Medicinrådet

Bilag til Medicinrådets vurdering af tislelizumab i kombination med platinbaseret kemoterapi som førstelinje-behandling af voksne patienter med inoperabelt, lokalt avanceret eller metastatisk planocellulær spiserørskræft

Patienter med PD-L1 TAP-score ≥ 5 %

Vers. 1.0

Bilagsoversigt

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

BeiGene Nordics, c/o Convendum, Gävlegatan 16, 113 30 Stockholm, Sweden – nordics@beigene.com

2025-05-19

Til Medicinrådet

På vegne af BeiGene vil jeg takke for muligheden for at give en tilbagemelding på udkast til vurderingsrapport for tislelizumab i kombination med platinbaseret kemoterapi som har indikation til førstelinjebehandling af voksne patienter med inoperabelt, lokalt avanceret eller metastatisk karcinom i spiserøret, hvis tumorer udtrykker PD-L1 med en tumorareal-positivitets (TAP)-score ≥ 5 %.

BeiGene ønsker ligeledes at takke for en god og konstruktiv dialog med sekretariatet igennem processen og vi har noteret at Medicinrådet synes enige i de antagelser der er valgt i ansøgningen.

BeiGene 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 anbefaling af tislelizumab.

Med venlig hilsen

Nicolai Bendtsen

Director, Nordic Market Access
BeiGene

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20.05.2025

DBS,KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	Juni 2025 (skriftlig proces)
Leverandør	BeiGene
Lægemiddel	Tevimbra (tislelizumab)
Ansøgt indikation	Tevimbra, i kombination med platinbaseret kemoterapi, til førstelinjebehandling af voksne patienter med inoperabelt, lokalt avanceret eller metastatisk planocellulær karcinom i spiserøret (OSCC), hvis tumorer udtrykker PD-L1 med en tumorareal-positivitets (TAP) score ≥ 5 %.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Tevimbra (tislelizumab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Tevimbra	10 mg/ml (10 ml)	19.315,00	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Konkurrencesituationen

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling/år (SAIP, DKK)
Tevimbra	10 mg/ml (10 ml)	200 mg hver 3. uge	[redacted]	[redacted]
Keytruda	25 mg/ml (4 ml)	2 mg/kg hver 3. uge eller 4 mg/kg hver 6. uge	[redacted]	[redacted]
Opdivo	100 mg (10 ml)	4,5 mg/kg hver 3. uge	[redacted]	[redacted]

*Patientvægt 76,5 kg

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til anbefaling
England	Under vurdering	Link til vurderingsstatus
Sverige	Under vurdering	Link til vurderingsstatus

Opsummering

[redacted]

Application for the assessment of Tevimbra (tislelizumab) in combination with platinum-based chemotherapy for the first-line treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%

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

Contact information

Contact information	
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	Please note that a power of attorney has been shared

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Tables and Figures

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Abbreviations

1L	First Line
2L	Second Line
AE	Adverse Event
BICR	Blinded Independent Central Review
BMI	Body Mass Index
BOR	Best Overall Response
CAPOX	Capecitabine and Oxaliplatin
CI	Confidence Interval
CrI	Credible Interval
CPS	Combined Positive Score
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DECG	Danish Esophagogastric Cancer Group
DKK	Danish Kroner
DMC	Danish Medicines Council
DOR	Duration of Response
DRG	Diagnosis Related Group
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for the Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-3L	EuroQoL 5-Dimensions 3- Levels
EQ-5D-5L	EuroQoL 5-Dimensions 5- Levels
EQ-VAS	EuroQoL Visual Analogue Scale
GHS	Global Health Status
HR	Hazard Ratio
ICC	Investigator-Chosen Therapy
ITC	Indirect Treatment Comparison
ITT	Intention-to-treat
N+C	Nivolumab plus Chemotherapy
N+I	Nivolumab plus Ipilimumab
NA	Not Applicable
NCI	National Cancer Institute
NMA	Network Meta Analysis
NR	Not Reported
OC	Oesophageal Cancer
OR	Odds Ratio
ORR	Overall Response Rate
OS	Overall Survival
OSCC	Oesophageal Squamous Cell Carcinoma
P+C	Placebo plus Chemotherapy
Pe+C	Pembrolizumab plus Chemotherapy
PD	Progressive Disease
PR	Partial response
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Cell Death Protein 1 Ligand
PD-L2	Programmed Cell Death Protein 2 Ligand
PFS	Progression Free Survival
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria for Solid Tumours
SAE	Serious adverse event
SD	Standard Deviation
SLR	Systematic Literature Review
SmPC	Summary of Product Characteristics
SOC	Standard of Care
SUCRA	Surface Area Under the Cumulative Ranking Curve
T+C	Tislelizumab plus Chemotherapy
TAP	Tumour Area Positivity
TEAE	Treatment Emergent Adverse Event
TNM	Tumour/Nodule/Metastasis
TPS	Tumour Proportion Score
TRAE	Treatment Related Adverse Event

1. Regulatory information on the medicine

Table 1 Overview of the medicine

Overview of the medicine [1–3]	
Proprietary name	Tevimbra
Generic name	Tislelizumab
Therapeutic indication as defined by EMA	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 tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.
Marketing authorization holder in Denmark	BeiGene
ATC code	LO1FF09
Combination therapy and/or co-medication	Platinum-based chemotherapy
Date of EC approval	November 2024
Has the medicine 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	Yes, indications provided below; **Non-small cell lung cancer (NSCLC)** Tevimbra in combination with pemetrexed and platinum-containing chemotherapy is indicated for the first-line treatment of adult patients with non-squamous NSCLC whose tumours have PD-L1 expression on ≥50% of tumour cells with no EGFR or ALK positive mutations and who have: - locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or - metastatic NSCLC. Tevimbra in combination with carboplatin and either paclitaxel or nab-paclitaxel is indicated for the first-line treatment of adult patients with squamous NSCLC who have:

Overview of the medicine [1–3]	
	- locally advanced NSCLC and are not candidates for surgical resection or platinum-based chemoradiation, or - 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 HER-2-negative locally advanced unresectable or metastatic gastric or gastroesophageal junction (G/GEJ) adenocarcinoma whose tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%. **Oesophageal squamous cell carcinoma (OSCC)** Tevimbra as monotherapy is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic OSCC after prior platinum-based chemotherapy.
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? Yes Is the product suitable for a joint Nordic assessment? No If no, why not? Tevimbra is already assessed/being assessed in the other Nordic countries.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Tislelizumab is available as 100 mg concentrate for solution for infusion. Each ml of the concentrate for solution for infusion contains 10 mg of tislelizumab. Each vial of 10 ml contains 100 mg tislelizumab. Tislelizumab will be available in single packs containing one vial.

2. Summary table

Table 2 Summary table

Summary	
Indication relevant for the assessment	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

Summary	
	tumours express PD-L1 with a tumour area positivity (TAP) score ≥ 5%.
Dosage regiment and administration	IV infusion: 200 mg once every 3 weeks
Choice of comparator	Nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy and Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy
Prognosis with current treatment (comparator)	By the time of diagnosis, patients with oesophageal squamous cell carcinoma (OSCC) most often have already reached the advanced stages of metastasis, resulting in poor prognosis and presenting difficulties in treatment [4]. High PD-L1 expression on tumour cells have been associated with lymph node metastasis and poor overall survival (OS) outcomes [5–7]. Additionally, the health-related quality of life (HRQoL) in patients with oesophageal cancer (OC) is reported to be linked to the worsening of symptoms and disease progression over time [8]. The prognosis of OC has historically been poor. According to data from 2018-2022, the relative 1-year and 5-year survival rates, were 47.4% and 20.2% for men, and 50.9% and 19.0% for women diagnosed with OC in Denmark [9]. Survival data for the Danish population following the recommendation of pembrolizumab combined with chemotherapy in 2022 and nivolumab combined with chemotherapy in 2023 have not yet been published.
Type of evidence for the clinical evaluation	Network meta-analysis (NMA).
Most important efficacy endpoints (Difference/gain compared to comparator)	OS, PFS, ORR, and grade ≥3 TRAEs between the intervention and comparators were compared in the NMA. From these endpoints the NMA showed, that tislelizumab combined with chemotherapy performed at least equally to both pembrolizumab and nivolumab combined with chemotherapy. The following are results from the ITT population published in the key clinical publications (excluding the gastroesophageal junction cancer population from KEYNOTE-590), as these were used in the NMA: **RATIONALE-306** Tislelizumab plus chemotherapy: - OS: 17.2 months - PFS: 7.3 months

Summary	
	- ORR: 63.5% Chemotherapy: - OS: 10.6 months - PFS: 5.6 months - ORR: 42.4% **KEYNOTE-590** Pembrolizumab plus chemotherapy: - OS: 12.6 months - PFS: 6.3 months - ORR: 43.8% Chemotherapy: - OS: 9.8 months - PFS: 5.8 months - ORR: 31.0% **CheckMate 648** Nivolumab plus chemotherapy: - OS: 13.2 months - PFS: 5.8 months - ORR: 47% Chemotherapy: - OS: 10.7 months - PFS: 5.6 months - ORR: 27% Section 6, presents the data used in the NMA, and data based on longer follow-up periods, when available.
Most important serious adverse events for the intervention and comparator	The NMA showed no statistically significant difference between pembrolizumab, tislelizumab, and nivolumab when comparing grade ≥3 TRAEs. Serious adverse events with a frequency of ≥ 5% for tislelizumab plus chemotherapy from data cut-off 28FEB2022, include: - Dysphagia n=[redacted] - Pneumonia n=[redacted] Serious adverse events with a frequency of ≥ 5% were not reported in the key clinical publications for both

Summary	
	pembrolizumab plus chemotherapy and nivolumab plus chemotherapy.
Impact on health-related quality of life	Clinical documentation: narrative comparison of the intervention and comparators based on life quality data from the key clinical trials compiled by EQ-5D and EQ-VAS. Health economic model: N/A, as a cost-minimisation approach were taken.
Type of economic analysis that is submitted	Cost-minimisation model.
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	Tislelizumab vs. nivolumab: [redacted] Tislelizumab vs. pembrolizumab: [redacted]
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	The clinical expert confirms Danish Medicines Council's estimate of 45 patients to be eligible per year
Budget impact (in year 5)	[redacted]

3. The patient population, intervention, choice of comparators and relevant outcomes

3.1 The medical condition

Disease description : Oesophageal cancer (OC) is the 8th most common cancer globally. Oesophageal squamous cell carcinoma (OSCC) and oesophageal adenocarcinoma are the two main histological types of OC, with OSCC comprising over 85% of all OC cases globally, approximately 50% of which present as advanced or metastatic unresectable disease at diagnosis [10–14]. OSCC is typically classified as early disease, locally advanced disease, or advanced/metastatic disease. Early OSCC is characterized by abnormal tissue growth in the oesophageal mucosa, with limited invasion of the superficial layer of the submucosa [15]. In locally advanced OSCC, the tumour invades local structures, leaving the lymph nodes and other distant tissues uninvolved [16]. Lastly, advanced/metastatic cancer is characterized by tumour invasion past the mucosa into the submucosal layer and to distant organs [16]. OSCC is further classified as either resectable (full surgical excision of the tumour remains a possible treatment option) or unresectable (the tumour is no longer restricted to the oesophagus and can no longer be removed completely through surgery) [15]. Surgical intervention is the standard of care (SOC) for resectable OC; however, approximately 80-85% of patients are ineligible and must consider alternative treatment options due to multiple factors, such as tumour location, disease severity, and patient willingness [17].

Staging: Accurate staging of OSCC is crucial as it directly affects the overall treatment and disease prognosis. OSCC is staged according to the American Joint Committee on Cancer TNM (Tumour/Nodule/Metastasis) classification system, the 8th and most recent edition of which has been in effect since 2018 [18]. The TNM framework evaluates the anatomical characteristics including tumour size and spread of a tumour into nearby tissue (T = tumour), the extent to which the cancer has spread to the local lymph node system (N = node), and the presence of metastases in distant tissues or organs (M = metastasis) [19].

Clinical presentation and diagnosis: By the time of diagnosis, patients with OSCC most often have already reached the advanced stages of metastasis, resulting in poor prognosis and presenting difficulties in its treatment [4]. This is a result of the disease remaining unnoticed in earlier stages due to asymptomatic presentation or the occurrence of mild, non-specific symptoms [20]. Until the disease has metastasized, finding evidence suggestive of OSCC can be challenging with physical examination alone. Dysphagia and unintentional weight loss are the two most common symptoms associated with OSCC, when symptomatic [21]. Other signs and symptoms of OSCC tumours may also include chest pain, upper abdominal pain, regurgitation, persistent cough, and chronic gastrointestinal blood loss [21]. The symptoms of OSCC are only

noticeable in advanced stages, making early diagnosis challenging [22]. As for diagnostic procedures, endoscopy is regarded as the gold standard for the detection and diagnosis of OSCC [22]. The diagnostic workup of OSCC typically involves an upper endoscopic biopsy, followed by a histologic examination determining the programmed cell death protein 1 ligand (PD-L1) status [23–25]. The cellular interaction between programmed cell death protein 1 (PD-1) and PD-L1 plays a critical role in tumour evasion, as PD-1 promotes tumour proliferation and evasion of the body's immune mechanism [26–28]. As a result, the PD-1/PD-L1 pathway has emerged as a promising therapeutic target in OSCC. PD-L1 overexpression generally appears to be associated with worse survival outcomes in patients with OSCC, however, some studies have reported conflicting evidence regarding its prognostic value [29–31]. Several studies support the association of high PD-L1 expression on tumour cells with lymph node metastasis and poor overall survival (OS) outcomes; however, its precise prognostic value may depend on the cellular type expressing PD-L1 [5–7]. There are several methods to measure the extent of membranous positivity of PD-L1 expression on immune cells and tumour cells. Whereas the tumour proportion score (TPS) only assesses PD-L1 expression in tumour cells, the combined positive score (CPS) and tumour area positivity (TAP) scoring methods detect expression in both immune and tumour cells [32–34].

Prognosis and HRQoL: The prognosis of OC has historically been extremely poor, with 5-year survival ranging between 10% and 30% in most countries, according to the latest data [35–37]. Based on Danish cancer data from 2018 to 2022, the relative survival at 1 year is 47.4% and 50.9% for men and women, respectively. The relative 5-year survival is 20.2% and 19.0% for men and women, respectively. Two out of three patients cannot be offered a curable treatment at the time of diagnosis due to disseminated disease or already being in a poor condition [9,25,38].Health-related quality of life (HRQoL) in patients with OC is reported to be linked to the worsening of symptoms and disease progression over time. A multi-center cross-sectional study from 2018 suggests that advanced cancer stages are associated with larger health utility decrements. The findings of the study showed that pain or discomfort was the most impacted dimension, followed by the anxiety or depression dimension. Patients with advanced disease were more likely to report problems in the mobility, self-care, and usual activities dimensions compared to those in the early stage. Further, patients in more advanced cancer stages had significantly poorer health status compared to those in the earlier stages, as shown in the lower health utility and EuroQol-Visual Analog scale (EQ-VAS) scores [8].

3.2 Patient population

In Denmark, OC is the 8th most common type of cancer with OSCC as the most common histological subtype [38]. In 2022, 264 patients were diagnosed with OC with an average age of 72 years. Of these patients, 9.1% received curative surgery while the remaining received either chemotherapy, medical treatment, other oncological treatment, or no treatment. The majority of the remaining patients were diagnosed with late-stage disease, including 87.5% of patients receiving medical treatment who had stage 4 OC [39]. In Table 3 the incidence and prevalence of OC in Denmark is presented. In the Danish Esophago Gastric Cancer Group (DECG) report from 2022, it is noted that the patients that earlier were registered as having OC, now are registered as OSCC [39]. The

incidence numbers shown in Table 3 are those referred to as oesophagus on the DEGC reports. The prevalences are based on numbers from NORDCAN, which does not provide insights to the histologic subtypes of OC.

Table 3 Incidence and prevalence of OC in Denmark in the past 5 years

Year	2018	2019	2020	2021	2022	Later
Incidence in Denmark [39,40]	288	320	282	279	264	N/A
Prevalence in Denmark [41]	1,407	1,398	1,425	1,396	1,412	N/A
Global prevalence* [42]	N/A	N/A	N/A	N/A	717,169	N/A

N/A: not applicable, as data is unavailable. *5-year prevalence

It is expected that patients with OSCC treated with nivolumab in combination with platinum- and fluoropyrimidine- based chemotherapy or pembrolizumab in combination with platinum- and fluoropyrimidine- based chemotherapy are eligible candidates for treatment with tislelizumab in combination with platinum-based chemotherapy. This population in Denmark includes patients with locally advanced inoperable or metastatic OSCC with high PD-L1 expression. In the prior DMC assessment, it was estimated that approximately 90 patients each year with advanced OSCC is offered palliative for relief and life extension, with 50% being assessed to be eligible for treatment with PD-L1 inhibitor. Based on this the DMC estimated the population eligible for treatment to be approximately 45 patients annually (See Table 4) **[43]**. The clinical expert validated this estimate but noted that it might be conservative.

Table 4 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark who are eligible for treatment in the coming years	45	45	45	45	45

3.3 Current treatment options

The DECG published in 2023 treatment guidelines for "*Onkologisk behandling af ikke-kurabel cancer i esophagus og ventrikel*". In these guidelines the treatment recommendations against non-curable squamous cell carcinoma in PD-L1 positive patients are:

- Treatment with pembrolizumab + platinum- and fluoropyrimidine is recommended in first line (1L) for patients in performance score (PS) 0-1 with squamous cell carcinoma and PD-L1 CPS ≥10.

- Treatment with nivolumab + platinum- and fluoropyrimidine is recommended in 1L for patients in PS 0-1 with squamous cell carcinoma and PD-L1 TPS ≥1%.
- Treatment with nivolumab + ipilimumab is recommended in 1L for patients in PS 0-1 with squamous cell carcinoma and PD-L1 TPS ≥1% [38].

Treatment with pembrolizumab in combination with platinum- and fluoropyrimidine is recommended by the DMC as 1L treatment of patients with locally advanced, unresectable, or metastatic OC or Human Epidermal growth factor Receptor 2-negative gastroesophageal junction adenocarcinoma, with PD-L1 CPS ≥ 10 [44]. Similarly, treatment with nivolumab in combination with platinum- and fluoropyrimidine is recommended by the DMC as 1L treatment for patients with unresectable advanced, recurrent, or metastatic OSCC and PD-L1 expression TPS ≥ 1 %. The two treatment options, nivolumab in combination with chemotherapy and pembrolizumab in combination with chemotherapy is assessed to be equivalent, thus the DMC recommends the regions use the combination with the lowest costs [43]. The combination of nivolumab + ipilimumab has not been assessed by the DMC as treatment in patients with OSCC [38]. No Danish data on the prognosis or survival of patients with OSCC treated with nivolumab plus chemotherapy or pembrolizumab plus chemotherapy have been published since the treatments were recommended by the DMC in 2023 and 2022, respectively [43,44]. However, according to data from 2018-2022, the relative 1-year and 5-year survival rates, expressed as percentages with [95% CI], were 47.4 [44.8-50.2] and 20.2 [18.0-22.6] for men, and 50.9 [46.8-55.3] and 19.0 [15.2-23.6] for women diagnosed with OC in Denmark [9].

3.4 The intervention – Tevimbra

Table 5 Overview of the intervention, Tevimbra

Overview of intervention [1]	
Indication relevant for the assessment	Tevimbra (tislelizumab), in combination with platinum-based chemotherapy, is indicated for the 1L treatment of adult patients with unresectable, locally advanced or metastatic OSCC whose tumours express PD-L1 with a TAP score ≥ 5%.
ATMP	No
Method of administration	For intravenous use after dilution.
Dosing	200 mg once every 3 weeks. Chemotherapy based on Danish clinical practice: Oxaliplatin: 130 mg/m^2 IV day 1 every three weeks for up to 6 -9 series [43]. Capecitabine: 2.000 mg/m^2 oral day 1 to 14 every three weeks for up to 9 series [43].
Dosing in the health economic model (including relative dose intensity)	200 mg of tislelizumab once every 3 weeks. The median RDI for tislelizumab or placebo was comparable between the two

Overview of intervention [1]	
	treatment arms. The mean RDI was [redacted]% (SD: [redacted]) in the tislelizumab arm and [redacted]% (SD: [redacted]) in the placebo arm.
Should the medicine be administered with other medicines?	Yes, platinum-based chemotherapy. However, the clinical expert noted that in Danish clinical practice, Tevimbra would be administered with capecitabine and oxaliplatin combined.
Treatment duration / criteria for EOT	Treatment until disease progression or unacceptable toxicity.
Necessary monitoring, both during administration and during the treatment period	Yes.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Testing for PD-L1 expression is required for both Tevimbra (tislelizumab) and the comparators, however the test is not included in the model.
Package size(s)	1 vial of 100 mg/10 ml.

Abbreviations: 1L, First Line; EOT, End of Treatment; IV, Intravenous; mg, Milligrams; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Cell-Death Ligand 1; RDI, Relative Dose Intensity; TAP, Tumour Area Positivity

Mechanism of action: Tislelizumab is a humanized immunoglobulin G4 anti-PD-1 monoclonal antibody. Tislelizumab binds the extracellular domain of human PD-1 and blocks its interaction with PD-L1 and programmed cell death protein 2 ligand (PD-L2), releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response [1].

3.4.1 The intervention in relation to Danish clinical practice

It is expected tislelizumab in combination with chemotherapy will be equivalent to both pembrolizumab plus chemotherapy, and nivolumab plus chemotherapy, thus tislelizumab plus chemotherapy will become an additional treatment option in the 1L treatment of patients with OSCC with PD-L1 expression. The PD-L1 expression is expressed in different scores; as either CPS ≥ 10, PD-L1 TPS ≥ 1 % or PD-L1 TAP ≥ 5 % depending on the indication of pembrolizumab, nivolumab and tislelizumab, respectively. The Danish clinical guidelines state all treatment eligible patients should have PD-L1 score determined by CPS and TPS before treatment. The clinical expert confirmed this but noted that a high PD-L1 score from one test might result in omitting the other test. Thus, both CPS and TPS are used to express PD-L1 score in Danish clinical setting. TAP score is currently not mentioned in the guidelines [38]. TAP is a newly developed method for assessing tumour cells and immune cells together via visual estimation. To determine the TAP score an immunohistochemistry slide is visually investigated to estimate the area PD-L1 positive tumour cells and tumour-associated immune cells covers compared to the total tumour area. TAP is an efficient scoring

measurement, with an average time spent on scoring of 5 minutes compared to an average time of 30 minutes for CPS scoring, shown in a study by Liu et al. (2023). It was shown TAP is equally as effective as CPS in detecting patients with a positive PD-L1 expression, with TAP being less time-consuming. TAP was also shown to be highly reproducible between different pathologists [32]. For information regarding the concordance of the PD-L1 scoring methods refer to section 7.1.1. Concerning tislelizumab, the European Medicines Agency (EMA) indication states tislelizumab should be administered in combination with platinum-based chemotherapy. However, the clinical expert noted that in Danish clinical practice, tislelizumab would be administered with capecitabine and oxaliplatin combined.

Body surface area: To estimate the dose of the chemotherapy therapy in the health economic evaluation, an estimation of the mean body surface areas is required. In alignment with a previous DMC assessment of an immunotherapy, a mean weight of 76.5 kg per patient with OSCC was used in the model [43]. In 2022 the mean height of the Danish men was 180.2 cm and the mean height for women was 166,7 cm [45]. This results in a mean height of 173.45 cm. From this a mean body surface area is calculated by [46]: Body surface area = weight ^{0,425} x height ^{0,725} x 0,007184. Which equals a mean body surface area at 1.91 m^2.

3.5 Choice of comparators

The relevant comparators for tislelizumab plus chemotherapy in a Danish treatment perspective are pembrolizumab plus chemotherapy and nivolumab plus chemotherapy. Both are recommended by the DMC and are assessed as equivalent, see section 3.3 for more information. Despite that the comparators have been assessed to be equivalent both will be presented in this submission, as the conducted indirect comparison comprises all three treatments, see section 7.

Table 6 Overview of the comparator - Pembrolizumab plus chemotherapy

Overview of comparator - Pembrolizumab plus chemotherapy	
Generic name	Pembrolizumab
ATC code	L01FF02
Mechanism of action	Pembrolizumab is a humanized monoclonal antibody that by binding blocks the PD-1 receptor's interaction with PD-L1 and PD-L2.
Method of administration	Administered intravenously over 30 minutes every 3 or 6 weeks using a sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line or add-on filter.

Overview of comparator - Pembrolizumab plus chemotherapy	
Dosing	Pembrolizumab: 200mg every three weeks or 400mg every six weeks per EMA indication [47]. However, the DMC recommends weight-based dosing of 2 mg/kg every three weeks [43]. Chemotherapy: according to the EMA SmPC, the SmPC for the concomitant therapy should be conferred [47]. According to DMC, oxaliplatin and capecitabine are preferred as platinum- and fluoropyrimidine-based chemotherapies in Danish clinical practice [43]. Oxaliplatin: 130 mg/m^2 IV day 1 every three weeks for up to 6 -9 series [43]. Capecitabine: 2.000 mg/m^2 oral day 1 to 14 every three weeks for up to 9 series [43].
Dosing in the health economic model (including relative dose intensity)	Fixed dosing of 200 mg every three weeks. The RDI was assumed as [redacted]%.
Should the medicine be administered with other medicines?	Yes, in combination with platinum and fluoropyrimidine-based chemotherapy.
Treatment duration/ criteria for EOT	Treatment should be continued until disease progression or unacceptable toxicity.
Need for diagnostics or other tests (i.e. companion diagnostics)	The tumour expression of PD-L1 should be confirmed by a validated test.
Package size(s)	Concentrate for solution 1 vial: 100 mg/4 mL

Source **[47]**
Abbreviations: DMC, Danish Medicines Council; EMA, European Medicines Agency; EOT, End of Treatment; mg, Milligrams; ml, Milliliters; PD-1, Programmed Cell-Death 1; PD-L1, Programmed Cell-Death Ligand 1; PD-L2, Programmed Cell-Death Ligand 2; RDI, Relative Dose Intensity; SmPC, Summary of Product Characteristics

The Summary of Product Characteristics (SmPC) for pembrolizumab states the recommended dose is 200mg every 3 weeks (or 400mg every 6 weeks), however, according to the DMC, in Danish clinical practice it is administered as weight based of 2mg/kg every 3 weeks **[44,47]**. Relative dose intensity (RDI) for pembrolizumab was not available, thus it was assumed to be equal to tislelizumab at [redacted]%.

Table 7 Overview of the comparator - Nivolumab plus chemotherapy

Overview of comparator – Nivolumab plus chemotherapy [48]	
Generic name	Nivolumab
ATC code	L01FF01

Overview of comparator – Nivolumab plus chemotherapy [48]	
Mechanism of action	Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), that by binding blocks the PD-1 receptor's interaction with PD-L1 and PD-L2.
Method of administration	Administered every 2-4 weeks IV over 30 minutes in combination with chemotherapy. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.
Dosing	Nivolumab: 240mg every two weeks or 480mg every four weeks per EMA indication [48]. However, the DMC recommends weight-based dosing of 4,5 mg/kg every three weeks [43]. Chemotherapy: the EMA SmPC do not specify the dosing of the concomitant therapy [48]. However, according to DMC oxaliplatin and capecitabin are preferred as platinum- and fluoropyrimidine-based chemotherapies in Danish clinical practice [43]. Oxaliplatin: 130 mg/m^2 IV day 1 every three weeks for up to 6 -9 series [43]. Capecitabine: 2.000 mg/m^2 oral day 1 to 14 every three weeks for up to 9 series [43].
Dosing in the health economic model (including relative dose intensity)	Fixed dose of 360mg every three weeks, to align treatment frequency with Danish clinical practice. Previous DMC assessment stated using a dose of 360mg every three weeks is not expected to impact the efficacy [43]. The RDI was assumed as [redacted]%.
Should the medicine be administered with other medicines?	Yes, in combination with fluoropyrimidine- and platinum-based chemotherapy.
Treatment duration/ criteria for EOT	Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
Need for diagnostics or other tests (i.e. companion diagnostics)	The tumour expression of PD-L1 should be confirmed by a validated test.
Package size(s)	Concentrate for solution for infusion - vials available as: - 40 mg/4 mL - 100 mg/10 mL - 120 mg/12 mL - 240 mg/24 mL

Abbreviations: DMC, Danish Medicines Council; EMA, European Medicines Agency; EOT, End of Treatment; HuMAb, Human Monoclonal Antibody; IgG4, Immunoglobulin G4; IV, Intravenous; mg, Milligrams; ml, Milliliters; PD-1, Programmed Cell-Death 1; PD-L1, Programmed Cell-Death Ligand 1; PD-L2, Programmed Cell-Death Ligand 2; RDI, Relative Dose Intensity; SmPC, Summary of Product Characteristics

The SmPC for nivolumab states the recommended dose is 240mg every 2 weeks or 480mg every 4 weeks, however, in Danish clinical setting the dosing frequency is adjusted to every 3 weeks (which results in a fixed dose of 360mg every 3 weeks). This adjustment is by the DMC assessed not to have an impact on the efficacy. Additionally, according to the DMC, nivolumab is in Danish clinical practice administered weight based as 4,5mg/kg every 3 weeks [43,48]. RDI for nivolumab was not available, thus it was assumed to be equal to tislelizumab at [redacted]%.

3.6 Cost-effectiveness of the comparators

Both nivolumab plus chemotherapy and pembrolizumab plus chemotherapy have previously been evaluated by the DMC and been assessed as equivalent. These are recommended as 1L treatment for OSCC PD-L1 positive patients [49].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

In the evaluations of nivolumab plus chemotherapy and pembrolizumab plus chemotherapy as 1L treatment of OC in PD-L1 positive patients the outcomes OS, PFS, safety, and life quality were deemed clinically relevant by the DMC [43,44]. Therefore, the relevant outcomes to assess the efficacy of tislelizumab compared to both nivolumab and pembrolizumab are OS, PFS, and treatment related adverse event (TRAE) grade ≥3. Additionally, ORR has been included in the indirect treatment comparison (ITC). Life quality data has not been included in the ITC however, life quality data are presented in section 10. The efficacy outcomes deemed relevant for the comparison of tislelizumab, nivolumab, and pembrolizumab all combined with chemotherapy are presented in Table 8. The follow-up time for efficacy outcomes in this submission are based on the key publications as the ITC solely uses this data. Under each section representing the clinical trials (6.1.4, 6.1.5, and 6.1.6), a subsection has been added to describe the newest available follow-up data.

Table 8 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
OS **[RATIONALE-306]**[50–52] **[KEYNOTE-590]**[53–55] **[CheckMate 648]**[56–58]	**RATIONALE-306:** Median follow-up was 16.3 months in the tislelizumab group and 9.8 months in the placebo group **KEYNOTE-590:** Median follow-	**RATIONALE-306**: OS is defined as the time from the date of randomization until the date of death due to any cause **KEYNOTE-590:** OS is defined as the time from randomization to death due to any cause.	N/R

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	up of 22.6 months **CheckMate 648**: The median follow-up was 12.1 months in the nivolumab plus chemotherapy group, 12.1 in the nivolumab plus ipilimumab group, and 9.5 months in the chemotherapy group.	**CheckMate 648:** OS is defined as the time between the date of randomization and the date of death.	
PFS **[RATIONALE-306]** [50–52] **[KEYNOTE-590]** [53–55] **[CheckMate 648]** [56–58]	**RATIONALE-306:** Same as OS **KEYNOTE-590:** Same as OS **CheckMate 648:** After a 12-month minimum follow-up	**RATIONALE-306:** PFS is defined as the time from the date of randomization to the date of first documentation of disease progression assessed by the investigator per RECIST v1.1 or death, whichever occurs first **KEYNOTE-590**: PFS was defined as the time from randomization to the first documented PD per RECIST 1.1 as assessed by the investigator, or death due to any cause, whichever occurred first. **CheckMate 648**: PFS was defined as the time from randomization to the date of the first documented PD per BICR on the basis of RECIST, version 1.1.	**RATIONALE-306:** Assessed by the investigator per RECIST v1.1 + BICR per RECIST v1.1 **KEYNOTE-590**: Assessed by the investigator per RECIST 1.1 **CheckMate 648**: BICR on the basis of RECIST, version 1.1.
ORR **[RATIONALE-306]** [50–52] **[KEYNOTE-590]** [53–55] **[CheckMate 648]** [56–58]	**RATIONALE-306:** Same as OS **KEYNOTE-590:** Same as OS	**RATIONALE-306:** ORR is defined as the proportion of participants whose BOR is CR or PRassessed by the investigator per RECIST v1.1	**RATIONALE-306**: Assessed by the investigator per RECIST v1.1 **KEYNOTE-590:** Assessed by the investigator per RECIST 1.1

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	CheckMate 648: Same as OS	**KEYNOTE-590**: ORR was defined as the percentage of participants in the analysis population who had a CR (disappearance of all target lesions) or a PR (≥30% decrease in the sum of diameters of target lesions) per RECIST 1.1. as assessed by the investigator. **CheckMate 648**: ORR is defined as the percentage of participants with a BOR of CR or PR. BOR is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1) or the date of subsequent anti-cancer therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm.	**CheckMate 648**: Determined by BICR on the basis of RECIST, version 1.1
Treatment related adverse event ≥ Grade 3 (TRAE 3+) **[RATIONALE-306]** [50–52] **[KEYNOTE-590]** [53–55] **[CheckMate 648]** [56–58]	**RATIONALE-306:** AEs were monitored throughout the trial and for a minimum of 30 days after treatment discontinuation **KEYNOTE-590**: AEs were monitored	**RATIONALE-306:** Included treatment-emergent AEs that were considered by the investigator to be related to the study drug or treatment-emergent AEs with a missing causality **KEYNOTE-590**: N/R **CheckMate 648**: Events reported between first	**RATIONALE-306**: NCI CTCAE version 4.03 **KEYNOTE-590:** CTCAE version 4.0 **CheckMate 648**: CTCAE v4.0 and the Medical Dictionary for Regulatory Activities, version 23.1 per Investigator assessment

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
	throughout the trial and for a minimum of 30 days after treatment discontinuation. **CheckMate 648**: TRAEs were reported from first dose and 30 days after last treatment dose.	dose and 30 days after last dose of study therapy. Treatment relatedness in the nivolumab plus chemotherapy group refers to nivolumab, at least one chemotherapy component, or both. Treatment relatedness in the nivolumab plus ipilimumab group refers to nivolumab, ipilimumab, or both.	
HRQoL **[RATIONALE-306]** [50–52] **[KEYNOTE-590]** [50–52,56] **[CheckMate 648]** [53–55,57]	**RATIONALE-306**: From baseline to EOT visit **KEYNOTE-590:** Time from baseline to week 18 **CheckMate 648**: N/R	**RATIONALE-306:** HRQoL Assessment of the Participant's Overall Health Status **KEYNOTE-590:** Changes from baseline in health-related quality of life using the EORTC QLQ-C30 and the EORTC QLQ-OES18. Characterize PRO utilities using EQ- 5D-5L questionnaire in all subjects **CheckMate 648:** HRQoL changes from baseline and differences between treatment groups were measured.	**RATIONALE-306:** EORTC QLQ-C30, EORTC QLQ-OES18, and EQ-5D-5L **KEYNOTE-590**: EORTC QLQ-30, QLQ-OES18 and EQ-5D-5L **CheckMate 648**: Functional Assessment of Cancer Therapy-Esophageal (including the GP5 item to assess impact of side effects) and EQ-5D-3L

*Longer follow-up data is presented later in the submission.
Abbreviations: AEs, Adverse Events; BICR, Blinded Independent Central Review; BOR, Best Overall Response; CR, Complete Response; CTCAE, Common Terminology Criteria for Adverse Events; EQ-5D-3L, EuroQol 5-Dimension 3-level; EQ-5D-5L, EuroQol 5-Dimension 5-level; EORTC-QLQ-30, European Organization of the Research and Treatment of Cancer- Quality of Life Questionnaire C30; EOT, End of Treatment; HRQoL, Health-related Quality of Life; N/R, Not Reported; NCI, National Cancer Institute; ORR, Objective Response; OS, Overall Survival; PD, Progressive Disease; PFS, Progression-Free Survival; PR, Partial Response; QLQ-OES18, Quality of Life Questionnaire Oesophageal Module; RECIST, Response Evaluation Criteria for Solid Tumours; TRAE, Treatment Related Adverse Events

Validity of outcomes

As described above the outcomes OS, PFS, safety, and life quality were earlier deemed clinically relevant by the DMC [43,44]. Additional to these outcomes, the ORR is also reported and compared for the treatment options, as ORR is an important parameter to assess the efficacy of the treatments [59]. To assess both PFS and ORR the RECIST v1.1 guidelines are used. RECIST v1.1 is a highly used and acknowledged tool for tumour

measurement [60]. To assess the safety the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) were used. To measure life quality different measurement tool have been used however, this submission focus on the data measured by EuroQol 5-dimension (EQ-5D), preferably by EuroQoL 5-Dimensions 5-Levels (EQ-5D-5L), as this generic questionnaire is preferred by the DMC [61].

