/24 [15]

Figure 27. Kaplan–Meier curves for PFS, CheckMate-9LA PD-L1 <1% and squamous subgroup

A



Source: CheckMate-9LA study, DCO at 22/11/24 [15]

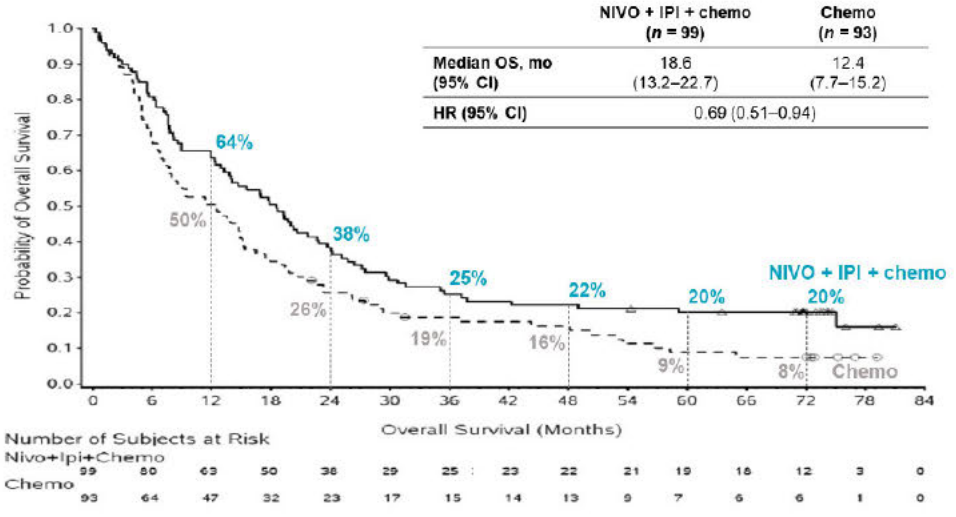
Table 53. OS, CheckMate-9LA ITT PD-L1 <1% and non-squamous subgroup

	N+I+CT (N = 99)	CT (N = 93)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	18.6 (13.2, 22.7)	12.4 (7.7, 15.2)
HR (95% CI)	0.68 (0.51, 0.94)	

Source: CheckMate-9LA study, DCO at 22/11/24 [15]

Figure 28. Kaplan–Meier curves for OS, CheckMate-9LA PD-L1 <1% and non-squamous subgroup

B



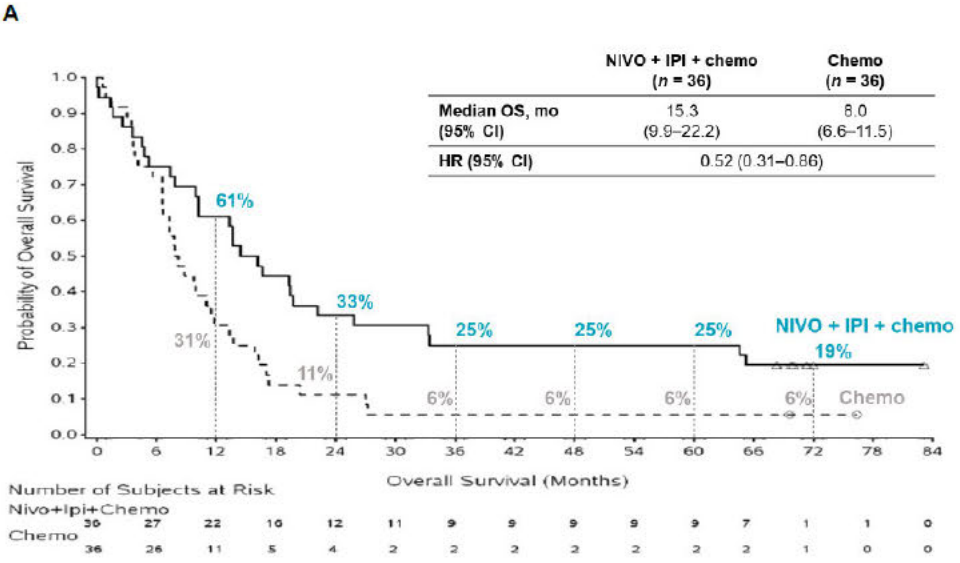
Source: CheckMate-9LA study, DCO at 22/11/24 [15]

Table 54. OS, CheckMate-9LA ITT PD-L1 <1% and squamous subgroup

	N+I+CT (N = 36)	CT (N = 36)
Events, n (%)	NA	NA
Median PFS, months (95% CI)	15.3 (9.9, 22.2)	8.0 (6.6, 11.5)
HR (95% CI)	0.52 (0.31, 0.86)	

Source: CheckMate-9LA study, DCO at 22/11/24 [15]

Figure 29. Kaplan–Meier curves for PFS, CheckMate-9LA PD-L1 <1% and squamous subgroup



Source: CheckMate-9LA study, DCO at 22/11/24 [15]

7. Comparative analyses

7.1 Method of analysis

7.1.1 Rationale for Matching-Adjusted Indirect Comparison (MAIC)

The method of analysis used in the provided sources primarily involves Matching-Adjusted Indirect Comparisons (MAICs), supplemented by Bucher Indirect Treatment Comparisons (ITCs) for safety outcomes, to evaluate the comparative effectiveness and safety of D+T+CT against other standard first-line treatments for mNSCLC with PD-L1 < 1%; P+CT in non-squamous and N+I+CT in squamous histology subgroup. This approach was necessary due to the absence of direct head-to-head clinical trials comparing these regimens. An assessment of these criteria was performed using data from the POSEIDON

trial (the intervention trial) and the comparator trials (KEYNOTE-189 and CheckMate-9LA).

To ensure that MAICs produce less biased estimates of relative efficacy than non-population-adjusted ITC methods, two criteria must be met; there are treatment effect modifiers (TEMs) present among the available patient baseline characteristics and there are imbalances in these TEMs between the clinical trials being compared.

TEMs are patient characteristics that significantly alter how effective a treatment is. For the MAIC analyses, TEMs were identified through exploratory analyses of the POSEIDON trial, which provided individual patient-level data (IPD) (see also Appendix D)

1. Global Interaction Test: An initial global interaction test was conducted to assess the consistency of treatment effects for D+T+CT versus CT on OS across various subgroups. The model included numerous baseline characteristics as covariates (e.g., histology, stage, PD-L1 expression, smoking status, age, race, brain metastases) and their interaction terms with treatment. The test yielded a p-value of 0.00714, indicating significant interactions between treatment and baseline characteristics.

2. Stepwise Backwards Selection Model: A stepwise backwards selection model further explored these interactions and identified race, smoking status, and histology as having significant interactions with treatment ($p<0.05$). Consequently, these three characteristics were designated as potential TEMs for the MAIC.

3. Directional Impact: Subgroup analyses of OS from POSEIDON indicated that D+T+CT had a greater treatment effect versus CT in non-Asian patients compared to Asian patients, current and former smokers compared to never smokers, and non-squamous histology compared to squamous histology. A similar trend was also observed for PFS, leading to the assumption that TEMs identified for OS could also be applied for PFS MAICs.

4. Consideration of Chemotherapy: Planned CT was not identified as a TEM based on the interaction tests. However, the CT options in POSEIDON were histology-dependent (e.g., pemetrexed for non-squamous, gemcitabine for squamous). The MAICs do not account for potential differences in CT agents within each histology subgroup, especially since gemcitabine + cisplatin/carboplatin, heavily used for squamous patients in POSEIDON, was not an option in CheckMate-9LA. This necessitates caution when interpreting results for squamous histology subgroups.

Significant imbalances in the identified TEMs were observed when comparing POSEIDON to the comparator trials, which underscored the necessity of MAICs:

- Race/Region: POSEIDON enrolled a much higher proportion of Asian patients (33.6%) compared to CheckMate-9LA (8.1%) and KEYNOTE-189 (1.6%).
- Smoking Status: POSEIDON had a lower proportion of current/former smokers (79.4%) compared to CheckMate-9LA (86.4%) and KEYNOTE-189 (88.1%).
- Histology: The proportion of non-squamous histology patients in POSEIDON (63.4%) was lower than in CheckMate-9LA (68.8%).

These substantial differences indicated that unadjusted comparisons would likely yield biased relative treatment estimates.

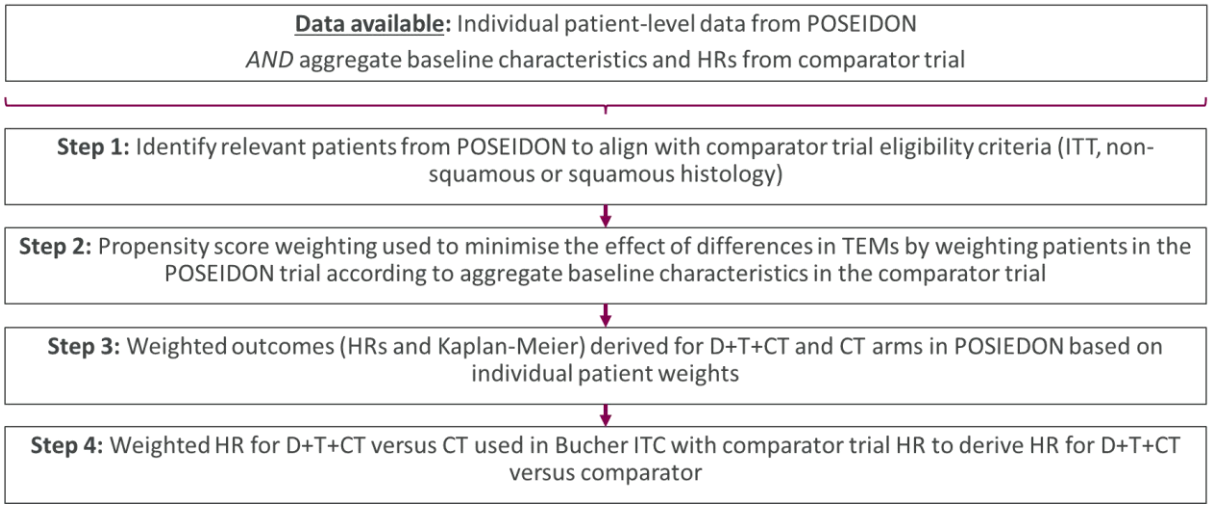
7.1.2 Implementing MAIC Methodology

Anchored MAICs were performed by re-weighting IPD from the POSEIDON trial. This re-weighting aimed to match the aggregate characteristics of the comparator trials (KEYNOTE-189 or CheckMate-9LA), thereby reducing heterogeneity and producing less biased estimates of relative efficacy.

The methodology followed these key steps:

The steps followed for conducting the MAICs are outlined in figure 1 and described below. Individual patient-level data were available from the POSEIDON trial, with only aggregate data available from the comparator trials.

Figure 30. Outline of MAIC methodology



Since the initial SLR was conducted, more recent OS data from the POSEIDON trial have become available (data cut-off date: 24th August 2023 [5-year OS analysis]), and survival data from longer duration of follow-up have been presented at clinical congresses for the KEYNOTE-189 (5-year follow-up) and CheckMate-9LA (4-year follow-up).[2-5] Results are presented for OS MAICs using the more recent data from the POSEIDON and comparator trials. PFS was not analysed at the 5-year OS analysis (or 4-year OS analysis) in POSEIDON and so no updates for PFS MAICs were conducted.

DCOs

Since the initial SLR was conducted, more recent OS data from the POSEIDON trial have become available (data cut-off date: 24th August 2023 [5-year OS analysis]), and survival data from longer duration of follow-up have been presented at clinical congresses for the KEYNOTE-189 (5-year follow-up) and CheckMate-9LA (4-year follow-up).[2-5] Results are presented for OS MAICs using the more recent data from the POSEIDON and

comparator trials. PFS was not analysed at the 5-year OS analysis (or 4-year OS analysis) in POSEIDON and so no updates for PFS MAICs were conducted.

ITT efficacy data

The OS and PFS HRs versus CT from POSEIDON and CheckMate-9LA for the POSIEDON ITT population are reported in Table 55.

Table 55. Efficacy data inputs from POSEIDON and comparator trials for POSEIDON ITT MAIC

Trial	OS HR vs CT (95% CI)	PFS HR vs CT (95% CI)	Data cut-off date / duration of follow-up	Source
POSEIDON	0.75 (0.63, 0.88)	0.72 (0.60, 0.86)	24th July 2019 (PFS) 11th March 2022 (OS) 46.5 months median duration follow-up (OS)	Johnson et al. presented at WCLC 2021 (PFS)[55] Johnson et al. presented at ESMO 2022 (OS)[56]
CheckMate-9LA	0.74 (0.62, 0.87)	0.70 (0.59, 0.83)	15th February 2022 36.1 month median follow-up	Paz-Ares 2023 [50]
More recent OS data				
	OS HR vs CT (95% CI)			
POSEIDON	0.76 (0.64, 0.89)		24th August 2023 63.4 months median duration follow-up (OS)	Peters et al. presented at ESMO-IO 2023[57]
CheckMate-9LA	0.74 (0.63, 0.87)		13th February 2023 54.5 months median follow-up	Carbone et al. presented at ASCO 2023[58]

Non-Squamous Subgroup efficacy data

The OS and PFS HRs versus CT from POSEIDON, KEYNOTE-189 and CheckMate-9LA for the non-squamous subgroup are reported in Table 56.

Table 56. Efficacy data inputs from POSEIDON and comparator trials for non-squamous histology MAIC

Trial	OS HR vs CT (95% CI)	PFS HR vs CT (95% CI)	Data cut-off date / duration of follow-up	Source
POSEIDON[a]	0.68 (0.55, 0.85)	0.66 (0.52, 0.84)	24th July 2019 (PFS) 11th March 2022 (OS) 46.5 months median duration follow-up (OS)	Johnson et al. presented at WCLC 2021 (PFS) Johnson et al. presented at ESMO 2022 (OS)
KEYNOTE-189	0.60 (0.50, 0.72)	0.50 (0.42, 0.60)	8th March 2022 64.6 months median follow-up	Garassino et al. 2023
CheckMate-9LA[a]	0.78 (0.63, 0.96)	0.72 (0.59. 0.88)	18th February 2021 30.7 months median follow-up	Reck et al. 2021
More recent OS data				
	OS HR vs CT (95% CI)			
POSEIDON[a]	0.69 (0.56, 0.85)		24th August 2023 63.4 months median duration follow-up (OS)	Peters et al. presented at ESMO-IO 2023
CheckMate-9LA[a]	0.80 (0.66, 0.97)		13th February 2023 54.5 months median follow-up	Carbone et al. presented at ASCO 2023

[a] *Based on subgroup analyses*

Squamous Subgroup efficacy data

The OS and PFS HRs versus CT from POSEIDON, KEYNOTE-407 and CheckMate-9LA for the squamous subgroup are reported in Table 57.

Table 57. Efficacy data inputs from POSEIDON and comparator trials for squamous histology MAIC

Trial	OS HR vs CT (95% CI)	PFS HR vs CT (95% CI)	Data cut-off date / duration of follow-up	Source
POSEIDON[a]	0.83 (0.64, 1.08)	0.77 (0.58, 1.01)	24th July 2019 (PFS) 11th March 2022 (OS) 46.5 months median duration follow-up (OS)	Johnson et al. presented at WCLC 2021 (PFS)[55] Johnson et al. presented at ESMO 2022 (OS)[56]
CheckMate-9LA[a]	0.63 (0.47, 0.85)	0.60 (0.44, 0.81)	18th February 2021 30.7 months median follow-up	Reck et al. 2021[4]
More recent OS data				
	OS HR vs CT (95% CI)			
POSEIDON[a]	0.85 (0.65, 1.10)		24th August 2023 63.4 months median duration follow-up (OS)	Peters et al. presented at ESMO-IO 2023[57]
CheckMate-9LA[a]	0.64 (0.48, 0.84)		13th February 2023 54.5 months median follow-up	Carbone et al. presented at ASCO 2023[58]

[a] Based on subgroup analyses

In the PDL-1 > 1% and non-squamous subgroup KeyNote189 reported PFS 0.68 (0.49, 0.93) and OS 0.55 (0.39, 0.76) (DCO 28.08.2020). In POSEIDON patients with PD-L1 <1% and non-squamous histology, the OS HRs for D+T+CT vs. CT was 0.81 (0.59, 1.13). Among patients with PD-L1 <1% and squamous histology, the OS HR was 0.80 (95% CI: 0.53, 1.23) for PD-L1 TC <1%.

Weighting of data

After weighting, baseline characteristics were re-examined to confirm that imbalances in TEMs had been adequately addressed. The distribution of weights and the ESS of the post-weighting POSEIDON population were assessed (See in in Appendix D, Figure 38, Figure 39 and Figure 40). Although adjustments were made, the use of aggregate data for comparator trials means that some residual confounding is possible for factors like region, chemotherapy regimen differences, or certain biomarker profiles that could not

be fully accounted for. However, clinical review suggested that the primary baseline characteristics crucial for outcomes and patient populations were sufficiently comparable for meaningful indirect comparison.

Table 58. Baseline characteristics of patients in POSEIDON before and after weighting to KEYNOTE-189, non-squamous subgroup

	POSEIDON non-squamous subgroup, before weighing (N=428)	POSEIDON non-squamous subgroup, after weighting (ESS=256.71)	KEYNOTE-189 ITT (N=616)
Age, <65 years %	54.7%	56.1%	50.6%
Sex, Male %	70.1%	71.7%	58.9%
Race[1], %			
Asian	36.7%	2.3%	1.6%
Non-Asian	63.3%	97.7%	98.4%
ECOG performance status, %			
0	33.2%	33.6%	43.2%
1	66.8%	66.4%	56.2%
Smoking status, %			
Never	25.2%	12.1%	11.9%
Current or former	74.8%	87.9%	88.1%
Metastases at baseline, %			
Liver[2]	18.7%	22.5%	-
Brain/CNS	13.3%	12.9%	17.5%
PD-L1 expression, %			
<1%	38.1%	43.1%	30.8%
≥1%	61.9%	56.9%	63.0%
≥50%	30.1%	27.3%	32.8%

[1]Region of enrolment used for 'Race' for comparator trials; [2]In POSEIDON, Liver = 'Hepatic (including gall bladder)'. **Note**: For the summary of baseline characteristics after weighting the patient-level weights were

rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1. **Source**: POSEIDON [2], POSEIDON CSR [43], KEYNOTE-189 [16]

Table 59. Baseline characteristics of patients in POSEIDON before and after weighting to CheckMate-9LA, squamous subgroup

	POSEIDON squamous subgroup, before weighing (N=246)	POSEIDON squamous subgroup, after weighting (ESS=205.87)	CheckMate-9LA ITT (N=719)
Age, <65 years %	54.1%	57.7%	49.2%
Sex, Male %	87.8%	86.2%	70.1%
Race[1], %			
Asian	26.4%	8.5%	8.1%
Non-Asian	73.6%	91.5%	91.9%
ECOG performance status, %			
0	35.4%	37.8%	31.3%
1	64.6%	62.2%	68.4%
Smoking status, %			
Never	12.2%	13.8%	13.6%
Current or former	87.8%	86.2%	86.4%
Metastases at baseline, %			
Liver[2]	28.0%	29.1%	21.4%
Brain/CNS	8.5%	6.1%	17.0%
PD-L1 expression, %			
<1%	37.4%	40.0%	36.7%
≥1%	62.6%	60.0%	56.6%
≥50%	27.6%	27.2%	24.2%

[1]Region of enrolment used for 'Race' for comparator trials; [2]In POSEIDON, Liver = 'Hepatic (including gall bladder)' .**Note**: For the summary of baseline characteristics after weighting the patient-level weights were rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1. Baseline characteristics including TEMs identified in this report were not available by histology

from CheckMate-9LA study. Consequently, we conducted histology-specific MAICs (squamous) for POSEIDON vs. CheckMate-9LA by deriving weights to align POSEIDON squamous with the CheckMate-9LA ITT population. **Source:** POSEIDON [2], POSEIDON CSR [43], CheckMate-9LA [12]

Table 60. Baseline characteristics of patients in POSEIDON before and after weighting to CheckMate-9LA, ITT population

	POSEIDON ITT, before weighing (N=675)	POSEIDON ITT, after weighting (ESS=491.1)	CheckMate-9LA ITT (N=719)
Age, <65 years %	54.5%	56.1%	49.2%
Sex, Male %	76.6%	76.4%	70.1%
Race[1], %			
Asian	33.6%	8.4%	8.1%
Non-Asian	66.4%	91.6%	91.9%
ECOG performance status, %			
0	33.9%	35.1%	31.3%
1	65.9%	64.9%	68.4%
Smoking status, %			
Never	20.4%	13.8%	13.6%
Current or former	79.4%	86.2%	86.4%
Metastases at baseline, %			
Liver[2]	22.1%	23.7%	21.4%
Brain/CNS	11.6%	10.7%	17.0%
PD-L1 expression, %			
<1%	37.8%	41.4%	36.7%
≥1%	62.2%	58.6%	56.6%
≥50%	29.3%	27.3%	24.2%

[1]Region of enrolment used for 'Race' for comparator trials; [2]In POSEIDON, Liver = 'Hepatic (including gall bladder)' **Note:** For the summary of baseline characteristics after weighting the patient-level weights were rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1.**Source:** POSEIDON [2], POSEIDON CSR [43], CheckMate-9LA [12]

Results after weighting

Table 61. HRs for D+T+CT vs CT before and after weighting to CheckMate-9LA (POSEIDON ITT)

HR (95% CI)	*Before weighting* D+T+CT vs CT	*After weighting* D+T+CT vs CT
OS (11th March 2022)	0.75 (0.63, 0.88)	0.61 (0.51, 0.74)
PFS	0.72 (0.60, 0.86)	0.64 (0.52, 0.79)
OS (24th August 2023)	0.74 (0.63, 0.88)	0.61 (0.51, 0.74)

Table 62. HRs for D+T+CT vs CT before and after weighting to KEYNOTE-189 (non-squamous)

HR (95% CI)	*Before weighting* D+T+CT vs CT	*After weighting to KN189* D+T+CT vs CT
OS	0.68 (0.55, 0.85)	0.55 (0.42, 0.73)
PFS	0.66 (0.52, 0.84)	0.61 (0.45, 0.83)
OS (24th August 2023)	0.69 (0.56, 0.85)	0.55 (0.42, 0.71)

Table 63. HRs for D+T+CT vs CT before and after weighting to CheckMate-9LA (squamous)

HR (95% CI)	*Before weighting* D+T+CT vs CT	*After weighting to CM9LA* D+T+CT vs CT
OS	0.83 (0.64, 1.08)	0.76 (0.63, 0.91)
PFS	0.77 (0.58, 1.01)	0.75 (0.56, 1.00)
OS (24th August 2023)	0.85 (0.65, 1.10)	0.77 (0.58, 1.02)

Note: *The before weighting HR from POSEIDON is from the stratified Cox proportional hazards model. The primary analysis in POSEIDON is based on analyses stratified for PD-L1 expression (PD-L1 ⩾50% vs PD-L1 <50%), histology (squamous versus non-squamous), and disease stage (Stage IVA versus Stage IVB) (primary analysis).[59]*

Results

The results for PFS and OS are presented in Table 64 – 68.

Conclusion

The impact of imbalances in TEMs between studies on the relative efficacy of D+T+CT versus P+CT and N+I+CT can be seen through comparison of HRs from ITCs before and after weighting in the MAIC. In each case, after adjusting for these differences in the MAIC the HRs for D+T+CT versus P+CT and N+I+CT are lower than the HRs from the ITC

before weighting. Conclusions on the relative efficacy of D+T+CT versus P+CT and N+I+CT should therefore consider the impact of these imbalances, with the ITCs after weighting in the MAIC providing less biased estimates of relative efficacy.

