Medicinrådet

Bilag til direkte indplacering af tislelizumab (Tevimbra) i Medicinrådets evidens-gennemgang vedrørende lægemidler til førstelinje-behandling af uhelbredelig ikke-småcellet lungekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat vedr. tislelizumab til NSCLC
2. Forhandlingsnotat fra Amgros vedr. tislelizumab til NSCLC
3. Ansøgers endelige ansøgning vedr. < tislelizumab til NSCLC

2025-10-22

Til Medicinrådet

På vegne af BeOne Medicines vil jeg takke for muligheden for at give en tilbagemelding på udkastet til tillægget til behandlingsvejledningen vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft. Tillægget omhandler tislelizumab i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel, som har indikation til førstelinjebehandling af voksne patienter med planocellulær NSCLC, der har lokalt fremskreden sygdom og ikke er kandidater til kirurgisk resektion eller platinbaseret kemoradioterapi, eller som har metastatisk NSCLC.

BeOne Medicines ønsker ligeledes at takke for en god og konstruktiv dialog med sekretariatet igennem processen og vi har noteret at Medicinrådet synes enige i de primære antagelser, der reflekteres i ansøgningen.

BeOne Medicines har et udtrykt ønske om hurtig adgang til behandling for patienter i Danmark og ser således ikke anledning til yderligere kommentarer.

Vi ser frem til Medicinrådets beslutning om anbefaling af tislelizumab

Med venlig hilsen

Nicolai Bendtsen
Director, Nordic Market Access

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

14.10.2025

LSC/DBS/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	19.11.2025
Leverandør	BeiGene
Lægemiddel	Tevimbra (tislelizumab)
Ansøgt indikation	Tevimbra i kombination med carboplatin og enten paclitaxel eller nab-paclitaxel til førstelinjebehandling af voksne patienter med planocellulær ikke-småcellet lungekræft (NSCLC) og PD-L1-ekspression ≥ 1 % og < 50 %, som har lokalt fremskreden NSCLC og ikke er kandidater til kirurgisk resektion eller platinbaseret kemoradioterapi, eller som har metastatisk NSCLC.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (direkte indplacering)

Prisinformation

Amgros har følgende priser på Tevimbra (tislelizumab):

Tabel 1: Udbudsresultat [redacted]

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Nuværende rabat ift. AIP
Tevimbra	100 mg, 1 stk.	19.315,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Tevimbra i kombination med kemoterapi indplaceres direkte i "Medicinrådets lægemiddelrekommandation og behandlingsvejledning vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft". Tevimbra forventes klinisk ligestillet med Keytruda (pembolizumab) i kombination med kemoterapi og Libtayo (cemiplimab) i kombination med kemoterapi til patienter med planocellulær NSCLC og PD-L1-ekspression ≥ 1 % og < 50 %.

Tevimbra er på nuværende tidspunkt også under vurdering i Medicinrådet til småcellet lungekræft. Der forventes at være konkurrence på denne indikation.

Tabel 2 viser lægemiddeludgiften på sammenlignelige lægemidler inkluderet i Medicinrådets behandlingsvejledning ved 24-ugers behandling for en gennemsnitlig patient med NSCLC og PD-L1-ekspression ≥ 1 % og < 50 % (jf. Tabel 11 i opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft). Lægemiddeludgiften til kemoterapi indgår ikke i udregningerne, da udgiften er på tilsvarende niveau i alle tre kombinationsbehandlinger, og udgør en minimal andel af den samlede lægemiddeludgift.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient for 24 ugers behandling

Lægemiddel	Styrke (pakningsstørrelse)	Dosering**	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. 24 ugers behandling (SAIP, DKK)
Tevimbra	100 mg (1 stk.)	200 mg (i.v.) hver 3. uge	[redacted]	[redacted]
Keytruda	25 mg/ml (4 ml)	2 mg/kg* (i.v.) hver 3. uge	[redacted]	[redacted]
Libtayo	350 mg (1 stk.)	350 mg (i.v.) hver 3. uge	[redacted]	[redacted]

*Patient vægt: 72 kg, jf. opsummering af Medicinrådets evidensgennemgang vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft.
**Udgift til kemoterapi indgår ikke i udregningen, da den er på et tilsvarende niveau i alle tre kombinationsbehandlinger.

Status fra andre lande

Tabel 3: Status fra andre lande

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

Opsummering

[redacted]

Application for the assessment of TEVIMBRA® (tislelizumab) by updating the treatment guideline for 1L squamous NSCLC with PD-L1 1-49%

Contact information

Contact information	
Name	**Nicolai Bendtsen / BeiGene**
Title	Market Access Director
Phone number	(+45) 28 12 41 16
E-mail	nicolai.bendtsen@beigene.com
Name (External representation)	**Julie Louise Lambrechtsen / Zealth**
Title	Healthcare Consultant
Phone number	(+45) 31 19 40 84
E-mail	jula@zealthcon.com
	Please note that a power of attorney has been shared

Table of contents

Tables and Figures

Figures

Abbreviations

Abbreviation	Description of abbreviation
1L	First line
AE	Adverse event
ALK	Anaplastic lymphoma kinase
AUC	Area under the curve
BICR	Blinded independent central review
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete remission
DCO	Data cut-off

DCR	Disease control rate
DMC	The Danish Medicines Council
DOR	Duration of response
DARE	Database of Abstracts of Reviews of Effects
EBM	Evidence-based medicine
EC	European Cooperative
ECOG	European Cooperative Oncology Group
ECOG-PS	European Cooperative Oncology Group performance status
EGFR	Epidermal growth factor receptor
EMC	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer quality of life questionnaire-cancer module 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer quality of life questionnaire-lung cancer module 13
EQ	EuroQol
EQ-5D-3L	EuroQol 5 dimensions 3 levels
G	Gastric
GEJ	Gastroesophageal junction
GHS	Global health status
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICF	Informed consent form
ImAE	Immune mediated adverse event
IRC	Independent review committee

ITC	Indirect treatment comparison
ITT	Intention to treat
IV	Intravenous
LS	Least square
LoT	Length of therapy
MESH	MedicaL subjects headings
mo	Months
N/A	Not applicable
NCI-CTCAE	National Cancer Institute common terminology criteria for adverse events
NE	Not estimated
n,N	Number
nPC	Nab-paclitaxel and carboplatin
NPC	Nasopharyngeal carcinoma
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OSCC	Oesophageal squamous cell carcinoma
p	Probability Value
PC	Carboplatin and paclitaxel
PD	Pharmacodynamics
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival

PICO	Population, intervention, comparator, outcome
PICOS	Population, intervention, comparator, outcome, study design
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
Q3W	Every three weeks
QLQ	Quality of Life Questionnaire
QLQ-C30	Quality of life questionnaire-cancer module 30
QLQ-LC13	Quality of life questionnaire-lung cancer module 13
QoL	Quality of life
RCT	Randomized controlled trial
RECIST	Response evaluation criteria in solid tumors
RoB	Risk of bias
RR	Relative risk
SAE	Serious Adverse Event
SCLC	Small cell lung cancer
SD	Standard Deviation
SE	Standard Error
SLR	Systematic literature review
SqNSCLC	Squamous Non-Small-Cell Lung Cancer
T	Tislelizumab
TC	Tumor Cell
TAP	Tumor area positivity
TEAE	Treatment emergent adverse event
TPS	Tumor Proportion Score
TTD	Time to discontinuation

1. Regulatory information on the pharmaceutical

Table 1: Overview of the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Tevimbra
Generic name	Tislelizumab
Therapeutic indication as defined by EMA	Tevimbra (tislelizumab) in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer (NSCLC) who have locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or patients having metastatic NSCLC.
Marketing authorization holder in Denmark	BeOne Medicines Ireland Limited 10 Earlsfort Terrace Dublin 02 T380 Ireland
ATC code	LO1FF09
Combination therapy and/or co-medication	Tevimbra (tislelizumab) plus carboplatin and either paclitaxel or nab-paclitaxel.
Date of EC approval	8th July 2024
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	NSCLC Tevimbra (tislelizumab) in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumors have programmed death ligand 1 (PD-L1) expression on ≥50% of tumor cells with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) positive mutations and who have:

Overview of the pharmaceutical	
	- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation - metastatic NSCLC Tevimbra as monotherapy is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC after prior platinum-based therapy. Patients with EGFR mutant or ALK-positive NSCLC should also have received targeted therapies before receiving tislelizumab. Gastric or gastroesophageal junction (G/GEJ) adenocarcinoma Tevimbra, in combination with platinum and fluoropyrimidine-based chemotherapy, is indicated for the first-line treatment of adult patients with human epidermal growth factor receptor-2 negative (HER2-) locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumors express PD-L1 with a tumor area positivity (TAP) score ≥ 5%. Oesophageal squamous cell carcinoma (OSCC) Tevimbra, in combination with platinum-based chemotherapy, is indicated for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumors express PD-L1 with a tumor area positivity (TAP) score ≥ 5%. Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy. Small cell lung cancer (SCLC) Tevimbra, in combination with etoposide and platinum chemotherapy, is indicated for the first-line treatment of adult patients with extensive-stage SCLC. Nasopharyngeal carcinoma (NPC) Tevimbra, in combination with gemcitabine and cisplatin, is indicated for the first-line treatment of adult patients with recurrent, not amenable to curative surgery or radiotherapy, or metastatic NPC.
Other indications that have been evaluated by the DMC (yes/no)	Recommended assessment: Tevimbra in combination with platinum-based chemotherapy as first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumors express PD-L1 with a TAP score ≥ 5%. Can be accessed here: https://medicinraadet.dk/tislelizumab-tevimbra-plus-kemoterapi-spiserorskraeft-1l Ongoing assessments: Tevimbra in combination with platinum and fluoropyrimidine-based chemotherapy for first-line treatment of adult patients with HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma

Overview of the pharmaceutical	
	whose tumors express PD-L1 with a TAP score ≥ 5%. Can be assessed here: https://medicinraadet.dk/tislelizumab-tevimbra-plus-kemoterapi-her2-negativ-adenokarcinom-1l
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Tevimbra (tislelizumab) is available as 100 mg concentrate for solution for infusion. Each milliliter of the concentrate for solution for infusion contains 10 mg of tislelizumab. Each vial of 10 ml contains 100 mg tislelizumab. Tevimbra (tislelizumab) is available in single packs containing one vial.

Abbreviations: ALK, anaplastic lymphoma kinase; CHMP, Committee for Medicinal Products for Human Use; EC, European Commission; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; G, gastric; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor-2; NSCLC, non-small-cell lung cancer; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death ligand 1; TAP, tumor area positivity.
Source: [1–3].

2. Summary table

Table 2: Summary table

Summary	
Therapeutic indication relevant for the assessment	Tevimbra (tislelizumab) in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer (NSCLC) who have locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or patients having metastatic NSCLC. This submission will focus on patients with PD-L1 expression ≥ 1 % and < 50 % as reflected in clinical question 6 in the treatment guidelines.
Dosage regiment and administration:	The recommended dose of tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks, in combination with carboplatin and either paclitaxel or nab-paclitaxel.
Choice of comparator	In this application, pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel is presented as comparator as agreed with the Danish Medicines Council and in alignment with the guideline for treating first-line NSCLC.
Most important efficacy endpoints (Difference/gain compared to comparator)	Efficacy documentation is based on the outcome measures relevant for clinical question 6 in the treatment guideline, i.e., overall survival (OS) and progression-free survival (PFS). OS and PFS are reported for both the intention to treat (ITT) population and the patient population who express PD-L1 between 1-49%

Summary	
	in the clinical trials RATIONALE-307 and KEYNOTE-407. Health-related quality of life (HRQoL) will be assessed in a narrative comparison and described in the respective sections 5.2.1 and 5.2.2. **RATIONALE-307, subgroup set PD-L1 1-49% (DCO: 30 September 2020)** Tislelizumab plus carboplatin and paclitaxel: - OS (95% CI): 26.1 months (15.2, 26.1) (HR (95% CI): 0.72 (0.32, 1.61)) - PFS (95% CI): 10.4 months (5.49, 20.04) (HR (95% CI): 0.40 (0.21, 0.76)) Tislelizumab plus carboplatin and nab-paclitaxel: - OS (95% CI): NE months (14.1, NE) (HR (95% CI): 0.73 (0.33, 1.64)) - PFS (95% CI): 10.1 months (7.39, 11.99) (HR (95% CI): 0.4 (0.22, 0.74)) Carboplatin and paclitaxel: - OS (95% CI): NE months (11.4, NE) - PFS (95% CI): 5.0 months (2.76, 6.54) **KEYNOTE-407, subgroup set PD-L1 1-49% (DCO: 23 February 2022)** Pembrolizumab plus carboplatin and (nab)paclitaxel: - OS (95% CI): 18.0 months (13.6, 22.8) (HR (95% CI): 0.61 (0.45, 0.83)) - PFS (95% CI): 8.2 months (6.2, 11.4) (HR (95% CI): 0.60 (0.45, 0.81)) Carboplatin and (nab)paclitaxel: - OS (95% CI): 13.1 months (9.1, 15.2) - PFS (95% CI): 6.0 months (4.2, 6.2)
Most important serious adverse events for the intervention and comparator	The safety data for both studies is comparable. This section will present only the relevant serious adverse events (SAEs). A qualitative description of safety data can be found in Section 5.2.6. **Serious events for Tevimbra (tislelizumab) (DCO: 30 September 2020):** In the safety population, serious TEAEs were more frequently reported in the tislelizumab plus carboplatin and paclitaxel arm compared to the control arm, including pneumonia (10.0% vs. 4.3%), pneumonitis (5.0% vs. 0.0%), and haemoptysis (3.3% vs. 0.9%). Similarly, in the tislelizumab plus carboplatin and nab-

paclitaxel arm, pneumonitis (5.9% vs. 0.0%), haemoptysis (3.4% vs. 0.9%), and febrile neutropenia (3.4% vs. 0.9%) were more frequent than in the control arm.

In the safety population, Grade 3–5 serious TEAEs in the tislelizumab plus carboplatin and paclitaxel group included febrile neutropenia (1.7%), decreased neutrophil count (3.3%), pneumonia (4.2%), and pneumonitis (2.5%). In the tislelizumab plus carboplatin and nab-paclitaxel group, the corresponding incidences were febrile neutropenia (3.4%), decreased neutrophil count (3.4%), pneumonia (5.1%), and pneumonitis (2.5%). This is compared to the carboplatin and paclitaxel alone group, where febrile neutropenia occurred in 0.9%, decreased neutrophil count in 1.7%, pneumonia in 1.7%, and no cases of pneumonitis (0.0%) were reported.

Serious adverse events for Keytruda (pembrolizumab) (DCO: 23 February 2022):

Serious adverse events are not reported for the DCO 23 February 2022. Instead Grade 3–5 TEAEs for the ITT population are reported. 74.8% (208/278) of patients receiving pembrolizumab plus chemotherapy, compared to 70.0% (196/280) in the chemotherapy-alone group experienced a Grade 3-5 TEAE. Treatment discontinuation due to adverse events occurred in 28.8% of patients in the pembrolizumab arm versus 13.2% in the control arm. The most frequent serious TEAEs (≥2%) in the pembrolizumab combination arm included febrile neutropenia (6%), pneumonia (6%), and urinary tract infection (3%).

Abbreviations: AE, adverse event; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; HRQoL, health-related quality of life; ITT, intention to treat; NE, not estimated; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; SAEs, serious adverse events.
Source:[3–6].

3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

The medical condition, patient population, and current treatment options are described in the treatment guideline '*Medicinrådets lægemiddelrekommandation vedrørende lægemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekræft'* for first-line non-small cell lung cancer (NSCLC). Tevimbra (tislelizumab) is relevant for clinical question 6, for which cemiplimab and pembrolizumab, both in combination with

chemotherapy, are recommended. For simplicity, pembrolizumab will be used as the comparator for first-line treatment of patients with squamous NSCLC and programmed death ligand 1 (PD-L1) expression ≥1% and <50%, as it is assessed as being equivalent to cemiplimab [6]. The approach has been verified by the Danish Medicines Council (DMC).

3.2 The intervention

Information on the intervention, Tevimbra (tislelizumab), is provided in the following Table 3.

Table 3: Overview of the intervention, Tevimbra (tislelizumab)

Overview of intervention	
Therapeutic indication relevant for the assessment	Tevimbra (tislelizumab) in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous non-small cell lung cancer (NSCLC) who have locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or patients having metastatic NSCLC.
Method of administration	Tevimbra (tislelizumab) is for intravenous use only.
Dosing	The recommended dose of tislelizumab is 200 mg administered by intravenous infusion once every 3 weeks.
Should the pharmaceutical be administered with other medicines?	Yes, in combination with carboplatin and either paclitaxel or nab-paclitaxel.
Treatment duration / criteria for end of treatment	Treatment until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Patients should be monitored for signs and symptoms of infusion-related reactions.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	The assessment of PD-L1 expression confirmed by a validated test is required for tislelizumab and pembrolizumab, however, costs associated with these tests are not described, as this application does not include any health economic model.
Package size(s)	Tevimbra (tislelizumab) is available as 100 mg concentrate for solution for infusion. Each milliliter of the concentrate for solution for infusion contains 10 mg of tislelizumab. Tevimbra (tislelizumab) is available in single packs containing one vial.

Abbreviations: NSCLC, non-small-cell lung cancer; PD-L1, programmed death ligand 1.
Source: [1–3].

3.2.1 The intervention in relation to Danish clinical practice

Tislelizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel is expected to be used as first-line treatment for patients with squamous NSCLC and PD-L1 expression ≥1% and <50%, in line with clinical question 6 of the DMC treatment guideline for first-line treatment of squamous NSCLC [6].

4. Overview of literature

A clinical systematic literature review (SLR) was conducted in the following databases: Embase®, MEDLINE®, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews, and the Health Technology Assessment database [5]. The objective of the SLR was, among others, to identify the evidence from randomized control trials (RCTs) with respect to efficacy, health-related quality of life (HRQoL), safety, and tolerability outcomes of platinum-based chemotherapy, immunotherapy, and targeted therapy for advanced, metastatic, newly diagnosed or recurrent NSCLC patients. The search appeared on the 24th of July 2024, and the DMC has accepted that the search has been conducted more than one year ago at the submission date (6 days in total).

In the Table 4, relevant studies for the submission can be found. A detailed description of the SLR is provided in Appendix D.

Ongoing trials

To ensure all relevant trials are captured, a search for active or unpublished trials that include the intervention and comparator on the intended patient population was conducted on the 13th of March 2025 on Clinicaltrials.gov and the European Union (EU) Clinical Trials Register. In the EU Clinical Trials Register, a search with a search combination of *non-small cell lung cancer AND tislelizumab AND pembrolizumab* is performed. Whereas in Clinicaltrials.gov, a search combination of *Non-small Cell Lung Cancer AND Tislelizumab AND Pembrolizumab* is performed. The searches resulted in no relevant hits for this specific population and treatment options.

Table 4: Overview of study design for studies included in the comparison for efficacy and safety

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
RATIONALE-307, NCT03594747 Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non–Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial -Wang J et al. (2021) [7] Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III	Open-label, randomized, multicenter phase III study	Patients were treated with tislelizumab until disease progression, unacceptable toxicity, or other discontinuation criteria were met	The trial was initiated in July 2018, and the last patient was randomized on 30 September 2020, with study completion date on April 28, 2023 Primary efficacy analysis: data cut-off date 6th December 2019 Final analysis: data cut-off 30th September 2020 Extended data cut-off: 28th April 2023	Adult patients with untreated, histologically confirmed, locally advanced or metastatic squamous NSCLC with ECOG-PS ≥1.	Arm A: Tislelizumab 200 milligrams (mg) plus paclitaxel 175 mg/m^2 and carboplatin AUC 5 on Day 1 administered IV Q3W. Arm B: Tislelizumab 200 mg on Day 1 plus nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 and carboplatin AUC 5 on Day 1 IV Q3W.	Arm C: Paclitaxel 175 mg/m^2 and carboplatin AUC 5 on Day 1 IV Q3W	6	**Primary outcomes:** Progression-free survival (PFS) by IRC per RECIST v1.1 or death, whichever occurs first, as of data cut-off 30SEP2020 (2 years, 2 months) **Secondary outcomes*:** OS through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) PFS by investigator assessment through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) PFS by IRC based on PD-L1 expression through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) EORTC QLQ-LC13, from baseline to cycle 5 EORTC QLQ-C30, from baseline to cycle 5

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
RATIONALE-307 trial - Wang J et al. (2024) [8] Data on file from BeiGene, as some data are not reported in the publications [5]								Number of participants with adverse events, from first dose to 30 days after the last dose, according to NCI-CTCAE v5.0
KEYNOTE-407, NCT02775435 A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients with Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407 - Paz-Ares et al. (2020) [9]	Double-blinded, randomized, multicenter phase III study	Participants received treatment or placebo for up to 2 years. Participants in the pembrolizumab arm with documented disease progression could receive second course of treatment for 1 year, and	The trial was initiated on June 9th, 2016 and completed on September 14th, 2023. Primary efficacy analysis cut-off: 7.8 months Final baseline analysis cut-off: 9th May 2019 (14.3 months)	Adult patients with untreated, histologically or cytologically confirmed diagnosis of stage IV squamous NSCLC.	Participants received pembrolizumab 200 mg IV prior to chemotherapy on Day 1 of each cycle (Q3W) for up to 35 cycles (~ 2 years) AND investigator's choice of paclitaxel (200 mg/m^2 IV on Day 1 of each cycle for 4 cycles) OR nab-paclitaxel (100	Participants received normal saline as placebo IV prior to chemotherapy on Day 1 of each cycle (Q3W) for up to 35 cycles (~ 2 years) AND paclitaxel (200 mg/m^2 IV on Day 1 of each cycle for 4 cycles) OR nab-paclitaxel (100 mg/m^2 IV on Days 1, 8, 15	6	**Primary outcomes:** PFS as assessed by blinded independent central review per RECIST 1.1 (up to approximately 19 months) OS, defined as time from randomization to death (up to approximately 19 months) **Secondary outcomes:** Number of patients experiencing an adverse event (up to approximately 83 months) Number of patients discontinuing study treatment due to an adverse event (up to approximately 29 months)

Trial name, NCT identifier and reference (Full citation incl. reference number)	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study - Novello et al. (2023) [10]		patients in the placebo arm could switch over to pembrolizumab for up to 2 years.	Extended analysis cut off: 40.1 months 5-year follow-up cut-off: 23 February 2022 (56.9 months)		mg/m^2 IV on Days 1, 8, 15 of each cycle for 4 cycles) AND carboplatin AUC 6 IV on Day 1 of each cycle for 4 cycles.	of each cycle for 4 cycles) AND carboplatin AUC 6 IV on Day 1 of each cycle for 4 cycles.		EORTC QLQ-LC13, from baseline to week 9 and 18 EORTC QLQ-C30, from baseline to week 9 and 18 EQ-5D-3L, from baseline to week 9 and 18

*Data are captured until 28th April 2023, however, this application reports data from DCO 30th September 2020 due to confidentiality.
Abbreviations: AUC, area under the curve; DOR, duration of response; ECOG-PS Eastern Cooperative Oncology Group performance status; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire-cancer module 30; EORTC QLQ-LC13, European Organization for Research and Treatment of Cancer quality of life questionnaire-lung cancer module 13; IRC, independent review committee; IV, intravenous; NCI-CTCAE, National Cancer Institute common terminology criteria for adverse events; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival; PICO, population, intervention, comparator, outcome; Q3W, every three weeks; RECIST, response evaluation criteria in solid tumors.
Source: [5,7-10].

5. Clinical question 6

5.1 Efficacy of tislelizumab in combination with chemotherapy compared to pembrolizumab for squamous NSCLC with PD-L1 expression ≥1 % and < 50 %

5.1.1 Relevant studies

Studies relevant to this clinical question are presented in Table 4. The population relevant for the treatment guideline is patients with squamous NSCLC and PD-L1 expression ≥ 1% and < 50% [6].

Both the RATIONALE-307 and KEYNOTE-407 studies present subgroup-specific analyses based on PD-L1 expression levels. In these studies, different PD-L1 expression thresholds have been considered, and for the purpose of this clinical question, the focus is on patients with PD-L1 expression levels of ≥1% and <50%. Both studies report this specific subgroup as patients with PD-L1 expression between 1% and 49% [6,8,9]. Therefore, in the context of this application, references to this subgroup will be made using the designation PD-L1 1-49% to ensure consistency with the reported data.

5.1.2 Comparability of studies

This section addresses the comparability between RATIONALE-307 and KEYNOTE-407. Both studies are multicenter, randomized, controlled phase III trials that include an immunotherapy treatment arm combined with carboplatin and either paclitaxel or nab-paclitaxel. Both studies report the relevant endpoints for this submission, i.e., progression-free survival (PFS), overall survival (OS), EORTC QLQ-C30 and safety [8–10].

Both the RATIONALE-307 and KEYNOTE-407 trials recruited adult patients with confirmed squamous NSCLC in the first-line setting. All patients had measurable disease according to response evaluation criteria in solid tumors (RECIST) v1.1. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 were considered. Both trials required tumor tissue samples at enrollment for PD-L1 status assessment. Furthermore, both age at baseline and number of smokers is consistent across the trials, with a median age ranging from 60-65 years and between 80% and 93.2% of patients who are currently or former smokers, representing the primary part of the study population. Efficacy outcomes are reported by disease subtype; however, baseline characteristics and safety outcomes are reported for all patients.

- Sample size: The sample size is higher in KEYNOTE-407 (intention to treat (ITT) population: 558, subgroup PD-L1 1-49%: 207 (approximately 37% of total population)), compared to RATIONALE-307 (ITT population: 360, subgroup PD-L1 1-49%: 91 (approximately 25% of total population)). This difference is not considered to significantly impact the indirect comparison, as both studies

maintain sufficient statistical power and report relevant efficacy and safety outcomes for the relevant patient group [11]. This consideration is validated by a Danish clinical expert.

- Stratification factors: In RATIONALE-307, patients are stratified based on disease stage and PD-L1 expression, whereas patients in KEYNOTE-407 are stratified based on choice of taxane-chemotherapy, geographic region, and PD-L1 expression [8–10]. The difference in stratification factors does not have an influence on the comparability between the studies regarding this application. The assumption is validated by a clinical expert.
- PD-L1 score: Different assays are used to evaluate the PD-L1 expression in the studies; VENTANA PD-L1 (SP263) assay for tislelizumab and PD-L1 IHC 22C3 pharmDx for pembrolizumab [7,9]. In the KEYNOTE-407 study the tumor PD-L1 expression is assessed at a central laboratory before randomization, likewise in RATIONALE-307 the tumor PD-L1 score is assessed before randomization using an interactive response technology system. Additionally, in RATIONALE-307 PD-L1 is assessed by tumor cell (TC) PD-L1 score, which categorize patients in the study based on the proportion of PD-L1-positive tumor cells in <1%, 1-49%, and ≥50%. In KEYNOTE-407 PD-L1 is assessed by tumor proportion score (TPS), which represents the percentage of viable tumor cells demonstrating partial or complete PD-L1 staining. Here the standard PD-L1 cut-offs in clinical evaluation include ≥1% and ≥50%, but presenting results divided in three stratifications (<1%, 1-49% and ≥50%) [8–10,12]. Both methods are standard practice, with TPS more widely used in Danish clinical practice. A systematic review of several studies investigated analytical concordance of the assays, highlighting high concordance between 22C3 and SP263-based assays in lung cancer when used to assess PD-L1 expression on tumor cells [13]. This is validated by a clinical expert.
- Treatment Regimen: Both studies evaluate the combination of a PD-1 inhibitor combined with chemotherapy. RATIONALE-307 involves a three-arm design, comparing two intervention arms (Arm A: Tislelizumab plus carboplatin and paclitaxel, and Arm B: Tislelizumab plus carboplatin and nab-paclitaxel) with one placebo arm [8]. In contrast, KEYNOTE-407 features a two-arm design, where pembrolizumab is combined with carboplatin and either paclitaxel or nab-paclitaxel is compared to placebo [10]. Both studies include a relevant and comparable comparator arm, enabling assessment of comparability analysis. The treatment follows the standard use of chemotherapy in Denmark meaning that the difference in study design, whether three arms or two arms respectively, does not need to be adjusted for in terms of comparability. This is validated by a Danish clinical expert.
- Dosage and administration: Both studies reflected a similar dosage of chemotherapy as well as the two different interventions [8–10]. In KEYNOTE-407, the patients are treated with 200mg pembrolizumab or placebo plus carboplatin and paclitaxel/nab-paclitaxel once every 3 weeks for four cycles. Patients in RATIONALE-307 are treated with 21-day cycles of respective treatment as followed; arm A: tislelizumab (200 mg, day 1) plus paclitaxel (175

mg/m2, day 1) and carboplatin (AUC of 5, day 1), arm B: tislelizumab (200 mg, day 1) plus nab-paclitaxel (100mg/m2, days 1, 8, and 15) and carboplatin (AUC of 5, day 1), and arm C: paclitaxel (175 mg/m2, day 1) and carboplatin (AUC of 5, day 1). Chemotherapies were administered for 4-6 cycles, at the investigator's discretion.