4. Health economic analysis

A cost-minimisation analysis has been chosen as the Network Meta Analysis (NMA) (see section 7) found no significant difference in efficacy between tislelizumab plus chemotherapy, nivolumab plus chemotherapy and pembrolizumab plus chemotherapy. For the cost-minimisation analysis, both nivolumab combined with platinum- and fluoropyrimidine-based chemotherapy and pembrolizumab combined with platinum- and fluoropyrimidine-based chemotherapy are included as comparators [43].

4.1 Model structure (N/A)

N/A due to a cost-minimisation approach.

4.2 Model features

The features of the health economic model are seen below in Table 9.

Table 9 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with OSCC with PD-L1 expression	Based on EMA indication and Danish clinical practice
Perspective	Limited societal perspective	According to DMC guidelines
Time horizon	Maximum one year (9 cycles corresponding to 6,24 months)	Based on treatment duration for intervention, comparator, chemotherapy and Danish clinical practice
Cycle length	3 weeks	Equivalent to one treatment cycle
Half-cycle correction	N/A	N/A
Discount rate	N/A	Not relevant as the time horizon is less than one year
Intervention	Tislelizumab in combination with capecitabine and oxaliplatin	Aligned with the SmPC and Danish clinical setting, validated by clinical expert.

Model features	Description	Justification
Comparator(s)	Nivolumab in combination with capecitabine and oxaliplatin. Pembrolizumab in combination with capecitabine and oxaliplatin.	According to DMC recommendations. Validated by clinical expert.
Outcomes	N/A	N/A as a cost-minimisation analysis is conducted

Abbreviations: DMC, Danish Medicines Council; EMA, European Medicines Agency; N/A, Non-Applicable; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Cell Death Protein 1 Ligand.

5. Overview of literature

5.1 Literature used for the clinical assessment

A comprehensive global clinical systematic literature review (SLR) was conducted on June 23, 2023, using the Ovid® search interface, the following electronic databases were searched: Embase, Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations), Ovid MEDLINE® Daily, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews. See Appendix H for detailed information on the SLR. Eight randomized control trials (RCT) studies met the inclusion criteria, including the key trials RATIONALE-306, KEYNOTE-590, and CheckMate 648, see Table 10. The remaining studies are presented in Table 93. The ITC compares tislelizumab, nivolumab and pembrolizumab, which is the relevant comparison in a Danish clinical setting. Therefore, the trials presented below will be limited to the three trials RATIONALE-306, KEYNOTE-590, and CheckMate 648. The DMC mandates that the SLR submitted must be no older than one year at the time of application. Therefore, an additional SLR was conducted to cover potentially new literature published from June 2023 until October 2024. In accordance with the Method Guide by the DMC, a literature search must be performed on effect and safety using, as a minimum, the databases of MEDLINE (via e.g. PubMed), and CENTRAL (via the Cochrane Library or Ovid) OR EMBASE (via e.g. embase.com). However, during a dialog with the DMC it was agreed the additional SLR only would be required to conducted in one database. Thus, an additional SLR was conducted in EMBASE using the searching method of the global SLR.
The additional search was carried out on October 17, 2024 in EMBASE to cover any relevant information published within the time frame from June 23, 2023 to October 17, 2024. The additional search was not as comprehensive as the global search but did follow the requirements outlined in the DMC's methods guide. The additional SLR was conducted with minor adjustments to the search strategy and eligibility criteria compared to comprehensive global clinical SLR. See Appendix H for detailed information on the additional SLR.
The additional SLR identified three different clinical trials from eight publications. The identified trials were previously identified in the comprehensive global clinical SLR and include RATIONALE-306, CheckMate 648, and KEYNOTE-590. The additional search did

not identify any new clinical trials or treatment comparisons between the interventions of the PICOS. However, new efficacy and safety follow-up data for the CheckMate 648 trial was identified through the search in two different abstracts covering the 29-month follow-up and the additional 45-month follow-up [62,63]. Safety data from the 45-month follow-up was insufficient and will thus not be presented however, efficacy data are included in the application in Section 6.1.5. Safety data from the 29-month follow-up will briefly be presented in Section 9.1.
Beyond the additional SLR, an abstract with 5-year follow-up data from the KEYNOTE-590 trial has been identified internally and added to the table below.

Table 10 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Full paper: Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic oesophageal squamous cell carcinoma (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study Xu, Jianming et al. The Lancet Oncology, Volume 24, Issue 5, 483 – 495 [51].	RATIONALE-306	NCT03783442	Start: 11/12/2018 Completion: 31/08/2024 Data cut-off: 28/02/2022	Tislelizumab vs. chemotherapy
Data on file [64] Data cutoff: February 28, 2022 + November 23, 2023				
Abstract: Global, randomized, phase III study of tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced/metastatic esophageal squamous cell carcinoma (RATIONALE-306 update): Minimum 3-year survival follow-up. Yoon, H et al. Journal of Clinical Oncology (2024) 42(16_suppl) 4032-4032 [65].			Start: 11/12/2018 Completion: 31/08/2024 Data cut-off: 23/11/2023	
Full paper: Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study Sun, Jong-Mu et al. The Lancet, Volume 398, Issue 10302, 759 – 771 [54].	KEYNOTE – 590	NCT03189719	Start: 25/07/2017 Completion: 10/07/2023 Data cut-off: 02/07/2020	Pembrolizumab vs chemotherapy
Abstract: First-line pembrolizumab (pembro) plus chemotherapy (chemo) for advanced esophageal cancer: 5-year outcomes from the phase 3 KEYNOTE-590 study.			Start: 25/07/2017 Completion: 10/07/2023	

Reference (Full citation incl. reference number)	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of
Shah, M et al. Journal of Clinical Oncology (2024) 42(3_suppl) 250 [66].			Data cut-off: 5-year follow up	
Full paper: Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma Doki, Yuichiro et al. The New England journal of medicine, 386(5), 449–462[57].	CheckMate 648	NCT03143153	Start: 29/06/2017 Completion: 13/01/2025	Nivolumab vs chemotherapy
Full paper: Nivolumab plus chemotherapy or ipilimumab versus chemotherapy in patients with advanced esophageal squamous cell carcinoma (CheckMate 648): 29-month follow-up from a randomized, open-label, phase III trial Kato, Doki et al. Cancer medicine, 13(9), e7235 [67].				
Abstract: Nivolumab (NIVO) plus chemotherapy (chemo) or ipilimumab (IPI) vs chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): 45-month (mo) follow-up of CheckMate 648 Chau, I et al. Ann Oncol, 2024, 45(suppl16), 4034 [63]				

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

Ongoing trials

A search for active or unpublished studies that include the intervention and comparator on the intended patient population was conducted the 11th of December on Clinicaltrials.gov and the EU Clinical Trials Register. The searches resulted in no hits for this specific population and treatment options.

5.2 Literature used for the assessment of health-related quality of life – (N/A)

A literature review was not conducted to identify health-related quality of life (HRQoL) data, because a cost-minimisation was performed to compare tislelizumab to the relevant comparators and therefore no HRQoL data was included in the model. However, as HRQoL data was collected in RATIONALE-306, KEYNOTE-590, and CheckMate 648, this data is presented in detail in section 10.

Table 11 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume(issue): pp [reference number]	E.g. First line metastatic recurrence	

5.3 Literature used for inputs for the health economic model – (N/A)

A literature review for inputs to the health economic model was not conducted, as this submission includes a simple cost-minimisation analysis.

Table 12 Relevant literature used for input to the health economic model (N/A)

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
-	-	-	-

6. Efficacy

6.1 Efficacy of tislelizumab plus chemotherapy compared to nivolumab plus chemotherapy and pembrolizumab plus chemotherapy

6.1.1 Relevant studies

For the comparative analyses the Intention-to-treat (ITT) analysis sets from all relevant trials have been utilized, see Table 13. Only the OSCC patients from the ITT analysis set in Keynote 590 has been utilized in this submission. Pre-specified subgroup analyses reflecting the PD-L1 positive populations have also been included whenever deemed relevant.

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

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
RATIONALE-306, NCT03783442 [51]	Global, randomized, double-blind, parallel-arm, placebo-controlled, phase 3 study that assessed the efficacy and safety of 1L treatment with either tislelizumab plus standard ICC doublet or placebo plus ICC doublet	The trial was initiated on December 11, 2018, with primary study completion on February 28, 2022	Patients with unresectable, locally advanced recurrent or metastatic OSCC	Tislelizumab + Chemotherapy: 200 mg tislelizumab administered IV on Day 1 of each cycle Q3W plus one of the following, Chemotherapy Doublet A: cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and 5-fluorouracil IV 750-800 mg/m^2 on Days 1 to 5 of each cycle Q3W. Chemotherapy Doublet B:	Matched placebo administered IV on Day 1 of each cycle Q3W plus one of the following until unacceptable toxicity, disease progression or withdrawal for other reasons; each cycle is 21 days. Chemotherapy Doublet A: cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and 5-	**Primary outcomes:** • OS defined as the time from randomisation to death due to any cause in all randomized patients (3 yr, 2 months) **Secondary outcomes:** • PFS defined as the time from randomisation to death due to any cause in all randomized patients (40 months) • ORR defined as the proportion of patients whose BOR was CR or PR, as assessed by the investigator per RECIST v1.1 (40 months) • OS in the PD-L1 Score ≥ 10% Subgroup defined as the time from randomisation until death due to any cause (40 months) • DOR defined as the time from the first determination of an objective response until the first documentation of progression, as assessed by the investigator per RECIST v1.1, or death, whichever comes first (40 months) • HRQoL Assessment of the Participant's Overall Health Status Using EORTC QLQ-C30 (40 months) • HRQoL Assessment of the Participant's Overall Health Status Using the EORTC QLQ-OES18 (40 months) • HRQoL Assessment of the Participant's Overall Health Status Using the Generic Health State Instrument 5D EQ-5D-5L (40 months)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and capecitabine orally 1000 mg/m^2 on Days 1 to 14 of each cycle, twice a day; or Chemotherapy Doublet C: cisplatin 60-80 mg/m^2 administered IV on Day 1 or 2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and paclitaxel 175 mg/m^2 IV on Day 1 of each	fluorouracil IV 750-800 mg/m^2 on Days 1 to 5 of each cycle Q3W. Chemotherapy Doublet B: cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and capecitabine orally 1000 mg/m^2 on Days 1 to 14 of each cycle, twice a day; or Chemotherapy Doublet C: cisplatin 60-80 mg/m^2 administered IV on Day 1 or 2 or oxaliplatin	• Number of Participants Experiencing AEs (40 months)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
				cycle Q3W; cisplatin may be given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines	130 mg/m^2 administered IV on Day 1 of each cycle Q3W and paclitaxel 175 mg/m^2 IV on Day 1 of each cycle Q3W; cisplatin may be given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines	
CheckMate 648, NCT03143153 [57,58]	Global, randomized, open-label, phase 3 trial evaluating efficacy and safety of nivolumab and ipilimumab or nivolumab combined with chemotherapy	The trial was initiated on June 29, 2017, with estimated study completion on January 13, 2025	Patients with unresectable advanced, recurrent, or metastatic previously untreated oesophageal squamous cell carcinoma	Nivolumab + chemotherapy: 240 mg nivolumab administered IV every 2 weeks (Q2W) plus chemotherapy consisting of a 4-week cycle of IV fluorouracil at 800 mg/m^2	Chemotherapy consisting of a 4-week cycle of IV fluorouracil at 800 mg/m^2 on days 1 through 5 and IV cisplatin at a dose of 80 mg/m^2 on day 1	**Primary outcomes:** • OS in patients with tumour cell PD-L1 defined as the time between the date of randomization and the date of death. For participants without documentation of death, OS will be censored on the last date the subject was known to be alive (up to approximately 20 months) • PFS in patients with tumour cell PD-L1 defined as the time from randomization to the date of the first documented PD per BICR per RECIST 1.1 criteria or death due to any cause. **Secondary outcomes:**

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
	versus chemotherapy			on day 1 through 5 and IV cisplatin at a dose of 80 mg/m^2 on day 1. or Nivolumab + ipilimumab: 3 mg/kg body weight nivolumab IV Q2W plus 1 mg/kg ipilimumab IV every 6 weeks		• OS in all randomized patients (up to approximately 16 months) • PFS in all randomized patients (up to approximately 7 months) • ORR as assessed by BICR defined as the percentage of participants with a BOR of CR or PR. BOR is defined as the best response designation as determined by BICR, recorded between the date of randomization and the date of objectively documented progression (per RECIST 1.1) or the date of subsequent anti-cancer therapy (including tumour-directed radiotherapy and tumour-directed surgery), whichever occurs first. PR is defined as at least a 30% decrease in the sum of diameters of target lesions. CR is defined as the disappearance of all target lesions and the reduction of any pathological lymph nodes to <10 mm (up to 40 months).
KEYNOTE-590, NCT03189719 [54,55]	Randomized, placebo-controlled, double-blind, phase 3 study evaluating efficacy and safety of pembrolizumab plus chemotherapy	The trial was initiated on July 25, 2017, with study completion on July 10, 2023	Patients with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable or metastatic	Pembrolizumab plus chemotherapy: 200 mg pembrolizumab IV Q3W plus cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2/day	Placebo plus chemotherapy: placebo to pembrolizumab (saline) IV Q3W plus cisplatin 80 mg/m^2 IV Q3W and 5-fluorouracil 800 mg/m^2/day continuous IV	**Primary outcomes:** • OS in patients with OSCC whose tumours are PD-L1 positive (CPS≥10). OS was defined as time from randomization to death due to any cause (up to approximately 34 months) • OS in patients with OSCC (up to approximately 34 months) • OS in patients with PD-L1 positive tumours (up to approximately 34 months) • OS in all patients (up to approximately 34 months)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
			oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer	continuous IV infusion on days 1 to 5 Q3W	infusion on days 1 to 5 Q3W	• PFS per RECIST 1.1 as assessed by investigator in patients with OSCC. PFS was defined as the time from randomization to the first documented progressive disease or death due to any cause, whichever occurred first (up to approximately 34 months) • PFS per RECIST 1.1 as assessed by investigator in patients with PD-L1 positive tumours. PFS was defined as the time from randomization to the first documented progressive disease or death due to any cause, whichever occurred first (up to approximately 34 months) • PFS per RECIST 1.1 as assessed by investigator in all patients. PFS was defined as the time from randomization to the first documented progressive disease or death due to any cause, whichever occurred first (up to approximately 34 months) **Secondary outcomes:** • ORR per RECIST 1.1 as assessed by investigator in all patients. ORR was defined as the percentage of patients in the analysis population who had a CR or PR per RECIST 1.1 (up to approximately 34 months) • ORR per RECIST 1.1 as assessed by investigator in patients with OSCC whose tumours are PD-L1 positive (CPS≥10) (up to approximately 34 months) • ORR per RECIST 1.1 as assessed by investigator in patients with OSCC (up to approximately 34 months)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• ORR per RECIST 1.1 as assessed by investigator in patients whose tumours are PD-L1 positive (CPS≥10) (up to approximately 34 months) • DOR per RECIST 1.1 as assessed by investigator in all patients. DOR was defined as the time from first documented evidence of confirmed CR or PR until PD or death due to any cause, whichever occurred first for patients who demonstrated confirmed CR or PR per RECIST 1.1. DOR for participants who had not progressed or died at the time of analysis was censored at the date of their last tumour assessment (up to approximately 34 months) • DOR per RECIST 1.1 as assessed by investigator in patients with OSCC whose tumours are PD-L1 positive (up to approximately 34 months) • DOR per RECIST 1.1 as assessed by investigator in patients with OSCC (up to approximately 34 months) • DOR per RECIST 1.1 as assessed by investigator in patients whose tumours are PD-L1 positive (up to approximately 34 months) • Number of patients with an AE (up to approximately 27 months) • EORTC QLQ-C30 GHS/QoL combined score in all patients (from baseline to week 18) • EORTC QLQ-C30 GHS/QoL combined score in patients with OSCC (from baseline to week 18)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
						• EORTC QLQ-C30 Global Health Status/Quality of Life (GHS/QoL) combined score in patients whose tumours are PD-L1 positive (from baseline to week 18) • EORTC QLQ-OES18 subscale scores in all patients (from baseline to week 18) • EORTC QLQ-OES18 subscale scores in patients with OSCC whose tumours are PD-L1 positive (from baseline to week 18) • EORTC QLQ-OES18 subscale scores in patients whose tumours are PD-L1 positive (from baseline to week 18) • EORTC QLQ-OES18 subscale scores in patients with OSCC (from baseline to week 18)

Abbreviations: 1L, First Line; AE, Adverse Events; BICR, Blinded Independent Central Review; BOR, Best Overall Response; CPS, Combined Positive Score; CR, Complete Response; DOR, Duration of Response; EORTC QLC-C30, European Organization of the Research and Treatment of Cancer- Quality of Life Questionnaire C30; EQ-5D-5L, EuroQol 5-Dimension 5-level; GHS, Global Health Status; HRQoL, Health-related Quality of Life; ICC, Investigator-Chosen Chemotherapy; IV, Intravenous; ORR, Objective Response Rate; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma; PD, Progressive Disease; PD-L1, Programmed Cell Death Protein 1 Ligand; PFS, Progression-Free Survival; PR, Partial Response; Q2W, Cycle Every 2 Weeks; Q3W, Cycle Every 3 Weeks; QLQ-OES18, Quality of Life Questionnaire Oesophageal Module; QoL, Quality of Life; RECIST, Response Evaluation Criteria for Solid Tumours.

6.1.2 Comparability of studies

The three trials were all multicenter, randomized controlled phase 3, and both RATIONALE-306 and KEYNOTE-590 were double blind whereas CheckMate 648 was an open label trial [51,54,57].

RATIONALE-306 and KEYNOTE-590 explicit stated that cross-over was not permitted between treatment groups, although CheckMate 648 did not report this, it is unlikely that cross-over occurred [51,54,57].

The trials included an immunotherapy treatment arm paired with chemotherapy. KEYNOTE-590 and CheckMate 648 assessed fluorouracil + cisplatin whereas RATIONALE-306 assessed multiple regimens, cisplatin or oxaliplatin + fluorouracil or capecitabine or paclitaxel. While differences in chemotherapy arms were noted, it was assumed that the chemotherapies were sufficiently similar to be combined into a single node in the NMA. RATIONALE-306 and KEYNOTE-590 included a placebo arm paired with chemotherapy, while CheckMate 648 included a chemotherapy-only arm. CheckMate 648 included also an arm of nivolumab and ipilimumab without chemotherapy. Differences in dose and dosing schedule were noted [51,54,57].

Although some differences in trial characteristics were noted, the trials were considered sufficiently similar to derive reasonable estimates of comparative efficacy via an ITC through an NMA. The clinical expert considered the three trials to be sufficiently similar, with no significant differences. The clinical expert deemed the trials comparable in an indirect analysis.

6.1.2.1 Comparability of patients across studies

In Table 14 the available baseline characteristics for the PD-L1 positive patient population from RATIONALE-306 and CheckMate 648 are presented. It was not possible to locate baseline characteristics of the PD-L1 positive patient population from KEYNOTE-590, thus KEYNOTE-590 was omitted from the table. The baseline characteristics from the ITT populations from each study are presented in Appendix K, Table 105. Comparing Table 105 and Table 14, no major deviations between the ITT population and the PD-L1 positive population, valid for both RATIONALE-306 and CheckMate 648.

Table 14 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety, PD-L1 positive population

	RATIONALE-306 [64]				CheckMate 648 [56,57]		
	Tislelizumab + Chemotherapy (N=116), TAP≥ 10%	Placebo + Chemotherapy (N=107), TAP≥ 10%	Tislelizumab + Chemotherapy (N=[redacted]), TAP≥ 5%	Placebo + Chemotherapy (N=[redacted]), TAP≥ 5%	Nivolumab + Chemotherapy (N=158), TPS ≥1%	Nivolumab + Ipilimumab (N=158), TPS ≥1%	Chemotherapy (N=157), TPS ≥1%
Age, years							
Median (range)	[redacted]	[redacted]	[redacted]	[redacted]	64 (40–85)	62 (28–81)	64 (26–81)
<65	[redacted]	[redacted]	[redacted]	[redacted]	NR		
≥65	[redacted]	[redacted]	[redacted]	[redacted]			
Sex, n (%)							
Female	[redacted]	[redacted]	[redacted]	[redacted]	33 (21)	27 (17)	26 (17)
Male	[redacted]	[redacted]	[redacted]	[redacted]	125 (79)	131 (83)	131 (83)
Geographical region, n (%)							
Asia	[redacted]	[redacted]	[redacted]	[redacted]	114 (72)	116 (73)	113 (72)
Rest of World	[redacted]	[redacted]	[redacted]	[redacted]	44 (28)	42 (27)	44 (28)

	RATIONALE-306 [64]				CheckMate 648 [56,57]		
	Tislelizumab + Chemotherapy (N=116), TAP≥ 10%	Placebo + Chemotherapy (N=107), TAP≥ 10%	Tislelizumab + Chemotherapy (N=[redacted]), TAP≥ 5%	Placebo + Chemotherapy (N=[redacted]), TAP≥ 5%	Nivolumab + Chemotherapy (N=158), TPS ≥1%	Nivolumab + Ipilimumab (N=158), TPS ≥1%	Chemotherapy (N=157), TPS ≥1%
Race, n (%)							
Asian	[redacted]	[redacted]	[redacted]	[redacted]	116 (73)	117 (74)	113 (72)
White	[redacted]	[redacted]	[redacted]	[redacted]	38 (24)	34 (22)	38 (24)
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]	[redacted]	NR		
Black/African American	[redacted]				1 (<1)	2 (1)	3 (2)
Not reported, unknown or other	[redacted]	[redacted]	[redacted]	[redacted]	3 (2)	5 (3)	3 (2)
Ethnicity, n (%)							
Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]	NR		
Not Hispanic or Latino	[redacted]	[redacted]	[redacted]	[redacted]			
Unknown	[redacted]	[redacted]	[redacted]	[redacted]			
Not reported	[redacted]	[redacted]	[redacted]	[redacted]			
BMI, kg/m^2, median (Q1,Q3)	[redacted]	[redacted]	[redacted]	[redacted]	NR		

	RATIONALE-306 [64]				CheckMate 648 [56,57]		
	Tislelizumab + Chemotherapy (N=116), TAP≥ 10%	Placebo + Chemotherapy (N=107), TAP≥ 10%	Tislelizumab + Chemotherapy (N=[redacted]), TAP≥ 5%	Placebo + Chemotherapy (N=[redacted]), TAP≥ 5%	Nivolumab + Chemotherapy (N=158), TPS ≥1%	Nivolumab + Ipilimumab (N=158), TPS ≥1%	Chemotherapy (N=157), TPS ≥1%
ECOG performance status, n (%)							
0	[redacted]	[redacted]	[redacted]	[redacted]	71 (45)	72 (46)	70 (45)
1	[redacted]	[redacted]	[redacted]	[redacted]	87 (55)	86 (54)	86 (55)
Smoking status, n (%)							
Never	[redacted]	[redacted]	[redacted]	[redacted]	33 (21)	33 (21)	38 (24)
Current	[redacted]	[redacted]	[redacted]	[redacted]	125 (79)	136 (86)	119 (76)
Former	[redacted]	[redacted]	[redacted]	[redacted]			
Missing	[redacted]	[redacted]	[redacted]	[redacted]	NR		
Alcohol consumption, n (%)							
Never	[redacted]	[redacted]	[redacted]	[redacted]	NR		

	RATIONALE-306 [64]				CheckMate 648 [56,57]		
	Tislelizumab + Chemotherapy (N=116), TAP≥ 10%	Placebo + Chemotherapy (N=107), TAP≥ 10%	Tislelizumab + Chemotherapy (N=[redacted]), TAP≥ 5%	Placebo + Chemotherapy (N=[redacted]), TAP≥ 5%	Nivolumab + Chemotherapy (N=158), TPS ≥1%	Nivolumab + Ipilimumab (N=158), TPS ≥1%	Chemotherapy (N=157), TPS ≥1%
Current	[redacted]	[redacted]	[redacted]	[redacted]			
Former	[redacted]	[redacted]	[redacted]	[redacted]			
Missing	[redacted]	[redacted]	[redacted]	[redacted]			
Disease status at study entry, n (%)							
Metastatic					85 (54)	107 (68)	89 (57)
Unresectable advanced					20 (13)	18 (11)	27 (17)
Recurrent, locoregional			[redacted]		13 (8)	9 (6)	14 (9)
Recurrent, distant					40 (25)	24 (15)	27 (17)
Number of organs with metastases, n (%)							
0					81 (51)	80 (51)	79 (50)
1			[redacted]				
2					77 (49)	78 (49)	78 (50)

	RATIONALE-306 [64]				CheckMate 648 [56,57]		
	Tislelizumab + Chemotherapy (N=116), TAP≥ 10%	Placebo + Chemotherapy (N=107), TAP≥ 10%	Tislelizumab + Chemotherapy (N=[redacted]), TAP≥ 5%	Placebo + Chemotherapy (N=[redacted]), TAP≥ 5%	Nivolumab + Chemotherapy (N=158), TPS ≥1%	Nivolumab + Ipilimumab (N=158), TPS ≥1%	Chemotherapy (N=157), TPS ≥1%
>2							
Histological type							
Squamous cell carcinoma			[redacted]		156 (99)	157 (>99)	155 (99)
Other					9 (3)	3 (<1)	6 (2)

Abbreviations: BMI, Body Mass Index; ECOG, Eastern Cooperative Oncology Group; NR, Not Reported; PD-L1, Programmed Cell-Death Ligand 1; TAP, Tumour Area Positivity; TPS, Tumour Proportion Score.
For RATIONALE-306: Percentages were based on N.
For CheckMate 648: Percentages may not total 100 because of rounding. Race was reported by the patients. ECOG performance status based on report form. ECOG performance status was not reported for one patient in the chemotherapy group.

Patient eligibility: The trials recruited adult patients with confirmed unresectable, locally advanced, or metastatic OSCC of the 1L and all evaluated measurable disease using RECIST v1.1. Of note, KEYNOTE-590 eligibility criteria included patients with adenocarcinoma of the oesophagus, or Siewert type 1 gastroesophageal junction adenocarcinoma. Efficacy outcomes were reported by disease subtype; however, baseline characteristics and safety outcomes were reported for all patients. All trials recruited adults and RATIONALE-306 and KEYNOTE-590 recruited patients with Eastern Cooperative Oncology Group (ECOG) PS 0-1, CheckMate 648 did not specify ECOG PS. RATIONALE-306 and KEYNOTE-590 required a tissue sample at enrolment to assess PD-L1 status, while CheckMate 648 did not. RATIONALE-306 and KEYNOTE-590 reported the time since last treatment as an eligibility criterion, which was 6 months and >14days from last radiation treatment, respectively, whereas CheckMate 648 did not specify time since last treatment and enrolment within eligibility criteria [51,54,57].

Baseline patient characteristics: Age at baseline was reported by and consistent across the trials, with a median age ranging from 62-64 years. Proportion of male participants ranged from 79% to 87% across the trials. The proportion of Asian participants ranged from 53% to 75%. The proportion of patients with metastatic disease ranged from 57% to 92% and advanced disease ranged from 8% to 16% across trials. The trial had slightly different definitions of advanced disease. Variation in PD-L1 expression across trials were noted concerning type of measurement used and chosen cut-offs for reporting [51,54,57].

Measurement of PD-L1 score: The three trials used different measurements for PD-L1 expression. In RATIONALE-306 PD-L1 is assessed by TAP score, in KEYNOTE-590 PD-L1 is assessed by CPS score, and in CheckMate 648 PD-L1 is assessed by TPS score, as seen in Table 15 [51,54,57].

Table 15 Overview of PD-L1 expression measurements

	RATIONALE-306 [50,51]	KEYNOTE-590 [53,54]	CheckMate 648 [56,57]
Type of PD-L1 measurement	Tumour area positivity (TAP)	Combined positive score (CPS)	Tumour proportion score (TPS)
Definition	Total percentage of tumour area (tumour and any desmoplastic stroma) covered by tumour cells with PD-L1 membrane staining at any intensity and tumour-associated immune cells with PD-L1 staining at any intensity	The number of PD-L1-positive cells (tumour cells, macrophages, and lymphocytes) divided by the total number of viable tumour cells.	The percentage of viable tumour cells with partial or complete membrane staining in at least 100 viable tumour cells.
Primary trial PD-L1 cut-off	PD-L1 TAP ≥10%: PD-L1 staining of any intensity in tumour cell membranes and tumour-associated immune cells	PD-L1 CPS ≥10	Tumour-cell PD-L1 expression ≥1%

	covering ≥10% of the tumour area

Abbreviations: CPS, Combined Positive Score; PD-L1, Programmed Cell-Death Ligand 1; TAP, Tumour Area Positivity; TPS, Tumour Proportion Score

For a description of the concordance between the measurement types refer to section 7.1.1. Although some differences in patient eligibility and patient characteristics were noted, the trials were deemed sufficiently similar by the clinical expert to derive reasonable estimates of comparative efficacy via an ITC through an NMA.

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

The patient population in RATIONALE-306 is according to the clinical expert representative of the Danish patient population that are eligible for tislelizumab. The clinical expert only highlighted the geographical difference but noted that this did not raise concerns regarding the efficacy and safety for the Danish population compared to the population from RATIONALE-306. The proportion of males included in the RATIONALE-306 trials were 87%, which is higher than the proportion of males diagnosed with OC in Denmark, this ranged from 66.3% in 2021 to 60.6% in 2022. Additionally, the median age of the included patients in the RATIONALE-306 trial was 64 years, which is slightly lower than the mean age among the Danish population diagnosed with OC in 2022 was 72 years [39,51]. In Table 16 the value for Danish patient weight used in the cost-minimisation analysis is presented, as per the rationale described in section 3.4.

Table 16 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Patient weight	76,5 kg	76,5 kg

6.1.4 Efficacy – results per RATIONALE-306

RATIONALE-306 (NCT03783442) is a randomized, placebo-controlled, double-blind, global phase 3 study that assessed the efficacy and safety of 1L treatment with either tislelizumab plus standard investigator-chosen chemotherapy (ICC) doublet or placebo plus ICC doublet in patients with unresectable, locally advanced recurrent or metastatic OSCC [51]. The protocol-specified data cut-off date for the interim analysis is 28 February 2022. A final analysis was originally planned but will not be pursued, as the superiority of tislelizumab plus chemotherapy (T+C) was confirmed in the interim analysis which will hereafter be referred to as the final analysis [51,64]. This section will include results from the final analysis (Data cutoff: February 28, 2022) and the three-year follow-up (Data cutoff: November 24, 2023) [51,65]. Data retrieved from the ITT population, the population with TAP PD-L1 score ≥10%, and the population with TAP PD-L1 score ≥5% will be presented in the following. This was decided in order to present the data used in the comparative analysis (ITT population), as well as the data used in the subgroup analysis in the comparative analysis (TAP ≥10% population) to demonstrate concordance

to currently used cut-offs in PD-L1 expression in Denmark, and the data representative of the EMA indication with a cut-off at TAP ≥5%.

[redacted] The proportion of patients in each group are seen in Table 17.

Table 17 Patients in each group from RATIONALE-306

Population	Tislelizumab + chemotherapy	Placebo + chemotherapy
ITT population	n=326	n=323
TAP PD-L1 score ≥10%	n=116	n=107
TAP PD-L1 score ≥5%	[redacted]	[redacted]

Abbreviations: ITT, Intent-to-Treat; PD-L1, programmed cell death ligand 1; TAP, tumour area positivity.
Source: **[64]**

6.1.4.1 Final Analysis (Data cutoff: February 28, 2022)

As of the data cut-off on 28 February 2022, the median follow-up time was 16.3 months (interquartile range (IQR): 8.6 to 21.8) for the T+C group and 9.8 months (IQR: 5.8 to 19.0) for the P+C group (67). The median duration of exposure was [redacted] months (range: [redacted] in the T+C arm and [redacted] months (range: [redacted]) in the P+C arm **[51]**.

6.1.4.1.1 Overall survival

ITT population: A statistically significant and clinically meaningful improvement in the primary endpoint, OS, was observed in the T+C arm relative to P+C (stratified Hazard Ratio (HR): 0.66 [95% CI: 0.54 to 0.80]; one-sided P < 0.0001). The median OS was 17.2 months (95% CI: 15.8 to 20.1) in the T+C arm and 10.6 months (95% CI: 9.3 to 12.1) in the P+C arm. The OS benefit in favour of tislelizumab was observed during most of the follow-up. Separation of the Kaplan–Meier curves started around 2 months after initially overlapping and the higher survival rates in the T+C arm were maintained thereafter, as seen in appendix L.1 Figure 15 **[51]**. The overall survival rate in the ITT population in the T+C arm at 12, 18 and 24 months were in % (95%CI) [redacted], [redacted] respectively, and for the P+C arm [redacted] and [redacted] as seen in appendix L.1 Figure 15 **[51,64]**. In appendix L.2 Figure 16 displays the Schoenfeld residual plot for OS in the ITT population **[64]**. The Schoenfeld residual plot for OS in the ITT population was the only plot available, thus for the remaining HRs no plots can be presented.

TAP PD-L1 score ≥10%: Additionally, OS results favoured T+C regardless of the baseline PD-L1 expression status [64]. Among patients with a PD-L1 score ≥10%, the median OS was [redacted] in the T+C arm and [redacted] in the P+C arm [redacted] [64]. The overall survival rate in the PD-L1 Score ≥ 10% population in the T+C arm at 12, 18 and 24 months were in % (95%CI) [redacted] and [redacted] respectively, and for the P+C arm [redacted] and [redacted] [64].

TAP PD-L1 Score ≥ 5%: Concerning the PD-L1 Score ≥ 5% population, the median OS was [redacted] in the T+C arm and [redacted] in the P+C arm [redacted], (see Figure [redacted] in appendix L.3). The overall survival rate in the PD-L1 Score ≥ 5% population in the T+C arm at 12, 18, and 24 months were in % (95%CI) [redacted] and [redacted] respectively, and for the P+C arm [redacted] and [redacted] respectively [64].

6.1.4.1.2 Progression-free survival

ITT population: PFS was a key secondary efficacy endpoint and as of the 28 February 2022 data cut-off date, the number of PFS events in the ITT population was 220 (67.5%) in the T+C arm and 254 (78.6%) in the P+C arm. The median PFS was significantly prolonged in the T+C arm, at 7.3 months (95% CI: 6.9 to 8.3 months), compared with 5.6 months in the P+C arm (95% CI: 4.9 to 6.0 months; HR: 0.62; [95% CI: 0.52 to 0.75]; $P < 0.0001$). A 38% reduction in the risk of disease progression or death was observed in the T+C arm relative to P+C. The Kaplan-Meier (KM) curves began to separate earlier than 2 months following randomization in favour of T+C and were consistently maintained thereafter [51]. The progression free survival rate in the ITT population in the T+C arm at 12 months were in % (95%CI) at [redacted] and for the P+C arm [redacted] as seen in Figure 18 in appendix L.4 [51,64].

PD-L1 TAP score ≥10%: In the PD-L1 TAP score ≥10% population PFS events was [redacted] in the T+C arm and [redacted] in the P+C arm. The median PFS was prolonged in the T+C arm, at [redacted] compared with [redacted] in the P+C arm [redacted] [64].The progression free survival rate in the PD-L1 TAP Score ≥ 10%: population in the T+C arm at [redacted] were in % (95%CI) at [redacted] and for the P+C arm [redacted] [64].

PD-L1 TAP score ≥5%: In the PD-L1 TAP score ≥5%, the number of PFS events was [redacted] in the T+C arm and [redacted] in the P+C arm. The median PFS was significantly prolonged in the T+C arm, at [redacted], compared with [redacted] in the P+C arm [redacted], see Figure 19 in appendix L.5. This difference in PFS is considered clinically meaningful. The progression free survival rate in the PD-L1 TAP score ≥5%, population in the T+C arm at 12 months were in % (95%CI) at [redacted], and for the P+C arm [redacted] [64].

6.1.4.1.3 Objective response rate

ITT population: Another key secondary efficacy endpoint was ORR. In the ITT population a total of [redacted] in the T+C arm and [redacted] in the P+C arm achieved an objective response. The T+C arm demonstrated a statistically significant and clinically relevant higher tumour response rate than P+C within the ITT Analysis Set, with a [redacted] and a [redacted]. Moreover, [redacted] and [redacted] had a CR in the T+C and P+C arms, respectively. In the T+C arm, [redacted] had a BOR of PD, compared with [redacted] in the P+C arm [50,64].

PD-L1 TAP score ≥10%: In the PD-L1 TAP score ≥10%: population [redacted] in the T+C arm and [redacted] in the P+C arm achieved an objective response. Resulting in an unstratified ORR difference of [redacted] and a [redacted] of [redacted] [50,64].

PD-L1 TAP score ≥5%: In the PD-L1 TAP score ≥5%: population [redacted] patients [redacted] in the T+C arm and [redacted] patients [redacted] in the P+C arm achieved an objective response. Resulting in an [redacted] difference of [redacted] and [redacted] of [redacted] [64].