Overall, the MAICs are considered to provide a less biased estimate of the relative efficacy of D+T+CT versus the comparators of interest, with respect to imbalances in TEMs identified from the POSEIDON trial. The MAICs suggest that after accounting for imbalances in TEMs between studies, numerical improvements in OS (HR<1) may be expected for D+T+CT versus P+CT (non-squamous) and versus N+I+CT (POSEIDON ITT and non-squamous), but the differences in OS are nominally not statistically significant, with the exception of the comparison versus N+I+CT in the non-squamous subgroup (nominally significant in favour of D+T+CT). MAICs in the squamous subgroup were also performed, with HRs after weighting in favour of the comparators (HRs>1), but these analyses should be interpreted with caution given the differences in chemotherapy regimens utilised in the trials, as described above.

7.1.3 Safety Analysis Methodology

Bucher ITCs were conducted using the odds ratio (OR) for D+T+CT versus CT in POSEIDON and the ORs for P+CT or N+I+CT versus CT in the KEYNOTE studies and CheckMate-9LA, respectively. The OR for each safety outcome was calculated based on the reported number of patients with AEs in each treatment arm, using the equivalent of the POSEIDON safety analysis set of all treated patients as the denominator. For the ITCs of safety outcomes, the follow-up period for reporting AEs and treatment exposure in the CT control arms has also been compared.

Across studies, the follow-up period for AEs (relative to the study treatment period) was generally consistent:

- **POSEIDON:** Events that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy (whichever occurred first)[60]
- **KEYNOTE-189:** Events that occurred during the trial period or within 30 days thereafter (within 90 days for serious events). Adverse events that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded[16, 61]
- **CheckMate-9LA:** Events reported between the first dose of study drug and 30 days after the last dose of study drug[12]

In each study, the CT control arm consisted of a planned number of chemotherapy cycles, with pemetrexed maintenance therapy permitted for trials including pemetrexed doublet chemotherapy as an option for patients with non-squamous histology.[12, 16, 60, 61] In CheckMate-9LA and the KEYNOTE study, the planned number of platinum-based chemotherapy cycles was four, whereas in the POSEIDON trial, patients were permitted to receive an additional two cycles of chemotherapy in the control arm, as clinically needed and at the investigator's discretion.[12, 16, 60, 61] Based on the primary publications of the comparator trials (where these data were reported), the

proportion of patients receiving four cycles of platinum-based chemotherapy, and the proportion of patients receiving pemetrexed maintenance therapy (where permitted), was consistent across studies.[12, 16, 61] In the POSEIDON trial, a similar proportion of patients received (at least) four cycles of platinum-based chemotherapy in the combination phase, with additional cycles (≥5 cycles) received by 27.3% patients (23.1% patients received ≥6 cycles).[60]

Despite some patients in the POSEIDON CT control arm receiving additional cycles of platinum-based chemotherapy compared to the comparator trials, the proportion of patients experiencing AEs in the CT control arms is largely comparable between trials. This is consistent with findings from a SLR/meta-analysis comparing outcomes for patients receiving six versus fewer planned cycles of platinum-based chemotherapy, which reported limited differences in severe toxicity between patients receiving 3–4 cycles of chemotherapy and those receiving six cycles.[62] The use of the POSEIDON CT control arm in anchored ITCs is therefore still considered acceptable.

Analyses done:

D+T+CT versus P+CT (non-squamous)

- AEs leading to discontinuation (any cause)
- Grade 3–5 AEs (any cause)

D+T+CT versus P+CT (squamous)

- AEs leading to discontinuation (any cause)
- Grade 3–5 AEs (any cause)

D+T+CT versus N+I+CT (mixed histology i.e. POSEIDON ITT)

- AEs leading to discontinuation (treatment related)
- Grade 3–4 AEs (treatment related)
- SAEs (treatment related)

Differences in outcomes between comparisons (versus P+CT and versus N+I+CT) were due to the differences in outcomes reported in each of the comparator trials:

- *Grade 3–5 AEs were reported in the KEYNOTE trial, whereas Grade 3–4 AEs were reported in the CheckMate-9LA trials*
- *Any cause AEs were reported in the KEYNOTE trial, whereas treatment-related AEs were reported in the CheckMate-9LA trials*
- *SAEs were not reported in the KEYNOTE trials*

Bucher ITCs were conducted using the odds ratio (OR) for D+T+CT versus CT in POSEIDON and the ORs for P+CT or N+I+CT versus CT in the KEYNOTE studies and CheckMate-9LA, respectively. The OR for each safety outcome was calculated based on the reported number of patients with AEs in each treatment arm, using the equivalent of the POSEIDON safety analysis set of all treated patients as the denominator.

A comparison of the studies included in the ITCs (i.e. POSEIDON, KEYNOTE studies and CheckMate-9LA) is provided in the MAIC report for efficacy outcomes. Additionally for the ITCs of safety outcomes, the follow-up period for reporting AEs and treatment exposure in the CT control arms has also been compared.

Across studies, the follow-up period for AEs (relative to the study treatment period) was generally consistent:

- POSEIDON: Events that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy (whichever occurred first)
- KEYNOTE-189 and KEYNOTE-407: Events that occurred during the trial period or within 30 days thereafter (within 90 days for serious events). Adverse events that occurred during crossover from the placebo-combination group to pembrolizumab monotherapy are excluded
- CheckMate-9LA: Events reported between the first dose of study drug and 30 days after the last dose of study drug

In each study, the CT control arm consisted of a planned number of chemotherapy cycles, with pemetrexed maintenance therapy permitted for trials including pemetrexed doublet chemotherapy as an option for patients with non-squamous histology.1-4 In CheckMate-9LA and the KEYNOTE studies, the planned number of platinum-based chemotherapy cycles was four, whereas in the POSEIDON trial, patients were permitted to receive an additional two cycles of chemotherapy in the control arm, as clinically needed and at the investigator's discretion.

Based on the primary publications of the comparator trials (where these data were reported), the proportion of patients receiving four cycles of platinum-based chemotherapy, and the proportion of patients receiving pemetrexed maintenance therapy (where permitted), was consistent across studies. In the POSEIDON trial, a similar proportion of patients received (at least) four cycles of platinum-based chemotherapy in the combination phase, with additional cycles ($\geq$5 cycles) received by 27.3% patients (23.1% patients received $\geq$6 cycles). Despite some patients in the POSEIDON CT control arm receiving additional cycles of platinum-based chemotherapy compared to the comparator trials, the proportion of patients experiencing AEs in the CT control arms is largely comparable between trials. The use of the POSEIDON CT control arm in anchored ITCs is therefore still considered acceptable.

Data from POSEIDON used in the ITCs were based on the OS final analysis (12th March 2021). SAEs were also analysed at the time of the latest OS analysis (11th March 2022), but the number of patients reporting an event in the D+T+CT and CT arms had not changed since the OS final analysis.

The comparator data used in the safety ITCs were derived from the latest data cut with a median duration follow-up for OS that did not exceed the median duration follow-up for the POSEIDON OS final analysis.

In the non-squamous ITC versus P+CT, D+T+CT was seen to have lower odds of AEs (any cause) leading to discontinuation when compared to P+CT (OR<1), but higher odds of Grade 3–5 AEs of any cause (OR>1) (Table 64). For both outcomes, the 95% confidence intervals for the estimated OR included 1.

Table 64. Odds ratios for D+T+CT vs P+CT in non-squamous histology ITC.

Population	Comparison	OR (95% CI)	
		AEs leading to discontinuation (any cause)	Grade 3–5 AEs (any cause)
Non-squamous	D+T+CT vs P+CT	0.70 (0.37, 1.34)	1.23 (0.72, 2.1)

In the ITC conducted in the POSEIDON ITT (mixed histology) versus N+I+CT, D+T+CT was seen to have lower odds of AEs leading to discontinuation, Grade 3–4 AEs, and SAEs when compared to N+I+CT (all outcomes based on treatment-related events) (Table 65). For each outcome, the 95% confidence intervals for the estimated ORs included 1.

Table 65. Odds ratios for D+T+CT vs P+CT in POSEIDON ITT (mixed histology) ITC

Population	Comparison	OR (95% CI)		
		AEs leading to discontinuation (treatment-related)	Grade 3–4 AEs (treatment-related)	SAEs (treatment-related)
POSEIDON ITT	D+T+CT vs N+I+CT	0.53 (0.28, 1.02)	0.87 (0.57, 1.34)	0.87 (0.52, 1.46)

Conclusion

Based on the results of the Bucher ITCs, the addition of tremelimumab to durvalumab and SoC chemotherapy (D+T+CT) is associated with safety outcomes (i.e. Grade 3–4 or 3–5 AEs, and SAEs) that are no worse than approved IO+CT regimens (P+CT; based on events of any cause) and which are favourable versus other approved IO+IO+CT regimens (N+I+CT; based on treatment-related events). Furthermore, compared to both P+CT and N+I+CT, there was a lower odds of discontinuation due to AEs with D+T+CT, indicating better tolerability with the POSEIDON regimen.

7.2 Results from the comparative analysis

Table 66. Results from the comparative analysis of D+T+CT vs. P+CT for first line mNSCLC non-squamous subgroup

Outcome	D+T+CT vs. CT (N=256)	P+CT vs. CT (N=616)	Result, D+T+CT vs. P+CT
PFS HR (95% CI)	0.61 (0.45, 0.83)	0.50 (0.41, 0.59)	1.22 (0.86, 1.73)
OS HR (95% CI)	0.55 (0.42, 0.71)	0.60 (0.50, 0.72)	0.91 (0.66, 1.26)

Note: The ITC reports did not present ESS disaggregated by individual treatment arm but presented ESS = 256.71 for the non-squamous subgroup from POSEIDON after weighting to KEYNOTE-189 (N=616). **Source**: POSEIDON DCO at 24/07/19 [48], POSEIDON DCO at 24/08/23 [29], KEYNOTE-189 DCO at 08/03/22 [45]

Table 67. Results from the comparative analysis of D+T+CT vs. P+CT for first line mNSCLC non-squamous subgroup with PD-L1 < 1 %

Outcome	D+T+CT vs. CT (N=108)	P+CT vs. CT (N= 196)	Result, D+T+CT vs. P+CT
PFS HR (95% CI)	0.60 (0.41, 0.89)	0.67 (0.49, 0.92)	0.90 (0.54, 1.49)
OS HR (95% CI)	0.61 (0.41, 0.92)	0.55 (0.39, 0.76)	1.11 (0.66, 1.88)

Note: The ITC reports did not present ESS disaggregated by individual treatment arm but presented ESS = 108 for the non-squamous subgroup with PD-L1<1% from POSEIDON after weighting to KEYNOTE-189, PD-L1<1% (N=196). **Source**: POSEIDON DCO at 24/07/19 [2], POSEIDON DCO at 24/08/23 [29], KEYNOTE-189 DCO at 08/03/22 [45]

Table 68. Results from the comparative analysis of D+T+CT vs. N+I+CT for 1L mNSCLC squamous subgroup

Outcome	D+T+CT vs. CT (N=206)	N+I+CT vs. CT (N= 719)	Result, D+T+CT vs. N+I+CT
PFS HR (95% CI)	0.75 (0.56, 1.00)	0.60 (0.44, 0.81)	1.25 (0.82, 1.90)
OS HR (95% CI)	0.77 (0.58, 1.02)	0.64 (0.48, 0.84)	1.21 (0.81, 1.79)

Note: The ITC reports did not present ESS disaggregated by individual treatment arm but presented ESS = 205.87 for the squamous subgroup from POSEIDON after weighting to CheckMate-9LA, ITT population (N=719). Baseline characteristics (i.e. Race) for the squamous subgroup from CheckMate-9LA were not available. **Source**: POSEIDON DCO at 24/07/19 [48], POSEIDON DCO at 24/08/23 [29], CheckMate-9LA DCO at 18/02/21 [4], CheckMate-9LA DCO at 13/02/23 [47]

Table 69. Results from the comparative analysis of D+T+CT vs. N+I+CT for 1L mNSCLC ITT population (mixed histology)

Outcome	D+T+CT vs. CT (N= 491)	N+I+CT vs. CT (N= 719)	Result, D+T+CT vs. N+I+CT
PFS HR (95% CI)	0.64 (0.52, 0.79)	0.67 (0.56, 0.79)	0.91 (0.70, 1.20)
OS HR (95% CI)	0.61 (0.51, 0.74)	0.74 (0.63, 0.87)	0.83 (0.65, 1.06)

Note: The ITC reports did not present ESS disaggregated by individual treatment arm but presented ESS = 491.1 for the ITT population from POSEIDON after weighting to CheckMate-9LA, ITT population (N=719). **Source**: POSEIDON DCO at 24/07/19 [2], POSEIDON DCO at 24/08/23 [29], CheckMate-9LA DCO at 15/02/22 [50], CheckMate-9LA DCO at 13/02/23 [47]

Table 70. Results from the comparative analysis of D+T+CT vs. N+I+CT for 1L mNSCLC ITT population with PD-L1 < 1 %

Outcome	D+T+CT vs. CT (N= 196)	N+I+CT vs. CT (N= 264)	Result, D+T+CT vs. N+I+CT
PFS HR (95% CI)	0.61 (0.45, 0.83)	0.71 (0.53, 0.94)	0.86 (0.57, 1.31)
OS HR (95% CI)	0.62 (0.46, 0.84)	0.67 (0.51, 0.88)	0.93 (0.62, 1.39)

Note: The ITC reports did not present ESS disaggregated by individual treatment arm but presented ESS = 196 for the ITT population with PD-L1<1% from POSEIDON after weighting to CheckMate-9LA, ITT with PD-L1<1% (N=264). **Source**: POSEIDON DCO at 24/07/19 [2], POSEIDON DCO at 24/08/23 [29], CheckMate-9LA DCO at 09/03/20 [12], CheckMate-9LA DCO at 15/02/22 [50]

7.3 Effect – results per outcome

See in Section 7.2.

8. Safety

8.1 Safety – results per POSEIDON

The safety analysis was based on POSEIDON DCO at 12/03/21 (median follow-up: 34.9 month) [2]. The safety population was predefined as all randomized patients who received at least one dose of study treatment, totalling 330 patients in the T+D+CT arm and 333 patients in the CT arm. The incidences of AEs were overall similar between the groups.

Table 71. Overview of adverse events, POSEIDON

	D+T+CT (N = 330)	CT (N =333)	Difference, % points	Difference, RR (95% CI)
All adverse events (AE), n (%)	321 (97.3%)	320 (96.1%)	1.2%	NA
Serious AE (SAE)[1], n (%)	146 (44.2%)	117 (35.1%)	9.1%	NA
AE grade 3/4, n (%)	176 (53.3%)	172 (51.7%)	1.6%	NA
Dose reduction due to AE, n (%)	Not reported	Not reported	-	-
Treatment discontinuation due to AE[2], n (%)	73 (22.1%)	51 (15.3%)	6.8%	NA

Note: [1]Serious adverse events (including AEs leading to death) were assessed by the investigator as possibly related to any study treatment that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy. [2]Treatment discontinuation due to AEs includes patients who permanently discontinued at least one study drug. **Source:** POSEIDON DCO at 12/03/21 [2]

Table 72. Proportion of patients with adverse events, occurring in ≥ 10% of patients in any group, POSEIDON

	D+T+CT (N = 330)		CT (N = 333)	
	All	**Grade 3/4**	**All**	**Grade 3/4**
Anaemia, n (%)	164 (49.7%)	68 (20.6%)	163 (48.9%)	75 (22.5%)
Nausea, n (%)	137 (41.5%)	6 (1.8%)	122 (36.6%)	7 (2.1%)
Neutropenia, n (%)	99 (30.0%)	56 (17.0%)	78 (23.4%)	41 (12.3%)
Decreased appetite, n (%)	93 (28.2%)	5 (1.5%)	82 (24.6%)	4 (1.2%)
Fatigue, n (%)	81 (24.5%)	8 (2.4%)	74 (22.2%)	9 (2.7%)
Constipation, n (%)	63 (19.1%)	0	79 (23.7%)	2 (0.6%)
Diarrhea, n (%)	71 (21.5%)	5 (1.5%)	51 (15.3%)	5 (1.5%)

	D+T+CT (N = 330)		CT (N = 333)	
Thrombocytopenia, n (%)	60 (18.2%)	18 (5.5%)	57 (17.1%)	17 (5.1%)
Vomiting, n (%)	60 (18.2%)	4 (1.2%)	45 (13.5%)	5 (1.5%)
Neutrophil count decreased, n (%)	39 (11.8%)	25 (7.6%)	59 (17.7%)	25 (7.5%)
ALT increased, n (%)	46 (13.9%)	5 (1.5%)	44 (13.2%)	7 (2.1%)
Rash, n (%)	64 (19.4%)	4 (1.2%)	22 (6.6%)	0
Asthenia, n (%)	56 (17.0%)	12 (3.6%)	41 (12.3%)	8 (2.4%)
AST increased, n (%)	42 (12.7%)	2 (0.6%)	38 (11.4%)	1 (0.3%)
Leukopenia, n (%)	42 (12.7%)	9 (2.7%)	39 (11.7%)	12 (3.6%)
Pneumonia, n (%)	47 (14.2%)	23 (7.0%)	32 (9.6%)	10 (3.0%)
Pyrexia, n (%)	53 (16.1%)	0	23 (6.9%)	0
Insomnia, n (%)	26 (7.9%)	0	29 (8.7%)	0
Cough, n (%)	33 (10.0%)	0	22 (6.6%)	1 (0.3%)
Arthralgia, n (%)	41 (12.4%)	1 (0.3%)	21 (6.3%)	1 (0.3%)
Alopecia, n (%)	33 (10.0%)	0	20 (6.0%)	0
Headache, n (%)	37 (11.2%)	0	25 (7.5%)	2 (0.6%)
Pruritus, n (%)	36 (10.9%)	0	15 (4.5%)	0
Hypothyroidism, n (%)	39 (11.8%)	0	4 (1.2%)	0

Source: POSEIDON DCO at 12/03/21 [2]

A list of all serious adverse events occurring in ≥ 1% of patients from POSEIDON study is provided in Appendix F, Table 108.

8.2 Safety – results per KEYNOTE-189

Table 73. Overview of adverse events, KEYNOTE-189

	P+CT (N = 405)	CT (N =202)	Difference, % points	Difference, RR (95% CI)
All adverse events (AE), n (%)	404 (99.8%)	200 (99.0%)	0.8%	NA
Serious AE (SAE), n (%)	NA	NA	NA	NA
AE grade 3 – 5, n (%)	292 (72.1%)	135 (66.8%)	5.3%	NA
Dose reduction due to AE, n (%)	NA	NA	NA	NA
Treatment discontinuation due to AE[1], n (%)	146 (36.0%)	35 (17.3%)	NA	NA

Note: [1]Reported in all patients who received 1 dose of study treatment. *Eight patients (2.0%) in the pembrolizumab combination group and two patients (1%) in the placebo combination group died from AEs attributed to study treatment by the investigator. **Source**: KEYNOTE-189, DCO at 20/05/19 [3]

Table 74. Proportion of patients with adverse events, occurring in ≥ 15% of patients in any group, POSEIDON

	P+CT (N = 405)		CT (N = 202)	
	All	**Grade 3 – 5**	**All**	**Grade 3 – 5**
Nausea	232 (57.3%)	14 (3.5%)	108 (53.5%)	8 (4.0%)
Anaemia	193 (47.7%)	75 (18.5%)	98 (48.5%)	35 (17.3%)
Fatigue	175 (43.2%)	31 (7.7%)	78 (38.6%)	7 (3.5%)
Constipation	144 (35.6%)	4 (1.0%)	67 (33.2%)	1 (0.5%)
Diarrhea	131 (32.3%)	21 (5.2%)	44 (21.8%)	6 (3.0%)

	P+CT (N = 405)		CT (N = 202)	
Decreased appetite	121 (29.9%)	5 (1.2%)	64 (31.7%)	2 (1.0%)
Neutropenia	114 (28.1%)	66 (16.3%)	50 (24.8%)	24 (11.9%)
Vomiting	106 (26.2%)	16 (4.0%)	48 (23.8%)	6 (3.0%)
Cough	104 (25.7%)	0	61 (30.2%)	0
Dyspnoea	102 (25.2%)	16 (4.0%)	53 (26.2%)	8 (4.0%)
Peripheral enema	101 (24.9%)	2 (0.5%)	34 (16.8%)	0
Asthenia	88 (21.7%)	27 (6.7%)	49 (24.3%)	7 (3.5%)
Pyrexia	88 (21.7%)	1 (0.2%)	34 (16.8%)	1 (0.5%)
Rash	88 (21.7%)	8 (2.0%)	26 (12.9%)	3 (1.5%)
Thrombocytopenia	76 (18.8%)	34 (8.4%)	30 (14.9%)	15 (7.4%)
Lacrimation increased	74 (18.3%)	0	22 (10.9%)	0
Back pain	68 (16.8%)	6 (1.5%)	27 (13.4%)	4 (2.0%)

Note: Reported in all patients who received 1 dose of study treatment. **Source**: KEYNOTE-189, DCO at 20/05/19 [3]

A list of all serious adverse events occurring in ≥ 1% of patients from KEYNOTE-189 study is provided in Appendix F, Table 109.

8.3 Safety – results per CheckMate-9LA

Table 75. Overview of adverse events, CheckMate-9LA

	N+I+CT (N = 358)	CT (N =349)	Difference, % points	Difference, RR (95% CI)
All adverse events (AE), n (%)	328 (91.6%)	306 (87.7%)	3.9%	NA
Serious AE (SAE), n (%)	109 (30.4%)	62 (17.8%)	12.6%	NA
AE grade 3/4, n (%)	173 (48.3%)	132 (37.8%)	10.5%	NA

	N+I+CT (N = 358)	CT (N =349)	Difference, % points	Difference, RR (95% CI)
Dose reduction due to AE, n (%)	Not reported in sources	Not reported in sources	-	-
Treatment discontinuation due to AE[1], n (%)	79 (22.1%)	29 (8.3%)	13.8%	NA

Note: [1]Includes events reported between first dose and 30 days after last dose of study drug. **Source:** CheckMate-9LA, DCO at 18/02/21 [4]

Table 76. Proportion of patients with adverse events, occurring in ≥ 10% of patients in any group, CheckMate-9LA

	D+T+CT (N = 358)		CT (N = 349)	
	All	**Grade 3/4**	**All**	**Grade ≥ 3/4**
Nausea	97 (27.1%)	5 (1.4%)	125 (35.8%)	6 (1.7%)
Anaemia	85 (23.7%)	21 (5.9%)	134 (38.4%)	25 (7.2%)
Pruritus	77 (21.5%)	3 (0.8%)	6 (1.7%)	0 (0.0%)
Diarrhea	76 (21.2%)	15 (4.2%)	42 (12.0%)	0 (0.0%)
Asthenia	74 (20.7%)	4 (1.1%)	63 (18.1%)	2 (0.6%)
Rash	71 (19.8%)	6 (1.7%)	11 (3.2%)	0 (0.0%)
Fatigue	62 (17.3%)	9 (2.5%)	38 (10.9%)	3 (0.9%)
Decreased appetite	59 (16.5%)	4 (1.1%)	57 (16.3%)	5 (1.4%)
Hypothyroidism	57 (15.9%)	1 (0.3%)	1 (0.3%)	0 (0.0%)
Vomiting	48 (13.4%)	6 (1.7%)	53 (15.2%)	5 (1.4%)
Neutropenia	35 (9.8%)	25 (7.0%)	60 (17.2%)	33 (9.5%)
Constipation	31 (8.7%)	0 (0.0%)	40 (11.5%)	0 (0.0%)

Note: Includes events reported between first dose and 30 days after last dose of study drug. **Source:** CheckMate-9LA, DCO at 18/02/21 [4]

A list of all serious adverse events occurring in ≥ 1% of patients from POSEIDON study is provided in Appendix F, Table 110.