- Cross-over: Both studies allowed cross-over from placebo to active treatment upon disease progression, resulting in a proportion of control arm patients receiving either tislelizumab or pembrolizumab, respectively. In KEYNOTE-407 DCO 2022, the cross-over rate is 50.9%, with 117 patients crossing to pembrolizumab and an additional 26 patients receiving subsequent anti-PD-L1 therapy outside the study [10]. In RATIONALE-307, the cross-over rate is reported at 36.0% at the 2020 DCO, with a median time to cross-over of 25.9 weeks; this metric is not reported for KEYNOTE-407 [5]. While the cross-over rates differ between studies, both trials allows cross-over under similar clinical circumstances, ensuring a comparable study design. KEYNOTE-407 applies mathematical methods to adjust for the impact of cross-over, whereas no adjusted analyses are reported for RATIONALE-307. Although cross-over could theoretically influence survival outcomes, it remains uncertain whether the observed differences have any meaningful impact. This is validated by a clinical expert. Given the randomized designs and the comparable cross-over approach, the impact on the indirect comparison is considered limited. No cross-over-adjusted hazard ratios for OS will be used to inform the indirect comparison.
- Follow-up duration: Both RATIONALE-307 and KEYNOTE-407 provided multiple data cut-offs. KEYNOTE-407 has a follow-up period, extending to a 5-year analysis with a median follow-up of 56.9 months, whereas RATIONALE-307's maximum follow-up of 44.8 months. However, in this application data from the final analysis (18.7 months) will be used, as data from the most recent DCO is confidential and not publicly available. Additionally, both studies show similar trends in prespecified initial follow-up durations, with their primary efficacy analyses conducted at approximately 7-8 months (8.6 months and 7.8 months for RATIONALE-307 and KEYNOTE-407, respectively) and their final analyses at 14-16 months (16.7 months and 14.3 months for RATIONALE-307 and KEYNOTE-407, respectively) [5,8–10]. Both extended follow-ups are considered adequately long to capture relevant events, however, the extended follow-up period for KEYNOTE-407 may allow for a more comprehensive evaluation of long-term effects and late-emerging impacts.
- Blinding: RATIONALE-307 is an open-label trial, whereas KEYNOTE-407 is a double-blinded trial. While blinding can reduce the risk of bias, particularly in subjective outcomes (e.g., HRQoL), the primary efficacy outcomes in both studies are objective measures. The difference in blinding is not expected to have a significant impact on the validity of the efficacy measures in this assessment. There is a chance that the difference in blinding can influence the reporting of safety outcomes; however, the difference is not expected to have

influence in this case as the two trials report safety and efficacy quite similarly. This is validated by a clinical expert.

- Number of men: Proportion of male participants ranged from 79.1% in RATIONALE-307 to 94.1% in KEYNOTE-407 [7,9]. The 15% higher inclusion of men compared to women in the studies is unlikely to significantly affect the results. This is validated by a clinical expert.
- Disease stage: In RATIONALE-307, patients with local advanced (stage IIIB) or metastatic (stage IV) squamous NSCLC are included, where KEYNOTE-407 included patients with metastatic (stage IV) squamous NSCLC. RATIONALE-307 has a higher percentage of stage IV patients, ranging from 63.6%-68.3%, compared to 31.7%-36.4% for stage IIIB patients, making the two study populations more comparable [5,9]. According to the clinical expert, this difference in stage is not considered significant, as the treatments are effective in both stages.
- Prior treatment: In RATIONALE-307, patients who have received prior neoadjuvant or adjuvant chemotherapy, radiotherapy, or chemoradiotherapy for non-metastatic disease are required to have a disease-free interval of at least 6 months before randomization [5]. In KEYNOTE-407, patients who receive previous systemic therapy for metastatic disease are ineligible [14]. This was not considered to have a reasonable influence on the comparability, which is validated by a clinical expert.

Despite the differences, the trials are considered sufficiently similar to derive reasonable estimates of comparative efficacy using a Bucher analysis for an indirect treatment comparison (ITC). According to the clinical expert, the studies are very similar, and an unadjusted comparable analysis can be justified.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Table 5: Baseline characteristics of patients included in studies (ITT population) for the comparative analysis of efficacy and safety

	RATIONALE-307 [7]			KEYNOTE-407 [9]	
	Tislelizumab plus carboplatin and paclitaxel (N=120)	Tislelizumab plus carboplatin and nab-paclitaxel (N=119)	Placebo plus carboplatin and paclitaxel (N=121)	Pembrolizumab plus carboplatin and (nab)-paclitaxel (N= 278)	Placebo plus carboplatin and (nab)-paclitaxel (N= 281)
Age, median (range)	60 (41-74)	63 (38-74)	62 (34-74)	65 (29-87)	65 (36-88)
Gender					

	RATIONALE-307 [7]			KEYNOTE-407 [9]	
	Tislelizumab plus carboplatin and paclitaxel (N=120)	Tislelizumab plus carboplatin and nab-paclitaxel (N=119)	Placebo plus carboplatin and paclitaxel (N=121)	Pembrolizumab plus carboplatin and (nab)-paclitaxel (N= 278)	Placebo plus carboplatin and (nab)-paclitaxel (N= 281)
Men, n (%)	107 (89.2)	112 (94.1)	111 (91.7)	220 (79.1)	235 (83.6)
Smoking status, n (%)					
Current/former	96 (80.0)	107 (89.9)	98 (81.0)	256 (92.1)	262 (93.2)
Never	24 (20.0)	12 (10.1)	23 (19.0)	22 (7.9)	19 (6.8)
Region of enrollment, n (%)					
East Asia	120 (100)	119 (100)	121 (100)	54 (19.4)	52 (18.5)
Rest of the world	0 (0)	0 (0)	0 (0)	224 (80.6)	229 (81.5)
ECOG status, n (%)					
0	31 (25.8)	22 (18.5)	32 (26.4)	73 (26.3)	90 (32.0)
1	89 (74.2)	97 (81.5)	89 (73.6)	205 (73.7)	191 (68.0)
Histology, n (%)					
Squamous	NR			272 (97,8)	274 (97,5)
Adeno squamous				6 (2.2)	7 (2.5)
Solid tumor stage, n (%)					
Stage IIIB	38 (31.7)	40 (33.6)	44 (36.4)	N/A	
Stage IV	82 (68.3)	79 (66.4)	77 (63.6)	278 (100)	281 (100)
PD-L1 expression on tumor cells, n (%)					
<1%	48 (40.0)	47 (39.5)	49 (40.5)	95 (34.2)	99 (35.2)
1-49%	30 (25.0)	30 (25.2)	31 (25.6)	103 (37.1)	104 (37.0)
≥50%	42 (35.0)	42 (35.3)	41 (33.9)	73 (26.3)	73 (26.0)

	RATIONALE-307 [7]			KEYNOTE-407 [9]	
	Tislelizumab plus carboplatin and paclitaxel (N=120)	Tislelizumab plus carboplatin and nab-paclitaxel (N=119)	Placebo plus carboplatin and paclitaxel (N=121)	Pembrolizumab plus carboplatin and (nab)-paclitaxel (N= 278)	Placebo plus carboplatin and (nab)-paclitaxel (N= 281)
Confirmed distant metastatic site(s), n (%)					
Bone	24 (20.0)	16 (13.4)	21 (17.4)	NR	
Liver	15 (12.5)	15 (12.6)	14 (11.6)		
Brain	2 (1.7)	3 (2.5)	1 (0.8)	20 (7.2)	24 (8.5)
Taxane chemotherapy, n (%)					
Paclitaxel	120 (100%)	0 (0%)	121 (100%)	169 (60.8)	167 (59.4)
Nab-Paclitaxel	0 (0%)	119 (100%)	0 (0%)	109 (39.2)	114 (40.6)

Data cut-off: 30th September 2020

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NR, not reported; PD-L1, programmed death ligand 1.

In addition, subgroup specific baseline characteristics for RATIONALE-307 can be found in Table 6. No subgroup specific baseline characteristics for KEYNOTE-407 were found publicly available.

Table 6: Baseline characteristics of patients included in studies (subgroup PD-L1 1-49% population) for the comparative analysis of efficacy and safety

	RATIONALE-307 [5]		
	Tislelizumab plus carboplatin and paclitaxel (N=30)	Tislelizumab plus carboplatin and nab-paclitaxel (N=30)	Placebo plus carboplatin and paclitaxel (N=31)
Age, median (range)	[redacted]	[redacted]	[redacted]
Gender			
Men, n (%)	[redacted]	[redacted]	[redacted]
Smoking status, n (%)			
Current	[redacted]	[redacted]	[redacted]

	RATIONALE-307[5]		
	Tislelizumab plus carboplatin and paclitaxel (N=30)	Tislelizumab plus carboplatin and nab-paclitaxel (N=30)	Placebo plus carboplatin and paclitaxel (N=31)
Former	[redacted]	[redacted]	[redacted]
Never	[redacted]	[redacted]	[redacted]
Region of enrollment, n (%)			
East Asia	[redacted]	[redacted]	[redacted]
Rest of the world	[redacted]	[redacted]	[redacted]
ECOG status, n (%)			
0	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]
Histology, n (%)			
Squamous	N/A		
Adeno squamous			
Solid tumor stage, n (%)			
Stage IIIB	N/A		
Stage IV			
PD-L1 expression on tumor cells, n (%)			
<1%	[redacted]	[redacted]	[redacted]
1-49%	[redacted]	[redacted]	[redacted]
≥50%	[redacted]	[redacted]	[redacted]
Confirmed distant metastatic site(s), n (%)			
Bone	N/A		

	RATIONALE-307[5]		
	Tislelizumab plus carboplatin and paclitaxel (N=30)	Tislelizumab plus carboplatin and nab-paclitaxel (N=30)	Placebo plus carboplatin and paclitaxel (N=31)
Liver			
Brain			
Taxane chemotherapy, n (%)			
Paclitaxel	[redacted]	[redacted]	[redacted]
Nab-Paclitaxel	[redacted]	[redacted]	[redacted]

Comparability of patients to a Danish setting

The patient populations in the two studies are representative of the Danish patient population that is eligible for first-line treatment. See Section 5.1.2 for a detailed analysis of the differences between the two studies and their comparability. Baseline characteristics for both studies are listed in Table 5 above.

Only age and proportion of women differ slightly from the Danish population. The median age of the included patients in the two studies is slightly lower than in Denmark (70-71 years vs. 60-65 years in the studies), and the proportion of women included in the studies are lower than the expected proportion of women with first-line squamous NSCLC as assessed by the DMC in the treatment guideline (about 50% vs. about 6-21% in the studies) [6]. Overall, the population in RATIONALE-307 is considered comparable to the Danish population, as individual differences are minor. The mean age is not substantially lower and analyses of treatment effect by sex have not revealed any clinically relevant differences. This assumption is validated by a clinical expert.

5.1.4 Subsequent treatment

In both KEYNOTE-407 and RATIONALE-307, patients are allowed to receive further systemic anticancer treatment following disease progression. The distribution of subsequent therapies, including cross-over to immunotherapy, is summarized in the table below for each study arm and treatment line.

In the RATIONALE-307 study, patients in the placebo plus paclitaxel and carboplatin could receive tislelizumab as monotherapy if they are determined to have an independent review committee confirmed disease progression. At the data cut-off on 30th of September 2020, 43 patients corresponding to 35.8% in the tislelizumab plus paclitaxel and carboplatin, 42 patients corresponding to 35.3% in the tislelizumab plus nab-paclitaxel and carboplatin, and 80 patients corresponding to 66.1% in the placebo

plus paclitaxel and carboplatin receive subsequent anticancer therapy. The proportion is particularly high in placebo plus paclitaxel and carboplatin, where 74 patients receive immunotherapy, and among these 68 patients (56.2%) cross over to tislelizumab following disease progression [5]. An overview of subsequent therapy in RATIONALE-307 can be found in Table 7.

Table 7: Subsequent therapy in RATIONALE-307 (DCO 2020)

	Tislelizumab plus paclitaxel and carboplatin	Tislelizumab plus nab-paclitaxel and carboplatin	Placebo plus paclitaxel and carboplatin
Any subsequent therapy, n (%)	43 (35.8%)	42 (35.3%)	80 (66.1%)
Subsequent immunotherapy, n (%)	–	–	74 (61.2%)
Crossover to tislelizumab, n (%)	–	–	68 (56.2%)
Median time from randomisation to crossover (weeks)	–	–	25.9
Median time from end of treatment to crossover (weeks)	–	–	10.1

Source: [5]

In the KEYNOTE-407 study, subsequent anticancer therapy was administered to 109 patients in the pembrolizumab plus paclitaxel and carboplatin group, of whom 33 received anti–PD-(L)1 therapy, including 12 patients who initiated a second course of pembrolizumab on-study. In the placebo plus paclitaxel and carboplatin group, 172 patients received subsequent therapy; 117 of these crossed over to pembrolizumab monotherapy on-study, while an additional 26 patients received anti–PD-(L)1 therapy outside the study, resulting in an effective crossover rate of 50.9%. Furthermore, 55 patients in the pembrolizumab plus chemotherapy group completed the planned 35 cycles of pembrolizumab, and 12 patients began a second treatment course with pembrolizumab [10]. In Table 8 an overview of the subsequent treatment in KEYNOTE-407 is depicted.

Table 8: Subsequent therapy in KEYNOTE-407 (DCO 2023)

Subsequent therapy	Pembrolizumab + paclitaxel and carboplatin (n=278)	Placebo + paclitaxel and carboplatin (n=280)

Any subsequent pharmacologic therapy	109 (39.2%)	172 (61.4%)
Anti–PD-(L)1 therapy	33 (11.9%)[a]	143 (51.1%)
On-study crossover to pembrolizumab	0	117 (41.8%)
Pembrolizumab (outside of study crossover)	7 (2.5%)	4 (1.4%)
Other anti–PD-(L)1 antibodies	5 (1.8%)	15 (5.4%)
Platinum-based chemotherapy (doublet ± third agent)	39 (14.0%)	14 (5.0%)
Non-platinum single-agent chemotherapy	50 (18.0%)	19 (6.8%)
Other regimens (VEGFR2 inhibitor combinations, TKIs, etc.)	12 (4.3%)	9 (3.2%)
Completed 35 cycles of pembrolizumab	55 (19.8%)	–
Second course of pembrolizumab	12 (4.3%)	–

The complete table is available in the published article by Novello et al. (2023). Source:[10]

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per RATIONALE-307

RATIONALE-307 evaluated the efficacy and safety of first-line treatment with either tislelizumab plus carboplatin and paclitaxel, tislelizumab plus carboplatin and nab-paclitaxel, or placebo plus carboplatin and paclitaxel in patients with advanced or metastatic squamous NSCLC [7]. The main objective is to compare PFS as assessed by the Independent Review Committee (IRC) per RECIST v1.1 in the ITT analysis set. Furthermore, both OS, adverse events (AEs), and discontinuation due to AEs are reported in the study. Several cut-offs are reported with two pre-specified analyses, together with one extension planned in the study design:

- Interim analysis, data cut-off date of 6th December 2019, in which the primary study endpoint was tested for significance.

- Final analysis data, cut-off date of 30th September 2020, where there was no subsequent significance testing of the primary endpoint, and the p-values are descriptive.
- An extended follow-up analysis was performed at study completion (data cut-off 28th April 2023), with no subsequent significance testing and with descriptive p-values. (Data not published or publicly available)

Both safety and efficacy data are available at multiple cut-offs, however, as the data for the extended follow-up of RATIONALE-307 is not yet publicly available, data will be presented for the final analysis, DCO of 30th September 2020.

Data will be presented for both the ITT population, the specific subgroup with PD-L1 1-49%, and the safety population. However, whenever possible, data for the subgroup PD-L1 1-49% will be presented.

A relative risk (RR) is calculated for comparing the incidence of safety events between the treatment groups. This provides a measure of the relative likelihood of an event occurring in the treatment group compared to the control group. The RR is presented together with a 95% CI to assess the uncertainty and statistical significance associated with the estimate.

5.2.1.1 ITT population – RATIONALE-307

For the ITT population, the efficacy outcomes demonstrate a clear benefit of tislelizumab plus carboplatin and either paclitaxel or nab-paclitaxel over placebo plus carboplatin and paclitaxel in terms of both OS and PFS.

Final analysis - data cut-off 30th of September 2020
Overall survival

At the final data cut-off, OS data demonstrates a favorable trend towards improved survival with tislelizumab plus chemotherapy compared to chemotherapy alone. In the arm receiving tislelizumab plus carboplatin and paclitaxel, the stratified OS HR versus Arm C is 0.68 (95% CI: 0.46, 1.01). In the tislelizumab plus carboplatin and nab-paclitaxel, the stratified OS HR is 0.75 (95% CI: 0.50, 1.12). The stratification factors involved disease stage (IIIB and IV) and PD-L1 expression in TCs. Although the differences are not statistically significant at this cut-off, the trends favored the tislelizumab arms. Median OS is 22.8 months (95% CI: 19.1, 26.1) for tislelizumab plus carboplatin and paclitaxel, NE (95% CI: 18.6, NE) for tislelizumab plus carboplatin and nab-paclitaxel, and 20.2 months (95% CI: 16.0, NE) for carboplatin and paclitaxel, see Figure 1 and Figure 2 [8].

In the RATIONALE-307 ITT population, the 12-months OS rate is 72.7% (95% CI: 63.7, 79.9) corresponding to 87 patients in the tislelizumab plus carboplatin and paclitaxel arm, 77.3% (95% CI: 68.4, 83.9) corresponding to 93 patients alive in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 71.4% (95% CI: 61.9, 79.0) corresponding to 86 patients in the placebo plus carboplatin and paclitaxel arm. At 18-months, the OS rate was 63.2% (95% CI: 53.8, 71.2) corresponding to 75 patients in the tislelizumab plus carboplatin and paclitaxel arm, 62.0% (95% CI: 52.1, 70.4) corresponding to 75 patients

in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 55.7% (95% CI: 45.3, 64.8) corresponding to 67 patients in the placebo plus carboplatin and paclitaxel arm [5].

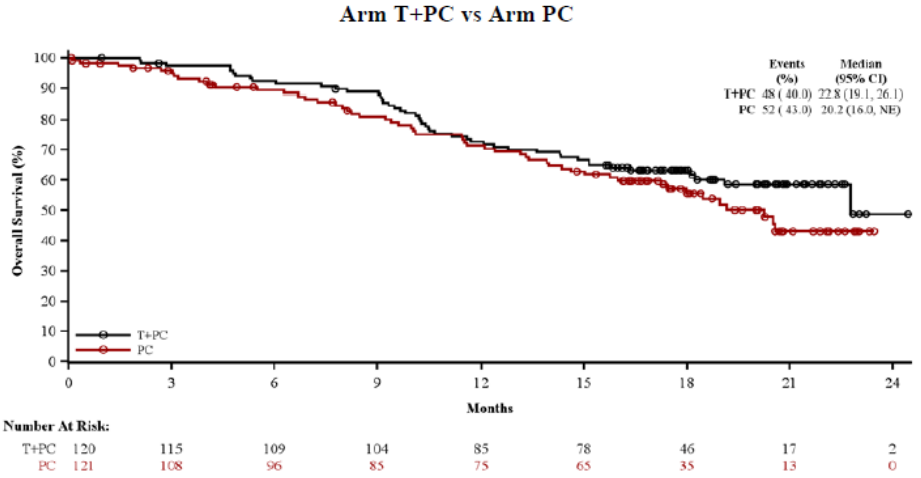


Figure 1: Kaplan-Meier plot of OS (ITT analysis set) for Arm A: tislelizumab plus carboplatin and paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307 (DCO: 2020)

Data cut-off: 30 September 2020
Abbreviations: CI, confidence interval; PC, carboplatin and paclitaxel; T, tislelizumab.
Source: [5].

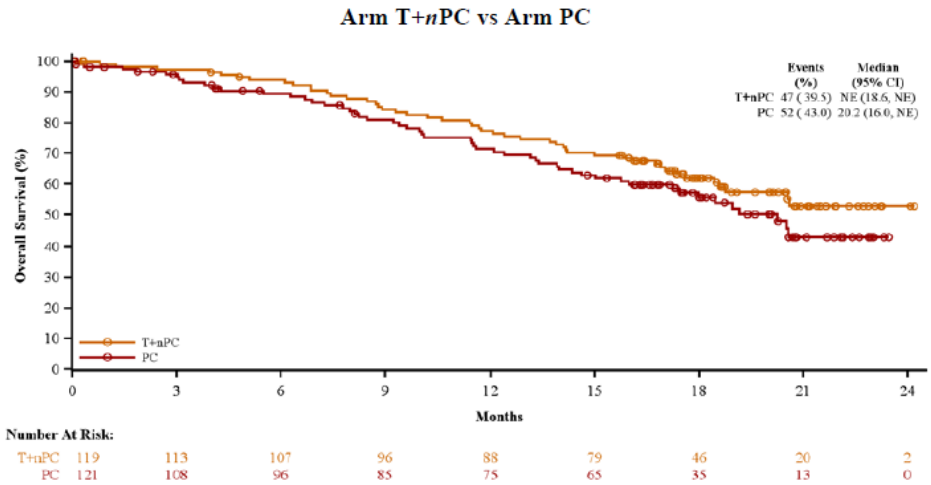


Figure 2: Kaplan-Meier plot of OS (ITT analysis set) for Arm A: tislelizumab plus carboplatin and paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307 (DCO:2020)

Data cut-off: 30 September 2020
Abbreviations: CI, confidence interval; PC, carboplatin and paclitaxel; T, tislelizumab.
Source: [5].

Progression-free survival

At the final data cut-off, a total of 245 IRC-assessed PFS events occurred across all treatment arms. Improvement in PFS is demonstrated for both the tislelizumab plus carboplatin and paclitaxel arm and the tislelizumab plus carboplatin and nab-paclitaxel

arm compared to the carboplatin and paclitaxel arm. For Arm A, the stratified PFS HR versus Arm C is 0.45 (95% CI: 0.33, 0.62), and for Arm B versus Arm C, the HR is 0.43 (95% CI: 0.31, 0.60). Both results are highly statistically significant ($P < 0.0001$). Median PFS is 7.7 months (95% CI: 6.7, 10.4) for Arm A and 9.6 months (95% CI: 7.4, 10.8) for Arm B, compared with 5.5 months (95% CI: 4.2, 5.6) in Arm C. These results confirm a substantial improvement in PFS with the addition of tislelizumab to platinum-based chemotherapy in the first-line treatment of advanced squamous NSCLC, see Figure 3 and Figure 4 [8].

In the RATIONALE-307 ITT-population, the PFS rate at 12-months is 36.5% (27.58, 45.44) corresponding to 44 patients in the tislelizumab plus carboplatin and paclitaxel, the PFS rate in the tislelizumab plus carboplatin and nab-paclitaxel is 33.1% (24.21, 42,26) corresponding to 40 patients. In the comparator arm, placebo plus carboplatin and (nab)-paclitaxel, the PFS rate at 12-months is 9.5% (4.48, 16.79) corresponding to 11 patients at 12-months. At 18 months, the PFS rate for the tislelizumab plus carboplatin and paclitaxel arm was 29.4% (20.79, 38.42), corresponding to 35 patients; in the tislelizumab plus carboplatin and nab-paclitaxel arm the PFS rate was 27.1% (18.70, 36.24), corresponding to 33 patients, and in the comparator arm the PFS rate was 6.8% (2.66, 13.58), corresponding to 8 patients [5].

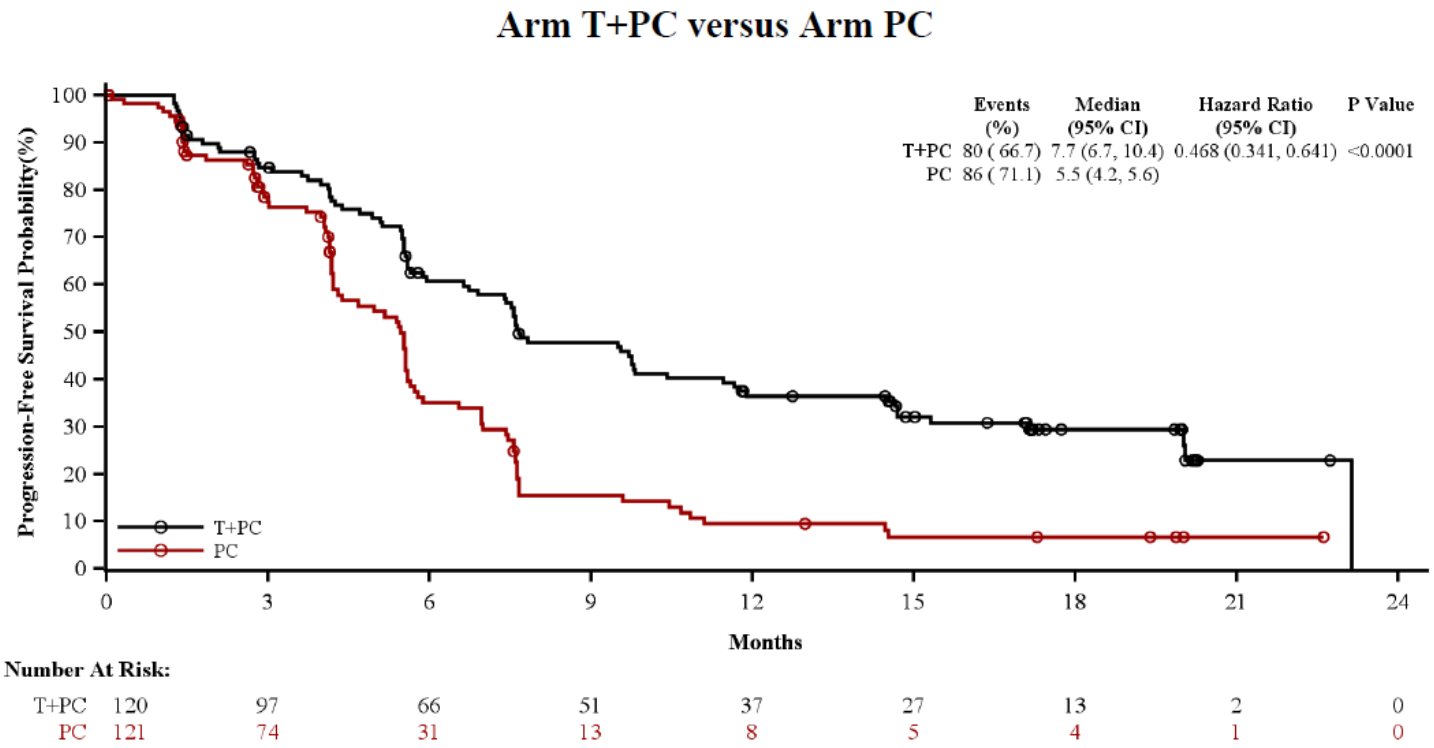


Figure 3: Kaplan-Meier plot of PFS (ITT analysis set) for Arm A: tislelizumab plus carboplatin and paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307 (DCO: 2020)

Data cut-off: 30 September 2020, Unstratified Hazard ratio (HR).

Abbreviations: CI, confidence interval; PC, carboplatin and paclitaxel; T, tislelizumab.

Source: [5].