6.1.4.2 Three-year survival follow-up (Data cutoff: November 24, 2023)

6.1.4.2.1 Overall Survival

ITT population + PD-L1 TAP score ≥10%: As of data cutoff on November 24, 2023, median exposure was longer for T+C [redacted] than for P+C [redacted], with [redacted] patients [redacted] treated with T+C for ≥36 months. Improvements in OS, PFS, and ORR were maintained relative to the final analysis with no new safety signals. T+C continued to prolong survival relative to P+C [redacted], including among patients with high PD-L1 expression (PD-L1 TAP score ≥10%: [redacted], [redacted] in appendix L.6. Similar benefits were observed across all other prespecified subgroups [64]. From the latest data cut-off only 24 months and 36 months overall survival rates are available for the ITT population, and for the PD-L1 TAP score ≥10% population. The overall survival rate in the ITT population in the T+C arm at 24 months and at 36 months were in % (95%CI) at 37.9 (32.5, 43.2) and 22.1 (17.6, 27.0) respectively, and for the P+C arm 24.8 (20.1, 29.8) and 14.1 (10.4, 18.4) [65]. The overall survival rate in the PD-L1 TAP score ≥10% population in the T+C arm at 24 months and at 36 months were in % (95%CI) at [redacted] and [redacted] respectively, and for the P+C arm [redacted] and [redacted] [64].

TAP PD-L1 Score ≥ 5%: Concerning the PD-L1 Score ≥ 5% population, the median OS was [redacted] in the T+C arm and [redacted] in the P+C arm [redacted]. The overall survival rate in the PD-L1 Score ≥ 5% population in the T+C arm at 18, 24 and 36 months were in % (95%CI) [redacted] and [redacted] respectively, and for the P+C arm [redacted], [redacted], and [redacted] [64]. See Kaplan-Meier plot in Figure [redacted] in appendix L.7.

6.1.4.2.2 Secondary endpoints

ITT population

In the ITT analysis set, clinically meaningful improvements in key secondary endpoints, PFS and ORR, were maintained with T+C versus P+C relative to the final analysis, as summarized in Table 18 [65].

Table 18 Summary of secondary efficacy results (ITT analysis set), RATIONALE-306 (3-year follow-up)

	Tislelizumab plus Chemotherapy (N = 326)	Placebo plus Chemotherapy (N = 323)
Median PFS (95% CI), months[a]	[redacted]	[redacted]
HR (95% CI)	[redacted]	
36-month PFS rate (95% CI), %[a]	15.0 (10.8, 19.9)	2.9 (1.1, 6.2)
ORR (95% CI), %[a]	[redacted]	[redacted]

Data cut-off: November 24, 2023. The ITT Analysis Set includes all randomized patients.
[a]Per investigator. [b]TIS plus ICC: N = 207; PBO plus ICC: N = 137. Abbreviations: CI, confidence interval; PFS, Progression-free survival. Source: **[64,65]**

TAP PD-L1≥10%: The median PFS was significantly prolonged in the T+C arm, at [redacted] months (95% CI: [redacted]), compared with [redacted] months in the P+C arm (95% CI: [redacted].In the PD-L1 TAP score ≥10%: population [redacted] in the T+C arm and [redacted] in the P+C arm achieved an objective response, with a [redacted] of [redacted] [64].

TAP PD-L1≥5%: In the PD-L1≥5% subgroup, as of the 24 November 2023 data cut-off date, PFS results remained consistent with the final analysis. The number of PFS events was [redacted] in the T+C arm and [redacted] in the P+C arm. The median PFS was significantly prolonged in the T+C arm, at [redacted], compared with [redacted] in the P+C arm [redacted], see Figure 22 in appendix L.8. A [redacted] reduction in the risk of disease progression or death was observed in the T+C arm relative to P+C. The progression free survival rate in the PD-L1 TAP score ≥5%, population in the T+C arm at 12 and 36 months were in % (95%CI) at [redacted], and [redacted], and for the P+C arm [redacted], and [redacted], respectively [64]. In the PD-L1 TAP score ≥5%: population [redacted] in the T+C arm and [redacted] in the P+C arm achieved an objective response [64].

6.1.5 Efficacy – results per CheckMate 648

CheckMate 648 (NCT03143153) is a global, randomized, open-label, phase 3 trial evaluating the efficacy and safety of nivolumab and ipilimumab or nivolumab combined with chemotherapy versus chemotherapy in patients with unresectable advanced, recurrent, or metastatic previously untreated OSCC. Primary endpoints were OS and PFS per RECIST v. 1.1, while secondary endpoints included ORR (per RECIST v. 1.1) among

others [57]. This section will include the results of nivolumab plus chemotherapy (N+C) compared to chemotherapy, as nivolumab is recommended by the DMC in combination with chemotherapy for 1L treatment of OSCC with PD-L1 TPS≥1% [43]. Results regarding nivolumab plus ipilimumab compared to chemotherapy will be excluded in this application as the combination of nivolumab plus ipilimumab has not been assessed by the DMC as treatment against OSCC [38]. Results from the primary pre-specified analysis, with a minimum of 13 months follow-up demonstrated a statistically significant improvement in OS with a median OS in the overall population of 13.2 months (95%CI: 11.1 to 15.7) for N+C and 10.7 months (95%CI: 9.4 to 11.9) for chemotherapy (HR=0.74, 99.1%CI: 0.58 to 0.96; P=0.002) see Figure 1. The 12-month overall survival was 54% in the N+C arm and 44% for chemotherapy in the overall population [57].

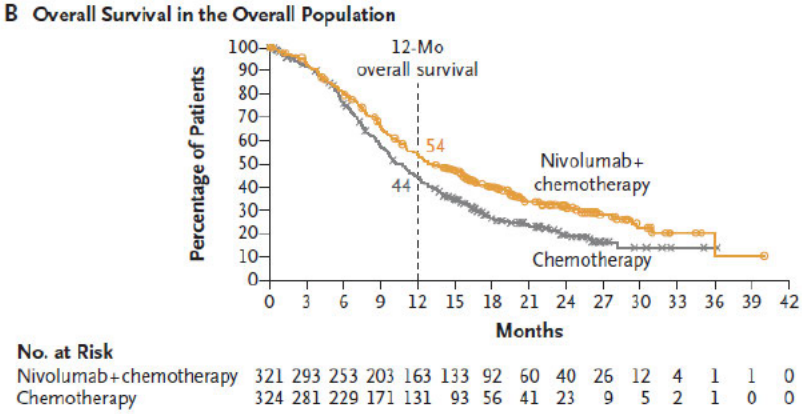


Figure 1 Kaplan-Meier plot of OS for the overall population, CheckMate 648
Abbreviations: CI, confidence interval; Mo, months; No, number; OS, overall survival
Source: [57]

Meanwhile, the median OS in patients with PD-L1 TPS ≥1% was 15.4 months (95%CI: 11.9 to 19.5) for N+C and 9.1 months (95%CI: 7.7 to 10.0) for chemotherapy (HR=0.54; 99.5%CI: 0.37 to 0.80; P<0.001), see Figure 2. The 12-month overall survival was 58% in the N+C arm and 37% for chemotherapy in the PD-L1 TPS ≥1% population [57].

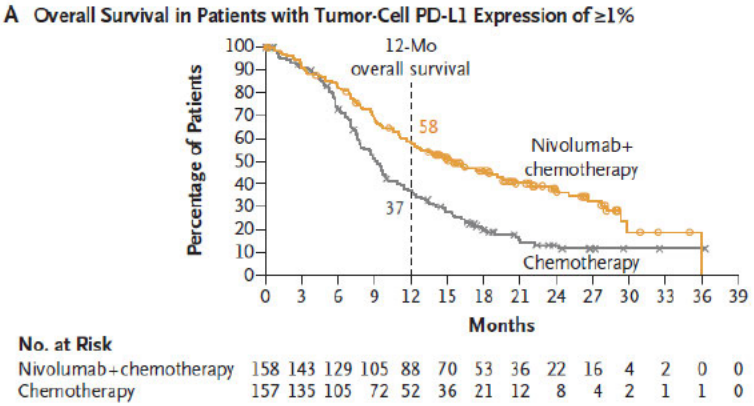


Figure 2 Kaplan-Meier plot of OS for patients with PD-L1 ≥1%, CheckMate 648
Abbreviations: CI, confidence interval; Mo, months; No, number; OS, overall survival
Source: [57].

The ORR was 47% (95% CI: 42 to 53) for N+C compared to 27% (95% CI: 22 to 32) for chemotherapy in the overall population. For the PD-L1 ≥1% population, ORR was 53% (95% CI: 45 to 61) for N+C compared to 20% (95% CI: 17 to 27) for chemotherapy.

Median PFS for the overall population did not meet the pre-specified boundary for significance (0.015) as it was 5.8 months (95%CI: 5.6 to 7.0) for N+C and 5.6 months (95%CI: 4.3 to 5.9) for chemotherapy (HR=0.81; 98.5%CI: 0.64 to 1.04, P=0.04), see Figure 3. The 12-month progression free survival was 24% in the N+C arm and 16% for chemotherapy in the overall population [57].

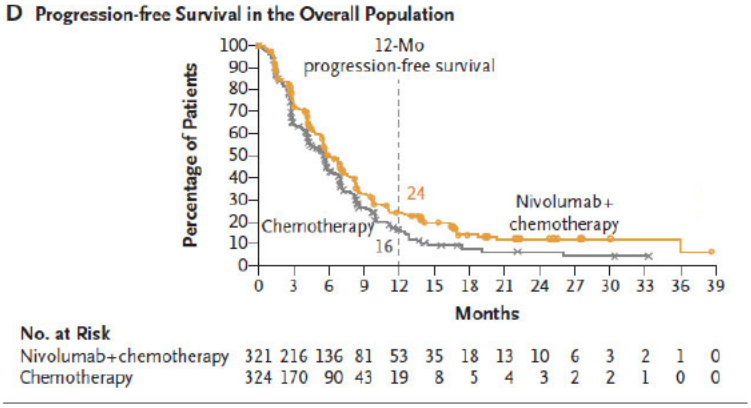


Figure 3 Kaplan-Meier plot of PFS for the overall population, CheckMate 648
Abbreviations: CI, confidence interval; Mo, months; No, number; PFS, progression-free survival
Source: [57]

However, among patients with PD-L1 TPS≥1% median PFS was 6.9 months (95% CI: 5.7, 8.3) for N+C compared to 4.4 months (95% CI: 2.9, 5.8) for chemotherapy (HR = 0.65; 98.5% CI: 0.46, 0.92, P=0.002), see Figure 4. The ORR among patients with PD-L1 TPS≥1% was 53% (95% CI: 45 to 61) for N+C compared to 20% (95% CI: 14, 27) for chemotherapy. The 12-month progression free survival was 25% in the N+C arm and 10% for chemotherapy in the PD-L1 TPS ≥1% population [57].

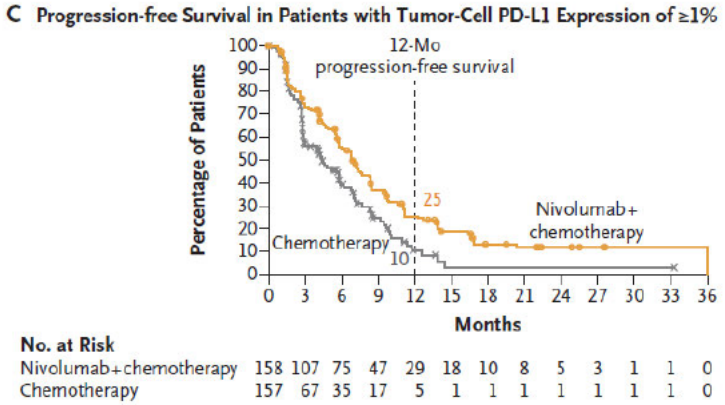


Figure 4 Kaplan-Meier plot of PFS for patients with PD-L1≥1%, CheckMate 648
Abbreviations: CI, confidence interval; Mo, months; No, number; PFS, progression-free survival
Source: [57]

Results from the 29-month follow-up was consistent with the primary analysis. Overall population results showed a median OS of 12.8 (95%CI: 11.1 to 15.7) months for N+C versus 10.7 (95%CI: 9.4 to 12.1) months for chemotherapy alone (HR = 0.78, 95% CI: 0.65.93). The 12- and 24-month overall survival was 53% and 29% in the N+C arm and 45% and 19% for chemotherapy in the overall population. Median PFS was 5.8 (95%CI: 5.5 to 7.0) months for N+C versus 5.6 months (95%CI: 4.3 to 5.9) for chemotherapy alone (HR = 0.83, 95% CI: 0.68-1.00). The 12- and 24-month progression free survival was 23% and 11% in the N+C arm and 17% and 4% for chemotherapy in the overall population per BICR. The ORR was 47% (95% CI: 42 to 53) for N+C compared to 27% (95% CI: 22 to 32) for chemotherapy. For the PD-L1 ≥1% population, median OS was 15 months (95% CI: 11.9, 18.6) for N+C versus 9.1 months (95% CI: 7.7 to 10.0) for chemotherapy alone (HR = 0.59, 95% CI: 0.46 to 0.76). The 12- and 24-month overall survival was 58% and 31% in the N+C arm and 37% and 12% for chemotherapy in the PD-L1 TPS ≥1% population. Median PFS was 6.8 months (95% CI: 5.7 to 8.3) for N+C versus 4.4 months (95% CI: 2.9 to 5.8) for chemotherapy alone (HR = 0.67, 95% CI: 0.51 to 0.89). The 12- and 24-month progression free survival was 25% and 12% in the N+C arm and 10% and 3% for chemotherapy in the PD-L1 TPS ≥1% population per BICR. The ORR among patients with PD-L1 TPS ≥1% was 53% (95% CI: 44 to 61) for N+C compared to 20% (95% CI: 14 to 27) for chemotherapy [67]. For the overall population, the 45-month follow-up results showed a median OS of 13.2 months (11.1 to 15.7) for N+C compared to 10.7 months (9.4 to 12.1) for chemotherapy alone (HR=0.77, 0.65 to 0.92). Median PFS was 5.8 months (5.5 to 7.0) for N+C versus 5.6 months (4.3 to 5.9) for chemotherapy alone (HR=0.82, 0.68 to 1.00). The ORR was 47% for N+C compared to 27% for chemotherapy. For the PD-L1 positive patients, the 45-month follow-up results showed a median OS of 15.0 months (11.9 to 18.7) for N+C compared to 9.1 months (7.7 to 10.0) for chemotherapy alone (HR=0.60, 0.47 to 0.77). Median PFS was 6.8 months (5.7 to 8.3) for N+C versus 4.4 months (2.9 to 5.8) for chemotherapy alone (HR=0.67, 0.51 to 0.88). The ORR was 53% for N+C compared to 20% for chemotherapy [68].

6.1.6 Efficacy – results per KEYNOTE-590

KEYNOTE-590 (NCT03189719) is a randomized, placebo-controlled, double-blind, phase 3 study evaluating the efficacy and safety of Pembrolizumab + chemotherapy (Pe+C) in patients with previously untreated, histologically or cytologically confirmed, locally advanced, unresectable, or metastatic oesophageal cancer or Siewert type 1 gastro-oesophageal junction cancer [54]. This section will include all available key efficacy results in the OSCC population, including PD-L1 positive (CPS≥10) patients as this is the populations relevant in this application. At the data cut-off (July 2, 2020) the median follow-up time was 22.6 months (IQR: 19.6 to 27.1). The median OS in the OSCC population was 12.6 months (95%CI: 10.2 to 14.3) for Pe+C compared to 9.8 months (95%CI: 8.6 to 11.1) for placebo plus chemotherapy (HR=0.72, 95%CI: 0.60 to 0.88; p=0.0006), see Figure 5. The 24-month overall survival rate was 29% in the Pe+C arm and 17% for placebo plus chemotherapy arm in the OSCC population. In the OSCC PD-L1 positive population, the median OS was 13.9 months (95%CI: 11.1 to 17.7) for Pe+C compared to 8.8 months (95%CI: 7.8 to 10.5) for placebo plus chemotherapy (HR= 0.57, 95%CI: 0.43 to 0.75; p<0.0001), see Figure 5. The 24-month overall survival rate was 31%

in the Pe+C arm and 15% for placebo plus chemotherapy in the OSCC PD-L1 CPS ≥10 population [54].

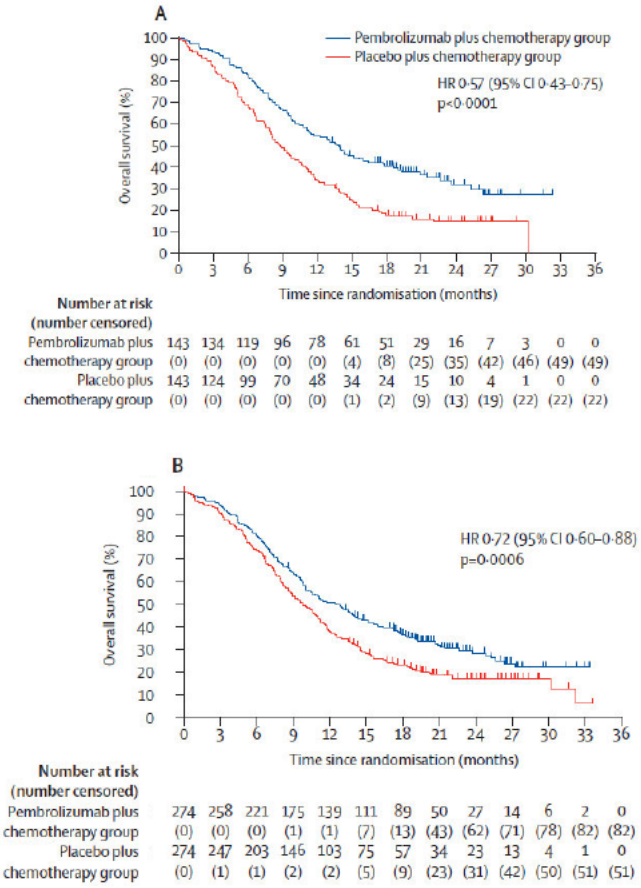


Figure 5 Kaplan-Meier plot of OS for (A) OSCC population and (B) OSCC PD-L1 positive population, KEYNOTE-590

Abbreviations: CI, confidence interval; Mo, months; No, number; OS, overall survival
Source: [54]

The ORR in the OSCC population was 43.8% (95% CI: 37.8 to 49.9) for the combination of Pe+C In comparison, the ORR for the placebo and chemotherapy combination was 31.0% (95% CI: 25.6 to 36.9) [55]. Median PFS in the OSCC population was 6.3 months (95%CI: 6.2 to 6.9) for Pe+C compared to 5.8 months (95%CI: 5.0 to 6.1) for placebo plus chemotherapy (HR=0.65, 95%CI: 0.54 to 0.78; p<0.0001) [54]. The median PFS in OSCC PD-L1 CPS ≥10 population 7.3 months (95% CI: 6.2-8.2) in the Pe+C arm and 5.4 months (95% CI: 4.2-6.0) for placebo plus chemotherapy, (HR=0.53, 95%CI: 0.40 to 0.69) [53]. Limited data from the 5-year follow up are available for the OSCC and the OSCC PD-L1 ≥10 population. The median OS HR (95% CI) for the OSCC population was 0.72 (0.62-0.84), and a 5-year OS rate at 11.8% for the Pe+C arm and 3.4% for placebo plus chemotherapy arm. The median PFS HR (95% CI) was 0.65 (0.54-0.78), and the ORR was 43.8% for the Pe+C arm and 31.0% for placebo plus chemotherapy arm. For the OSCC PD-L1 ≥10 population the median OS HR (95% CI) was 0.60 (0.46-0.76), and a 5-year OS rate at 13.8% for the Pe+C arm and 3.7% for placebo plus chemotherapy arm. The

median PFS HR (95% CI) was 0.53 (0.41-0.69), and the ORR was 51.0% for the Pe+C arm and 28.0% for placebo plus chemotherapy arm [66].

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

Assessment of efficacy outcomes: The efficacy outcomes used in the ITC comprise OS, PFS, and ORR (TRAE grade 3+ for safety, see section 9.1). OS, PFS, and ORR were reported and consistently defined across the trials. TRAE grade 3+ were reported across the trials but the version of CTCAE used to report this varied across the trials. PFS and ORR were not evaluated completely similar in each study, for pembrolizumab they were assessed by the investigator per RECIST 1.1, for nivolumab they were assessed by BICR on the basis of RECIST 1.1, and for tislelizumab both investigator and BICR per RECIST 1.1 were used for PFS but only investigator for ORR. When a BICR-assessed datapoint was not reported, investigator-assessed values were used in the ITC. Despite the noted differences, minimal heterogeneity exists between the trials, and they were considered sufficiently similar to obtain reasonable indirect estimates of safety and efficacy.

PD-L1 scores: An additional difference between the trials were noted as they used different measurement types to report PD-L1 scores. Based on RATIONALE-306, the concordance of different PD-L1 measurements has been investigated, and a considerable concordance and good correlation between TAP and CPS scores in OSCC was found. The correlation showed an interclass correlation coefficient of ICC=0.85 [0.80, 0.88], which indicates a good correlation between TAP and CPS score. The concordance of TAP and CPS at 1%, 5%, and 10% cut-offs were substantial by overall percent agreement and Cohen's Kappa. Thus, at matched cut-offs TAP and CPS scores (i.e. TAP=10% vs CPS=10) demonstrated substantial concordance in OSCC [69]. The PD-L1 expression was investigated in the RATIONALE-306 population, by assessing CPS score post hoc using the same slide the prespecified TAP score was determined with [50]. The results from this investigation are presented in Table 19.

Table 19 PD-L1 expression status by CPS or TAP scoring methods in all randomised patients from RATIONALE-306

PD-L1 status	Tislelizumab plus chemotherapy (n=326)	Placebo plus chemotherapy (n=323)	Total (n=649)
PD-L1 status on CPS*			
CPS ≥10	115 (35%)	113 (35%)	228 (35%)
CPS <10	149 (46%)	160 (50%)	309 (48%)
Unknown†	62 (19%)	50 (15%)	112 (17%) ‡

PD-L1 status on TAP score			
TAP ≥10%	116 (36%)	107 (33%)	223 (34%)
TAP <10%	151 (46%)	168 (52%)	319 (49%)
Unknown†	59 (18%)	48 (15%)	107 (16%)

Data are n (%).
Abbreviations: CPS, Combined Positive Score; PD-L1, Programmed Death Ligand-1; TAP, Tumour Area Positivity
*PD-L1 CPS score were assessed post hoc using the same slide the prespecified TAP score was assessed with (stained with the VENTANA PD-L1 [SP263] platform). †Unknown refers to patients without sample collection, with non-evaluable samples, or with scored unqualified samples (patients with scored unqualified samples were identified and reclassified as unknown after database lock). ‡5 samples with evaluable TAP score were found not evaluable for CPS scoring because the negative reagent control slide faded **[50]**.

Table 20 Prevalence of PD-L1 Subgroups by TAP and CPS

PD-L1 status TAP/CPS score	TAP Tislelizumab plus chemotherapy (n=[redacted])	TAP Placebo plus chemotherapy (n=[redacted])	CPS Tislelizumab plus chemotherapy (n=[redacted]	CPS Tislelizumab plus chemotherapy (n=[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Data are n (%).
Abbreviations: CPS, Combined Positive Score; PD-L1, Programmed Death Ligand-1; TAP, Tumour Area Positivity **[64]**.

Table 20 presents an overview of the prevalence of PD-L1 subgroups by TAP and CPS from the RATIONALE-306 trial.

From these it is evident that the amount identified at cut-off 10% with TAP is almost identical to the amount identified at cut-off CPS 10%, it is therefore assumed that in general there is a big overlap between patients with a TAP ≥10% and a CPS ≥10 score. Liu et al. 2023 also demonstrated a high concordance between TAP and CPS scores, although a higher concordance at TAP=5% vs CPS=1 cut-offs was exhibited [32]. Alongside the proven concordance of TAP and CPS, a sensitivity analysis was run in the ITC for OS using CPS data from RATIONALE-306. This showed similar results to base case data, supporting the assumption of equivalence between the scoring systems [64]. Considering these arguments, it is not expected that the different measurement tools for PD-L1 will affect the results. Thus, TAP 10%, CPS 10, and TPS 1% were assumed to be equivalent in the ITC analysis [64].

PD-L1 assays: In the RATIONALE-306 trial PD- L1 expression was stained using VENTANA PD-L1 (SP263) assay, in KEYNOTE-590 PD-L1 was assessed using the PD-L1 IHC 22C3 assay, and in CheckMate 648 PD-L1 was assessed using the Dako PD-L1 IHC 28-8 pharmDx assay [47,48,64] . [redacted]

7.1.2 Method of synthesis

For the comparison of the efficacy of T+C, N+C, and Pe+C a network of meta-analysis was performed. A brief description of the choice, method, and feasibility assessment are outlined below, for more detailed information see Appendix C. The three RCTs RATIONALE-306, KEYNOTE-590, and CheckMate 648 were identified through the SLR. Therefore, for the ITC the results for tislelizumab were based on data from the data cut-off date 28 February 2022, and the data for the comparators were from the key trial publications. Trial design characteristics, patient eligibility criteria, baseline patient characteristics, outcome characteristics (i.e., definitions and methods of reporting outcomes) were extracted from the RCTs and used to assess the feasibility of a network meta-analysis to compare T+C, N+C, and Pe+C [64]. The evidence network for all outcomes is outlined in Figure 6.

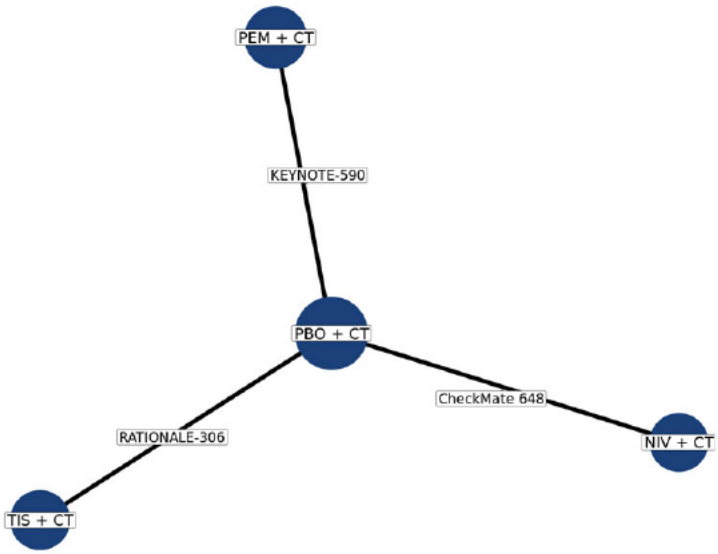


Figure 6 Evidence network for all outcomes [64]

Abbreviations: TIS+CT, Tislelizumab plus Chemotherapy; PEM+CT, Pembrolizumab plus Chemotherapy; NIV+CT, Nivolumab plus Chemotherapy

Outcomes of interest for the feasibility assessment were survival outcomes PFS, OS, and response outcome ORR and safety outcome grade ≥3 TRAE. These were selected based on the key outcomes evaluated in the RATIONALE-306 trial. Following the qualitative assessment of heterogeneity and clinical opinion, it was considered feasible to conduct ITCs between the RATIONALE-306 trial and the other two trials. The recommended ITC

was an NMA, as (a) the trials were sufficiently similar to be compared without requiring population level adjustment, (b) there is precedent for conducting NMAs in this patient population, (c) the differences observed between patient populations could be assessed via subgroup analyses, (d) NMAs allow for comparisons among all relevant treatments in a single analysis, and finally, (e) NMAs are reproducible. Based on the results of the feasibility assessment, NMAs were feasible and recommended for the following outcomes: OS, PFS, ORR, and grade ≥3 TRAE, under the assumption that all chemotherapy backbone treatments are comparable and can be pooled together into a single note. The relative efficacy of T+C compared with these agents was evaluated via [redacted] for key efficacy outcomes PFS, OS, and ORR and grade ≥3 TRAE. Subgroup analyses were conducted for PD-L1 expression status. A [redacted] was used for the analysis. For time-to-event outcomes (OS, PFS), [redacted] whereas for response and safety outcomes (ORR and grade ≥3 TRAEs), the [redacted]. KM curves, estimated median survival, and estimated survival rates are not presented, as these have not been calculated in the NMA. The proportional hazards (PH) assumption for OS and PFS between the treatments were assessed via [redacted] and by [redacted]. There were no clear violations of the PH assumption among the treatments for both OS and PFS. [redacted] are seen in [redacted] and [redacted] respectively, and for PFS in [redacted] and [redacted], respectively, for the ITT populations [64]. [redacted]

7.1.3 Results from the comparative analysis

The results from the NMA are outlined in Table 21 for the intention to treat (ITT) population from each trial. The results from Pe+C vs N+C are not presented as these have already been assessed as equivalent by the DMC [43,64]. Absolute results, estimated median survival, and survival rates are not presented, as these were not calculated from the NMA.

Table 21 Results from the comparative analysis of T + C vs. P + C and for N + C for ITT.

Outcome measure	T + C (N=326)	Pe + C (N=274)	Result	T + C (N=326)	N + C (N=321)	Result
OS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PFS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ORR	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NOTE: An HR > 1 indicates T + C has greater hazard than the comparator therapy. An HR < 1 indicates T + C has a lesser hazard than the comparator therapy. An OR > 1 indicates T + C has greater odds of a response than the comparator therapy. An OR < 1 indicates the odds of a response are lower in T + C compared to the comparator therapy. Bold font indicates statistical significance at the 0.05 level. **[64]** Abbreviations: C, chemotherapy; N, nivolumab; OS, overall survival; PFS, progression free survival; Pe, pembrolizumab; T, tislelizumab; ITT, intent-to-treat.

PD-L1 subgroup analysis:

To support the indication for tislelizumab analyses were conducted for PD-L1 positive subgroups from each trial, using the following cutoff: PD-L1 10% (TAP 10%, CPS 10, or TPS 1%) and [redacted] Based on studies evaluating the concordance of TAP and CPS in patients with 1L OSCC and that of TAP, CPS, and TPS in patients with second-line (2L) OSCC, an assumption was made that TAP 10% and CPS 10 were equivalent, and that TPS 1% was equivalent to TAP 10% and CPS 10 **[69,71]**. Where more than one measure of PD-L1 was provided by a trial, the order of preference for selecting a measure for analysis was [redacted], based on TAP as the primary PD-L1 measurement for the RATIONALE-306 trial. To test the assumption of equivalence between TAP 10% and CPS 10, a sensitivity analysis was run for OS using CPS data from RATIONALE-306. [redacted]. The results from the subgroup analyses for [redacted], are presented in Table 22. [redacted] [64].

Table 22 Results from the comparative analysis of T + C vs. P + C and for N + C, PD-L1 positive population

Outcome measure	T + C	Pe + C	Result	T + C	N + C	Result
[redacted]						

Outcome measure	T + C	Pe + C	Result	T + C	N + C	Result
[redacted]						

NOTE: An HR > 1 indicates T + C has greater hazard than the comparator therapy. An HR < 1 indicates T + C has a lesser hazard than the comparator therapy. An OR > 1 indicates T + C has greater odds of a response than the comparator therapy. An OR < 1 indicates the odds of a response are lower in T + C compared to the comparator therapy. Bold font in the results indicates statistical significance at the 0.05 level. **[64]**
Abbreviations: C, chemotherapy; N, nivolumab; OS, overall survival; PFS, progression free survival; Pe, pembrolizumab; T, tislelizumab.

7.1.4 Efficacy – results per OS

ITT population: In the OS analysis, T+C performed similarly to Pe+C ([redacted]), and to N+C ([redacted]). No statistically significant differences were observed between active treatments. Surface Under the Cumulative Ranking curve (SUCRA) values and probability best values are presented in Table 23. Aligned with the league table, T+C was associated with the highest Surface Area Under the Cumulative Ranking Curve (SUCRA) value of [redacted] [64].

Table 23 Summary of SUCRA values from the [redacted] NMA for OS

Treatment Arm	SUCRA (%)	Probability Best (%)
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]

N + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; OS, overall survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab.**[64]**

This proves that T+C is at least as effective as Pe+C and N+C, when comparing OS, and therefore they can be considered as equivalent.

PD-L1 positive population: In the OS analyses for both the PD-L1 5% and 10% subgroup, T+C performed similarly to Pe+C, and to N+C. No statistically significant differences were observed between active treatments. Surface Under the Cumulative Ranking curve (SUCRA) values and probability best values are presented in Table 24 and Table 25 **[64]**.

Table 24 Summary of SUCRA values from the [redacted] NMA for OS, PD-L1 10% positive

Treatment Arm	SUCRA (%)	Probability Best (%)
N + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]
T + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; PFS, Progression-free survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab. **[64]**

Table 25. Summary of SUCRA values from the [redacted] NMA for OS, PD-L1 5% positive

Treatment Arm	SUCRA (%)	Probability Best (%)
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]
N + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; PFS, Progression-free survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab. **[64]**

7.1.5 Efficacy – results per PFS

ITT population: In the PFS analysis, T+C was significantly more effective than N+C ([redacted]), and performed similarly to pembrolizumab plus placebo ([redacted]). SUCRA values and probability best values are presented in Table 26. Aligned with the league table, T+C was associated with the highest SUCRA value of [redacted] [64].

Table 26 Summary of SUCRA values from the [redacted] NMA for PFS

Treatment Arm	SUCRA (%)	Probability Best (%)

T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]
N + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; PFS, Progression-free survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab. **[64]**

This proves that T+C is at least as or more effective than Pe+C and N+C, when comparing PFS, and therefore it is reasonable to consider these as equivalent.

PD-L1 positive population: In the PFS analysis, T+C performed similarly to Pe+C, and to N+C for the PD-L1 10% subgroup, meaning no statistically significant differences were observed between active treatments. In the PD-L1 5% subgroup, T+C was significantly more effective than N+C, and performed similarly to Pe+C. Surface Under the Cumulative Ranking curve (SUCRA) values and probability best values are presented in Table 27 and Table 28 [64].

Table 27 Summary of SUCRA values from the [redacted] NMA for PFS, PD-L1 10% positive

Treatment Arm	SUCRA (%)	Probability Best (%)
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]
N + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; PFS, Progression-free survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab. **[64]**

Table 28. Summary of SUCRA values from the [redacted] NMA for PFS, PD-L1 5% positive

Treatment Arm	SUCRA (%)	Probability Best (%)
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]
N + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA, network meta-analysis; PFS, Progression-free survival; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab. **[64]**

7.1.6 Efficacy – results per ORR

ITT population: In the ORR analysis, T+C performed similarly to Pe+C ([redacted]) and N+C ([redacted]). SUCRA and probability best values are presented in Table 29. N+C was associated with the highest SUCRA value of [redacted]. T+C had the second highest SUCRA value of [redacted] [64].

Table 29 Summary of SUCRA values from the [redacted] NMA for ORR

Treatment Arm	SUCRA (%)	Probability Best (%)
N + C	[redacted]	[redacted]
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA,network meta-analysis; ORR, objective response rare; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab [64].

This proves that there is no significant difference between T+C compared to Pe+C and N+C, when comparing ORR, and therefore it is reasonable to consider these as equivalent.

PD-L1 10% positive population: In the ORR analysis, T+C performed similarly to Pe+C, and to N+C. No statistically significant differences were observed between active treatments. Surface Under the Cumulative Ranking curve (SUCRA) values and probability best values are presented in Table 30 [64].

Table 30 Summary of SUCRA values from the [redacted] NMA for ORR, PD-L1 10% positive

Treatment Arm	SUCRA (%)	Probability Best (%)
N + C	[redacted]	[redacted]
T + C	[redacted]	[redacted]
Pe + C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA,network meta-analysis; ORR, objective response rare; Pe, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab [64].

8. Modelling of efficacy in the health economic analysis (N/A)

Section 8 is not applicable since a cost-minimisation analysis was performed.

8.1 Presentation of efficacy data from the clinical documentation used in the model (N/A)

8.1.1 Extrapolation of efficacy data (N/A)

8.1.1.1 Extrapolation of [effect measure 1] (N/A)

Table 31 Summary of assumptions associated with extrapolation of [effect measure] (N/A)

Method/approach	Description/assumption
Data input	
Model	
Assumption of proportional hazards between intervention and comparator	
Function with best AIC fit	
Function with best BIC fit	
Function with best visual fit	
Function with best fit according to evaluation of smoothed hazard assumptions	
Validation of selected extrapolated curves (external evidence)	
Function with the best fit according to external evidence	
Selected parametric function in base case analysis	
Adjustment of background mortality with data from Statistics Denmark	
Adjustment for treatment switching/cross-over	
Assumptions of waning effect	
Assumptions of cure point	

8.1.1.2 Extrapolation of [effect measure 2] (N/A)

8.1.2 Calculation of transition probabilities (N/A)

Table 32 Transitions in the health economic model (N/A)

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence		

	Death
Recurrence	Death
Health state/Transition	

8.2 Presentation of efficacy data from [additional documentation] (N/A)

8.3 Modelling effects of subsequent treatments (N/A)

8.4 Other assumptions regarding efficacy in the model (N/A)

8.5 Overview of modelled average treatment length and time in model health state (N/A)

Table 33 Estimates in the model (N/A)

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
[Name of intervention]			

Table 34 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) (N/A)

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
[Intervention]			
[Comparator]			

9. Safety

9.1 Safety data from the clinical documentation

In RATIONALE-306, safety was assessed in all randomized patients who received at least one dose of study drug and analysed using descriptive statistics (i.e., safety population). All treatment-emergent adverse events (TEAEs) were monitored and recorded using the NCI-CTCAE grading criteria (version 4.03). TEAEs were defined as adverse events that had an onset date or a worsening in severity from baseline on or after the first dose of study drug and up to 30 days following study drug discontinuation or initiation of new anti-cancer therapy, whichever occurs first. TRAEs included TEAEs that was assessed related to the study drug by the investigator or TEAEs with a missing causality. Serious adverse events (SAEs) were defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalisation or prolonging of existing hospitalisation, results in disability/incapacity, is a congenital anomaly, is considered a significant adverse event (AE) by the investigator **[51]**.