9. Extrapolation of patient transitions

9.1 Clinical data for extrapolation of patient transitions

Not applicable

9.2 Extrapolation using parametric extrapolation models

9.2.1 Extrapolation of [clinical endpoint 1]

Table 77. Overview of assumptions regarding extrapolation of [clinical endpoint]

Method/approach	Description/assumption
Not applicable	

9.2.2 Extrapolation of [clinical endpoint 2]

Not applicable

9.3 Extrapolation using transition probabilities

Table 78. Transition probabilities in the health economic model

From health state	To health state	Transition probability, including calculation	Assumption	Reference
Not applicable				

Table 79. Transition matrix for [intervention/comparator]

Off/On	State A	State B	State C	...
Not applicable				

9.4 Summary and validity of extrapolated patient transitions

Table 80. Modelled averages in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	[Intervention]	[Comparator]	Difference
Not applicable			

10. Health-related quality of life

10.1 Overview

Table 81. Overview of included instruments for health-related quality of life

Instrument	Median follow-up time and data-cut	Use	Source	Reference to description
EQRTC QLQ-C30	12.52 months, DCO at 12/03/21	Measurement of global health status/QoL	POSEIDON CSR [43]	Section 10.2.1
EQ-5D-5L VAS	12.52 months, DCO at 12/03/21	Measurement of overall health status	POSEIDON CSR [43]	Section 10.2.2
EORTC QLQ-C30	10.5 months, DCO at 08/11/27	Measurement of global health status/QoL	KEYNOTE-189 [52]	Section 10.2.3
EQ-5D-3L VAS	30.7 months, DCO at 18/02/21	Measurement of overall health status	CheckMate-9LA [53]	Section 10.2.4

Table 82. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
Not applicable			

10.2 Instruments

10.2.1 EORTC QLQ-C30, POSEIDON study

10.2.1.1 Study design and instrument

The European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire (EQRTC QLQ-C30) was utilized in the POSEIDON study as a pre-specified secondary endpoint to assess disease-related symptoms, functioning, and HRQoL. This instrument consists of thirty questions categorized into five functional scales covering cognitive, emotional, physical, role, and social domains, alongside three symptom scales for fatigue, pain, and nausea/vomiting. Additionally, it includes six single-item symptom measures for appetite loss, constipation, diarrhea, dyspnoea, insomnia, and perceived financial difficulties, as well as a dedicated scale for global health status and QoL.

Within the POSEIDON study design, the specific measure of interest prioritized from this tool was global health status. The study administered the QLQ-C30 (version 3) on an intent-to-treat basis using electronic tablets (ePRO), which allowed patients to complete the assessments unassisted during clinic visits before any other study procedures were performed.

10.2.1.2 Data collection

Data collection occurred at baseline, on the first day of every treatment cycle and then every four weeks until second progression or death. The analysis focused on the time to deterioration (TTD), which was defined as the duration from randomization to the first confirmed clinically meaningful deterioration—prespecified as an absolute change of ten or more points from baseline—or death. Results were scored on a standardized scale from 0 to 100, where higher scores indicated either a better level of functioning and quality of life or a greater severity of symptoms. Compliance for this instrument was high, with 96% of randomized patients completing the baseline questionnaire and scores remaining generally comparable across all treatment arms at the start of the study.

Overview of responses for D+T+CT arm and CT arm are presented in Appendix G, Table 111 and Table 112, respectively. The instrument was not utilized for calculating utility values.

Table 83. Overview of responses by health state [create a table for both intervention and comparator]

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
Not applicable		

10.2.1.3 Results

Figure 32 presents mean change of QLQ-C30 global health status/QoL from baseline over the follow-up period in both arms. See more details for QLQ-C30 results in Appendix G, Table 119.

Figure 31. EORTC QLQ-C30: GHS/QoL mean change from baseline, POSEIDON



Source: POSEIDON CSR [43]

10.2.2 EQ-5D-VAS, POSEIDON study

10.2.2.1 Study design and instrument

The POSEIDON study incorporated the EQ-5D-5L health state utility index as an exploratory objective to assess the impact of the investigational treatments and disease state on patients' HRQoL. This instrument was specifically chosen to derive health state utility through patient-reported data, which includes a visual analogue scale (VAS) component. The use of this patient-reported outcome (PRO) instrument was vital for understanding the totality of clinical benefit.

10.2.2.2 Data collection

Patients were asked to complete the EQ-5D-5L questionnaire, which includes the EQ VAS, at regular intervals: every four weeks until second progression or death. This systematic approach aimed to capture changes in health state utility throughout the treatment and follow-up periods.

Overall compliance rates for the EQ-5D-5L were acceptable to good, demonstrating the feasibility of its use in this clinical setting. Compliance in the D+T+CT arm was 72.8%

(observed up to Week 56), compared with 64.7% in the CT arm (up to Week 32). Analysis of the collected data indicated that both the EQ VAS scores generally remained stable or showed improvement over time across the treatment arms. These findings reinforced the ability of the investigational treatments to not only impact survival but also to delay deterioration in HRQoL, as evidenced by longer time to deterioration and greater improvement rates in global health status/QoL and functioning scales in D+T+CT compared to CT. Overview of responses for D+T+CT arm and CT arm are presented in Appendix G, Table 113 and Table 114, respectively. The instrument was not utilized for calculating utility values.

10.2.2.3 Results

Figure 33 presents mean change of QLQ-C30 global health status/QoL from baseline over the follow-up period in both arms. See more details for QLQ-C30 results in Appendix G, Table 120.

Figure 32. EQ-5D-VAS mean change from baseline, POSEIDON



Source: POSEIDON CSR [43]

10.2.3 EORTC QLQ-C30, KEYNOTE-189 study

10.2.3.1 Study design and instrument

The KEYNOTE-189 study incorporated PROs as a prespecified exploratory objective to evaluate whether P+CT could maintain or improve HRQOL, using the EORTC QLQ-C30.

10.2.3.2 Data collection

PRO data were collected electronically by patients during clinic visits prior to any medical evaluations or treatment administration to minimize reporting bias. The data collection schedule was frequent during the early stages of treatment, occurring at cycles 1 through 5, and then continued until disease progression or treatment discontinuation. Analysis was performed on a QoL analysis set, which included all randomized patients who received at least one dose of study medication and completed at least one PRO assessment. Overview of responses for D+T+CT arm and CT arm are presented in Appendix G, Table 115 and Table 116, respectively.

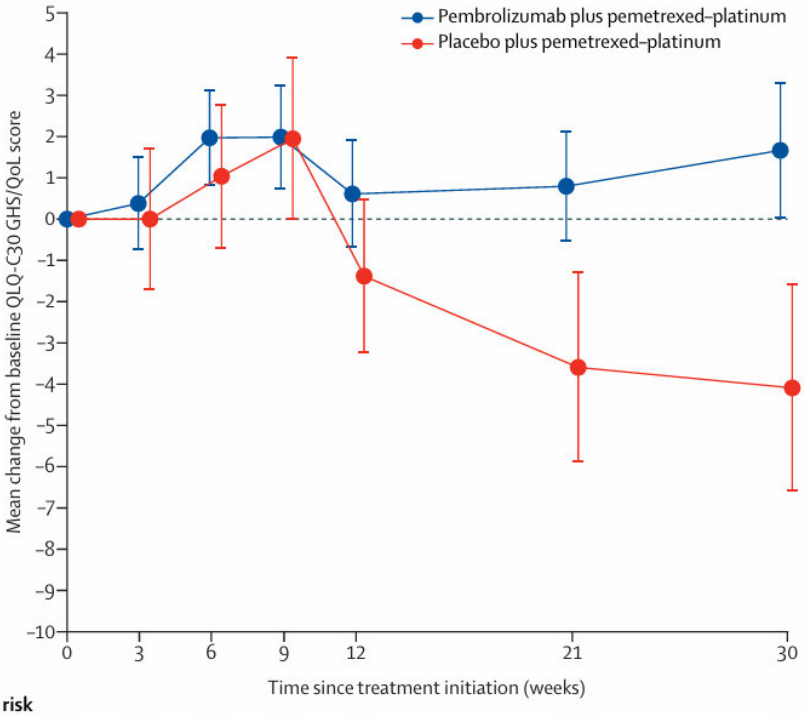
Table 84. Overview of responses by health state

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
Not applicable		

10.2.3.3 Results

Figure 34 presents mean change of QLQ-C30 global health status/QoL from baseline over the follow-up period in both arms.

Figure 33. EORTC QLQ-C30: GHS/QoL mean change from baseline, KEYNOTE-189



Source: KEYNOTE-189 [52]

10.2.4 EQ-5D-VAS, CheckMate-9LA

10.2.4.1 Study design and instrument

The EQ-5D-3L VAS was utilized in the CheckMate-9LA study as a prespecified exploratory endpoint to assess the overall health status of patients with mNSCLC. This instrument was selected to provide a patient-centred perspective on whether the survival benefits of the nivolumab plus ipilimumab regimen were maintained without negatively impacting QoL, particularly given the risk of immune-related side effects. The study followed an international, randomized, open-label, phase 3 design, collecting data from the randomized population to monitor disease and treatment impact over time.

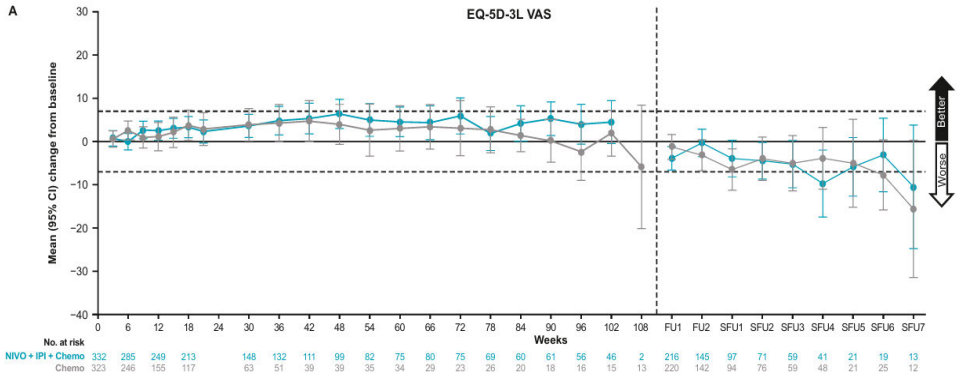
10.2.4.2 Data collection

Data collection was strictly integrated into the clinical workflow, with assessments administered electronically prior to treatment on day 1 of each cycle for the first six months, and then every six weeks during the treatment phase. To capture long-term health trends beyond the treatment period, collection continued at two post-treatment follow-up visits and persisted through survival follow-up via telephone assessments conducted every three to six months. Overview of responses for N+I+CT arm and CT arm are presented in Appendix G, Table 117 and Table 118, respectively.

10.2.4.3 Results

Figure 35 presents mean change of QLQ-C30 global health status/QoL from baseline over the follow-up period in both arms.

Figure 34. EQ-5D-VAS mean change from baseline, CheckMate-9LA



Source: CheckMate-9LA [53]

10.2.5 Summary when reporting multiple instruments

Across the studies, different HRQoL instruments such as EORTC QLQ-C30 and EQ-VAS were employed to capture various aspects of patient well-being, from disease-specific symptoms and functional scales to overall health status and health state utility values. Despite minor variations in patient demographics among the POSEIDON, KEYNOTE-189, and CheckMate-9LA, the overall impact of the immuno-oncology interventions on HRQoL consistently points towards the maintenance or improvement of patients' QoL, generally showing similar outcomes across the different immuno-oncology treatment arms. The EQ-5D-5L/VAS data in POSEIDON, for example, indicated that scores generally remained stable or showed improvement over time across the treatment arms, suggesting these interventions delay deterioration in HRQoL.

10.3 Utility values

10.3.1 Dataset(s)

Not applicable

10.3.2 Calculation of utility values

Not applicable

10.3.3 Adverse events, comorbidity and other state-specific adjustments to the utility values

Not applicable

10.3.4 Results for utility values

Not applicable

Table 85. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Not applicable			

11. Cost calculations

11.1 Drug costs

11.1.1 Drug costs for intervention and comparator

Not applicable

11.1.2 Drug costs for subsequent treatment

Not applicable

11.2 Hospital costs

11.2.1 Administration

Not applicable

Table 86. Assumptions regarding administrative costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
Not applicable			

11.2.2 Disease management

Not applicable

Table 87. Assumptions regarding costs for disease management

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Not applicable					

11.2.3 Treatment monitoring

Not applicable

Table 88. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Not applicable					

11.2.4 Management of adverse events

Not applicable

Table 89. Assumptions regarding costs for management of adverse events

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	[Intervention]	[comparator]			
Not applicable					

11.2.5 Other hospital costs

Not applicable

11.3 Patient costs

Not applicable

Table 90. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transport time	Note
Not applicable				

11.4 Other costs

Not applicable

12. Results

Table 91. Results, discounted estimates, half-cycle corrected (where relevant) and adjusted for background mortality

	[Intervention]	[Comparator]	Difference
Not applicable			

Table 92. Results per drug if combination treatments (more than one drug)

	Drug costs
Not applicable	

12.1 Sensitivity analyses

12.1.1 Deterministic sensitivity analyses

Table 93. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Incremental costs	Incremental QALYs	ICER
Not applicable			

12.1.2 Probabilistic sensitivity analyses (PSA)

Not applicable

13. Budget impact analysis

Table 94. Budget impact (non-discounted estimates), DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Not applicable					

14. List of experts

NA

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Appendix A. Study characteristics

Table 95. Main characteristics of included studies, POSEIDON

POSEIDON	NCT number: NCT03164616
Purpose	To determine the efficacy and safety of durvalumab or durvalumab + tremelimumab in combination with platinum-based chemotherapy compared with chemotherapy alone as first-line treatment for metastatic EGFR/ALK-wild-type NSCLC.
Publications – title, author, journal, year	Durvalumab ± Tremelimumab + Chemotherapy as First-line Treatment for mNSCLC: Results from the Phase 3 POSEIDON Study, Johnson M, et al. World Conference on Lung Cancer (WCLC) 2021 (Abstract PL02.01) / Journal of Thoracic Oncology, 2021 [48] Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non–Small-Cell Lung Cancer: The Phase III POSEIDON Study, Jonson ML, et al., Journal of Clinical Oncology, 2023 [2] Patient-reported outcomes with durvalumab, with or without tremelimumab, plus chemotherapy as first-line treatment for metastatic non-small-cell lung cancer (POSEIDON), Garon EB, et al., Lung Cancer, 2023 [51] A Brief Report of Durvalumab With or Without Tremelimumab in Combination With Chemotherapy as First-Line Therapy for Metastatic Non-Small-Cell Lung Cancer: Outcomes by Tumor PD-L1 Expression in the Phase 3 POSEIDON Study, Garon EB, et al., Clin Lung Cancer, 2024 [49] Durvalumab With or Without Tremelimumab in Combination With Chemotherapy in First-Line Metastatic NSCLC: Five-Year Overall Survival Outcomes From the Phase 3 POSEIDON, Peters S, et al., Journal of Thoracic Oncology, 2025 [29]
Study type and design	Phase III, randomized, open-label, multi-centre study. Patients were randomized 1:1:1 to D+T+CT, D+CT, or CT alone using a centralized randomization system. The trial was open-label (no blinding), no crossover was permitted.
Number of trial participants (N)	1,186 participants enrolled. Randomized population in publications: 1,013 patients (338 in D+T+CT, 338 in D+CT, and 337 in CT arm)
Primary inclusion criteria	Adults with histologically or cytologically confirmed mNSCLC, Tumours lacking EGFR-activating mutations and ALK fusions, No prior systemic therapy for metastatic disease, ECOG PS 0–1, Available tumour tissue for PD-L1 testing, Adequate organ function
Primary exclusion criteria	Known sensitizing EGFR or ALK alterations, Untreated or unstable CNS metastases, Active autoimmune disease requiring systemic therapy,

POSEIDON	NCT number: NCT03164616
	Prior exposure to PD-1, PD-L1, or CTLA-4 inhibitors, Significant uncontrolled comorbidities
Intervention	T+D+CT arm (n=338): Durvalumab 1500 mg Q3W + tremelimumab 75 mg Q3W for 4 cycles with platinum-based chemotherapy, one additional tremelimumab dose at week 16, durvalumab maintenance 1500 mg Q4W until progression D+CT arm (n=338): Durvalumab 1500 mg Q3W + platinum-based chemotherapy for 4 cycles, durvalumab maintenance Q4W
Comparator(s)	CT alone (n=337): Up to 6 cycles of platinum-based chemotherapy (regimen per histology: pemetrexed-platinum for non-squamous disease; gemcitabine- or nab-paclitaxel-based regimens for squamous disease), optional pemetrexed maintenance in non-squamous disease
Follow-up time	Primary publication: 34.9 months (median) [2], updated OS: 63.4 months (median) [29]
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary endpoints: OS and PFS for D+CT vs CT Key secondary endpoints: OS and PFS for T+D+CT vs CT, ORR, DoR, Safety and tolerability, HRQoL Exploratory endpoints: Subgroup analyses (PD-L1, histology, TMB, KRAS/STK11/KEAP1 mutations), PFS2, long-term OS Outcomes included in this application: OS, PFS, QLQ-C30, EQ-5D-VAS Other outcomes: None
Analysis method	Efficacy analyses were conducted in the ITT population and the pre-specified subgroups. Kaplan–Meier methods were used for time-to-event endpoints. Treatment comparisons were based on stratified log-rank tests and stratified Cox proportional hazards models, adjusted for PD-L1 status, disease stage, and histology.
Subgroup analyses	Subgroup analyses performed for: Histology (non-squamous, squamous), PD-L1 expression (<1%, ≥1%, ≥50%), smoking status (current, former, never), race (Asian, non-Asian), stage (IVA, IVB), and genomic subgroups (KRAS, STK11, KEAP1) Methods: ITT-based Cox models; analyses were pre-specified for major demographic/clinical subgroups but exploratory for biomarker-defined and long-term follow-up subgroups.

POSEIDON	NCT number: NCT03164616
Other relevant information	The CT arm allowed up to 6 cycles, more than KEYNOTE-189 and CheckMate-9LA. The study enrolled a globally diverse population across Europe, Asia, North America, and Latin America. No crossover was permitted.

Table 96. Main characteristics of included studies, KEYNOTE-189

KEYNOTE-189	NCT number: NCT02578680
Purpose	To evaluate the efficacy and safety of pembrolizumab + pemetrexed/platinum chemotherapy versus pemetrexed/platinum chemotherapy alone as first-line treatment for metastatic non-squamous NSCLC without EGFR or ALK genomic alterations.
Publications – title, author, journal, year	Pembrolizumab plus chemotherapy in metastatic non–small-cell lung cancer, Gandhi L, et al, New England Journal of Medicine, 2018 [16] Patient-reported outcomes following pembrolizumab or placebo plus pemetrexed and platinum in patients with previously untreated, metastatic, non-squamous non-small-cell lung cancer (KEYNOTE-189): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial, Garassino MC, et al., Lancet Oncology, 2020 [52] Updated analysis from KEYNOTE-189: Pembrolizumab or placebo plus pemetrexed and platinum for previously untreated metastatic nonsquamous non-small-cell lung cancer, Gadgeel S, et al., Journal of Clinical Oncology, 2020 [63] Pembrolizumab + Pemetrexed-Platinum vs Pemetrexed-Platinum for Metastatic NSCLC: 4-Year Follow-up From KEYNOTE-189, Gray J, et al., Journal of Thoracic Oncology (WCLC 2020 Abstract), 2021 [46] Pemetrexed plus platinum with or without pembrolizumab in patients with previously untreated metastatic nonsquamous NSCLC: protocol-specified final analysis from KEYNOTE-189, Rodríguez-Abreu D, et al., Annals of Oncology, 2021 [3] Pembrolizumab Plus Pemetrexed and Platinum in Nonsquamous Non–Small-Cell Lung Cancer: 5-Year Outcomes From the Phase 3 KEYNOTE-189 Study, Garassino MC, et al., Journal of Clinical Oncology, 2023 [45]
Study type and design	Phase III, multicentre, double-blind, randomised, placebo-controlled trial. Patients were randomised 2:1 to P+CT vs CT. No crossover permitted initially, but crossover was allowed upon progression in the control arm.
Number of trial participants (N)	616 randomized participants (410 in P+CT arm, 206 in CT arm).

KEYNOTE-189	NCT number: NCT02578680
Primary inclusion criteria	Histologically or cytologically confirmed stage IV metastatic non-squamous NSCLC, EGFR- and ALK-negative disease (no indication for targeted therapy), No prior systemic therapy for metastatic disease, ECOG PS 0–1, Adequate contraception for participants of reproductive potential, Tumour tissue available for PD-L1 testing ECOG PS 0–1, Available tumour tissue for PD-L1 testing, Adequate organ function
Primary exclusion criteria	Prior treatment with PD-1/PD-L1/CTLA-4 inhibitors. Prior systemic therapy for mNSCLC, Active CNS metastases, Active autoimmune disease requiring systemic therapy, Recent participation in another investigational study <4 weeks
Intervention	P+CT arm (n=410): Pembrolizumab 200 mg IV Q3W for up to 35 cycles, pemetrexed 500 mg/m² + cisplatin 75 mg/m² or carboplatin AUC 5 (investigator's choice) Q3W × 4 cycles, then pemetrexed maintenance
Comparator(s)	CT arm (n=206): Saline placebo Q3W, same pemetrexed/platinum chemotherapy regimen as above for 4 cycles, then pemetrexed maintenance
Follow-up time	Protocol-specified final OS analysis: 31.0 months (median) [3]. Updated analyses: 46.3 months (median) [46], 64.6 months (median) [45].
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary endpoints: OS, PFS Secondary endpoints: ORR, DOR, QLQ-C30 Exploratory endpoints: PFS2, Outcomes by PD-L1 expression, long-term OS (≥5 years) Outcomes included in this application: OS, PFS, QLQ-C30 Other outcomes: None
Analysis method	Analyses were conducted in the ITT population and pre-specified subgroups. Kaplan-Meier used for time-to-event endpoints. Stratified log-rank test for OS & PFS comparisons. HRs estimated with stratified Cox proportional hazards model. RECIST v1.1 used for tumour assessment.
Subgroup analyses	Subgroups examined included PD-L1 categories (<1%, 1–49%, ≥50%), baseline brain/liver metastases, age, sex, and geographic region. Analyses used stratified Cox regression; most subgroup analyses were pre-specified, but later long-term analyses (5-year) were post hoc.
Other relevant information	High crossover rate: 57% of placebo-arm patients received subsequent anti-PD-(L)1 therapy [45]. Double-blind design maintained through

KEYNOTE-189	NCT number: NCT02578680
	primary analyses. Amendment in 2019 unblinded ongoing participants and removed placebo.