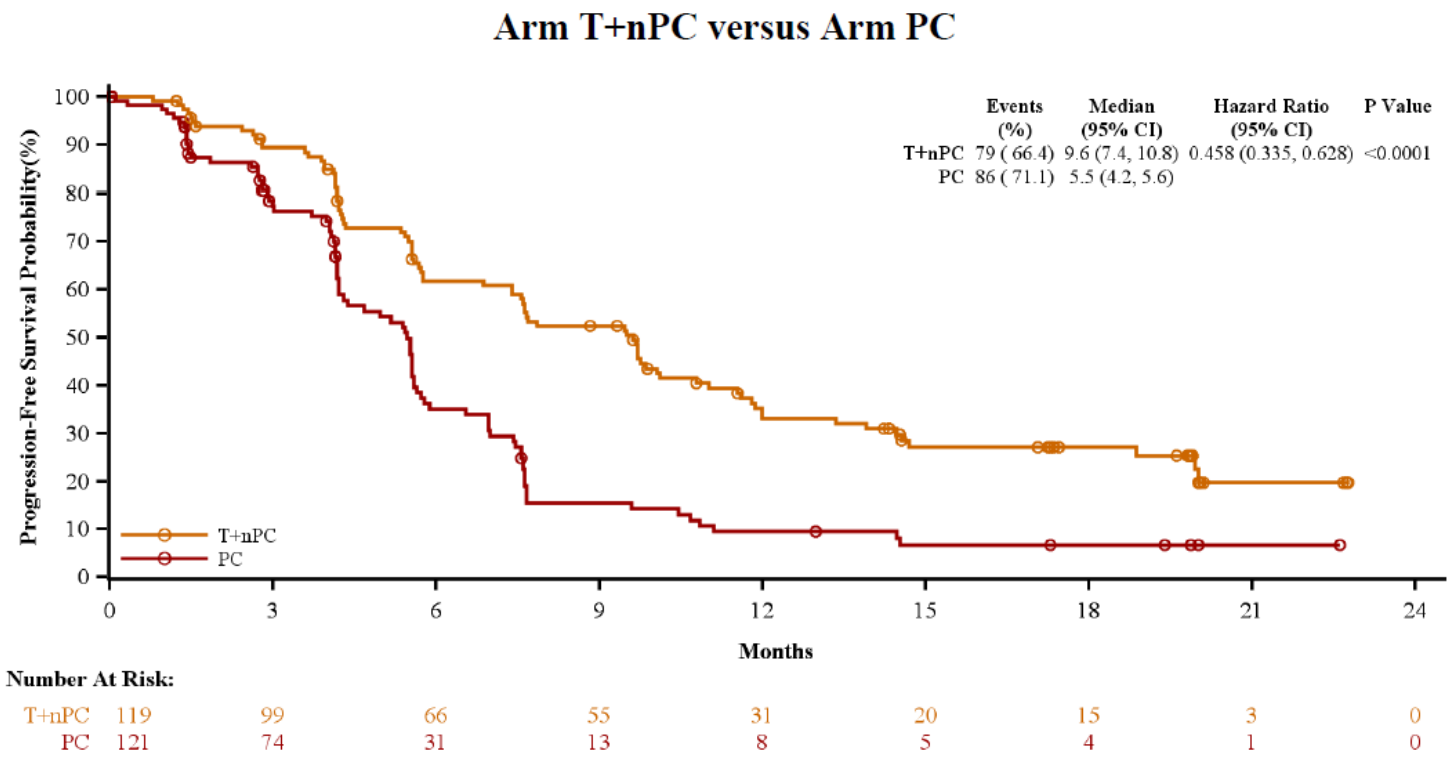


Figure 4: Kaplan-Meier plot of PFS (ITT analysis set) for Arm A: tislelizumab plus carboplatin and paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307 (DCO: 2020)

Data cut-off: 30 September 2020, Unstratified Hazard ratio (HR).
Abbreviations: CI, confidence interval; PC, carboplatin and paclitaxel; T, tislelizumab.
Source: [5].

Safety

The safety population included all patients who received at least one dose of the assigned treatment. In the tislelizumab plus carboplatin and paclitaxel arm, all patients received treatment. In the tislelizumab plus carboplatin and nab-paclitaxel arm, one patient was not treated, and in the carboplatin and paclitaxel arm, four patients did not receive treatment.

The rate of grade ≥3 TEAEs is 89.2% (107/120) of patients in the tislelizumab plus carboplatin and paclitaxel group and 87.3% (103/118) of patients in the tislelizumab plus carboplatin and nab-paclitaxel group. In comparison, 84.6% (99/117) of patients receiving carboplatin and paclitaxel alone report grade ≥3 AEs [8]. The incidence of TEAEs leading to treatment discontinuation is higher in Arm B with 32.2% (38/118) than that in Arm A with 17.5% (21/120) and Arm C with 15.4% (18/117) [15].

Serious TEAEs of Grade 3-5 were reported separately. In the tislelizumab plus carboplatin and paclitaxel arm, 38 patients (31.7%) experienced at least one serious TEAE of Grade 3–5. In the tislelizumab plus carboplatin and nab-paclitaxel group, the corresponding number was 42 patients (35.6%). In comparison, only 16 patients (13.7%) in the carboplatin and paclitaxel (control) group experienced at least one serious TEAE of Grade 3–5 [5].

Table 9: Summary of efficacy and safety results (ITT and Safety analysis set), RATIONALE-307

Endpoint	Data cut-off 30th September 2020		
	Tislelizumab carboplatin paclitaxel (N=120)	Tislelizumab carboplatin nab-paclitaxel (N=119)	Carboplatin paclitaxel (N=121)
Overall survival			
Median OS, mo. (95% CI)	22.8 (19.1, NE)	NE (18.6, NE)	20.2 (16.0, NE)
OS HR versus carboplatin paclitaxel (95% CI)	0.68 (0.46, 1.01)	0.75 (0.50, 1.12)	-
Absolute effect in median OS, versus carboplatin paclitaxel mo. (95% CI)*	2.6 (NE)	NE	-
Progression-free survival			
Median PFS, mo. (95% CI)	7.7 (6.7, 10.4)	9.6 (7.4, 10.8)	5.5 (4.2, 5.6)
PFS HR versus carboplatin paclitaxel (95% CI)	0.45 (0.33, 0.62)	0.43 (0.31, 0.60)	-
Absolute effect in median PFS versus carboplatin paclitaxel, mo. (95% CI)*	2.2 (0.22, 4.18)	4.1 (2.26, 5.94)	-

Discontinuation due to AEs			
N (%)	21/120 (17.5%)	38/118 (32.2%)	18/117 (15.4%)
RR versus carboplatin paclitaxel (95% CI)	1.14 (0.64, 2.02)	1.05 (0.95, 1.16)	-
Adverse events grade 3-5			
N (%)	107/120 (89.2%)	103/118 (87.3%)	99/117 (84.6%)
RR versus carboplatin paclitaxel (95% CI)	2.09 (1.27, 3.45)	1.03 (0.93, 1.14)	-

Data cutoff: 30 September 2020
Abbreviations: CI, confidence interval; HR, hazard ratio; mo., months; OS, overall survival; PFS, progression-free survival; RR, relative risk.
*The absolute effect and 95% confidence interval (CI) were determined using statistical methods based on the median months (95% CI).
Source: [8].

5.2.1.2 Subgroup PD-L1 1-49% - RATIONALE-307

For the PD-L1 1-49% subgroup, the results indicate that tislelizumab plus carboplatin and (nab)-paclitaxel demonstrates a favorable effect on both PFS and OS compared to carboplatin and paclitaxel alone.

Final analysis - data cut-off 30th of September 2020
Overall survival

The median OS is 26.1 months (95% CI: 15.2, 26.1) for patients treated with tislelizumab plus carboplatin and paclitaxel, and NE (95% CI: 14.1, NE) for patients treated with tislelizumab plus carboplatin and nab-paclitaxel. Patients receiving carboplatin and paclitaxel alone also have a NE median OS (95% CI: 11.4, NE). The stratified HR (stratified by disease IIIB versus IV) for OS is 0.60 (95% CI: 0.27, 1.36) for tislelizumab plus carboplatin and paclitaxel and 0.71 (95% CI: 0.31, 1.61) for tislelizumab plus carboplatin and nab-paclitaxel, indicating a trend towards improved survival outcomes in both treatment arms [4]. The unstratified HR for OS is 0.72 (95% CI: 0.32, 1.61) for tislelizumab plus carboplatin and paclitaxel and 0.73 (95% CI: 0.33, 1.64) for tislelizumab plus carboplatin and nab-paclitaxel [5]. No Kaplan-Meier plot is available for OS for the subgroup PD-L1 1-49%.

In the subgroup PD-L1 1-49% population, the 12-month OS rate is 79.3% (95% CI: 59.64, 90.13) corresponding to around 24 patients in the tislelizumab plus carboplatin and paclitaxel arm, 75.9% (95% CI: 55.94, 87.69) corresponding to 23 patients in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 63.1% (95% CI: 43.25, 77.67) corresponding to 20 patients in the carboplatin and paclitaxel arm. At 18-months, the PFS rate is 61.9% (95% CI: 41.79, 76.79) corresponding to 18 patients in the tislelizumab plus carboplatin and paclitaxel arm, 64.9% (95% CI: 44.48, 79.41) corresponding to 19 patients in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 59.4% (95% CI: 39.56, 74.63) corresponding to 18 patients in the carboplatin and paclitaxel arm [5].

Progression-free survival

For patients with PD-L1 expression 1-49%, the median PFS is 10.4 months (95% CI: 5.49, 20.04) for patients treated with tislelizumab plus carboplatin and paclitaxel, compared to 5.0 months (95% CI: 2.76, 6.54) for patients treated with carboplatin and paclitaxel alone. The unstratified HR is 0.40 (95% CI: 0.21, 0.76). The median PFS is 10.1 months (95% CI: 7.39, 11.99) for patients treated with tislelizumab plus carboplatin and nab-paclitaxel. The unstratified HR is 0.4 (95% CI: 0.22, 0.74), suggesting a consistent PFS benefit with tislelizumab across both treatment regimens in this PD-L1 subgroup, see Figure 5 and Figure 6 [4].

In the subgroup PD-L1 1-49% population, the 12-month PFS rate is 48.3% (95% CI: 29.47, 64.78) corresponding to around 14 patients in the tislelizumab plus carboplatin and paclitaxel arm, 29.6% (95% CI: 13.5, 47.9) corresponding to 9 patients in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 8.4% (95% CI: 1.5, 23.3) corresponding to 3 patients in the carboplatin and paclitaxel arm. At 18-months, the PFS rate is 35.8% (95% CI: 16.7, 55.4) corresponding to 11 patients in the tislelizumab plus carboplatin and paclitaxel arm, 21.2% (95% CI: 7.8, 38.8) corresponding to 6 patients in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 8.4% (95% CI: 1.5, 23.3) corresponding to 3 patients in the carboplatin and paclitaxel arm [5].

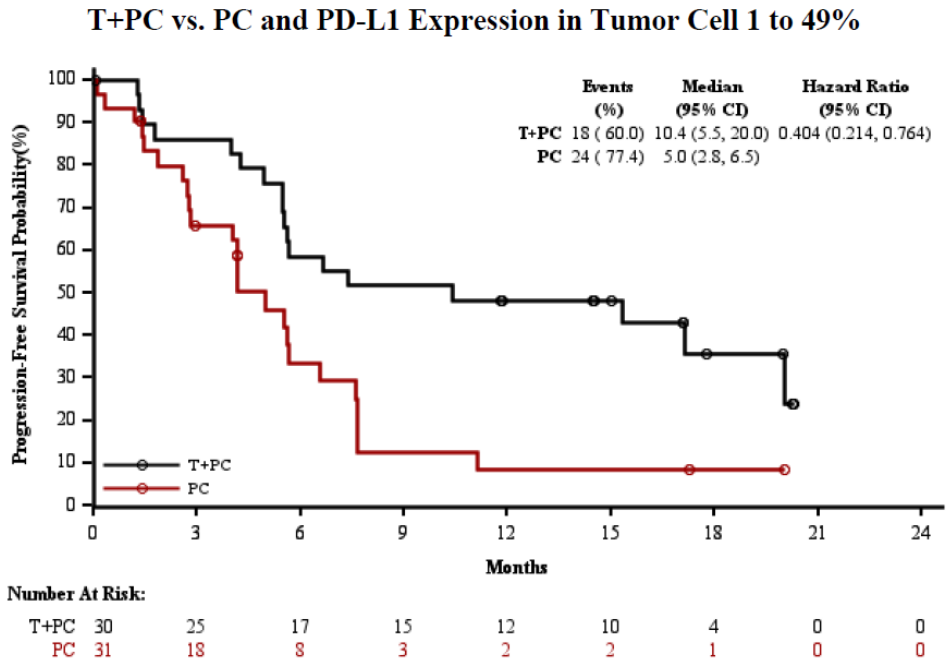


Figure 5: Kaplan-Meier plot of PFS (PD-L1 1-49% analysis set) for Arm A: tislelizumab plus carboplatin and paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307
Data cut-off: 30 September 2020
Abbreviations: PC, carboplatin and paclitaxel; T, tislelizumab.
Source: [5].

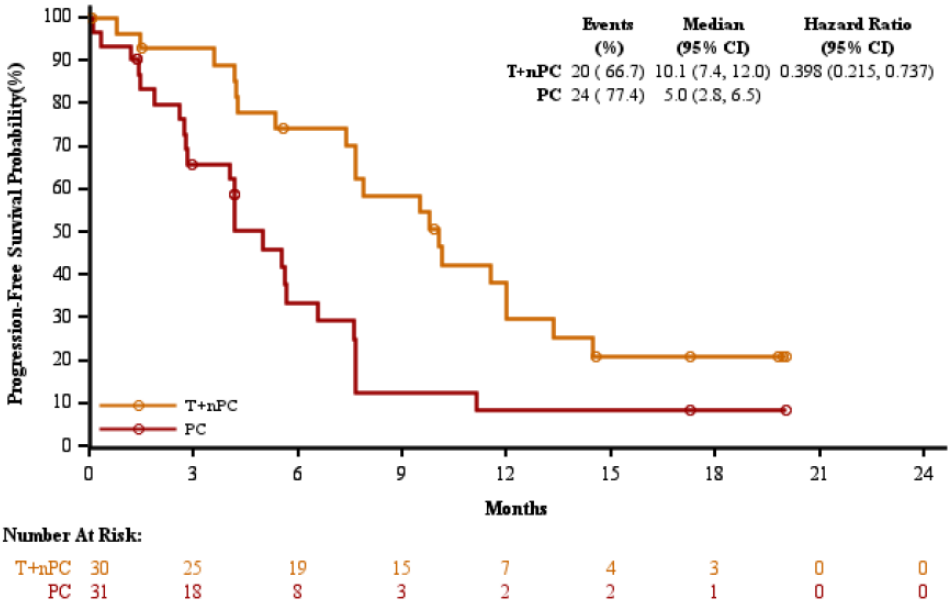


Figure 6: Kaplan-Meier plot of PFS (PD-L1 1-49% analysis set) for Arm B: tislelizumab plus carboplatin and nab-paclitaxel vs. Arm C: placebo plus carboplatin and paclitaxel, RATIONALE-307

Data cut-off: 30 September 2020

Abbreviations: nPC, nab-paclitaxel and carboplatin; PC, carboplatin and paclitaxel; T, tislelizumab.

Source: [5].

Table 10: Summary of efficacy and safety results (Subgroup PD-L1 1-49% analysis set), RATIONALE-307

Endpoint	Data cut-off 30th September 2020		
	Tislelizumab carboplatin paclitaxel (N=30)	Tislelizumab carboplatin nab-paclitaxel (N=30)	Carboplatin paclitaxel (N=31)
Overall survival			
Median OS, mo. (95% CI)	26.1 (15.2, 26.1)	NE (14.1, NE)	NE (11.4, NE)
OS HR versus carboplatin paclitaxel (95% CI)	0.72 (0.32, 1.61)	0.73 (0.33, 1.64)	-
Absolute effect median OS versus carboplatin paclitaxel, mo. (95% CI)*	NE	NE	-
Progression-free survival			
Median PFS, mo. (95% CI)	10.4 (5.49, 20.04)	10.1 (7.39, 11.99)	5.0 (2.76, 6.54)
PFS HR versus carboplatin paclitaxel (95% CI)	0.40 (0.21, 0.76)	0.4 (0.22, 0.74)	-

Absolute effect median PFS versus carboplatin paclitaxel, mo. (95% CI)*	5.4 (-2.12, 12.92)	5.1 (2.12, 8.08)	-

Data cutoff: 30 September 2020
Abbreviations: CI, confidence interval; HR, hazard ratio; mo., months; OS, overall survival; PFS, progression-free survival; RR, relative risk.
*The absolute effect and 95% confidence interval (CI) were determined using statistical methods based on the median months (95% CI).
Source: [4,5]

5.2.2 Efficacy and safety – results per KEYNOTE-407

KEYNOTE-407 is a multicenter, randomized, double-blinded, phase III clinical trial comparing the efficacy and safety of pembrolizumab plus carboplatin combined with paclitaxel/nab-paclitaxel and placebo plus carboplatin and paclitaxel/nab-paclitaxel for first-line treatment in patients with metastatic or advanced squamous NSCLC. Efficacy analyses are conducted on the ITT population and relevant subgroups as well, while safety analyses are based on all patients who received at least one dose of study treatment. Data is available at four different cut-offs:

- Primary efficacy analysis cut-off at 7.8 months
- Final baseline analysis cut-off date of 9th May 2019 (14.3 months)
- Extended analysis cut-off at 40.1 months
- 5-year follow-up cut-off date 23 February 2022, with a median time from random assignment to database cut-off at 56.9 months

The subgroup of patients with PD-L1 expression <1% is based on a predefined stratification factor, whereas the subgroup of patients with PD-L1 expression ≥1% and <50% represents a subpopulation within the stratified group of patients with PD-L1 expression ≥1%. This ensures that randomization remains preserved for the subgroup of patients with PD-L1 expression <1%, supporting the validity of subgroup comparisons. This application addresses efficacy and safety data for clinical question 6 involving patients with PD-L1 expression ≥1% and <50%, thus data within this subgroup will primarily be presented, as well as data for the overall ITT population. The subgroup will be described as PD-L1 1-49% as presented in the study [10]. The 5-year DCO will be considered, unless otherwise noted.

The following section outlines the efficacy and safety outcomes relevant in the treatment guideline, including PFS, OS, discontinuation due to AEs, and grade 3-5 AEs [6]. For safety data, RRs were calculated and reported for applicable outcomes.

5.2.2.1 ITT population – KEYNOTE-407

Overall survival

As for the ITT population, OS is improved with pembrolizumab and carboplatin plus (nab)-paclitaxel versus placebo and carboplatin plus (nab)-paclitaxel (HR, 0.71; 95% CI, 0.59 to 0.85), see Figure 7.

In the KEYNOTE-407 ITT-population, the OS rate is 64.7% corresponding to 180 patients in the pembrolizumab plus carboplatin and (nab)-paclitaxel. In the comparator arm, placebo plus carboplatin and (nab)-paclitaxel, the OS rate is 49.6% corresponding to 137 patients [10].

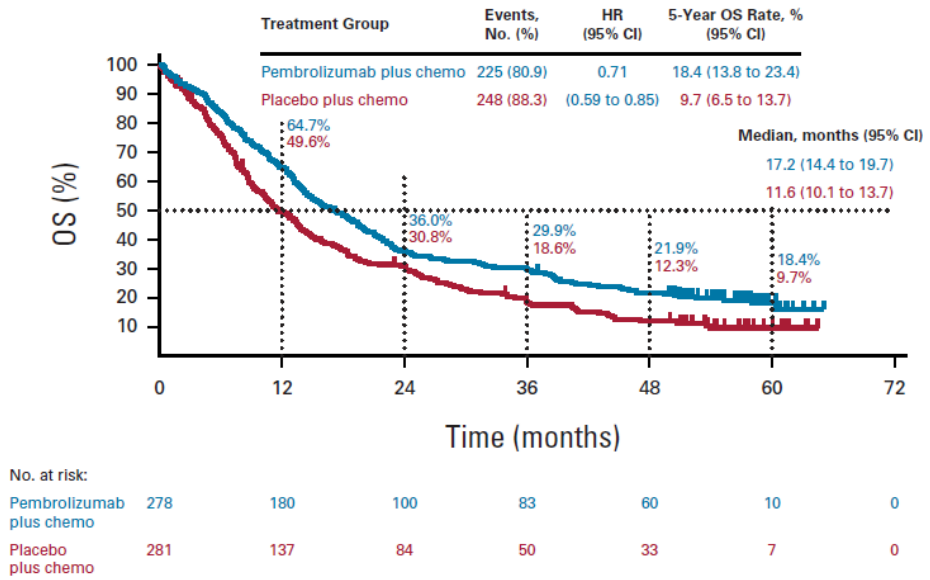


Figure 7: Kaplan-Meier plot of OS (ITT analysis set), KEYNOTE-407
Data cut-off: 23 February 2022.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: [10].

Progression-free survival

PFS improved with pembrolizumab and carboplatin plus (nab)-paclitaxel versus placebo and carboplatin plus (nab)-paclitaxel (HR, 0.62; 95% CI, 0.52 to 0.74), see Figure 8.

In the KEYNOTE-407 ITT-population, the PFS rate is 36.3% corresponding to 100 patients in the pembrolizumab plus carboplatin and (nab)-paclitaxel. In the comparator arm, placebo plus carboplatin and (nab)-paclitaxel, the PFS rate is 19.2% corresponding to 53 patients [10].

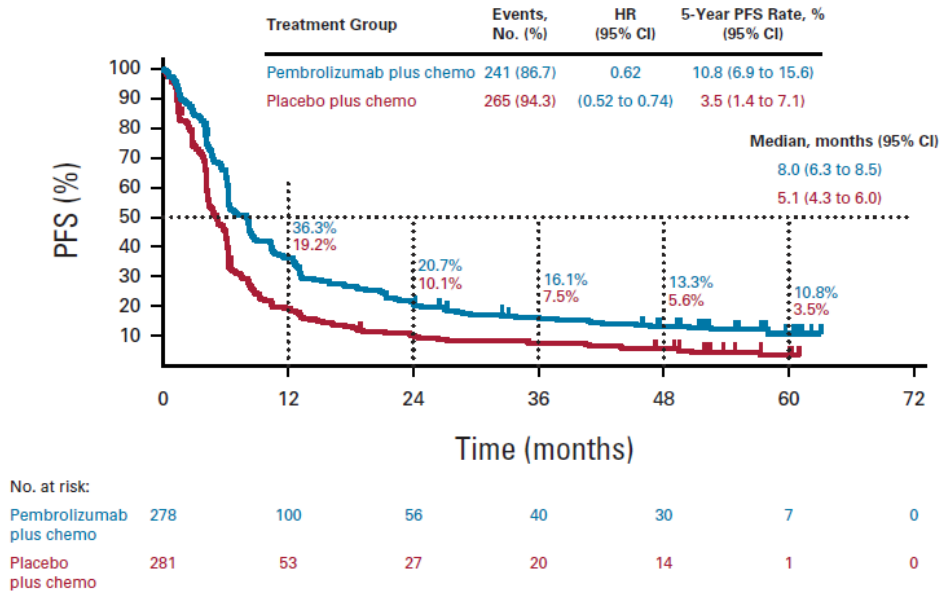


Figure 8: Kaplan-Meier plot of PFS (ITT analysis set), RATIONALE-407

Data cut-off: 23 February 2022.
Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.
Source: [10].

Safety

Safety data showed 28.8% and 13.2% of patients receiving pembrolizumab and carboplatin plus (nab)-paclitaxel and placebo and carboplatin plus (nab)-paclitaxel, respectively, discontinued the treatment due to AEs. Grade 3 to 5 AEs affected 74.8% of patients in the pembrolizumab group and 70.0% in the placebo group (see Table 11) [10].

Table 11: Summary of efficacy and safety results (ITT analysis set), KEYNOTE-407

Endpoint	Data cut-off 23 February 2022 Pembrolizumab carboplatin paclitaxel/nab-paclitaxel (N=278)	Carboplatin-paclitaxel (N=280)
Overall survival		
Median OS, mo. (95% CI)	17.2 (14.4, 19.7)	11.6 (10.1, 13.7)
OS HR (95% CI)	0.71 (0.59, 0.85)	-
Absolute effect (95% CI)*	5.6 (2.4, 8.80)	-
Progression-free survival		
Median PFS, mo. (95% CI)	8.0 (6.3, 8.5)	5.1 (4.3, 6.0)
PFS HR (95% CI)	0.62 (0.52, 0.74)	-

Absolute effect (95% CI)*	2.9 (1.51, 4.29)	-
Discontinuation due to AEs		
N (%)	80/278 (28.8%)	37/280 (13.2%)
RR (95% CI)	2.18 (1.53; 3.10)	-
Adverse events grade 3-5		
N (%)	208/278 (74.8%)	196/280 (70.0%)
RR (95% CI)	1.07 (0.96, 1.18)	-

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; mo., months; N, number; OS, overall survival; PFS, progression-free survival; RR, relative risk.
Source: [10].

5.2.2.2 Subgroup PD-L1 1-49% - KEYNOTE-407

Overall survival

Among patients with PD-L1 1-49%, the median OS is 18.0 months (95% CI: 13.6, 22.8) in the pembrolizumab and carboplatin plus (nab)-paclitaxel arm and 13.1 (95% CI: 9.1, 15.2) in the placebo and carboplatin plus (nab)-paclitaxel arm, with a relative effect HR: 0.61 (95% CI: 0.45, 0.83), see Figure 9.

In the KEYNOTE-407 subgroup PD-L1 1-49% population, the OS rate is 66.0% corresponding to 68 patients at risk in the pembrolizumab plus carboplatin and (nab)-paclitaxel. In the comparator arm, placebo plus carboplatin and (nab)-paclitaxel, the OS rate is 53.4% corresponding to 55 patients at risk.

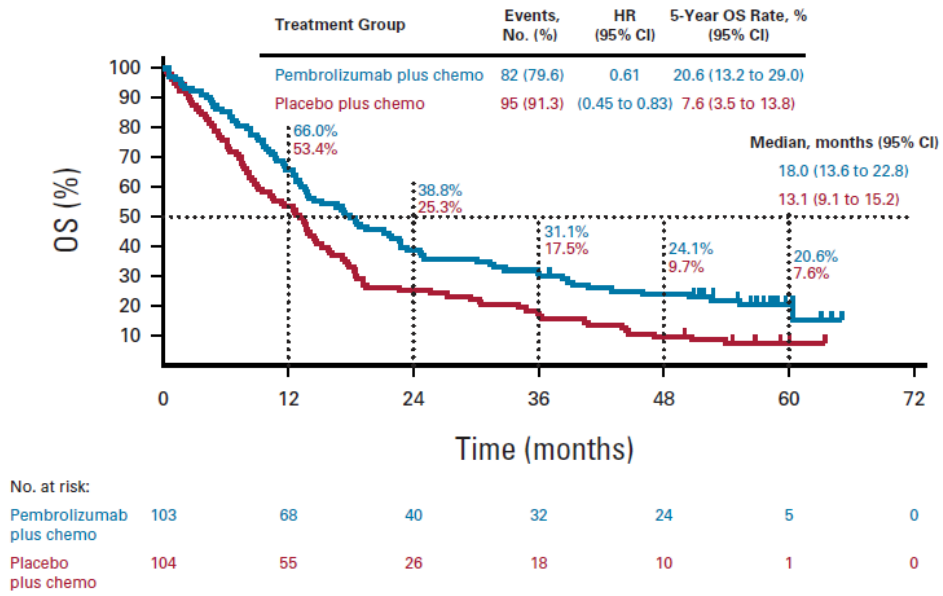


Figure 9: Kaplan-Meier plot of OS (Sub-group PD-L1 1-49% analysis set), KEYNOTE-407

Data cut-off: 23 February 2022.
Abbreviations: CI, confidence interval; HR, hazard ratio; OS, overall survival.
Source: [10].

Progression-free survival

Regarding PFS a median PFS of 8.2 (95% CI: 6.2, 11.4) are found in the pembrolizumab and carboplatin plus (nab)-paclitaxel arm and a median PFS of 6.0 (95% CI: 4.2, 6.2) are presented for placebo and carboplatin plus (nab)-paclitaxel, with a relative effect HR: 0.60 (95% CI: 0.45, 0.81) [10], see Figure 14. No subgroup-specific safety data is reported.

In the KEYNOTE-407 subgroup PD-L1 1-49% population, the PFS rate is 39.8% corresponding to 41 patients at risk in the pembrolizumab plus carboplatin and (nab)-paclitaxel. In the comparator arm, placebo plus carboplatin and (nab)-paclitaxel, the PFS rate is 19.2% corresponding to 20 patients at risk.