In both KEYNOTE-590 and CheckMate 648 TEAE were N/R, and the definition of TRAEs were not reported in KEYNOTE-590. The definition of TRAEs in CheckMate 648 were events reported between first dose and 30 days after last dose of study therapy. Treatment relatedness in the nivolumab plus chemotherapy group refers to nivolumab, at least one chemotherapy component, or both **[57]**. SAEs in KEYNOTE-590 were defined similar to the definition in RATIONALE-306, and the definition was not reported in CheckMate 648.

Table 35 presents an overview of the safety events of the key publications of the clinical trials RATIONALE-306, CheckMate 648, and KEYNOTE-590, as these are applied in the indirect comparison of the treatments. Please note that assessing the number of any event in the table must take into account that exposure to tislelizumab is longer than placebo (median duration of exposure: [redacted] months in the T+C arm and [redacted] months in the P+C arm) **[64]**.

Table 35. Overview of safety events.

	RATIONALE-306			CheckMate 648		KEYNOTE-590	
	Tislelizumab + chemotherapy (N=324) [50,51,64]	Placebo + chemotherapy (N=321) [50,51,64]	Difference, % (95 % CI)	Nivolumab + Chemotherapy (N=310) [56,57]	Chemotherapy (N=304) [56,57]	Pembrolizumab + Chemotherapy (N=370) [53,54]	Placebo + Chemotherapy (N=370) [53,54]
Number of AEs, n	[redacted]	[redacted]	NR	NR	NR	NR	NR
Number and proportion of patients with ≥1 AEs, n (%)	[redacted]	[redacted]	NR	NR	NR	370 (100)	386 (99)
Number of SAEs, n	[redacted]	[redacted]	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 SAEs, n (%)	[redacted]	[redacted]	NR	74 (24)†	49 (16)†	NR	NR
Number of CTCAE grade ≥ 3 events, n	[redacted]	[redacted]	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events, n (%)	[redacted]	[redacted]	NR	147 (47)†	108 (36)†	318 (86)	308 (83)
Number of ARs, n	NR	NR	NR	NR	NR	NR	NR
Number and proportion of patients with ≥ 1 ARs, n (%)	NR	NR	NR	297 (96)	275 (90)	364 (98)	360 (97)
Number and proportion of patients who had a dose modification due to TEAEs, n (%)	[redacted]	[redacted]	NR	Cisplatin: 105 (34) Fluorouracil: 65 (21)	Cisplatin: 75 (25) Fluorouracil: 36 (12)	NR	NR

	RATIONALE-306			CheckMate 648		KEYNOTE-590	
	Tislelizumab + chemotherapy (N=324) [50,51,64]	Placebo + chemotherapy (N=321) [50,51,64]	Difference, % (95 % CI)	Nivolumab + Chemotherapy (N=310) [56,57]	Chemotherapy (N=304) [56,57]	Pembrolizumab + Chemotherapy (N=370) [53,54]	Placebo + Chemotherapy (N=370) [53,54]
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	286 (88.3)	306 (95.3)	NR	285 (91.9)	300 (98.7)	328 (88.6)	359 (97.0%)
Number and proportion of patients who discontinue treatment due to AEs, n (%)	[redacted]	[redacted]	NR	106 (34)[†]	59 (19)[†]	90 (24)	74 (20%)

[†]Treatment-related adverse events. Abbreviations: AEs, Adverse Events; AR, Adverse Reaction; CI, Confidence Interval; CTCAE, Common Terminology Criteria for Adverse Events; NR, Not Reported; SAE, Serious Adverse Events; TEAE, Treatment Emergent Adverse Events

The most commonly reported adverse events by System Organ Class were [redacted] between the 2 treatment arms in RATIONALE-306. The most common events [redacted] by preferred term in the T+C Arm and the P+C Arm were [redacted] [64].

Additional safety analysis was performed to determine if there was any difference in safety associated with T+C in the subgroup of patients with PD-L1≥5% compared to the overall population. The safety profile of T+C in this subgroup was consistent with that reported for the overall safety analysis set. No increases in safety risks were identified at the data from 28FEB2022. The incidence of tislelizumab/placebo-related TEAEs with ≥ Grade 3 severity was evaluated for the PD-L1≥5% subgroup. Consistent with the overall population, higher incidence of treatment-related TEAEs was observed for the T+C arm ([redacted]) compared to the P+C arm ([redacted]). The incidence of events by preferred term in this subgroup was largely consistent with the overall population [64].

At data cutoff 24 November 2023 (3-years follow-up), median exposure was longer for T+C [redacted] than for P+C [redacted] with [redacted] treated with T+C for ≥36 months. A total of [redacted] discontinued from treatment [redacted] for various reasons, including progressive disease ([redacted]), withdrawal by patient ([redacted]), AE ([redacted]), physician decision ([redacted]), treatment interruption ([redacted]), and non-compliance with study drug ([redacted]). A total of [redacted] patients ([redacted]) discontinued the study (T+C: [redacted]; P+C: [redacted] Consistent with the findings at interim analysis, the frequency of any-grade ([redacted] and grade ≥3 TRAEs ([redacted]) were comparable between the T+C and P+C treatment arms, respectively. T+C therapy was associated with a greater incidence of TEAEs leading to treatment discontinuation ([redacted] with P+C), as well as more frequently occurring serious TRAEs ([redacted]), respectively. However, rates of TRAEs leading to death were similar between both groups ([redacted] [64].

In the CheckMate 648 study (29 months follow-up), the safety data for the N+C arm was consistent with the primary analysis with 74 patients (24%) experiencing SAE. Additionally, 151 patients (49%) had ≥1 CTCAE grade ≥3 events. Furthermore, the number of patients with at least one TEAE was 297 (96%) [67].

The SAEs with frequency of ≥ 5% from the three trials are reported below in Table 36, Table 37 and Table 38, respectively. SAEs with an incidence ≥ 1% and the frequency of different SAEs from the clinical trials, RATIONALE-306, CheckMate 648 and KEYNOTE-590 are presented in Appendix E [64].

Table 36 Serious adverse events (time point), RATIONALE-306

RATIONALE-306 (Data cut-off: February 28, 2022) [64]				
Adverse events	**Tislelizumab + chemotherapy (N=324)**		**Placebo + chemotherapy (N=321)**	
	Number of patients with AEs	**Number of AEs**	**Number of patients with AEs**	**Number of AEs**
Dysphagia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Pneumonia, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: AEs, Adverse Events; NR, Not Reported

Table 37. Serious adverse events (time point), CheckMate 648

CheckMate 648 [58]				
Adverse events	**Nivolumab + Chemotherapy (N = 310)**		**Chemotherapy (N=304)**	
	Number of patients with AEs	**Number of AEs**	**Number of patients with AEs**	**Number of AEs**
Dysphagia, n (%)	20 (6.45)	NR	16 (5.26)	NR
Pneumonia, n (%)	33 (10.65)	NR	20 (6.58)	NR
Malignant neoplasm progression, n (%)	56 (18.06)	NR	62 (20.39)	NR

Note: Results posted on Clinicaltrials.gov, with a time frame for up to 43 months . Abbreviations: AEs, Adverse Events; NR, Not Reported

Table 38. Serious adverse events (time point), KEYNOTE-590

KEYNOTE-590 [55]				
Adverse events	**Pembrolizumab + Chemotherapy (N = 370)**		**Placebo + Chemotherapy (N=370)**	
	Number of patients with AEs	**Number of AEs**	**Number of patients with AEs**	**Number of AEs**
Pneumonia, n (%)	38 (10.27)	40	32 (8.65)	36

Note: Results posted on Clinicaltrials.gov, with a time frame for up to approximately 70 months
Abbreviations: AEs, Adverse Events; NR, Not Reported

Comparative safety analysis

As no head-to-head study is available for T+C compared to N+C and Pe+C, an ITC was conducted for grade ≥3 TRAEs. This analysis was based on ITT populations from each study. For a detailed description of the ITC synthesis and method see section 7 and Appendix C [64]. The number of patients included in the safety analysis is outlined in Table 39. [redacted]

Table 39 Number of patients included in the Grade ≥3 TRAE network, by treatment arm [64]

Treatment Arm	Number of patients
T+C	[redacted]
Pe+C	[redacted]
N+C	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; Pe, pembrolizumab; T, tislelizumab

The results from the safety analysis showed that T+C had a comparable safety profile to, Pe+C, and N+C. The results are seen in Table 40.

Table 40 Pairwise comparisons from the [redacted] NMA for Grade ≥3 TRAE (reported as OR [95% CI]) [64]

Outcome measure	T+C (N=[redacted])	Pe+C (N=[redacted])	Result OR (95% CI)	T+C (N=[redacted])	N+C (N=[redacted])	Result OR (95% CI)
Grade ≥3 TRAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NOTE: An OR > 1 indicates TIS + CT has greater odds of a response than the comparator therapy. An OR < 1 indicates the odds of a response are lower in TIS + CT compared to the comparator therapy. Bold font indicates statistical significance at the 0.05 level.
Abbreviations: C, chemotherapy; NMA, Network meta-analysis; N, nivolumab; OS,overall survival; PFS, progression free survival; Pe, pembrolizumab; T, tislelizumab; ITT, intent-to-treat.

SUCRA values and probability best values are presented in Table 41. T+C had the highest SUCRA value of [redacted] [64].

Table 41 Summary of SUCRA values from the [redacted] NMA for Grade ≥3 TRAE [64]

Treatment Arm	SUCRA (%)	Probability Best (%)
T+C	[redacted]	[redacted]
P+C	[redacted]	[redacted]
N+C	[redacted]	[redacted]

Abbreviations: C, chemotherapy; N, nivolumab; NMA , network meta-analysis; ORR, objective response rare; P, pembrolizumab; SUCRA, Surface Area Under the Cumulative Ranking Curve; T, tislelizumab.

Thus, no significant difference between T+C, P+C, and N+C were found when comparing grade ≥3 TRAEs. As the ≥3 TRAEs are not significantly different between the treatments, AEs have not been included in the health economic model [64].

Table 42. Adverse events used in the health economic model (N/A)

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Adverse event, n (%)				

9.2 Safety data from external literature applied in the health economic model (N/A)

Table 43 Adverse events that appear in more than X % of patients (N/A)

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

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

In the following sections HRQoL data from RATIONALE-306, KEYNOTE-590, and CheckMate 648 will be presented. HRQoL was measured by EQ-5D and EQ-VAS in all of the three trials (Table 44).

Table 44 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L + EQ-VAS	RATIONALE-306	Clinical effectiveness
EQ-5D-5L + EQ-VAS	KEYNOTE-590	Clinical effectiveness
EQ-5D-3L + EQ-VAS	CheckMate 648	Clinical effectiveness

Abbreviations: EQ-5D-3L, EuroQol 5-Dimension 3-Level; EQ-5D-5L, EuroQol 5-Dimension 5-Level; EQ-VAS, EuroQol Visual Analogue Scale

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument – RATIONALE-306

RATIONALE-306 was a randomized, double-blind, parallel-arm, placebo-controlled, phase 3 study. See section 6 for a more detailed description. A secondary endpoint in the RATIONALE-306 study was HRQoL measured by three validated patient reported outcome; the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ)-C30), its oesophageal cancer module - EORTC QLQ-OES18 (OES18), and the European Quality of Life 5-Dimension 5-Level (EQ-5D-5L) descriptive module and EQ-VAS. In this submission, EQ-VAS data for the ITT population are presented [50].

10.1.2 Study design and measuring instrument – KEYNOTE-590

KEYNOTE-590 was a randomized, double-blind, placebo-controlled, phase 3 study. See section 6 for a more detailed description. To measure HRQoL the three validated tools QLQ-C30, OES18, and EQ-5D-5L including EQ-VAS were used. The HRQoL was assessed among all randomized patients who had received at least one treatment dose and completed at least 1 HRQoL assessment during the follow-up period [72].

10.1.3 Study design and measuring instrument – CheckMate 648

CheckMate 648 was a randomized, open-label, phase 3 study. See section 6 for a more detailed description. Information regarding HRQoL measurement in the study was only accessible in abstract form from 2022 ASCO Gastrointestinal Cancers Symposium. The HRQoL was measured by the Functional Assessment of Cancer Therapy-Esophageal

(including the GP5 item to assess impact of side effects) and EuroQoL 5-Dimensions 3-levels (EQ-5D-3L). The HRQoL analyses were performed on all randomized patients and on the subgroup with PD-L1 expression ≥1% [73].

10.1.4 Data collection – RATIONALE-306

The HRQoL was assessed at baseline, after randomization, prior to dosing or any clinical activities at every treatment cycle for the first 6 cycles, then every other cycle afterwards, and at the end-of-treatment (EOT) Visit [50]. Only patients who completed the questionnaire at baseline and had ≥ 1 postbaseline assessment were included in the analysis. The completion rates correspond to the number of patients who completed the questionnaire divided by the total number of patients on study treatment at relevant visits in relevant treatment arm. The pattern of missing data and completion can be found in Table 45 below.

Table 45 Pattern of missing data and completion

	Tislelizumab + chemotherapy				Placebo + chemotherapy			
Time point	**HRQoL population N**	**Missing N (%)**	**Expected to complete N**	**Completion N (%)**	**HRQoL population N**	**Missing N (%)**	**Expected to complete N**	**Completion N (%)**
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

	Tislelizumab + chemotherapy				Placebo + chemotherapy			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

	Tislelizumab + chemotherapy				Placebo + chemotherapy			
Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								
[redacted]								

Abbreviations: EOT, End of Treatment; HRQoL, Health-related Quality of life

10.1.5 Data collection – KEYNOTE-590

The questionnaire was completed at baseline and for cycles 1-9, after the completion of cycle 9, the questionnaire was completed every 3 cycles up to a year or until the EOT. At the EOT and at the follow-up visit 30 days after a questionnaire was also completed. The population who received at least one dose and completed at least one HRQoL assessment comprised the HRQoL population of 730 patients. Compliance and complement rate for baseline are not reported. However, the compliance rate was high (≥90%) at week 18, whereas completion rate was ≥56% [72].

10.1.6 Data collection – CheckMate 648

In total 970 patients were randomized into the three groups and 90% of these were included in the HRQoL population, as these completed an assessment at baseline and at least one on-treatment assessment [73].

10.1.7 HRQoL results – RATIONALE-306

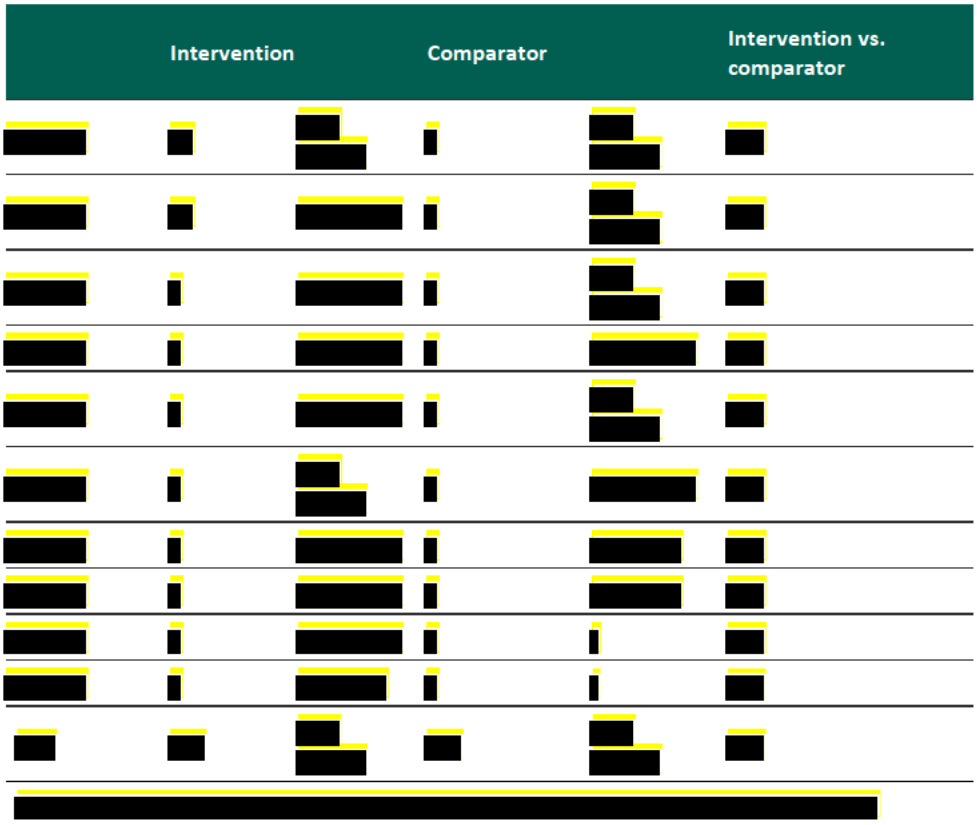
No statistically significant or clinically meaningful differences were observed between the T+C and P+C treatment arms for the HRQoL assessments at either Cycle [redacted] These cycles were the [redacted], respectively. Tislelizumab was overall well-tolerated and its combination with chemotherapy was associated with delayed worsening in general QoL, as measured by EQ-5D-5L [64]. The results from the EQ-VAS were at baseline comparable between treatment arms [redacted]. Mean change from baseline in the VAS showed a smaller decrease in health status in the T+C arm compared with patients in the P+C arm up to Cycle [redacted] Mean change from baseline (SD) in VAS was [redacted] in the T+C arm versus [redacted] in the P+C arm at Cycle [redacted] and was [redacted] in the T+C arm versus to [redacted] in the P+C arm at Cycle [redacted] [64]. [redacted] and Table 46 presents the EQ-VAS score results.

[redacted]

[redacted]

Table 46 HRQoL: EQ-VAS Score summary statistics [64]

	Intervention		Comparator		Intervention vs. comparator
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]



10.1.8 HRQoL results – KEYNOTE-590

The result of the EQ-VAS showed the mean score at baseline and at week 18 were similar between the treatment arms (see Table 47). There was no clinically meaningful difference between the groups from baseline to week 18 (least squares mean difference, 1.20; 95% CI, −1.61 to 4.01; 2-sided nominal P = .4016). In conclusion, HRQoL was maintained from baseline to week 18 throughout treatment with Pe+C [72].

Table 47 HRQoL EQ-VAS summary statistics – KEYNOTE-590

	Pembrolizumab plus chemotherapy		Placebo plus chemotherapy		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	360	72.59 (18.65)	352	74.43 (17.14)	N/R
Week 18	226	72.41 (18.55)	204	74.03 (16.59)	N/R

Abbreviations: SE, Standard Error; CI, Confidence interval; NR, Not reported
Source **[72]**

10.1.9 HRQoL results – CheckMate 648

At baseline the scores were similar across treatment arms. There were no statistically significant changes from baseline however, the groups treated with N+C and nivolumab + ipilibumab (N+I) favoured a better HRQoL compared to chemotherapy alone. The results from the subgroup analysis for the population with PD-L1 expression ≥1% were similar to the overall HRQoL population. In conclusion, the analysis showed that HRQoL is maintained throughout treatment with N+CT and N+I [73].

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

The HRQoL results from the RATIONALE-306, KEYNOTE-590 and CheckMate 648 trials demonstrated maintained HRQoL while patients received treatment. It is assumed that the treatments are equal in maintaining the patients' HRQoL during treatment.

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

Not applicable to this application.

10.2.1 HSUV calculation (N/A)

10.2.1.1 Mapping (N/A)

10.2.2 Disutility calculation (N/A)

10.2.3 HSUV results (N/A)

Table 48 Overview of health state utility values [and disutilities] (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
-				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy (N/A)

Not applicable to this application.

10.3.1 Study design (N/A)

10.3.2 Data collection (N/A)

10.3.3 HRQoL Results (N/A)

10.3.4 HSUV and disutility results (N/A)

Table 49 Overview of health state utility values [and disutilities] (N/A)

Results [95% CI]	Instrument	Tariff (value set) used	Comments
-			

Table 50 Overview of literature-based health state utility values (N/A)

Results[95% CI]	Instrument	Tariff (value set) used	Comments
-			

11. Resource use and associated costs

All relevant costs linked to the treatment of OSCC with PD-L1 expression with tislelizumab combined with chemotherapy compared to nivolumab in combination with chemotherapy and pembrolizumab in combination with chemotherapy, respectively. The clinical expert recommended that the model must use the capecitabine and oxaliplatin regimen as chemotherapy as this reflects clinical practice in Denmark.
Data from the study trials, the SmPCs and assumptions validated by a Danish clinical expert was applied when identifying inputs for the model. The medicine costs are presented as pharmacy purchasing prices (PPP) identified through medicinpriser.dk on the 11th of December [74].

11.1 Medicines - intervention and comparator

Packages: For an overview of available packages presented with PPP see Table 51. If several packages were available the ones with the lowest cost per mg were used, and if price was equal regardless of package size the most convenient was chosen. The model only includes the packages that have been deemed relevant for comparison based on what is stated above.

Table 51 Overview of available packages and pharmacy purchasing price, November 2024

Medicine	Strength	Packages	Pharmacy purchasing price [DKK]	Source
Tislelizumab	100mg/10mL	1 vial	[redacted]	BeiGene
Pembrolizumab	100mg/4mL	1 vial	28,709.70	Medicinpriser.dk[74]

Nivolumab	40mg/4mL	1 vial	4,580.40	Medicinpriser.dk[74]
	100mg/10mL	1 vial	11,353.50	Medicinpriser.dk[74]
	120mg/12mL	1 vial	13,620.80	Medicinpriser.dk[74]
	240 mg/24mL	1 vial	27,224.80	Medicinpriser.dk[74]
Capecitabine	150mg	60 pcs	847.40	Medicinpriser.dk[74]
	500mg	120pcs	768.95	Medicinpriser.dk[74]
Oxaliplatin	50 mg/10mL	1 vial	71.60	Medicinpriser.dk[74]
	100mg/20mL	1 vial	108.35	Medicinpriser.dk[74]
	200mg/40mL	1 vial	186.85	Medicinpriser.dk[74]

Medicine waste: Aligned with the DMC assessment of nivolumab, waste has not been included in the health economic analysis, as the hospital pharmacies as far possible ensure to share the vials between patients [43].

Treatment duration: The treatment duration is based on the duration of treatment exposure in each of the respective studies. PFS was not chosen as it does not reflect the patients who discontinue due to toxicity. In Xu et al. 2023 treatment was continued until investigator-assessed disease progression, unacceptable toxicity, death or withdrawal of consent. The median time of treatment exposure was 6.4 months (IQR 3.3-11.1) in the tislelizumab group compared to 4.9 (IQR 2.5-8.3) in the placebo group [51]. In Doki et al. 2022 treatment was continued until disease progression, unacceptable toxicity, withdrawal of consent or the end of the trial. Nivolumab must not be administered for more than 2 years. The median duration of treatment in the N+C group was 5.7 months compared to 3.4 months in the chemotherapy group [57]. In Sun et al. 2021 treatment was continued until disease progression, unacceptable toxicity, illness, withdrawal decided by either patient or physician, non-compliance, reaching completion of 35 cycles, CR or discontinuation due to administrative reasons. The mean treatment duration of pembrolizumab +chemotherapy was 7.7 months (SD 6.84) compared to 5.8 months (SD 4.76) in the placebo+ chemotherapy group [54]. The treatment duration is similar for tislelizumab, nivolumab and pembrolizumab. The slight differences expressed might be explained by different reporting measures as the time is presented as a mean for pembrolizumab, and as a median for both tislelizumab and nivolumab. A mean is more sensitive towards outliers and the SD is quite high, which could be a factor in the small difference in treatment duration. The clinical expert mentioned that the treatment duration in Danish patients is usually somewhere between [redacted] months which is in alignment with the data from the clinical trials. The treatment duration in the health economic model reflects that capecitabine and oxaliplatin (CAPOX) can only be administered up to 9 cycles corresponding to 6,24 months. It is assumed that this treatment duration is plausible based on the input from the clinical expert and the fact that the treatments are considered as equal.

Time horizon: The time horizon has been chosen to be 9 cycles (corresponding to 6,24 months) to reflect maximum treatment length with CAPOX, which the clinical expert defined as being the most sufficient and common chemotherapy regimen for combination therapy with tislelizumab, nivolumab or pembrolizumab in OSCC patients.

Relative dose intensity: RDI has been assumed to be [redacted]% for both tislelizumab, nivolumab, and pembrolizumab. The assumption was made since RDI for nivolumab and pembrolizumab could not be found. Since all immunotherapies relevant for this submission should be administered as fixed doses based on the SmPCs, the base case reflects this. See Table 52 below for an overview.

Table 52 Medicines used in the model

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Tislelizumab in combination with platinum-based chemotherapy	Tislelizumab: 200mg CAPOX -capecitabine (2000 mg/m² orally. on days 1-14 every 3 weeks) and oxaliplatin (130 mg/m² IV on day 1 every 3 weeks).	The mean RDI was [redacted]% (SD: [redacted]) [64].	Every 3 weeks	Yes
Nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy	Nivolumab: 360mg CAPOX -capecitabine (2000 mg/m² orally. on days 1-14 every 3 weeks) and oxaliplatin (130 mg/m² IV on day 1 every 3 weeks).	Assumed same as tislelizumab: [redacted]%.	Every 3 weeks	Yes
Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy	Pembrolizumab: 200mg CAPOX -capecitabine (2000 mg/m² orally. on days 1-14 every 3 weeks) and oxaliplatin (130 mg/m² IV on day 1 every 3 weeks).	Assumed same as tislelizumab: [redacted]%.	Every 3 weeks	Yes

Abbreviations: RDI, Relative Dose Intensity; SD, Standard Deviation; CAPOX, Capecitabine and Oxaliplatin; IV, Intravenous

11.2 Medicines– co-administration (N/A)

Not applicable as no co-administration is needed for the intervention and comparators.

11.3 Administration costs (N/A)

Since the treatment duration has a cut-off at 9 cycles, all treatments will involve the same administration costs within this time frame and is therefore omitted in the analysis.

Table 53 Administration costs used in the model (N/A)

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
-	-	-	-	-

11.4 Disease management costs (N/A)

Since the treatment duration has a cut-off at 9 cycles, all treatments will involve the same disease management costs within this time frame and is therefore omitted in the analysis.

Table 54 Disease management costs used in the model (N/A)

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
-	-	-	-	-

11.5 Costs associated with management of adverse events (N/A)

No costs related to the management of adverse events have been included in the model, as the NMA showed that there was no significant difference between the three treatment options when comparing Grade ≥3TRAEs.

Table 55 Cost associated with management of adverse events (N/A)

	DRG code	Unit cost/DRG tariff
-	-	-

11.6 Subsequent treatment costs (N/A)

As the efficacy of the three treatment options have been assumed equivalent and an identical treatment duration is assumed, the subsequent treatment is deemed irrelevant to include in the model.

Table 56 Medicines of subsequent treatments (N/A)

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
-	-	-	-	-

11.7 Patient costs (N/A)

Patient costs are considered as being equal regardless of received treatment and therefore omitted in the health economic analysis. The first dose of tislelizumab should be infused over 60 minutes, however, if this is tolerated the infusion time of the subsequent doses may be decreased to 30 minutes [1,64]. Nivolumab and pembrolizumab are administered as infusion over 30 minutes [47,48]. It is assumed that this cost has a very small impact on the total result if reflected in the analysis.

Table 57 Patient costs used in the model (N/A)

Activity	Time spent
Activity	-

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

Since tislelizumab, nivolumab, and pembrolizumab are PD-L1 inhibitors, it is necessary to conduct a test to determine the PD-L1 score before commencing treatment. Currently, CPS and TPS are utilized to measure PD-L1 scores in Danish clinical practice, which is consistent with the use of nivolumab and pembrolizumab [38]. Whereas treatment with tislelizumab relies on estimating PD-L1 score using TAP score. TAP has been shown to be an efficient method, with an average time spent on scoring of 5 minutes [32]. Compared to CPS, TAP appears to be less time-consuming, suggesting that using TAP to determine the PD-L1 score might also be less costly. Consequently, the costs associated with determining PD-L1 score were excluded, as it is anticipated that the cost of PD-L1 scoring for treatment with tislelizumab would be comparable to or less than the cost of PD-L1 scoring for treatment with nivolumab or pembrolizumab. The clinical expert was consulted regarding this but could not provide a valid answer since a pathologist must be consulted as well.

12. Results

12.1 Base case overview

An overview of the central aspects in the base case is found in Table 58.

Table 58 Base case overview

Feature	Description
Comparator	Nivolumab in combination with platinum- and fluoropyrimidine-based chemotherapy and

Feature	Description
	Pembrolizumab in combination with platinum- and fluoropyrimidine-based chemotherapy
Type of model	Cost-minimisation model
Time horizon	Maximum one year (9 cycles corresponding to 6,24 months)
Treatment line	1L
Measurement and valuation of health effects	N/A
Costs included	Medicine costs
Dosage of medicine	Fixed dosage
Average time on treatment	Intervention and comparators: 6.24 months (due to restrictions with administration of CAPOX)
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	No
Average time in model health state	N/A
Health state 1	
Health state 2	
Health state 3	
Death	

Abbreviations: 1L, First Line; CAPOX, Capecitabine and Oxaliplatin; NA, Not Applicable; PFS, Progression-Free Survival; OS, Overall Survival

12.1.1 Base case results

The base case results for comparison to nivolumab and pembrolizumab are found in Table 59 and Table 60, respectively.

Table 59 Base case results, tislelizumab vs. nivolumab

	Tislelizumab	Nivolumab	Difference
Medicine costs	[redacted]	346,620.4 DKK	[redacted]

	Tislelizumab	Nivolumab	Difference
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Total costs			
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs		[redacted]	

Abbreviations: N/A, Non-Applicable; QALY, Quality-adjusted life year

Table 60 Base case results, tislelizumab vs. pembrolizumab

	Tislelizumab	Pembrolizumab	Difference
Medicine costs	[redacted]	483,727.2 DKK	[redacted]

	Tislelizumab	Pembrolizumab	Difference
Medicine costs – co-administration	N/A	N/A	N/A
Administration	N/A	N/A	N/A
Disease management costs	N/A	N/A	N/A
Costs associated with management of adverse events	N/A	N/A	N/A
Subsequent treatment costs	N/A	N/A	N/A
Patient costs	N/A	N/A	N/A
Palliative care costs	N/A	N/A	N/A
Total costs			
Life years gained (health state A)	N/A	N/A	N/A
Life years gained (health state B)	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs (state A)	N/A	N/A	N/A
QALYs (state B)	N/A	N/A	N/A
QALYs (adverse reactions)	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs		[redacted]	

Abbreviations: N/A, Non-Applicable; QALY, Quality-adjusted life year

12.2 Sensitivity analyses

As the employed model was a simple cost-minimisation, no deterministic or probabilistic sensitivity analyses were utilized, however, two scenario analyses were performed: one

scenario analysis demonstrating weight-based dosing of nivolumab and pembrolizumab due to DMC's inputs in a previous DMC assessment, and one scenario analysis reflecting that tislelizumab should only be administered with platinum-based chemotherapy based on SmPC.

Scenario analysis 1: Weight-based dosing

According to the DMC nivolumab and pembrolizumab are administered per weight-based dosing in Danish clinical practice, and a scenario analysis was performed to consider this aspect. Tislelizumab should reflect the SmPC based on the statement from the clinical expert and is therefore kept as fixed dose. In alignment with the previous DMC assessment of immunotherapies a mean weight of 76,5kg was assumed in the model [43]. No waste has been assumed due to vial sharing, with the same rationale as in the base case analysis. Table 61 presents the inputs used in the scenario analysis and Table 62 shows the results of the scenario analysis.

Table 61 Inputs for the scenario analysis

Medicine	Weight-based dose	Mean weight	Total mean dose
Tislelizumab	N/A	76,5kg	200 mg
Nivolumab	4,5mg/kg [43]	76,5kg	344,25mg
Pembrolizumab	2mg/kg [43]	76,5kg	153mg

Table 62 Scenario analysis results

Medicine	Medicine costs	Incremental (intervention vs. comparator)
Tislelizumab	[redacted]	-
Nivolumab	331,816.4 DKK	[redacted]
Pembrolizumab	371,988.4 DKK	[redacted]

Scenario analysis 2: Tislelizumab in combination with platinum-based chemotherapy

Based on tislelizumab's indication it should only be administered with platinum-based chemotherapy [1]. If all input parameters in the base case model are fixed, but capecitabine (the fluoropyrimidine regime) is removed from the tislelizumab costs, tislelizumab continues to be a cost-saving alternative; the incremental cost compared to nivolumab is [redacted] DKK and the incremental cost compared to pembrolizumab is [redacted] DKK.

12.2.1 Deterministic sensitivity analyses (N/A)

Table 63 One-way sensitivity analyses results (N/A)

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	-	-	-

12.2.2 Probabilistic sensitivity analyses (N/A)

13. Budget impact analysis

Number of patients (including assumptions of market share)

It was previously stated that 45 patients are eligible for treatment with the intervention and comparators. The clinical expert expects [redacted] why a [redacted] market share is used in the non-recommendation scenario and a [redacted] market share is used in the recommendation scenario. The number of patients used in the budget impact analysis is presented below in Table 64.

Table 64 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Tislelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			Non-recommendation		
Tislelizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Budget impact

The result of the budget impact analysis is presented in Table 65.