Table 97. Main characteristics of included studies, CheckMate-9LA

CheckMate-9LA	NCT number: NCT03215706
Purpose	To evaluate whether nivolumab + ipilimumab + two cycles of platinum-doublet chemotherapy improve efficacy outcomes compared with four cycles of chemotherapy alone in untreated mNSCLC without EGFR/ALK alterations
Publications – title, author, journal, year	First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial, Paz-Ares L, et al., Lancet Oncolog, 2021 [12] First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in advanced non-small-cell lung cancer: CheckMate 9LA 2-year update, Reck M, et al., ESMO Open, 2021 [4] First-line nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone for metastatic NSCLC in CheckMate 9LA: 3-year clinical update and outcomes in patients with brain metastases or select somatic mutations, Paz-Ares LG, et al., Journal of Thoracic Oncology, 2023 [50] First-line (1L) nivolumab (N) + ipilimumab (I) + chemotherapy (C) vs C alone in patients (pts) with metastatic NSCLC (mNSCLC) from CheckMate 9LA: 4-y clinical update and outcomes by tumor histologic subtype (THS), Carbone DP, et al., Journal of Clinical Oncology (ASCO Abstract), 2023 [47] First-line nivolumab plus ipilimumab with two cycles of chemotherapy versus chemotherapy alone (four cycles) in metastatic non-small cell lung cancer: CheckMate 9LA 2-year patient-reported outcomes, Reck M, et al., European Journal of Cancer, 2023 [53] Four-year clinical update and treatment switching-adjusted outcomes with first-line nivolumab plus ipilimumab with chemotherapy for metastatic non-small cell lung cancer in the CheckMate 9LA randomized trial, Carbone DP, et al., Journal for Immunotherapy of Cancer, 2024 [13] Five-year outcomes with first-line nivolumab plus ipilimumab with 2 cycles of chemotherapy versus 4 cycles of chemotherapy alone in patients with metastatic non-small cell lung cancer in the randomized CheckMate 9LA trial, Reck M, et al., European Journal of Cancer, 2024 [14]

CheckMate-9LA	NCT number: NCT03215706
	Nivolumab plus ipilimumab with chemotherapy as first-line treatment of patients with metastatic non-small-cell lung cancer: final, 6-year outcomes from CheckMate 9LA, Carbone DP, et al., ESMO Open, 2025 [15]
Study type and design	Phase III, international, randomised, open-label, active-controlled trial. Randomisation 1:1 to N+I+CT vs CT alone; stratified by histology, sex, and PD-L1 expression. No protocol-permitted crossover between arms.
Number of trial participants (N)	719 randomized patients (361 in N+I+CT arm. 358 in CT arm).
Primary inclusion criteria	Stage IV or recurrent NSCLC, squamous or non-squamous, No prior systemic therapy for metastatic disease, EGFR/ALK-negative tumours, ECOG PS 0–1, Tumour tissue available for PD-L1 testing
Primary exclusion criteria	Known sensitising EGFR mutations or ALK fusions, Active autoimmune disease requiring systemic therapy, Uncontrolled or symptomatic CNS metastases, Prior treatment with PD-1, PD-L1, or CTLA-4 inhibitors, No adequate tumour sample for PD-L1 testing
Intervention	N+I+CT arm (n=361): Nivolumab 360 mg Q3W, Ipilimumab 1 mg/kg Q6W, 2 cycles of histology-based platinum-doublet chemotherapy (non-squamous: pemetrexed-based; squamous: paclitaxel-based), Immunotherapy continued up to 2 years unless progression/intolerable toxicity
Comparator(s)	CT arm (n=358): 4 cycles of histology-based platinum-doublet chemotherapy (non-squamous: pemetrexed-based ± pemetrexed maintenance; squamous: carboplatin + paclitaxel), maintenance pemetrexed allowed in non-squamous histology only.
Follow-up time	The primary analysis: 13.2 months (median) [12], updated analyses: 30.7 months (median) [4], 54.5 months (median) [47], 75.8 months (median) [15]
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Primary endpoints: OS Secondary endpoints: PFS, ORR, DOR Exploratory endpoints: PFS2, EQ-5D-VAS, Outcomes by PD-L1, histology, CNS metastases, smoking status, age, Outcomes in patients who discontinued N+I+CT due to TRAEs Outcomes included in this application: OS, PFS, EQ-5D-VAS Other outcomes: None

CheckMate-9LA	NCT number: NCT03215706
Analysis method	Analyses were conducted in the ITT population and pre-specified subgroups. Kaplan–Meier estimator was used for time-to-event analyses. Treatment comparisons used stratified Cox proportional hazards models and stratified log-rank tests, stratified by histology, sex, and PD-L1 expression.
Subgroup analyses	Subgroups analysed included histology, PD-L1 categories, CNS metastases, smoking status, age, and sex. Analyses used stratified Cox models (descriptive); pre-specified for key demographics/clinical factors, exploratory for biomarker-defined groups.
Other relevant information	N+I+CT uses only 2 cycles of chemotherapy. Subsequent immunotherapy was common in the CT arm (37% after PFS event). Dual-checkpoint therapy resulted in higher TRAE-related discontinuation but maintained durable responses even post-discontinuation.

Appendix B. Results regarding effectiveness per study

Table 98. Results (effectiveness) per study, POSEIDON

Results of POSEIDON (NCT03164616)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Ref.
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS, months	D+T+CT	338	14.0 (11.7, 16.1)	2.4	-0.2, 5.0	NA	HR:0.76	0.64, 0.89	NA	The median OS is based on the Kaplan-Meier estimator. The HR for the ITT population is based on a stratified Cox proportional hazards model adjusted for the variables used for stratification (PD-L1 expression status, tumour histologic type, and disease stage), using the Efron method to control for ties.	[29]
	CT	337	11.6 (10.5, 13.1)								
OS rate at 12 months (%)	D+T+CT	338	54.8 (49.3 – 60.0)	5.8	-1.8, 13.4	NA	NA	NA	NA	The landmark OS rates are based on the Kaplan–Meier estimator.	[29]
	CT	337	49.0 (43.5 – 54.3)								
OS rate at 24	D+T+CT	338	32.8 (27.8 – 37.9)	11	4.3, 17.7	NA	NA	NA	NA		

Results of POSEIDON (NCT03164616)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Ref.
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
months (%)	CT	337	21.8 (17.5 – 26.4)								
OS rate at 36 months (%)	D+T+CT	338	24.9 (20.4 – 29.7)	11.6	5.7, 17.5	NA	NA	NA	NA		
	CT	337	13.3 (9.9 – 17.3)								
OS rate at 48 months (%)	D+T+CT	338	20.9 (16.7 – 25.4)	12.4	7.1, 17.7	NA	NA	NA	NA		
	CT	337	8.5 (5.8 – 11.9)								
OS rate at 60 months (%)	D+T+CT	338	15.7 (12.0 – 19.9)	8.9	4.1, 13.7	NA	NA	NA	NA		
	CT	337	6.8 (4.4 – 10.0)								
Median PFS, months	D+T+CT	338	6.2 (5.0 – 6.5)	1.4	0.4, 2.4	NA	HR:0.72	0.60, 0.86	NA	The median PFS is based on the Kaplan-Meier estimator. The HR for the ITT population is based on a stratified Cox proportional hazards model adjusted for the variables used	[2, 48]
	CT	337	4.8 (4.6 – 5.8)								

Results of POSEIDON (NCT03164616)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Ref.
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										for stratification (PD-L1 expression status, tumour histologic type, and disease stage), using the Efron method to control for ties	
PFS rate at 12 months (%)	D+T+CT	338	26.6 (21.7 to 31.7)	13.5	7.0, 20.0	NA	NA	NA	NA	The landmark PFS rates are based on the Kaplan–Meier estimator.	[2]
	CT	337	13.1 (9.3 to 17.6)								
PFS rate at 24 months (%)	D+T+CT	338	NA	NA	NA	NA	NA	NA	NA		
	CT	337	NA								
PFS rate at 36 months (%)	D+T+CT	338	NA	NA	NA	NA	NA	NA	NA		
	CT	337	NA								
PFS rate at 48	D+T+CT	338	NA	NA	NA	NA	NA	NA	NA		
	CT	337	NA								

Results of POSEIDON (NCT03164616)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	Ref.
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
months (%)											
PFS rate at 60 months (%)	D+T+CT	338	NA	NA	NA	NA	NA	NA	NA		
	CT	337	NA								

Note: Differences in median OS/PFS and landmark OS/PFS rates were calculated as absolute between-arm differences. Confidence intervals were approximated using a normal-theory delta method based on published Kaplan–Meier estimates and their reported 95% confidence intervals, assuming asymptotic normality and independence between treatment arms.

Table 99. Results (effectiveness) per study, KEYNOTE-189

Results of KEYNOTE (NCT02578680)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS, months	P+CT	410	22.0 (19.5 – 24.5)	11.4	7.9, 14.9	NA	HR: 0.60	0.50, 0.72	NA	The median OS is based on the Kaplan-Meier estimator. The HR for the ITT population is based on a Cox proportional hazards model, with	[45]
	CT	206	10.6 (8.7 – 13.6)								

Results of KEYNOTE (NCT02578680)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										benefits observed regardless of PD-L1 expression status.	
OS rate at 12 months (%)	P+CT	410	69.8 (NA)	21.8	NA	NA	NA	NA	NA	The landmark OS rates are based on the Kaplan-Meier estimator.	[45]
	CT	206	48.0 (NA)								
OS rate at 24 months (%)	P+CT	410	45.7 (NA)	18.4	NA	NA	NA	NA	NA		9[45]
	CT	206	27.3 (NA)								
OS rate at 36 months (%)	P+CT	410	31.3 (NA)	13.9	NA	NA	NA	NA	NA		[45]
	CT	206	17.4 (NA)								
OS rate at 48 months (%)	P+CT	410	23.6 (NA)	9.8	NA	NA	NA	NA	NA		[45]
	CT	206	13.8 (NA)								

Results of KEYNOTE (NCT02578680)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS rate at 60 months (%)	P+CT	410	19.4 (15.7, 23.4)	8.1	2.3, 13.9	NA	NA	NA	NA		[45]
	CT	206	11.3 (7.4, 16.1)								
Median PFS, months	P+CT	410	9.0 (8.1–10.4)	4.1	2.9, 5.3	NA	HR: 0.50	0.41, 0.59	NA	The median PFS are based on the Kaplan-Meier estimator. The HR for the ITT population is based on a Cox proportional hazards model, with benefits observed regardless of PD-L1 expression status.	[46]
	CT	206	4.9 (4.7–5.5)								
PFS rate at 12 months (%)	P+CT	410	39.8 (NA)	12.1	NA	NA	NA	NA	NA	The landmark PFS rates are based on the Kaplan-Meier estimator.	[45]
	CT	206	17.7 (NA)								
PFS rate at 24 months (%)	P+CT	410	21.3 (NA)	17.0	NA	NA	NA	NA	NA		[45]
	CT	206	4.3 (NA)								
	P+CT	410	13.1 (NA)	11.2	NA	NA	NA	NA	NA		[45]

Results of KEYNOTE (NCT02578680)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS rate at 36 months (%)	CT	206	1.9 (NA)								
PFS rate at 48 months (%)	P+CT	410	10.2 (NA)	8.9	NA	NA	NA	NA	NA		[45]
	CT	206	1.3 (NA)								
PFS rate at 60 months (%)	P+CT	410	7.5 (5.1, 10.5)	6.9	3.8, 10.0	NA	NA	NA	NA		[45]
	CT	206	0.6 (0.1, 3.1)								

Note: Differences in median OS/PFS and landmark OS/PFS rates were calculated as absolute between-arm differences. Confidence intervals were approximated using a normal-theory delta method based on published Kaplan–Meier estimates and their reported 95% confidence intervals, assuming asymptotic normality and independence between treatment arms.

Table 100. Results (effectiveness) per study, CheckMate-9LA

Results of CheckMate-9LA (NCT03215706)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS, months	N+I+CT	361	15.8 (NA)	4.8	NA	NA	HR: 0.74	0.63, 0.87	NA	The median OS is based on the Kaplan-Meier methodology. The HR for the ITT population is based on a stratified Cox proportional hazards model adjusted for the variables used for stratification: PD-L1 expression status, tumour histology, and sex.	[47]
	CT	358	11.0 (NA)								
OS rate at 12 months (%)	N+I+CT	361	63 (NA)	16	NA	NA	NA	NA	NA	The landmark OS rates are based on the Kaplan–Meier estimator.	[15]
	CT	358	47 (NA)								
OS rate at 24 months (%)	N+I+CT	361	38 (NA)	12	NA	NA	NA	NA	NA		
	CT	358	26 (NA)								
OS rate at 36 months (%)	N+I+CT	361	27 (NA)	8	NA	NA	NA	NA	NA		
	CT	358	19 (NA)								
	N+I+CT	361	21 (NA)	5	NA	NA	NA	NA	NA		

Results of CheckMate-9LA (NCT03215706)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
OS rate at 48 months (%)	CT	358	16 (NA)								
OS rate at 60 months (%)	N+I+CT	361	18 (NA)	7	NA	NA	NA	NA	NA		
	CT	358	11 (NA)								
OS rate at 72 months (%)	N+I+CT	361	16 (13, 20)	6	1.4, 10.6	NA	NA	NA	NA		
	CT	358	10 (7, 13)								
Median PFS, months	N+I+CT	361	6.7 (5.6 – 7.8)	1.4	NA	NA	HR: 0.67	0.56-0.79	NA	The median PFS is based on the Kaplan-Meier methodology. The HR for the ITT population is based on a stratified Cox proportional hazards model adjusted for the variables used for stratification: PD-L1 expression status, tumour histology, and sex.	[4]
	CT	358	5.3 (4.4 – 5.6)								
	N+I+CT	361	32 (NA)	13	NA	NA	NA	NA	NA		[15]

Results of CheckMate-9LA (NCT03215706)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS rate at 12 months (%)	CT	358	19 (NA)							The landmark PFS rates are based on the Kaplan–Meier methodology.	
PFS rate at 24 months (%)	N+I+CT	361	19 (NA)	10	NA	NA	NA	NA	NA		
	CT	358	9 (NA)								
PFS rate at 36 months (%)	N+I+CT	361	14 (NA)	8	NA	NA	NA	NA	NA		
	CT	358	6 (NA)								
PFS rate at 48 months (%)	N+I+CT	361	11 (NA)	6	NA	NA	NA	NA	NA		
	CT	358	5 (NA)								
PFS rate at 60 months (%)	N+I+CT	361	9 (NA)	4	NA	NA	NA	NA	NA		
	CT	358	5 (NA)								

Results of CheckMate-9LA (NCT03215706)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS rate at 72 months (%)	N+I+CT	361	9 (NA)	6	NA	NA	NA	NA	NA		
	CT	358	3 (NA)								

Note: Differences in median OS/PFS and landmark OS/PFS rates were calculated as absolute between-arm differences. Confidence intervals were approximated using a normal-theory delta method based on published Kaplan–Meier estimates and their reported 95% confidence intervals, assuming asymptotic normality and independence between treatment arms.

Appendix C. Subsequent treatment

Table 101. Results (subsequent treatment) per study, POSEIDON

Treatment Arm	Any Subsequent Therapy, n (%)	Radiotherapy, n (%)	Any Systemic Therapy, n (%)	Cytotoxic Chemotherapy, n (%)	Immunotherapy, n (%)	Targeted Therapy, n (%)	Other, n (%)
D+T+CT (N=338)	145 (42.9%)	50 (14.8%)	128 (37.9%)	113 (33.4%)	25 (7.4%)	14 (4.1%)	5 (1.5%)
CT (N=337)	205 (60.8%)	66 (19.6%)	195 (57.9%)	122 (36.2%)	112 (33.2%)	22 (6.5%)	5 (1.5%)

Source: POSEIDON [29]

Table 102. Results (subsequent treatment) per study, KEYNOTE-189

Treatment Category	Any Subsequent Pharmacologic Therapy	Any Anti–PD-(L)1 Therapy (Any line)	First Subsequent							
			Pembrolizumab (including in-study crossover)	Other anti–PD-(L)1 antibody	Single-agent non-platinum CT	Platinum-based CT	Non-platinum CT + targeted therapy	Targeted therapy	VEGF inhibitor + CT	Other
P+CT (N=405)	224 (55.3%)	103 (25.4%)	30 (7.4%)	30 (7.4%)	70 (17.3%)	34 (8.4%)	26 (6.4%)	14 (3.5%)	14 (3.5%)	6 (1.5%)
CT (N=202)	130 (64.4%)	118 (58.4%)	91 (44.7%)	22 (10.9%)	7 (3.5%)	2 (1.0%)	2 (1.0%)	4 (2.0%)	1 (0.5%)	1 (0.5%)

Source: KEYNOTE-189 [45]

Table 103. Results (subsequent treatment) per study, CheckMate-9LA

Therapy Category	Any Subsequent Therapy	Radiotherapy	Surgery	Systemic chemotherapy				
				Immunotherapy	Targeted Therapy*	Non-platinum CT	Platinum-doublet CT	Overall
N+I+CT (N=361)	158 (44%)	68 (19%)	7 (2%)	29 (8%)	28 (8%)	128 (36%)	73 (20%)	137 (38%)
CT (N=358)	199 (56%)	62 (17%)	3 (1%)	133 (37%)	30 (8%)	101 (28%)	23 (6%)	178 (50%)

Source: CheckMate-9LA [15]

Appendix D. Comparative analyses

As described in NICE TSD DSU 18, in order to justify the use of a population-adjusted ITC, such as a MAIC, evidence needs to be presented to suggest that these analyses will produce less biased estimates of relative efficacy than would be produced via non-population-adjusted ITC methods [64]. Specifically, both of the criteria need to be met; there are TEMs among the patient baseline characteristics that are available and there are imbalances in these TEMs between the two clinical trials. The identification of TEMs was based on exploratory analyses of the POSEIDON trial, for which IPD were available.

Identification of Treatment Effect Modifiers

A global interaction test was conducted to first assess the consistency of treatment effects for D+T+CT versus CT for OS across subgroups (based on POSEIDON OS final analysis; DCO at 12/03/21). A model which included all of the following baseline characteristics as covariates (histology [squamous versus non-squamous], stage [IVA versus IVB], PD-L1 expression [<50% versus ≥50%], smoking status [current, former versus never], ECOG performance status [0 versus 1], age [<65 year versus ≥65 years], planned chemotherapy [Abraxane, gemcitabine versus pemetrexed], sex [female versus male], race [Asian versus non-Asian], brain metastases [yes versus no], bTMB [<20, ≥20 versus unknown]), plus all interaction terms for covariate and treatment, was compared against a model which excluded all interaction terms. The list of characteristics included in the model was based on the characteristics that were planned for the pre-specified subgroup analyses of the POSEIDON trial. The results of the global interaction test (p=0.00714) provided evidence to suggest that significant interactions between treatment and baseline characteristics exist, when all subgroups were considered.

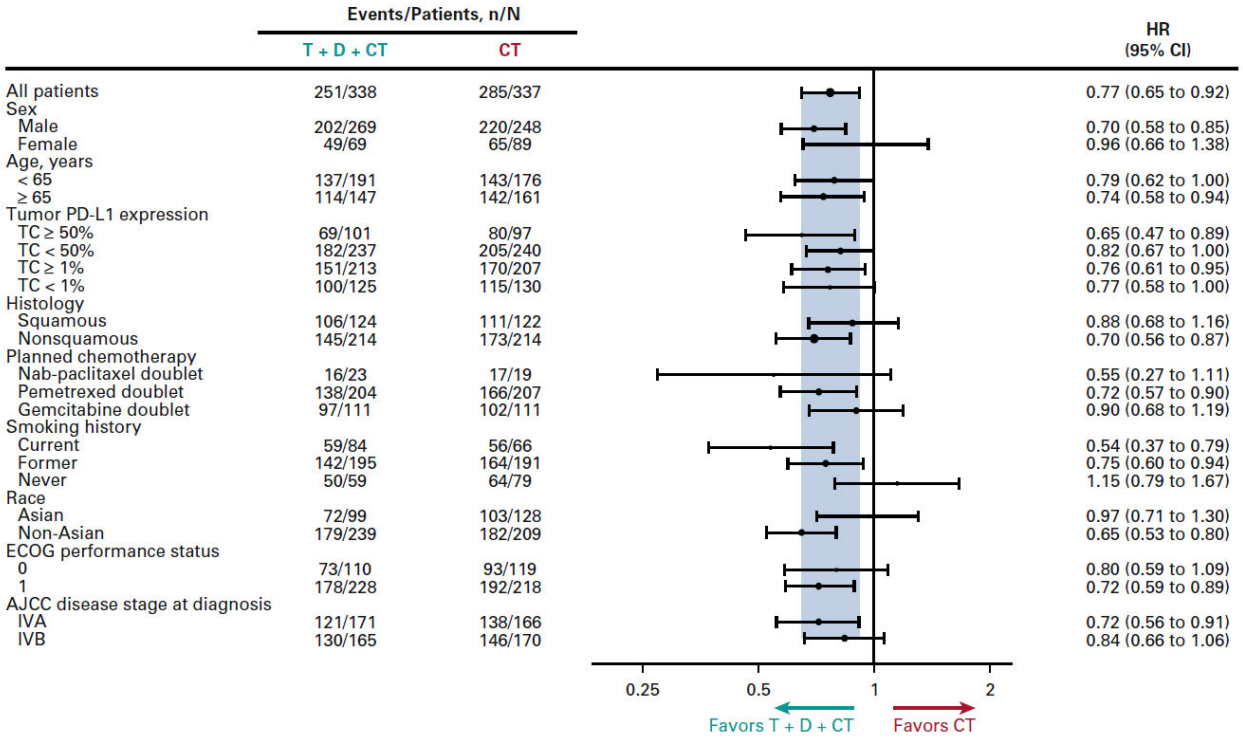
Interactions between treatment and baseline characteristics for D+T+CT versus CT for OS were further explored using a stepwise backwards selection model. In this approach, the least significant interaction terms are removed from the model one-by-one until a final model is reached where all interactions are significant and all excluded interactions are non-significant, with a significance threshold of 0.1. Of the baseline characteristics explored, race, smoking status and histology were identified as having a significant interaction with treatment (p<0.05) in the stepwise backwards selection model. Based on evidence of significant interaction between treatment and each of these baseline characteristics in the POSEIDON trial for D+T+CT versus CT for OS, race, smoking status and histology were considered as potential TEMs for the MAIC.

As seen in the OS subgroup analyses for POSEIDON (Figure 36), when looking at the directional impact of these potential TEMs, D+T+CT appears to have a greater treatment effect versus CT in non-Asian versus Asian (race), current and former versus never (smoking status), non-squamous versus squamous (histology). A similar trend was also observed in subgroup analyses for PFS (Figure 37). As a simplifying assumption, it was assumed that TEMs identified based on OS from POSEIDON could also be applied for MAICs for PFS.

For the comparisons vs. P+CT and vs. N+I+CT in the non-squamous and squamous histology subgroups, it was also assumed that the TEMs identified in the POSEIDON ITT population would also be applicable in each of the histology subgroups. Given the preponderance of patients with squamous histology to be current/former smokers (see Section 6.1.2, 6.2.2, and 6.3.2), the impact of smoking status as a TEM in the squamous subgroup MAICs may be limited, regardless of the magnitude of effect modification in this subgroup.