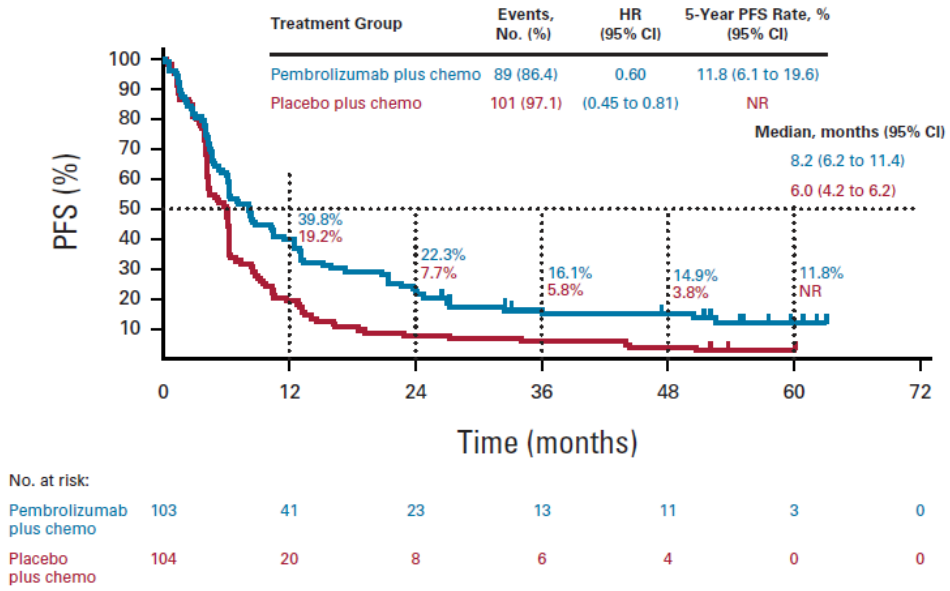


Figure 14: Kaplan-Meier plot of PFS (Sub-group PD-L1 1-49% analysis set), KEYNOTE-407

Data cut-off: 23 February 2022.

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Source: [10].

Table 12: Summary of efficacy results (Subgroup PD-L1 1-49% analysis set), KEYNOTE-407

Data cut-off 23 February 2022		
Endpoint	**Pembrolizumab carboplatin paclitaxel/nab-paclitaxel (N=103)**	**Carboplatin-paclitaxel (N=104)**
Overall survival		
Median OS, mo. (95% CI)	18.0 (13.6, 22.8)	13.1 (9.1, 15.2)
OS HR (95% CI)	0.61 (0.45, 0.83)	-
Absolute effect, mo. (95% CI)*	4.9 (-0.62, 10.42)	-
Progression-free survival		
Median PFS, mo. (95% CI)	8.2 (6.2, 11.4)	6.0 (4.2, 6.2)
PFS HR (95% CI)	0.60 (0.45, 0.81)	-
Absolute effect, mo. (95% CI)*	2.2 (-0.59, 4.99)	-

Abbreviations: CI, confidence interval; HR, hazard ratio; mo, months; OS, overall survival; PFS, progression-free survival.

Source: [10].

5.2.3 Health-related quality of life results in RATIONALE-307

A total of 355 patients (Arm A: 120; Arm B: 118; and Arm C: 117) who received at least one dose of study treatments and completed at least one HRQoL assessment are included in the analysis of HRQoL. The evaluation was performed using data with a cutoff of 6th of December 2019. The study evaluated HRQoL using the European Organization for Research and Treatment of Cancer Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) global health status (GHS)/quality of life (QoL) as well as lung cancer-related symptoms including coughing, dysphagia, dyspnoea, haemoptysis, pain in arms and shoulders, chest pain, and peripheral neuropathy symptoms estimated by Quality of Life Questionnaire-Lung Cancer Module 13 (QLQ-LC13) [5,16]. EQ-5D specific QoL data are not reported for the RATIONALE-307 trial and will therefore not be presented in this application.

Table 13: HRQoL data collection and analysis in RATIONALE-307

HRQoL data collection and analysis in RATIONALE-307	
Population	355 patients (Arm A: 120; Arm B: 118; Arm C: 117) included in PRO analysis set (≥1 post-baseline HRQoL assessment).
Instruments	EORTC QLQ-C30 and QLQ-LC13
Timing of assessments	At baseline and every 6 weeks during treatment (until Week 12 in comparator arm). Questionnaires were always completed prior to clinical procedures.
Endpoints	Primary PRO endpoints were mean change from baseline in QLQ-C30 GHS/QoL at Week 6 and Week 12, and time to definitive deterioration (TTD). Supportive endpoints included mean change over time in QLQ-C30 and QLQ-LC13 subscales.
Completion and compliance	Completion was defined as ≥1 item answered, compliance was calculated as completed assessments relative to patients at risk (alive, not discontinued, scheduled visit).
Handling of missing data	Constrained longitudinal data analysis under MAR assumption with fixed effects for treatment, visit, treatment-by-visit, and stratification factors.

In the two treatment arms QLQ-C30 and QLQ-LC13 are assessed at baseline and at every 6 weeks through the end of treatment, whereas it was assessed through week 12 in the comparator arm. See Table 13 for overview of methodologies. All questionnaires are completed prior to any clinical activity. EORTC QLQ-C30 and QLQ-LC13 HRQoL was evaluated with key PRO endpoints of mean change from baseline to Week 6 and Week 12 in QLQ-C30 GHS/QoL and TTD in GHS/QoL. Supportive PRO endpoints were mean changes from baseline over time in QLQ-C30 and QLQ-LC13 subscales, descriptive summaries were produced for mean changes at Week 18, Week 24, Week 30, and Week

36. Week 6 (on chemotherapy) and Week 12 (post chemotherapy) were chosen to limit missingness due to progression or death. Analyses used the PRO analysis set (all randomized patients who received ≥1 dose and completed ≥1 post-baseline HRQoL assessment). A PRO assessment was counted if ≥1 item was answered. Completion was the % with ≥1 PRO assessment at each visit in the PRO set, compliance was the proportion with ≥1 item among those expected to complete (not discontinued and with a scheduled visit). Mean change to Week 6/Week 12 was estimated via constrained longitudinal data analysis under missing-at-random with fixed effects for treatment, visit, treatment-by-visit, and randomization stratification factors (tumor-cell PD-L1, disease stage); between-group effects are reported as LS-mean from baseline with 95% CI and two-sided nominal p-values. No multiplicity adjustment was applied across PRO endpoints. TTD was time from randomization to the first confirmed ≥10-point decrease from baseline in GHS/QoL (confirmation by a subsequent ≥10-point decrease). Kaplan Meier was used for TTD curves and a stratified Cox model with Efron ties for between-group comparisons. To meet the request, we will include pattern-of-missingness, completion and compliance tables by arm/visit for QLQ-C30 and QLQ-LC13, and results tables (not only graphs) with baseline, LS-mean changes and LS-mean differences at Week 6/Week 12 (95% CI, nominal p), plus descriptive mean-change tables for Week 18/Week 24/Week 30/Week 36 [16].

Completion and compliance rates for HRQoL questionnaires were high across all treatment arms, with nearly full completion at baseline and consistently high compliance at all time points. Declining completion over time was primarily due to disease progression, AEs or discontinuation. As QLQ-C30 and QLQ-LC13 were administered together, completion and compliance followed the same pattern.

Table 14: Completion and compliance for QLQ-C30 in RATIONALE-307

Time point	Arm A (N=120)	Arm B (N=118)	Arm C (N=117)
Baseline	120 (100%) / 100%	117 (99.2%) / 100%	117 (100%) / 100%
Week 6	107 (89.2%) / 98.2%	106 (89.8%) / 98.1%	103 (88.0%) / 99.0%
Week 12	96 (80.0%) / 98.0%	92 (78.0%) / 96.8%	59 (50.4%) / 96.7%
Week 18	90 (75.0%) / 100%	86 (72.9%) / 100%	0 / 0
Week 24	73 (60.8%) / 97.3%	67 (56.8%) / 95.7%	0 / 0
Week 30	50 (41.7%) / 98.0%	52 (44.1%) / 100%	0 / 0
Week 36	26 (21.7%) / 96.3%	32 (27.1%) / 100%	0 / 0

Source: [16].

Table 15: Completion and compliance for QLQ-LC30 in RATIONALE-307

Time point	Arm A (N=120)	Arm B (N=118)	Arm C (N=117)
Baseline	120 (100%) / 100%	117 (99.2%) / 100%	117 (100%) / 100%
Week 6	107 (89.2%) / 98.2%	106 (89.8%) / 98.1%	103 (88.0%) / 99.0%
Week 12	96 (80.0%) / 98.0%	92 (78.0%) / 96.8%	59 (50.4%) / 96.7%
Week 18	90 (75.0%) / 100%	86 (72.9%) / 100%	0 / 0
Week 24	73 (60.8%) / 98.6%	67 (56.8%) / 95.7%	0 / 0
Week 30	50 (41.7%) / 98.0%	52 (44.1%) / 100%	0 / 0
Week 36	26 (21.7%) / 96.3%	32 (27.1%) / 100%	0 / 0

Source: [16]

QLQ-C30 GHS/QoL scores at baseline for cutoff of 6th of December 2019 are similar among the treatment arms: the tislelizumab plus carboplatin and paclitaxel arm resulted in a mean score of 66.6 (SD: 22.13), tislelizumab plus carboplatin and nab-paclitaxel arm resulted in a mean score of 65.7 (19.93), and carboplatin plus paclitaxel alone arm resulted in a mean score of 66.5 (20.10). At week 6, all treatment arms showed improvement relative to baseline, although the between-group least square (LS) mean differences did not show statistically significant differences. LS mean differences at week 6 were 0.5 (95% CI: -4.2, 5.2; p=0.8330) for tislelizumab plus carboplatin and paclitaxel versus carboplatin plus paclitaxel alone and 2.1 (95% CI: -2.6, 6.8; p=0.3842) for tislelizumab plus carboplatin and nab-paclitaxel versus carboplatin plus paclitaxel alone. At week 12, the GHS/QoL score increased in both tislelizumab plus carboplatin and (nab)-paclitaxel arms, while it remained stable in the carboplatin plus paclitaxel alone arm. LS mean differences at week 12 were 3.4 (95% CI: -2.4, 9.2; p=0.2536) for tislelizumab plus carboplatin and paclitaxel versus carboplatin plus paclitaxel alone and 3.4 (95% CI: -2.5, 9.3; p=0.2541) for tislelizumab plus carboplatin and nab-paclitaxel versus carboplatin plus paclitaxel alone. The long-term change in QLQ-C30 GHS/QoL from baseline is maintained after week 12 in both tislelizumab plus carboplatin and (nab)-paclitaxel arms [16]. The mean changes from baseline in QoL for RATIONALE-307 are presented in Figure 15 and Table 16.

Table 16: QLQ-C30 GHS/QoL results in RATIONALE-307 (DCO 2019)

Time point	Arm A (95% CI)	Arm B (95% CI)	Arm C (95% CI)	Diff A/B vs C (95% CI)	p-value

Week 6	2.1 (–1.4, 5.6)	3.7 (0.2, 7.1)	1.6 (–1.9, 5.1)	A: 0.5 (–4.2, 5.2) / B: 2.1 (–2.6, 6.8)	0.83 / 0.38
Week 12	3.8 (–0.2, 7.8)	3.8 (–0.2, 7.8)	0.4 (–4.4, 5.2)	A: 3.4 (–2.4, 9.2) / B: 3.4 (–2.5, 9.3)	0.25 / 0.25

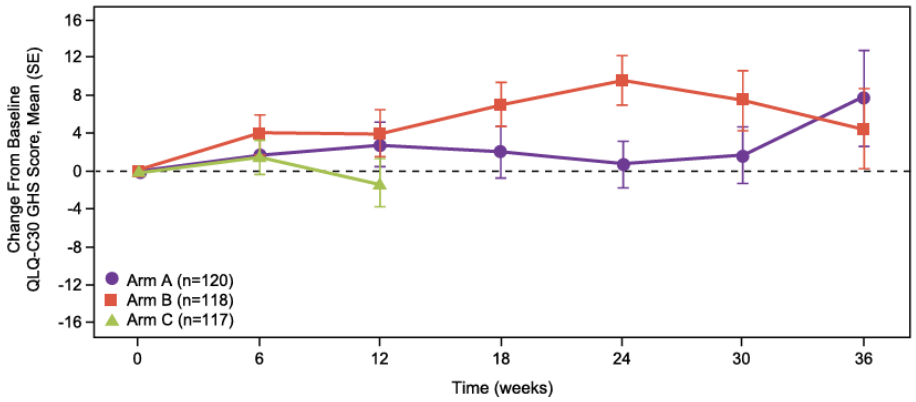


Figure 15: Mean change from baseline in QLQ-C30 scale score for RATIONALE-307. Arm A represents tislelizumab plus carboplatin and paclitaxel, Arm B represents tislelizumab plus carboplatin and nab-paclitaxel, and Arm C represents placebo plus carboplatin and paclitaxel (DCO: 06 December 2019).

Abbreviations: GHS, global health status; SE, standard error; QLQ, Quality of Life Questionnaire; QoL, quality of life.

Source: [16].

In terms of QLQ-LC13, an overview of the results for the subscales can be found in Table 17.

Table 17: QLQ-LC13 selected subscale results in RATIONALE-307 (DCO: 2019)

Endpoint	Week	Arm A	Arm B	Arm C
Coughing	6	–14.0	–11.6	–12.3
	12	–20.1	–12.7	–7.3
Dyspnea	6	–1.5	–2.4	–1.1
	12	–1.9	–1.8	+2.4
Hemoptysis	6	–7.5	–9.4	–3.9
	12	–9.4	–9.4	–2.3

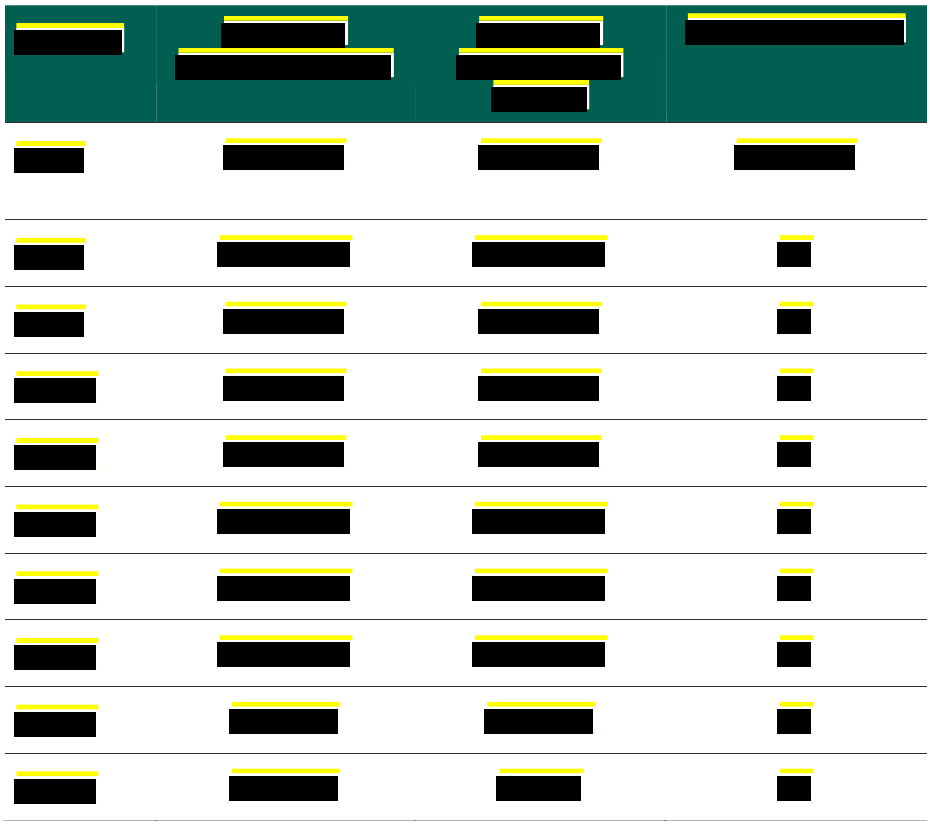
Chest pain	6	–5.9	–7.5	–6.8
	12	–5.9	–5.8	–5.6

Source: [16]

The most recent, unpublished data is presented in Figure 10, supplementary to the 06 December 2019 DCO. Information about compliance rates is listed in Table 18 below.

Source: [5]

(DCO: 30 September 2020)



Abbreviations: HRQoL, health-related quality of life; QLQ, Quality of Life Questionnaire
Source: [5]

For the QLQ-C30 subscales of fatigue and physical functioning, all three arms experienced numerically similar increases in fatigue and reductions in physical functioning at weeks 6 and 12 compared to baseline. For the QLQ-LC13 subscales, patients in the intervention arms experience greater improvement in coughing at weeks 6 and 12 compared to patients in the carboplatin plus paclitaxel alone arm. Throughout the treatment, the mean score of dyspnoea decrease in patients in the tislelizumab plus carboplatin and (nab)-paclitaxel arms, whereas it increases in the carboplatin plus paclitaxel alone arm. Haemoptysis decreases in all three treatment arms, with the tislelizumab plus carboplatin and paclitaxel arm and tislelizumab plus carboplatin and nab-paclitaxel arm showing the largest decreases. All three arms saw worsening of peripheral neuropathy; however, the tislelizumab plus carboplatin and nab-paclitaxel arm had the smallest increase. Similar pain relief is observed across all three arms, including chest pain and pain in the arm and shoulder. The median TTD for the composite of cough, chest pain, and dyspnoea in QLQ-LC13 is reached only in the tislelizumab plus carboplatin and paclitaxel arm at 5.7 months (95% CI: 3.06, NE) [16].

5.2.4 Health-related quality of life results in KEYNOTE-407

In the KEYNOTE-407 study, HRQoL is assessed and reported utilizing the same questionnaire and modules (EORTC QLQ-C30 and QLQ-LC13) that are employed in RATIONALE-307. The endpoints are reported as mean score change from baseline to weeks 9 and 18. Data was provided from the data cut-off of 3rd April 2018, median follow-up 7.8 months. 559 patients were randomly assigned between August 19, 2016

and December 28, 2017. Among the patients, the PRO analysis population comprised 554 patients who completed at least 1 QLQ-C30 assessment and 553 patients who completed at least 1 QLQ-LC13 assessment. Additionally, EuroQoL (EQ)-5D-3L data were collected for KEYNOTE-407, but were not reported in the publication. All questionnaires were administered by trained personnel and completed using a tablet before any study procedures (drug administration, AE evaluation, and disclosure of disease status) at cycle 1-7 and then every third cycle while on treatment through week 48, as well as at treatment discontinuation and the 30-day safety follow-up. The questionnaires were presented in order of EQ-5D-5L, then QLQ-C30 and lastly QLQ-LC13. Prespecified PRO endpoints were mean change from baseline in QLQ-C30 GHS/QoL at week 9 and 18 and time to definitive deterioration in a composite of cough (QLQ-LC13, item 1), chest pain (QLQ-LC13, item 10, and dyspnea (QLQ-C30, item 8). Supportive endpoints included mean changes over time across QLQ-C30 and QLQ-LC13 subscales and the numbers of patients categorized as improved, stable, or deteriorated at weeks 9 and 18. Weeks 9 (during therapy) and week 18 (post therapy) were chosen to capture assessments during and after chemotherapy and to minimize missing data because of progression or death. A ≥ 10-point change from baseline on each scale defined improvement or deterioration and was considered clinically meaningful. In Table 19 an overview of the HRQoL collection are depicted [17].

Table 19: HRQoL data collection and analysis in KEYNOTE-407

HRQoL data collection and analysis in KEYNOTE-407	
Population	554 patients for QLQ-C30 and 553 for QLQ-LC13 included in PRO analysis population (≥1 assessment completed).
Instruments	EORTC QLQ-C30 and QLQ-LC13, plus EQ-5D, not reported.
Timing of assessments	At cycle 1–7 and then every third cycle through Week 48, plus treatment discontinuation and 30-day follow-up. Administered by trained staff before any study procedures (treatment, AE evaluation, disease disclosure).
Endpoints	Prespecified endpoints included mean change from baseline in QLQ-C30 GHS/QoL at Weeks 9 and 18, and TTD in composite of cough, chest pain, and dyspnea. Supportive endpoints: mean changes across all subscales, proportions improved/stable/deteriorated.
Completion and compliance	Completion was defined as ≥1 item answered, compliance was calculated as completed assessments relative to patients at risk (alive, not discontinued, scheduled visit).
Handling of missing data	Constrained longitudinal data analysis; no formal multiplicity adjustment across PRO endpoints.

Patients were considered to have completed a PRO assessment if they answered ≥1 item on the instrument. The completion rate was the percentage of patients with ≥1 PRO assessment at each time point in the full-analysis population; compliance was defined as the proportion who completed ≥1 item among those expected to complete the questionnaires (i.e., alive, not discontinued, translation available, and a scheduled visit). Mean change from baseline to weeks 9 and 18 was evaluated using a constrained longitudinal data analysis with fixed effects for treatment-by-visit and randomization stratification factors, and between-group differences were reported as least-squares mean differences with 95% CIs and nominal p-values. No formal family-wise multiplicity control across PRO endpoints was applied, therefore, inferential results for PROs should be interpreted descriptively [17].The baseline mean QLQ-C30 GHS/QoL scores are similar between the pembrolizumab plus carboplatin and (nab)-paclitaxel arm (63.9 (20.4)) and the placebo plus carboplatin and (nab)-paclitaxel arm (62.7 (21.3)). At week 9, LS mean (95% CI) QLQ-C30 GHS/QoL scores are stable in the pembrolizumab plus carboplatin and (nab)-paclitaxel arm with an increase of 1.8 points (-0.9 to 4.4), and in the placebo plus carboplatin and (nab)-paclitaxel arm, there is a LS mean score of -1.8 points (-4.4 to 0.7). The LS mean difference in score between groups at week 9 is 3.6 points (95% CI, 0.3 to 6.9; P = .0337). At week 18, the LS mean (95% CI) QLQ-C30 GHS/QoL score improve from baseline in the pembrolizumab plus carboplatin and (nab)-paclitaxel arm, showing an increase of 4.3 points (1.7 to 6.9), while in the placebo plus carboplatin and (nab)-paclitaxel arm, it remained stable with a LS mean score of -0.6 points (-3.3 to 2.2). The LS mean difference in score between groups at week 18 is 4.9 points (95% CI, 1.4 to 8.3; P = .0060) [17]. See Figure 16 and Table 20 for the presentation of mean changes from baseline in QoL for KEYNOTE-407.

Table 20: QLQ-C30 GHS results in KEYNOTE-407 (DCO 2018)

Time point	Arm A (95% CI)	Arm B (95% CI)	Diff A vs. B (95% CI)	p-value
Week 9	1.8 (-0.9, 4.4)	-1.8 (-4.4, 0.7)	3.6 (0.3, 6.9)	0.0337
Week 18	4.3 (1.7, 6.9)	-0.6 (-3.3, 2.2)	4.9 (1.4, 8.3)	0.0060

Source: [17]

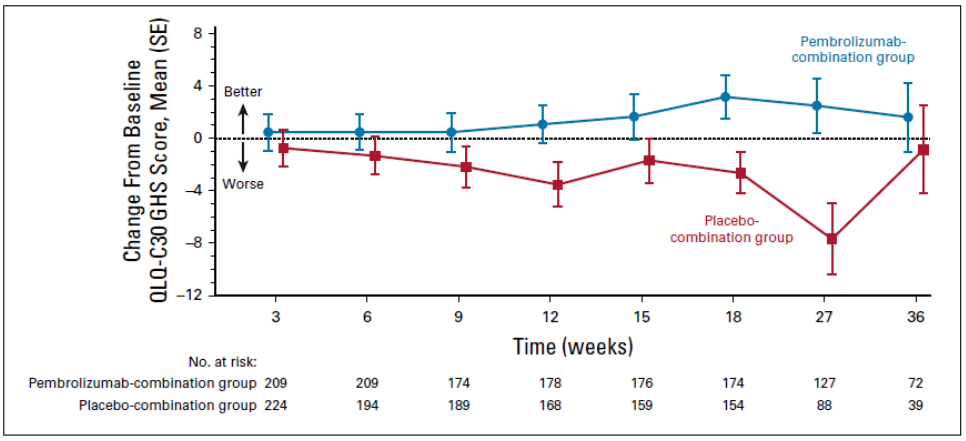


Figure 16: Mean change from baseline in QLQ-C30 GHS scale score for KEYNOTE-407

Abbreviations: QLQ-C30, Quality of Life Questionnaire Core 30.
Source: [17].

In terms of QLQ-LC13 outcomes, some subgroup results were presented individually, while others were reported in combination with QLQ-C30. The median time to deterioration in the composite endpoint of cough, chest pain, or dyspnea was not reached in either treatment arm; a trend favored pembrolizumab plus carboplatin and (nab)-paclitaxel over placebo plus carboplatin and (nab)-paclitaxel (HR 0.79; 95% CI: 0.58–1.06; p=0.125). Consistent with this, patients in the pembrolizumab arm generally reported a lower symptom burden for fatigue, pain, dyspnea, and insomnia, whereas gastrointestinal symptoms such as diarrhea and constipation were slightly more frequent in the pembrolizumab arm and less prominent in the placebo arm [17].

5.2.5 Narrative description of the comparison of HRQoL in the clinical trials

Results from HRQoL evaluations in RATIONALE-307 and KEYNOTE-407 have demonstrated that patients maintained their quality of life during treatment. Both studies indicate that the addition of either tislelizumab or pembrolizumab to the treatment regimen for patients with squamous NSCLC leads to improvements or maintenance of HRQoL. By week 6 in RATIONALE-307, HRQoL improves across all treatment arms, though without statistical significance. At week 12, GHS/QoL increase in the tislelizumab arms but remain stable with chemotherapy alone [5]. At week 9 in KEYMOTE-407, HRQoL maintains in the pembrolizumab arm but declined in the placebo group, yielding a statistically significant between-group difference (3.6 points; p=0.0337). By week 18, the pembrolizumab arm demonstrates a significant QoL improvement compared to the control group (4.9 points; *p*=0.0060) [17]. The methods of measurement applied are consistent with those used in comparable studies, as well as those recommended in current clinical treatment guidelines [6].

5.2.6 Qualitative description of safety data

Safety data from RATIONALE-307 were based on the safety analysis set (n=355) from cutoff of 30th September 2020. A treatment-emergent adverse event (TEAE) was defined as an AE that had an onset date or a worsening in severity from baseline (pretreatment) or after the first dose of study treatment up to 30 days after the last dose of the study

treatment or initiation of new anticancer therapy, whichever occurred first. TEAE also included all imAEs identified as per the algorithmic approach, recorded up to 90 days after the last dose of the randomized study treatment [8].

In RATIONALE-307, the most frequently reported TEAEs of all grades were anaemia, alopecia, and decreased neutrophil count. TEAEs by system organ class for all grades are blood and lymphatic system disorders, laboratory abnormalities, metabolism and nutrition disorders, and skin and subcutaneous tissue in all three treatment arms [5]. The incidence of TEAEs of any grade or Grade 3-5 is similar in all 3 treatment arms. In tislelizumab plus carboplatin and paclitaxel (100.0%) and tislelizumab plus carboplatin and nab-paclitaxel (99.2%) compared to carboplatin and paclitaxel alone (100.0%). Serious TEAEs was higher when treated with tislelizumab than with carboplatin and paclitaxel alone, with 43.3% in tislelizumab plus carboplatin and paclitaxel, 42.4% in tislelizumab plus carboplatin and nab-paclitaxel, and 24.8% in the carboplatin and paclitaxel arm [8].

Patients in the tislelizumab plus carboplatin and paclitaxel arm experience serious TEAE with a higher incidence compared to patients in the carboplatin and paclitaxel alone arm, including [redacted] Serious TEAEs with a higher incidence in the tislelizumab plus carboplatin and nab-paclitaxel arm compared with the carboplatin and paclitaxel alone arm are [redacted] [5].

For serious TEAEs of Grade 3-5, the distribution pattern shows slightly more events in the tislelizumab arms, 31.7% of patients receiving tislelizumab plus carboplatin and paclitaxel, 35.6% of patients receiving tislelizumab plus carboplatin and nab-paclitaxel, and 13.7% of patients receiving carboplatin and paclitaxel alone [8]. Grade 3–5 serious TEAEs in tislelizumab plus carboplatin and paclitaxel included decreased neutrophil count (53.3%), neutropenia (33.3%), decreased white blood cell count (23.3%), and leukopenia (15.8%). In the tislelizumab plus carboplatin and nab-paclitaxel grade 3-5 serious TEAEs included decreased neutrophil count (45.8%), decreased white blood cell count (27.1%), neutropenia (27.1%), and leukopenia (25.4%) compared to decreased neutrophil count (45.3%), decreased white blood cell count (23.9%), neutropenia (40.2%), and leukopenia (18.8%) in the carboplatin and paclitaxel group. Overall, 89.2% (107/120) of patients in the tislelizumab and carboplatin and paclitaxel group and 87.3% (103/118) of those in the tislelizumab plus carboplatin and nab-paclitaxel group shows Grade 3-5 TEAEs. In comparison, 84.6% (99/117) of patients receiving carboplatin and paclitaxel alone report Grade 3-5 AEs [8,15]. In Table 21 a presentation of AEs of all grades and grade 3-5.