Table 65 Expected budget (in DKK) impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	[redacted]				
The medicine under consideration is NOT recommended	[redacted]				
Budget impact of the recommendation	[redacted]				

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 66 Main characteristic of RATIONALE-306. [50,51,75]

Trial name: RATIONALE-306	**NCT number: 03783442**
Objective	To assess tislelizumab plus chemotherapy versus placebo plus chemotherapy as 1L treatment for advanced or metastatic OSCC.
Publications – title, author, journal, year	A Randomized, Placebo-Controlled, Double-Blind Phase 3 Study to Evaluate the Efficacy and Safety of Tislelizumab (BGB-A317) in Combination with Chemotherapy as First-Line Treatment in Patients with Unresectable, Locally Advanced Recurrent or Metastatic Oesophageal Squamous Cell Carcinoma. Xu J. et al. Lancet Oncol. 2023.
Study type and design	Randomized, double-blinded, parallel-arm, placebo-controlled, phase 3 study conducted at 162 medical centres across Asia, Europe, Oceania, and North America. Patients were randomly assigned (1:1), using permuted block randomization (block size of four), and stratified by investigator-chosen chemotherapy, region, and previous definitive therapy. Cross-over between treatment groups during the study treatment period was prohibited, even after unmasking. Investigators, patients, and sponsor staff or designees were masked to treatment.
Sample size (n)	649
Main inclusion criteria	• Pathologically (histologically) confirmed diagnosis of OSCC. • ≥18 years of age. • Stage IV unresectable OSCC at first diagnosis OR unresectable, locally advanced recurrent or metastatic disease, if there was prior neoadjuvant/adjuvant therapy with platinum-based chemotherapy, a treatment-free interval of at least 6 months was required.
Main exclusion criteria	• Brain or leptomeningeal metastases that were symptomatic or required treatment. • Evidence of complete oesophageal obstruction not amenable to treatment. • Evidence of fistula. • Active autoimmune diseases. • Medical conditions requiring systemic corticosteroids or immunosuppressants. • Previous therapies targeting PD-1, PD-L1, or PD-L2.
Intervention	Tislelizumab + Chemotherapy (n=326): Tislelizumab 200 mg administered IV on Day 1 of each cycle Q3W plus one of the following until unacceptable toxicity, disease progression, or withdrawal for other reasons; each cycle is 21 days: • Chemotherapy Doublet A: cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and 5-fluorouracil IV 750-800 mg/m^2 on Days 1 to 5 of each cycle Q3W; or

Trial name: RATIONALE-306	NCT number: 03783442
	• Chemotherapy Doublet B: cisplatin 60-80 mg/m^2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and capecitabine orally 1000 mg/m^2 on Days 1 to 14 of each cycle, twice a day; or • Chemotherapy Doublet C: cisplatin 60-80 mg/m^2 administered IV on Day 1 or 2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and paclitaxel 175 mg/m^2 IV on Day 1 of each cycle Q3W; cisplatin may be given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines.
Comparator	Placebo + Chemotherapy (n=323): Matched placebo administered IV on Day 1 of each cycle Q3W plus one of the following until unacceptable toxicity, disease progression, or withdrawal for other reasons; each cycle is 21 days: • Chemotherapy Doublet A: cisplatin 60-80 mg/m^{2}or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and 5-fluorouracil IV 750-800 mg/m^2 on Days 1 to 5 of each cycle Q3W; or • Chemotherapy Doublet B: cisplatin 60-80 mg/m^{2}or oxaliplatin 130 mg/m^{2}administered IV on Day 1 of each cycle Q3W and capecitabine orally 1000 mg/m^{2}on Days 1 to 14 of each cycle, twice a day; or • Chemotherapy Doublet C: cisplatin 60-80 mg/m^2 administered IV on Day 1 or 2 or oxaliplatin 130 mg/m^2 administered IV on Day 1 of each cycle Q3W and paclitaxel 175 mg/m^2 IV on Day 1 of each cycle Q3W; cisplatin may be given in 3 divided doses on Days 1, 2, and 3 depending on local guidelines.
Follow-up time	As of data cutoff (Feb 28, 2022), median study follow-up (from randomization to data cutoff, death, or study discontinuation due to other reason, whichever came first) was 16.3 months (IQR 8·6–21·8) in the tislelizumab group and 9.8 months (5·8–19·0) in the placebo group.
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was OS. The secondary endpoints were PFS, ORR, Overall Survival in the subgroup with a PD-L1 TAP score of ≥10%, DOR, HRQoL as assessed by QLQ-C30, QLQ-OES18, and EQ-5D-5L, and safety. **Other endpoints:** Exploratory endpoints included investigator-assessed disease control rate (proportion of patients whose BOR was CR, partial response, or stable disease, per RECIST version 1.1), and blinded independent review committee-assessed PFS, ORR, DOR, and disease control rate.
Method of analysis	Efficacy analyses were done in the ITT analysis set, which included all patients randomly assigned to treatment. Safety was assessed in all patients who received at least one dose of study treatment (safety population).
Subgroup analyses	Pre-specified subgroup analyses for the primary endpoint, OS:

Trial name: RATIONALE-306	NCT number: 03783442
	• Investigator-chosen chemotherapy (platinum plus fluoropyrimidine *vs* platinum plus paclitaxel). • Geographical region (Asia vs. Rest of the World, Asia (excluding Japan) vs. Japan vs. Rest of World) • ECOG performance Score (0 vs. 1) • Age (<65 years, ≥65 years) • Sex (female, male) • Smoking status at entry (former/current smoker, non-smoker) • Race (White, Asian, and Other) • Disease status (Locally advanced vs. metastatic) • Prior definitive therapy (yes/no) • Baseline PD-L1 expression category using TAP score: PD-L1 score>= 10%, PD-L1 score< 10%, Unknown Post-hoc subgroup analyses for the primary endpoint, OS: • Choice of chemotherapy doublet regimen • PD-L1 expression status using CPS and tumour cell score. Pre-specified subgroup analyses for the secondary endpoint, PFS: • Geographical region (Asia *vs* other regions) • PD-L1 expression status (TAP score <10% *vs* ≥10% *vs* unknown) Post-hoc subgroup analyses for the secondary endpoint, PFS: • Investigator-chosen chemotherapy (platinum plus fluoropyrimidine *vs* platinum plus paclitaxel). A prespecified multivariable analysis was conducted for OS, adjusting for key baseline characteristics and prognostic factors based on a stratified Cox regression model, including treatment group, baseline PD-L1 TAP score, age, sex, smoking status, ECOG performance status, and disease stage as covariates, and pooled geographical region, previous definitive therapy, and investigator-chosen chemotherapy as strata. ORR was tested using the Cochran-Mantel-Haenszel test, adjusting for prespecified stratification factors; the two-sided 95% CI for odds ratio (OR) was calculated alongside Clopper-Pearson 95% CIs of overall response rate (ORR) in each treatment group. Prespecified subgroup analyses were conducted for ORR as per the PFS analyses. DOR was calculated in a similar way to PFS; medians were also calculated. Safety data were analysed using descriptive statistics.
Other relevant information	N/A

Abbreviations: 1L, First Line; CI, Confidence Interval; CPS, Combined Positive Score; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; EQ-5D-5L, EuroQol 5-Dimension 5-Level; HRQoL, Health-Related Quality of Life; ITT, Intent-to-Treat; IV, Intravenous; MG, Milligrams; N/A, Not Applicable; OR, Odds Ratio; ORR, Objective Response Rate; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma;

PD-1, Programmed Death 1; PD-L1, Programmed Death Ligand 1; PD-L2, Programmed Death Ligand 2; PFS, Progression-Free Survival; Q3W, Every 3 Weeks; QLQ-C30, Quality of Life Questionnaire C30; QLQ-OES18, Quality of Life Questionnaire Oesophageal Module; RECIST, Response Evaluation Criteria for Solid Tumours; TAP, Tumour Area Positivity

Table 67 Main characteristics of CheckMate 648 [56–58]

Trial name: CheckMate 648	**NCT number: 03143153**
Objective	To assess nivolumab plus chemotherapy versus nivolumab plus monoclonal antibody and placebo plus chemotherapy as 1L treatment for advanced or metastatic OSCC.
Publications – title, author, journal, year	Nivolumab Combination Therapy in Advanced Oesophageal Squamous-Cell Carcinoma. Doki Y. et al. The New England Journal of Medicine. 2022.
Study type and design	Randomized, open-label, phase 3 trial. Enrolled patients were randomly assigned in 1:1:1.
Sample size (n)	970
Main inclusion criteria	• Histologically confirmed diagnosis of OSCC or adenosquamous-cell carcinoma. • ≥18 years of age. • Had unresectable advanced, recurrent, or metastatic OSCC, regardless of PD-L1 expression status; had disease that was not amenable to curative treatments; and did not receive previous systemic therapy for advanced disease.
Main exclusion criteria	• Presence of tumour cells in the brain of spinal cord which are symptomatic or require treatment • Active known or suspended autoimmune disease • Any serious or uncontrolled medical disorder or active infection • Known history of positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome • Any positive test result for hepatitis B or C indicating acute or chronic infection and/or detectable virus
Interventions	Nivolumab plus chemotherapy (fluorouracil plus cisplatin) (N=321): Nivolumab was administered IV at a dose of 240 mg at day one of every cycle (cycle consisting of 2 weeks). Chemotherapy, fluorouracil at a dose of 800 mg pr square meter of body-surface area was administered intravenously at days one through five of every cycle (cycle consisting of 4 weeks) and intravenous cisplatin at a dose of 80 mg per square meter body-surface area on day one. Nivolumab plus ipilimumab (n=325): Nivolumab was administered intravenously at a dose of 3 mg per kg of bodyweight on day one of cycle (cycle of 2 weeks) plus ipilimumab administered intravenously at a dose of 1 mg per kilogram bodyweight on the first day of each cycle (cycle consisting of 6 weeks).

Trial name: CheckMate 648	NCT number: 03143153
	Treatment continued until disease progression, unacceptable toxic effects, withdrawal of consent, or the end of trial. Patients could receive nivolumab plus chemotherapy or nivolumab plus ipilimumab for a maximum of 2 years.
Comparator(s)	Placebo plus chemotherapy (fluorouracil plus cisplatin) (N=324): Chemotherapy, fluorouracil at a dose of 800 mg pr square meter of body-surface area was administered intravenously at days one through five of every cycle (cycle consisting of 4 weeks) and intravenous cisplatin at a dose of 80 mg per square meter body-surface area on day one.
Follow-up time	Nivolumab plus chemotherapy: Median follow-up of 12.1 months (range 01-40.0) Chemotherapy: Median follow-up of 9.5 months (range 0.0-36.2)
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoints were OS and PFS. The secondary endpoints were the percentage of patients with an objective response according to RECIST version 1.1. PD-L1 expression of 1% or greater, DOR, OS in subgroups according to tumour-cell PD-L1 expression and PD-L1 CPS. Adverse events were assessed according to the NCI CTCAE version 4.0. Patient-reported outcomes were evaluated with the Functional Assessment of Cancer Therapy-Oesophageal questionnaire. **Other endpoints:** The study did not include exploratory endpoints.
Method of analysis	PFS was assessed by BICR in all patients including the subgroup with tumour cell PD-L1 expression ≥ 1%. OS and PFS analyses were conducted using two-sided log-rank test, stratified by ECOG performance status (0 vs 1) and the number of organs with metastases (≤ 1 vs. ≥ 2) comparing the treatment groups. The HR of OS and PFS with associated two-sided 100(1-α)% Cis were estimated using a stratified Cox model with treatment arm as the covariate model. Median OS and PFS for each arm were estimated and plotted using Kaplan-Meier product limit method. Median OS, PFS and 95% CIs were constructed based on a log-log transformed CI for the survival function.
Subgroup analyses	Pre-specified subgroup analyses for the primary endpoint, OS: • Overall population

Trial name: CheckMate 648	NCT number: 03143153
	• Patients with tumour-cell PD-L1 expression subgroups (≥ 1%, ≥ 5% and ≥ 10% cutoffs) • Geographic region • ECOG performance-status score • The number of organs with metastases Post-hoc subgroup analyses for the primary endpoint, OS • PD-L1 expression status using combined positive score and tumour cell score.
Other relevant information	N/A

Abbreviations: 1L, First Line; AE, Adverse Events; BICR, Blinded Independent Central Review; CI, Confidence Interval; CPS, Combined Positive Score; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; HR, Hazard Ratio; IV, Intravenous; KG, Kilogram; mg, Milligrams; NA, Not Applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Death Ligand 1; PFS, Progression-Free Survival; RECIST, Response Evaluation Criteria for Solid Tumours

Table 68 Main characteristics of KEYNOTE-590 [53–55]

Trial name: KEYNOTE-590	NCT number: 03189719
Objective	To assess efficacy of pembrolizumab plus chemotherapy versus placebo plus chemotherapy for 1L treatment in advanced oesophageal cancer and Siewert type 1 gastro-oesophageal junction cancer.
Publications – title, author, journal, year	Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590: a randomized, placebo-controlled, phase 3 study. Sun et al. Lancet Oncol. 2021.
Study type and design	Randomized, double-blinded, placebo-controlled phase 3 trial. Enrolled patients had locally advanced unresectable or metastatic adenocarcinoma or squamous cell carcinoma of the oesophagus or advanced or metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction.
Sample size (n)	n=749 (n=548 for OSCC)
Main inclusion criteria	• Has histologically confirmed diagnosis of locally advanced adenocarcinoma or squamous cell carcinoma of the oesophagus. • Adenocarcinoma or squamous cell carcinoma is locally advanced, unresectable or metastatic. • ECOG performance status between 0 and 1.

Trial name: KEYNOTE-590		NCT number: 03189719
	• Has measurable adenocarcinoma or squamous cell carcinoma by RECIST version 1.1, as determined by local site investigator or radiology assessment. • Female participants must have a negative urine or serum pregnancy test within 72 hours prior to randomization and be willing to use adequate contraception. • Male participants must use an adequate method of contraception. • Has adequate organ function	
Main exclusion criteria	• Has locally advanced oesophageal carcinoma that is resectable or potentially curable with radiation therapy. • Has had previous therapy for advanced or metastatic adenocarcinoma or squamous cell cancer of the oesophagus or advanced or metastatic Siewert type 1 adenocarcinoma of the esophagogastric junction. • Has had major surgery, biopsy or significant traumatic injury within 28 days prior to randomization. • Has anticipation of the need for major surgery during course of study treatment. • Has additional malignancy that is progressing and requires active treatment. • Has known metastases active in the central nervous system • Has had an active autoimmune disease that required systemic treatment within the past 2 years. • Has diagnosed immunodeficiency or is receiving chronic systemic steroid or other immunosuppressive treatment, within the last 7 days prior to study treatment. • Has a history of organ or stem cell transplant. • Has a history of non-infectious pneumonitis that required steroid treatment. • Has active infection that requires systemic treatment. • Is pregnant, breastfeeding or expecting to conceive or father children within the duration of the study. • Has received prior therapy with antibodies targeting PD-1, PD-L1 or PD-L2 or with another co-inhibitory T-cell receptor or has previously participated in a pembrolizumab clinical trial. • Has severe hypersensitivity (≥ Grade 3) to any part of the study treatment.	

Trial name: KEYNOTE-590	NCT number: 03189719
	• Has a history of positive hepatitis B or Hepatitis C • Has received live vaccine within 30 days prior to the first dose of study treatment. • As had radiotherapy within 14 days of randomization. • Must have fully recovered from radiotherapy >14 days prior to randomization.
Intervention	Participants in intervention group (n=373) received pembrolizumab 200 mg plus chemotherapy (5-fluorooouracil 800 mg/m^2 on days 1-5 plus cisplatin 80 mg/m^2 on day 1, for a maximum of 6 cycles) once every 3 weeks for up to 35 cycles. All treatments were administered IV. Treatments was continued until disease progression or unacceptable toxicity, illness, physician or patient decision to withdraw, non-compliance, completion of 35 cycles, CR, or discontinuation for administrative reasons. No crossover between groups was allowed. Tumor response was assessed per RECIST version 1.1 by investigators at week 9 and every 9 weeks thereafter.
Comparator(s)	Participants in placebo group (n=376) received saline placebo plus chemotherapy (5-fluorooouracil 800 mg/m^2 on days 1-5 plus cisplatin 80 mg/m^2 on day 1, for a maximum of 6 cycles) once every 3 weeks for up to 35 cycles. All treatments were administered intravenously. Treatments was continued until disease progression or unacceptable toxicity, illness, physician or patient decision to withdraw, non-compliance, completion of 35 cycles, CR, or discontinuation for administrative reasons. No crossover between groups was allowed. Tumour response was assessed per RECIST version 1.1 by investigators at week 9 and every 9 weeks thereafter.
Follow-up time	Median follow-up of 22.6 months (range 19.6-27.1)
Is the study used in the health economic model?	No
Primary, secondary and exploratory endpoints	Pre-specified subgroup analyses for the primary endpoints: • OS in participants with OSCC and participants with OSCC whose tumours were PD-L1 biomarker-positive CPS ≥10 as well as all other participants. • Progression-free survival in participants with OSCC and participants with OSCC whose tumours were PD-L1 biomarker-positive CPS ≥10 as well as all other participants. Subgroup analyses for the secondary endpoints • ORR • DOR

Trial name: KEYNOTE-590	NCT number: 03189719
	• Number of participants with an AE • Number of participants discontinuing study treatment due to AE • Change from baseline to week 18 in EORTC QLQ-C30 Subgroup analyses of secondary endpoints were assessed in participants with OSCC and participants with OSCC whose tumours were PD-L1 biomarker-positive CPS ≥10 as well as all other participants.
Method of analysis	Primary efficacy analyses were performed in the ITT population of all randomized participants. Safety was assessed in all randomized participants who received at least one dose of intervention treatment. The Kaplan-Meier method was used to estimate OS, PFS, and DOR. Log-rank test was performed to assess to determine between-group differences. The stratified Miettinen and Nurminen method was used to determine differences in objective response. Between-group treatment effect (95% CI) across pre-specified subgroups was estimated for primary endpoints in patients with OSCC and PD-L1 CPS ≥10, OSCC, PD-L1 CPS ≥10, and all randomized patients. Estimation of HR and associated 95% CI was assessed using stratified Cox proportional hazards model with Efron's method of tie. A sensitivity analysis of PFS was performed per RECIST version 1.1 by masked independent central review was done to assess the robustness of the PFS by investigator assessment endpoint. Exploratory analysis was performed to examine between-group differences in treatment in participants with by PD-L1 status, and in patients from Asian and non-Asian regions. Post hoc analysis was performed to study between-group treatment differences in PD-L1 biomarker status and histology.
Subgroup analyses	For each pre-specified group of participants (OSCC and PD-L1 CPS ≥10) were divided into subgroups by: • Years of age • ECOG performance status • Geographical region (Asia vs non-Asia) • Histology • PD-L1 status
Other relevant information	N/A

Abbreviations: 1L, First Line; AE, Adverse Events; CI, Confidence Interval; CPS, Combined Positive Score; CR, Complete Response; DOR, Duration of Response; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30; HR, Hazard Ratio; IV, Intravenous; mg, Milligrams; NA, Not Applicable; ORR, Objective Response Rate; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Death Ligand 1; PD-L2, Programmed Death Ligand 2; RECIST, Response Evaluation Criteria for Solid Tumours

Appendix B. Efficacy results per study

Table 69 Results of RATIONALE-306 (Data cut-off: February 28, 2022)

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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 OS	Tislelizumab + chemo-therapy	326	17.2 (15.8–20.1) months	6.6	NA	NA	[redacted]	[redacted]	[redacted]	The median overall survival is based on the Kaplan-Meier estimator. The HR is based on a Cox regression model including treatment as covariate, and pooled geographic region, prior definitive therapy, and Investigator chemotherapy choice as strata.	[51,75]
	Placebo + chemotherapy	323	10.6 (9.3–12.1) months								
Median OS	Tislelizumab + chemo-therapy	116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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**		
TAP PD-L1 ≥ 10%	Placebo + chemotherapy	107	[redacted]								[51,75]
Median OS TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene
	Placebo + chemotherapy	[redacted]	[redacted]								[51,75]
Median PFS	Tislelizumab + chemo-therapy	326	7.3 (6.9– 8.3) months	1.7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[51,75]
	Placebo + chemotherapy	323	5.6 (4.9–6.0) months								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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 PFS TAP PD-L1 ≥ 10%	Tislelizumab + chemo-therapy										[51,75]
	Placebo + chemotherapy										
Median PFS TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy										Data on file from Beigene [64]
	Placebo + chemotherapy										

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
ORR	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
ORR TAP PD-L1 ≥ 10%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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**		
ORR TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								
Median DOR	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [50,64]
	Placebo + chemotherapy	[redacted]	[redacted]								
Median DOR	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
TAP PD-L1 ≥ 10%	Placebo + chemotherapy	[redacted]	[redacted]								
Median DOR TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								
Number and proportion of patients (%) with ≥ 1 CTCAE grade ≥ 3 events	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
Patients who discontinue regardless of reason	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
Number of AEs	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								
Number and proportion of patients with ≥1 adverse events, n (%)	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								
Number of SAEs*, n	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
	Placebo + chemotherapy	321	[redacted]								
Number and proportion of patients with ≥ 1 SAEs, n (%)	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								
Number of CTCAE grade ≥ 3 events, n	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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**		
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								
Number of ARs, n	Tislelizumab + chemo-therapy	324	NA	NA	NA	NA	NA	NA	NA		[50,51]
	Placebo + chemotherapy	321	NA								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
Number and proportion of patients with ≥ 1 ARs, n (%)	Tislelizumab + chemo-therapy	324	NA	NA	NA	NA	NA	NA	NA		[50,51]
	Placebo + chemotherapy	321	NA								
Number and proportion of patients who had a dose modification due to TEAEs, n (%)	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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		
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	Tislelizumab + chemo-therapy	324	286 (88.3)	-20	NA	NA	NA	NA	NA		[50,51]
	Placebo + chemotherapy	321	306 (95.3)								
Number and proportion of patients who discontinue treatment due to	Tislelizumab + chemo-therapy	324	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	321	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: February 28, 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**		
adverse events, n (%)											
EQ-VAS Change of Mean SD from Baseline to Cycle 8. (36 months)	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Abbreviations: AEs, Adverse Events; CI, Confidence Interval; DOR, Duration of Response; EQ-VAS, EuroQol Visual Analogue Scale; HR, Hazard Ratio; NA, Not Applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Objective Response Rate; OS, Overall Survival; PD-L1, Programmed Death Ligand 1; PFS, Progression-Free Survival; SAEs, Serious Adverse Events; SD, Standard Deviation; TAP, Tumour Area Positivity; TEAE, Treatment Emergent Adverse Events

Table 70 Results of RATIONALE-306 (Data cut-off: November 24, 2023)

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)												
				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	Tislelizumab + chemo-therapy	326	17.2 (15.8–20.1) months	6.6	NA	NA	[redacted]	[redacted]	[redacted]	The median overall survival is based on the Kaplan-Meier estimator. The HR is based on a Cox regression model including treatment as covariate, and pooled geographic region, prior definitive therapy, and Investigator chemotherapy choice as strata.	Data on file from Beigene [64]
	Placebo + chemotherapy	323	10.6 (9.3–12.0) months								
Median overall survival TAP PD-L1 ≥ 10%	Tislelizumab + chemo-therapy	116	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	107	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)											
				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	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
TAP PD-L1 ≥ 5%	Placebo + chemotherapy	[redacted]	[redacted]								
Median Progression-free Survival	Tislelizumab + chemo-therapy	326	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	323	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)												
				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 Progression-free Survival TAP PD-L1 ≥ 10%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								
Median Progression-free Survival TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)											
				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		
Objective response rate	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								
Objective Response Rate TAP PD-L1 ≥ 10%	Tislelizumab + chemo-therapy	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
	Placebo + chemotherapy	[redacted]	[redacted]								

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)												
				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**		
Objective Response Rate TAP PD-L1 ≥ 5%	Tislelizumab + chemo-therapy										Data on file from Beigene [64]
	Placebo + chemotherapy										
Median duration of response	Tislelizumab + chemo-therapy	326									Data on file from Beigene [64]
	Placebo + chemotherapy	323									

Results of RATIONALE-306 (NCT number: 03783442) (Data cut-off: November 24, 2023)												
				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 duration of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
TAP PD-L1 ≥ 10%	[redacted]	[redacted]	[redacted]								
Median duration of response	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Data on file from Beigene [64]
TAP PD-L1 ≥ 5%	[redacted]	[redacted]	[redacted]								

Abbreviations: AEs, Adverse Events; CI, Confidence Interval; DOR, Duration of Response; EQ-VAS, EuroQol Visual Analogue Scale; HR, Hazard Ratio; NA, Not Applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Objective Response Rate; OS, Overall Survival; PD-L1, Programmed Death Ligand 1; PFS, Progression-Free Survival; SAEs, Serious Adverse Events; SD, Standard Deviation; TAP, Tumour Area Positivity; TEAE, Treatment Emergent Adverse Events

Table 71 Results of CheckMate 648 (Data cut-off: January 18, 2021)

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off: January 18, 2021)											
				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	CI	P value		
Median overall survival TPS PD-L1 ≥1%	Nivolumab + chemotherapy	158	15.4 (11.9-19.5) months	6.3	NA	NA	HR: 0.54	99.5% CI 0.37-0.80	<0.001	OS analysis was conducted using two-sided log-rank test, stratified by ECOG performance status (0 vs 1) and the number of organs with metastases (≤ 1 vs. ≥ 2) comparing the treatment groups. The HR of OS with associated two-sided 100(1-α)% CIs were estimated using a stratified Cox model with treatment arm as the covariate model. Median OS for each arm were estimated and plotted using Kaplan-Meier product limit method. Median OS 95% CIs were constructed based on a log-log transformed CI for the survival function.	[43,57]
	Chemotherapy alone	157	9.1 (7.7-10.0) months								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off: January 18, 2021)											
				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	CI	P value		
Median OS Overall Population	Nivolumab + chemotherapy	321	13.2 (11.1-15.7) months	2.5	NA	NA	HR: 0.74	99.1% CI 0.58-0.96	0.002	Same as above	[57]
	Chemotherapy alone	324	10.7 (9.4-11.9) months								
Median PFS TPS PD-L1 ≥1%	Nivolumab + chemo-therapy	158	6.9 (5.7-8.3) months	2.5	NA	NA	HR: 0.65	98.5% CI 0.46-0.92	0.002	The median PFS is based on the Kaplan-Meier estimator. The HR is based on a Cox regression model including treatment as covariate, and pooled geographic region, prior definitive therapy, and Investigator chemotherapy choice as strata.	
	Chemotherapy alone	157	4.4 (2.9-5.8) months								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off: January 18, 2021)												
				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	CI	P value		
Median PFS Overall Population	Nivolumab + chemo-therapy	321	5.8 (5.6-7.0) months	0.2	NA	NA	HR: 0.81	98.5% CI 0.64-1.04	0.04	Same as above	[57]
	Chemotherapy alone	324	5.6 (4.3-5.9) months								
ORR TPS PD-L1 ≥1%	Nivolumab + chemo-therapy	158	53 (45 –61) %	33	NA	NA	NA	NA	NA	The percentages of patients with an objective response, and the corresponding two-sided 95% CIs, were calculated with the use of the Clopper–Pearson method	[57]
	Chemotherapy alone	157	20 (14-27) %								
ORR	Nivolumab + chemo-therapy	321	47 (42-53) %	20	NA	NA	NA	NA	NA	Same as above	[57]

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off: January 18, 2021)												
				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	CI	P value		
Overall Population	Chemotherapy alone	324	27 (22-32) %								
Median DOR TPS PD-L1 ≥1%	Nivolumab + chemo-therapy	158	8.4 (6.9-12.4) months	2.7	NA	NA	NA	NA	NA	NA	[57]
	Chemotherapy alone	157	5.7 (4.4–8.7) months								
Median DOR Overall Population	Chemotherapy alone	321	8.2 (6.9-9.7) months	1.1	NA	NA	NA	NA	NA	NA	[57]
	Chemotherapy alone	324	7.1 (5.7-8.2) months								
TRAEs ≥Grade 3	Nivolumab + chemo-therapy	310	147 events	39	NA	NA	NA	NA	NA	TRAEs were reported according to the NCI CTCAE version 4.0 per investigator assessment.	[56,57]

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off: January 18, 2021)												
				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	CI	P value		
	Chemotherapy alone	304	108 events							TRAEs leading to discontinuation of any treatment were recorded in a cumulative manner throughout the duration of treatment.	
TRAEs leading to death	Nivolumab + chemo-therapy	310	5 events	1	NA	NA	NA	NA	NA	Same as TRAE ≥Grade 3	[56,57]
	Chemotherapy alone	304	6 events								
TRAEs leading to discontinuation	Nivolumab + chemo-therapy	310	106 events	47	NA	NA	NA	NA	NA	Same as TRAE ≥Grade 3	[56,57]
	Chemotherapy alone	304	59 events								

Abbreviations: CI, Confidence Interval; DOR, Duration of Response; HR, Hazard Ratio; NA, Not Applicable; NR, Not Reached; ORR, Objective Response Rate; OS, Overall Survival; PD-L1, Programmed Death Ligand 1; TPS, Tumour Proportion Score; TEAE, Treatment-Related Adverse Events

Table 72 Results of CheckMate 648 (Data cut-off May 17, 2022)

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off May 17, 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 OS TPS PD-L1 ≥1%	Nivolumab + chemotherapy	158	15.0 (11.9-18.6) months	5.9	NA	NA	HR: 0.59	0.46-0.76	NA	The Kaplan–Meier method was used to estimate the median overall survival and progression-free survival, and the corresponding CIs were calculated using a log–log transformation method	[67]
	Chemotherapy alone	157	9.1 (7.7-10.0) months								
Median OS Overall population	Nivolumab + chemo-therapy	321	12.8 (11.1–15.7) months	2.1	NA	NA	HR; 0.78	0.65-0.93	NA	Same as above	[67]
	Chemotherapy alone	324	10.7 (9.4–12.1) months								
Median PFS	Nivolumab + chemo-therapy	158	6.8 (5.7-8.3) months	NA	NA	NA	HR: 0.67	0.51–0.89	N/A	Same as above	[67]

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off May 17, 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		
TPS PD-L1 ≥1%	Chemotherapy alone	157	4.4 (2.9-5.8) months								
Median PFS Overall population	Nivolumab + chemo-therapy	321	5.8 (5.5– 7.0) months	0.2	NA	NA	HR: 0.83	0.68-1.00	NA	Same as above	[67]
	Chemotherapy alone	324	5.6 (4.3–5.9) months								
ORR TPS PD-L1 ≥ 1%	Nivolumab + chemo-therapy	158	53 (44–61) %	33	NA	NA	NA	NA	NA	The ORR and the corresponding two-sided 95% Cis were calculated using the Clopper-Pearson method and the estimates of differences between treatment groups were calculated using the Cochran-Mantel-Haenszel test,	[67]
	Chemotherapy alone	157	20 (14-27) %								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off May 17, 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**		
										with adjustment for stratification factors	
ORR Overall population	Nivolumab + chemo-therapy	321	47 (42-53) %	20	NA	NA	NA	NA	NA	Same as above	
	Chemotherapy alone	324	27 (22-32) %								
Median DOR TPS PD-L1 ≥ 1%	Nivolumab + chemo-therapy	158	8.4 (6.9-12.4) months	2.7	NA	NA	NA	NA	NA	NA	[67]
	Chemotherapy alone	157	5.7 (4.4–8.7) months								
Median DOR	Nivolumab + chemo-therapy	321	8.2 (6.9-9.7) months	1.1	NA	NA	NA	NA	NA	NA	[67]

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off May 17, 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**		
Overall population	Chemotherapy alone	324	7.1 (5.7-8.2) months								
TRAEs ≥Grade 3 Overall population	Nivolumab + chemo-therapy	310	151 events	41	NA	NA	NA	NA	NA	TRAEs were reported according to the NCI CTCAE version 4.0 per investigator assessment. TRAEs leading to discontinuation of any treatment were recorded in a cumulative manner throughout the duration of treatment.	[67]
	Chemotherapy alone	304	110 events								
TRAEs leading to death Overall population	Nivolumab + chemo-therapy	310	5 events	0	NA	NA	NA	NA	NA	Same as TRAE ≥Grade 3	[67]
	Chemotherapy alone	304	5 events								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off May 17, 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**		
TRAEs leading to discontinuation	Nivolumab + chemo-therapy	310	107 events	44	NA	NA	NA	NA	NA	Same as TRAE ≥Grade 3	[67]
Overall population	Chemotherapy alone	304	63 events								

Abbreviations: CI, Confidence Interval; DOR, Duration of Response; HR, Hazard Ratio; NA, Not Applicable; NR, Not Reached; ORR, Objective Response Rate; OS, Overall Survival; PD-L1, Programmed Death Ligand 1; TPS, Tumour Proportion Score; TRAE, Treatment-Related Adverse Events;

Table 73 Results of CheckMate 648 (NCT number: 03143153) (Data cut-off 45-month follow-up)

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off 45-month follow-up)											
				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 OS PD-L1 ≥1%	Nivolumab + chemotherapy	158	15.0 (11.9-18.7) months	5.9	NA	NA	HR: 0.60	0.47–0.77	NA	NA	[63]
	Chemotherapy alone	157	9.1 (7.7-10.0) months								
Median OS Overall population	Nivolumab + chemotherapy	321	13.2 (11.1-15.7) months	2.5	NA	NA	HR: 0.77	0.65–0.92	NA	NA	[63]
	Chemotherapy alone	324	10.7 (9.4-12.1) months								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off 45-month follow-up)											
				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 PFS PD-L1 ≥1%	Nivolumab + chemo-therapy	158	6.8 (5.7-8.3) months	2.4	NA	NA	HR: 0.67	0.51–0.88	NA	NA	[63]
	Chemotherapy alone	157	4.4 (2.9-5.8) months								
Median PFS Overall population	Nivolumab + chemotherapy	321	5.8 (5.5-7.0) months	0.2	NA	NA	HR: 0.82	0.68–1.00	NA	NA	[63]
	Chemotherapy alone	324	5.6 (4.3-5.9) months								
ORR	Nivolumab + chemo-therapy	158	53%	33	NA	NA	NA	NA	NA	NA	[63]

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off 45-month follow-up)												
				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**		
PD-L1 ≥ 1%	Chemotherapy alone	157	20%								
ORR Overall population	Nivolumab + chemo-therapy	321	47%	20	NA	NA	NA	NA	NA	NA	[63]
	Chemotherapy alone	324	27%								
Median DOR PD-L1 ≥ 1%	Nivolumab + chemo-therapy	158	8.4 (6.9-12.4) months	2.7	NA	NA	NA	NA	NA	NA	[63]
	Chemotherapy alone	157	5.7 (4.4–8.7) months								

Results of CheckMate 648 (NCT number: 03143153) (Data cut-off 45-month follow-up)												
				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 DOR Overall population	Nivolumab + chemo-therapy	321	8.2 (6.9-9.7) months	1.1	NA	NA	NA	NA	NA	NA	[63]
	Chemotherapy alone	324	7.1 (5.7–8.2) months								

Abbreviations: CI, Confidence Interval; DOR, Duration of Response; NA, Not Applicable; ORR, Objective Response Rate; OS, Overall Survival; PFS, Progression-Free Survival

Table 74 Results of KEYNOTE-590 (Data cut-off date July 2, 2020)

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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 OS OSSC PD-L1 CPS ≥10	Pembrolizumab + chemotherapy	143	13.9 (11.1-17.7) months	5.1	NA	NA	HR: 0.57	0.43–0.75	<0.0001	Kaplan-Meier method was used to estimate overall survival and, progression free survival and duration of response. Between-group differences in OS, and PFS were assessed using stratified log-rank test.	[54]
	Placebo + chemotherapy	143	8.8 (7.8-10.5) months								
Median OS OSCC	Pembrolizumab + chemotherapy	274	12.6 (10.2-14.3) months	2.8	NA	NA	HR: 0.72	0.60-0.88	0.0006	Same as above	[54]
	Placebo + chemotherapy	274	9.8 (8.6-11.1) months								

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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 PFS OSSC PD-L1 CPS ≥10	Pembrolizumab + chemotherapy	143	7.3 (6.2-8.2) months	1.9	NA	NA	HR: 0.53	0.40-0.69	NA	Same as above	[53]
	Placebo + chemotherapy	143	5.4 (4.2-6.0) months								
Median PFS OSCC	Pembrolizumab + chemo-therapy	274	6.3 (6.2-6.9) months	0.5	NA	NA	HR: 0.65	0.54–0.78	0.0001	Same as above	[54]
	Placebo + chemotherapy	274	5.8 (5.0-6.1) months								
ORR	Pembrolizumab +	143	51.0 (42.6-59.5) %	23	11.6-33.4	<0,0001	NA	NA	NA	Differences in objective response rate were assessed	[55]

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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**		
OSSC PD-L1 CPS ≥10 (Up to 34 months)	chemo-therapy									with the stratified Miettinen and Nurminen method.	
	Placebo + chemotherapy	143	28.0 (20.8-36.1) %								
ORR OSCC (Up to 34 months)	Pembrolizumab + chemo-therapy	274	43.8 (37.8-49.9) %	12.8	4.7-20.7	0,0009	NA	NA	NA	Same as above	[55]
	Placebo + chemotherapy	274	31.0 (25.6-36.9) %								
AEs of ≥Grade 3	Pembrolizumab + chemo-therapy	370	318 events (86%)	10	NA	NA	NA	NA	NA	An AE was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and	[53,54]

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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**		
	Placebo + chemotherapy	370	308 events (83%)							which did not necessarily have to have a causal relationship with this treatment. AEs were evaluated and graded by qualified physician according to NCI CTCAE version 4.0. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs.	
TRAEs	Pembrolizumab + chemo-therapy	370	364 events (98%)	4	NA	NA	NA	NA	NA	AEs were evaluated and graded by qualified physician according to NCI CTCAE version 4.0. Safety data in this study was conducted from All Subjects as Treated population, who had received one dose of study treatment. Safety and tolerability were assessed by clinical review of all relevant parameters including AEs.	[53,54]
	Placebo + chemotherapy	370	360 events (97%)								

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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		
TRAEs ≥Grade 3	Pembrolizumab + chemo-therapy	370	266 events (72%)	16	NA	NA	NA	NA	NA	Same as above	[53,54]
	Placebo + chemotherapy	370	250 events (68%)								
AEs leading to discontinuation	Pembrolizumab + chemo-therapy	370	90 events (24%)	16	NA	NA	NA	NA	NA	Same as adverse events ≥Grade 3	[53,54]
	Placebo + chemotherapy	370	74 events (20%)								
	Pembrolizumab +	370	28 events (8%)	10	NA	NA	NA	NA	NA	NA	[53,54]

Results of KEYNOTE-590 (NCT number: 03189719) (Data cut-off date July 2, 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**		
AEs leading to death	chemo-therapy										
	Placebo + chemotherapy	370	38 events (10%)								

Abbreviations: AE, Adverse Events; CPS, Combined Positive Score; HR, Hazard Ratio; NA, Not Applicable; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, Objective Response Rate; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Death Ligand 1; PFS, Progression-Free Survival; TRAE, Treatment-Related Adverse Events

Table 75. Results of KEYNOTE-590 (5-year follow up data)

Results of KEYNOTE-590 (NCT number: 03189719) – 5-year follow up data												
				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 OS OSSC PD-L1 CPS ≥10	Pembrolizumab + chemotherapy	143	NA	NA	NA	NA	HR: 0.60	0.46–0.76	NA	Kaplan-Meier estimate.	[66]
	Placebo + chemotherapy	143	NA								
Median OS OSCC	Pembrolizumab + chemotherapy	274	NA	NA	NA	NA	HR: 0.71	0.60-0.85	NA	Same as above	[66]
	Placebo + chemotherapy	274	NA								

Results of KEYNOTE-590 (NCT number: 03189719) – 5-year follow up data												
				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 OS, 5-year rate, OSSC PD-L1 CPS ≥10	Pembrolizumab + chemotherapy	143	13.8%	10.1	NA	NA	NA	NA	NA	Same as above	[66]
	Placebo + chemotherapy	143	3.7%								
Median OS, 5-year rate, OSSC	Pembrolizumab + chemotherapy	274	11.8%	8.4	NA	NA	NA	NA	NA	Same as above	[66]
	Placebo + chemotherapy	274	3.4%								
	Pembrolizumab +	143	NA	NA	NA	NA	HR: 0.53	0.41-0.69	NA	Same as above	[66]

Results of KEYNOTE-590 (NCT number: 03189719) – 5-year follow up data												
				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 PFS OSSC PD-L1 CPS ≥10	chemotherapy Placebo + chemotherapy	143	NA								
Median PFS OSCC	Pembrolizumab + chemo-therapy Placebo + chemotherapy	274 274	NA NA	NA	NA	NA	HR: 0.65	0.54–0.78	NA	Same as above	[66]
ORR	Pembrolizumab +	143	51.0%	23	NA	NA	NA	NA	NA	Same as above	[66]

Results of KEYNOTE-590 (NCT number: 03189719) – 5-year follow up data												
				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**		
OSSC PD-L1 CPS ≥10	chemo-therapy										
	Placebo + chemotherapy	143	28.0%								
ORR OSCC	Pembrolizumab + chemo-therapy	274	43.8 %	12.8	NA	NA	NA	NA	NA	Same as above	[66]
	Placebo + chemotherapy	274	31.0%								

Abbreviations: CPS, Combined Positive Score; HR, Hazard Ratio; NA, Not Applicable; ORR, Objective Response Rate; OS, Overall Survival; OSCC, Oesophageal Squamous Cell Carcinoma; PD-L1, Programmed Death Ligand 1; PFS, Progression-Free Survival

Appendix C. Comparative analysis of efficacy

A network meta-analysis (NMA) was conducted to compare tislelizumab plus chemotherapy to pembrolizumab plus chemotherapy, and nivolumab plus chemotherapy.