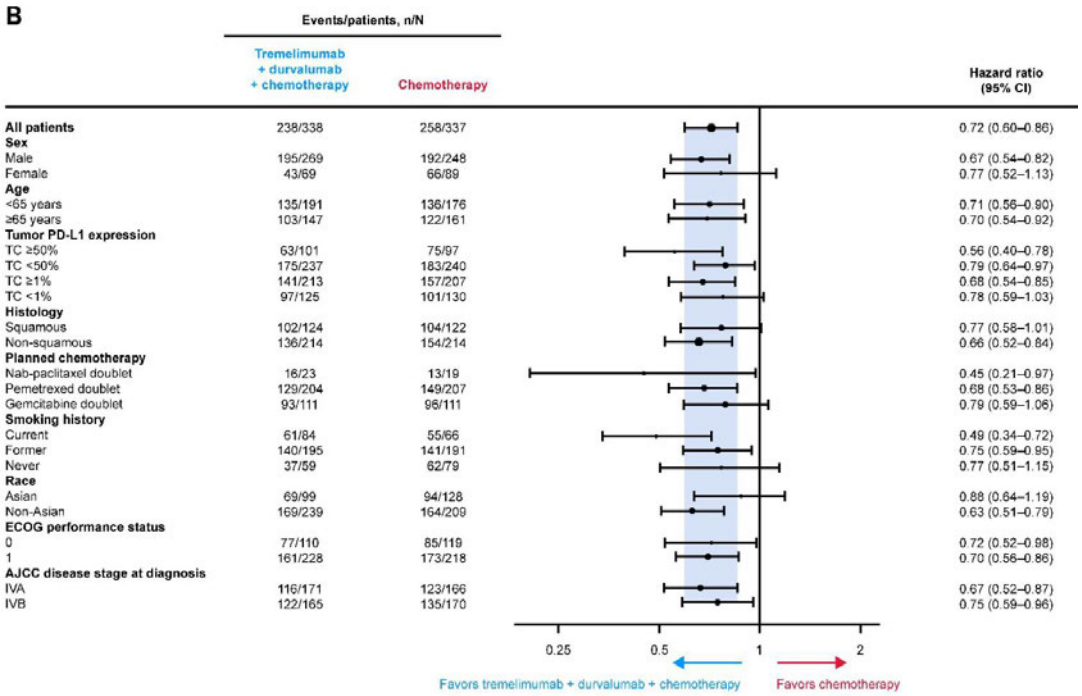
Planned CT was not identified as a TEM based on the results of the interaction tests. Given that the CT options used in the POSEIDON trial were dependent on histology to a large extent (e.g. pemetrexed doublet only for patients with non-squamous histology and gemcitabine doublet only for patients with squamous histology), weighting based on histology in the POSEIDON ITT MAICs will also impact the distribution of CT agents received. However, the MAICs do not account for potential differences in the CT agents received within each histology subgroup. In the POSEIDON trial, gemcitabine + cisplatin/carboplatin was highly utilised as an option for patients with squamous histology, but was not an option in CheckMate-9LA (nab-paclitaxel or paclitaxel + carboplatin only). In POSEIDON, patients receiving gemcitabine + cisplatin/carboplatin appeared to have lower treatment benefit with D+T+CT versus CT compared with those receiving nab-paclitaxel + carboplatin (see Figure 36 and Figure **37** 35), but the results of these subgroup analyses should be interpreted with caution given the small sample sizes. Restricting the ITC to only those patients with squamous histology treated with nab-paclitaxel + carboplatin (in order to align with the CT regimens available in the MAIC comparator trials) was not considered possible due to the prohibitively small number of patients receiving nab-paclitaxel + carboplatin in POSEIDON [65]. Consequently, the results of the MAICs (including patients with squamous histology) should also be interpreted with caution given that the possible impact that the use of different CT regimens (for squamous histology) between trials might have on treatment effects is not accounted for in the ITCs.

Figure 35. Forest plot of OS by subgroup in POSEIDON (full analysis set), D+T+CT versus CT



Source: POSEIDON DCO at 24/07/19 [2]

Figure 36. Forest plot of PFS based on BICR assessments per RECIST by subgroup in POSEIDON (full analysis set), D+T+CT versus CT



Source: POSEIDON DCO at 24/07/19 [2]

Implementation of matching adjusted indirect comparison

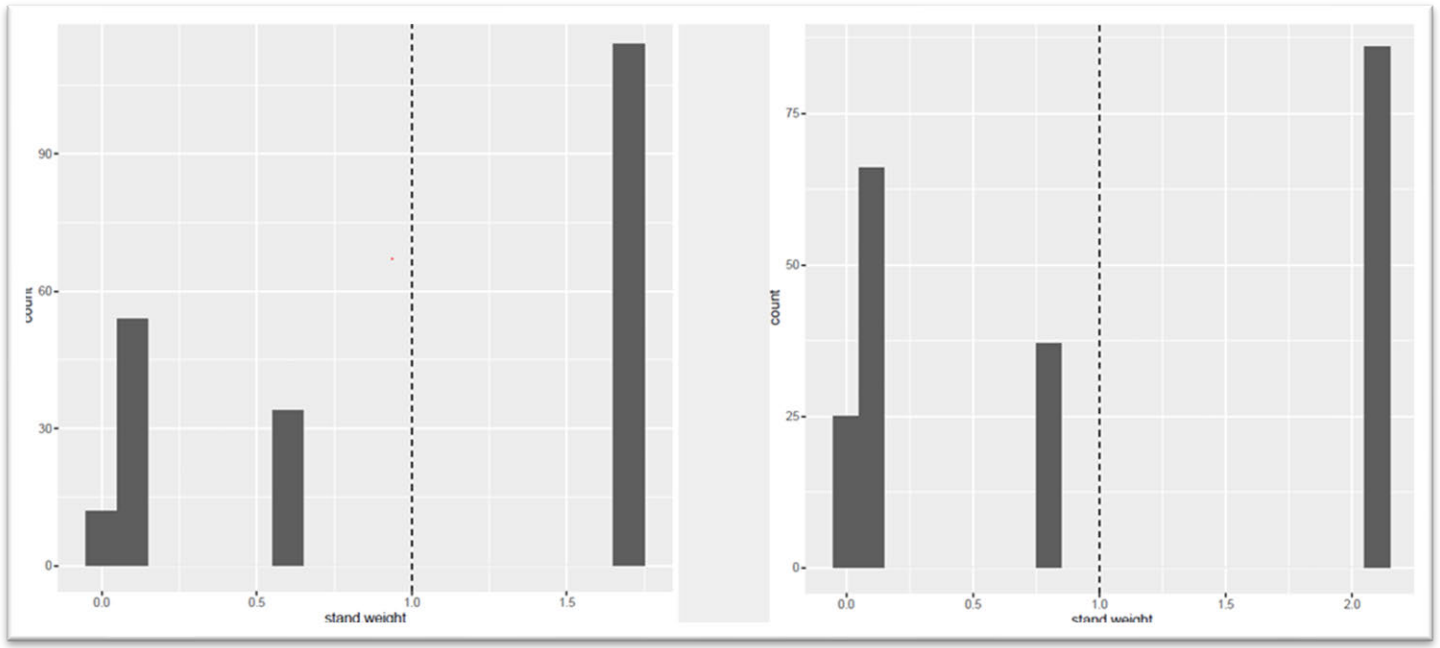
IPD were available from the POSEIDON trial, with only aggregate data available from the comparator trials.

Patients in the relevant patient population for the comparisons (ITT, non-squamous and squamous) were identified from POSEIDON in order to match the eligibility criteria of the comparator trials. In all other respects, the main eligibility criteria were considered similar between studies. In order to adjust for the imbalances in TEM between studies, patients from the D+T+CT and CT arms in the relevant POSIEDON subset (ITT, non-squamous or squamous) were weighted according to the competitor trial baseline characteristics (race, smoking status and histology [where applicable]) using propensity score weighting, such that the weighted mean baseline characteristics for these TEMs in the pooled D+T+CT and C+T POSEIDON subset matched those in the competitor trial. Patient-level weights were derived from a logistic regression model which included only the relevant TEMs for each analysis. These weights represent the odds of an individual being enrolled in the POSEIDON subset versus the comparator trial given their race, smoking status and histology (where applicable). With only aggregate data available from the comparator trial, the method of moments was used to estimate the patient-level weights such that the mean baseline characteristics after weighting match those in the comparator trials. Kaplan-Meier plots for survival outcomes were generated from the weighted D+T+CT and CT arms and HRs for D+T+CT versus CT were derived from weighted Cox proportional hazards models. Standard errors for weighted survival outcomes in the MAIC were derived using robust sandwich estimators. The weighted HR for D+T+CT versus CT was included in a Bucher ITC with the HR from the comparator trial (e.g. P+CT versus CT) in order to estimate a HR for D+T+CT versus the MAIC comparator (e.g. D+T+CT vs P+CT). As per NICE DSU TSD 18 guidance for anchored MAICs, only TEMs and not prognostic factors were included in this propensity score weighting [64].

Validation

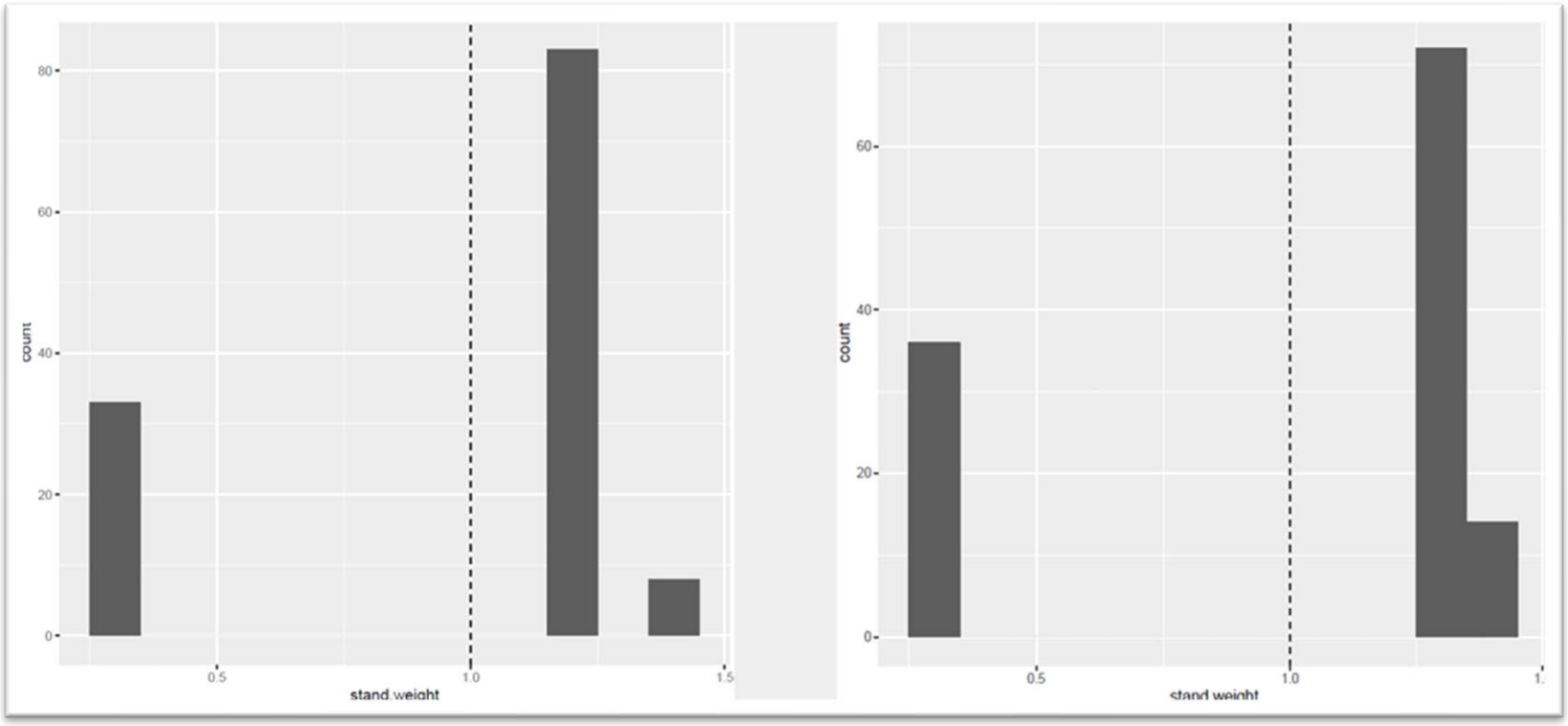
After weighting, baseline characteristics were also compared across trials to ensure that imbalances in TEMs had been addressed. The distribution of weights in POSEIDON following the propensity score weighting was inspected to identify whether the analyses were highly sensitive to extreme weights. The weights were also used to estimate the effective sample size (ESS) of the post-weighting POSEIDON population. A low ESS is reflective of an uneven distribution of weights and limited overlap between study populations with respect to TEMs, with the outcomes in the post-weighting POSEIDON population driven by a small number of individual patients. The analyses were conducted using the statistical software ‘R’ version 4.1. The MAIC matching analysis was performed using maic version 0.1.4 package, per Signorovitch et al. 2012, as recommended in the NICE DSU guidelines [64, 66].

Figure 37. Distribution of rescaled weights for POSEIDON D+T+CT arm (left) and CT arm (right) – weighting to KEYNOTE-189 (non-squamous)



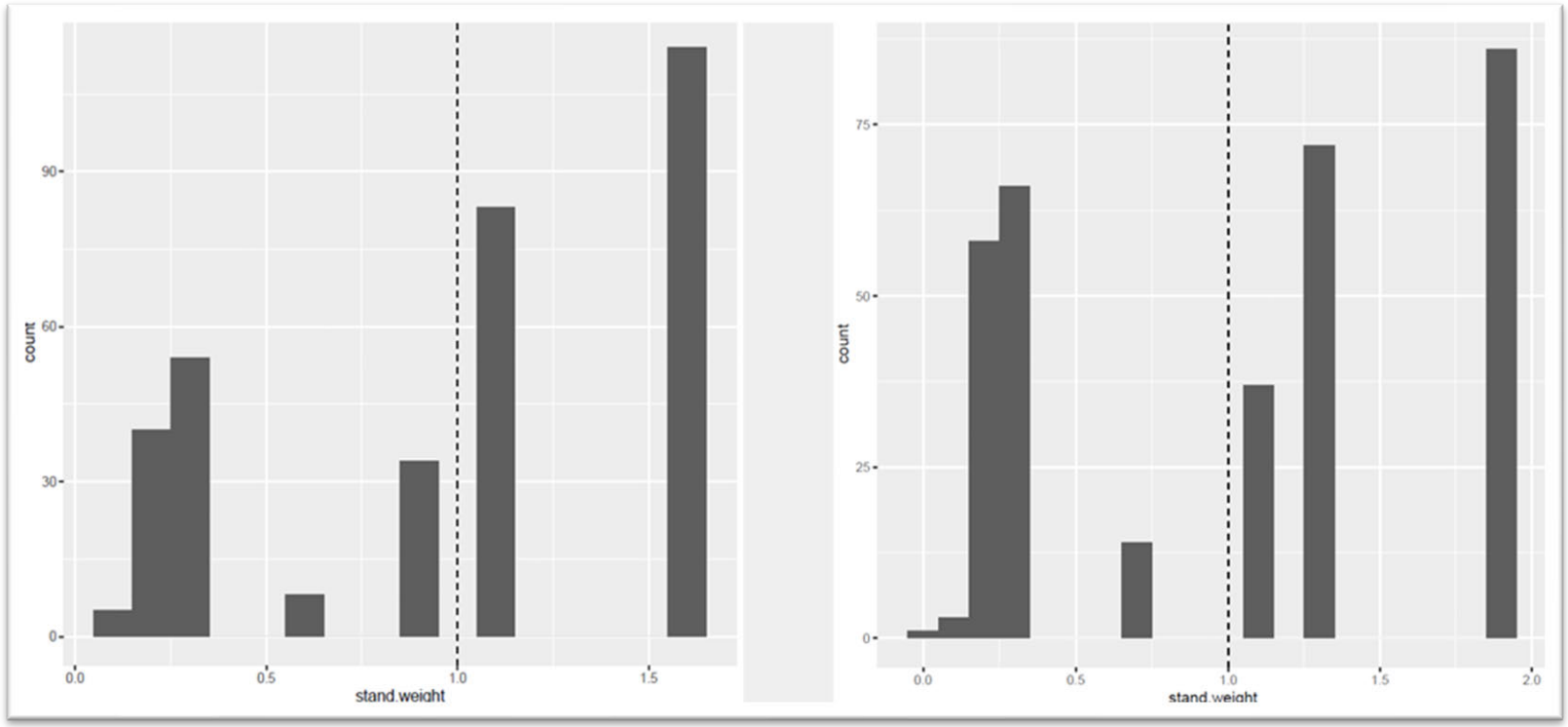
Patient-level weights were rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1

Figure 38. Distribution of rescaled weights for POSEIDON D+T+CT arm (left) and CT arm (right) – weighting to CheckMate-9LA (squamous)



Patient-level weights were rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1

Figure 39. Distribution of rescaled weights for POSEIDON D+T+CT arm (left) and CT arm (right) – weighting to CheckMate-9LA (POSEIDON ITT)



Patient-level weights were rescaled such that the mean weights across patients in the D+T+CT and CT arms included in the weighting equalled 1

Figure 40. Distribution of rescaled weights for POSEIDON non-squamous subgroup, D+T+CT (Durva+Treme+SoC) and CT (SoC) – weighting to KEYNOTE-189, and POSEIDON ITT D+T+CT and CT – weighting CheckMate-9LA (ITT)

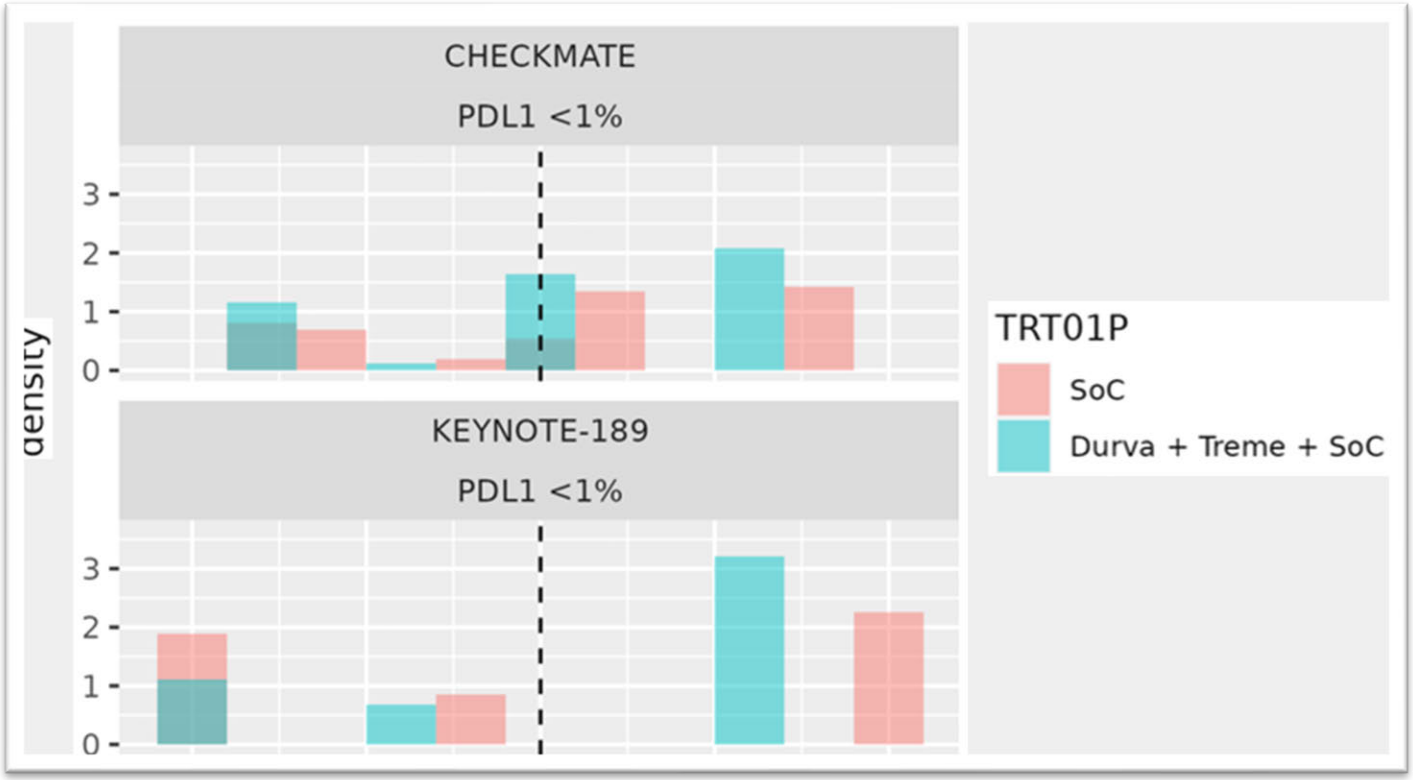


Table 104. Summary distribution of weights of POSEIDON after weighting

	Weighting to KEYNOTE-189 (non-squamous)		Weighting to CheckMate-9LA (squamous)		Weighting to CheckMate-9LA (POSEIDON ITT)	
	D+T+CT (N=214)	CT (N=214)	D+T+CT (N=124)	CT (N=122)	D+T+CT (N=338)	CT (N=337)
Mean (SD)	0.73 (0.53)	0.58 (0.54)	0.89 (0.38)	0.88 (0.40)	0.86 (0.49)	0.75 (0.49)
Median (min–max)	1.21 (0.018–1.21)	0.46 (0.018–1.21)	1.11 (0.26–1.24)	1.11 (0.26–1.24)	0.94 (0.091–1.42)	0.80 (0.00–1.42)

Table 105. Comparative analysis of studies comparing D+T+CT with P+CT for patients with mNSCLC in non-squamous subgroup

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
OS	POSEIDON DCO at 24/08/23 [29], KEYNOTE-189 DCO at 08/03/22 [45]	N/A	N/A	N/A	HR: 0.91	(0.66, 1.26)	N/A	Bucher ITCs after weighting to KEYNOTE-189	No

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
PFS	POSEIDON DCO at 24/07/19 [2, 48], KEYNOTE-189 DCO at 08/03/22 [45]	N/A	N/A	N/A	HR: 1.22	(0.86, 1.73)	N/A	Bucher ITCs after weighting to KEYNOTE-189	No

Table 106. Comparative analysis of studies comparing D+T+CT with N+I+CT for patients with mNSCLC in squamous subgroup

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
OS	POSEIDON DCO at 24/08/23 [29], CheckMate-9LA DCO at 13/02/23 [47]	N/A	N/A	N/A	HR: 1.21	(0.81, 1.79)	N/A	Bucher ITCs after weighting to CheckMate-9LA	No
PFS	POSEIDON DCO at 24/07/19 [2, 48], CheckMate-9LA DCO at 18/02/21 [4]	N/A	N/A	N/A	HR: 1.25	(0.82, 1.90)	N/A	Bucher ITCs after weighting to CheckMate-9LA	No

Table 107. Comparative analysis of studies comparing D+T+CT with N+I+CT for patients with mNSCLC (ITT population)

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
OS	POSEIDON DCO at 24/08/23 [29], CheckMate-9LA DCO at 13/02/23 [47]	N/A	N/A	N/A	HR: 0.83	(0.65, 1.06)	N/A	Bucher ITCs after weighting to CheckMate-9LA	No
PFS	POSEIDON DCO at 24/07/19 [2, 48], CheckMate-9LA DCO at 15/02/22 [4]	N/A	N/A	N/A	HR: 0.91	(0.70, 1.20)	N/A	Bucher ITCs after weighting to CheckMate-9LA	No

Appendix E. Extrapolation of patient transitions

E.1 Parametric extrapolation models

Not applicable

E.1.1 Extrapolation of [clinical endpoint 1]

E.1.1.1 Log-cumulative hazard plots and residual plots

E.1.1.2 Internal validity

E.1.1.2.1 Assessment of statistical and visual fit (AIC and BIC)

E.1.1.2.2 Assessment of smoothed hazard functions

E.1.1.3 External validity

E.1.1.4 Other assumptions

E.1.2 Extrapolations of [clinical endpoint 2]

E.2 Transition probabilities

Not applicable

E.2.1 Internal validity

E.2.2 External validity

E.2.3 Other assumptions

Appendix F. Serious adverse events

Table 108. Treatment-related serious adverse events ≥ 1%, POSEIDON

	D+T+CT (N = 330)	CT (N = 333)
Any serious event	91 (27.6%)	59 (17.7%)
Anaemia	15 (4.5%)	20 (6.0%)
Pneumonia	12 (3.6%)	8 (2.4%)
Thrombocytopenia	8 (2.4%)	3 (0.9%)
Febrile neutropenia	7 (2.1%)	4 (1.2%)
Diarrhea	6 (1.8%)	2 (0.6%)
Colitis	5 (1.5%)	0 (0.0%)
Pneumonitis	5 (1.5%)	1 (0.3%)
Neutropenia	4 (1.2%)	3 (0.9%)
Pyrexia	4 (1.2%)	0 (0.0%)
Sepsis	4 (1.2%)	0 (0.0%)

Note: Includes serious adverse events assessed by the investigator as possibly related to any study treatment that occurred during the treatment period and up to 90 days after the last dose of study treatment or up to the start of any subsequent therapy (whichever occurred first) **Source:** POSEIDON DCO at 12/03/21) [2].

Table 109. Treatment-related serious adverse events (grade 3-5) ≥ 1%, KEYNOTE-189

	P+CT (N = 405)	CT (N = 202)
Anaemia	75 (18.5%)	35 (17.3%)
Neutropenia	66 (16.3%)	24 (11.9%)
Thrombocytopenia	34 (8.4%)	15 (7.4%)
Fatigue	31 (7.7%)	7 (3.5%)
Asthenia	27 (6.7%)	7 (3.5%)
Diarrhea	21 (5.2%)	6 (3.0%)

Vomiting	16 (4.0%)	6 (3.0%)
Dyspnoea	16 (4.0%)	8 (4.0%)
Nausea	14 (3.5%)	8 (4.0%)
Pneumonitis	12 (3.0%)	4 (2.0%)
Severe skin reactions	10 (2.5%)	4 (2.0%)
Rash	8 (2.0%)	3 (1.5%)
Colitis	7 (1.7%)	0 (0.0%)
Nephritis	6 (1.5%)	0 (0.0%)
Hepatitis	6 (1.5%)	0 (0.0%)
Back pain	6 (1.5%)	4 (2.0%)
Decreased appetite	5 (1.2%)	2 (1.0%)
Constipation	4 (1.0%)	1 (0.5%)

Source: KEYNOTE-189 DCT at 20/05/19) [3]

Table 110. Treatment-related serious adverse events ≥ 1%, CheckMate-9LA

	N+I+CT (N = 358)	CT (N = 349)
Any serious events	93 (26%)	51 (15%)
Neutropenia	25 (7%)	33 (9%)
Anaemia	21 (6%)	52 (15%)
Hepatitis	16 (4%)	Not Reported
Diarrhea or Colitis	15 (4%)	3 (1%)
Rash	14 (4%)	0 (0%)
Pneumonitis	10 (3%)	Not Reported
Fatigue	9 (2%)	5 (1%)
Vomiting	6 (2%)	1 (<1%)
Hypophysitis	6 (2%)	Not Reported
Nausea	5 (1%)	2 (1%)

Adrenal Insufficiency	5 (1%)	Not Reported
Decreased appetite	4 (1%)	5 (1%)
Asthenia	4 (1%)	8 (2%)
Pruritus	3 (1%)	0 (0%)
Hypothyroidism/Thyroiditis	2 (1%)	Not Reported

Source: CheckMate-9LA DCO at 18/02/21) [4]

Appendix G. Health-related quality of life

G.1 Data collection – overview of responses

Table 111. Overview of responses of EORTC QLQ-C30 in POSEIDON D+T+CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	[redacted]			
Week 3				
Week 6				
Week 9				
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36				
Week 40				
Week 44				
Week 48				
Week 52				
Week 56				
Week 60				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 64	[redacted]			
Week 68				
Week 72				
Week 76				
Week 80				
Week 84				
Week 88				
Week 92				
Week 96				
Week 100				
Week 104				
Week 108				
Week 112				
Week 116				
Week 120				
Week 124				
Week 128				
Week 132				
Week 136				
Week 140				
Week 144				
Week 148				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 152	[redacted]			
Week 156				
Week 160				
Week 164				
Week 168				
Week 172				
Week 176				
Week 180				
Week 184				
Week 188				

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: POSEIDON CSR [43]

Table 112. Overview of responses of EORTC QLQ-C30 in POSEIDON CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	[redacted]			
Week 3				
Week 6				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 9	[redacted]			
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36				
Week 40				
Week 44				
Week 48				
Week 52				
Week 56				
Week 60				
Week 64				
Week 68	[redacted]			
Week 72				
Week 76				
Week 80				
Week 84				
Week 88				
Week 92				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 96	[redacted]			
Week 100				
Week 104				
Week 108				
Week 112				
Week 116				
Week 120				
Week 124				
Week 128				
Week 132				
Week 136				
Week 140				
Week 144				
Week 148				
Week 152				
Week 156				
Week 160				
Week 164				
Week 168				
Week 172				
Week 176				
Week 180				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 184	[redacted]			
Week 188				

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: POSEIDON CSR [43]

Table 113. Overview of responses of EQ-5D-VAS in POSEIDON D+T+CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	[redacted]			
Week 3				
Week 6				
Week 9				
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36				
Week 40				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 44	[redacted]			
Week 48				
Week 52				
Week 56				
Week 60				
Week 64				
Week 68				
Week 72				
Week 76				
Week 80				
Week 84				
Week 88				
Week 92				
Week 96				
Week 100				
Week 104				
Week 108				
Week 112				
Week 116				
Week 120				
Week 124				
Week 128				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 132	[redacted]			
Week 136				
Week 140				
Week 144				
Week 148				
Week 152				
Week 156				
Week 160				
Week 164				
Week 168				
Week 172				
Week 176				
Week 180				
Week 184				
Week 188				

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: POSEIDON CSR [43]

Table 114. Overview of responses of EQ-5D-VAS in POSEIDON CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	[redacted]			
Week 3				
Week 6				
Week 9				
Week 12				
Week 16				
Week 20				
Week 24				
Week 28				
Week 32				
Week 36				
Week 40				
Week 44				
Week 48				
Week 52				
Week 56				
Week 60				
Week 64				
Week 68				
Week 72				
Week 76				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 80	[redacted]			
Week 84				
Week 88				
Week 92				
Week 96				
Week 100				
Week 104				
Week 108				
Week 112				
Week 116				
Week 120				
Week 124				
Week 128				
Week 132				
Week 136				
Week 140				
Week 144				
Week 148				
Week 152				
Week 156				
Week 160				
Week 164				

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 168	[redacted]			
Week 172				
Week 176				
Week 180				
Week 184				
Week 188				

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: POSEIDON CSR [43]

Table 115. Overview of responses of EORTC QLQ-C30 in KEYNOTE-189 P+CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	402	359	89.3%	89.3%
Week 3	389	362	93.1%	90.0%
Week 6	360	342	95.0%	85.1%
Week 9	342	308	90.1%	76.6%
Week 12	354	319	90.1%	79.4%
Week 21	326	249	76.4%	61.9%
Week 30	278	210	75.5%	52.2%

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number

of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: KEYNOTE-189, Garassino MC, et al., 2020 [52]

Table 116. Overview of responses of EORTC QLQ-C30 in KEYNOTE-189 CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	200	180	90.0%	90.0%
Week 3	186	171	91.9%	85.5%
Week 6	175	154	88.0%	77.0%
Week 9	158	140	88.6%	70.0%
Week 12	167	149	89.2%	74.5%
Week 21	143	91	63.6%	45.5%
Week 30	88	63	71.6%	31.5%

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Source: KEYNOTE-189, Garassino MC, et al., 2020 [52]

Table 117. Overview of responses of EORTC QLQ-C30 in CheckMate-9LA N+I+CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	361	350	97.0%	97.0%
Week 3	338	304	89.9%	84.2%
Week 6	324	293	90.4%	81.2%
Week 9	304	287	94.4%	79.5%

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 12	274	258	94.2%	71.5%
Week 15	255	239	93.7%	66.2%
Week 18	239	216	90.4%	59.8%
Week 21	214	199	93.0%	55.1%
Week 24	191	96	50.3%	26.6%
Week 30	170	150	88.2%	41.6%
Week 36	144	134	93.1%	37.1%
Week 42	128	112	87.5%	31.0%
Week 48	113	99	87.6%	27.4%
Week 54	100	83	83.0%	23.0%
Week 60	92	76	82.6%	21.1%
Week 66	87	81	93.1%	22.4%
Week 72	81	76	93.8%	21.1%
Week 78	76	70	92.1%	19.4%
Week 84	69	61	88.4%	16.9%
Week 90	65	62	95.4%	17.2%
Week 96	63	57	90.5%	15.8%
Week 102	48	46	95.8%	12.7%
Week 108	2	2	100.0%	0.6%
Week 114–150	0	0	0.0%	0.0%

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation. Source: CheckMate-9LA, Reck M et al., 2023 [53]

Table 118. Overview of responses of EORTC QLQ-C30 in CheckMate-9LA CT arm

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Baseline	358	343	95.8%	95.8%
Week 3	323	306	94.7%	85.5%
Week 6	283	251	88.7%	70.1%
Week 9	265	246	92.8%	68.7%
Week 12	176	159	90.3%	44.4%
Week 15	153	142	92.8%	39.7%
Week 18	129	119	92.2%	33.2%
Week 21	109	101	92.7%	28.2%
Week 24	90	42	46.7%	11.7%
Week 30	71	63	88.7%	17.6%
Week 36	58	52	89.7%	14.5%
Week 42	45	41	91.1%	11.5%
Week 48	43	40	93.0%	11.2%
Week 54	41	36	87.8%	10.1%
Week 60	40	35	87.5%	9.8%
Week 66	36	30	83.3%	8.4%
Week 72	30	24	80.0%	6.7%
Week 78	27	27	100.0%	7.5%
Week 84	22	21	95.5%	5.9%
Week 90	20	19	95.0%	5.3%
Week 96	19	17	89.5%	4.7%

Time	Number of patients "at risk"* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk" at time t** %	Proportion of responses out of the number of patients at randomisation*** %
Week 102	17	15	88.2%	4.2%
Week 108	14	14	100.0%	3.9%
Week 114	11	10	90.9%	2.8%
Week 120	9	7	77.8%	2.0%
Week 126	8	8	100.0%	2.2%
Week 132	6	5	83.3%	1.4%
Week 138	5	3	60.0%	0.8%
Week 144	2	2	100.0%	0.6%
Week 150	1	0	0.0%	0.0%

Note: *Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted. **Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*. ***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation. Source: CheckMate-9LA, Reck M et al., 2023 [53]

G.2 Reporting of domains

Table 119. Results for QLQ-C30, POSEIDON

Time	D+T+CT	CT	Difference
	Average (SD)	Average (SD)	Difference (95%CI)
Baseline	[redacted]		
Week 3			
Week 6			
Week 9			
Week 12			
Week 16			

Time	D+T+CT	CT	Difference
Week 20	[redacted]		
Week 24			
Week 28			
Week 32			
Week 36			
Week 40			
Week 44			
Week 48			
Week 52			
Week 56			
Week 60			
Week 64			
Week 68			
Week 72			
Week 76			
Week 80			
Week 84			
Week 88			
Week 92			
Week 96			
Week 100			
Week 104			
Week 108			
Week 112			
Week 116			

Time	D+T+CT	CT	Difference
Week 120	[redacted]		
Week 124			
Week 128			
Week 132			
Week 136			
Week 140			
Week 144			
Week 148			
Week 152			
Week 156			
Week 160			
Week 164			
Week 168			
Week 172			
Week 176			
Week 180			
Week 184			
Week 188			

[redacted]

Source: POSEIDON CSR [43]

Table 120. Results for EQ-5D-VAS, POSEIDON

Time	D+T+CT	CT	Difference
	Average (SD)	Average (SD)	Difference (95%CI)
Baseline	[redacted]		
Week 3			

Time	D+T+CT	CT	Difference
Week 6	[redacted]		
Week 9			
Week 12			
Week 16			
Week 20			
Week 24			
Week 28			
Week 32			
Week 36			
Week 40			
Week 44			
Week 48			
Week 52			
Week 56			
Week 60			
Week 64			
Week 68			
Week 72			
Week 76			
Week 80			
Week 84			
Week 88			
Week 92			
Week 96			
Week 100			

Time	D+T+CT	CT	Difference
Week 104	[redacted]		
Week 108			
Week 112			
Week 116			
Week 120			
Week 124			
Week 128			
Week 132			
Week 136			
Week 140			
Week 144			
Week 148			
Week 152			
Week 156			
Week 160			
Week 164			
Week 168			
Week 172			
Week 176			
Week 180			
Week 184			
Week 188			

[redacted]

Source: POSEIDON CSR [43]

G.3 Mapping

Not applicable

G.4 Calculation of utility values

Not applicable

Appendix H. Literature searches for the clinical assessment

H.1 Effect and safety of intervention and comparators

The literature search was conducted to identify all clinical efficacy and safety evidence for first-line treatment of mNSCLC without sensitizing EGFR or ALK mutations, specifically as relevant to Danish clinical practice and reimbursement context.

The initial SLR was comprehensively conducted to inform the core evidence base on March 10, 2022. The initial SLR followed PRISMA and Cochrane guidelines, encompassing:

- Adult patients with untreated mNSCLC, EGFR-wildtype, ALK-wildtype
- Interventions: Durvalumab ± Tremelimumab + chemotherapy, and other first-line recommended comparators
- Outcomes: OS, PFS, response rate, safety, HRQoL
- Study types: Phase 2/3 RCTs, English language
- Databases: MEDLINE, EMBASE, PubMed, Cochrane CENTRAL, major oncology conference abstracts, clinical trial registries

To comply with the requirement for the most recent evidence, the first supplementary search was performed on August 20, 2025, and the second on February 23, 2026. The supplementary searches focused on PubMed and targeting pivotal studies, interventions, and comparators aligned with Danish practice and reimbursement status. PubMed was selected for practical reasons and for its comprehensive coverage of peer-reviewed research relevant to clinical practice in most European countries, including Danmark. No unpublished or ongoing studies were identified or included as only published, peer-reviewed RCTs deemed relevant and accessible at the time of search.

Table 121. Bibliographic databases

Database	Platform/Website	Date of search
Embase	Embase.com (no period restriction for search)	10.03.2022
MEDLINE	Embase.com (no period restriction for search)	10.03.2022
	PubMed (10.03.2022 and onwards)	20.08.2025
	PubMed (20.08.2025 and onwards)	23.02.2026
CENTRAL	The Cochrane Library (no period restriction for search)	10.03.2022

On 31 March 2022, trial registries were searched on ClinicalTrials.gov and the EU Clinical Trials Register (EUCTR). The ClinicalTrials.gov search returned 109 records, and the EUCTR search returned 34 records. Search terms for each registry were adapted from those used in the electronic database searches and tailored to the requirements and format of each platform.

Table 122. Other sources

Source	Website	Search strategy/keywords used	Source
ClinicalTrials.gov	https://clinicaltrials.gov/	NSCLC Stage IV; Filters: Recruiting, Not yet recruiting, Active, not recruiting, Completed, Enrolling by invitation, Unknown status Studies | Studies With Results | Interventional Studies | Adult, Older Adult | Phase 2, 3, 4	31.03.2022
EU Clinical Trials Register (EUCTR)	https://www.clinicaltrialsregister.eu/ctr-search/search	(nsclc OR 'non small cell lung cancer') AND (Atezolizumab OR Cemiplimab OR Nivolumab OR Pembrolizumab OR Sintilimab OR Toripalimab); Filters: Ongoing, Completed, Adult, Older Adult | Phase 2, 3, 4	31.03.2022

Table 123 below lists the conferences searched as part of the hand searches of the clinical SLR. Only conference proceedings year 2019 onwards were retrieved.

Table 123. Conference material

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO)	https://conferences.asco.org/am/abstracts	Manual search in year 2019-2022	First-line therapy (after filtering for NSCLC + years + abstracts + Annual Meeting)	31.03.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Society for Medical Oncology (ESMO)	https://www.esmo.org/meetings/past-meetings/esmo-congress-2021/abstracts	Manual search in year 2019-2021	Non-small cell lung cancer + abstract filters	31.03.2023
European Lung Cancer Conferences (ELCC)	https://www.esmo.org/meetings/european-lung-cancer-congress-2022/abstracts	Manual search in year 2019-2021	Non-small cell lung cancer + abstract filters	31.03.2023
International Association for the Study of Lung Cancer World Conference on Lung Cancer (WCLC)	https://www.iaslc.org/meetings-webinars/past-meetings-webinars	Manual search in year 2019-2021	"stage IV nsclc"	31.03.2023
American Association for Cancer Research (AACR)	https://aacrjournals.org/pages/meeting-abs	Manual search in year 2019-2021	Searched under "clinical trials" and "clinical research" headings	31.03.2023
ESMO Asia	https://oncologypro.esmo.org/meeting-resources/esmo-asia-virtual-congress-2020?hit=ESMO-Abstracts	Manual search in year 2019-2020	Non-small cell lung cancer + abstract filters	31.03.2023
ESMO Immuno-oncology Congress	https://oncologypro.esmo.org/meeting-resources/esmo-immuno-oncology-congress	Manual search in year 2019-2021	Non-small cell lung cancer + abstract filters	31.03.2023

HTA reports were searched via the INAHTA database, covering following agencies:

- UK: National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC) and All Wales Medicines Strategy Group (AWMSG)
- France: Haute Autorité de Santé (HAS)
- Germany: Gemeinsamer Bundesausschuss (GBA) and Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesenis (IQWiG)
- Australia: Pharmaceutical Benefits Advisory Committee (PBAC)

- Canada: Canadian Agency for Drugs and Technologies in Health (CADTH)
- NIHR HTA Programme

Table 124. HTA reports

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
INAHTA (Australia, Canada, France, Germany, UK, and the US)	https://www.inahta.org/	Manual search in year 2012-2022	((non small cell lung cancer)) OR (nsclc)	31.03.2023

The following tables describe the search strategies for the original search on March 10, 2022. The additional searches in MEDLINE using PubMed were conducted on August 20, 2025, and February 23, 2026.

Table 125. Search strategy table for Embase and MEDLINE via embase.com (March 10, 2022)

No.	Query	Results
#1	'non small cell lung cancer'/exp	181992
#2	nsclc:ab,ti	94596
#3	'lung cancer*':ti,ab	274718
#4	(lung NEXT/1 carcinom*):ab,ti	29517
#5	(lung NEXT/1 neoplasm*):ab,ti	1429
#6	(lung NEXT/1 tumor*):ti,ab	19765
#7	(lung NEXT/1 tumour*):ti,ab	3258
#8	'non small cell*':ti,ab	116552
#9	'nonsmall cell*':ti,ab	6271
#10	'non-small cell':ab,ti	116489
#11	(#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9 OR #10)	118584
#12	#1 OR #2 OR #11	198882
#13	'first line':ti,ab OR 'first-line':ti,ab OR 'front line':ti,ab OR 'frontline':ti,ab OR naive:ti,ab OR untreated:ti,ab OR 'not treated':ti,ab OR 'not previously treated':ti,ab OR (new*:ti,ab AND ((diagnos* NEAR/3 (advanc* OR metasta*)):ti,ab))	713407

#14	'durvalumab'/exp OR imfinzi OR 'medi 4736' OR medi4736	6479
#15	'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'	27921
#16	'pembrolizumab'/exp OR 'keytruda' OR 'lambrolizumab' OR 'mk 3475' OR 'mk3475' OR 'pembrolizumab' OR 'sch 900475' OR 'sch900475'	25968
#17	'ipilimumab'/exp OR 'bms 734016' OR 'bms734016' OR 'ipilimumab' OR 'mdx 010' OR 'mdx 101' OR 'mdx010' OR 'mdx101' OR 'strentarga' OR 'yervoy'	19480
#18	'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'	9992
#19	'ticilimumab'/exp OR 'cp 675 206' OR 'cp 675, 206' OR 'cp 675206' OR 'cp675 206' OR 'cp675, 206' OR 'cp675206' OR tremelimumab	3189
#20	'bevacizumab'/syn OR abevmy OR 'abp 215' OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR 'ask b1202' OR askb1202 OR avastin OR aybintio OR 'bat 1706' OR bat1706 OR 'bcd 021' OR bcd021 OR bevax OR 'bevz 92' OR bevz92 OR 'bi 695502' OR bi695502 OR boyounuo OR bryxta OR byvasda OR 'cbt 124' OR cbt124 OR 'chs 5217' OR chs5217 OR cizumab OR 'ct p16' OR ctp16 OR equidacent OR 'fkb 238' OR fkb238 OR 'gb 222' OR gb222 OR 'hd 204' OR hd204 OR 'hlx 04' OR hlx04 OR 'ibi 305' OR ibi305 OR 'jyv028' OR jy028 OR krabeva OR kyomarc OR lextemy OR 'ly 01008' OR ly01008 OR 'mb 02' OR mb02 OR 'milv0' OR mil60 OR mvasi OR 'myl 14020' OR 'myl 1402o' OR myl14020 OR myl1402o OR 'nsc 704865' OR nsc704865 OR onbevzi OR 'ons 1045' OR 'ons 5010' OR ons1045 OR ons5010 OR oyavas OR 'pf 06439535' OR 'pf 6439535' OR pf06439535 OR pf6439535 OR pusintin OR 'ql 1101' OR ql1101 OR 'r 435' OR r435 OR 'rg 435' OR rg435 OR 'rhumab vegf' OR 'ro 4876646' OR ro4876646 OR 'rph 001' OR rph001 OR 'sb 8' OR sb8 OR 'sct 510' OR sct510 OR 'stc 103' OR stc103 OR 'tab 008' OR tab008 OR 'tot 102' OR tot102 OR 'trs 003' OR trs003 OR 'tx 16' OR tx16 OR versavo OR zirabev OR 'zrc 113' OR zrc113	67827
#21	'cemiplimab'/exp OR 'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR libtayo OR 'regn 2810' OR regn2810 OR 'sar 439684' OR sar439684	903
#22	'sugemalimab'/exp OR 'cs 1001' OR cs1001 OR 'wbp 315' OR 'wbp 3155' OR wbp315 OR wbp3155	39
#23	'sintilimab'/exp OR 'ibi 308' OR ibi308 OR tyvyt	522
#24	'toripalimab'/exp OR 'js 001' OR js001 OR 'tab 001' OR tab001 OR teripalimab OR treipril OR treprizumab OR tripleitriumab OR triprizumab OR tuoyi	485
#25	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24	115268
#26	'cisplatin'/exp OR cisplatin OR 'platinum diamminodichloride' OR 'cis-platinum' OR 'cis platinum' OR 'cisplatinum' OR 'dichlorodiammineplatinum' OR 'cis-diamminedichloroplatinum' OR 'cis	209653

	diamminedichloroplatinum' OR 'cis-dichlorodiammineplatinum' OR 'platinol' OR 'platidiam' OR 'platino' OR biocisplatinum	
#27	'carboplatin'/exp OR carboplatin 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	79611
#28	#26 OR #27	250163
#29	'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 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	129814
#30	'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	17006
#31	'gemcitabine'/exp OR 'gemcitabine hydrochloride' OR 'gemcite' OR 'gemzar'	63889
#32	'vinorelbine'/exp OR 'eunades' OR 'exelbine' OR 'navelbin' OR 'navelbine' OR 'navirel' OR 'vinbine' OR 'vinelbine' OR 'vinorelbine ditartrate' OR 'vinorelbine tartrate'	19340
#33	'docetaxel'/exp OR 'nsc 628503' OR nsc628503 OR oncodocel OR 'rp 56976' OR rp56976 OR taxespira OR taxoter OR taxotere OR texot OR daxotel OR dexotel OR docefrez OR 'docetaxel accord' OR 'lit 976' OR lit976	65259
#34	#29 OR #30 OR #31 OR #32 OR #33	219703
#35	#28 AND #34	89049
#36	((platin* NEAR/5 chemotherap*):ti,ab) AND (combin*:ti,ab OR doubl*:ti,ab)	8956
#37	#35 OR #36	95400
#38	#25 OR #37	192502
#39	#12 AND #13 AND #38	9632
#40	'randomized controlled trial'/exp	610311

#41	'controlled clinical trial'/exp	781347
#42	random*:ti,ab	1543847
#43	'randomization'/exp	87095
#44	'intermethod comparison'/exp	262939
#45	placebo:ti,ab	307459
#46	compare:ti OR compared:ti OR comparison:ti	533284
#47	(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)	2120960
#48	(open NEXT/1 label):ti,ab	79442
#49	((double OR single OR doubly OR singly) NEXT/1 (blind OR blinded OR blindly)):ti,ab	234343
#50	'double blind procedure'/exp	173879
#51	parallel:ti,ab AND group*:ti,ab	74190
#52	crossover:ti,ab OR (cross:ti,ab AND over:ti,ab)	208857
#53	((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	176
#54	assigned:ti,ab OR allocated:ti,ab	389244
#55	(controlled NEXT/7 (study OR design OR trial)):ti,ab	332862
#56	volunteer:ti,ab OR volunteers:ti,ab	248365
#57	'human experiment'/exp	503778
#58	trial.ti	1
#59	#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	4980909
#60	(random* NEXT/1 sampl* NEXT/7 ('cross section*' OR questionnaire*1 OR survey* OR database*1)):ti,ab	1646
#61	'comparative study'/exp OR 'controlled study'/exp OR 'randomi?ed controlled:ti,ab or randomly assigned:ti,ab'	8600392
#62	#60 NOT #61	1216
#63	'cross-sectional study'/exp	353939

#64	'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'	7690261
#65	#63 NOT #64	237634
#66	(case NEXT/1 control) AND random*	25178
#67	randomi?ed:ti,ab AND controlled:ti,ab	413725
#68	#66 NOT #67	21525
#69	systematic:ti AND review:ti NOT (trial:ti OR study:ti)	151972
#70	nonrandom*:ti,ab NOT random*:ti,ab	16159
#71	random AND field*:ti,ab	17051
#72	random:ti,ab AND ((cluster NEXT/3 sampl*):ti,ab)	3542
#73	review:ab AND review:it NOT trial:ti	795876
#74	'we searched':ab AND (review:ti OR review:pt)	17005
#75	'update review':ab	104
#76	(databases NEXT/4 searched):ab	25019
#77	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	2352372
#78	'animal experiment'/exp	2567067
#79	#77 AND #78	1067994
#80	'animal experiment'/exp NOT ('human experiment'/exp OR 'human'/exp)	2251440
#81	#62 OR #65 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #79 OR #80	3485934
#82	#59 NOT #81	4936378
#83	#39 AND #82	4284
#84	#83 AND ('Article'/it OR 'Article in Press'/it)	1769

Table 126. Search strategy table for CDSR and CENTRAL via Cochrane library (March 10, 2022)

No.	Query	Results
#1	MeSH descriptor: [Carcinoma, Non-Small-Cell Lung] explode all trees	4666
#2	("nsclc"):ti,ab,kw (Word variations have been searched)	10203
#3	(lung cancer*):ti,ab,kw	26960
#4	(lung carcinom*):ti,ab,kw	9184
#5	(lung neoplasm*):ti,ab,kw	11298
#6	(lung tumor*):ti,ab,kw	9541
#7	(lung tumour*):ti,ab,kw	1548
#8	(non small cell*):ti,ab,kw	17143
#9	(nonsmall cell*):ti,ab,kw	9630
#10	(non-small cell):ti,ab,kw	14386
#11	(#3 OR #4 OR #5 OR #6 OR #7) AND (#8 OR #9 OR #10)	14719
#12	#1 OR #2 OR #11	15398
#13	first line OR "first-line" OR "front line" OR "frontline" OR naive OR untreated OR "not treated" OR "not previously treated" OR ("new*" AND ("diagnos*" AND ("advanc*" OR "metasta*")))	64624
#14	durvalumab OR imfinzi OR "medi 4736" OR medi4736	801
#15	nivolumab OR "bms 936558" OR "bms936558" OR "cmab 819" OR "cmab819" OR "mdx 1106" OR mdx1106 OR "ono 4538" OR ono4538 OR opdivo	2240
#16	pembrolizumab OR keytruda OR lambrolizumab OR "mk 3475" OR mk3475 OR "sch 900475" OR sch900475	2183
#17	ipilimumab OR "bms 734016" OR bms734016 OR "mdx 010" OR "mdx 101" OR "mdx010" OR "mdx101" OR "strentarga" OR "yervoy"	1478
#18	atezolizumab OR "monoclonal antibody mpdl 3280a" OR "monoclonal antibody mpdl3280a" OR "mpdl 3280a" OR "mpdl3280a" OR "rg 7446" OR "rg7446" OR "tecentriq" OR "tecntriq"	1093
#19	tremelimumab OR "ticilimumab" OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR "cp675206"	339
#20	bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR	7025

	avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR "nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113	
#21	'cemiplimab' OR 'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR libtayo OR 'regn 2810' OR regn2810 OR 'sar 439684' OR sar439684	74
#22	'sugemalimab' OR 'cs 1001' OR cs1001 OR 'wbp 315' OR 'wbp 3155' OR wbp315 OR wbp3155	216
#23	'sintilimab' OR 'ibi 308' OR ibi308 OR tyvyt	82
#24	'toripalimab' OR 'js 001' OR js001 OR 'tab 001' OR tab001 OR teripalimab OR treipril OR treprizumab OR tripleitriumab OR triprizumab OR tuoyi	10188
#25	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #20	23136
#26	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	15611
#27	carboplatin 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	7841
#28	#26 OR #27	20756
#29	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	14597

	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	
#30	'gemcitabine' OR 'gemcitabine hydrochloride' OR 'gemcite' OR 'gemzar'	6458
#31	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	2294
#32	'vinorelbine' OR 'eunades' OR 'exelbine' OR 'navelbin' OR 'navelbine' OR 'navirel' OR 'vinbine' OR 'vinelbine' OR 'vinorelbine ditartrate' OR 'vinorelbine tartrate'	1968
#33	'docetaxel' OR 'nsc 628503' OR nsc628503 OR oncodocel OR 'rp 56976' OR rp56976 OR taxespira OR taxoter OR taxotere OR texot OR daxotel OR dexotel OR docefrez OR 'docetaxel accord' OR 'lit 976' OR lit976	7929
#34	#29 OR #30 OR #31 OR #32 OR #33	27732
#35	#28 AND #34	10011
#36	((platin* NEAR/5 chemotherap*) AND (combin* OR doubl*)):ti,ab,kw	2605
#37	#35 OR #36	11825
#38	#25 OR #37	32625
#39	#12 AND #13 AND #38	2703
#40	Restricted to PubMed (734), Embase (1435), CINAHL (10), Reviews (19) Excluded ICTRP (407) and CT.gov (405), Cochrane protocols (7), Clinical Answers (4)	2198

Table 127. Search strategy table for MEDLINE & In-Process via PubMed (March 10, 2022)

No.	Query	Results
#1	(('non small cell lung cancer'[MeSH Terms]) OR (nsclc [TIAB]) OR ((("lung cancer*"[TIAB]) OR ("lung carcinom*"[TIAB]) OR ("lung neoplasm*"[TIAB]) OR ("lung tumor*"[TIAB]) OR ("lung tumour*"[TIAB])) AND (("non small cell*"[TIAB]) OR ("nonsmall cell*"[TIAB]) OR ("non-small cell"[TIAB])))) AND ("first line"[TIAB] OR "first-line"[TIAB] OR "front line"[TIAB] OR "frontline"[TIAB] OR naive[TIAB] OR untreated[TIAB] OR "not treated"[TIAB] OR "not previously treated"[TIAB] OR ("new*"	2,593

AND ("diagnos*" AND ("advanc*" OR "metasta*")))) AND (("clinical trial" OR clinical trial [pt]) OR ("randomized controlled trial" OR randomized controlled trial [pt] OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials") OR ("controlled clinical trial" OR controlled clinical trial [pt]) OR ("multicenter study" OR multicenter study [pt]) OR ("phase 1 clinical trial" OR ‘phase 1 clinical trial’[MeSH Major Topic]) OR ("phase 2 clinical trial" OR 'phase 2 clinical trial'[MeSH Major Topic]) OR ("phase 3 clinical trial" OR ‘phase 3 clinical trial’[MeSH Major Topic]) OR ("phase 4 clinical trial" OR 'phase 4 clinical trial'[MeSH Major Topic]) OR (randomization OR "random allocation"[MeSH Terms]) OR ("single blind procedure" OR "Single-Blind Method"[Mesh]) OR ("double blind procedure" OR "double-blind procedure" OR Double-Blind Method[Mesh]) OR ("crossover procedure" OR "Cross-Over Studies"[Mesh]) OR (placebo OR "Placebos"[Mesh]) OR ("rct"[tiab]) OR (random* AND allocat*) OR ((allocated AND random*) OR (random* AND assign*) OR random*) OR ((double [tiab] OR single [tiab] OR doubly [tiab] OR singly [tiab] OR triple[tiab] OR treble[tiab]) AND (blind [tiab] OR blinded [tiab] OR blindly [tiab] OR mask [tiab] OR masked [tiab])) OR (placebo [tiab]) OR ((control* OR equivalence OR superiority OR "non inferiority" OR noninferiority OR pragmatic OR practical OR quasiexperimental OR "quasi experimental" OR experimental OR phase) AND (study OR studies OR trial* OR group*)) OR ("prospective study" OR "Prospective Studies"[Mesh]) OR (controlled [tiab] AND (study [tiab] OR design [tiab] OR trial [tiab])))) AND (((durvalumab OR imfinzi OR "medi 4736" OR medi4736) OR ("nivolumab"[MeSH Terms] OR "bms 936558" OR "bms936558" OR "cmab 819" OR "cmab819" OR "mdx 1106" OR "mdx1106" OR "nivolumab" OR "ono 4538" OR "ono4538" OR "opdivo") OR ("pembrolizumab" OR "keytruda" OR "lambrolizumab" OR "mk 3475" OR "mk3475" OR "sch 900475" OR "sch900475") OR ("ipilimumab" OR "bms 734016" OR "bms734016" OR "ipilimumab" OR "mdx 010" OR "mdx 101" OR "mdx010" OR "mdx101" OR "strentarga" OR "yervoy") 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") OR ("tremelimumab" OR "ticilimumab" OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR "cp675206") OR (bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR

"nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113) OR ('cemiplimab' OR 'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR libtayo OR 'regn 2810' OR regn2810 OR 'sar 439684' OR sar439684) OR ('sugemalimab' OR 'cs 1001' OR cs1001 OR 'wbp 315' OR 'wbp 3155' OR wbp315 OR wbp3155) OR ('sintilimab' OR 'ibi 308' OR ibi308 OR tyvyt) OR ('toripalimab' OR 'js 001' OR js001 OR 'tab 001' OR tab001 OR teripalimab OR treipril OR treprizumab OR tripleitriumab OR triprizumab OR tuoyi)) 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) OR (carboplatin 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)) AND ((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) OR ('gemcitabine' OR 'gemcitabine hydrochloride' OR 'gemcite' OR 'gemzar') 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) OR ('vinorelbine' OR 'eunades' OR 'exelbine' OR 'navelbin' OR 'navelbine' OR 'navirel' OR 'vinbine' OR 'vinelbine' OR 'vinorelbine ditartrate' OR 'vinorelbine tartrate') OR ('docetaxel' OR 'nsc 628503' OR nsc628503 OR oncodocel OR 'rp 56976' OR rp56976 OR taxespira OR taxoter OR taxotere OR texot OR daxotel OR dexotel OR docefrez OR 'docetaxel accord' OR 'lit 976' OR lit976))) OR ((platin*[TIAB] AND

chemotherap*[TIAB]) AND (combin*[TIAB] OR doubl*[TIAB]))) - Saved search

Table 128. Search strategy table for MEDLINE via PubMed, first supplemental search (August 20, 2025)

No.	Query	Results
#1	(('non small cell lung cancer'[MeSH Terms]) OR (nsclc [TIAB]) OR (((("lung cancer*"[TIAB]) OR ("lung carcinom*"[TIAB]) OR ("lung neoplasm*"[TIAB]) OR ("lung tumor*"[TIAB]) OR ("lung tumour*"[TIAB])) AND (("non small cell*"[TIAB]) OR ("nonsmall cell*"[TIAB]) OR ("non-small cell"[TIAB])))) AND ("first line"[TIAB] OR "first-line"[TIAB] OR "front line"[TIAB] OR "frontline"[TIAB] OR naive[TIAB] OR untreated[TIAB] OR "not treated"[TIAB] OR "not previously treated"[TIAB] OR ("new*" AND ("diagnos*" AND ("advanc*" OR "metasta*")))) AND (("clinical trial" OR clinical trial [pt]) OR ("randomized controlled trial" OR randomized controlled trial [pt] OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials") OR ("controlled clinical trial" OR controlled clinical trial [pt]) OR ("multicenter study" OR multicenter study [pt]) OR ("phase 1 clinical trial" OR 'phase 1 clinical trial'[MeSH Major Topic]) OR ("phase 2 clinical trial" OR 'phase 2 clinical trial'[MeSH Major Topic]) OR ("phase 3 clinical trial" OR 'phase 3 clinical trial'[MeSH Major Topic]) OR ("phase 4 clinical trial" OR 'phase 4 clinical trial'[MeSH Major Topic]) OR (randomization OR "random allocation"[MeSH Terms]) OR ("single blind procedure" OR "Single-Blind Method"[Mesh]) OR ("double blind procedure" OR "double-blind procedure" OR Double-Blind Method[Mesh]) OR ("crossover procedure" OR "Cross-Over Studies"[Mesh]) OR (placebo OR "Placebos"[Mesh]) OR ("rct"[tiab]) OR (random* AND allocat*) OR ((allocated AND random*) OR (random* AND assign*) OR random*) OR ((double [tiab] OR single [tiab] OR doubly [tiab] OR singly [tiab] OR triple[tiab] OR treble[tiab]) AND (blind [tiab] OR blinded [tiab] OR blindly [tiab] OR mask [tiab] OR masked [tiab])) OR (placebo [tiab]) OR ((control* OR equivalence OR superiority OR "non inferiority" OR noninferiority OR pragmatic OR practical OR quasiexperimental OR "quasi experimental" OR experimental OR phase) AND (study OR studies OR trial* OR group*)) OR ("prospective study" OR "Prospective Studies"[Mesh]) OR (controlled [tiab] AND (study [tiab] OR design [tiab] OR trial [tiab]))) AND (((durvalumab OR imfinzi OR "medi 4736" OR medi4736) OR ("nivolumab"[MeSH Terms] OR "bms 936558" OR "bms936558" OR "cmab 819" OR "cmab819" OR "mdx 1106" OR "mdx1106" OR "nivolumab" OR "ono 4538" OR "ono4538" OR "opdivo") OR ("pembrolizumab" OR "keytruda" OR "lambrolizumab" OR "mk 3475" OR "mk3475" OR "sch 900475" OR "sch900475") OR ("ipilimumab" OR "bms 734016" OR "bms734016" OR "ipilimumab" OR "mdx 010" OR "mdx 101" OR	3,353

"mdx010" OR "mdx101" OR "strentarga" OR "yervoy") 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") OR ("tremelimumab" OR "ticilimumab" OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR "cp675206") OR (bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR "nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113) OR ('cemiplimab' OR 'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR libtayo OR 'regn 2810' OR regn2810 OR 'sar 439684' OR sar439684) OR ('sugemalimab' OR 'cs 1001' OR cs1001 OR 'wbp 315' OR 'wbp 3155' OR wbp315 OR wbp3155) OR ('sintilimab' OR 'ibi 308' OR ibi308 OR tyvyt) OR ('toripalimab' OR 'js 001' OR js001 OR 'tab 001' OR tab001 OR teripalimab OR treipril OR treprizumab OR tripleitriumab OR triprizumab OR tuoyi)) 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) OR (carboplatin 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)) AND ((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) OR ('gemcitabine' OR 'gemcitabine hydrochloride' OR 'gemcite' OR 'gemzar') 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) OR ('vinorelbine' OR 'eunades' OR 'exelbine' OR 'navelbin' OR 'navelbine' OR 'navirel' OR 'vinbine' OR 'vinelbine' OR 'vinorelbine ditartrate' OR 'vinorelbine tartrate') OR ('docetaxel' OR 'nsc 628503' OR nsc628503 OR oncodocel OR 'rp 56976' OR rp56976 OR taxespira OR taxoter OR taxotere OR texot OR daxotel OR dexotel OR docefrez OR 'docetaxel accord' OR 'lit 976' OR lit976))) OR ((platin*[TIAB] AND chemotherap*[TIAB]) AND (combin*[TIAB] OR doubl*[TIAB]))))) - Saved search	
#2	#1 AND ("2022/03/10"[Date - Publication] : "3000"[Date - Publication])	758

Table 129. Search strategy table for MEDLINE via PubMed, second supplemental search (February 23, 2026)

No.	Query	Results
#1	(('non small cell lung cancer'[MeSH Terms]) OR (nsclc [TIAB]) OR ((("lung cancer*"[TIAB]) OR ("lung carcinom*"[TIAB]) OR ("lung neoplasm*"[TIAB]) OR ("lung tumor*"[TIAB]) OR ("lung tumour*"[TIAB])) AND (("non small cell*"[TIAB]) OR ("nonsmall cell*"[TIAB]) OR ("non-small cell"[TIAB])))) AND ("first line"[TIAB] OR "first-line"[TIAB] OR "front line"[TIAB] OR "frontline"[TIAB] OR naive[TIAB] OR untreated[TIAB] OR "not treated"[TIAB] OR "not previously treated"[TIAB] OR ("new*" AND ("diagnos*" AND ("advanc*" OR "metasta*")))) AND (("clinical trial" OR clinical trial [pt]) OR ("randomized controlled trial" OR randomized controlled trial [pt] OR "randomised controlled trial" OR "randomized controlled trials" OR "randomised controlled trials") OR ("controlled clinical trial" OR controlled clinical trial [pt]) OR ("multicenter study" OR multicenter study [pt]) OR ("phase 1 clinical trial" OR 'phase 1 clinical trial'[MeSH Major Topic]) OR ("phase 2 clinical trial" OR 'phase 2 clinical trial'[MeSH Major Topic]) OR ("phase 3 clinical trial" OR 'phase 3 clinical trial'[MeSH Major Topic]) OR ("phase 4 clinical trial" OR 'phase 4 clinical trial'[MeSH Major Topic]) OR (randomization OR "random allocation"[MeSH Terms]) OR ("single blind procedure" OR "Single-Blind Method"[Mesh]) OR ("double blind procedure" OR "double-blind procedure" OR Double-Blind Method[Mesh]) OR ("crossover procedure" OR "Cross-Over Studies"[Mesh]) OR (placebo OR "Placebos"[Mesh])	3,490

OR ("rct"[tiab]) OR (random* AND allocat*) OR ((allocated AND random*) OR (random* AND assign*) OR random*) OR ((double [tiab] OR single [tiab] OR doubly [tiab] OR singly [tiab] OR triple[tiab] OR treble[tiab]) AND (blind [tiab] OR blinded [tiab] OR blindly [tiab] OR mask [tiab] OR masked [tiab])) OR (placebo [tiab]) OR ((control* OR equivalence OR superiority OR "non inferiority" OR noninferiority OR pragmatic OR practical OR quasiexperimental OR "quasi experimental" OR experimental OR phase) AND (study OR studies OR trial* OR group*)) OR ("prospective study" OR "Prospective Studies"[Mesh]) OR (controlled [tiab] AND (study [tiab] OR design [tiab] OR trial [tiab]))) AND (((durvalumab OR imfinzi OR "medi 4736" OR medi4736) OR ("nivolumab"[MeSH Terms] OR "bms 936558" OR "bms936558" OR "cmab 819" OR "cmab819" OR "mdx 1106" OR "mdx1106" OR "nivolumab" OR "ono 4538" OR "ono4538" OR "opdivo") OR ("pembrolizumab" OR "keytruda" OR "lambrolizumab" OR "mk 3475" OR "mk3475" OR "sch 900475" OR "sch900475") OR ("ipilimumab" OR "bms 734016" OR "bms734016" OR "ipilimumab" OR "mdx 010" OR "mdx 101" OR "mdx010" OR "mdx101" OR "strentarga" OR "yervoy") 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") OR ("tremelimumab" OR "ticilimumab" OR "cp 675 206" OR "cp 675, 206" OR "cp 675206" OR "cp675 206" OR "cp675, 206" OR "cp675206") OR (bevacizumab OR abevmy OR "abp 215" OR abp215 OR ainex OR altuzan OR alymsys OR ankeda OR "ask b1202" OR askb1202 OR avastin OR aybintio OR "bat 1706" OR bat1706 OR "bcd 021" OR bcd021 OR bevax OR "bevz 92" OR bevz92 OR "bi 695502" OR bi695502 OR boyounuo OR bryxta OR byvasda OR "cbt 124" OR cbt124 OR "chs 5217" OR chs5217 OR cizumab OR "ct p16" OR ctp16 OR equidacent OR "fkb 238" OR fkb238 OR "gb 222" OR gb222 OR "hd 204" OR hd204 OR "hlx 04" OR hlx04 OR "ibi 305" OR ibi305 OR "jyv028" OR jy028 OR krabeva OR kyomarc OR lextemy OR "ly 01008" OR ly01008 OR "mb 02" OR mb02 OR "milv0" OR mil60 OR mvasi OR "myl 14020" OR "myl 1402o" OR myl14020 OR myl1402o OR "nsc 704865" OR nsc704865 OR onbevzi OR "ons 1045" OR "ons 5010" OR ons1045 OR ons5010 OR oyavas OR "pf 06439535" OR "pf 6439535" OR pf06439535 OR pf6439535 OR pusintin OR "ql 1101" OR ql1101 OR "r 435" OR r435 OR "rg 435" OR rg435 OR "rhumab vegf" OR "ro 4876646" OR ro4876646 OR "rph 001" OR rph001 OR "sb 8" OR sb8 OR "sct 510" OR sct510 OR "stc 103" OR stc103 OR "tab 008" OR tab008 OR "tot 102" OR tot102 OR "trs 003" OR trs003 OR "tx 16" OR tx16 OR versavo OR zirabev OR "zrc 113" OR zrc113) OR ('cemiplimab' OR 'cemiplimab rwlc' OR 'cemiplimab-rwlc' OR libtayo OR 'regn 2810' OR regn2810 OR 'sar 439684' OR sar439684) OR ('sugemalimab' OR 'cs 1001' OR cs1001 OR 'wbp 315' OR 'wbp 3155' OR wbp315 OR wbp3155) OR ('sintilimab' OR 'ibi 308' OR ibi308 OR tyvyt) OR ('toripalimab' OR 'js 001' OR js001 OR 'tab 001' OR tab001 OR teripalimab OR treipril OR treprizumab OR tripleitriumab OR triprizumab OR tuoyi)) 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) OR (carboplatin 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)) AND ((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) OR ('gemcitabine' OR 'gemcitabine hydrochloride' OR 'gemcite' OR 'gemzar') 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) OR ('vinorelbine' OR 'eunades' OR 'exelbine' OR 'navelbin' OR 'navelbine' OR 'navirel' OR 'vinbine' OR 'vinelbine' OR 'vinorelbine ditartrate' OR 'vinorelbine tartrate') OR ('docetaxel' OR 'nsc 628503' OR nsc628503 OR oncodocel OR 'rp 56976' OR rp56976 OR taxespira OR taxoter OR taxotere OR texot OR daxotel OR dexotel OR docefrez OR 'docetaxel accord' OR 'lit 976' OR lit976))) OR ((platin*[TIAB] AND chemotherap*[TIAB]) AND (combin*[TIAB] OR doubl*[TIAB])))) - Saved search	
#2	#1 AND ("2025/08/20"[Date - Publication] : "3000"[Date - Publication])	154

H.2 Systematic selection of studies and references

The study eligibility criteria were developed using the population, intervention, comparator, outcomes, study design (PICOs) framework, and are shown in Table 130 for the original SLR and the SLR updates. As the global SLRs did not restrict studies based on intervention or comparator, the relevant PICOs in Denmark of interest were those that might represent potential comparators to durvalumab in adults with mNSCLC with no EGFR mutations or ALK rearrangements, PD-L1 < 1%.

In accordance with DMC guidelines, the PICO from the global SLR was adjusted to the reflect the Danish setting, where N+I+CT is the SoC for patients with PD-L1 <1% in squamous histology and P+CT is the SoC for patients with PD-L1 <1% in non-squamous histology. In addition, reporting of HR for OS and PFS was important to include for the ITC for relative efficacy estimation (Table 130).

Table 130. Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	• Adults with untreated mNSCLC without sensitizing EGFR mutations or ALK fusions (including both squamous and non-squamous NSCLC) • Mixed population (with or without EGFR mutations or ALK fusions) with the distribution of mutations available (70-80% of patients are EGFR and/or ALK wildtype) • No restrictions based on patients' PD-L1 status	None	Adults with untreated mNSCLC without sensitizing EGFR mutations or ALK fusions (including both squamous and non-squamous NSCLC), PD-L1 < 1%
Intervention	Durvalumab + Tremelimumab + SoC (CT) Durvalumab + SoC (CT)	None	Durvalumab + Tremelimumab + SoC (CT)
Comparators	**For non-squamous NSCLC**: • Atezolizumab + SoC (CT) • Atezolizumab • Cemiplimab • Nivolumab + ipilimumab + SoC (CT) • Nivolumab + ipilimumab • SoC (CT) • Pembrolizumab + SoC (CT) • Pembrolizumab monotherapy **For squamous NSCLC:** • Atezolizumab • Cemiplimab • SoC (CT) • Nivolumab + ipilimumab + SoC (CT) • Nivolumab + ipilimumab • Pembrolizumab + SoC (CT) • Pembrolizumab	None	**For non-squamous NSCLC**: • Nivolumab + ipilimumab + SoC (CT) **For squamous NSCLC:** • Pembrolizumab + SoC (CT)

Outcomes	• Overall survival (OS) • Progression-free survival (PFS) • PFS2 • Time to distant metastasis or death • Response rate • Duration of response • Time to response • Time to treatment failure (TTF) • Time to treatment discontinuation (TTD) • Time to progression (TTP) • Time to first subsequent treatment (TFST) • Time to second subsequent treatment (TSST) • Percentage of subsequent treatment (Immuno-oncology treatment) • Any treatment-related adverse events (AEs) ≥ grade 3, any SAE, Immune-mediated AEs, any AE of special interest, discontinuation due to AE • Health-related quality of life (HRQoL)	None	• OS • PFS
Study design/publication type	RCTs	None	RTCs
Language restrictions	English	None	English

Titles and abstracts of studies identified from the search strategy were reviewed independently by two researchers in accordance with the pre-specified inclusion criteria. Potentially relevant articles were then further reviewed for eligibility. The full-text review of these articles was also conducted by two researchers independently and in parallel, per the pre-specified inclusion criteria. Any discrepancy at either the title/abstract or full-text review stage was resolved by discussion with a third reviewer. Data extraction was done in a pre-specified data extraction grid. After initial extraction, all of the evidence extracted was subject to a quality check for accuracy and completeness.

The processes for both the initial global SLR and the supplementary searches to reflect the Danish clinical practice are illustrated in Figure 42, Figure 43, and Figure 44.

Figure 41. PRISMA flow diagram for studies identified in the original SLR, March 10, 2022, with Danish adaptation

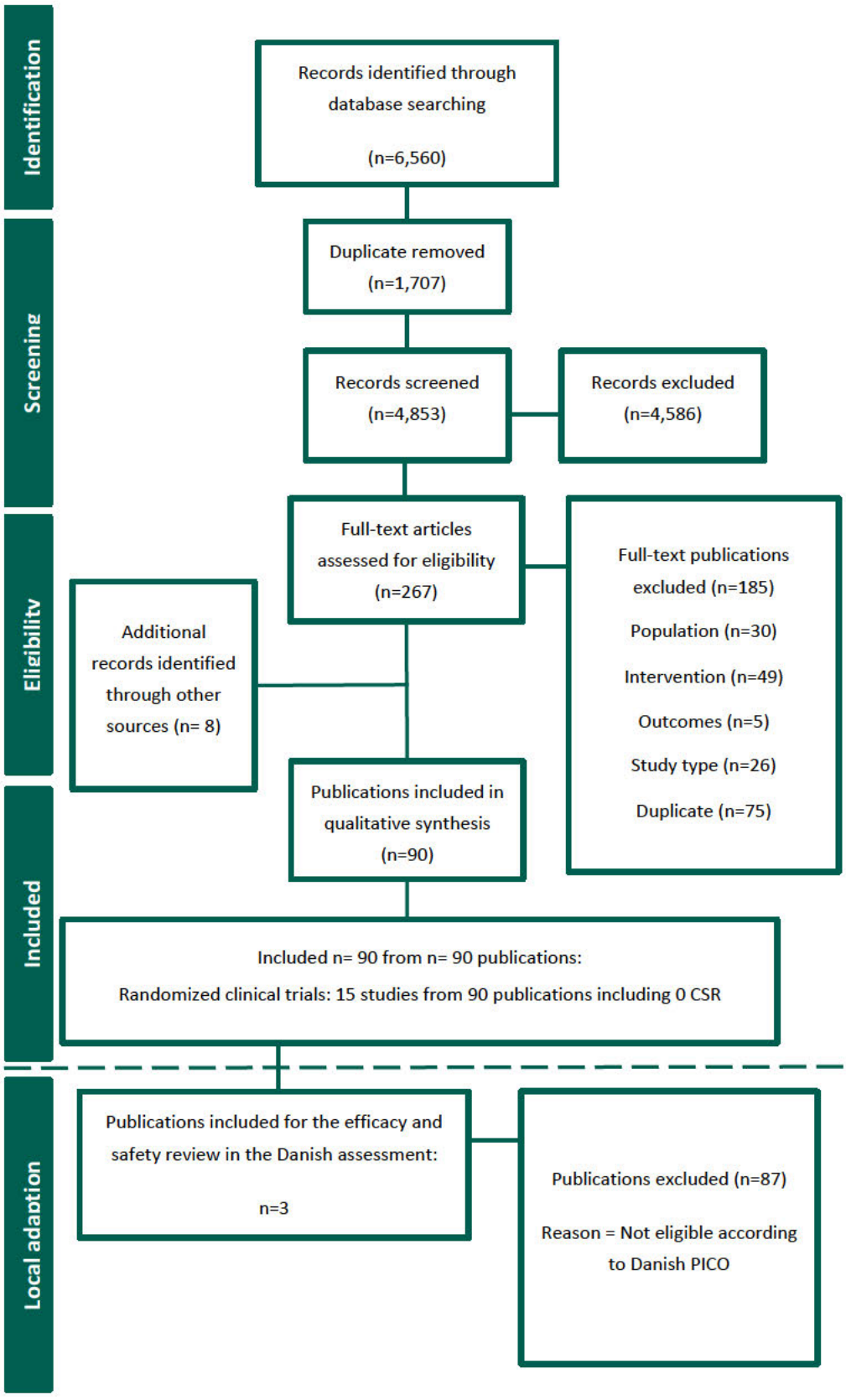


Figure 42. PRISMA flow diagram for studies identified in the updated SLR, August 20, 2025

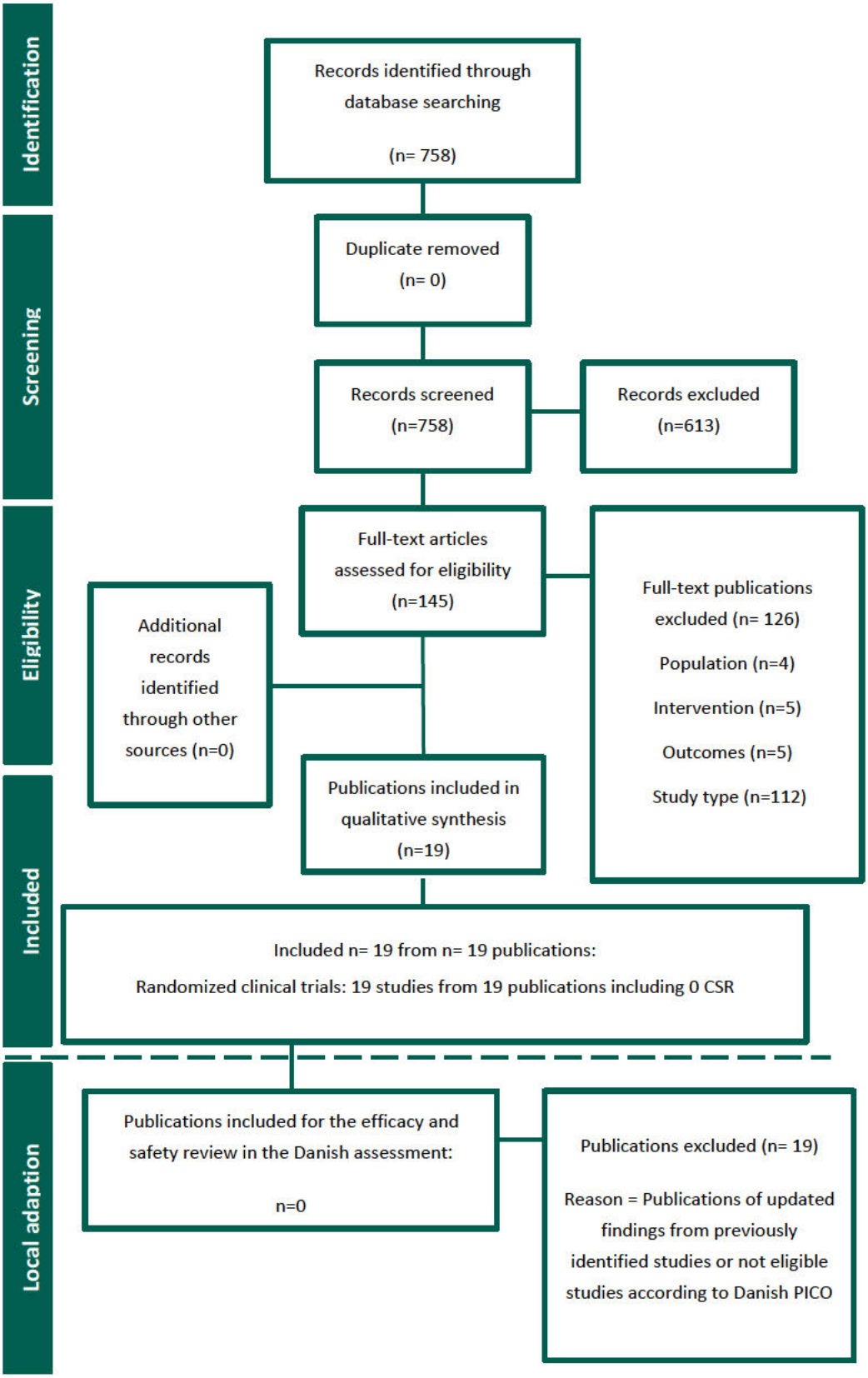
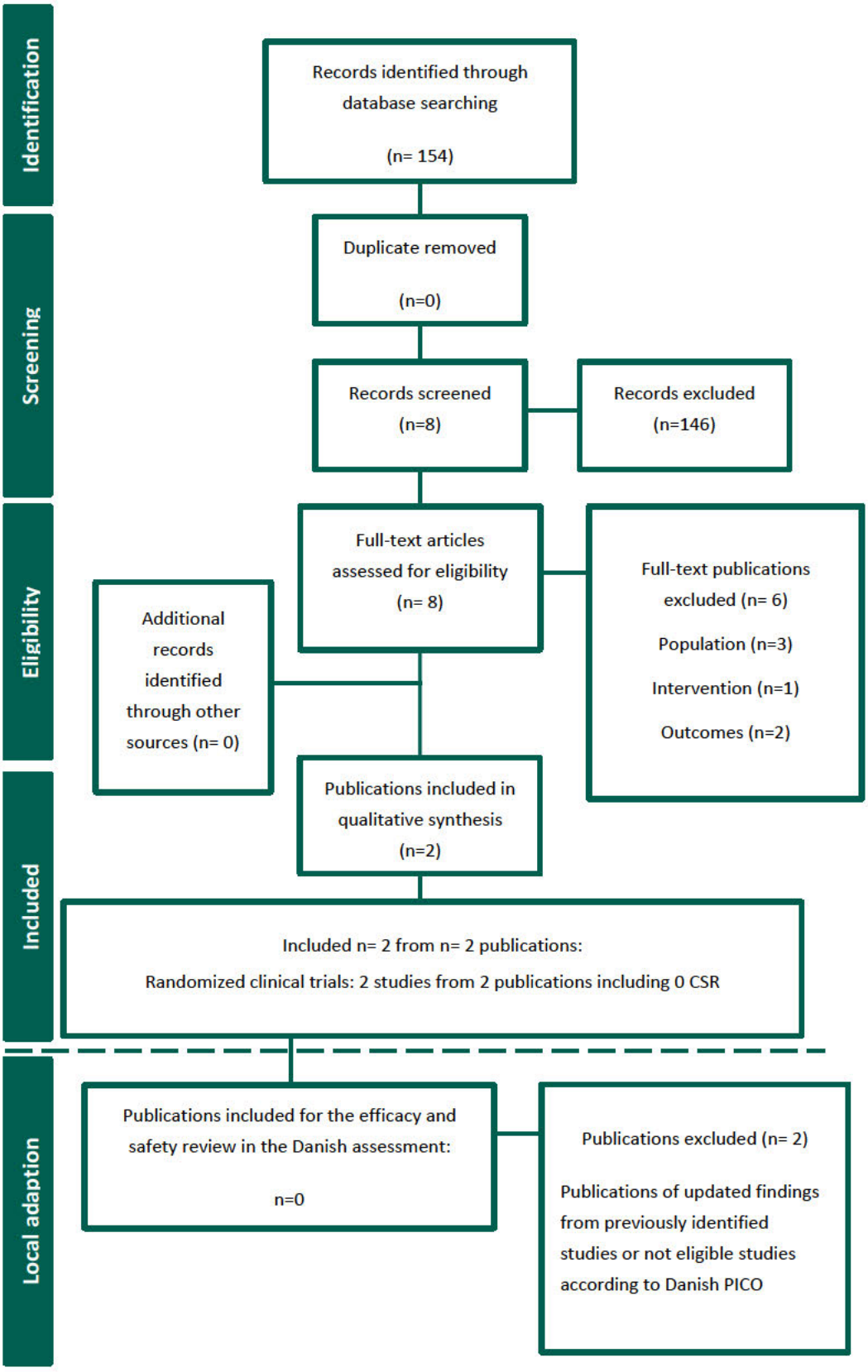


Figure 43. PRISMA flow diagram for studies identified in the updated search, February 23, 2026



The initial systematic literature review identified 15 studies, primarily large randomized controlled trials evaluating the efficacy and safety of first-line treatments for adult patients with mNSCLC who EGFR/ALK wild-type are. These studies span both squamous and non-squamous histology and include patient's representative of real-world advanced NSCLC populations globally.

Although the original and updated SLRs identified RCTs across various therapeutic options, only three studies were considered relevant for the ITCs based on the adapted Danish PICO and current SoC:

- POSEIDON as the relevant evidence for D+T+CT
- KEYNOTE-189 as the relevant evidence for a comparison versus P+CT
- CheckMate-9LA as the relevant evidence for the comparison versus N+I+CT

Table 131. Studies/references included in the Danish assessment

Study	Reference(s)
POSEIDON	See Table 95
KEYNOTE-189	See Table 96
CheckMate-9LA	See Table 97

Table 132. Excluded studies/references

Study	Reference(s)
CheckMate 227	Hellmann, 2019, Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer Paz-Ares, 2022, First-Line Nivolumab Plus Ipilimumab in Advanced NSCLC: 4-Year Outcomes From the Randomized, Open-Label, Phase 3 CheckMate 227 Part 1 Trial Reck, 2021, First-Line Nivolumab Plus Ipilimumab Versus Chemotherapy in Advanced NSCLC With 1% or Greater Tumor PD-L1 Expression: Patient-Reported Outcomes From CheckMate 227 Part 1 Ramalingam, 2021, Nivolumab (NIVO) + ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced NSCLC (aNSCLC) in CheckMate 227 Part 1: efficacy by KRAS, STK11, and KEAP1 mutation status

Study	Reference(s)
ERACLE	Galetta, 2015, Cisplatin/pemetrexed followed by maintenance pemetrexed versus carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab in advanced nonsquamous lung cancer: the GOIM (Gruppo Oncologico Italia Meridionale) ERACLE phase III randomized trial.
IMpower130	West, 2019, Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial.
IMpower150	Socinski, 2018, Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. Socinski, 2021, IMpower150 Final Overall Survival Analyses for Atezolizumab Plus Bevacizumab and Chemotherapy in First-Line Metastatic Nonsquamous Reck, 2020, Safety and Patient-Reported Outcomes of Atezolizumab Plus Chemotherapy With or Without Bevacizumab Versus Bevacizumab Plus Chemotherapy in Non-Small-Cell Lung Cancer West, 2022, Clinical efficacy of atezolizumab plus bevacizumab and chemotherapy in KRAS-mutated non-small cell lung cancer with STK11, KEAP1, or TP53 comutations: subgroup results from the phase III IMpower150 trial
Keynote 024	Reck, 2016, Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer Reck, 2021, Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non-Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50 Brahmer, 2017, Health-related quality-of-life results for pembrolizumab versus chemotherapy in advanced, PD-L1-positive NSCLC (KEYNOTE-024): a multicentre, international, randomised, open-label phase 3 trial
Keynote 042	Mok, 2019, Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Castro, 2021, KEYNOTE-042 5-year survival update: Pembrolizumab versus chemotherapy in patients with previously untreated, PD-l1-positive, locally advanced or metastatic non-small-cell lung cancer
KEYNOTE-407	Paz-Ares, 2018, Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer Robinson, 2021, First-line pembrolizumab plus chemotherapy for patients with advanced squamous NSCLC: 3-year follow-up from KEYNOTE-407

Study	Reference(s)
	Mazieres, 2019, Health-Related Quality of Life With Carboplatin-Paclitaxel or nab-Paclitaxel With or Without Pembrolizumab in Patients With Metastatic Squamous Non–Small-Cell Lung Cancer
IMpower110	Herbst, 2020, Atezolizumab for First-Line Treatment of PD-L1–Selected Patients with NSCLC Jassem, 2021, Updated Overall Survival Analysis From IMpower110: Atezolizumab Versus Platinum-Based Chemotherapy in Treatment-Naive Programmed Death-Ligand 1-Selected NSCLC
EMPOWER LUNG-1	Sezer 2021, Cemiplimab monotherapy for first-line treatment of advanced non-small-cell lung cancer with PD-L1 of at least 50%: a multicentre, open-label, global, phase 3, randomised, controlled trial.
KEYNOTE-021 Cohort G	Langer 2016, Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study Awad M 2021, Long-Term Overall Survival From KEYNOTE-021 Cohort G: Pemetrexed and Carboplatin With or Without Pembrolizumab as First-Line Therapy for Advanced Nonsquamous NSCLC
PRONOUNCE	Zinner RG 2015, PRONOUNCE: randomized, open-label, phase III study of first-line pemetrexed + carboplatin followed by maintenance pemetrexed versus paclitaxel + carboplatin + bevacizumab followed by maintenance bevacizumab in patients with advanced nonsquamous non-small-cell lung cancer.
BEYOND	Zhou C 2015, BEYOND: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Study of First-Line Carboplatin/Paclitaxel Plus Bevacizumab or Placebo in Chinese Patients With Advanced or Recurrent Nonsquamous Non–Small-Cell Lung Cancer.
Impower-151	Zhou C, 2025, Atezolizumab plus bevacizumab and chemotherapy in metastatic nonsquamous NSCLC: the randomized double-blind phase 3 IMpower151 trial
TASUKI-52	Lee KH, 2025, First-line nivolumab plus platinum chemotherapy and bevacizumab for advanced nonsquamous non-small cell lung cancer: A 3-year follow-up of the phase 3 randomized TASUKI-52 trial
KEYLYNK-006	Grey JE, 2025, The Phase 3 KEYLYNK-006 Study of Pembrolizumab Plus Olaparib Versus Pembrolizumab Plus Pemetrexed as Maintenance Therapy for Metastatic Nonsquamous NSCLC
PEARL	Lu S, 2025, Durvalumab Versus Chemotherapy as First-line Treatment for Metastatic NSCLC With Tumor PD-L1 Expression of 25% or Higher: Results From the Randomized Phase 3 PEARL Study

Study	Reference(s)
ONO-4538-52	Kim HR, 2023, First-line nivolumab, paclitaxel, carboplatin, and bevacizumab for advanced non-squamous non-small cell lung cancer: Updated survival analysis of the ONO-4538-52/TASUKI-52 randomized controlled trial
IMPOWER132	Nishio M, 2024, Integrated analysis of older adults and patients with renal dysfunction in the IMpower130 and IMpower132 randomized controlled trials for advanced non-squamous non-small cell lung cancer Lu S, 2023, Results from the IMpower132 China cohort: Atezolizumab plus platinum-based chemotherapy in advanced non-small cell lung cancer
HARMONIC	Bodor JN, 2025, Phase II Trial of LP-300 in Combination With Carboplatin and Pemetrexed in Never Smoker Patients With Relapsed Advanced Primary Adenocarcinoma of the Lung After Treatment With Tyrosine Kinase Inhibitors
TRITON	Skoulidis F, 2025, Rationale and design for a phase IIIb trial of first-line tremelimumab plus durvalumab versus pembrolizumab, in combination with chemotherapy, in patients with non-squamous metastatic non-small-cell lung cancer and mutations or co-mutations in STK11, KEAP1, or KRAS: the TRITON study

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

I.1 Systematic search

Not applicable

I.2 Focused search

Not applicable

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

J.1 Systematic search

Not applicable

J.2 Focused search

Not applicable

Appendix K. Reasons for confidential information

Our redactions pertain to unpublished comparative efficacy (MAIC) and comparative safety analysis (Bucher ITC) analyses conducted in the absence of head-to-head trials as well as unpublished study data extracted from the POSEIDON CSR. The MAIC and Bucher ITC analyses rely on CSR-derived inputs not available in the public domain. Public disclosure would allow competitors to appropriate our analytical approach, undermine our first-to-publish position, and prejudice ongoing and planned submissions and publications. Similarly, the CSR-sourced PROs (EQRTC QLQ-C30 and EQ-5D-5L VAS) are proprietary, unpeer-reviewed components of our internal evidence base; releasing them would expose sensitive information and enable reverse-engineering of our analyses.

Table 133. Justifications regarding confidential information

Parameter	Justification
EORTC QLQ-C30 results from the CSR	These patient-reported outcomes are unpublished CSR-derived data, and disclosure would expose proprietary evidence and compromise planned publications.
EQ-5D-5L VAS results from the CSR	These patient-reported outcomes are unpublished CSR-derived data, and disclosure would expose proprietary evidence and compromise planned publications.

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