Table 21: Incidence of treatment-emergent adverse events (occurring in ≥20% of patients in any arm) by preferred term and by decreasing frequency of all grade events in Arm A (DCO 2020)

	Tislelizumab + carboplatin and paclitaxel (n=120)	Tislelizumab + carboplatin and nab-paclitaxel (n=118)	Carboplatin and paclitaxel (n=117)

Preferred term with ≥1 event	All Grades (%)	Grade 3-5 (%)	All Grades (%)	Grade 3-5 (%)	All Grades (%)	Grade 3-5 (%)
Patients with ≥1 event	120 (100)	107 (89.2)	117 (99.2)	103 (87.3)	117 (100)	99 (84.6)
Anemia	107 (89.2)	12 (10)	111 (94.1)	27 (22.9)	94 (80.3)	15 (12.8)
Alopecia	78 (65)	0 (0)	82 (69.5)	0 (0)	72 (61.5)	0 (0)
Neutrophil count decreased	78 (65)	64 (53.3)	72 (61)	54 (45.8)	68 (58.1)	53 (45.3)
White blood cell decrease	67 (55.8)	28 (23.3)	68 (57.6)	32 (27.1)	62 (53)	28 (23.9)
Leukopenia	58 (48.3)	19 (15.8)	66 (55.9)	30 (25.4)	57 (48.7)	22 (18.8)
ALT increased	56 (46.7)	3 (2.5)	43 (36.4)	2 (1.7)	27 (23.1)	0 (0)
Decreased appetite	54 (45)	2 (1.7)	55 (46.6)	2 (1.7)	37 (31.6)	1 (0.9)
Neutropenia	53 (44.2)	40 (33.3)	50 (42.4)	32 (27.1)	56 (47.9)	47 (40.2)
AST increased	49 (40.8)	2 (1.7)	42 (35.6)	1 (0.8)	14 (12.0)	0 (0.0)
Platelet count decreased	44 (36.7)	6 (5.0)	52 (44.1)	16 (13.6)	29 (24.8)	2 (1.7)
Constipation	40 (33.3)	0 (0.0)	36 (30.5)	0 (0.0)	27 (23.1)	0 (0.0)
Pain in extremity	40 (33.3)	3 (2.5)	18 (15.3)	0 (0.0)	27 (23.1)	0 (0.0)
Nausea	37 (30.8)	1 (0.8)	54 (45.8)	0 (0.0)	35 (29.9)	1 (0.9)
Thrombocytopenia	35 (29.2)	8 (6.7)	49 (41.5)	15 (12.7)	33 (28.2)	7 (6.0)
Hypoalbuminemia	30 (25.0)	1 (0.8)	25 (21.2)	0 (0.0)	19 (16.2)	0 (0.0)
Asthenia	30 (25.0)	0 (0.0)	24 (20.3)	0 (0.0)	24 (20.5)	1 (0.9)
Blood bilirubin increased	30 (25.0)	0 (0.0)	18 (15.3)	0 (0.0)	15 (12.8)	0 (0.0)
Vomiting	28 (23.3)	1 (0.8)	27 (22.9)	0 (0.0)	20 (17.1)	2 (1.7)

Hypoesthesia	27 (22.5)	0 (0.0)	13 (11.0)	0 (0.0)	20 (17.1)	0 (0.0)
Rash	26 (21.7)	4 (3.3)	28 (23.7)	2 (1.7)	4 (3.4)	0 (0.0)
Hyponatremia	26 (21.7)	2 (1.7)	25 (21.2)	2 (1.7)	20 (17.1)	3 (2.6)
Arthralgia	26 (21.7)	0 (0.0)	23 (19.5)	0 (0.0)	20 (17.1)	0 (0.0)
Hypokalemia	26 (21.7)	3 (2.5)	20 (16.9)	2 (1.7)	16 (13.7)	2 (1.7)
Pneumonia	26 (21.7)	6 (5.0)	19 (16.1)	6 (5.1)	13 (11.1)	3 (2.6)
Pyrexia	25 (20.8)	0 (0.0)	24 (20.3)	0 (0.0)	18 (15.4)	0 (0.0)
Hemoptysis	24 (20.0)	2 (1.7)	20 (16.9)	4 (3.4)	13 (11.1)	0 (0.0)
Malaise	24 (20.0)	3 (2.5)	19 (16.1)	1 (0.8)	19 (16.2)	0 (0.0)

Table adapted from the supplementary material of Wang et al. (2024), Supplementary Table S4.

Source: [15]

The incidence of TEAEs leading to treatment discontinuation is comparable between tislelizumab plus carboplatin and paclitaxel (17.5%) and carboplatin plus paclitaxel alone arms (15.4%), while it is 32.2% in the tislelizumab plus carboplatin and nab-paclitaxel arm. There are 11 patients (9.2%) in the tislelizumab plus carboplatin and paclitaxel arm, 31 patients (26.3%) in the tislelizumab plus carboplatin and nab-paclitaxel arm, and 18 patients (15.4%) in the carboplatin and paclitaxel alone arm who permanently discontinued any component of chemotherapy (carboplatin, paclitaxel, or nab-paclitaxel) due to TEAEs. The incidence of TEAEs leading to tislelizumab discontinuation is comparable between tislelizumab plus carboplatin and paclitaxel (17 patients (14.2%)) and tislelizumab plus carboplatin and nab-paclitaxel (15 patients (12.7%)). Furthermore, the incidence of TEAE leading to death and of infusion-related reactions is comparable among the three treatments [5].

Immune-mediated adverse events (imAE) are only expected with tislelizumab due to the mechanism of action. An incidence of any grade imAE was 44.2% (53 patients) in the tislelizumab plus carboplatin and paclitaxel arm, and 50.8% (60 patients) in the tislelizumab plus carboplatin and nab-paclitaxel arm. ImAEs led to discontinuation of tislelizumab in 6.7% of patients in tislelizumab plus carboplatin and paclitaxel arm, and 6.8% of patients in tislelizumab plus carboplatin and nab-paclitaxel [5].

At final analysis, TEAEs resulting in death are found to be 3.3% (4 patients) in the tislelizumab plus carboplatin and paclitaxel, 5.9% (7 patients) in the tislelizumab plus carboplatin and nab-paclitaxel, and 4.3% (5 patients) in the carboplatin and paclitaxel arm, respectively [5].

Deaths are reported in [redacted] patients receiving tislelizumab plus carboplatin and paclitaxel, [redacted] of patients in the tislelizumab plus carboplatin and nab-paclitaxel group, and [redacted] of patients in the placebo plus carboplatin and paclitaxel group. The most common cause of death across the 3 treatment arms is [redacted] in tislelizumab plus carboplatin and paclitaxel arm, [redacted] in tislelizumab plus carboplatin and nab-paclitaxel arm, and [redacted] in the placebo plus carboplatin and paclitaxel arm. [redacted] [5].

In the KEYNOTE-407 study, 98.6% of patients receiving pembrolizumab plus carboplatin and (nab)-paclitaxel and 98.2% of patients receiving placebo plus carboplatin and (nab)-paclitaxel experience one or more AEs. The most common AEs are anemia, alopecia, neutropenia, and nausea. AEs led to discontinuation more frequently in the intervention arm (28.8%) than in the comparator arm (13.2%). Grade 3 to 5 AEs affect 74.8% of patients in the pembrolizumab group and 70.0% in the placebo group [9,10]. ImAEs and infusion reactions occur more frequently in patients treated with pembrolizumab plus carboplatin and (nab)-paclitaxel (35.3%) compared to patients treated with placebo plus carboplatin and (nab)-paclitaxel (8.9%).

5.2.6.1 Comparability of safety data

Both studies utilized CTCAE criteria for AE classification and RECIST v1.1 for response evaluation, which ensures a high level of methodological comparability in the outcome assessments. The classification of TEAEs and imAEs is also broadly aligned between the studies, with imAEs being defined based on clinical presentation and, in some cases, the need for immunosuppressive therapy [5,9,10].

The incidence of Grade 3-5 AEs is comparable between the two studies, ranging from 89.2% to 84.6% in the RATIONALE-307 and from 74.8% to 70.0% in the KEYNOTE-407. Discontinuation due to TEAEs is more frequent in the intervention arm in KEYNOTE-407 (28.8% vs. 13.2% in the control group) than in RATIONALE-307, where the incidence is 17.5% in the tislelizumab plus paclitaxel arm, 32.2% in the tislelizumab plus nab-paclitaxel arm, and 15.4% in the control arm. Both studies report anemia, alopecia, and neutropenia as the most reported TEAEs, with nearly all patients experiencing at least one TEAE of any grade [9,10,15].

ImAEs are only expected in the experimental arms of RATIONALE-307 (44.2% and 50.8%), while their incidence is higher in KEYNOTE-407 (35.3% vs. 8.9% in the control arm) [5,9,10]. Generally, both studies show comparable safety profiles.

5.2.6.2 Difference in definitions of outcomes

The RATIONALE-307 and KEYNOTE-407 studies both report OS, PFS, safety, and HRQoL using similar definitions. Table 22 provides a comparison of these outcome definitions and a clinician's assessment of their similarity.

Table 22: Definition of relevant outcomes in RATIONALE-307 and KEYNOTE-407

Definitions of outcomes			
Endpoint	**RATIONALE-307**	**KEYNOTE-407**	**Comparability assessed by a clinical expert**
Overall survival	Time from randomization to death independent of reason. Estimated using the nonparametric Kaplan-Meier methods, and treatment difference were assessed with a stratified Cox proportional hazard.	Time from randomization to progression or death, with patients being censored at the last contact if no death occurred. Response was assessed according to RECIST, version 1.1 by BICR. Estimated using the nonparametric Kaplan-Meier methods, and treatment difference were assessed with a stratified Cox proportional hazard.	The methods are considered highly comparable, as clinical practice appears consistent. Differences are primarily related to variations in methodological descriptions, which are not deemed to have a significant impact on the outcomes.
Progression-free survival	Time from randomization to documented progression. Assessed by independent review committee and as secondary outcome by investigator assessment.	Time from randomization to documented progression. Response was assessed according to RECIST, version 1.1 by BICR.	The methods are considered highly comparable, as clinical practice appears consistent.
Discontinuation due to adverse events **Adverse events Grade 3-5**	Safety was assessed throughout the trial by monitoring AEs. It was generally graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and coded using Medical Dictionary for Regulatory activities version 23.0.	Adverse events were generally graded according to the National Cancer Institute Common Terminology Criteria, version 4.03.	The methods are considered generally comparable, with minor differences primarily related to wording. As safety assessments are more subjective, some variability is expected; however, these differences are not deemed to have a significant impact on the overall comparability.
Health related quality of life	HRQoL were assessed by EORTC QLQ-C30 GHS/QoL as well as lung	Assessed by EORTC QLQ-C30 GHS/QoL and lung cancer-related	The two measurement approaches are

	cancer-related symptoms including coughing, dysphagia, dyspnoea, haemoptysis, pain in arms and shoulders, chest pain, and peripheral neuropathy symptoms estimated by QLQ-LC13.	symptoms including coughing, dysphagia, dyspnoea, haemoptysis, pain in arms and shoulders, chest pain, and peripheral neuropathy symptoms assessed by QLQ-LC13. Furthermore, EQ-5D-3L was collected.	comparable, with the only difference being the inclusion of EQ-5D-3L for pembrolizumab.

Abbreviations: BICR, blinded independent central review; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer quality of life questionnaire-cancer module 30; EQ-5D-3L, EuroQol 5 dimensions 3 levels; GHS, global health status; HRQoL, health related quality of life; QLQ-LC13, quality of life questionnaire-lung cancer module 13; QoL, quality of life; N/A, not applicable; RECIST, response evaluation criteria in solid tumors.
Source: [8,10,16,17].

5.2.7 Method of synthesis

This section explains the methodology used for comparative analysis. Due to lack of head-to-head RCTs comparing tislelizumab plus carboplatin and either paclitaxel or nab-paclitaxel to other first-line treatments for locally advanced or metastatic NSCLC, a Bucher ITC is employed to assess relative clinical efficacy and safety. A standardized statistical Bucher's is performed by following the standard protocol [18].

The ITC is performed using a common comparator, carboplatin combined with paclitaxel or nab-paclitaxel, to estimate the relative efficacy and safety of tislelizumab plus chemotherapy compared to pembrolizumab plus chemotherapy. This method depends on the assumption of transitivity, meaning that the studies must be sufficiently comparable in terms of patient populations, study design, and outcome assessments to ensure valid comparisons. RATIONALE-306 and KEYNOTE-407 are considered comparable both in terms of study population and design. Therefore, a Bucher's analysis is applied, based on evidence from RCTs identified through SLR, see description in Appendix D. This method is chosen in alignment with the DMC. Due to the three-arm design of the RATIONALE-307 study, comprising two intervention arms and one comparator arm, two separate Bucher's analyses are conducted as part of the comparative analysis. Specifically, Arm A of RATIONALE-307 is compared to Arm A of KEYNOTE-407, and likewise, Arm B of RATIONALE-307 is compared to Arm A of KEYNOTE-407.

By performing a Bucher's analysis, an evidence-based estimate of the relative efficacy of tislelizumab and pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel are provided. This method is applied to the relevant efficacy and safety outcomes outlined in the treatment guidelines, including OS, PFS, discontinuation due to AE, and AEs of Grade 3-5 [6]. A detailed description of the methodology can be found in Appendix C.

5.2.8 Results from the comparative analysis

To ensure alignment with the clinical question 6, subgroup-specific data are utilized for OS and PFS. For safety, the safety population has been chosen for the comparative

analysis in accordance with the approach in the treatment guidelines. The results from the indirect comparison with Bucher method are listed in Table 23 and Table 24 below.

As 12 and 18-months rates for OS and PFS are not available for the PD-L1 1-49% subgroups from RATIONALE-307, no comparative analyses have been prepared for these outcomes in this application.

Results from the comparative analysis for DCO 2020 for Tevimbra

Table 23: Results from the comparative analysis of Tevimbra (tislelizumab) vs. Keytruda (pembrolizumab) for first-line treatment of squamous NSCLC – comparison of Arm A in RATIONALE-307 and Arm A in KEYNOTE-407

Outcome measure	Tislelizumab carboplatin paclitaxel (DCO: 18.7 months (30th September 2020))	Pembrolizumab carboplatin paclitaxel/nab-paclitaxel (DCO: 56.9 months (23 February 2022))	Relative difference
Subgroup specific data for subgroup PD-L1 1-49%			
Overall survival, HR (95% CI)	0.72 (0.32, 1.61)	0.61 (0.45, 0.83)	**1.18 (0.51, 2.80)**
Overall survival median, absolute effect (95% CI)	N/A	4.9 (-0.62, 10.42)	**N/A**
Progression-free survival, HR (95% CI)	0.4 (0.21, 0.76)	0.60 (0.45, 0.81)	**0.67 (0.33, 1.35)**
Progression-free survival median, absolute effect (95% CI)	5.4 (-2.12, 12.92)	2.2 (-0.59, 4.99)	**3.2 (-4.72, 11.12)**
Data for safety population (as-treated/ITT population)			
Discontinuation due to AEs, RR (95% CI)	1.14 (0.64, 2.02)	2.18 (1.53, 3.10)	**0.52 (0.27, 1.03)**
Grade 3-5 AEs, RR (95% CI)	2.09 (1.27, 3.45)	1.07 (0.96, 1.18)	**1.95 (1.17, 3.25)**

Number of patients: Arm A (RATIONALE-307) 30 patients in subgroup PD-l1 1-49% and 120 in ITT population. Arm A (KEYNOTE-407) 103 patients in subgroup PD-l1 1-49% and 278 in ITT population.
Abbreviations: AE, adverse event; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intention to treat; N/A, not applicable; NR, not reported; PD-L1, programmed death ligand 1; RR, relative risk.
Source: [4,10] .

The estimated HR for OS is 0.72 (95% CI: 0.32, 1.61) for tislelizumab plus carboplatin and paclitaxel and 0.61 (95% CI: 0.45, 0.83) for pembrolizumab plus carboplatin and (nab)-paclitaxel, yielding an indirect HR of 1.18 (95% CI: 0.51, 2.80). Although the point estimate numerically favors pembrolizumab plus carboplatin and (nab)-paclitaxel, the confidence interval overlaps 1.0, indicating no significant difference. The absolute

difference in median OS is not possible to calculate, as the median was not reached for tislelizumab plus carboplatin and paclitaxel at the 2020 DCO.

For PFS, the HR is 0.40 (95% CI: 0.21, 0.76) for tislelizumab plus carboplatin and paclitaxel and 0.60 (95% CI: 0.45, 0.81) for pembrolizumab plus carboplatin and (nab)-paclitaxel, resulting in an indirect HR of 0.67 (95% CI: 0.33, 1.35), suggesting a potential advantage for tislelizumab plus carboplatin and paclitaxel. The absolute effect of PFS for tislelizumab plus carboplatin and paclitaxel 5.4 (95% CI: -2.12, 12.92) and 2.2 (95% CI: -0.59, 4,99) for pembrolizumab plus carboplatin (nab)-paclitaxel resulting in an indirect difference of 3.2 (95% CI: -4.72, 11.12).

In terms of safety outcomes (assessed in the safety population), the risk of Grade 3-5 AEs is RR: 2.09; 95% CI: 1.27–3.45 for tislelizumab plus carboplatin and paclitaxel compared with RR: 1.07; 95% CI: 0.96–1.18 for pembrolizumab plus carboplatin and (nab)-paclitaxel, resulting in an indirect RR of 1.95 (95% CI: 1.17–3.25), indicating a significantly higher risk of Grade 3-5 AEs with tislelizumab plus carboplatin and paclitaxel. For treatment discontinuation due to AEs, the RR is 1.14 (95% CI: 0.64–2.02) for tislelizumab plus carboplatin and paclitaxel and 2.18 (95% CI: 1.53–3.10) for pembrolizumab plus carboplatin and (nab)-paclitaxel, giving an indirect RR of 0.52 (95% CI: 0.27–1.03), which is not statistically significant.

Table 24: Results from the comparative analysis of Tevimbra (tislelizumab) vs. Keytruda (pembrolizumab) for first-line treatment of squamous NSCLC – comparison of Arm B in RATIONALE-307 and Arm A in KEYNOTE-407

Outcome measure	Tislelizumab carboplatin nab-paclitaxel (DCO: 18.7 months (30 September 2020))	Pembrolizumab carboplatin paclitaxel/nab-paclitaxel (DCO: 56.9 months (23 February 2022))	Relative difference
Subgroup specific data for subgroup PD-L1 1-49%			
Overall survival, HR (95% CI)	0.73 (0.33, 1.64)	0.61 (0.45, 0.83)	**1.19 (0.51, 2.82)**
Overall survival median, absolute effect (95% CI)	N/A	4.9 (-0.62, 10.42)	**N/A**
Progression-free survival, HR (95% CI)	0.4 (0.22, 0.74)	0.60 (0.45, 0.81)	**0.67 (0.34, 1.31)**
Progression-free survival median, absolute effect (95% CI)	5.1 (2.12, 8.08)	2.2 (-0.59, 4.99)	**2.9 (--1.1, 6.79)**
Data for safety population (as-treated/ITT population)			

Outcome measure	Tislelizumab carboplatin nab-paclitaxel (DCO: 18.7 months (30 September 2020))	Pembrolizumab carboplatin paclitaxel/nab-paclitaxel (DCO: 56.9 months (23 February 2022))	Relative difference
Discontinuation due to AEs, RR (95% CI)	1.05 (0.95, 1.16)	2.18 (1.53, 3.10)	**0.48 (0.33 0.71**
Grade 3-5 AEs, RR (95% CI)	1.03 (0.93, 1.14)	1.07 (0.96, 1.18)	**0.96 (0.83, 1.11)**

Number of patients: Arm B (RATIONALE-307) 30 patients in subgroup PD-L1 1-49% and 120 in ITT population. Arm A (KEYNOTE-407) 103 patients in subgroup PD-L1 1-49% and 278 in ITT population.
Abbreviations: AE, adverse event; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intention to treat; PD-L1, programmed death ligand 1; RR, relative risk.
Source: [4,10].

For OS, the HR is 0.73 (95% CI: 0.33, 1.64) for tislelizumab plus carboplatin and nab-paclitaxel and 0.61 (95% CI: 0.45, 0.83) for pembrolizumab plus carboplatin and (nab)-paclitaxel, resulting in an indirect HR of 1.19 (95% CI: 0.51, 2.82). This suggests a numerical benefit for pembrolizumab plus carboplatin and (nab)-paclitaxel, although the confidence interval includes 1.0, indicating no significant difference. A relative difference for the absolute effect of OS is not possible to estimate.

Regarding PFS, the HR is 0.40 (95% CI: 0.22, 0.74) for tislelizumab plus carboplatin and nab-paclitaxel and 0.60 (95% CI: 0.45, 0.81) for pembrolizumab plus carboplatin and (nab)-paclitaxel, leading to an indirect HR of 0.67 (95% CI: 0.34–1.31), which favors tislelizumab plus carboplatin and nab-paclitaxel but is not statistically significant. The absolute PFS benefit is 5.1 months (95% CI: 2.12, 8.08) for tislelizumab plus carboplatin and nab-paclitaxel versus 2.2 (95% CI: -0.59, 4.99) months for pembrolizumab plus carboplatin and (nab)-paclitaxel, corresponding to a difference of 2.9 months (95% CI: -1.1, 6.79), again not statistically significant.

For safety outcomes, the RR for treatment discontinuation due to AEs is 1.05 (95% CI: 0.95, 1.16) for tislelizumab plus carboplatin and nab-paclitaxel and 2.18 (95% CI: 1.53, 3.10) for pembrolizumab plus carboplatin and (nab)-paclitaxel, yielding an indirect RR of 0.48 (95% CI: 0.33, 0.71), suggesting a significantly lower risk of discontinuation for tislelizumab plus carboplatin and nab-paclitaxel. The risk of Grade 3–5 AEs is similar between the two treatments, with an RR of 1.03 (95% CI: 0.93, 1.14) for tislelizumab plus carboplatin and nab-paclitaxel and 1.07 (95% CI: 0.96, 1.18) for pembrolizumab plus carboplatin and (nab)-paclitaxel, leading to an indirect RR of 0.96 (95% CI: 0.83, 1.11), indicating no meaningful difference.

Both treatment regimens, tislelizumab plus carboplatin and (nab)-paclitaxel, and pembrolizumab plus carboplatin and (nab)-paclitaxel, demonstrate similar efficacy and safety profiles in patients with squamous NSCLC PD-L1 1-49%. No statistically significant differences in OS or PFS are observed in the Bucher analysis based on RATIONALE-307 and KEYNOTE-407, and both regimens showed comparable rates of Grade 3–5 AEs.

These findings support the conclusion that both treatment options offer equivalent clinical benefit within this patient population.

6. List of experts

Anders Mellemgaard, Medical Doctor in Oncology, MD, PhD

7. References

1. European Medicines Agency. Tevimbra - EPAR. https://www.ema.europa.eu/en/medicines/human/EPAR/tevimbra. 2023.

2. European Medicines Agency. Tevimbra - opinion on variation to marketing authorisation. https://www.ema.europa.eu/en/medicines/human/variation/tevimbra. 2024.

3. European Medicines Agency. Summary of Product Characteristics - Tevimbra. 2023.

4. BeiGene (Shanghai). Summary Report of Benefit-Risk Assessment - Tevimbra. 2024 Feb.

5. BeiGene. Data on file - BeiGene. 2024.

6. Medicinrådet. Tillaeg til Medicinrådets behandlingsvejledning vedrørende laegemidler til førstelinjebehandling af uhelbredelig ikke-småcellet lungekraeft. 2024 Feb.

7. Wang J, Lu S, Yu X, Hu Y, Sun Y, Wang Z, et al. Tislelizumab plus chemotherapy vs chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer a phase 3 randomized clinical trial. JAMA Oncol. 2021 May 1;7(5):709–17.

8. Wang J, Lu S, Yu X, Hu Y, Zhao J, Sun M, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III RATIONALE-307 trial. ESMO Open [Internet]. 2024 Oct;9(10):103727. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2059702924014972

9. Paz-Ares L, Vicente D, Tafreshi A, Robinson A, Soto Parra H, Mazières J, et al. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients With Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407. In: Journal of Thoracic Oncology. Elsevier Inc.; 2020. p. 1657–69.

10. Novello S, Dariusz ;, Kowalski M, Luft ; Alexander, Mahmut ;, David Vicente ;, et al. Pembrolizumab Plus Chemotherapy in Squamous Non-Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study. J Clin Oncol [Internet]. 2023;41:1999–2006. Available from: https://doi.

11. Kang M, Ragan BG, Park J-H. Issues in outcomes research: an overview of randomization techniques for clinical trials. J Athl Train. 2008;43(2):215–21.

12. Agilent. Fundamentals of Tumor Proportion Score (TPS). https://pathology-education.agilent.com/en-gb/home/training/pd-l1-ihc-22c3/fundamentals-of-tumor-proportion-score-tps.html.

13. Prince EA, Sanzari JK, Pandya D, Huron D, Edwards R. Analytical concordance of PD-L1 assays utilizing antibodies from FDA-approved diagnostics in advanced cancers: a systematic literature review. JCO Precis Oncol. 2021;5:953–73.

14. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. New England Journal of Medicine. 2018 Nov 22;379(21):2040–51.

15. Wang J, Lu S, Yu X, Hu Y, Zhao J, Sun M, et al. Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III RATIONALE-307 trial - Supplementary. ESMO Open. 2024;9(10):103727.

16. Wang J, Yu X, Barnes G, Leaw S, Bao Y, Tang B. The effects of tislelizumab plus chemotherapy as first-line treatment on health-related quality of life of patients with advanced squamous non-small cell lung cancer: Results from a phase 3 randomized clinical trial. Cancer Treat Res Commun. 2022 Jan 1;30.

17. Mazieres J, Kowalski D, Luft A, Vicente D, Tafreshi A, Laktionov K, et al. 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. J Clin Oncol [Internet]. 2019;37. Available from: https://doi.

18. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997;50(6):683–91.

19. BeiGene. A Study of Tislelizumab in Combination With Chemotherapy Versus Chemotherapy in Advanced Lung Cancer. https://clinicaltrials.gov/study/NCT03594747. 2024.

20. Merck Sharp and Dohme LLC. A Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With First Line Metastatic Squamous Non-small Cell Lung Cancer (MK-3475-407/KEYNOTE-407). https://clinicaltrials.gov/study/NCT02775435. 2016.

21. Higgins JP. Cochrane handbook for systematic reviews of interventions. Cochrane Collaboration and John Wiley & Sons Ltd. 2008;

22. Dissemination U of YorkNHSC for R&. Undertaking Systematic Reviews of Research on Effectiveness: CRD's Guidance for Those Carrying Out Or Commissioning Reviews. Centre for Reviews and Dissemination, University of York; 2001.

23. Pilkington G, Boland A, Brown T, Oyee J, Bagust A, Dickson R. A systematic review of the clinical effectiveness of first-line chemotherapy for adult patients with

locally advanced or metastatic non-small cell lung cancer. Thorax. 2015;70(4):359–67.