For the analyses, dosages for these were obtained from their respective pivotal phase 3 RCTs (i.e., RATIONALE-306 [tislelizumab], KEYNOTE-590 [pembrolizumab], and CheckMate 648 [nivolumab]).

Feasibility assessment was performed for the trials which showed that although some differences in trial characteristics, patient eligibility, patient characteristics, and outcome definitions were noted. Ultimately, these differences were considered minor, and the trials were considered sufficient similar to derive reasonable estimates of comparative efficacy via an NMA.

The choice of outcomes for the NMAs was informed by the RCTs and NMA feasibility assessment, which showed the following outcomes were sufficient similar to derive reasonable estimates of comparative efficacy. The four outcomes that were assessed in the NMAs included:

- OS (survival, HR)
- PFS (survival, HR)
- ORR (binary, OR)
- Grade ≥3 TRAEs (binary, OR) [64]

NMAs were conducted for each outcome of interest using a [redacted] framework as described in the NICE Evidence Synthesis Decision Support Unit (DSU) Technical Support Document (TSD) series [76].

All analyses were performed using [redacted], and were based on [redacted]. Point estimates and [redacted] credible intervals (CrIs) were modelled for outcomes using [redacted] methods. The probability that each treatment was the most efficacious regimen (P-Best), the second best, the third best, and so on, were assessed. The Surface area Under the

Cumulative Ranking curve (SUCRA) values, reported as percentages, were calculated to reflect the relative probability of an intervention being among the best options [77].

A normal model with [redacted] was used with vague priors for treatment effects, and an [redacted] [78,79]. For time-to-event outcomes (OS, PFS), [redacted] for these outcomes. [redacted] and its [redacted] was derived for the analysis by taking the [redacted] and dividing the [redacted] For response and safety outcomes (ORR and grade ≥3 TRAEs), the [redacted]. Studies reporting only number of responders/events or percentage of response/events had [redacted] [64].

Model fit was based on the [redacted] With only a single study informing each [redacted] [80,81]. Therefore, [redacted] was the selected model for the analyses.

PH assumption was assessed for OS and PFS see section 7.1.2.

To form connected network diagrams, all chemotherapy backbone treatments were assumed to be comparable and were therefore pooled together into a single node. As such, each node represents a different treatment in addition to a chemotherapy backbone treatment, regardless of the chemotherapy regimen assessed in the trial (i.e., tislelizumab plus chemotherapy, nivolumab plus chemotherapy, etc.) [64].

ITT analysis:
This was of a base case analysis, which used the intent-to-treat (ITT) populations for each trial, however, due to relevance only the OSCC population from KEYNOTE-590 was included.

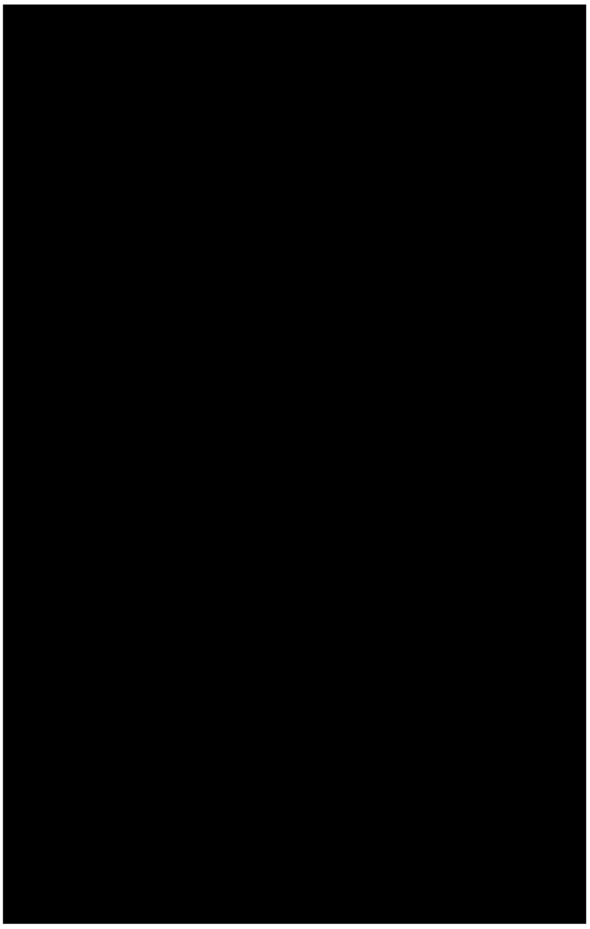
The number of patients included in the ITT population OS, PFS, and ORR analyses by treatment arm us outlined in Table 76 [64].

Table 76 Number of patients included in the OS, PFS and ORR network, by treatment arm

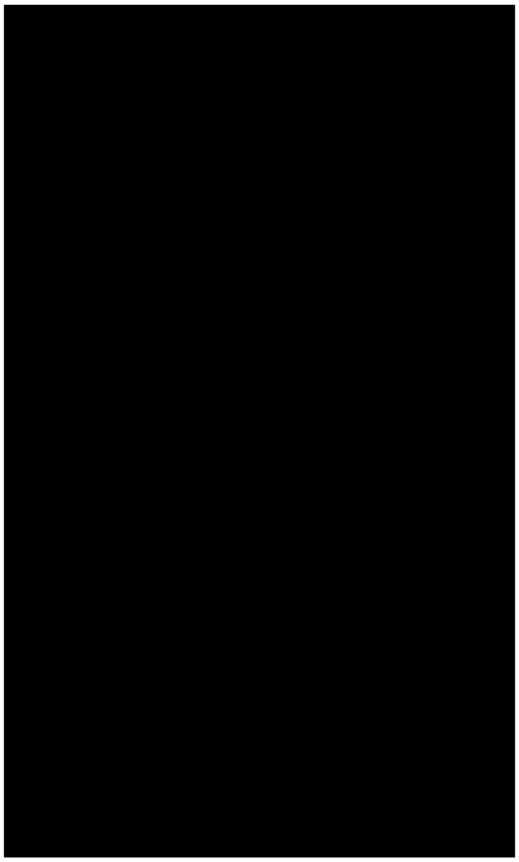
Treatment Arm	Number of Patients
TIS + CT	326
PEM + CT	274
NIV + CT	321

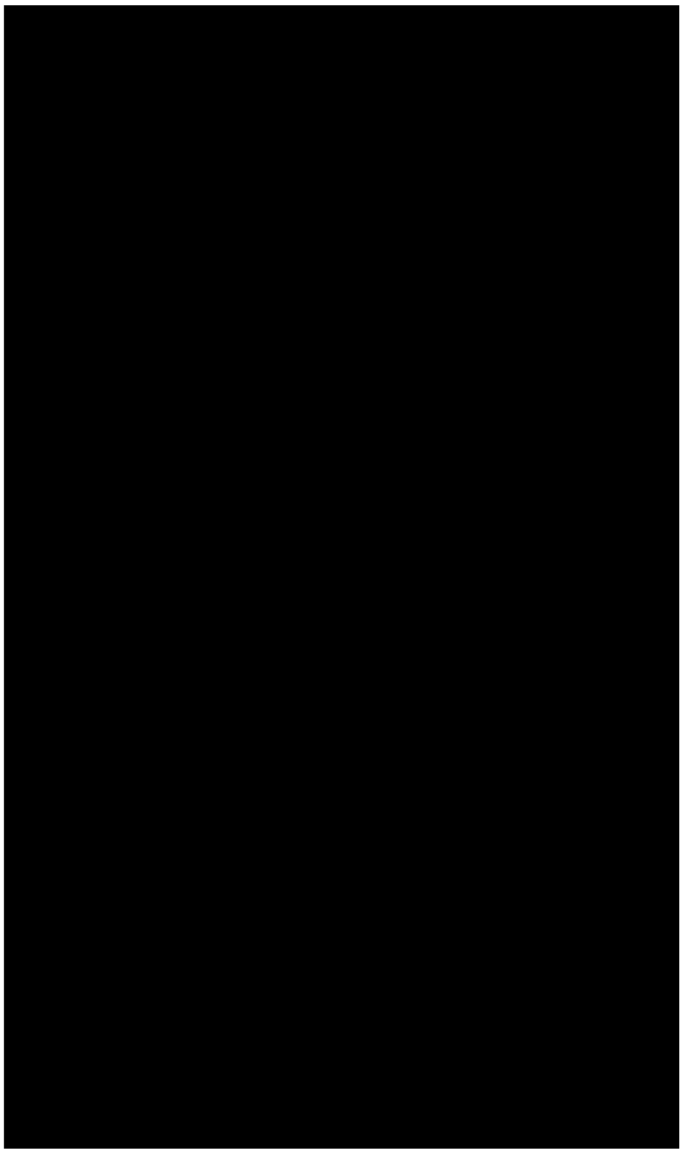
Abbreviations: CT, chemotherapy; NIV, nivolumab; PEM, pembrolizumab; PFS, progression-free survival; TIS, tislelizumab, OS, overall survival; ORR, objective response rate **[64]**.

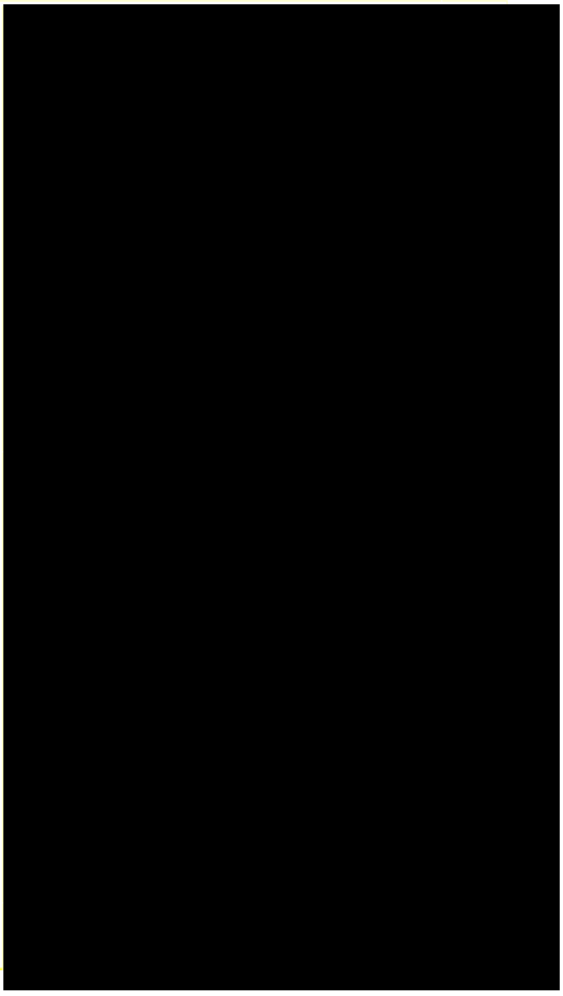
For the results of the base case analysis see section 7.1.3.



Abbreviations: TIS+CT, Tislelizumab plus Chemotherapy; PEM+CT, Pembrolizumab plus Chemotherapy; NIV+CT, Nivolumab plus Chemotherapy







PD-L1 subgroup analysis:
To support the indication for tislelizumab analyses were conducted for PD-L1 positive subgroups from each trial, using the following cutoff:

- PD-L1 10% (TAP 10%, CPS 10, or TPS 1%)

Based on studies evaluating the concordance of TAP and CPS in patients with 1L OSCC and that of TAP, CPS, and TPS in patients with second-line (2L) OSCC, an assumption was made that TAP 10% and CPS 10 were equivalent, and that TPS 1% was equivalent to TAP 10% and CPS 10 [69,71].

Where more than one measure of PD-L1 was provided by a trial, the order of preference for selecting a measure for analysis was [redacted], based on TAP as the primary PD-L1 measurement for the RATIONALE-306 trial. To test the assumption of equivalence between TAP 10% and CPS 10, a sensitivity analysis was run for OS using CPS data from RATIONALE-306.

The results from the subgroup analysis showed no statistically significant differences between active treatments for OS, PFS, and ORR [64].

Table 77 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] (N/A)

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
-	-	-	-	-	-	-	-	-	-

Appendix D. Extrapolation (N/A)

D.1 Extrapolation of [effect measure 1] (N/A)

D.1.1 Data input (N/A)

D.1.2 Model (N/A)

D.1.3 Proportional hazards (N/A)

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

D.1.5 Evaluation of visual fit (N/A)

D.1.6 Evaluation of hazard functions (N/A)

D.1.7 Validation and discussion of extrapolated curves (N/A)

D.1.8 Adjustment of background mortality (N/A)

D.1.9 Adjustment for treatment switching/cross-over (N/A)

D.1.10 Waning effect (N/A)

D.1.11 Cure-point (N/A)

D.2 Extrapolation of [effect measure 2] (N/A)

Appendix E. Serious adverse events

Table 78 Serious TEAEs with an incidence of ≥1%, RATIONALE-306

PT	Tislelizumab + Chemotherapy (N = 324) n (%)	Placebo + Chemotherapy (N = 321) n (%)
[redacted]		

PT	Tislelizumab + Chemotherapy (N = 324) n (%)	Placebo + Chemotherapy (N = 321) n (%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Data cut-off: 28FEB2022. [redacted]
Note: Percentages were based on N as denominator. Patients with multiple events for a given PT were counted only once at the worst severity for the PT. PTs filtered by incidence ≥1% in either arm. AE terms were coded using MedDRA version 24.0. AEs are sorted by descending frequency of PT in the T+C column.
Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Drug Regulatory Affairs; PT, preferred term; T+C, tislelizumab plus chemotherapy; TEAE, treatment-emergent adverse event.

Source: [64]

Table 79 Serious adverse event with an incidence of ≥1%, CheckMate 648 [58]

PT	Nivolumab + Chemotherapy (N = 310) n (%)	Chemotherapy (N = 304) n (%)
Patients with ≥1 serious adverse event	217 (70.0)	172 (56.58)
Anaemia	5 (1.61)	6 (1.97)
Febrile neutropenia	6 (1.94)	5 (1.64)
Colitis	5 (1.61)	0 (0.0)
Diarrhoea	6 (1.94)	3 (0.99)
Dysphagia	20 (6.45)	16 (5.26)
Nausea	4 (1.29)	5 (1.64)
Oesophageal obstruction	3 (0.97)	5 (1.64)
Oesophageal stenosis	9 (2.90)	13 (4.28)

PT	Nivolumab + Chemotherapy (N = 310) n (%)	Chemotherapy (N = 304) n (%)
Stomatitis	5 (1.61)	0 (0.0)
Vomiting	4 (1.29)	12 (3.95)
Pyrexia	7 (2.26)	7 (2.30)
Pneumonia	33 (10.65)	20 (6.58)
Neutrophil count decreased	4 (1.29)	1 (0.33)
Decreased appetite	4 (1.29)	7 (2.30)
Dehydration	4 (1.29)	6 (1.97)
Hypercalcaemia	4 (1.29)	4 (1.32)
Hypokalaemia	4 (1.29)	2 (0.66)
Hyponatraemia	4 (1.29)	4 (1.32)
Malignant neoplasm progression	56 (18.06)	62 (20.39)
Tumour pain	0 (0.0)	4 (1.32)
Acute kidney injury	9 (2.90)	4 (1.32)
Pleural effusion	5 (1.61)	1 (0.33)
Pneumonia aspiration	5 (1.61)	8 (2.63)
Pneumonitis	6 (1.94)	1 (0.33)
Respiratory failure	5 (1.61)	1 (0.33)

For a complete list of serious adverse events visit clinicaltrials.gov. **[58]**

Table 80 Serious adverse event with an incidence of ≥1%, KEYNOTE-590 [55]

PT	Pembrolizumab + Chemotherapy (N = 370) n (%)	Placebo + Chemotherapy (N = 370) n (%)
Patients with ≥1 serious adverse event	207 (55.95)	204 (55.14)

PT	Pembrolizumab + Chemotherapy (N = 370) n (%)	Placebo + Chemotherapy (N = 370) n (%)
Anaemia	3 (0.81)	10 (2.70)
Febrile neutropenia	9 (2.43)	13 (3.51)
Neutropenia	5 (1.35)	3 (0.81)
Colitis	4 (1.08)	1 (0.27)
Diarrhoea	7 (1.89)	5 (1.35)
Dysphagia	17 (4.59)	13 (3.51)
Nausea	5 (1.35)	3 (0.81)
Oesophageal obstruction	5 (1.35)	13 (4.28)
Oesophageal stenosis	1 (0.27)	7 (1.08)
Stomatitis	4 (1.08)	5 (1.35)
Upper gastrointestinal haemorrhage	4 (1.08)	6 (1.62)
Vomiting	9 (2.43)	6 (1.62)
Death	2 (0.54)	7 (1.89)
Fatigue	3 (0.81)	6 (1.62)
Mucosal inflammation	1 (0.27)	4 (1.08)
Pyrexia	5 (1.35)	1 (0.27)
Pneumonia	38 (10.27)	32 (8.65)
Pneumonia aspiration	11 (2.97)	7 (1.89)
Sepsis	1 (0.27)	5 (1.35)
Neutrophil count decreased	4 (1.08)	6 (1.62)
Platelet count decreased	5 (1.35)	10 (2.70)
White blood cell count decreased	2 (0.54)	4 (1.08)
Decreased appetite	6 (1.62)	6 (1.62)

PT	Pembrolizumab + Chemotherapy (N = 370) n (%)	Placebo + Chemotherapy (N = 370) n (%)
Dehydration	6 (1.62)	8 (2.16)
Hypokalaemia	7 (1.89)	6 (1.62)
Hyponatraemia	7 (1.89)	6 (1.62)
Acute kidney injury	11 (2.97)	6 (1.62)
Pneumonitis	12 (3.24)	0 (0.0)
Pulmonary embolism	7 (1.89)	7 (1.89)

For a complete list of serious adverse events visit clinicaltrials.gov. [55]

Appendix F. Health-related quality of life (N/A)

Appendix G. Probabilistic sensitivity analyses (N/A)

Table 81 Overview of parameters in the PSA (N/A)

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
-				

Appendix H. Literature searches for the clinical assessment

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

Comprehensive global clinical systematic literature search (June 23, 2023)

The objective of this was to conduct a SLR of clinical evidence to summarize the efficacy and safety data from RCTs for immuno-oncology regimens in first-line, unresectable, locally advanced, or metastatic OSCC.

Searches for RCTs were conducted with multiple databases using the Ovid interface. Using the Ovid® search interface, the following electronic databases were searched: Embase, Ovid MEDLINE® (including Epub Ahead of Print and In-Process & Other Non-Indexed Citations), Ovid MEDLINE® Daily, Cochrane Central Register of Controlled Trials, and the Cochrane Database of Systematic Reviews as per DMC guidelines. These searches were performed on June 23, 2023 [64].

Table 82 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 June 22, 2023	23.06.2023
Ovid MEDLINE® (Daily) (including, Epub Ahead of Print and In-Process & Other Non-Indexed Citations)	Ovid - Ovid MEDLINE®	1946 to June 22, 2023	23.06.2023
Cochrane Central Register of Controlled Trials	www.cochranelibrary.com/central	N/R	23.06.2023
Cochrane Database of Systematic Reviews	www.cochranelibrary.com/cdsr/reviews	2005 – June 20, 2023	23.06.2023

Abbreviations: N/R, not reported.

Table 83 Registers included in the literature search

Source name	Location/source	Search strategy	Date of search
Australian New Zealand Clinical Trials Registry (ANZCTR)	https://www.anzctr.org.au/	N/R	23.06.2023
ClinicalTrials.gov	https://www.clinicaltrials.gov/	N/R	23.06.2023
International Clinical Trials Registry Platform (ICTRP)	https://www.who.int/clinical-trials-registry-platform	N/R	23.06.2023

Abbreviations: N/R, not reported.

Table 84 Conference material included in the literature search (N/A) – see section H.2

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

Additional SLR (October 17, 2024)

The additional SLR aimed to identify new literature published from July 23, 2023, to October 17, 2024, concerning clinical evidence of efficacy and safety of immuno-oncology regimens for first-line treatment of unresectable, locally advanced, or metastatic OSCC in adult patients. The search was conducted in Embase on October 17, 2024 [64].

Table 85 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	www.embase.com	July 23, 2023 to October 17, 2024	17.10.2024

H.1.1 Search strategies

Comprehensive global clinical systematic literature search (June 23, 2023)

The search was limited to include RCTs, SLRs, and meta-analyses only. Furthermore, the search was limited to humans and adults aged 18 years and older. The search included last 2 years of abstracts retained in Embase and CENTRAL, while protocols and opinion publications were removed.

The search was performed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and reported in alignment with the Preferred Reporting Items for Systematic Literature Reviews and Meta-Analyses (PRISMA) statement. The Population, Intervention, Comparator, Outcome, Study design (PICOS) framework was used to develop the search strategy and structure the reporting of the eligibility criteria.

The search strategy was developed and tested through an iterative process by a medical information specialist in consultation with the review team. The strategy was peer-reviewed independently by another senior medical information specialist before execution using the Peer Review of Electronic Search Strategies (PRESS) checklist [82]. The search strategy was developed based on the pre-defined PICOS criteria. Search strategies utilized a combination of controlled vocabulary and keywords (eg, "OSCC") to cover all aspects of the PICOS framework. Modified versions of the Cochrane Highly Sensitive Search Strategy filter for identifying RCTs in MEDLINE® and Embase were applied, in addition to filters for SLRs [82]. Vocabulary and syntax were adjusted across databases. The search strategy was not restricted by language. Animal-only and opinion pieces were removed from the results.

Grey literature searches of ANZCTR, ClinicalTrials.gov, ICTRP, and reference lists of previously published reviews were conducted [64].

Table 86 Search strategy table for MEDLINE

No.	Query	Results
#1	Esophageal Squamous Cell Carcinoma/ or (((esophag$ or oesophag$) adj5 (squamous$ or SC or adenosquamous$ or adeno-squamous$ or epidermoid$ or planocellular$ or prickle cell?) adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or malignan$ or oncolog$ or adenocancer$ or adeno-cancer$ or adenoma$ or adenocarcinoma$ or adeno-carcinoma$ or blastoma$ or carcinosarcoma$ or carcino-sarcoma$ or adenoacanthoma$ or adeno-acanthoma$ or epithelioma$ or melanoma$ or mesenchymoma$ or sarcoma$ or thymoma$ or granuloma$ or choriocarcinoma$ or cancerogenes?s or carcinoid$)) or ((esophag$ or oesophag$) adj3 SCC) or (OSCC and (esophag$ or oesophag$))).ti,ab,kw,kf. [OSCC TERMS]	48,203
#2	exp Neoplasm Metastasis/ or Neoplasm Recurrence, Local/ or ((meta adj sta$) or metastas$ or metastatic$ or recur$ or secondar$ or relaps$ or advance$ or inoperab$ or disseminat$ or spread or migration or lethal$ or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasive$ or aggressive$ or (late? adj2 stage$) or ((stage? or grade? or type?) adj2 (3a$ or 3b$ or 3c$ or III$ or 4a$ or 4b$ or IV or IVa or IVb or IVc)) or "stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).ti,ab,kw,kf. [METASTASIS]	13,763,733

No.	Query	Results
#3	#1 and #2	29,095
#4	(tislelizumab$2 or tirelizumab$2 or bgb-a317 or bgba317 or bgn-1 or bgn1 or jhl-2108 or jhl2108 or vdt-482 or vdt482 or 1858168-59-8 or 0kvo411b3n).ti,ab,kw,kf,ot,hw,rn,nm. [TISLELIZUMAB TERMS]	1,731
#5	(atezolizumab$2 or anti-PDL1 or MPDL-3280A or MPDL3280A or RG-7446 or RG7446 or ro-5541267 or ro5541267 or Tecentriq$2 or Tecntriq$2 or 1380723-44-3 or 0INE2SFD9E or 52CMI0WC3Y).ti,ab,kw,kf,ot,hw,rn,nm. [ATEZOLIZUMAB TERMS]	20,778
#6	(avelumab$2 or bavencio$2 or msb-0010682 or msb-0010718c or msb0010682 or msb0010718c or msb-10682 or msb-10718c or msb10682 or msb10718c or pf-06834635 or pf-6834635 or pf06834635 or pf6834635 or KXG2PJ551I or 1537032-82-8).ti,ab,kw,kf,ot,hw,rn,nm. [AVELUMAB TERMS]	7,547
#7	(camrelizumab$2 or "anti-pd-1 monoclonal antibody" or shr-1210 or shr1210 or carilizumab$2 or carrelizumab$2 or 73096E137E or 1798286-48-2).ti,ab,kw,kf,ot,hw,rn,nm. [CAMRELIZUMAB TERMS]	3,604
#8	(durvalumab$2 or imfinzi$2 or medi-4736 or medi4736 or 28X28X9OKV or 1428935-60-7).ti,ab,kw,kf,ot,hw,rn,nm. [DURVALUMAB TERMS]	12,734
#9	Nivolumab/ or (nivolumab$2 or bms-936558 or bms-986213 or bms-986298 or cmab819 or bms936558 or bms986213 or bms986298 or cmab-819 or mdx-1106 or mdx1106 or ono-4538 or ono4538 or opdivo$2 or opdualag$2 or 31YO63LBSN or 946414-94-4).ti,ab,kw,kf,ot,hw,rn,nm. [NIVOLUMAB TERMS]	50,869
#10	(pembrolizumab$2 or keytruda$2 or lambrolizumab$2 or mk3475 or mk-1308a or mk-3475 or mk7684a or sch-900475 or sch900475 or "keylynk-010 component" or DPT0O3T46P or 1422183-02-5 or 1374853-91-4).ti,ab,kw,kf,ot,hw,rn,nm. [PEMBROLIZUMAB TERMS]	49,240
#11	(2072873-06-2 or 8fu7fq8upk or ibi308 or ibi-308 or sintilimab$2 or tyvyt$2 or who-10801).ti,ab,kw,kf,ot,hw,rn,nm. [SINTILIMAB TERMS]	2,269
#12	(1924598-82-2 or 8jxn261vva or js001 or js-001 or tab001 or tab-001 or teripalimab$2 or toripalimab$2 or treipril$2 or treprizumab$2 or tripleitriumab$2 or triprizumab$2 or tuoyi$2 or who-10820 or CHS-007).ti,ab,kw,kf,ot,hw,rn,nm. [TORIPALIMAB TERMS]	1,649
#13	(2231029-82-4 or hlx10 or hlx-10 or s3gqz2k36v or serplulimab$2).ti,ab,kw,kf,ot,hw,rn,nm. [SERPLULIMAB TERMS]	101
#14	(2256084-03-2 or 90iqr2i6tr or cs1001 or cs-1001 or sugemalimab$2 or wbp315 or wbp-315 or wbp3155 or wbp-3155).ti,ab,kw,kf,ot,hw,rn,nm. [SUGEMALIMAB TERMS]	148

No.	Query	Results
#15	Ipilimumab/ or (ipilimumab$2 or bms-734016 or bms734016 or cs-1002 or cs1002 or ibi-310 or ibi310 or mdx-ctla-4 or mdx-010 or mdx-101 or mdx010 or mdx101 or strentarga$2 or yervoy$2 or 6T8C155666 or 477202-00-9).ti,ab,kw,kf,ot,hw,rn,nm. [IPILIMUMAB TERMS]	32,330
#16	(tremelimumab$2 or ticilimumab$2 or cp-675 or cp675 or cp675-cpd or cp-675 or cp-675-206 or cp-675206 or cp675206 or cp675-206 or pf-06753388 or QEN1X95CIX or 745013-59-6).ti,ab,kw,kf,ot,hw,rn,nm. [TREMELIMUMAB TERMS]	5,163
#17	Immune Checkpoint Inhibitors/ or ((Programmed Cell Death 1 Receptor/ or Programmed Cell Death 1 Ligand 2 Protein/) and (inhibit? or block?).ti,ab,kw,kf.) or ((immune$ adj3 checkpoint? adj3 (inhibit? or block?)) or (((programmed adj3 cell adj3 death) or PD-1 or PD-1-PD-L1 or PDCD1) adj3 (ligand? or inhibit? or block?)) or ((B7-H1 or B7H1 or "B7 homolog 1" or CD274 or CD273 or PDCD1LG1 or PDCD1LG2) adj3 (antigen? or protein?)) or ((Cytotoxic-T-Lymphocyte-Associated Protein-4 Inhibitor? or CTLA-4) adj3 (inhibit? or block?)) or ((ICI or ICIs) and "Immune Checkpoint") or BMS-1 or EX-A947 or HY-19991 or J-690233 or MFCD28978741 or s7911 or D000082082 or SCHEMBL16555159 or ZINC230477930 or 1675201-83-8).ti,ab,kw,kf,ot,hw,rn,nm. [IMMUNE CHECKPOINT PROTEINS TERMS]	74,124
#18	or/ #4-#17	157,412
#19	(randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly or trial or groups).ti,ab. or drug therapy.fs. [RCTs – MEDLINE sensitive Filter – Cochrane HSSS, 2019]	15,836,332
#20	exp Randomized Controlled Trials as Topic/ or Clinical Trial, Phase II/ or Clinical Trial, Phase III/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo$ or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-3, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2,541,648
#21	#19 or #20 [RCTs ONLY]	16,128,490
#22	(systematic review or systematic literature review or systematic scoping review or systematic narrative review or systematic qualitative review or systematic evidence review or systematic quantitative review or "systematic meta-review" or systematic critical review or systematic mixed studies review or systematic mapping review or systematic cochrane review or "systematic search and review" or systematic integrative review).ti. not comment.pt. not (protocol or protocols).ti. not MEDLINE.st.	312,794

No.	Query	Results
#23	(1469-493X or 1361-6137).is. and review.pt.	29,334
#24	systematic review.pt.	240,370
#25	#22 or #23 or #24 [Ovid Expert Searches: SLR filter 2019]	563,697
#26	(meta-analy$ or metanaly$ or metaanaly$ or met-analy$).mp,pt. or review.pt. [SLR & MA - modified; Montori, 2004 - Balanced query, sn>sp Filter]	6,796,804
#27	Network Meta-Analysis/ or ((network adj1 (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs or ITC or ITCs or STC or STCs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kw,kf. [Additional terms for MA, NMA, ITC]	66,206
#28	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	69,774
#29	(systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$ or synthes$)) or meta-review$ or meta-overview$ or meta-synthes$ or metareview$ or metaoverview$ or metasynthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs).tw,kw,kf. [Additional terms for synonyms for systematic reviews and HTAs based on SLRs]	230,795
#30	or/#25-#29 [SLR & MA FILTERS - Combined]	7,030,579
#31	#21 or #30 [RCTs & SLRs & MAs Filters]	21,280,620
#32	#3 and #18 and #31 [mOSCC & Drugs & Study Types TERMS]	1,200
#33	(Adolescent/ or exp Child/ or exp Infant/) not (exp Adult/ and (Adolescent/ or exp Child/ or exp Infant/)) [CHILDREN <19 REMOVE]	4,728,322
#34	exp Animals/ not (exp Animals/ and Humans/) [ANIMAL STUDIES ONLY - REMOVE - MEDLINE]	16,826,944
#35	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. [Opinion publications - Remove -MEDLINE]	4,936,789
#36	Clinical Trial Protocol.pt.	571,668

No.	Query	Results
#37	#32 not (#33 or #34 or #35 or #36) [CHILD <19, ANIMAL STUDIES, TRIAL PROTOCOLS and OPINION PUBLICATIONS - REMOVED - MEDLINE]	1,089
#38	37 use ppez [MEDLINE results]	237

Table 87 Search strategy table for Embase

No.	Query	Results
#1	esophageal squamous cell carcinoma/ or (((esophag$ or oesophag$) adj5 (squamous$ or SC or adenosquamous$ or adeno-squamous$ or epidermoid$ or planocellular$ or prickle cell?) adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or malignan$ or oncolog$ or adenocancer$ or adeno-cancer$ or adenoma$ or adenocarcinoma$ or adeno-carcinoma$ or blastoma$ or carcinosarcoma$ or carcino-sarcoma$ or adenoacanthoma$ or adeno-acanthoma$ or epithelioma$ or melanoma$ or mesenchymoma$ or sarcoma$ or thymoma$ or granuloma$ or choriocarcinoma$ or cancerogenes?s or carcinoid$)) or ((esophag$ or oesophag$) adj3 SCC) or (OSCC and (esophag$ or oesophag$))).ti,ab,kw,kf. [OSCC TERMS]	48,203
#2	exp metastasis/ or exp cancer recurrence/ or exp advanced cancer/ or ((meta adj sta$) or metastas$ or metastatic$ or recur$ or secondar$ or relaps$ or advance$ or inoperab$ or disseminat$ or spread or migration or lethal$ or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasive$ or aggressive$ or (late? adj2 stage$) or ((stage? or grade? or type?) adj2 (3a$ or 3b$ or 3c$ or III$ or 4a$ or 4b$ or IV or IVa or IVb or IVc)) or "stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).ti,ab,kw,kf. [METASTASIS]	13,769,518
#3	#1 and #2	29,195
#4	tislelizumab/ or (tislelizumab$2 or tirelizumab$2 or bgb-a317 or bgba317 or bgn-1 or bgn1 or jhl-2108 or jhl2108 or vdt-482 or vdt482 or 1858168-59-8 or 0kvo411b3n).ti,ab,kw,kf,ot,rn,dq. [TISLELIZUMAB TERMS]	1,731
#5	atezolizumab/ or (atezolizumab$2 or anti-PDL1 or MPDL-3280A or MPDL3280A or RG-7446 or RG7446 or ro-5541267 or ro5541267 or Tecentriq$2 or Tecntriq$2 or 1380723-44-3 or 0INE2SFD9E or 52CMI0WC3Y).ti,ab,kw,kf,ot,rn,dq. [ATEZOLIZUMAB TERMS]	20,594
#6	avelumab/ or (avelumab$2 or bavencio$2 or msb-0010682 or msb-0010718c or msb0010682 or msb0010718c or msb-10682 or msb-10718c or msb10682 or msb10718c or pf-06834635 or pf-6834635 or pf06834635 or pf6834635 or KXG2PJ551I or 1537032-82-8).ti,ab,kw,kf,ot,rn,dq. [AVELUMAB TERMS]	7,543
#7	camrelizumab/ or (camrelizumab$2 or "anti-pd-1 monoclonal antibody" or shr-1210 or shr1210 or carilizumab$2 or carrelizumab$2 or	3,603

No.	Query	Results
	73096E137E or 1798286-48-2).ti,ab,kw,kf,ot,rn,dq. [CAMRELIZUMAB TERMS]	
#8	durvalumab/ or (durvalumab$2 or imfinzi$2 or medi-4736 or medi4736 or 28X28X9OKV or 1428935-60-7).ti,ab,kw,kf,ot,rn,dq. [DURVALUMAB TERMS]	12,732
#9	nivolumab/ or (nivolumab$2 or bms-936558 or bms-986213 or bms-986298 or cmab819 or bms936558 or bms986213 or bms986298 or cmab-819 or mdx-1106 or mdx1106 or ono-4538 or ono4538 or opdivo$2 or opdualag$2 or 31YO63LBSN or 946414-94-4).ti,ab,kw,kf,ot,rn,dq. [NIVOLUMAB TERMS]	50,849
#10	pembrolizumab/ or (pembrolizumab$2 or keytruda$2 or lambrolizumab$2 or mk3475 or mk-1308a or mk-3475 or mk7684a or sch-900475 or sch900475 or "keylynk-010 component" or DPT0O3T46P or 1422183-02-5 or 1374853-91-4).ti,ab,kw,kf,ot,rn,dq. [PEMBROLIZUMAB TERMS]	49,222
#11	sintilimab/ or (2072873-06-2 or 8fu7fq8upk or ibi308 or ibi-308 or sintilimab$2 or tyvyt$2 or who-10801).ti,ab,kw,kf,ot,rn,dq. [SINTILIMAB TERMS]	2,269
#12	toripalimab/ or (1924598-82-2 or 8jxn261vva or js001 or js-001 or tab001 or tab-001 or teripalimab$2 or toripalimab$2 or treipril$2 or treprizumab$2 or tripleitriumab$2 or triprizumab$2 or tuoyi$2 or who-10820 or CHS-007).ti,ab,kw,kf,ot,rn,dq. [TORIPALIMAB TERMS]	1,649
#13	serplulimab/ or (2231029-82-4 or hlx10 or hlx-10 or s3gqz2k36v or serplulimab$2).ti,ab,kw,kf,ot,rn,dq. [SERPLULIMAB TERMS]	101
	sugemalimab/ or (2256084-03-2 or 90iqr2i6tr or cs1001 or cs-1001 or sugemalimab$2 or wbp315 or wbp-315 or wbp3155 or wbp-3155).ti,ab,kw,kf,ot,rn,dq. [SUGEMALIMAB TERMS]	148
#14	ipilimumab/ or (ipilimumab$2 or bms-734016 or bms734016 or cs-1002 or cs1002 or ibi-310 or ibi310 or mdx-ctla-4 or mdx-010 or mdx-101 or mdx010 or mdx101 or strentarga$2 or yervoy$2 or 6T8C155666 or 477202-00-9).ti,ab,kw,kf,ot,rn,dq. [IPILIMUMAB TERMS]	32,310
#15	tremelimumab/ or (tremelimumab$2 or ticilimumab$2 or cp-675 or cp675 or cp675-cpd or cp-675 or cp-675-206 or cp-675206 or cp675206 or cp675-206 or pf-06753388 or QEN1X95CIX or 745013-59-6).ti,ab,kw,kf,ot,rn,dq. [TREMELIMUMAB TERMS]	5,161
#16	immune checkpoint inhibitor/ or ((programmed death 1 receptor/ or programmed death 1 ligand 2/) and (inhibit? or block?).ti,ab,kw,kf.) or ((immune$ adj3 checkpoint? adj3 (inhibit? or block?)) or (((programmed adj3 cell adj3 death) or PD-1 or PD-1-PD-L1 or PDCD1) adj3 (ligand? or inhibit? or block?)) or ((B7-H1 or B7H1 or "B7 homolog 1" or CD274 or CD273 or PDCD1LG1 or PDCD1LG2) adj3 (antigen? or protein?)) or	65,484

No.	Query	Results
	((Cytotoxic-T-Lymphocyte-Associated Protein-4 Inhibitor? or CTLA-4) adj3 (inhibit? or block?)) or ((ICI or ICIs) and "Immune Checkpoint") or BMS-1 or EX-A947 or HY-19991 or J-690233 or MFCD28978741 or s7911 or D000082082 or SCHEMBL16555159 or ZINC230477930 or 1675201-83-8).ti,ab,kw,kf,ot,rn,dq. [IMMUNE CHECKPOINT PROTEINS TERMS]	
#17	or/#4-16 [INTERVENTIONS & COMPARATORS TERMS]	150,225
#18	Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or (crossover or cross over) or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or (assigned or allocated) or (controlled adj7 (study or design or trial)) or (volunteer or volunteers)).ti,ab.	11,789,668
#19	(Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or ((((case adj control$) and random$) not randomi?ed controlled) or (nonrandom$ not random$) or "Random field$" or (random cluster adj3 sampl$)).ti,ab. or (Systematic review not (trial or study)).ti. or ((review.ab. and review.pt.) not trial.ti.) or ("we searched".ab. and (review.ti. or review.pt.)) or ("update review" or (databases adj4 searched)).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/))	6,169,445
#20	#18 not #19 [RCTs – Embase sensitive Filter – Cochrane HSSS, 2019]	10,724,925
#21	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/ or (equivalence trial or pragmatic clinical trial).pt. or (randomised or randomi#ation? or RCT or placebo* or ((singl$ or doubl$ or trebl$ or tripl$) adj (mask$ or blind$ or dumm$)) or ((study or trial or CT) adj3 (phase 2 or phase 2a or phase 2b or phase 2c or phase II or phase IIa or phase IIb or phase IIc or phase 3 or phase 3a or phase 3b or phase 3c or phase III or phase IIIa or phase IIIb or phase IIIc or "phase? 2/3" or "phase? II/III" or "phase? 3/4" or "phase? III/IV")) or open label$).tw,kw,kf. [PHASE 2-4, OPEN LABEL - ADDITIONAL TERMS TO SUPPLEMENT RCTs FILTER]	2,244,647
#22	#20 or #21 [RCTs ONLY]	10,985,410
#23	exp meta analysis/ or ((meta adj analy$) or metaanalys$).mp. or (systematic adj (review? or overview?)).tw. or (cancerlit or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal	1,278,732

No.	Query	Results
	or science citation index or bids or reference lists or bibliograph$ or hand-search$ or manual search$ or relevant journals).ab.	
#24	(data extraction or selection criteria).ab. and review.pt.	73,445
#25	#23 or #24 [SLR & MA FILTER - Ovid Expert Searches: SLR filter 2019]	1,290,450
#26	(meta-analy$ or metanaly$ or metaanaly$ or met-analy$).mp. or review.pt. [SLR & MA FILTER - modified and translated; Montori, 2004 - Balanced query, sn>sp Filter]	6,796,804
#27	network meta-analysis/ or ((network adj1 (MA or MAs)) or (NMA or NMAs or MTC or MTCs or MAIC or MAICs or ITC or ITCs or STC or STCs) or indirect$ compar$ or (indirect treatment$ adj1 compar$) or (mixed treatment$ adj1 compar$) or (multiple treatment$ adj1 compar$) or (multi-treatment$ adj1 compar$) or simultaneous$ compar$ or mixed comparison?).tw,kw,kf. [Additional terms for MA, NMA, ITC]	66,206
#28	(cochrane or health technology assessment or evidence report or systematic reviews).jw.	69,774
#29	(systematic overview$ or evidence-based review$ or evidence-based overview$ or (evidence adj3 (review$ or overview$ or synthes$)) or meta-review$ or meta-overview$ or meta-synthes$ or metareview$ or metaoverview$ or metasynthes$ or rapid review$ or "review of reviews" or umbrella review? or technology assessment$ or HTA or HTAs).tw,kw,kf. [Additional terms for synonyms for systematic reviews and HTAs based on SLRs]	230,795
#30	or/#25-#29 [SLR & MA FILTERS - Combined]	7,166,075
#31	#22 or #30 [RCTs & SLRs & MAs Filters]	17,568,409
#32	#3 and #17 and #31	940
#33	(exp adolescent/ or exp child/ or exp fetus/) not (exp adult/ and (exp adolescent/ or exp child/ or exp fetus/)) [CHILDREN <18 REMOVE]	4,472,111
#34	(exp animal/ or exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experimentation/ or exp human experiment/) [ANIMAL STUDIES ONLY - REMOVE - EMBASE]	12,428,674
#35	(editorial or note or short survey or tombstone).pt. or (letter.pt. not randomized controlled trial/) [OPINION PIECES REMOVE - Embase]	5,298,209
#36	conference abstract.pt. [CONFERENCE ABSTRACTS]	4,798,845
#37	#32 not (#33 or #34 or #35) [CHILD <19, ANIMAL STUDIES and OPINION PUBLICATIONS - REMOVED - Embase]	934

No.	Query	Results
#38	#36 and #37 [CONFERENCE ABSTRACTS ONLY]	198
#39	limit #38 to yr="2021 -Current"	124
#40	#37 not #36 [CONFERENCE ABSTRACTS REMOVED]	736
#41	#39 or #40 [LAST 2 YRS OF ABSTRACTS RETAINED - Embase]	860
#42	#41 use oemezd [Embase results]	506

Table 88 Search strategy table for CENTRAL (Cochrane Central Register of Controlled Trials)

No.	Query	Results
#1	Esophageal Squamous Cell Carcinoma/ or (((esophag$ or oesophag$) adj5 (squamous$ or SC or adenosquamous$ or adeno-squamous$ or epidermoid$ or planocellular$ or prickle cell?) adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or malignan$ or oncolog$ or adenocancer$ or adeno-cancer$ or adenoma$ or adenocarcinoma$ or adeno-carcinoma$ or blastoma$ or carcinosarcoma$ or carcino-sarcoma$ or adenoacanthoma$ or adeno-acanthoma$ or epithelioma$ or melanoma$ or mesenchymoma$ or sarcoma$ or thymoma$ or granuloma$ or choriocarcinoma$ or cancerogenes?s or carcinoid$)) or ((esophag$ or oesophag$) adj3 SCC) or (OSCC and (esophag$ or oesophag$))).ti,ab,kw. [OSCC TERMS]	47,895
#2	exp Neoplasm Metastasis/ or Neoplasm Recurrence, Local/ or ((meta adj sta$) or metastas$ or metastatic$ or recur$ or secondar$ or relaps$ or advance$ or inoperab$ or disseminat$ or spread or migration or lethal$ or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasive$ or aggressive$ or (late? adj2 stage$) or ((stage? or grade? or type?) adj2 (3a$ or 3b$ or 3c$ or III$ or 4a$ or 4b$ or IV or IVa or IVb or IVc)) or "stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).ti,ab,kw. [METASTASIS]	13,723,366
#3	#1 and #2	28,930
#4	(tislelizumab$2 or tirelizumab$2 or bgb-a317 or bgba317 or bgn-1 or bgn1 or jhl-2108 or jhl2108 or vdt-482 or vdt482 or 1858168-59-8 or 0kvo411b3n).ti,ab,kw. [TISLELIZUMAB TERMS]	985
#5	(atezolizumab$2 or anti-PDL1 or MPDL-3280A or MPDL3280A or RG-7446 or RG7446 or ro-5541267 or ro5541267 or Tecentriq$2 or Tecntriq$2 or 1380723-44-3 or 0INE2SFD9E or 52CMI0WC3Y).ti,ab,kw. [ATEZOLIZUMAB TERMS]	11,551
#6	(avelumab$2 or bavencio$2 or msb-0010682 or msb-0010718c or msb0010682 or msb0010718c or msb-10682 or msb-10718c or msb10682 or msb10718c or pf-06834635 or pf-6834635 or pf06834635	3,295

No.	Query	Results
	or pf6834635 or KXG2PJ551I or 1537032-82-8).ti,ab,kw. [AVELUMAB TERMS]	
#7	(camrelizumab$2 or "anti-pd-1 monoclonal antibody" or shr-1210 or shr1210 or carilizumab$2 or carrelizumab$2 or 73096E137E or 1798286-48-2).ti,ab,kw. [CAMRELIZUMAB TERMS]	2,504
#8	(durvalumab$2 or imfinzi$2 or medi-4736 or medi4736 or 28X28X9OKV or 1428935-60-7).ti,ab,kw. [DURVALUMAB TERMS]	6,293
#9	Nivolumab/ or (nivolumab$2 or bms-936558 or bms-986213 or bms-986298 or cmab819 or bms936558 or bms986213 or bms986298 or cmab-819 or mdx-1106 or mdx1106 or ono-4538 or ono4538 or opdivo$2 or opdualag$2 or 31YO63LBSN or 946414-94-4).ti,ab,kw. [NIVOLUMAB TERMS]	50,689
#10	(pembrolizumab$2 or keytruda$2 or lambrolizumab$2 or mk3475 or mk-1308a or mk-3475 or mk7684a or sch-900475 or sch900475 or "keylynk-010 component" or DPT0O3T46P or 1422183-02-5 or 1374853-91-4).ti,ab,kw. [PEMBROLIZUMAB TERMS]	30,325
#11	(2072873-06-2 or 8fu7fq8upk or ibi308 or ibi-308 or sintilimab$2 or tyvyt$2 or who-10801).ti,ab,kw. [SINTILIMAB TERMS]	1,281
#12	(1924598-82-2 or 8jxn261vva or js001 or js-001 or tab001 or tab-001 or teripalimab$2 or toripalimab$2 or treipril$2 or treprizumab$2 or tripleitriumab$2 or triprizumab$2 or tuoyi$2 or who-10820 or CHS-007).ti,ab,kw. [TORIPALIMAB TERMS]	853
#13	(2231029-82-4 or hlx10 or hlx-10 or s3gqz2k36v or serplulimab$2).ti,ab,kw. [SERPLULIMAB TERMS]	71
	(2256084-03-2 or 90iqr2i6tr or cs1001 or cs-1001 or sugemalimab$2 or wbp315 or wbp-315 or wbp3155 or wbp-3155).ti,ab,kw. [SUGEMALIMAB TERMS]	99
#14	Ipilimumab/ or (ipilimumab$2 or bms-734016 or bms734016 or cs-1002 or cs1002 or ibi-310 or ibi310 or mdx-ctla-4 or mdx-010 or mdx-101 or mdx010 or mdx101 or strentarga$2 or yervoy$2 or 6T8C155666 or 477202-00-9).ti,ab,kw. [IPILIMUMAB TERMS]	32,267
#15	(tremelimumab$2 or ticilimumab$2 or cp-675 or cp675 or cp675-cpd or cp-675 or cp-675-206 or cp-675206 or cp675206 or cp675-206 or pf-06753388 or QEN1X95CIX or 745013-59-6).ti,ab,kw. [TREMELIMUMAB TERMS]	1,974
#16	Immune Checkpoint Inhibitors/ or ((Programmed Cell Death 1 Receptor/ or Programmed Cell Death 1 Ligand 2 Protein/) and (inhibit? or block?).ti,ab,kw,kf.) or ((immune$ adj3 checkpoint? adj3 (inhibit? or block?)) or (((programmed adj3 cell adj3 death) or PD-1 or PD-1-PD-L1 or PDCD1) adj3 (ligand? or inhibit? or block?)) or ((B7-H1 or B7H1 or "B7	63,965

No.	Query	Results
	homolog 1" or CD274 or CD273 or PDCD1LG1 or PDCD1LG2) adj3 (antigen? or protein?)) or ((Cytotoxic-T-Lymphocyte-Associated Protein-4 Inhibitor? or CTLA-4) adj3 (inhibit? or block?)) or ((ICI or ICIs) and "Immune Checkpoint") or BMS-1 or EX-A947 or HY-19991 or J-690233 or MFCD28978741 or s7911 or D000082082 or SCHEMBL16555159 or ZINC230477930 or 1675201-83-8).ti,ab,kw. [IMMUNE CHECKPOINT PROTEINS TERMS]	
#17	or/#4-#16[INTERVENTIONS & COMPARATORS TERMS]	141,693
#18	#3 and #17	1,329
#19	(Adolescent/ or exp Child/ or exp Infant/) not (exp Adult/ and (Adolescent/ or exp Child/ or exp Infant/)) [CHILDREN <19 REMOVE]	4,728,322
#20	(editorial or note or comment or clinical trial protocol).pt. or (letter.pt. not randomized controlled trial/) [PROTOCOLS and OPINION PIECES REMOVE - CENTRAL]	5,792,290
#21	#18 not (#19 or #20) [PROTOCOLS and OPINION PIECES REMOVED - CENTRAL]	1,196
#22	Conference proceeding.pt. [CONFERENCE ABSTRACTS/PROCEEDINGS]	221,325
#23	#21 and #22 [CONFERENCE ABSTRACTS ONLY]	76
#24	limit #23 to yr="2021 -Current"	43
#25	#21 not #22 [CONFERENCE ABSTRACTS REMOVED]	1,120
#26	#24 or #25 [LAST 2 YRS OF ABSTRACTS RETAINED]	1,163
#27	#26 use cctr [CENTRAL results]	73

Table 89 Search strategy table for Cochrane Database of Systematic Reviews

No.	Query	Results
#1	(((esophag$ or oesophag$) adj5 (squamous$ or SC or adenosquamous$ or adeno-squamous$ or epidermoid$ or planocellular$ or prickle cell?) adj5 (neoplas$ or cancer$ or tumo?r$ or carcinoma$ or malignan$ or oncolog$ or adenocancer$ or adeno-cancer$ or adenoma$ or adenocarcinoma$ or adeno-carcinoma$ or blastoma$ or carcinosarcoma$ or carcino-sarcoma$ or adenoacanthoma$ or adeno-acanthoma$ or epithelioma$ or melanoma$ or mesenchymoma$ or sarcoma$ or thymoma$ or granuloma$ or choriocarcinoma$ or cancerogenes?s or carcinoid$)) or ((esophag$ or oesophag$) adj3 SCC) or (OSCC and (esophag$ or oesophag$))).ti,ab,kw. [OSCC TERMS]	42,946

No.	Query	Results
#2	((meta adj sta$) or metastas$ or metastatic$ or recur$ or secondar$ or relaps$ or advance$ or inoperab$ or disseminat$ or spread or migration or lethal$ or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasive$ or aggressive$ or (late? adj2 stage$) or ((stage? or grade? or type?) adj2 (3a$ or 3b$ or 3c$ or III$ or 4a$ or 4b$ or IV or IVa or IVb or IVc)) or "stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).ti,ab,kw. [METASTASIS]	13,540,197
#3	#1 and #2	25,371
#4	(tislelizumab$2 or tirelizumab$2 or bgb-a317 or bgba317 or bgn-1 or bgn1 or jhl-2108 or jhl2108 or vdt-482 or vdt482 or 1858168-59-8 or 0kvo411b3n).ti,ab,kw. [TISLELIZUMAB TERMS]	985
#5	(atezolizumab$2 or anti-PDL1 or MPDL-3280A or MPDL3280A or RG-7446 or RG7446 or ro-5541267 or ro5541267 or Tecentriq$2 or Tecntriq$2 or 1380723-44-3 or 0INE2SFD9E or 52CMI0WC3Y).ti,ab,kw. [ATEZOLIZUMAB TERMS]	11,551
#6	(avelumab$2 or bavencio$2 or msb-0010682 or msb-0010718c or msb0010682 or msb0010718c or msb-10682 or msb-10718c or msb10682 or msb10718c or pf-06834635 or pf-6834635 or pf06834635 or pf6834635 or KXG2PJ551I or 1537032-82-8).ti,ab,kw. [AVELUMAB TERMS]	3,295
#7	(camrelizumab$2 or "anti-pd-1 monoclonal antibody" or shr-1210 or shr1210 or carilizumab$2 or carrelizumab$2 or 73096E137E or 1798286-48-2).ti,ab,kw. [CAMRELIZUMAB TERMS]	2,504
#8	(durvalumab$2 or imfinzi$2 or medi-4736 or medi4736 or 28X28X9OKV or 1428935-60-7).ti,ab,kw. [DURVALUMAB TERMS]	6,293
#9	(nivolumab$2 or bms-936558 or bms-986213 or bms-986298 or cmab819 or bms936558 or bms986213 or bms986298 or cmab-819 or mdx-1106 or mdx1106 or ono-4538 or ono4538 or opdivo$2 or opdualag$2 or 31YO63LBSN or 946414-94-4).ti,ab,kw. [NIVOLUMAB TERMS]	31,963
#10	(pembrolizumab$2 or keytruda$2 or lambrolizumab$2 or mk3475 or mk-1308a or mk-3475 or mk7684a or sch-900475 or sch900475 or "keylynk-010 component" or DPT0O3T46P or 1422183-02-5 or 1374853-91-4).ti,ab,kw. [PEMBROLIZUMAB TERMS]	30,325
#11	(2072873-06-2 or 8fu7fq8upk or ibi308 or ibi-308 or sintilimab$2 or tyvyt$2 or who-10801).ti,ab,kw. [SINTILIMAB TERMS]	1,281
#12	(1924598-82-2 or 8jxn261vva or js001 or js-001 or tab001 or tab-001 or teripalimab$2 or toripalimab$2 or treipril$2 or treprizumab$2 or tripleitriumab$2 or triprizumab$2 or tuoyi$2 or who-10820 or CHS-007).ti,ab,kw. [TORIPALIMAB TERMS]	853

No.	Query	Results
#13	(2231029-82-4 or hlx10 or hlx-10 or s3gqz2k36v or serplulimab$2).ti,ab,kw. [SERPLULIMAB TERMS]	71
	(2256084-03-2 or 90iqr2i6tr or cs1001 or cs-1001 or sugemalimab$2 or wbp315 or wbp-315 or wbp3155 or wbp-3155).ti,ab,kw. [SUGEMALIMAB TERMS]	99
#14	(ipilimumab$2 or bms-734016 or bms734016 or cs-1002 or cs1002 or ibi-310 or ibi310 or mdx-ctla-4 or mdx-010 or mdx-101 or mdx010 or mdx101 or strentarga$2 or yervoy$2 or 6T8C155666 or 477202-00-9).ti,ab,kw. [IPILIMUMAB TERMS]	17,771
#15	(tremelimumab$2 or ticilimumab$2 or cp-675 or cp675 or cp675-cpd or cp-675 or cp-675-206 or cp-675206 or cp675206 or cp675-206 or pf-06753388 or QEN1X95CIX or 745013-59-6).ti,ab,kw. [TREMELIMUMAB TERMS]	1,974
#16	((immune$ adj3 checkpoint? adj3 (inhibit? or block?)) or (((programmed adj3 cell adj3 death) or PD-1 or PD-1-PD-L1 or PDCD1) adj3 (ligand? or inhibit? or block?)) or ((B7-H1 or B7H1 or "B7 homolog 1" or CD274 or CD273 or PDCD1LG1 or PDCD1LG2) adj3 (antigen? or protein?)) or ((Cytotoxic-T-Lymphocyte-Associated Protein-4 Inhibitor? or CTLA-4) adj3 (inhibit? or block?)) or ((ICI or ICIs) and "Immune Checkpoint") or BMS-1 or EX-A947 or HY-19991 or J-690233 or MFCD28978741 or s7911 or D000082082 or SCHEMBL16555159 or ZINC230477930 or 1675201-83-8).ti,ab,kw. [IMMUNE CHECKPOINT PROTEINS TERMS]	41,803
#17	or/#4-#16 [INTERVENTIONS & COMPARATORS TERMS]	106,569
#18	#3 and #17	1,015
#19	#18 use coch [CDSR results]	0

Additional SLR (October 17, 2024)

The search strategy for the additional SLR, (see Table 90) was designed to align closely with the comprehensive global clinical SLR, incorporating minor adjustments to better fit the Danish clinical practice. The modifications primarily focused on the PICOS framework, ensuring relevance to the local context. The population criteria remained consistent with the comprehensive global clinical SLR, targeting patients with unresectable, locally advanced, or metastatic OSCC. A primary adjustment involved the selection of interventions. In the additional SLR, the interventions were narrowed to include only those treatments that are pertinent to Danish clinical practice. Thus, the review focused exclusively on tislelizumab, nivolumab, and pembrolizumab as interventions. The comparators, outcomes, and study design criteria remained consistent with the comprehensive global SLR. The PICOS criteria are presented in Table 92 [64].

Table 90 Search strategy table for additional SLR in Embase

No.	Query	Results
#1	**'esophageal squamous cell carcinoma'**/exp OR ((**esophag***:ti,ab,kw OR **oesophag***:ti,ab,kw) AND (**squamous***:ti,ab,kw OR **sc**:ti,ab,kw OR **adenosquamous***:ti,ab,kw OR **'adeno squamous*'**:ti,ab,kw OR **epidermoid***:ti,ab,kw OR **planocellular***:ti,ab,kw OR **prickle**:ti,ab,kw) AND **cell?**:ti,ab,kw AND (**neoplas***:ti,ab,kw OR **cancer***:ti,ab,kw OR **tumo?r***:ti,ab,kw OR **carcinoma***:ti,ab,kw OR **malignan***:ti,ab,kw OR **oncolog***:ti,ab,kw OR **adenocancer***:ti,ab,kw OR **'adeno cancer*'**:ti,ab,kw OR **adenoma***:ti,ab,kw OR **adenocarcinoma***:ti,ab,kw OR **'adeno carcinoma*'**:ti,ab,kw OR **blastoma***:ti,ab,kw OR **carcinosarcoma***:ti,ab,kw OR **'carcino sarcoma*'**:ti,ab,kw OR **adenoacanthoma***:ti,ab,kw OR **'adeno acanthoma*'**:ti,ab,kw OR **epithelioma***:ti,ab,kw OR **melanoma***:ti,ab,kw OR **mesenchymoma***:ti,ab,kw OR **sarcoma***:ti,ab,kw OR **thymoma***:ti,ab,kw OR **granuloma***:ti,ab,kw OR **choriocarcinoma***:ti,ab,kw OR **cancerogenes?s**:ti,ab,kw OR **carcinoid***:ti,ab,kw)) OR ((**esophag***:ti,ab,kw OR **oesophag***:ti,ab,kw) AND **scc**:ti,ab,kw) OR (**escc**:ti,ab,kw AND (**esophag***:ti,ab,kw OR **oesophag***:ti,ab,kw))	30,421
#2	**'metastasis'**/exp OR **'cancer recurrence'**/exp OR **'advanced cancer'**/exp OR (**meta**:ti,ab,kw AND **sta***:ti,ab,kw) OR **metastas***:ti,ab,kw OR **metastatic***:ti,ab,kw OR **recur***:ti,ab,kw OR **secondar***:ti,ab,kw OR **relaps***:ti,ab,kw OR **advance***:ti,ab,kw OR **inoperab***:ti,ab,kw OR **disseminat***:ti,ab,kw OR **spread**:ti,ab,kw OR **migration**:ti,ab,kw OR **lethal***:ti,ab,kw OR **incurable**:ti,ab,kw OR **noncurable**:ti,ab,kw OR **'non curable'**:ti,ab,kw OR **uncurable**:ti,ab,kw OR **progressive**:ti,ab,kw OR **terminal**:ti,ab,kw OR **invasive***:ti,ab,kw OR **aggressive***:ti,ab,kw OR (**late?**:ti,ab,kw AND **stage***:ti,ab,kw) OR ((**stage?**:ti,ab,kw OR **grade?**:ti,ab,kw OR **type?**:ti,ab,kw) AND (**3a***:ti,ab,kw OR **3b***:ti,ab,kw OR **3c***:ti,ab,kw OR **iii***:ti,ab,kw OR **4a***:ti,ab,kw OR **4b***:ti,ab,kw OR **iv**:ti,ab,kw OR **iva**:ti,ab,kw OR **ivb**:ti,ab,kw OR **ivc**:ti,ab,kw)) OR **'stage 3'**:ti,ab,kw OR **'stage 4'**:ti,ab,kw OR **met**:ti,ab,kw OR **mets**:ti,ab,kw OR **n1**:ti,ab,kw OR **n2?**:ti,ab,kw OR **n3?**:ti,ab,kw OR **pn1?**:ti,ab,kw OR **pn2?**:ti,ab,kw OR **pn3?**:ti,ab,kw	8,410,077
#3	#1 AND #2	19,000
#4	**'tislelizumab'**/exp OR tislelizumab*:ti,ab,kw,rn OR tirelizumab*:ti,ab,kw,rn OR tevimbra*:ti,ab,kw,rn OR **'bgb a317'**:ti,ab,kw,rn OR **bgba317**:ti,ab,kw,rn OR **'bgn 1'**:ti,ab,kw,rn OR **bgn1**:ti,ab,kw,rn OR **'jhl 2108'**:ti,ab,kw,rn OR **jhl2108**:ti,ab,kw,rn OR **'vdt 482'**:ti,ab,kw,rn OR **vdt482**:ti,ab,kw,rn OR **'1858168 59 8'**:ti,ab,kw,rn OR **0kvo411b3n**:ti,ab,kw,rn	3,221
#5	**'nivolumab'**/exp OR nivolumab*:ti,ab,kw,rn OR **'bms 936558'**:ti,ab,kw,rn OR **bms936558**:ti,ab,kw,rn OR **'bms 986213'**:ti,ab,kw,rn OR **bms986213**:ti,ab,kw,rn OR **'bms 986298'**:ti,ab,kw,rn OR **bms986298**:ti,ab,kw,rn OR **'cmab 819'**:ti,ab,kw,rn OR **cmab819**:ti,ab,kw,rn OR **'mdx 1106'**:ti,ab,kw,rn OR **mdx1106**:ti,ab,kw,rn OR **'ono 4538'**:ti,ab,kw,rn	48,827

No.	Query	Results
	OR **ono4538**:ti,ab,kw,rn OR opdivo*:ti,ab,kw,rn OR opdualag*:ti,ab,kw,rn OR **31yo63lbsn**:ti,ab,kw,rn OR **'946414 94 4'**:ti,ab,kw,rn	
#6	**'pembrolizumab'**/exp OR pembrolizumab*:ti,ab,kw,rn OR keytruda*:ti,ab,kw,rn OR lambrolizumab*:ti,ab,kw,rn OR **'mk 3475'**:ti,ab,kw,rn OR **mk3475**:ti,ab,kw,rn OR **'mk 1308a'**:ti,ab,kw,rn OR **mk1308a**:ti,ab,kw,rn OR **'mk 7684a'**:ti,ab,kw,rn OR **mk7684a**:ti,ab,kw,rn OR **'sch 900475'**:ti,ab,kw,rn OR **sch900475**:ti,ab,kw,rn OR **'keylynk-010 component'**:ti,ab,kw,rn OR **'keylynk 010'**:ti,ab,kw,rn or **keylynk010**:ti,ab,kw,rn OR **dpt0o3t46p**:ti,ab,kw,rn OR **'1422183 02 5'**:ti,ab,kw,rn OR **'1374853 91 4'**:ti,ab,kw,rn	50,431
#7	#4 OR #5 OR #6	75,800
#8	**'randomized controlled trial'**/exp OR **'controlled clinical study'**/exp OR **'randomization'**/exp OR **'intermethod comparison'**/exp OR **'double blind procedure'**/exp OR **'human experiment'**/exp OR **compare**:ti OR **compared**:ti OR **comparison**:ti OR **trial**:ti OR **assigned**:ti,ab OR **allocated**:ti,ab OR **volunteer**:ti,ab OR **volunteers**:ti,ab OR ((**evaluated**:ab OR **evaluate**:ab OR **evaluating**:ab OR **assessed**:ab OR **assess**:ab) AND (**compare**:ab OR **compared**:ab OR **comparing**:ab OR **comparison**:ab)) OR ((**random***:ti,ab OR **placebo**:ti,ab OR (**open**:ti,ab AND **label**:ti,ab) OR ((**double**:ti,ab OR **single**:ti,ab OR **doubly**:ti,ab OR **singly**:ti,ab) AND (**blind**:ti,ab OR **blinded**:ti,ab OR **blindly**:ti,ab)) OR **parallel**:ti,ab) AND **group***:ti,ab) OR ((**crossover**:ti,ab OR **cross**:ti,ab) AND **over**:ti,ab) OR ((**assign***:ti,ab OR **match**:ti,ab OR **matched**:ti,ab OR **allocation**:ti,ab) AND (**alternate**:ti,ab OR **group***:ti,ab OR **intervention***:ti,ab OR **patient***:ti,ab OR **subject***:ti,ab OR **participant***:ti,ab)) OR (**controlled**:ti,ab AND (**study**:ti,ab OR **design**:ti,ab OR **trial**:ti,ab))	7,004,592
#9	**'cross-sectional study'**/exp NOT (((**'randomized controlled trial'**/exp OR **'controlled clinical study'**/exp OR **'controlled study'**/exp OR **randomi?ed**) AND **controlled**:ti,ab OR **control**) AND **group***:ti,ab) OR (**case**:ti,ab AND **control***:ti,ab AND **random***:ti,ab NOT **randomi?ed**:ti,ab AND **controlled**:ti,ab) OR (**nonrandom***:ti,ab NOT **random***:ti,ab) OR **'random field*'**:ti,ab OR (**random**:ti,ab AND **cluster**:ti,ab AND **sampl***:ti,ab) OR (**systematic**:ti AND **review**:ti NOT (**trial**:ti OR **study**:ti)) OR (**review**:ab AND **review**:pt NOT **trial**:ti) OR (**'we searched'**:ab AND (**review**:ti OR **review**:pt)) OR **'update review'**:ab OR (**databases**:ab AND **searched**:ab) OR ((**rat**:ti OR **rats**:ti OR **mouse**:ti OR **mice**:ti OR **swine**:ti OR **porcine**:ti OR **murine**:ti OR **sheep**:ti OR **lambs**:ti OR **pigs**:ti OR **piglets**:ti OR **rabbit**:ti OR **rabbits**:ti OR **cat**:ti OR **cats**:ti OR **dog**:ti OR **dogs**:ti OR **cattle**:ti OR **bovine**:ti OR **monkey**:ti OR **monkeys**:ti OR **trout**:ti OR **marmoset***:ti) AND **'animal experiment'**/exp) OR (**'animal experiment'**/exp NOT (**'human experiment'**/exp OR **'human'**/exp))	3,905,228
#10	#8 NOT #9	6,182,248

No.	Query	Results
#11	**'phase 2 clinical trial'**/exp OR **'phase 3 clinical trial'**/exp OR **'phase 4 clinical trial'**/exp OR ((**equivalence**:pt AND **trial**:pt OR **pragmatic**:pt) AND **clinical**:pt AND **trial**:pt) OR **randomised**:kw OR **randomi*ation?**:kw OR **rct**:kw OR **placebo***:kw OR ((**singl***:kw OR **doubl***:kw OR **trebl***:kw OR **tripl***:kw) AND (**mask***:kw OR **blind***:kw OR **dumm***:kw)) OR ((**study**:kw OR **trial**:kw OR **ct**:kw) AND **phase**:kw AND (**2**:kw OR **2a**:kw OR **2b**:kw OR **2c**:kw OR **ii**:kw OR **iia**:kw OR **iib**:kw OR **iic**:kw OR **3**:kw OR **3a**:kw OR **3b**:kw OR **3c**:kw OR **iii**:kw OR **iiia**:kw OR **iiib**:kw OR **iiic**:kw)) OR **'phase? 2/3'**:kw OR **'phase? ii/iii'**:kw OR **'phase? 3/4'**:kw OR **'phase? iii/iv'**:kw OR (**open**:kw AND **label***:kw)	221,756
#12	#10 OR #11	6,247,006
#13	**'meta analysis'**/exp OR (**meta** AND **analy***) OR **metaanalys*** OR (**systematic** AND (**review?** OR **overview?**)) OR (((((**cancerlit**:ab OR **cochrane**:ab OR **embase**:ab OR **psychlit**:ab OR **psyclit**:ab OR **psychinfo**:ab OR **psycinfo**:ab OR **cinahl**:ab OR **cinhal**:ab OR **science**:ab) AND **citation**:ab AND **index**:ab OR **bids**:ab OR **reference**:ab) AND **lists**:ab OR **bibliograph***:ab OR **'hand search*'**:ab OR **manual**:ab) AND **search***:ab OR **relevant**:ab) AND **journals**:ab)	645,483
#14	(**data** AND **extraction** OR **selection**) AND **criteria** AND **review**	71,779
#15	#13 OR #14	676,795
#16	**'meta analy*'** OR **metanaly*** OR **metaanaly*** OR **'met analy*'** OR **review**	6,495,444
#17	**'network meta-analysis'**/exp OR ((((**network**:kw AND (**ma**:kw OR **mas**:kw) OR **nma**:kw OR **nmas**:kw OR **mtc**:kw OR **mtcs**:kw OR **maic**:kw OR **maics**:kw OR **itc**:kw OR **itcs**:kw OR **stc**:kw OR **stcs**:kw OR **indirect***:kw) AND **compar***:kw OR (**indirect**:kw AND **treatment***:kw AND **compar***:kw) OR (**mixed**:kw AND **treatment***:kw AND **compar***:kw) OR (**multiple**:kw AND **treatment***:kw AND **compar***:kw) OR (**'multi treatment*'**:kw AND **compar***:kw) OR **simultaneous***:kw) AND **compar***:kw OR **mixed**:kw) AND **comparison?**:kw)	10,891
#18	(((**cochrane** OR **health**) AND **technology** AND **assessment** OR **evidence**) AND **report** OR **systematic**) AND **reviews**	181,456
#19	(((((**systematic** AND **overview*** OR **'evidence based'**) AND **review*** OR **'evidence based'**) AND **overview*** OR (**evidence** AND (**review*** OR overview$ OR **synthes***)) OR **'meta review*'** OR **'meta overview*'** OR **'meta synthes*'** OR **metareview*** OR **metaoverview*** OR **metasynthes*** OR **rap id**) AND **review*** OR **'review of reviews'** OR **umbrella**) AND **review?** OR **technology**) AND **assessment*** OR **hta** OR **htas**	393,930
#20	#15 OR #16 OR #17 OR #18 OR #19	6,796,649
#21	#15 OR #16 OR #17 OR #18 OR #19	12,277,147

No.	Query	Results
#22	#3 AND #7 AND #21	666
#23	#22 AND [adult]/lim AND [humans]/lim AND [embase]/lim AND [23-07-2023]/sd NOT [18-11-2024]/sd	**81**

H.1.2 Systematic selection of studies

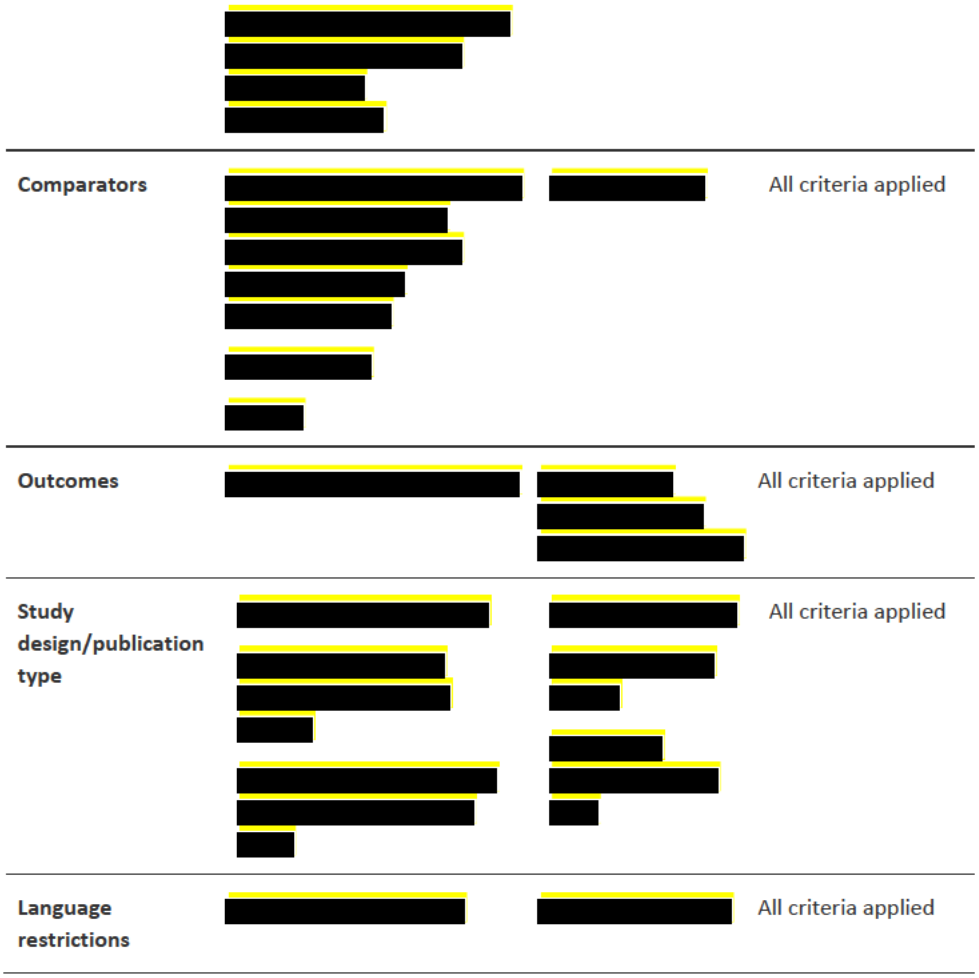
Comprehensive global clinical systematic literature search (June 23, 2023)

Records identified from the electronic database searches were imported into EndNote X9 and duplicates were removed prior to exporting to the systematic review software for study selection. Study selection was conducted by two reviewers who independently reviewed the study records, citation titles, and abstracts to assess eligibility based on the pre-defined inclusion and exclusion criteria (Table 91). Duplicates were quarantined from the final screening list prior to study selection. Reviewers documented their reasons for exclusion and any discrepancies between the two reviewers were resolved by consensus or were referred to and resolved by a third independent reviewer not involved in the study selection process.

Records considered to describe potentially eligible studies were independently reviewed by two reviewers in full-text form for formal inclusion in the review. Records that did not meet the inclusion criteria were excluded and the reason for exclusion was recorded at the full-text screening. Any discrepancies between the two reviewers were resolved by consensus or were referred to and resolved by a third independent reviewer not involved in the study selection process. Included full-text articles were further validated for inclusion during the data extraction phase. This involved reviewing the study design details, baseline population characteristics, and efficacy and safety endpoints [64].

Table 91 Inclusion and exclusion criteria used for assessment of studies (June 23, 2023)

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	[redacted]	[redacted]	All criteria applied
Intervention	[redacted]	[redacted]	All criteria applied


Comparators
All criteria applied
Outcomes
All criteria applied
Study design/publication type
All criteria applied
Language restrictions
All criteria applied

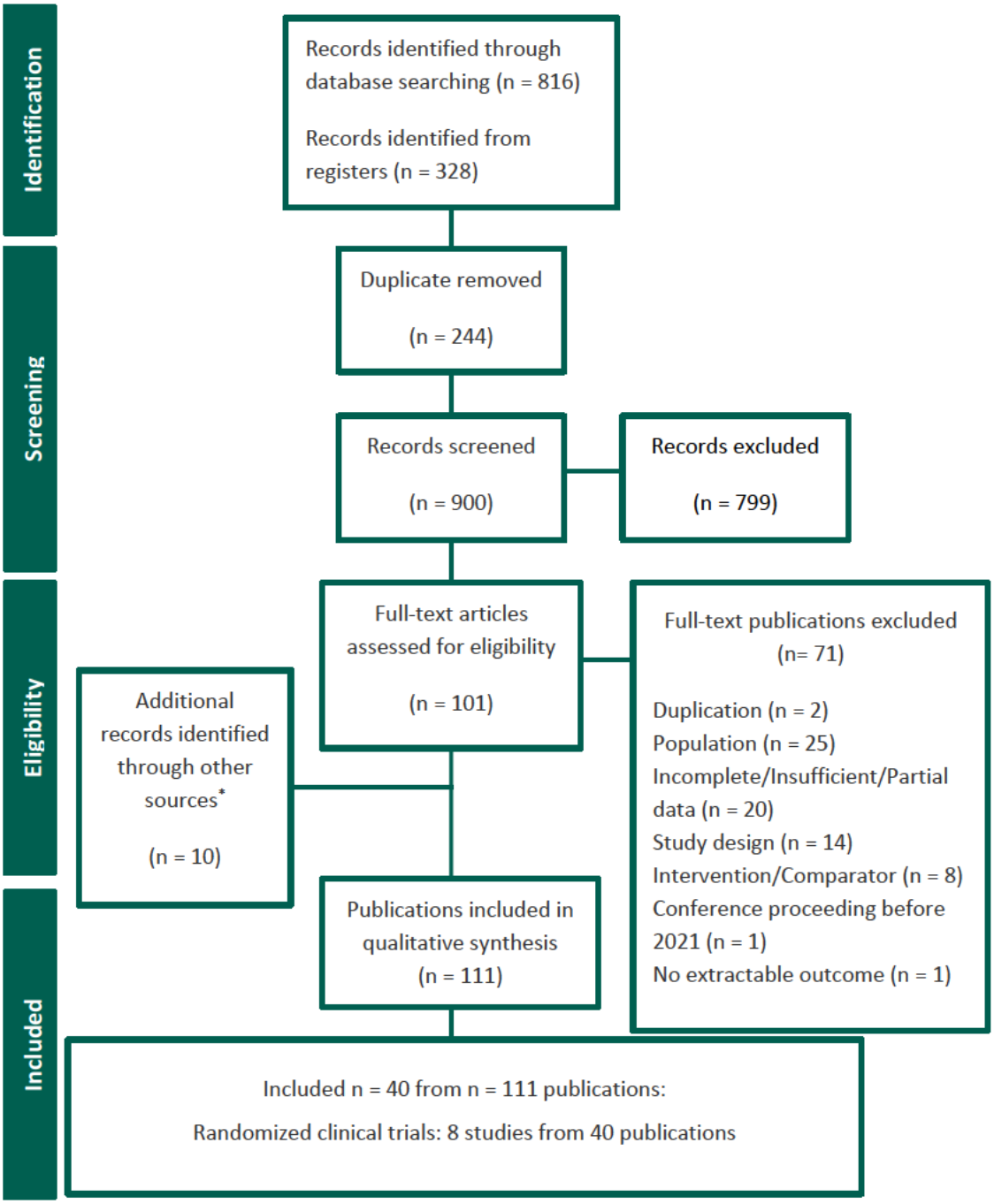


Figure 12 PRISMA flow diagram of clinical evidence identified June 23, 2023

*An elaborate presentation of identification of studies via other methods is presented in Appendix H.2.

Additional SLR (October 17, 2024)

The systematic selection of studies was identical to that of the comprehensive global clinical SLR. However, as described previously there were minor adjustments to the PICOS framework applied to more accurately fit the Danish clinical practice. The pre-defined PICOS eligibility criteria are presented in Table 92 [64].

Table 92 Inclusion and exclusion criteria used for assessment of studies (October 17, 2024)

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	[redacted]	[redacted]	All criteria applied
Interventions	[redacted]	[redacted]	All criteria applied
Comparators	[redacted]	[redacted]	All criteria applied
Outcomes	[redacted]	[redacted]	All criteria applied
Study Design	[redacted]	[redacted]	All criteria applied
Language	[redacted]	[redacted]	All criteria applied

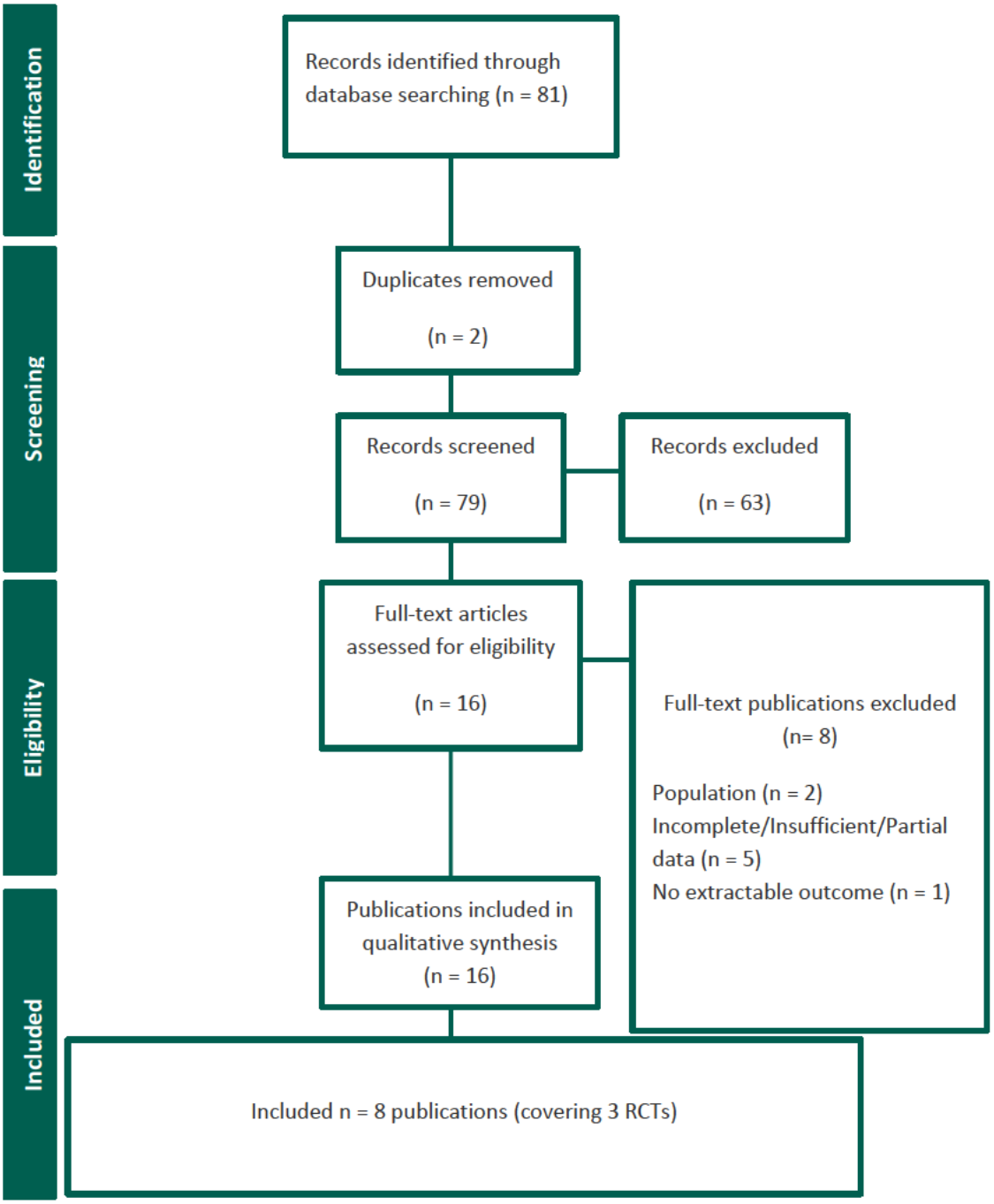


Figure 13 PRISMA flow diagram of clinical evidence identified October 17, 2024

Table 93 Overview of study design for studies included in the analyses (Comprehensive global clinical systematic literature review [June 23, 2023])

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-306 [52] NCT03783442	Evaluation of efficacy and safety of tislelizumab as 1L treatment in combination with chemotherapy compared to placebo and chemotherapy	Phase 3, multicenter, double-blinded RCT	Participants with advanced unresectable/metastatic OSCC	Tislelizumab plush chemotherapy (n=326) vs placebo plus chemotherapy (n=323)	OS (Time frame: up to approximately 3 years and 2 months)	PFS, ORR, DoR, OS in PD-L1 Score ≥10% Subgroup, HRQoL (Time frame: approximately 40 months from date of the first participant randomization)
CheckMate 648 [58] NCT03143153	Comparison of how long subjects live overall or without disease progression after receiving nivolumab and ipilimumab or nivolumab and chemotherapy compared to chemotherapy alone	Phase 3, multicenter, open-label RCT	Subjects with unresectable advanced, recurrent or metastatic previously untreated OSCC	Nivolumab plus chemotherapy (n=321) or nivolumab plus ipilimumab (n=325) vs chemotherapy alone (n=324)	OS in patients with tumour cell PD-L1 (Time frame: up to approximately 20 months) PFS in patients with tumour cell PD-L1 (time frame: up to approximately 9 months)	OS in all patients (Time frame: up to approximately 16 months) PFS in all patients (time frame: up to approximately 7 months) ORR (time frame: up to approximately 40 months)
KEYNOTE-590 [55] NCT03189719	Evaluation of efficacy and safety of pembrolizumab plus chemotherapy	Phase 3, multicenter, double-blinded RCT	Participants with locally advanced or metastatic	Pembrolizumab plus chemotherapy (n=373) vs placebo	OS in Participants with OSCC whose tumours are PD-L1 Biomarker-Positive,	ORR in Participants with OSCC whose tumours are PD-L1 Biomarker-Positive,

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
	compared to placebo plus chemotherapy as first-line treatment		oesophageal carcinoma	plus chemotherapy (n=376)	Participants with OSCC, Participants whose tumours are PD-L1 Biomarker-Positive, and in all participants (Time Frame: Up to approximately 34 months) PFS in Participants with OSCC whose tumours are PD-L1 Biomarker-Positive, Participants with OSCC, Participants whose tumours are PD-L1 Biomarker-Positive, and in all participants (Time Frame: Up to approximately 34 months)	Participants with OSCC, Participants whose tumours are PD-L1 Biomarker-Positive, and in all participants (Time Frame: Up to approximately 34 months) DoR in Participants with OSCC whose tumours are PD-L1 Biomarker-Positive, Participants with OSCC, Participants whose tumours are PD-L1 Biomarker-Positive, and in all participants (Time Frame: Up to approximately 34 months) Number of participants with AEs (Time frame: up to approximately 28 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
						HRQoL (Time frame: baseline to week 18)
ASTRUM-007 [83] NCT03958890	Comparison of clinical efficacy and safety of serplulimab or placebo combined with chemotherapy in first-line treatment of locally advanced/metastatic OSCC patients	Phase 3, multicenter, double-blinded RCT	Patients with locally advanced/metastatic OSCC	Serplulimab plus chemotherapy (n=368) vs placebo plus chemotherapy (n=183)	PFS and OS (Time frame: up to 2 years)	ORR and DoR (Time frame: up to 2 years)
JUPITER-06 [84] NCT03829969	Comparison of effectiveness and safety of toripalimab combined with chemotherapy vs placebo combined with chemotherapy in patients with advanced or metastatic OSCC	Phase 3, multicenter, double-blinded RCT	Patients with advanced or metastatic OSCC without previous systemic chemotherapy	Toripalimab plus chemotherapy (n=257) vs placebo plus chemotherapy (n=257)	PFS and OS (Time frame: up to 2 years)	ORR, DCR, and DoR (Time frame: up to 2 years)
ORIENT-15 [85] NCT03748134	Comparison of efficacy and safety of sintilimab or placebo in combination with	Phase 3, multicenter, double-blinded RCT	Subjects with unresectable, locally advanced recurrent or metastatic OSCC	Sintilimab plus chemotherapy (n=327) vs placebo	OS in overall and PD-L1 positive population (Time	ORR, PFS, DCR, and DoR in overall and PD-L1 positive populations (Time

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
	chemotherapy as first-line treatment in subjects with unresectable, locally advanced recurrent or metastatic OSCC			plus chemotherapy (n=332)	frame: up to 40 months)	frame: up to 28 months)
ESCORT-1st [86] NCT03691090	Comparison of efficacy and safety of camrelizumab plus chemotherapy vs placebo plus chemotherapy as 1L therapy for advanced OC patients	Phase 3, multicenter, double-blinded RCT	Patients with untreated advanced or metastatic OSCC in China	Camrelizumab plus chemotherapy (n=298) vs placebo plus chemotherapy (n=298)	PFS and OS (Time frame: approximately 22 months)	OS rate (Time frame: approximately 6 and 9 months) ORR, DCR, DoR, and AE (Time frame: approximately 22 months)
GEMSTONE-304 [87] NCT04187352	Investigation of efficacy and safety of sugemalimab or placebo in combination with chemotherapy as 1L treatment in patients with unresectable locally advance, recurrent or metastatic OSCC	Phase 3, multicenter, double-blinded RCT	Patients with unresectable locally advance, recurrent or metastatic OSCC	Sugemalimab plus chemotherapy (n=358) vs placebo plus chemotherapy (n=182)	PFS and OS (Time frame: approximately 43 months)	PFS, ORR, and DoR (Time frame: approximately 43 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

Abbreviations: AE, adverse event; DCR, disease control rate; DoR, duration of response; HRQoL, health-related quality of life; ORR, overall response-rate; OSCC, oesophageal squamous cell carcinoma; PD-L1, programmed death ligand 1; PFS, progression-free survival

Additional SLR (October 17, 2024)

The additional SLR identified three different clinical studies from eight publications. The identified studies were previously identified in the comprehensive global clinical SLR and include RATIONALE-306, CheckMate 648, and KEYNOTE-590. The additional search did not identify any new clinical studies or indirect treatment comparisons between the interventions of the PICOS. However, new efficacy and safety follow-up data for the CheckMate 648 study was identified through the search. This data is included in the application in Section 6.1.5 [64].

H.1.3 Excluded full-text references

Table 94 Overview of the excluded full-text references with reasons, SLR from June 2023

Bibliography	Exclusion Reason
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population

Bibliography	Exclusion Reason
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population

Bibliography	Exclusion Reason
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population
[redacted]	Population

Bibliography	Exclusion Reason
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator
[redacted]	Intervention/comparator

Bibliography	Exclusion Reason
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design

Bibliography	Exclusion Reason
[redacted]	
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Study design
[redacted]	Outcome
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data

Bibliography	Exclusion Reason
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
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Bibliography	Exclusion Reason
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
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[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data
[redacted]	Incomplete/insufficient/partial data

Bibliography	Exclusion Reason
[redacted]	
[redacted]	Duplicate
[redacted]	Duplicate
[redacted]	"other" (conference proceeding before 2021)

Table 95 Overview of the excluded full-text references with reasons, SLR October 2024

Bibliography	Exclusion Reason
[redacted]	Population

Bibliography	Exclusion Reason
[redacted]	Insufficient data
[redacted]	Insufficient data
[redacted]	Insufficient data
[redacted]	No extractable outcome
[redacted]	Insufficient data
[redacted]	Population

Bibliography	Exclusion Reason
[redacted]	Insufficient data

H.1.4 Quality assessment

A key strength of this review was its adherence to best practices for the conduct and reporting of systematic reviews. Notably, all searches were performed by an experienced medical information specialist and peer-reviewed by a second information specialist. As per the PRISMA statement, the current review reports detailed search strategies, PICOS, a PRISMA flow diagram, full included/excluded study lists, and risk of bias assessments using appropriate tools.

A limitation of this review was that the language was restricted to include English-only articles at the study selection stage. Given that most of the key studies identified were published in English journals, it is likely that this was a minor limitation. However, it should be noted that this restriction was not applied to the search strategy.

H.1.5 Unpublished data

Any unpublished data utilized to present the efficacy and safety of tislelizumab have been attained from the clinical trial RATIONALE-306, from e.g. the clinical study report, ad hoc analyses or longer follow-up data than the published data. There is no publication plan available for this data.

H.2 Identification of studies via other methods

Comprehensive global clinical systematic literature search (June 23, 2023)

Additional searches of the following grey literature sources were conducted to maximize the inclusion of all relevant studies.

Websites of six key clinical conferences confirmed not to be indexed within Embase were hand searched for relevant abstracts from 2021 onward (Table 96). Key HTA agencies (National Institute for Health and Care Excellence [NICE], Health Insurance Review & Assessment Service [HIRA], and Pharmaceutical Benefits Advisory Committee [PBAC]) were also hand searched for relevant technology appraisals

Table 97). Searches of two Korean databases (KMBase and KoreaMed) were also conducted (Table 98) [64].

Table 96 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ASCO 2023	e.g. conference website	A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ESMO-Asia 2021	Journal supplement [insert reference]	A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023
Blood 2021, 2022		A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023
ISPOR 2021, 2022		A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023
ISPOR EU 2021		A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023
WCGI 2022, 2023		A hand search of the conference website was performed	Conference abstracts from last 2 years (2021, 2022, 2023	23.06.2023

Abbreviations: ASCO, American Society of Clinical Oncology; ESMO, European Society of Medical Oncology; ISPOR The International Society for Pharmacoeconomics and Outcomes Research; WCGI, The World Congress on Gastrointestinal Cancer

Table 97 Additional registers included in the literature search

Source name	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Hand searched for relevant technology appraisals	23.06.2023
Health Insurance Review & Assessment Service [HIRA]		Hand searched for relevant technology appraisals	23.06.2023

Source name	Location/source	Search strategy	Date of search
Pharmaceutical Benefits Advisory Committee [PBAC]		Hand searched for relevant technology appraisals	23.06.2023
Bibliographic search of select relevant SLRs		Search of bibliographies of key relevant SLRs	23.06.2023

Abbreviations: HIRA, Health Insurance Review & Assessment Service; PBAC, Pharmaceutical Benefits Advisory; SLR, systematic literature review

Table 98 Additional databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
KMBase	http://en.medric.or.kr/	N/R	23.06.2023
KoreaMed	https://koreamed.org/	N/R	23.06.2023

Hand searches and study selection of all grey literature sources described above were conducted by a single reviewer and verified by a second reviewer. A third reviewer was consulted if the two reviewers did not reach an agreement. The PRISMA flow diagram for identification of studies via both databases, registers, and other methods is illustrated in [redacted]

Appendix I. Literature searches for health-related quality of life (N/A)

I.1 Health-related quality-of-life search (N/A)

Table 99 Bibliographic databases included in the literature search (N/A)

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com		dd.mm.yyyy
Medline	Ovid		dd.mm.yyyy
Specific health economics databases[1]			dd.mm.yyyy

Abbreviations:

Table 100 Other sources included in the literature search (N/A)

Source name	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
CEA Registry	Tufts CEA - Tufts CEA		dd.mm.yyyy

Abbreviations: CEA; cost-effectiveness analysis; NICE, National Institute of Health and Care Excellence

Table 101 Conference material included in the literature search (N/A)

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
Conference name	e.g. conference website	Electronic search	List individual terms used to search in the congress material:	dd.mm.yyyy

[1] Papaioannou D, Brazier J, Paisley S. Systematic searching and selection of health state utility values from the literature. Value Health. 2013;16(4):686-95.

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
	Journal supplement [insert reference]	Skimming through abstract collection		dd.mm.yyyy

I.1.1 Search strategies (N/A)

Table 102 Search strategy for [name of database] (N/A)

No.	Query	Results
#1		88244
#2		85778
#3		115048
#4		7011
#5		10053
#6		12332
#7		206348
#8		211070
#9	#7 OR #8	272517
#10	#3 AND #6 AND #9	37

I.1.2 Quality assessment and generalizability of estimates (N/A)

I.1.3 Unpublished data (N/A)

Appendix J. Literature searches for input to the health economic model (N/A)

J.1 External literature for input to the health economic model (N/A)

J.1.1 Example: Systematic search for [...] (N/A)

Table 103 Sources included in the search (N/A)

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates] (N/A)

Table 104 Sources included in the targeted literature search (N/A)

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

Appendix K. Baseline Characteristics, ITT population

Table 105. Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Age, years							
Median (range)	64 (59-68)	65 (58-70)	64 (40-90)	63 (28-81)	64 (26-81)	64 (28-94)	62 (27-89)
<65	176 (54%)	161 (50%)	NR			201 (54)	226 (60)
≥65	150 (46%)	162 (50%)				172 (46)	150 (40)
Sex, n (%)							
Female	44 (13)	42 (13)	68 (21)	56 (17)	49 (15)	67 (18)	57 (15)
Male	282 (87)	281 (87)	253 (79)	269 (83)	275 (85)	306 (82)	319 (85)

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Geographical region, n (%)							
Asia	243 (75)	243 (75)	225 (70)	229 (70)	226 (70)	196 (53)	197 (52)
Europe	79 (24)	77 (24)	NR				NR
North America	1 (<1)	1 (<1)					
Oceania	3 (1)	2 (1)					
Race, n (%)							
Asian	243 (75)	243 (75)	227 (71)	231 (71)	227 (70)	201 (54)	199 (53)
White	79 (24)	76 (24)	85 (26)	79 (24)	84 (26)	139 (37)	139 (37)
American Indian or Alaska Native	0 (0)	1 (<1)	NR	NR	NR	9 (2)	12 (3)
Black/African American	NR	NR	1 (<1)	4 (1)	6 (2)	5 (1)	2 (1)

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Not reported, unknown or other	4 (1)	3 (1)	8 (2)	11 (3)	7 (2)	19 (5)	24 (6)
BMI, kg/m^2	21.2 (19.4, 23.4)	21.2 (18.9, 24.1)	NR	NR	NR	NR	NR
ECOG performance status, n (%)							
0	109 (33)	104 (32)	150 (47)	151 (46)	154 (48)	149 (40)	150 (40)
1	217 (67)	219 (68)	171 (53)	174 (54)	170 (52)	223 (60)	225 (60)
Smoking status, n (%)							
Never	68 (21)	81 (25)	67 (21)	57 (18)	68 (21)	NR	
Current or former	247 (76)	231 (72)	254 (79)	268 (82)	256 (79)		
Missing	11 (3)	11 (3)	NR	NR	NR		
Disease status at study entry, n (%)							

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Metastatic	279 (86)	282 (87)	184 (57)	196 (60)	187 (58)	344 (92)	339 (90)
Unresectable locally advanced	47 (14)	41 (13)	44 (14)	31 (10)	52 (16)	29 (8)	37 (10)
Recurrent, locoregional	NR		21 (7)	25 (8)	25 (8)	NR	
Recurrent, distant			72 (22)	73 (22)	60 (19)		
Number of metastatic sites at study entry, n (%)							
0	47 (14%)	41 (13%)	158 (49)	160 (49)	158 (49)	NR	
1	144 (44%)	143 (43%)					
2	81 (25%)	80 (25%)	163 (51)	165 (51)	166 (51)		
>2	54 (17%)	59 (18%)					
Histological type							

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Squamous cell carcinoma	325 (>99%)	323 (100%)	311 (97)	322 (>99)	318 (98)	274 (73)	274 (73)
Other	1 (<1%)	0	9 (3)	3 (<1)	6 (2)	99 (27)	102 (27)
Previous definitive therapy							
Definitive surgery	107 (33)	107 (33)	NR			NR	
Definitive radiotherapy	40 (12)	40 (12)					
Definitive surgery and radiotherapy	4 (1)	6 (2)					
No previous definitive therapy	183 (56)	182 (56)					
PD-L1 expression, n (%)	TAP ≥10%		TPS ≥1%			CPS ≥10	
Positive	116 (36)	107 (33)	158 (49)	158 (49)	157 (48)	186 (50)	197 (52)
Negative	151 (46)	168 (52)	163 (51)	164 (50)	165 (50)	175 (47)	172 (46)

	RATIONALE-306 [50,51]		CheckMate 648 [56,57]			KEYNOTE-590 [53,54]	
	Tislelizumab + Chemotherapy (N=326)	Placebo + Chemotherapy (N=323)	Nivolumab + Chemotherapy (N=321)	Nivolumab + Ipilimumab (N=325)	Chemotherapy (N=324)	Pembrolizumab + Chemotherapy (373)	Placebo + Chemotherapy (N=376)
Unknown	59 (18)	48 (15)	0 (0)	3 (<1)	2 (<1)	12 (3)	7 (2)

Abbreviations: BMI, Body Mass Index; CPS, Combined Positive Score; ECOG, Eastern Cooperative Oncology Group; NR, Not Reported; PD-L1, Programmed Cell-Death Ligand 1; TAP, Tumour Area Positivity; TPS, Tumour Proportion Score.

Appendix L. Figures related to tislelizumab

L.1 Kaplan–Meier plot of OS (ITT analysis set), RATIONALE-306

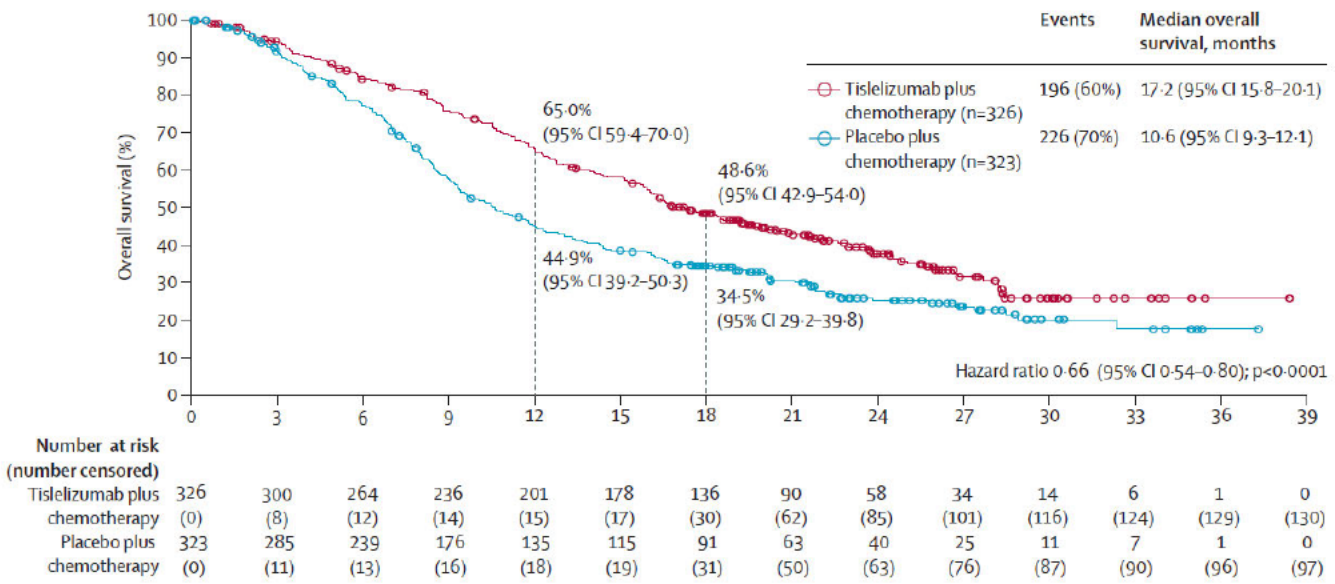

Figure 15 Kaplan–Meier plot of OS (ITT analysis set), RATIONALE-306

Data cut-off: 28FEB2022.

Note: One-sided P-value was estimated from log-rank test stratified by pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum with fluoropyrimidine vs. platinum with paclitaxel) per IRT. HR (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum with fluoropyrimidine vs. platinum with paclitaxel) per IRT as strata.

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; IRT, interactive response technology; ITT, Intent-to-Treat

Source: [51]

[redacted]

Source: [64]

L.3

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; PFS, progression-free survival.
Source: **[64]**

L.4 Kaplan-Meier plot of PFS assessment by investigator (ITT analysis set), RATIONALE-306

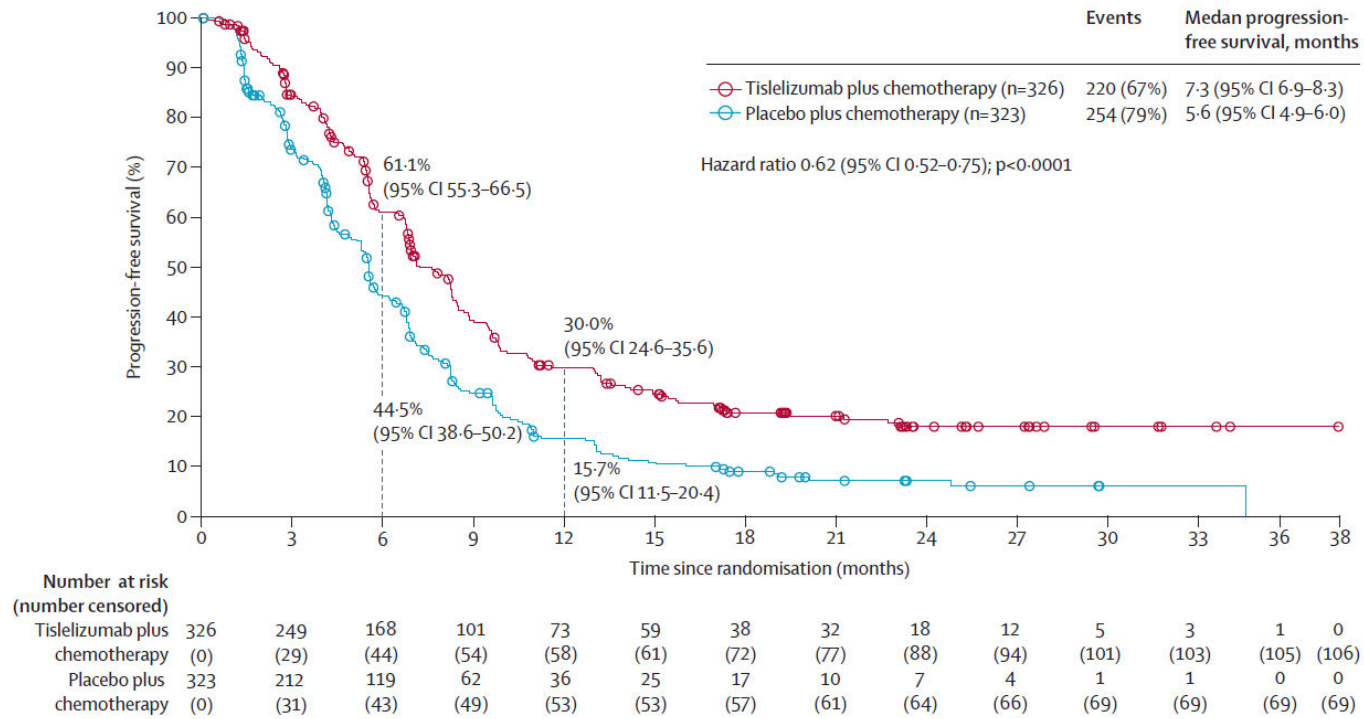

Figure 18 Kaplan-Meier plot of PFS assessment by investigator (ITT analysis set), RATIONALE-306

Data cut-off: 28FEB2022.

Note: One-sided P-value was estimated from log-rank test stratified by pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum with fluoropyrimidine vs. platinum with paclitaxel) per IRT. HR (T+C vs. P+C) was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs. Rest of World) per IRT, prior definitive therapy (yes vs. no) per IRT and ICC option (platinum with fluoropyrimidine vs. platinum with paclitaxel) per IRT as strata.

Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; IRT, interactive response technology; ITT, Intent-to-Treat; P+C, placebo plus chemotherapy; PFS, progression-free survival; T+C, tislelizumab plus chemotherapy.

Source: [51]

L.5 [redacted]

[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; PFS, progression-free survival.
Source: **[64]**

L.6 [redacted]

[redacted])

Data cut-off: November 24, 2023.
The ITT Analysis Set includes all randomized patients. HR was based on Cox regression model including treatment as covariate, and pooled geographic region (Asia vs Rest of World) per IRT, prior definitive therapy (yes vs no) per IRT, and ICC option (platinum with fluoropyrimidine vs platinum with paclitaxel) per IRT as strata. Abbreviations: CI, confidence interval; HR, hazard ratio; ICC, investigator-chosen chemotherapy; IRT, interactive response technology; ITT, intent-to-treat; OS, overall survival; PBO, placebo; PD-L1, programmed death-ligand 1; TAP, tumour area positivity; TIS, tislelizumab.
Source: **[64]**

L.7 [redacted]

[redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; PFS, progression-free survival.
Source: **[64]**

L.8 [redacted]

Abbreviations: CI, confidence interval; HR, hazard ratio; ITT, Intent-to-Treat; PFS, progression-free survival.
Source: **[64]**

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