Appendix A. Main characteristics of studies included

Table 25: Main characteristics for RATIONALE-307

Trial name: RATIONALE-307	NCT number: NCT03594747
Objective	The overall objective was to compare the efficacy and safety of tislelizumab combined with chemotherapy versus chemotherapy only as first-line treatment in advanced and metastatic squamous NSCLC.
Publications – title, author, journal, year	Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-Line Treatment for Advanced Squamous Non-Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial, Wang J et al, JAMA Oncol, 2021. Randomized Phase III Study of Tislelizumab plus Chemotherapy versus Chemotherapy Alone as First-Line Treatment for Advanced Squamous Non-Small Cell Lung Cancer (Sq-NSCLC): RATIONALE-307 Updated Analysis, Wang J et al, ESMO Open, 2024.
Study type and design	An open-label, randomized, multicenter, phase 3 study. Patients were randomized (1:1:1) to treatment by using an interactive response technology system.
Sample size (n)	360 (91 for PD-L1 1-49%)
Main inclusion criteria	1. Age 18-75 years old, male or female, and signed informed consent form (ICF) 2. Advanced NSCLC diagnosed by pathological or clinical physicians 3. Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 4. Participants must have ≥ 1 measurable lesion as defined per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 5. Must be treatment-naive for locally advanced or metastatic squamous NSCLC 6. Life expectancy ≥ 12 weeks 7. Participants must have adequate organ function 8. Male/Female is willing to use a highly effective method of birth control

Trial name: RATIONALE-307	NCT number: NCT03594747
Main exclusion criteria	1. Diagnosed with NSCLC but with epidermal growth factor receptors (EGFR)-sensitizing mutation or anaplastic lymphoma kinase (ALK) gene translocation 2. Received any approved systemic anticancer therapy 3. Received prior treatment with EGFR inhibitors or ALK inhibitors 4. Received prior therapies targeting programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1) 5. With history of interstitial lung disease 6. Clinically significant pericardial effusion 7. Severe infections, active leptomeningeal disease or uncontrolled, untreated brain metastasis 8. Any major surgical procedure before randomization 9. Human immunodeficiency virus infection 10. Untreated hepatitis B virus (HBV)/hepatitis C virus (HCV) 11. Active autoimmune diseases or history of autoimmune diseases 12. History of allergic reactions to chemotherapy
Intervention	Arm A: Tislelizumab plus Carboplatin and Paclitaxel. Tislelizumab 200 mg plus paclitaxel 175 mg/m^2 and carboplatin area under the plasma or serum concentration-time curve (AUC) 5 on Day 1 administered intravenously once every 3 weeks until unacceptable toxicity, withdrawal of consent, loss of clinical benefit, or disease progression; paclitaxel and carboplatin were administered for 4 to 6 cycles (each cycle is 21 days). 120 patients received this intervention. Arm B: Tislelizumab plus Carboplatin and Nab-paclitaxel. Tislelizumab 200 mg on Day 1 plus Nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 and carboplatin AUC 5 on Day 1 administered intravenously once every 3 weeks until unacceptable toxicity, withdrawal of consent, loss of clinical benefit, or disease progression; Nab-paclitaxel and carboplatin were administered for 4 to 6 cycles (each cycle is 21 days). 119 patients received this intervention.
Comparator(s)	Arm C: Carboplatin plus Paclitaxel. Paclitaxel 175 mg/m^2 and carboplatin AUC 5 on Day 1 administered intravenously once every 3 weeks for 4 to 6 cycles (each cycle is 21 days). 121 patients received this comparator.
Follow-up time	Primary interim analysis: 6th December 2019 (median study follow-up: 8.6 months) Final analysis: 30th September 2020 (median study follow-up: 18.7 months)

Trial name: RATIONALE-307	NCT number: NCT03594747
	Extended follow-up: 28th April 2023 (median study follow-up: 44.8 months)
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** RATIONALE-307 reported several endpoints including PFS assessed by IRC per RECIST v 1.1 or death as primary endpoints. Secondary endpoints included OS and PFS by investigator assessment, HRQoL as assessed by EORTC QLQ-LC13 and EORTC QLQ-C30, and safety. **Other endpoints:** ORR and DOR by IRC assessment and ORR and DOR by investigator assessment were included as secondary endpoints in this study but was not included in this submission.
Method of analysis	All efficacy analyses were assessed in the ITT population, defined as all randomized patients. Time-to-event end points were estimated using Kaplan-Meier analysis; the Brookmeyer and Crowley method was used to construct 95% CIs for the median PFS, OS, and DOR of each treatment arm. Hazard ratios for comparisons between arms A or B with arm C were estimated using the stratified Cox proportional hazards model; a stratified 1-sided log-rank test calculated the significance between treatment arms. The stratified Cochran-Mantel-Haenszel $\chi 2$ test assessed differences in ORR. The stratification factors of PD-L1 expression (<1% vs 1%-49% vs ≥50%) and disease stage (IIIB vs IV) were applied to all stratified analyses. Safety analyses were assessed in the safety analysis set, defined as all patients receiving any dose of tislelizumab and/or chemotherapy. Safety outcomes were analyzed using descriptive statistics. Specifically, categorical safety variables – such as the incidence of specific AEs, or the proportion of patients with severe (grade ≥3) toxicities – were summarized as number and percentage of patients in each treatment arm experiencing those event.
Subgroup analyses	Pre-specified subgroup analysis for OS and PFS: PD-L1 expression status (TC 1%-49%)* Efficacy analyses for this subpopulation were assessed as described for the ITT population.
Other relevant information	N/A

Abbreviations: ALK, anaplastic lymphoma kinase; AUC, area under the curve; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EORTC QLQ-C30, European Organization For Research and Treatment Of Cancer core quality of life questionnaire-cancer module 30; EORTC QLQ-LC13, European Organization For Research and Treatment Of Cancer core quality of life questionnaire-lung cancer module 13; HBV, hepatitis B virus; HCV, hepatitis C virus; HRQoL, health-related quality of life; ICF, informed consent form; IRC, independent review committee; ITT, intention to treat; N/A, not applicable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PFS, progression-free survival; PS, performance status; RECIST, response evaluation criteria in solid tumors.

*In this application, only subgroup data for PD-L1 1-49% subgroup is utilized. However, subgroup specific analysis was performed for various PD-L1 expression groups.
Source: [5,7,8,19].

Table 26: Main characteristics of KEYNOTE-407

Trial name: KEYNOTE-407	NCT number: NCT02775435
Objective	The overall objective was to compare the efficacy and safety of pembrolizumab combined with chemotherapy versus chemotherapy only as first-line treatment in metastatic squamous NSCLC.
Publications – title, author, journal, year	Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study, Novello et al., Journal of Clinical Oncology, 2023. A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients with Metastatic Squamous NSCLC: Protocol-Specified Final Analysis of KEYNOTE-407, Paz-Arez, Journal of Thoracic Oncology, 2020.
Study type and design	A randomized, double-blinded, phase III trial. Patients were randomized (1:1) to receive carboplatin and paclitaxel/nab-paclitaxel and pembrolizumab or placebo. Randomization was stratified by choice of taxane, geography, and PD-L1 TPS.
Sample size (n)	559 (207 for PD-L1 1-49%)
Main inclusion criteria	1. Aged 18 years and older 2. Histologically or cytologically confirmed diagnosis of stage IV squamous NSCLC 3. Measurable disease based on RECIST version 1.1 4. Not previously received systemic treatment for metastatic NSCLC 5. Provided tumor tissue for the determination of PD-L1 status 6. Life expectancy of at least 3 months 7. ECOG performance status of 0 or 1 8. Adequate organ function as assessed by laboratory parameters
Main exclusion criteria	1. Non-squamous NSCLC 2. Previous systemic cytotoxic chemotherapy for metastatic disease 3. Major surgical procedure within 3 weeks before treatment 4. Received radiation therapy to the lung that was greater than 30 Gy within 6 months or completed palliative radiotherapy within 7 days before treatment 5. Required any form of antineoplastic therapy

Trial name: KEYNOTE-407		NCT number: NCT02775435
	6. History of previous malignancy 7. Had active central nervous system metastases or carcinomatous meningitis 8. Had peripheral neuropathy grade 2 or greater 9. Had active autoimmune disease requiring systemic treatment within 2 years 10. Received long-term systemic steroids 11. Previous treatment with any other anti-PD-1, PD-L1, or PD-L2 agent 12. Had interstitial lung disease or a history of pneumonitis that required steroid therapy	
Intervention	Pembrolizumab in combination with carboplatin and paclitaxel/nab-paclitaxel 278 participants received pembrolizumab 200 mg IV prior to chemotherapy on Day 1 of each cycle (Q3W) for up to 35 cycles (~ 2 years) AND investigator's choice of paclitaxel (200 mg/m^2 IV on Day 1 of each cycle for 4 cycles) OR nab-paclitaxel (100 mg/m^2 IV on Days 1, 8, 15 of each cycle for 4 cycles) AND carboplatin AUC 6 IV on Day 1 of each cycle for 4 cycles.	
Comparator(s)	Placebo in combination with carboplatin and paclitaxel/nab-paclitaxel 281 participants received normal saline as placebo IV prior to chemotherapy on Day 1 of each cycle (Q3W) for up to 35 cycles (~ 2 years) AND paclitaxel (200 mg/m^2 IV on Day 1 of each cycle for 4 cycles) OR nab-paclitaxel (100 mg/m^2 IV on Days 1, 8, 15 of each cycle for 4 cycles) AND carboplatin AUC 6 IV on Day 1 of each cycle for 4 cycles.	
Follow-up time	Primary efficacy analysis cut-off: 7.8 months Final baseline analysis cut-off: 9 May 2019 (14.3 months) Extended analysis cut-off: 40.1 months 5-year follow-up cut-off: 23 February 2022 (56.9 months)	
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** KEYNOTE-407 reported several endpoints, including PFS as assessed by blinded independent central review per RECIST 1.1 and OS, defined as time from randomization to death, both evaluated over approximately 19 months as primary endpoints. Secondary endpoints included HRQoL as assessed by EORTC QLQ-LC13 and EORTC QLQ-C30, and safety. **Other endpoints:**	

Trial name: KEYNOTE-407	NCT number: NCT02775435
	ORR and DOR by RECIST 1.1 t were included as secondary endpoints in this study but were not included in this submission.
Method of analysis	All efficacy analyses were conducted in the ITT population, which included all randomized patients. Time-to-event endpoints, including OS, PFS, and DOR, were estimated using Kaplan-Meier methodology. The magnitude of treatment differences (HR and 95% CI) was assessed with a stratified Cox proportional hazards model and the Efron method of tie handling. Randomization stratification factors were applied to the stratified Cox model. Safety analyses included all randomized patients who received at least one dose of study treatment. AEs that occurred during crossover pembrolizumab treatment were excluded from the primary safety comparison between treatment arms. Safety outcomes were summarized using descriptive statistics: categorical variables (e.g., incidence of specific AEs or grade 3-5 AEs) were reported as counts and percentages by treatment arm. No formal statistical hypothesis testing was conducted for between-group comparisons of adverse event rates. Immune-mediated adverse events and infusion reactions were analyzed using predefined groupings of preferred terms, regardless of investigator attribution.
Subgroup analyses	Subgroup analysis: PD-L1 expression (1%-49%)* Efficacy analyses for this subpopulation were assessed as described for the ITT population.
Other relevant information	N/A

Abbreviations: AE, adverse event; CI, confidence interval; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention to treat; N/A, not applicable; NSCLC, non-small-cell lung cancer; OS, overall survival; PD-L1, programmed death ligand 1; PD-L2, programmed death ligand 2; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors
* In this application, only the subgroup data for the PD-L1 1-49% category is utilized. However, in the study, subgroup-specific data was analyzed to account for geographical differences and varying levels of PD-L1 expression among patients.
Source: [9,10,20].

Appendix B. Efficacy results per study

Results per study

In Table 27 and Table 28 below, the relevant efficacy results for this submission are presented.

Table 27: Results per RATIONALE-307 (DCO: 2020)

Results of RATIONALE-307 (NCT03594747) DCO: 30th September 2020											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival (ITT population), DCO: 30th September 2020	Tislelizumab + carboplatin and paclitaxel	120	22.8 (19.1, NE)	2.6 months	(-9.86, 15.06)	N/A	HR: 0.68	0.46, 1.01	NR	Median overall survival was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. The HR is based on a Cox proportional hazards model l, and a stratified log-rank test was carried out to test the difference between treatment arms. The absolute effect was calculated by subtracting the median survival in months, and the CI was derived based on	[8]
	Tislelizumab + carboplatin and nab-paclitaxel	119	NE (18.6, NE)	N/A		N/A	HR: 0.75	0.50, 1.12	NR		
	Carboplatin + paclitaxel	121	20.2 (16.0, NE)								

Results of RATIONALE-307 (NCT03594747) DCO: 30th September 2020											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										the CIs for the individual medial survival estimates.	
Median overall survival (Subgroup: PD-L1 1-49%), DCO: 30th September 2020	Tislelizumab + carboplatin and paclitaxel	30	26.1 (15.1, 26.1)	N/A	X	N/A	HR: 0.72	0.32, 1.61	NR	Median overall survival was estimated by Kaplan-Meier method with 95% CIs estimated using the method of Brookmeyer and Crowley. The HR is based on a Cox proportional hazards model l, and a stratified log-rank test was carried out to test the difference between treatment arms. The absolute effect was calculated by subtracting the median survival in months, and the CI was derived based on the Cis for the individual medial survival estimates.	[4]
	Tislelizumab + carboplatin and nab-paclitaxel	30	NE (14.1, NE)	N/A	X	N/A	HR: 0.73	0.33, 1.64	NR		
	Carboplatin + paclitaxel	31	NE (11.4, NE)								
Progression-free survival (ITT	Tislelizumab + carboplatin and paclitaxel	120	7.7 (6.7, 10.4)	2.2 months	(0.22, 4.18)	N/A	HR: 0.45	0.33, 0.62	NR	Progression-free survival was defined as the time from randomization to the first documented disease progression or death from any	[8]

Results of RATIONALE-307 (NCT03594747) DCO: 30th September 2020											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
population) DCO: 30th September 2020	Tislelizumab + carboplatin and nab-paclitaxel	119	9.6 (7.4, 10.8)	4.1 months	(2.26, 5.94)	N/A	HR: 0.43	0.31, 0.60	NR	cause, whichever occurred first. PFS was assessed by an independent review committee using RECIST v1.1 criteria. Median PFS was estimated using the Kaplan–Meier method, and the 95% confidence intervals were calculated using the Brookmeyer and Crowley method. Hazard ratios (HRs) and corresponding 95% CIs were derived from a Cox proportional hazards model.	
	Carboplatin + paclitaxel	121	5.5 (4.2, 5.6)								
Progression-free survival (Subgroup: PD-L1 1-49%), DCO: 30th September 2020	Tislelizumab + carboplatin and paclitaxel	30	10.4 (5.49, 20.04)	5.4 months	(-2.12, 12.92)	N/A	HR: 0.40	0.21, 0.76	NR	Progression-free survival was defined as the time from randomization to the first documented disease progression or death from any cause, whichever occurred first. PFS was assessed by an independent review committee using RECIST v1.1 criteria. Median PFS was estimated using the Kaplan–Meier method, and the 95%	[4]
	Tislelizumab + carboplatin and nab-paclitaxel	30	10.1 (7.39, 11.99)	5.1 months	(2.12, 8.08)	N/A	HR: 0.4	0.22, 0.74	NR		

Results of RATIONALE-307 (NCT03594747) DCO: 30th September 2020											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										confidence intervals were calculated using the Brookmeyer and Crowley method. Hazard ratios (HRs) and corresponding 95% CIs were derived from a Cox proportional hazards model.	
	Carboplatin + paclitaxel	31	5.0 (2.76, 6.54)								
Discontinuation due to AEs (ITT population). DCO: 30th September 2020	Tislelizumab + carboplatin and paclitaxel	120	21/120 (17.5%)	NR	NR	NR	RR: 1.14	0.64, 2.02	NR	The proportion of patients who discontinued treatment due to AEs was calculated as a proportion of the total population. It was generally graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and coded using Medical Dictionary for Regulatory activities version 23.0.	[4]
	Tislelizumab + carboplatin and nab-paclitaxel	119	38/118 (32.2%)	NR	NR	NR	RR: 1,05	0.95, 1.16	NR		
	Carboplatin + paclitaxel	121	18/117 (15.4%)								

Results of RATIONALE-307 (NCT03594747) DCO: 30th September 2020											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Adverse events grade 3-5 (ITT population). DCO: 30th September 2020	Tislelizumab + carboplatin and paclitaxel	120	107/120 (89.2%)	NR	NR	NR	RR: 2.09	1.27, 3.45	NR	AEs grade 3-5 was assessed throughout the trial by monitoring AEs and assessed by the investigator. It was generally graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 and coded using Medical Dictionary for Regulatory activities version 23.0.	[4]
	Tislelizumab + carboplatin and paclitaxel	119	103/118 (87.3%)	NR	NR	NR	RR: 1.03	0.93, 1.14	NR		
	Carboplatin + paclitaxel	121	99/117 (84.6%)								

Abbreviations: AE, adverse event; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intention to treat; N/A, not applicable; NE, not estimated; NR, not reported; PD-L1, programmed death ligand 1; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors; RR, relative risk.
Source: [4,5,8].

Table 28: Results per KEYNOTE-407

Results of KEYNOTE-407 (NCT02775435) DCO: 23 February 2022											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Median overall survival (ITT population), DCO: 23 February 2022	Pembrolizumab + carboplatin and (nab)-paclitaxel	278	17.2 (14.4, 19.7)	5.6	2.4, 8.80	N/A	HR: 0.71	0.59, 0.85	NR	Overall survival was defined as the time from randomization to death due to any cause. Subjects without a documented death at the time of analysis were censored at the date of last known contact. Median OS and 95% confidence intervals were estimated using the Kaplan–Meier method. Hazard ratios and corresponding confidence intervals were calculated using a Cox proportional hazards model.	[10]
	Carboplatin + (nab)-paclitaxel	280	11.6 (10.1, 13.7)								
Median overall survival (Subgroup: PD-L1 1-	Pembrolizumab + carboplatin and (nab)-paclitaxel	103	18.0 (13.6, 22.8)	4.9	-0.62, 10.42	N/A	HR: 0.61	0.45, 0.83	NR	Overall survival was defined as the time from randomization to death due to any cause. Subjects without a documented death at the time	[10]

Results of KEYNOTE-407 (NCT02775435) DCO: 23 February 2022											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
49%), DCO: 23 February 2022	Carboplatin + (nab)-paclitaxel	104	13.1 (9.1, 15.2)							of analysis were censored at the date of last known contact. Median OS and 95% confidence intervals were estimated using the Kaplan–Meier method. Hazard ratios and corresponding confidence intervals were calculated using a Cox proportional hazards model.	
Progression-free survival (ITT population), DCO: 23 February 2022	Pembrolizumab + carboplatin and (nab)-paclitaxel	278	8.0 (6.3, 8.5)	2.9	1.51, 4.29	N/A	0.62	0.52, 0.74	NR	Progression-free survival was defined as the time from randomization to the first documented disease progression (per RECIST version 1.1) or death from any cause, whichever occurred first. PFS was assessed both by a blinded independent central imaging review and by the investigator. Median PFS was estimated using the Kaplan–Meier method, and 95%	[10]
	Carboplatin + (nab)-paclitaxel	280	5.1 (4.3, 6.0)								

Results of KEYNOTE-407 (NCT02775435) DCO: 23 February 2022											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
										confidence intervals were calculated using the method of Brookmeyer and Crowley. Hazard ratios and confidence intervals were derived from a Cox proportional hazards model.	
Progression-free survival (Subgroup: PD-L1 1-49%), DCO: 23 February 2022	Pembrolizumab + carboplatin and (nab)-paclitaxel	103	8.2 (6.2, 11.4)	2.2	-0.59, 4.99	N/A	HR: 0.60	0.45, 0.81	NR	Progression-free survival was defined as the time from randomization to the first documented disease progression (per RECIST version 1.1) or death from any cause, whichever occurred first. PFS was assessed both by a blinded independent central imaging review and by the investigator. Median PFS was estimated using the Kaplan–Meier method, and 95% confidence intervals were calculated using the method of Brookmeyer and Crowley.	[10]
	Carboplatin + (nab)-paclitaxel	104	6.0 (4.2, 6.2)								

Results of KEYNOTE-407 (NCT02775435) DCO: 23 February 2022											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
										Hazard ratios and confidence intervals were derived from a Cox proportional hazards model.	
Discontinuation due to AEs (ITT population)	Pembrolizumab + carboplatin and (nab)-paclitaxel	278	80/278 (28.8%)	N/A	N/A	N/A	RR: 2.18	1.53, 3.10	NR	Discontinuation due to adverse events was reported as the proportion of patients who permanently discontinued treatment during the trial or within 30 days thereafter (or within 90 days for serious adverse events), regardless of attribution by the investigator. The relationship between AEs and study treatment was assessed by the investigator based on various factors. AEs were generally graded according to the National cancer institute common terminology criteria, version 4.03.	[10]
	Carboplatin + (nab)-paclitaxel	280	37/280 (13.2%)								

Results of KEYNOTE-407 (NCT02775435) DCO: 23 February 2022											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
AEs grade 3-5 (ITT population)	Pembrolizumab + carboplatin and (nab)-paclitaxel	278	208/278 (74.8%)	N/A	N/A	N/A	RR: 1.07	0.96, 1.18	NR	AEs grade 3 to 5 were recorded from the time of first dose until 30 days after the last dose of study treatment. AEs were coded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Events were considered treatment-related based on the investigator's assessment. Results were summarized descriptively as proportions of the ITT population.	[10]
	Carboplatin + (nab)-paclitaxel	280	196/280 (70.0%)								

Abbreviations: AE, adverse event; CI, confidence interval; DCO, data cut-off; HR, hazard ratio; ITT, intention to treat; N/A, not applicable; NCI CTCAE, National Cancer Institute common terminology criteria for adverse events; NR, not reported; OS, overall survival; PFS, progression-free survival; RECIST, response evaluation criteria in solid tumors.
Source: [10].

Appendix C. Comparative analysis of efficacy

Due to absence of a head-to-head study comparing tislelizumab plus carboplatin and either paclitaxel or nab-paclitaxel to alternative first-line treatments for locally advanced or metastatic NSCLC a Bucher ITC was performed. Bucher analysis is a simple statistical method used to estimate the relative effect or risk between two treatments that have been compared to a common comparator.

The method maintains the principles of randomized comparisons by preserving the internal validity of the included trials. It assumes that the estimations of relative or absolute effect in the different trials can be compared, provided that the trials are sufficiently similar in terms of design, population characteristics, outcome definitions and other relevant factors.

For relative measures like HR comparison, the method uses logarithmic transformation (in this case the natural logarithm) to show their multiplicative nature. To calculate the relative difference the following equations were used:

$$Relative\ difference = \frac{HR(tislelizumab)}{HR(pembrolizumab)}$$

Then the 95% CI was to be estimated for the relative difference. This can be performed in various steps, however, in the application a two-step approach was applied. Firstly, the standard error (SE) was calculated from the 95% CI of the respective HRs. Secondly, the 95% CI was calculated from the estimations of SE (16). The different equations can be seen here:

$$SE(tislelizumab) = \frac{Ln\big(HR(tislelizumab)\big) - Ln\big(HR(pembrolizumab)\big)}{2 * 1.96}$$

$$95\%\ CI = Exp\left(Ln(relative\ difference) \pm \sqrt{SE(tislelizumab)^2 + SE(pembrolizumab)^2}\right)$$

In contrast, when considering an absolute effect an ITC is performed directly on the differences without interpretation of logarithmic transformations [18].

The outcome of a Bucher ITC reflects an indirect estimate of the comparative efficacy or safety between two interventions. However, uncertainty in relation to the estimations should be reflected. In this application a Bucher analysis comparing the two arms A and B in RATIONALE-307 individually against Arm A in KEYNOTE-407 have been performed. This was done to demonstrate the comparability of the arms when no head-to-head study exists. No adjustments were made in connection with the analysis.

The results for each relevant outcome for all comparisons are depicted in Table 29 and Table 30.

Table 29: Comparative analysis (Bucher ITC) of tislelizumab plus carboplatin and paclitaxel (Arm A) to pembrolizumab plus carboplatin and (nab)-paclitaxel (Arm A) for patients with squamous NSCLC

Outcome		Absolute difference in effect		Relative difference in effect		Method used for quantitative synthesis
	Studies included in the analysis	Difference	95% CI	Difference	95% CI	
Overall survival	RATIONALE-307 and KEYNOTE-407	N/A	N/A	HR: 1.18	0.51, 2.80	An ITC was performed using the standard Bucher method. Hazard ratios and calculated absolute effects for tislelizumab (RATIONALE-307) and pembrolizumab (KEYNOTE-407) were compared via a shared control arm. The method assumes trial similarity in patient population, study design, and outcome definitions.
Progression-free survival	RATIONALE-307 and KEYNOTE-407	3.2	-4.72, 11.12	HR: 0.67	0.33, 1.35	An ITC was performed using the standard Bucher method. Hazard ratios and calculated absolute effects fortislelizumab (RATIONALE-307) and pembrolizumab (KEYNOTE-407) were compared via a shared control arm. The method assumes trial similarity in patient population, study design, and outcome definitions.
Grade 3-5 AEs	RATIONALE-307 and KEYNOTE-407	N/A	N/A	1.95	1.17, 3.25	A Bucher indirect comparison was applied to relative risks of grade ≥3 adverse events, based on safety data reported in the ITT population in the included studies.

Outcome		Absolute difference in effect		Relative difference in effect		Method used for quantitative synthesis
	Studies included in the analysis	Difference	95% CI	Difference	95% CI	
Discontinuation due to AEs	RATIONALE-307 and KEYNOTE-407	N/A	N/A	0.52	0.27, 1.03	A Bucher indirect comparison was applied to relative risks of discontinuation due to adverse events, based on safety data reported in the ITT population in the included studies.

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention to treat; N/A, not applicable; NR, not reported.
Source:[5,10].

Table 30: Comparative analysis (Bucher ITC) of tislelizumab plus carboplatin and nab-paclitaxel (Arm B) to pembrolizumab plus carboplatin and (nab)-paclitaxel (Arm A) for patients with squamous NSCLC

Outcome		Absolute difference in effect		Relative difference in effect		Method used for quantitative synthesis
	Studies included in the analysis	Difference	95% CI	Difference	95% CI	
Overall survival	RATIONALE-307 and KEYNOTE-407	N/A	N/A	HR: 1.19	0.51, 2.82	An ITC was performed using the standard Bucher method. Hazard ratios and calculated absolute effects for tislelizumab (RATIONALE-307) and pembrolizumab (KEYNOTE-407) were compared via a shared control arm. The method assumes trial similarity in patient population, study design, and outcome definitions.
Progression-free survival	RATIONALE-307 and KEYNOTE-407	2.9	-1.1, 6.79	HR: 0.67	0.34, 1.31	An ITC was performed using the standard Bucher method. Hazard ratios and calculated absolute effects for tislelizumab (RATIONALE-307) and pembrolizumab (KEYNOTE-407) were compared via

Outcome		Absolute difference in effect		Relative difference in effect		Method used for quantitative synthesis
	Studies included in the analysis	Difference	95% CI	Difference	95% CI	
						a shared control arm. The method assumes trial similarity in patient population, study design, and outcome definitions.
Grade 3-5 AEs	RATIONALE-307 and KEYNOTE-407	N/A	N/A	0.96	0.83, 0.71	A Bucher indirect comparison was applied to relative risks of grade ≥3 adverse events, based on safety data reported in the ITT population in the included studies.
Discontinuation due to AEs	RATIONALE-307 and KEYNOTE-407	N/A	N/A	0.48	0.33, 0.71	A Bucher indirect comparison was applied to relative risks of discontinuation due to adverse events, based on safety data reported in the ITT population in the included studies

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention to treat; N/A, not applicable.
Source: [4,10].

Appendix D. Literature searches for the clinical assessment

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

A comprehensive global clinical systematic literature review was conducted in the following databases: Embase®, MEDLINE® and Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews, and the Health Technology Assessment database of Effects in the Cochrane Library. These databases have been summarized in Table 31 below. The comprehensive SLR aimed to identify evidence from RCTs on efficacy, HRQoL, safety, and tolerability of relevant treatments for NSCLC [5].

The search was conducted in compliance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in accordance with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement [21,22].

Table 31: Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	www.embase.com	1974 to July 22, 2024	Original SLR: 2nd November 2022 Third update: 24 July 2024
Medline	https://pubmed.ncbi.nlm.nih.gov/advanced	1946 to July 22, 2024	Original SLR: 2 November 2022 Third update: 24 July 2024
Cochrane Central Register of Controlled Trials, or referred to as CENTRAL Including the following databases: Cochrane Database of Systematic	www.cochranelibrary.com/central	2005 to July 17, 2024	Original SLR: 2 November 2022 Third update: 24 July 2024

Database	Platform/source	Relevant period for the search	Date of search completion
Reviews, Database of Abstracts of Reviews, and the Health Technology Assessment database of Effects			

Abbreviations: SLR, systematic literature review.

Furthermore, searches for conference posters were performed at the same time as the original SLR and the three updates to capture the most recent unpublished or ongoing trials. A single reviewer reviewed the relevant websites that were not indexed in Embase® [5]. The following conferences were included: World Conference on Lung Cancer; International Lung Cancer Research Association; American Association for Cancer Research Annual Meeting; The European Lung Cancer Congress; Society for Immunotherapy of Cancer; International Society for Quality-of-Life Research; Chinese Society of Clinical Oncology; International Society for Pharmacoeconomics and Outcomes Research; Academy of Managed Care Pharmacy Foundation.

Table 32: Other sources included in the literature search (N/A)

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

Table 33: Conference material included in the literature search (N/A)

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

The original SLR builds on findings from a published SLR for first-line chemotherapy in advanced, unresectable, or metastatic NSCLC patients from Pilkington 2015 which captured studies from 2001 until 2009 [23]. The original SLR was limited to include studies from the past 12 years (2010 to 2022) [5]. Several updates of the SLR have been performed, and the latest was conducted on the 24th of July 2024. An overview of the updates is provided in the Table 34 below.

Table 34: SLR update overview

Title	Description of update	Search time frame
2022 Original SLR	Original clinical SLR	2001 to November 7, 2022
2023 First SLR update	Inclusion of two additional comparator: Camrelizumab and toripalimab	2010 to August 2, 2023

2023 Second SLR update	Update of the original SLR and first SLR update*	November 7, 2022, to October 10, 2023
	Inclusion of two additional comparators: Serplulimab and retifanlimab	2010 to October 10, 2023
2024 third SLR update	Update of the original SLR and first SLR and second SLR update*	October 10, 2023, to July 24, 2024
	Inclusion of nine additional comparators: ivonescimab, cadonilimab, adebrelimab, SHR1701, HLX-301, fianlimab, cobolimab, dostarlimab and envafolimab	2010 to July 24, 2024

Abbreviations: SLR, systematic literature review.
*The additional comparators of the first SLR and second SLR update were also included in the third SLR update to align all comparators.

D.1.2 Search strategies

The Population, Intervention, Comparator, Outcome, Study design (PICOS) framework was employed to develop the search strategy and to structure the reporting of the eligibility criteria. The eligibility criteria are found in the next section "D.1.3 Systematic selection of studies".
Search strategies combined free text and indexing terms (e.g. medical subject headings (MESH), EMTREE terms) for NSCLC with Boolean operators (e.g., AND, OR, NOT) to focus on disease, interventions, and study design. The search strings were appropriately modified to fit each database-specific syntax [5]. The search strings for the original SLR and the newest SLR update (third) are provided in the tables (see Table 35, Table 36, Table 37, Table 38, Table 39, and Table 4040) below for each respective database.

Table 35: Of search strategy table for the original SLR for 1L NSCLC, Embase®

No.	Query	Results
#1	exp non small cell lung cancer/	139315
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab.	138797
#3	or/1-2	195615
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and 'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab.	1913257
#5	3 and 4	81552
#6	exp Programmed death 1 receptor/ or exp programmed death 1 ligand 1/	70508
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab.	76297
#8	exp tislelizumab/	747
#9	(tislelizumab or BGB-A317 or BGBA317 or tisle$).ti,ab.	381

No.	Query	Results
#10	exp pembrolizumab/	30159
#11	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	15924
#12	exp nivolumab/	31807
#13	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab.	17276
#14	exp Durvalumab/	8158
#15	(Durvalumab or Imfinz or MEDI 4736).ti,ab.	3078
#16	exp atezolizumab/	11837
#17	(atezolizumab or MPDL3280A or RG7446 or Tecentriq).ti,ab.	5118
#18	exp avelumab/	5081
#19	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab.	1678
#20	exp ipilimumab/	21420
#21	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab.	9649
#22	exp ticilimumab/	3606
#23	(ticilimumab or tremelimumab or CP675206 or CP 675206).ti,ab.	925
#24	exp cemiplimab/	1268
#25	(cemiplimab or REGN2810 or REGN 2810).ti,ab.	545
#26	exp bevacizumab/	69210
#27	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab.	35030
#28	exp sintilimab/	1024
#29	(sintilimab or Tyvyt or IBI308).ti,ab.	491
#30	exp sugemalimab/	50
#31	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab.	35

No.	Query	Results
#32	exp zimberelimab/	69
#33	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab.	52
#34	exp prolgolimab/	14
#35	exp penpulimab/	67
#36	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab.	48
#37	exp Bavituximab/	215
#38	(Bavituximab or PGN401 or Tarvacin).ti,ab.	124
#39	exp tiragolumab/	146
#40	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab.	41
#41	exp vibostolimab/	66
#42	(vibostolimab or MK-7684A or MK7684A).ti,ab.	29
#43	exp ociperlimab/	31
#44	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab.	17
#45	exp domvanalimab/	22
#46	exp ganetespib/	806
#47	(Ganetespib or STA9090 or STA9090).ti,ab.	350
#48	exp sitravatinib/	178
#49	(sitravatinib or MGCD516 or MGCD-516).ti,ab.	82
#50	BMS-986207.ti,ab.	3
#51	exp afatinib/	7378
#52	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab.	3785
#53	exp erlotinib/	30606
#54	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab.	13294

No.	Query	Results
#55	exp Ramucirumab/	4081
#56	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY3009806).ti,ab.	2041
#57	*docetaxel/	15712
#58	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab.	32083
#59	*paclitaxel/	31937
#60	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab.	62888
#61	*irinotecan/	8954
#62	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab.	19224
#63	*Capecitabine/	7289
#64	(Capecitabine or xeloda).ti,ab.	14896
#65	*Cisplatin/	64431
#66	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab.	111336
#67	*Ifosfamide/	6313
#68	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or	20354

No.	Query	Results
	IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab.	
#69	*Carboplatin/	15287
#70	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab.	32028
#71	*Etoposide/	17635
#72	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab.	39160
#73	*Gemcitabine/	15738
#74	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab.	33313
#75	*Oxaliplatin/	11171
#76	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab.	22674
#77	*pemetrexed/	3829
#78	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab.	13773
#79	*vinorelbine tartrate/	586
#80	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab.	6753
#81	*mitomycin/	6346
#82	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab.	21837
#83	*topotecan/	2436
#84	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab.	4842
#85	*nedaplatin/	741

No.	Query	Results
#86	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab.	1217
#87	*gimeracil-oteracil potassium-tegafur/	2193
#88	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab.	27
#89	or/6-88	533578
#90	*clinical trial/	17640
#91	exp randomized controlled trial/	736157
#92	exp Randomization/	95717
#93	exp Double blind procedure/	200255
#94	exp Single blind procedure/	48113
#95	exp Crossover Procedure/	71926
#96	exp Placebo/	387304
#97	"randomi?ed controlled trial$".ti,ab,kw.	308158
#98	RCT.ti,ab,kw.	51248
#99	(random$ adj2 (allocat$ or assign$)).ti,ab,kw.	218636
#100	(cross-over or crossover).ti,ab,kw.	119029
#101	(clinical adj1 trial$).ti,ab,kw.	649748
#102	((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab,kw.	271370
#103	placebo$.ti,ab,kw.	351433
#104	*Prospective Study/	37708
#105	or/90-104	1945302
#106	5 and 89 and 105	10678
#107	(animal$ not human$).ti,ab.	1055962
#108	animal/ not (animal/ and human/)	1166703
#109	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	9054356

No.	Query	Results
#110	(comment or letter or case reports).pt.	1244395
#111	(case report$ or case stud$ or case histor$).ti.	440204
#112	or/107-111	10787985
#113	106 not 112	9696
#114	limit 113 to yr="2010 -Current"	8021
#115	conference.so.	631281
#116	conference abstract.pt.	4581294
#117	or/115-116	4594873
#118	limit 117 to yr="2010 - 2019"	3637663
#119	114 not 118	4993
#120	limit 119 to english language	4798

Table 36: Of search strategy table for the third SLR update for 1L NSCLC, Embase®

No.	Query	Results
#1	exp non small cell lung cancer/	171904
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab.	159378
#3	or/1-2	229956
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and 'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab.	2206365
#5	3 and 4	94909
#6	exp Programmed death 1 receptor/ or exp programmed death 1 ligand 1/	92485
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab.	100664
#8	exp tislelizumab/	2272
#9	(tislelizumab or BGB-A317 or BGBA317 or tisle$).ti,ab	901
#10	exp pembrolizumab/	43214

No.	Query	Results
#11	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	21452
#12	exp nivolumab/	43110
#13	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab.	21909
#14	exp Durvalumab/	12384
#15	(Durvalumab or Imfinz or MEDI 4736 or MEDI4736).ti,ab.	4623
#16	exp atezolizumab/	18260
#17	(atezolizumab or MPDL3280A or RG7446 or MPDL-3280A or RG-7446 or Tecentriq).ti,ab.	7661
#18	exp avelumab/	7312
#19	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab.	2270
#20	exp ipilimumab/	27331
#21	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab.	11666
#22	exp ticilimumab/	4870
#23	(ticilimumab or tremelimumab or CP675206 or CP 675206).ti,ab.	1235
#24	exp cemiplimab/	2314
#25	(cemiplimab or REGN2810 or REGN 2810).ti,ab.	934
#26	exp bevacizumab/	78939
#27	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab.	39361
#28	exp sintilimab/	2703
#29	(sintilimab or Tyvyt or IBI308 or IBI-308).ti,ab.	1025
#30	exp sugemalimab/	145
#31	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab.	67

No.	Query	Results
#32	exp zimberelimab/	163
#33	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab.	86
#34	exp prolgolimab/	29
#35	exp penpulimab/	186
#36	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab.	91
#37	exp Bavituximab/	232
#38	(Bavituximab or PGN401 or PGN-401 or Tarvacin).ti,ab.	133
#39	exp tiragolumab/	300
#40	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab.	77
#41	exp vibostolimab/	151
#42	(vibostolimab or MK-7684A or MK7684A).ti,ab.	55
#43	exp ociperlimab/	79
#44	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab.	31
#45	exp domvanalimab/	62
#46	exp Toripalimab/	1939
#47	(Toripalimab or Tuoyi or Loqtorzi or JS001 or TAB001 or JS-001 or TAB-001).ti,ab.	671
#48	exp camrelizumab/	2800
#49	(camrelizumab or SHR-1210 or Airuika or HR-301210 or INCSHR-1210 or HR301210 or INCSHR1210 or SHR1210 or SHR01210).ti,ab.	1115
#50	serplulimab/	132
#51	(serplulimab or HLX-10 or HLX10 or Hansizhuang).ti,ab.	77
#52	retifanlimab/	213
#53	(retifanlimab or Zynyz or retifanlimab-dlwr or INCMGA00012 or INCMGA-00012 or MGA012 or MGA-012).ti,ab.	94
#54	exp ganetespib/	934

No.	Query	Results
#55	(Ganetespib or STA9090 or STA9090 or STA-9090 or STA-9090).ti,ab.	426
#56	exp sitravatinib/	278
#57	(sitravatinib or MGCD516 or MGCD-516).ti,ab.	113
#58	(BMS-986207 or BMS986207).ti,ab.	9
#59	exp afatinib/	8995
#60	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab.	4287
#61	exp erlotinib/	33506
#62	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab.	14194
#63	exp Ramucirumab/	5153
#64	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY3009806 or LY-3009806 or LY-3009806).ti,ab.	2420
#65	*docetaxel/	16912
#66	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab.	35194
#67	*paclitaxel/	34570
#68	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab.	69668
#69	*irinotecan/	9600
#70	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab.	20862
#71	*Capecitabine/	7958
#72	(Capecitabine or xeloda).ti,ab.	16700
#73	*Cisplatin/	68240
#74	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis	121165

No.	Query	Results
	diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab.	
#75	*Ifosfamide/	6472
#76	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab.	22382
#77	*Carboplatin/	16351
#78	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab.	35531
#79	*Etoposide/	18196
#80	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab.	42319
#81	*Gemcitabine/	17145
#82	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab.	37399
#83	*Oxaliplatin/	12406
#84	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab.	25549
#85	*pemetrexed/	4128
#86	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab.	15375
#87	*vinorelbine tartrate/	694

No.	Query	Results
#88	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab.	7129
#89	*mitomycin/	6707
#90	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab.	22803
#91	*topotecan/	2540
#92	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab.	5169
#93	*nedaplatin/	784
#94	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab.	1318
#95	*gimeracil-oteracil potassium-tegafur/	0
#96	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab.	31
#97	or/6-96	615824
#98	exp cadonilimab/	136
#99	(cadonilimab or AK-104 or AK104).ti,ab.	63
#100	exp ivonescimab/	29
#101	(ivonescimab or AK-112 or AK112 or SMT-112 or SMT112).ti,ab.	19
#102	exp Adebrelimab/	62
#103	(Adebrelimab or HTI-1088 or HTI1088 or SHR-1316 or SHR1316).ti,ab.	40
#104	(SHR1701 or SHR-1701).ti,ab.	22
#105	(HLX-301 or HLX301).ti,ab.	0
#106	exp fianlimab/	78
#107	(fianlimab or REGN 3767 or REGN3767 or WHO 11182 or WHO11182).ti,ab.	24
#108	exp cobolimab/	97
#109	(cobolimab or "TSR 022" or TSR022 or WBP-296A or WBP296A).ti,ab.	15

No.	Query	Results
#110	exp dostarlimab/	813
#111	(Jemperli or Dostarlimab or dostarlimab-gxly or GSK-4057190 or GSK4057190 or "TSR 042" or TSR042 or WBP-285 or WBP285).ti,ab.	327
#112	or/98-111	1201
#113	*clinical trial/	17641
#114	exp randomized controlled trial/	837697
#115	exp Randomization/	100161
#116	exp Double blind procedure/	221968
#117	exp Single blind procedure/	55748
#118	exp Crossover Procedure/	79029
#119	exp Placebo/	415968
#120	"randomi?ed controlled trial$".ti,ab,kw.	365021
#121	RCT.ti,ab,kw.	61300
#122	(random$ adj2 (allocat$ or assign$)).ti,ab,kw.	245048
#123	(cross-over or crossover).ti,ab,kw.	129837
#124	(clinical adj1 trial$).ti,ab,kw.	751051
#125	((singl$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$)).ti,ab,kw.	295717
#126	placebo$.ti,ab,kw.	384073
#127	*Prospective Study/	44263
#128	or/113-127	2183531
#129	5 and 97 and 128	12392
#130	(animal$ not human$).ti,ab.	1136798
#131	animal/ not (animal/ and human/)	1225284
#132	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	9876843
#133	(comment or letter or case reports).pt.	1334503

No.	Query	Results
#134	(case report$ or case stud$ or case histor$).ti.	506182
#135	or/130-134	11762824
#136	129 not 135	11199
#137	limit 136 to yr="2023 -Current"	1220
#138	limit 137 to english language	1203
#139	5 and 112 and 128	80
#140	139 not 135	62
#141	limit 140 to yr="2010 -Current"	62
#142	limit 141 to english language	62
#143	conference.so.	716469
#144	conference abstract.pt.	5201624
#145	or/143-144	5215573
#146	limit 145 to yr="2010 - 2021"	4276576
#147	142 not 146	55
#148	138 or 147	1223

Table 37: Of search strategy table for the original SLR for 1L NSCLC, MEDLINE®

No.	Query	Results
#1	exp Carcinoma, Non-Small-Cell Lung/	66962
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab.	81078
#3	or/1-2	93079
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and 'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab.	1361673
#5	3 and 4	37632
#6	exp Programmed Cell Death 1 Receptor/	10888

No.	Query	Results
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab.	36212
#8	(tislelizumab or BGB-A317 or BGBA317 or tisle$).ti,ab.	118
#9	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	6587
#10	exp nivolumab/	4704
#11	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab.	7344
#12	(Durvalumab or Imfinz or MEDI 4736).ti,ab.	1078
#13	(atezolizumab or MPDL3280A or RG7446 or Tecentriq).ti,ab.	2139
#14	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab.	705
#15	exp ipilimumab/	2736
#16	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab.	4190
#17	(ticilimumab or tremelimumab or CP675206 or CP 675206).ti,ab.	359
#18	(cemiplimab or REGN2810 or REGN 2810).ti,ab.	257
#19	exp bevacizumab/	13693
#20	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab.	19144
#21	(sintilimab or Tyvyt or IBI308).ti,ab.	271
#22	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab.	12
#23	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab.	12
#24	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab.	13
#25	(Bavituximab or PGN401 or Tarvacin).ti,ab.	35
#26	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab.	9
#27	(vibostolimab or MK-7684A or MK7684A).ti,ab.	2

No.	Query	Results
#28	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab.	2
#29	(Ganetespib or STA9090 or STA9090).ti,ab.	149
#30	(sitravatinib or MGCD516 or MGCD-516).ti,ab.	16
#31	BMS-986207.ti,ab.	1
#32	exp afatinib/	957
#33	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab.	1823
#34	exp Erlotinib Hydrochloride/	4336
#35	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab.	6875
#36	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY3009806).ti,ab.	1090
#37	*docetaxel/	899
#38	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab.	17579
#39	*paclitaxel/	15123
#40	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab.	39447
#41	*irinotecan/	426
#42	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab.	11361
#43	*Capecitabine/	683
#44	(Capecitabine or xeloda).ti,ab.	7369
#45	*Cisplatin/	23567
#46	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or	76991

No.	Query	Results
	blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab.	
#47	*Ifosfamide/	1611
#48	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab.	11306
#49	*Carboplatin/	3577
#50	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab.	17054
#51	*Etoposide/	4120
#52	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab.	25289
#53	*Gemcitabine/	0
#54	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab.	18334
#55	*Oxaliplatin/	743
#56	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab.	13030
#57	*pemetrexed/	364
#58	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab.	8776
#59	*Vinorelbine/	93

No.	Query	Results
#60	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab.	3975
#61	*mitomycin/	4137
#62	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab.	17935
#63	*topotecan/	1019
#64	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab.	3207
#65	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab.	849
#66	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab.	9
#67	or/6-66	277162
#68	exp Randomized controlled trials as Topic/	162256
#69	exp Randomized controlled trial/	581382
#70	exp Random allocation/	106890
#71	exp Double blind method/	173437
#72	exp Single blind method/	32264
#73	*Clinical trial/	0
#74	*Clinical Trials as Topic/	32024
#75	(clinic$ adj trial$).ti,ab,tw.	453636
#76	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,tw.	192303
#77	Placebos/	35923
#78	Placebo$.ti,ab,tw.	240364
#79	RCT.ti,ab,tw.	29026
#80	(randomi#ed adj1 control$ adj1 (trial$ or stud$)).ti,ab,tw.	262991
#81	(random$ adj2 (allocat$ or assign$)).ti,ab,tw.	173986
#82	exp Cross-Over Studies/	54235

No.	Query	Results
#83	(cross-over or crossover).ti,ab,tw.	95487
#84	*Prospective Studies/	444
#85	or/68-84	1453965
#86	5 and 67 and 85	4273
#87	(animal$ not human$).ti,ab.	892912
#88	animal/ not (animal/ and human/)	5027207
#89	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	7189654
#90	(comment or letter or case reports).pt.	3753565
#91	(case report$ or case stud$ or case histor$).ti.	363185
#92	or/87-91	10965517
#93	86 not 92	3997
#94	limit 93 to yr="2010 -Current"	2606
#95	limit 94 to english language	2526

Table 38: Of search strategy table for the third SLR update for 1L NSCLC, MEDLINE®

No.	Query	Results
#1	exp Carcinoma, Non-Small-Cell Lung/	75439
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab.	93050
#3	or/1-2	105880
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and 'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab.	1568199
#5	3 and 4	43119
#6	exp Programmed Cell Death 1 Receptor/	12841
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab.	49266

No.	Query	Results
#8	(tislelizumab or BGB-A317 or BGBA317 or tisle$).ti,ab.	362
#9	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab.	9057
#10	exp nivolumab/	5808
#11	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab.	9435
#12	(Durvalumab or Imfinz or MEDI 4736 or MEDI4736).ti,ab.	1718
#13	(atezolizumab or MPDL3280A or RG7446 or MPDL-3280A or RG-7446 or Tecentriq).ti,ab.	3332
#14	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab.	974
#15	exp ipilimumab/	3197
#16	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab.	5058
#17	(ticilimumab or tremelimumab or CP675206 or CP 675206).ti,ab.	516
#18	(cemiplimab or REGN2810 or REGN 2810).ti,ab.	427
#19	exp bevacizumab/	14955
#20	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab.	21526
#21	(sintilimab or Tyvyt or IBI308 or IBI-308).ti,ab.	609
#22	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab.	40
#23	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab.	24
#24	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab.	28
#25	(Bavituximab or PGN401 or Tarvacin).ti,ab.	37
#26	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab.	29
#27	(vibostolimab or MK-7684A or MK7684A).ti,ab.	5
#28	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab.	4

No.	Query	Results
#29	(Ganetespib or STA9090 or STA-9090).ti,ab.	183
#30	(sitravatinib or MGCD516 or MGCD-516).ti,ab.	33
#31	(BMS-986207 or BMS986207).ti,ab.	2
#32	exp afatinib/	1076
#33	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab.	2123
#34	exp Erlotinib Hydrochloride/	4521
#35	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab.	7455
#36	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY-3009806).ti,ab.	1305
#37	*docetaxel/	991
#38	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab.	19246
#39	*paclitaxel/	15540
#40	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab.	43267
#41	*irinotecan/	480
#42	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab.	12238
#43	*Capecitabine/	728
#44	(Capecitabine or xeloda).ti,ab.	8199
#45	*Cisplatin/	24386
#46	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or	82992

No.	Query	Results
	citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab.	
#47	*Ifosfamide/	1629
#48	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab.	12157
#49	*Carboplatin/	3631
#50	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab.	18537
#51	*Etoposide/	4154
#52	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab.	26581
#53	*Gemcitabine/	254
#54	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab.	20408
#55	*Oxaliplatin/	831
#56	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab.	14785
#57	*pemetrexed/	382
#58	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab.	9809
#59	*Vinorelbine/	100
#60	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab.	4169

No.	Query	Results
#61	*mitomycin/	4194
#62	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab.	18541
#63	*topotecan/	1044
#64	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab.	3383
#65	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab.	921
#66	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab.	11
#67	(Toripalimab or Tuoyi or Loqtorzi or JS001 or TAB001 or JS-001 or TAB-001).ti,ab.	336
#68	(camrelizumab or SHR-1210 or Airuika or HR-301210 or INCSHR-1210 or HR301210 or INCSHR1210 or SHR1210 or SHR01210).ti,ab.	693
#69	(serplulimab or HLX-10 or HLX10 or Hansizhuang).ti,ab.	52
#70	(retifanlimab or Zynyz or retifanlimab-dlwr or INCMGA00012 or INCMGA-00012 or MGA012 or MGA-012).ti,ab.	20
#71	or/6-70	312691
#72	(cadonilimab or AK-104 or AK104).ti,ab.	28
#73	(ivonescimab or AK-112 or AK112 or SMT-112 or SMT112).ti,ab.	6
#74	(Adebrelimab or HTI-1088 or HTI1088 or SHR-1316 or SHR1316).ti,ab.	24
#75	(SHR1701 or SHR-1701).ti,ab.	8
#76	(HLX-301 or HLX301).ti,ab.	0
#77	(fianlimab or REGN 3767 or REGN3767 or WHO 11182 or WHO11182).ti,ab.	2
#78	(cobolimab or "TSR 022" or TSR022 or WBP-296A or WBP296A).ti,ab.	2
#79	(Jemperli or Dostarlimab or dostarlimab-gxly or GSK-4057190 or GSK4057190 or "TSR 042" or TSR042 or WBP-285 or WBP285).ti,ab.	138
#80	or/72-79	207
#81	exp Randomized controlled trials as Topic/	176048

No.	Query	Results
#82	exp Randomized controlled trial/	619744
#83	exp Random allocation/	107424
#84	exp Double blind method/	179625
#85	exp Single blind method/	33766
#86	*Clinical trial/	0
#87	*Clinical Trials as Topic/	32617
#88	(clinic$ adj trial$).ti,ab,tw.	520041
#89	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,tw.	206798
#90	Placebos/	35976
#91	Placebo$.ti,ab,tw.	258380
#92	RCT.ti,ab,tw.	34991
#93	(randomi#ed adj1 control$ adj1 (trial$ or stud$)).ti,ab,tw.	311198
#94	(random$ adj2 (allocat$ or assign$)).ti,ab,tw.	194403
#95	exp Cross-Over Studies/	57140
#96	(cross-over or crossover).ti,ab,tw.	103011
#97	*Prospective Studies/	484
#98	or/81-97	1597096
#99	(animal$ not human$).ti,ab.	951009
#100	animal/ not (animal/ and human/)	5207624
#101	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	7474025
#102	(comment or letter or case reports).pt.	3967324
#103	(case report$ or case stud$ or case histor$).ti.	419269
#104	or/99-103	11487422
#105	5 and 71 and 98	4773

No.	Query	Results
#106	105 not 104	4468
#107	limit 106 to yr="2023 -Current"	454
#108	limit 107 to english language	449
#109	5 and 80 and 98	4
#110	109 not 104	4
#111	limit 110 to yr="2010 -Current"	4
#112	limit 111 to english language	4
#113	108 or 112	449

Table 39: Of search strategy table for the original SLR for 1L NSCLC, CENTRAL

No.	Query	Results
#1	exp Carcinoma, Non-Small-Cell Lung/	5001
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab,tw.	15883
#3	or/1-2	16303
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and 'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab,tw.	132179
#5	3 and 4	12138
#6	exp Programmed Cell Death 1 Receptor/	115
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab,tw.	5393
#8	(tislelizumab or BGB-A317 or BGBA317 or tisle*).ti,ab,tw.	150
#9	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab,tw.	2567
#10	exp nivolumab/	604
#11	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab,tw.	2606

No.	Query	Results
#12	(Durvalumab or Imfinz or MEDI 4736).ti,ab,tw.	890
#13	(atezolizumab or MPDL3280A or RG7446 or Tecentriq).ti,ab,tw.	1213
#14	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab,tw.	351
#15	exp ipilimumab/	277
#16	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab,tw.	1675
#17	(ticilimumab or CP675206 or CP 675206).ti,ab,tw.	8
#18	(cemiplimab or REGN2810 or REGN 2810).ti,ab,tw.	87
#19	exp bevacizumab/	2234
#20	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab,tw.	7321
#21	(sintilimab or Tyvyt or IBI308).ti,ab,tw.	122
#22	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab,tw.	14
#23	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab,tw.	16
#24	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab,tw.	18
#25	(Bavituximab or PGN401 or Tarvacin).ti,ab,tw.	31
#26	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab,tw.	36
#27	(vibostolimab or MK-7684A or MK7684A).ti,ab,tw.	23
#28	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab,tw.	18
#29	(Ganetespib or STA9090 or STA9090).ti,ab,tw.	40
#30	(sitravatinib or MGCD516 or MGCD-516).ti,ab,tw.	12
#31	BMS-986207.ti,ab,tw.	3
#32	exp afatinib/	71
#33	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab.	496

No.	Query	Results
#34	exp Erlotinib Hydrochloride/	572
#35	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab.	1798
#36	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY3009806).ti,ab.	622
#37	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab,tw.	7891
#38	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab,tw.	11269
#39	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab,tw.	3678
#40	(Capecitabine or xeloda).ti,ab,tw.	4271
#41	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,tw.	15657
#42	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab,tw.	2097
#43	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab,tw.	7710
#44	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or	4701

No.	Query	Results
	NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab,tw.	
#45	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab,tw.	6587
#46	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab,tw.	4885
#47	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab,tw.	3031
#48	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab,tw.	1889
#49	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab,tw.	2850
#50	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab,tw.	804
#51	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab.	230
#52	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab.	18
#53	or/6-52	60600
#54	exp Randomized controlled trials as Topic/	8616
#55	exp Randomized controlled trial/	118
#56	exp Random allocation/	20692
#57	exp Double blind method/	148401
#58	exp Single blind method/	23267
#59	*Clinical trial/	0
#60	*Clinical Trials as Topic/	0
#61	(clinic$ adj trial$).ti,ab,tw.	226688
#62	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,tw.	315683
#63	Placebos/	24481
#64	Placebo$.ti,ab,tw.	354776

No.	Query	Results
#65	RCT.ti,ab,tw.	41639
#66	(randomi#ed adj1 control$ adj1 (trial$ or stud$)).ti,ab,tw.	290207
#67	(random$ adj2 (allocat$ or assign$)).ti,ab,tw.	215723
#68	exp Cross-Over Studies/	40884
#69	(cross-over or crossover).ti,ab,tw.	105951
#70	*Prospective Studies/	0
#71	or/54-70	1006621
#72	5 and 53 and 71	3202
#73	(animal$ not human$).ti,ab,tw.	10574
#74	animal/ not (animal/ and human/)	11291
#75	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	11298
#76	(comment or letter or case reports).pt.	10287
#77	(case report$ or case stud$ or case histor$).ti.	1365
#78	or/73-77	32506
#79	72 not 78	3185
#80	limit 79 to yr="2010 -Current" [Limit not valid in DARE; records were retained]	2561
#81	limit 80 to english language [Limit not valid in CDSR,DARE; records were retained]	2528

Table 40: Of search strategy table for the third SLR update for 1L NSCLC, CENTRAL

No.	Query	Results
#1	exp Carcinoma, Non-Small-Cell Lung/	6789
#2	(NSCLC or ('non-small cell lung' adj1 (cancer or carcinoma))).ti,ab,tw.	17067
#3	or/1-2	17657
#4	(advanc$ or metastat$ or unopera$ or ('non' adj2 resect$) or nonresect$ or unresect$ or inopera$ or ('late' adj2 'stage') or 'stage iii' or (stage and	142887

No.	Query	Results
	'iii') or 'stage-3' or 'stage iv' or (stage and 'iv') or 'stage 4' or 'stage-4').ti,ab,tw.	
#5	3 and 4	13193
#6	exp Programmed Cell Death 1 Receptor/	223
#7	("programmed cell death 1 protein" or pd-1 or pd-l1 or pd1 or pdl1).ti,ab,tw.	6914
#8	(tislelizumab or BGB-A317 or BGBA317 or tisle*).ti,ab,tw.	301
#9	(pembrolizumab or keytruda or lambrolizumab or mk 3475 or mk3475 or sch 900475 or sch900475).ti,ab,tw.	3379
#10	exp nivolumab/	974
#11	(nivolumab or 'bms 936558' or bms936558 or 'cmab 819' or cmab819 or 'mdx 1106' or mdx1106 or 'ono 4538' or ono4538 or opdivo).ti,ab,tw.	3181
#12	(Durvalumab or Imfinz or MEDI 4736 or MEDI4736).ti,ab,tw.	1318
#13	(atezolizumab or MPDL3280A or RG7446 or MPDL-3280A or RG-7446 or Tecentriq).ti,ab,tw.	1557
#14	(avelumab or MSB-0010682 or MSB0010682 or bavencio or MSB0010718C or MSB-0010718C).ti,ab,tw.	440
#15	exp ipilimumab/	574
#16	(Ipilimumab or Yervoy or "MDX 010" or MDX010 or MDXCTLA4 or MDX CTLA 4).ti,ab,tw.	1937
#17	(ticilimumab or CP675206 or CP 675206).ti,ab,tw.	11
#18	(cemiplimab or REGN2810 or REGN 2810).ti,ab,tw.	172
#19	exp bevacizumab/	3075
#20	(Mvasi or bevacizumab or Avastin or ABP215 or ABP-215 or Altuzan).ti,ab,tw.	7831
#21	(sintilimab or Tyvyt or IBI308 or IBI-308).ti,ab,tw.	232
#22	(sugemalimab or CS-1001 or CS1001 or WBP3155 or WBP-3155 or Cejemly).ti,ab,tw.	28
#23	(zimberelimab or AB-122 or AB122 or GLS-010 or GLS010 or GS-0122 or GS0122 or WBP-3055 or WBP 3055).ti,ab,tw.	33

No.	Query	Results
#24	(prolgolimab or penpulimab or AK105 or AK-105).ti,ab,tw.	41
#25	(Bavituximab or PGN401 or PGN-401 or Tarvacin).ti,ab,tw.	30
#26	(tiragolumab or MTIG7192A or MTIG-7192A).ti,ab,tw.	69
#27	(vibostolimab or MK-7684A or MK7684A).ti,ab,tw.	50
#28	(ociperlimab or BGB-A1217 or BGBA1217).ti,ab,tw.	28
#29	(Ganetespib or STA9090 or STA-9090).ti,ab,tw.	40
#30	(sitravatinib or MGCD516 or MGCD-516).ti,ab,tw.	17
#31	(BMS-986207 or BMS986207).ti,ab,tw.	4
#32	Toripalimab.ti,ab,tw.	185
#33	(Tuoyi or Loqtorzi or JS001 or TAB001 or JS-001 or TAB-001).ti,ab,tw.	33
#34	camrelizumab.ti,ab,tw.	261
#35	(SHR-1210 or Airuika or HR-301210 or INCSHR-1210 or HR301210 or INCSHR1210 or SHR1210 or SHR01210).ti,ab,tw.	58
#36	serplulimab.ti,ab,tw.	30
#37	(HLX-10 or HLX10 or Hansizhuang).ti,ab,tw.	16
#38	retifanlimab.ti,ab,tw.	26
#39	(Zynyz or retifanlimab-dlwr or INCMGA00012 or INCMGA-00012 or MGA012 or MGA-012).ti,ab,tw.	22
#40	exp afatinib/	113
#41	(afatinib or Gilotrif or Giotrif or BIBW2992 or BIBW-2992 or Tovok or Tomtovok).ti,ab,tw.	498
#42	exp Erlotinib Hydrochloride/	720
#43	(erlotinib or Tarceva or CP-358774 or CP358774 or R-1415 or R1415).ti,ab,tw.	1832
#44	(Ramucirumab or IMC-1121B or IMC1121B or LY3009806 or LY3-009806).ti,ab,tw.	694
#45	(docetaxel or taxotere or rp 56976 or rp56976 or NSC 628503 or NSC628503).ti,ab,tw.	8378

No.	Query	Results
#46	(paclitaxel or "abi 007" or abi007 or bms 181339 or bms181339 or bmy 45622 or bmy45622 or anzatax or NSC 125973 or NSC125973 or apealea or asotax or biotax or nab paclitaxel or pacxel or padexol or Taxol or Paxene or Praxel or Onxol).ti,ab,tw.	12237
#47	(irinotecan or Camptothecin-11 or Camptothecin11 or camptosar or Irinotecan Hydrochloride or SN 38 11 or SN3811 or CPT-11 or CPT11).ti,ab,tw.	3860
#48	(Capecitabine or xeloda).ti,ab,tw.	4670
#49	(Cisplatin$ or GemCit or Platinol$ or platamin or Neoplatin or Cismaplat or CDDP or Biocisplatinum or dichlorodiammineplatinum or nsc-119875 or platidiam or platino or platinum diamminodichloride or cis diamminedichloroplatinum or cis-diamminedichloroplatinum or cis platinum or cis-platinum or L01XA01 or Abiplatin or biocysplatinum or blastolem or briplatin or cddp ti or cis ddp or (cis adj3 (platinum or platino?s or diamine or diaminechloroplatinum)) or cisplatyl or citoplatino or cytoplatin or cytosplat or docistin or elvecis or kemoplat or lederplatin or lipoplatin or mpi 5010 or mpi5010 or neoplatin or niyaplat or nk 801 or noveldexis or nsc 119875 or platamine or platiblastin or platidiam or platimine or platinex or platinil or platinoxan or (platinum adj3 (diamine or diaminodichloride or diamminedichloride)) or platiran or platistil or platistin or platosin or randa or romcis or sicatem or "spi 077" or tecnoplatin).ti,ab,tw.	16510
#50	(Ifosfamide or Ifomide or iphosphamid or iphosphamide or isoendoxan or iso-Endoxan or isophosphamide or naxamide or ifex or Holoxan$ or IFO-Cell or Ifolem or Ifomida or Ifoxa or Mitoxana or Tronoxal or IFF or IFO or IFX or IPP or Asta Z-4942 or MJF-9325 or Z 4942 or NSC109724 or NSC-109-724).ti,ab,tw.	2127
#51	(Carboplatin$ or Blastocarb or Carboplat or Carbosin or Carbosol or Carbotec or Displata or Ercar or Nealorin or Novoplatinum or Paraplatin or Platinwas or Ribocarbo or CBDCA or JM-8 or JM8 or Neocarbo or NSC-241240 or NSC241240).ti,ab,tw.	8363
#52	(Etoposid$ or Etopophos or Toposar or VePesid or Lastet or EPEG or VP-16 or VP16 or VP-16-213 or VP16213 or Eto-GRY or EtoGRY or Exitop or NSC-141540 or NSC141540 or Onkoposid or Riboposid or Teva or Etomedac or Eposin).ti,ab,tw.	5006
#53	(Gemcitabine or Gemzar or LY 188011 or LY-188011 or L01BC05 or difluorodeoxycytidine or gemcite or dFdCyd).ti,ab,tw.	6991
#54	(oxaliplatin or eloxatin or eloxatine or L-OHP Cpd or oxaliplatine or "ACT 078" or ACT078).ti,ab,tw.	5285
#55	(pemetrexed or MTA or LY231514 or LY 231 514 or LY-231514 or Alimta).ti,ab,tw.	3405

No.	Query	Results
#56	(5' Nor anhydrovinblastine or KW 2307 or KW2307 or Navelbine or vinorelbine).ti,ab,tw.	1938
#57	(Mitomycin or Mitocin or NSC 26980 or NSC26980 or Ametycine or Mutamycin).ti,ab,tw.	2974
#58	(Topotecan or Nogitecan or F-104864-A or F104864A or Hycamtin or NSC-609699 or NSC609699 or Hycamtamine).ti,ab,tw.	825
#59	(nedaplatin or NSC-375101D or NSC375101D or 254-S or 254S or Aqupla).ti,ab,tw.	248
#60	(Teysuno or gimeracil-oteracil potassium-tegafur).ti,ab,tw.	20
#61	or/6-60	66247
#62	(cadonilimab or AK-104 or AK104).ti,ab,tw.	36
#63	(ivonescimab or AK-112 or AK112 or SMT-112 or SMT112).ti,ab,tw.	13
#64	(Adebrelimab or HTI-1088 or HTI1088 or SHR-1316 or SHR1316).ti,ab,tw.	33
#65	(SHR1701 or SHR-1701).ti,ab,tw.	13
#66	(HLX-301 or HLX301).ti,ab,tw.	0
#67	(fianlimab or REGN 3767 or REGN3767 or WHO 11182 or WHO11182).ti,ab,tw.	12
#68	(cobolimab or "TSR 022" or TSR022 or WBP-296A or WBP296A).ti,ab,tw.	9
#69	(Jemperli or Dostarlimab or dostarlimab-gxly or GSK-4057190 or GSK4057190 or "TSR 042" or TSR042 or WBP-285 or WBP285).ti,ab,tw.	103
#70	or/62-69	208
#71	exp Randomized controlled trials as Topic/	48470
#72	exp Randomized controlled trial/	37
#73	exp Random allocation/	26027
#74	exp Double blind method/	171391
#75	exp Single blind method/	27474
#76	*Clinical trial/	0
#77	*Clinical Trials as Topic/	0

No.	Query	Results
#78	(clinic$ adj trial$).ti,ab,tw.	257664
#79	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,tw.	347635
#80	Placebos/	27051
#81	Placebo$.ti,ab,tw.	385472
#82	RCT.ti,ab,tw.	44801
#83	(randomi#ed adj1 control$ adj1 (trial$ or stud$)).ti,ab,tw.	315374
#84	(random$ adj2 (allocat$ or assign$)).ti,ab,tw.	243172
#85	exp Cross-Over Studies/	48192
#86	(cross-over or crossover).ti,ab,tw.	114246
#87	*Prospective Studies/	0
#88	or/71-87	1122102
#89	animal/ not (animal/ and human/)	19633
#90	animal/ or animal experiment/ or animal model/ or animal tissue/ or nonhuman/	19636
#91	(comment or letter or case reports).pt.	14876
#92	(case report$ or case stud$ or case histor$).ti.	1297
#93	or/89-92	35609
#94	5 and 61 and 88	3750
#95	94 not 93	3735
#96	limit 95 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	423
#97	limit 96 to english language [Limit not valid in CDSR,DARE; records were retained]	421
#98	5 and 70 and 88	21
#99	98 not 93	21
#100	limit 99 to yr="2010 -Current" [Limit not valid in DARE; records were retained]	21

No.	Query	Results
#101	limit 100 to english language [Limit not valid in CDSR,DARE; records were retained]	21
#102	97 or 101	428

D.1.3 Systematic selection of studies

A list of the eligibility criteria for a systematic selection of studies in the SLRs are provided in the Table 41 below.

Table 41: Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Patients ≥18 years of age with advanced unresectable or metastatic NSCLC (Stage IIIb or IV)	Population <18 years old Non-human Patients without advanced unresectable or metastatic NSCLC
Intervention	Immunotherapy: Tislelizumab, Pembrolizumab, Nivolumab, Durvalumab, Atezolizumab, Avelumab, Ipilizumab, Ticilimumab, Cemiplimab, Sintilimab, Sugemalimab, Zimberelimab, Prolgolimab, Bavituximab, Vibostolimab, Ociperlimab, Tiragolumab, Domvanalimab, BMS-986207, Camrelizumab, Toripalimab, Serplulimab, Retifanlimab, Ivonescimab, Candonilimab, Adebrelimab, SHR1701, HLX-301, Fianlimab, Cobolimab, Dostarlimab, Envafolimab Chemotherapy: Docetaxel, Paclitaxel, Irinotecan, Capecitabine, Cisplatin, Gemcitabine, Transplantin, Ifosfamide, Cyclophosphamide, Carboplatin, Etoposide, Oxaliplatin, Pemetrexed, Vinorelbine tartrate, Mitomycin, Topotecan, Nedaplatin, Tegafur gimeracil oteracil Target therapy: Ganetespib, SItravatinib, Adatinib, Erlotinib, Bevacizumab, Ramucirumab Placebo	Any treatments/ therapies class not listed in the inclusion criteria. Consolidation therapy Vaccines Biosimilars Herbal medicines

Comparators	Same as for interventions	Same as for intervention
Outcomes	PFS, OS, AEs, DOR, ORR, DCR, CR, PR, SD, PD, Discontinuation, QoL	Studies not providing data on the specific outcomes of interest
Study design/publication type	RCT (Phase II and III clinical trials only) SLR	Phase I clinical trials Dose comparison studies Studies comparing same intervention in both arm (schedule/formulation/ mode of administration etc.) Review Case report Comment/ Editorial Guideline/Interview Lectures/Letter Monograph/News/Tutorial Terminated/ pre-maturely closed/ halted studies
Language restrictions	English	Non-English language studies

Abbreviations: AE, adverse event; CR, complete remission; DCR, disease control rate; DOR, duration of response; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; SD, standard deviation; SLR, systematic literature review.

Screening process

All records identified from the databases were imported into EndNote® and duplicates were removed prior to exporting to the systematic review software. Based on specific predefined eligibility criteria, titles and abstracts of retrieved records were independently assessed for inclusion by two reviewers. In cases where there was uncertainty or misalignment between the two reviewers, a resolution was achieved either through a discussion between the two reviewers or through a third independent reviewer. Prior to proceeding with the abstract review process, a pilot screening phase involving 150 abstracts was completed.

Full-text publications of potentially relevant studies retained from abstract screening were then independently reviewed by two reviewers and misalignment was resolved through discussion between the two reviewers or, through a third independent reviewer. Prior to proceeding with the full-text review process, a pilot screening phase involving 20 full-texts was completed. Following the screening process, data from the included studies were extracted into a standardized data extraction template.

SLR results

A total of 10,230 records were identified from electronic database searches conducted on 07 November 2022 (MEDLINE®: 2,666; Embase®: 4,957; Evidence based medicine (EBM) reviews: 2,607), 2,694 duplicates were removed, the remaining 7,536 records were screened. Considering the eligibility criteria, 6,353 records were excluded during the title and abstract screening stage, leaving 1,183 potentially relevant records for full-text review. At full text review, a further 635 records were excluded based on the PICOS eligibility criteria, resulting in 548 publications being included following full-text review [5].
An additional manual search (i.e., screening of specific conferences, clinical trial registries and bibliography checks of systematic literature reviews and meta-analyses) was conducted based on the same eligibility criteria, which retrieved 98 additional publications. Therefore, a total of 646 publications, describing 459 unique studies, were identified in this SLR.

The third SLR update identified 2,102 records from electronic databases (MEDLINE®: 450; Embase®: 1,223; Cochrane®: 429). After deduplication from the original SLR, first and second SLR update, the remaining 865 publications were screened. After the title and abstract screening, 747 references were excluded according to the eligibility criteria and 118 potentially relevant references were retrieved for full-text assessment. During the full-text review, a further 61 records were excluded based on PICOS eligibility criteria and 57 records were included [5]. From the hand-search, 11 additional records were identified that met the inclusion criteria. Therefore, a total of 68 publications reporting on 20 unique studies were identified in this third SLR update.

From the identified publications, studies focusing on treatment with immunotherapy versus chemotherapy was assessed. Once studies related to pembrolizumab and tislelizumab was extracted, we identified RATIONALE-307 and KEYNOTE-407 to be relevant for this submission, and they are described in Table 42.

The PRISMA diagram for the original SLR and the third SLR update are presented in the Figure 11 and Figure 12, respectively.

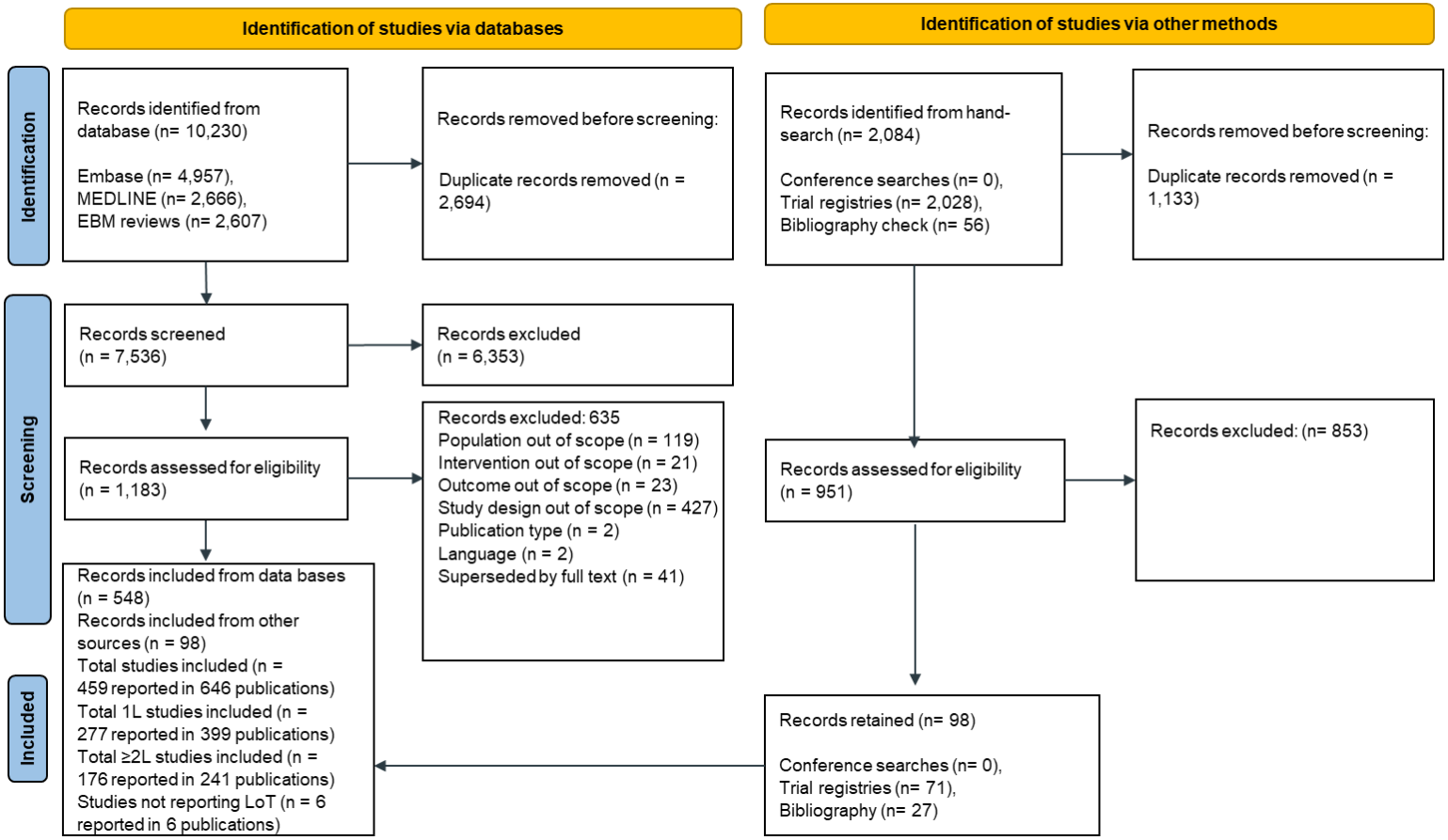


Figure 11: PRISMA diagram for the original SLR

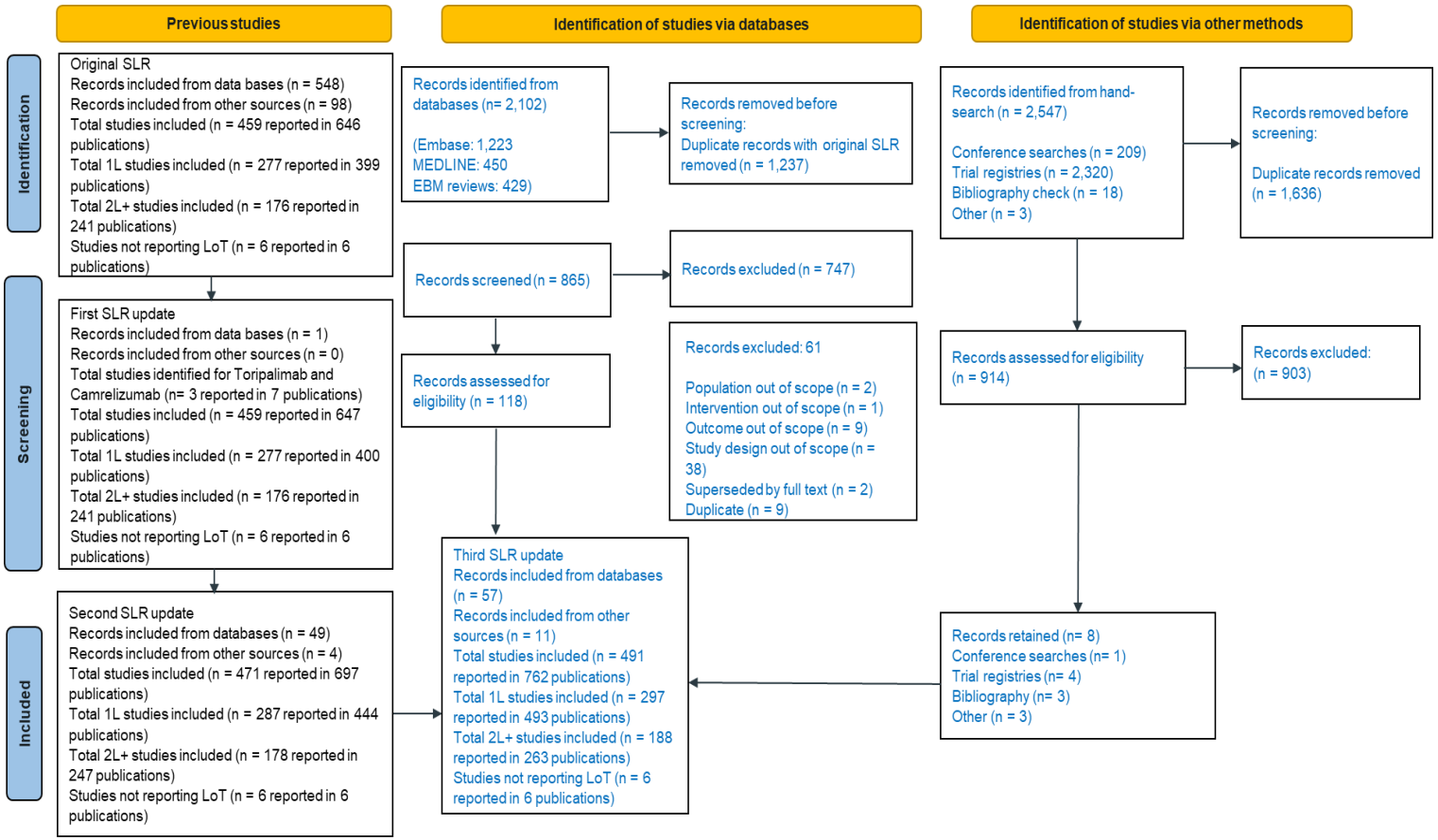


Figure 12: PRISMA diagram for the third SLR update (indicated by the blue text)

Table 42: Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
RATIONALE-307 Tislelizumab Plus Chemotherapy vs Chemotherapy Alone as First-line Treatment for Advanced Squamous Non–Small-Cell Lung Cancer: A Phase 3 Randomized Clinical Trial -Wang J et al. (2021) [7] Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous non-small-cell lung cancer: final analysis of the randomized, phase III	To assess efficacy and safety/tolerability of tislelizumab plus chemotherapy vs chemotherapy as first-line treatment of advanced squamous NLCLC	Multicenter, controlled, open label, randomized, Phase 3 study	Adult patients with untreated, histologically confirmed, locally advanced or metastatic stage IIIB/IV squamous NSCLC and PD-L1 expression of <1% vs 1-49% vs >50%	Intervention: Tislelizumab plus carboplatin and paclitaxel (n=120) or tislelizumab plus carboplatin and nab-paclitaxel (n=119) Comparator: paclitaxel with carboplatin (n=121)	PFS in the ITT population by IRC per RECIST v1.1 or death, whichever occurs first, as of data cut-off 30SEP2020 (2 years, 2 months)	OS through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) ORR by IRC assessment through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) ORR by investigator assessment through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) DOR by IRC assessment through study completion data cut-off 28APR2023 (up to

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
RATIONALE-307 trial - Wang J et al. (2024) [8] Data on file from BeiGene, as the data from the extended follow-up cut-off of 28th April 2023 has not been posted as of today [5]						approximately 4 years, 9 months) DOR by investigator assessment through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) PFS by investigator assessment through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) PFS by IRC based on PD-L1 expression through study completion data cut-off 28APR2023 (up to approximately 4 years, 9 months) EORTC QLQ-LC13, from baseline to cycle 5

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
						EORTC QLQ-C30, from baseline to cycle 5 Number of participants with adverse events, from first dose to 30 days after the last dose according to NCI-CTCAE v5.
KEYNOTE-407 Pembrolizumab plus Chemotherapy for Squamous Non-Small-Cell Lung Cancer – Paz-Ares et al. (2018) [14] A Randomized, Placebo-Controlled Trial of Pembrolizumab Plus Chemotherapy in Patients with Metastatic Squamous NSCLC: Protocol-Specified Final Analysis	To assess whether previously untreated squamous NSCLC patients had improved survival outcomes vs patients treated with placebo and chemotherapy.	Double-blinded, randomized, multicenter phase III study	Adult patients with untreated, histologically or cytologically confirmed diagnosis of stage IV squamous NSCLC and PD-L1-expression ≥ 1 % and < 50 %	Intervention: Pembrolizumab in combination with chemotherapy (n=278) Comparator: placebo in combination with chemotherapy (n=281)	PFS as assessed by blinded independent central review per RECIST 1.1 (up to approximately 19 months) OS defined as time from randomization to death (up to approximately 19 months)	ORR as assessed by RECIST 1.1 (up to approximately 19 months) DOR as assessed by RECIST 1.1 (up to approximately 19 months) Number of patients experiencing an adverse event (up to approximately 83 months)

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
of KEYNOTE-407 - Paz-Ares et al. (2020) [9] Pembrolizumab Plus Chemotherapy in Squamous Non–Small-Cell Lung Cancer: 5-Year Update of the Phase III KEYNOTE-407 Study - Novello et al. (2023) [10]						Number of patients discontinuing study treatment due to an adverse event (up to approximately 29 months)

Abbreviations: AE, adverse event; DOR, duration of response; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival.
Source: [5,7,9,10,12]

D.1.4 Quality assessment

The quality of the randomized clinical trials retained for data extraction was assessed using the revised Cochrane Risk of Bias (RoB 2.0) tool, with assessment of five components: D1 of randomisation process, D2 of deviations from intended interventions, D3 of missing outcome data, D4 of measurement of the outcome and D5 of the selection of the reported results [5]. The overall risk of study bias was rated by low risk, some concerns or high risk. High-quality studies were considered to report clearly on almost all items, while studies of low quality did not report on most items. The results of the quality assessment were not explicitly used in the narrative synthesis but serve as an additional source of information to determine the quality of the evidence base when interpreting the results.

A significant strength of the literature search was its comprehensive nature, covering a wide range of relevant studies and ensuring the inclusion of various comparators within immunotherapy, chemotherapy, and targeted therapy. The methods for data extraction and quality assessment followed standardized protocols, providing transparency and allowing for the relevance of the found studies to be evaluated. According to the PRISMA statement, the current review includes detailed search strategies, PICOS criteria, clear screening method, a PRISMA flow diagram, complete lists of included and excluded studies, and risk of bias assessments using appropriate tools.

Limitations were identified in the methodology, as this SLR was built based on previously published SLRs, and further criteria were applied to restrict the number of studies for reporting purposes. Other limitations were due to inconsistent reporting of outcomes, population, variation in terms of sample size, definition of outcomes, and time points, thus limiting inter-study comparisons between the interventions.

D.1.5 Unpublished data

Any unpublished data utilized to present the efficacy and safety of tislelizumab have been attained from the clinical trial RATIONALE-307, from e.g. the clinical study report or longer follow-up data than the published data. An abstract will be published later this year presenting data from the extended analysis, DCO 2023.

Medicinrådet

Danish Medicines Council
Secretariat
Dampfærgevej 21-23, 3rd floor
DK-2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk