

## 5.22 TISLELIZUMAB, Solution concentrate for IV infusion 100 mg in 10 mL, Tevimbra<sup>®</sup>, BeiGene Aus Pty Ltd.

### 1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 100, (Efficient Funding of Chemotherapy Program) Authority Required (Streamlined), listing for tislelizumab for the first-line treatment of patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC). The submission stated that treatment would be given in combination with chemotherapy consisting of platinum + fluoropyrimidine. The Pre-Sub-Committee Response (PSCR) proposed that treatment could alternatively be given with paclitaxel plus a platinum drug.
- 1.2 Listing was requested on the basis of a cost-minimisation approach (CMA) versus nivolumab plus chemotherapy, as described in Table 1.

**Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)**

Component	Description
Population	Patients with unresectable, locally advanced recurrent, or metastatic oesophageal squamous cell carcinoma, who are treatment naïve to systemic therapy.
Intervention	Tislelizumab 200 mg every 3 weeks, intravenous infusion administration in combination with chemotherapy. Treatment to be continued until progressive disease or 24 months from treatment initiation, whichever comes first.
Comparator	Main: Nivolumab in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy. Near-market: Pembrolizumab in combination with platinum-containing plus fluoropyrimidine-containing chemotherapy.
Outcomes	Overall survival, progression-free survival, objective response rate, duration of response, TEAE, TRAE, WAE.
Clinical claim	In patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma, regardless of PD-L1 expression status, treatment naïve or first-line, treatment with tislelizumab is non-inferior in efficacy and non-inferior but manageable in terms of safety compared to nivolumab in combination with chemotherapy doublet.

Source: Table ES.1, p2 of the submission.

PD-L1: Programmed death-ligand 1; TEAE: treatment emergent adverse events; TRAE: treatment-related adverse events; WAE: withdrawal due to adverse events

### 2 Background

#### **Registration status**

- 2.1 Tislelizumab was included on the Australian Register of Therapeutic Goods (ARTG) on 30 May 2024:
- as monotherapy for the treatment of adult patients with unresectable, recurrent, locally advanced or metastatic OSCC after prior chemotherapy.

- in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with locally advanced or metastatic squamous non-small cell lung cancer (NSCLC).
  - as monotherapy for the treatment of patients with locally advanced or metastatic NSCLC after prior chemotherapy.
- 2.2 This submission was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration the TGA Delegate’s Overview was available. The Delegate proposed to approve tislelizumab for the first-line treatment of patients with unresectable, locally advanced or metastatic OSCC.
- 2.3 The pre-PBAC Response stated that a TGA application seeking approval of tislelizumab for use in combination with platinum and fluoropyrimidine-based chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic gastric cancer/gastro-oesophageal junction cancer (GC/GOJC), that is not HER-2 positive, was lodged in February 2024 and that a Clinical Evaluation Report was available.

For more detail on PBAC’s view, see section 7 PBAC outcome.

### 3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	No. of Rpts
TISLELIZUMAB	\$7,192.61 published price (public hospital)	200 mg	6
	\$7,335.71 published price (private hospital)		
<b>Available brands</b>			
Tevimbra Tislelizumab, 100mg/10mL, vial.			

Source: ES.3, p4 of the submission.

#### Initial/continuing treatment

<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy
<b>Prescriber type:</b> <input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/>
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (STREAMLINED)
<b>Indication:</b> Unresectable locally advanced recurrent or metastatic oesophageal squamous cell carcinoma.
<b>Clinical criteria:</b> Patient must have/ have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1,
<b>AND</b>
<b>Clinical criteria:</b> Patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for oesophageal squamous cell carcinoma
<b>AND</b>
<b>Clinical criteria:</b> The treatment must be in combination with chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug.

<p><b>Treatment criteria:</b> Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.</p>
<p><b>Administrative Advice:</b> When administering tislelizumab in combination with chemotherapy, administer tislelizumab before chemotherapy when both are given on the same day.</p>

**Grandfather treatment**

<p><b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy</p>
<p><b>Prescriber type:</b> <input type="checkbox"/>Dental <input checked="" type="checkbox"/>Medical Practitioners <input type="checkbox"/>Nurse practitioners <input type="checkbox"/>Optometrists <input type="checkbox"/></p>
<p><b>Restriction type:</b> <input checked="" type="checkbox"/>Authority Required</p>
<p><b>Indication:</b> Unresectable locally advanced recurrent or metastatic oesophageal squamous cell carcinoma.</p>
<p><b>Clinical criteria:</b> Patient must have previously received non-PBS-subsidised treatment with this drug for the above indication prior to [PBS listing date of tislelizumab]</p>
<p><b>AND</b></p>
<p><b>Clinical criteria:</b> The treatment must be in combination with chemotherapy containing at least a fluoropyrimidine drug plus a platinum drug.</p>
<p><b>Treatment criteria:</b> Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.</p>
<p><b>Administrative Advice:</b> When administering tislelizumab in combination with chemotherapy, administer tislelizumab before chemotherapy when both are given on the same day.</p>

- 3.1 The submission proposed a published ex-manufacturer price of \$3,551.24 per 100 mg vial, with the effective price to be calculated on the basis of a CMA using the nivolumab effective price.
- 3.2 The submission proposed restrictions for initial and continuing treatment and a grandfathering restriction to allow patients currently receiving tislelizumab via compassionate access to continue treatment. The PSCR stated that a compassionate access program is proposed to commence in first quarter 2025 with an expected uptake of 4 or 5 patients a month.
- 3.3 The proposed restriction was consistent with the draft Product Information (PI). The proposed restriction for tislelizumab included only 'Population 2' in the current nivolumab restriction, which is first-line treatment of OSCC.
- 3.4 The RATIONALE-306 trial on which the submission relied allowed treating clinicians to replace the fluoropyrimidine drug with paclitaxel, according to local guidelines, and approximately half of randomised patients received paclitaxel. The proposed restriction for tislelizumab requires use of platinum and a fluoropyrimidine, but the submission did not present results separately for those patients. The PSCR stated that the sponsor amended the requested PBS restriction for tislelizumab to allow for use of tislelizumab in combination with either fluoropyrimidine plus a platinum OR

paclitaxel plus a platinum drug. The TGA approval for paclitaxel does not include treatment of OSCC. The PBS listing of paclitaxel is unrestricted, and the nanoparticle albumin-bound paclitaxel has a restricted listing that does not include OSCC.

- 3.5 The pre-PBAC Response proposed that the PBAC may wish to consider if it is appropriate to recommend listing tislelizumab for an aligned, broad restriction across gastro-oesophageal cancers i.e., overlapping with Population 1 (first-line gastric cancer, gastro-oesophageal junction cancer, oesophageal adenocarcinoma), Population 2 (first-line OSCC) and Population 3 (second-line OSCC) of the existing nivolumab PBS listing. The pre-PBAC response proposed restriction criteria consistent with the current nivolumab PBS listing with the exception of allowing concomitant use with paclitaxel for the OSCC population (as discussed in paragraph 3.5).

*For more detail on PBAC's view, see section 7 PBAC outcome.*

## 4 Population and disease

- 4.1 Oesophageal cancers are the 20<sup>th</sup> most common cancer in Australia, of which approximately 40% are squamous cell carcinomas.<sup>1</sup> However, the prevalence of squamous cell carcinoma of the oesophagus is falling, and that of adenocarcinoma is rising in parallel with changes in risk factors (smoking and alcohol consumption for squamous cell carcinoma vs obesity for adenocarcinoma).<sup>2</sup>
- 4.2 Most patients with early oesophageal cancer are asymptomatic or have non-specific symptoms, and the majority of early-stage oesophageal cancers are found incidentally. Most oesophageal cancers diagnosed following the development of symptoms such as dysphagia are locally advanced. The 5-year survival rates of US patients with oesophageal cancer are: for localised disease 37.5% for men and 38.8% for women, for regionally advanced disease 28.2% for men and 26.4% for women, and for disease with distant metastases 6.6% for men and 4.3% for women.<sup>3</sup> Over the past 20 years 5-year survival rates for patients with localised or regionally advanced disease have increased significantly, but those for patients with distant metastases have not.
- 4.3 Currently nivolumab, in combination with fluoropyrimidine and platinum-based chemotherapy, is listed on the PBS for the treatment of unresectable, advanced, recurrent, or metastatic OSCC irrespective of PD-L1 status. Pembrolizumab was recommended for listing for a similar indication in March 2022, but has not progressed to listing.
- 4.4 The submission noted that the PBAC has previously considered that “there was unlikely to be any difference between pembrolizumab and nivolumab in clinical

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<sup>1</sup> The submission stated that the age-standardised incidence of OSCC in Australia is 1.2/100,000 with mortality 2.4/100,000 (p13); this is incorrect - the mortality cited is for all oesophageal cancer, not only OSCC.

<sup>2</sup> Liu C-Q, Ma Y-L, Qin Q, Wang P-H, Luo Y, Xu P-F, Cui Y. Epidemiology of esophageal cancer in 2020 and projections to 2030 and 2040. *Thoracic Cancer* 2023; 14:2-11.

<sup>3</sup> SEER\*Explorer: An interactive website for SEER cancer statistics. Surveillance Research Program, National Cancer Institute; 2024 Apr 17, updated: 2024 Jun 27; <https://seer.cancer.gov/statistics-network/explorer/> accessed 18 July 2024.

practice for the first line treatment of gastro-oesophageal cancers in terms of clinical benefit, tolerability and treatment duration” (Paragraph 14.4, Pembrolizumab Public Summary Document (PSD), May 2022 PBAC Meeting) and the submission proposed that tislelizumab should be considered equivalent to pembrolizumab/nivolumab.

- 4.5 The submission proposed that tislelizumab, as another PD-L1 inhibitor, should be listed in combination with fluoropyrimidine and platinum-based chemotherapy (amended to also include combination use with paclitaxel and a platinum drug in the PSCR), for first-line treatment of unresectable, advanced, recurrent, or metastatic OSCC irrespective of PD-L1 status and be considered as one of a ‘class’ of PD-L1 inhibitors. It was proposed as another option for first-line treatment as an alternative to nivolumab.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **5 Comparator**

- 5.1 The submission nominated nivolumab, in combination with fluoropyrimidine + platinum-based chemotherapy as the main comparator, as the treatment most likely to be replaced. The ESC considered the comparator was appropriate.
- 5.2 The submission nominated pembrolizumab in combination with fluoropyrimidine + platinum-based chemotherapy as a secondary, near market comparator on the grounds that it has been recommended by the PBAC for use for the same indication as that requested for tislelizumab and that it may be listed in the future.
- 5.3 In the context of the cost-minimisation approach taken by the submission, a further consideration for PBAC is that, under Section 101(3B) of the *National Health Act 1953*, when the proposed medicine is substantially more costly than an alternative therapy, the committee cannot make a positive recommendation unless it is satisfied that, for some patients, the proposed medicine provides a significant improvement in efficacy and/or reduction of toxicity over the alternative therapy. If the committee is so satisfied, it must make a statement to this effect.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## **6 Consideration of the evidence**

### ***Sponsor hearing***

- 6.1 There was no hearing for this item.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from 3 organisations (Rare Cancers Australia, Pancare Foundation and the Medical Oncology Group of Australia) via the Consumer Comments facility on the PBS website. The comments described the poor prognosis for patients with oesophageal cancer, the morbidity associated with the disease, and

the possibility that treatments for the disease will improve overall survival while having tolerable toxicity. The PBAC noted that this advice was supportive of the evidence provided in the submission.

- 6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the tislelizumab submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for tislelizumab, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>4</sup>, based on a comparison with placebo in RATIONALE-306.

### ***Clinical trials***

- 6.4 The submission was based on an indirect treatment comparison (ITC) of tislelizumab + chemotherapy versus nivolumab + chemotherapy, using chemotherapy alone as the common comparator. The comparison used the RATIONALE-306 trial for tislelizumab + chemotherapy versus placebo + chemotherapy (referred to herein as tislelizumab versus placebo) and the CheckMate-648 trial for nivolumab + chemotherapy versus chemotherapy (referred to herein as nivolumab versus chemotherapy). The submission also presented an ITC of tislelizumab + chemotherapy and pembrolizumab + chemotherapy using efficacy outcomes in the RATIONALE-306 and KEYNOTE-590 trials, with placebo + chemotherapy as the common comparator. (The comparison in KEYNOTE-590 is referred to herein as pembrolizumab versus placebo).
- 6.5 The submission referred to an unpublished network meta-analysis commissioned by the sponsor, which used the RATIONALE-306, CheckMate-648 and KEYNOTE-590 trials (Eversana, 2024).
- 6.6 Details of the trials presented in the submission are provided in Table 2.

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<sup>4</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

**Table 2 : Primary trial reports and meta-analyses presented in the submission**

Study ID	Report/Publication Title	Citation
RATIONALE-306 NCT03783442	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 Esophageal Squamous Cell Carcinoma. Protocol Number BGB-A317-306.	Interim Analysis Clinical Study Report 2022 – Data cutoff date 28 February 2022
	BeiGene Analysis of 3-year Follow-Up in Rationale 306 study.	Sponsor internal document, 2023
	Tislelizumab plus chemotherapy versus placebo plus chemotherapy as first-line treatment for advanced or metastatic OSCC (RATIONALE-306): a global, randomised, placebo-controlled, phase 3 study.	Xu J et al. Lancet Oncol 2023; <a href="https://doi.org/10.1016/S1470-2045(23)00108-0">https://doi.org/10.1016/S1470-2045(23)00108-0</a>
CheckMate-648 NCT03143153	Nivolumab combination therapy in advanced esophageal squamous cell carcinoma.	Doki Y, et al. N Engl J Med 2022;386:449-62.
KEYNOTE-590 NCT03189719	Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590: A randomised, placebo-controlled, phase 3 study).	Sun J-M, et al. Lancet 2021; 398:759-771.
Eversana, 2024	A network meta-analysis of treatments for unresectable, locally advanced, or metastatic esophageal squamous cell carcinoma in the first line setting.	Sponsor internal document, 2024

Source: Table 2.2, pp25-27 of the submission.

6.7 Key features of the included trials are shown in Table 3. Overall, the risk of bias in the trials was either low or unclear. The risk of bias in the CheckMate-648 trial was considered unclear since it was open-label; this would tend to favour nivolumab, and in the context of a claim of non-inferiority the evaluation considered this to be acceptable.

**Table 3: Key features of the included evidence – indirect comparisons**

Study	N	Design/ duration	Risk of bias	Patient population	Primary Outcome(s)	Use in modelled evaluation
<b>Tislelizumab + CT vs placebo + CT</b>						
RATIONALE-306	649	R, DB, MC, 24 months; 1:1 tislelizumab + ICCT <sup>1</sup> or placebo + ICCT, stratified by choice of CT	Low	OSCC, Stage 4 unresectable if newly diagnosed or locally advanced recurrent or metastatic, no prior systemic treatment except neoadjuvant > 6 months before (no prior PD-L1 inhibitor)	OS	Used
<b>Nivolumab + CT vs CT</b>						
CheckMate-648	970 randomised, 645 to nivolumab + CT or CT <sup>2</sup>	R, OL, MC, 24 months, 1:1:1 nivolumab + CT (Arm B) or CT (Arm C) or nivolumab + ipilimumab (Arm A)	Unclear	OSCC or adenosquamous cell carcinoma, unresectable advanced, recurrent, or metastatic, no prior systemic treatment except for CT as adjuvant, neoadjuvant or primary with curative intent	OS and PFS in patients with tumour cell PD-L1 expression ≥ 1%	Used
<b>Pembrolizumab + CT vs placebo + CT</b>						
KEYNOTE-590	749 (548 had OSCC)	R, DB, MC, 24 months; 1:1 pembrolizumab + CT or placebo + CT, <sup>2</sup> stratified by OSCC vs adenocarcinoma	Low	Unresectable, locally advanced or metastatic oesophageal cancer (squamous cell or adenocarcinoma) or Siewert Type1 GJ cancer; no prior treatment	OS and PFS in OSCC and PD-L1 combined positive score ≥ 10 and in all randomised patients	Not used for economic evaluation, used for ITC and network meta-analysis.

<sup>1</sup> Cisplatin or oxaliplatin and fluorouracil or capecitabine or paclitaxel.

<sup>2</sup> Fluorouracil and cisplatin.

Source: Constructed during the evaluation.

CT = chemotherapy; DB = double blind; GJ = gastro-oesophageal junction; ICCT = investigator-chosen chemotherapy; ITC = indirect treatment comparison; MC = multi-centre; OS = overall survival; OSCC = oesophageal squamous cell carcinoma; R = randomised.

6.8 Baseline characteristics of the patients in the trials are shown in Table 4. KEYNOTE-590 enrolled fewer Asian patients but the trial populations were otherwise similar. While there were differences in the outcomes of the trials and the populations studied as detailed below, the ESC considered there were no significant transitivity issues:

- The CheckMate-648 (nivolumab) and KEYNOTE-590 (pembrolizumab) studies had as primary outcomes overall survival in patients whose tumours expressed PD-L1 above a threshold level, while RATIONALE-306 measured primary outcome regardless of PD-L1 status.
- There were differences in the chemotherapy regimens used in the trials, because in RATIONALE-306 treating clinicians could replace fluoropyrimidine with paclitaxel. About half the patients in RATIONALE-306 received paclitaxel instead of a fluoropyrimidine.
- The KEYNOTE-590 study included patients with adenocarcinoma and squamous cell oesophageal carcinoma, but results for OSCC were reported separately.

**Table 4: Baseline characteristics of patients in the submitted trials**

	RATIONALE-306		CheckMate-648		KEYNOTE-590	
	Tislelizumab N = 326	Placebo N = 323	Nivolumab N = 321	CT N = 324	Pembrolizumab N = 373	Placebo N = 376
Age, years						
Median (range)	64 (26-84)	65 (40-84)	64 (40-90)	64 (28-81)	64 (28-94)	62 (27-89)
≥ 65 n (%)	150 (46%)	162 (50%)	NR	NR	172 (46%)	150 (40%)
Male, n (%)	282 (87%)	281 (87%)	253 (79%)	275 (85%)	306 (82%)	319 (85%)
Race, n (%)						
Asian	243 (75%)	243 (75%)	227 (71%)	227 (70%)	201 (54%)	199 (53%)
White	79 (24%)	76 (24%)	85 (26%)	84 (26%)	139 (37%)	139 (37%)
OSCC, n (%)	325 (>99%)	323 (100%)	311 (97%)	318 (98%)	274 (73%)	274 (73%)
OSCC and PD-L1 CPS						
≥ 10, n (%)	115 (35%)	113 (35%)	NR	NR	143 (38%)	143 (38%)
< 10, n (%)	149 (46%)	160 (50%)	NR	NR	121 (32%)	126 (34%)
ECOG, n (%)						
0	109 (33%)	104 (32%)	150 (47%)	154 (48%)	149 (40%)	150 (40%)
1	217 (67%)	219 (68%)	171 (53%)	170 (52%)	223 (60%)	225 (60%)
Disease status at entry, n (%)						
Locally advanced	47 (14%)	41 (13%)	44 (14%)	52 (16%)	29 (8%)	37 (10%)
Metastatic/recurrent	279 (86%)	282 (87%)	277 (86%)	272 (84%)	344 (92%)	339 (90%)

Source: Table 2.11, pp41-42 of the submission; Sun et al, Lancet 2021; 398:759-771.

CT = chemotherapy; ECOG = Eastern co-operative oncology group performance status; OSCC = oesophageal squamous cell carcinoma; PD-L1 CPS = programmed death ligand 1 combined positive score.

### **Comparative effectiveness**

6.9 The results for the key outcomes in the trials are shown in Table 5 and Table 6.

**Table 5: Summary of progression free survival**

	Proposed medicine	Comparator	Absolute difference	HR (95% CI)
<b>RATIONALE-306</b>	<b>Tislelizumab N=326</b>	<b>Placebo N=323</b>		
Events, n (%)	220 (67.5)	254 (78.6)	-	
Median PFS, months (95% CI)	7.3 (6.9, 8.3)	5.6 (4.9, 6.0)	1.7	0.62 (0.52, 0.75)
% not progressed at 6 months (95% CI)	61.1 (55.3, 66.5)	44.5 (38.6, 50.2)	16.6	
12 months (95% CI)	30.3 (24.6, 35.6)	15.7 (11.5, 20.4)	14.6	
<b>CheckMate-648</b>	<b>Nivolumab</b>	<b>CT</b>		
<b>ITT population</b>	<b>N=321</b>	<b>N=324</b>		
Events, n (%)	NR	NR		
Median PFS, months (95% CI)	5.8 (5.6, 7.0)	5.6 (4.3, 5.9)	0.2	0.81 (0.64, 1.04)
% not progressed at 12 months (95% CI)	24 (NR)	16 (NR)	8	
<b>PD-L1 ≥ 1%</b>	<b>N=158</b>	<b>N=157</b>		
Events, n (%)	NR	NR		
Median PFS, months (95% CI)	6.9 (5.7, 8.3)	4.4 (2.9, 5.8)	2.5	0.65 (0.46, 0.92)
% not progressed at 12 months (95% CI)	25 (NR)	10 (NR)	15	
<b>KEYNOTE-590, OSCC only, PD-L1 agnostic</b>	<b>Pembrolizumab N = 274</b>	<b>Placebo N = 274</b>		
Events, n (%)	NR	NR		
Median PFS, months (95% CI)	6.3 (6.2, 6.9)	5.8 (5.0, 6.1)	0.5	0.65 (0.54, 0.78)

Source: Constructed during the evaluation from Table 2.17, p51, Table 2.20, p54, Table 2.22, p57, Table 2.23 p57, and Sun et al, Lancet 2021 398 759-771.

CT = chemotherapy; NA = not applicable; OSCC = oesophageal squamous cell carcinoma; PD-L1 = programmed cell death ligand. CI = confidence interval; n = number of participants reporting data; N = total participants in group; NR = not reported

**Table 6: Summary of overall survival**

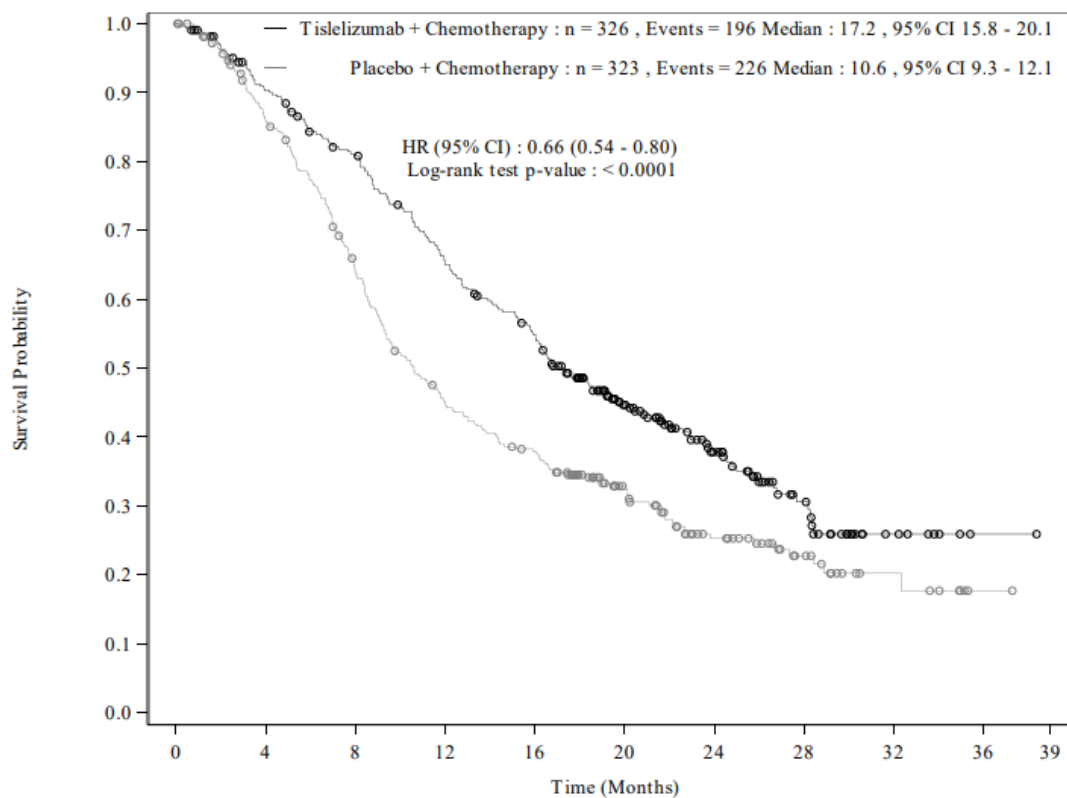
	Proposed medicine	Comparator	Absolute difference	HR (95% CI)
<b>RATIONALE-306</b>	<b>Tislelizumab N=326</b>	<b>Placebo N=323</b>		
Events, n (%)	196 (60.1)	226 (70.0)	-	
Median OS, months (95% CI)	17.2 (15.8, 20.1)	10.6 (9.3, 12.1)	6.6	0.66 (0.54, 0.80)
Survival rate at ... % (95% CI)				
3 months	94.4 (91.3, 96.4)	91.5 (87.8, 94.1)	2.9	-
6 months	84.3 (79.8, 87.9)	77.3 (72.2, 81.5)	7.0	-
12 months	65.0 (59.4, 70.0)	44.9 (39.2, 50.3)	20.1	-
24 months	37.8 (31.9, 43.6)	25.3 (20.1, 30.7)	12.5	-
<b>CheckMate-648</b>	<b>Nivolumab</b>	<b>CT</b>		
<b>ITT population</b>	<b>N=321</b>	<b>N=324</b>		
Events, n (%)	NR	NR		
Median OS, months (95% CI)	13.2 (11.1, 15.7)	10.7 (9.4, 11.9)	2.5	0.74 (0.58, 0.96)
Survival rate at 12 months, % (95% CI)	54 (NR)	44 (NR)	10	-
<b>PD-L1 ≥ 1%</b>	<b>N=158</b>	<b>N=157</b>		
Events, n (%)	NR	NR		
Median OS, months (95% CI)	15.4 (11.9, 19.5)	9.1 (7.7, 10.0)	6.3	0.54 (0.37, 0.80)
% alive at 12 months (95% CI)	58 (NR)	37 (NR)	21	-
<b>KEYNOTE-590, OSCC only, PD-L1 agnostic</b>	<b>Pembrolizumab N = 274</b>	<b>Placebo N = 274</b>		
Events, n (%)	NR	NR		
Median OS, months (95% CI)	12.6 (10.2, 14.3)	9.8 (0.60, 0.88)	2.8	0.72 (0.60, 0.88)

Source: Constructed during the evaluation from Table 2.17, p51, Table 2.20, p54, Table 2.22, p57, Table 2.23 p57, Sun et al, Lancet 2021; 398 759-771, RATIONALE-306 CSR, Table 14, p84

CI = confidence interval; CT = chemotherapy; n = number of participants reporting data; N = total participants in group; NA = not applicable; NR= not reported; OSCC = oesophageal squamous cell carcinoma; PD-L1 = programmed cell death ligand.

6.10 Kaplan-Meier plots for overall survival (OS) and progression-free survival (PFS) in RATIONALE-306 and CheckMate-648 are shown in the figures below.

Figure 1: Kaplan-Meier plot of overall survival in RATIONALE-306

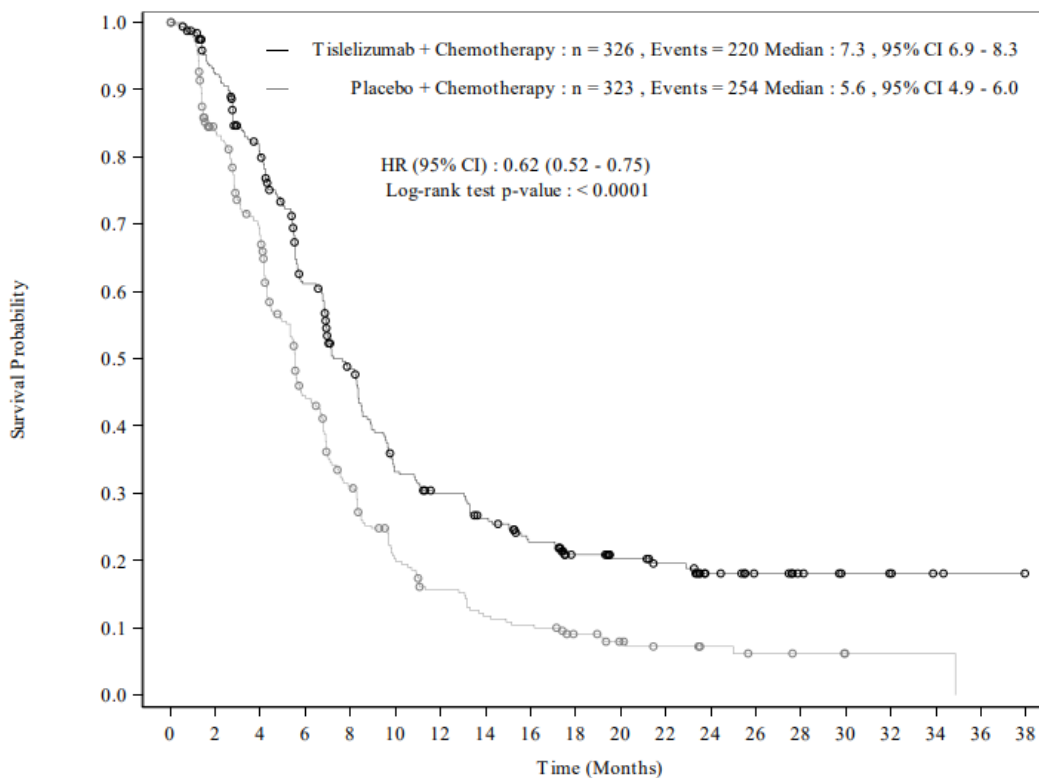


Number of Patients at Risk:

Time:	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + Chemotherapy	326	311	287	264	253	227	201	183	167	136	101	79	58	41	28	14	8	4	1	1
Placebo + Chemotherapy	323	304	268	239	195	158	135	122	112	91	71	54	40	32	22	11	8	6	1	0

Source: Figure 2.5, p52 of the submission.  
 CI: confidence interval; HR: hazard ratio

Figure 2: Kaplan-Meier plot of progression-free survival in RATIONALE-306



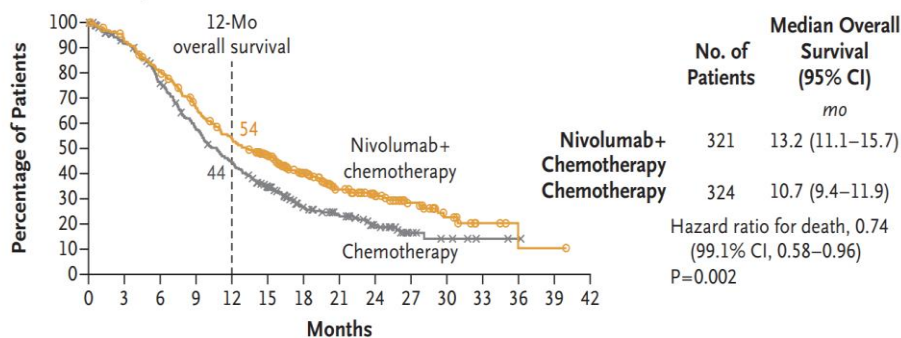
Number of Patients at Risk:

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38
Tislelizumab + Chemotherapy	326	283	236	168	125	84	73	62	50	38	32	27	18	12	8	5	4	2	1	0
Placebo + Chemotherapy	323	248	196	119	80	49	36	27	24	17	12	9	7	4	3	1	1	1	0	0

Source: Figure 2.8, p55 of the submission.

CI: confidence interval; HR: hazard ratio

Figure 3: Kaplan-Meier plot of overall survival (whole population) in CheckMate-648

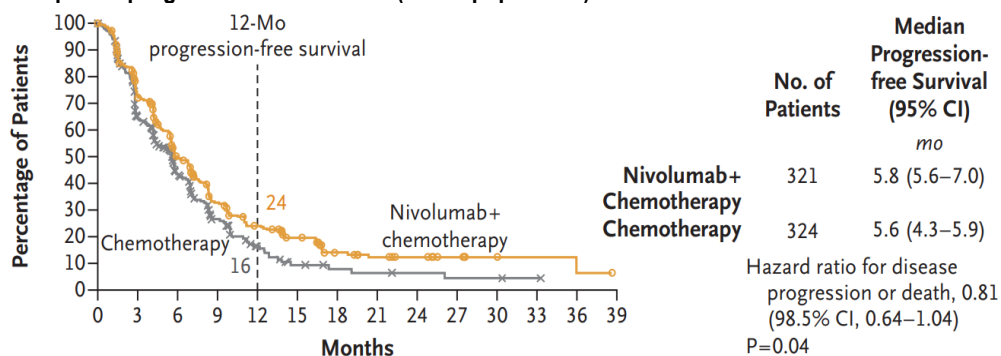


No. at Risk

Nivolumab+chemotherapy	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemotherapy	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

Source: Figure 2.10, p57 of the submission.: CI = confidence interval.

Figure 4: Kaplan-Meier plot of progression-free survival (whole population) in CheckMate-648



**No. at Risk**

Nivolumab+chemotherapy	321	216	136	81	53	35	18	13	10	6	3	2	1	0
Chemotherapy	324	170	90	43	19	8	5	4	3	2	2	1	0	0

Source: Figure 2.11, p58 of the submission.

CI: confidence interval

- 6.11 Relevant secondary outcome and sub-group data for overall survival in the submitted trials are shown in Table 7.
- 6.12 There were no clear differences between sub-groups for either tislelizumab or nivolumab. The most important of these, in the context of the proposed listing for tislelizumab to be used together with platinum + fluoropyrimidine, was that the benefits to overall and progression-free survival associated with tislelizumab were not affected by the use of chemotherapy with paclitaxel versus chemotherapy with fluoropyrimidine. The sponsor reiterated this point in the PSCR and stated that the submission is requesting use of tislelizumab in combination with either a platinum plus fluoropyrimidine, or platinum plus paclitaxel.

Table 7: Secondary outcomes from the trials

Trial	Hazard ratio (95% CI)
<b>RATIONALE-306</b>	<b>Tislelizumab vs placebo</b>
<b>Overall survival</b>	
Age < 65 years	0.73 (0.56, 0.95)
Age ≥ 65 years	0.62 (0.47, 0.82)
Platinum + fluoropyrimidine	0.66 (0.49, 0.88)
Platinum + paclitaxel	0.69 (0.54, 0.89)
ECOG 0	0.72 (0.51, 1.04)
ECOG 1	0.66 (0.53, 0.83)
Race	
Asian and other	0.69 (0.56, 0.87)
White	0.61 (0.41, 0.89)
Metastatic disease at entry	0.72 (0.59, 0.88)
Locally advanced disease at entry	0.44 (0.25, 0.78)
PD-L1 CPS score ≥ 10%	0.65 (0.47, 0.89)
PD-L1 CPS score < 10%	0.71 (0.55, 0.92)
<b>Progression-free survival</b>	
Platinum + fluoropyrimidine	0.66 (0.51, 0.86)
Platinum + paclitaxel	0.57 (0.45, 0.74)
PD-L1 CPS score ≥ 10%	0.50 (0.37, 0.68)
PD-L1 CPS score < 10%	0.68 (0.53, 0.87)
<b>CheckMate-648</b>	<b>Nivolumab vs chemotherapy</b>
<b>Overall survival</b>	
Age < 65 years	0.80 (0.62, 1.04)
Age ≥ 65 years	0.67 (0.51, 0.88)
Region	0.74 (0.59, 0.94)
Asia	0.74 (0.54, 1.02)
Not Asia	
ECOG 0	0.71 (0.54, 0.95)
ECOG 1	0.76 (0.59, 0.97)
Metastatic disease at entry	0.63 (0.49, 0.81)
Locally advanced disease at entry	0.73 (0.45, 1.16)
PD-L1 CPS score ≥ 10%	0.63 (0.47, 0.84)
PD-L1 CPS score < 10%	0.78 (0.60, 1.01)

Source: RATIONALE-306 CSR, Figure 4, p90; Table 17, p99; p102; pp109-111. Figure S3, panel B, p26; Figure S4, panel B, p30, Supplementary Appendix to Doki Y et al. N Engl J Med 2022; 386:449-62.

CI = confidence interval; ECOG = Eastern co-operative oncology group performance status; PD-L1 = programmed death ligand 1.

- 6.13 Results of the ITCs presented in the submission are shown in Table 8.
- 6.14 The ESC noted there were no statistically significant differences in overall survival or progression-free survival between tislelizumab and nivolumab in the ITCs.
- 6.15 The ESC noted there were no statistically significant differences in either overall survival (for the overall population or for patients with PD-L1 <1% or PD-L1 ≥1%) or in progression-free survival between tislelizumab and pembrolizumab in the ITC.

**Table 8: Indirect treatment comparison (ITC) of overall and progression-free survival**

	Trial and comparison	Overall survival HR (95% CI)	Progression-free survival HR (95% CI)
Overall population	RATIONALE-306 Tis vs placebo	0.66 (0.54, 0.80)	0.62 (0.52, 0.75)
	CheckMate-648 Niv vs CT	0.74 (0.61, 0.89)	0.81 (0.64, 1.04)
	KEYNOTE-590 Pembro vs placebo	0.72 (0.60, 0.88)	0.65 (0.54, 0.78)
	ITC, Tis vs Niv	0.89 (0.68, 1.17)	0.76 (0.59, 1.00)
	ITC, Tis vs Pembro	0.92 (0.70, 1.21)	0.95 (0.74, 1.24)
TC ≥ 1%	RATIONALE-306 Tis vs placebo	0.65 (0.49, 0.87)	NR
	CheckMate-648 Niv vs CT	0.54 (0.42, 0.71)	
	ITC, Tis vs Niv	1.20 (0.82, 1.78)	
TC < 1%	RATIONALE-306 Tis vs placebo	0.79 (0.57, 1.09)	NR
	CheckMate-648 Niv vs CT	0.98 (0.76, 1.28)	
	ITC, Tis vs Niv	0.81 (0.53, 1.22)	

Source: Table 2-35, p70, Table 2-36, p71 of the submission.

CI = confidence interval; CT = chemotherapy; HR = hazard ratio; Niv = nivolumab; Pembro = pembrolizumab; TC = tumour cells positive for Programmed cell death receptor -1 receptor; Tis = tislelizumab

6.16 The submission presented an unpublished meta-analysis (Eversana, 2024) that was supportive of the ITCs.

### **Comparative harms**

6.17 Adverse events in the trials are shown in Table 9.

6.18 There were no clear differences in adverse event frequency. All serious treatment-emergent adverse events (TEAEs), anaemia, and decreased neutrophil counts were more common with tislelizumab than with nivolumab and pembrolizumab but were also more common in the placebo arm of RATIONALE-306 than in the placebo arm of KEYNOTE-590 and in the chemotherapy arm of CheckMate-648.

**Table 9: Adverse events**

	RATIONALE-306		CheckMate-648		KEYNOTE-590	
	Tislelizumab N = 324	Placebo N = 321	Nivolumab N = 310	Chemo N = 321	Pembro N = 370	Placebo N = 370
Any TEAE, n (%)	323 (99.7%)	319 (99.4%)	297 (96%)	275 (90%)	370 (100%)	368 (99%)
Serious TEAE, n (%)	156 (48.1%)	127 (39.6%)	74 (24%)	49 (16%)	NR	NR
Grade 3+ TEAE, n (%)	254 (78.4%)	249 (77.6%)	147 (18%)	108 (36%)	318 (86%)	308 (83%)
Treatment discontinuation due to TEAE, n (%)	103 (31.8%)	72 (22.4%)	106 (34%)	59 (19%)	90 (24%)	74 (20%)
Death due to TEAE, n (%)	17 (5.2%)	17 (5.3%)	5 (2%)	6 (2%)	28 (8%)	38 (10%)
Hyponatremia	72 (22.2%)	60 (18.7%)	NR	NR	32 (9.0%)	40 (10.8%)
Hyponatremia Grade ≥ 3	36 (11.1%)	18 (5.6%)	NR	NR	20 (5.0%)	20 (5.4%)
Hypothyroidism	30 (9.3%)	14 (4.4%)	18 (5.8%)	0 (0%)	38 (10.3%)	22 (5.9%)
Anaemia	197 (60.8%)	180 (56.1%)	93 (30.0%)	67 (20.9%)	143 (39%)	162 (44%)
Anaemia Grade ≥ 3	56 (17.3%)	50 (15.6%)	30 (9.7%)	17 (5.3%)	46 (12%)	54 (15%)
Decreased neutrophil count	154 (47.5%)	156 (48.6%)	65 (21.0%)	52 (16.2%)	135 (36%)	109 (29%)
Decreased neutrophil count Grade ≥ 3	100 (30.9%)	107 (33.3%)	25 (8.1%)	24 (7.5%)	84 (23%)	62 (17%)
Decreased platelet count	62 (19.1%)	55 (17.1%)	NR	NR	61 (16%)	56 (15%)
Nausea	123 (38.0%)	136 (42.4%)	182 (58.7%)	158 (49.2%)	233 (63%)	220 (59%)
Nausea Grade ≥ 3	9 (2.8%)	5 (1.6%)	11 (3.5%)	8 (2.5%)	26 (7%)	24 (6%)
Fatigue	64 (19.8%)	57 (17.8%)	61 (19.7%)	50 (15.6%)	135 (36%)	107 (29%)
Fatigue Grade ≥ 3	17 (5.2%)	9 (2.8%)	7 (2.3%)	11 (3.4%)	23 (6%)	20 (5%)
Stomatitis	63 (19.4%)	48 (15.0%)	98 (31.6%)	71 (22.1%)	96 (26%)	93 (25%)
Stomatitis Grade ≥ 3	13 (4.0%)	7 (2.2%)	20 (6.4%)	5 (1.6%)	21 (6%)	14 (4%)
Dysphagia	44 (13.6%)	35 (10.9%)	NR	NR	NR	NR
Dysphagia Grade ≥ 3	20 (6.2%)	13 (4.0%)	NR	NR	NR	NR

Source: Tables 23, pp125-126; Table 24, pp127-128, Table 26, pp130-131, RATIONALE-306 CSR; Table 2.28, p61 of the submission; Table 2, Sun et al, Lancet 2021; 398:759-771. TEAE = treatment-emergent adverse event; Pembro = Pembrolizumab; Chemo = Chemotherapy.

6.19 The submission presented results of an ITC for tislelizumab and nivolumab for any treatment-related adverse event (TRAE), and for any severe TRAE (Grade 3 or worse). The results are shown in Table 10.

**Table 10: Indirect treatment comparison of adverse events tislelizumab vs nivolumab**

	Trial and comparison	OR (95% CI)	HR (95% CI)	Number of events, active treatment (N)	Number of events, placebo (N)
Any TRAE	RATIONALE-306 Tis vs placebo	1.01 (0.52, 1.98)	0.66 (0.54, 0.80)	306 (324)	303 (321)
	CheckMate-648 Niv vs CT	2.41 (1.23, 4.73)	0.7 (0.6, 0.8)	297 (310)	275 (304)
	ITC, Tis vs Niv	0.42 (0.16, 1.09)	0.94 (0.74, 1.20)	-	-
Any TRAE Grade 3 or 4	RATIONALE-306 Tis vs placebo	1.08 (0.79, 1.50)	NR	209 (324)	201 (321)
	CheckMate-648 Niv vs CT	1.64 (1.18, 2.26)	NR	147 (310)	108 (304)
	ITC, Tis vs Niv	0.66 (0.42, 1.05)	NR	-	-

Source: Table 2-37, Table 2-38, p72 of the submission. CI = confidence interval; HR = hazard ratio; ITC = indirect treatment comparison; Niv = nivolumab; NR = not reported; OR = odds ratio; TRAE = treatment-related adverse event.

- 6.20 The ESC considered the ITC of tislelizumab versus nivolumab did not suggest differences in TRAEs or treatment-related severe adverse events between tislelizumab and nivolumab. The submission presented an unpublished meta-analysis (Eversana, 2024) that was supportive of the ITC.
- 6.21 No formal comparison of all adverse events or of TEAEs between tislelizumab and nivolumab was conducted.
- 6.22 A formal ITC of adverse events was not conducted for tislelizumab vs pembrolizumab.

### ***Benefits/harms***

- 6.23 A benefits and harms table was not presented as the submission made a claim of non-inferiority.

### ***Clinical claim***

- 6.24 The submission claimed that tislelizumab + chemotherapy is non-inferior in terms of effectiveness and safety compared with nivolumab + chemotherapy.
- 6.25 The ESC considered this claim was adequately supported with respect to both effectiveness and safety.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable.
- 6.27 The PBAC noted the submission had presented an ITC of tislelizumab compared to pembrolizumab based on the results of the RATIONALE-306 and the KEYNOTE-590 trials. The Committee considered the ITC supported the claim of non-inferior comparative effectiveness and safety of tislelizumab compared to pembrolizumab.

### ***Economic analysis***

- 6.28 The submission presented a CMA versus nivolumab. The key components and assumptions of the CMA are presented in Table 11. As the effective price of nivolumab is confidential, the analysis was conducted using the published price of nivolumab.

**Table 11: Key components and assumptions of the cost-minimisation approach**

Component	Claim or assumption
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be non-inferior.
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be non-inferior.
Evidence base	Indirect comparison of tislelizumab and nivolumab, based on RATIONALE-306 and CheckMate-648.
Equi-effective doses	Tislelizumab 200 mg, IV, Q3W is equi-effective with nivolumab 240 mg, IV, Q2W or nivolumab 360 mg, IV, Q3W. These three therapies are taken until disease progression or unacceptable toxicity. The ESC noted the equi-effective doses were revised in the Pre-Sub-Committee Response (PSCR).
Direct medicine costs	Tislelizumab: \$87,100.12 Nivolumab: \$87,100.12 The direct medicine costs were revised in the PSCR and the pre-PBAC Response.
Other costs or cost offsets	None - the submission assumed that the administration costs will be same in the base case and acknowledged that there may be differences in administration costs for a 3-weekly vs 2-weekly regimen. The administration costs were revised in the PSCR and the pre-PBAC Response in line with the revised equi-effective doses.

Source: Table 3.1, p89 of the submission.

- 6.29 The equi-effective doses presented in the submission were estimated as tislelizumab 200 mg 3-weekly and nivolumab 240 mg 2-weekly OR nivolumab 360 mg 3-weekly. Although patients in the CheckMate-648 trial were scheduled to receive nivolumab 240 mg 2-weekly, the approved PI for nivolumab states that, in combination with fluoropyrimidine-containing and platinum-containing chemotherapy, dosing can be 240 mg every 2 weeks or 480 mg every 4 weeks for patients with OSCC. The PBAC noted the recommended nivolumab dose for patients with gastric cancer, gastro-oesophageal cancer and oesophageal adenocarcinoma is 240 mg every 2 weeks or 360 mg every 3 weeks.
- 6.30 The submission stated that it “assumed that all patients will receive 3-weekly tislelizumab based on the current proposed 3-weekly dosing regimen”. The submission noted that “this leads to a slight cost-offset in MBS costs compared with the 2-weekly nivolumab regimen given the more frequent administration of 2-weekly nivolumab”. The submission stated that the base case CMA compares tislelizumab with only 3-weekly nivolumab so that tislelizumab is cost neutral to the PBS (i.e., assumes no cost offsets associated with 3-weekly vs 2-weekly administration). The PSCR stated that the sponsor is seeking TGA approval for both 2-weekly and 4-weekly dosing for tislelizumab.
- 6.31 The base case CMA compared 3-weekly treatment regimens for both tislelizumab and nivolumab.
- 6.32 In calculating equi-effective doses, the submission assumed that the mean treatment duration in RATIONALE-306 (8.8 months) would apply to both tislelizumab and nivolumab, which gives an expected mean number of doses of 12.9 for tislelizumab and 19.3 for nivolumab. The submission used the actual mean number of doses for tislelizumab = 11.7, and calculated  $11.7/12.9 \times 19.3 = 17.5$  as the mean number of doses for nivolumab.

- 6.33 The CMA in the submission was undertaken using dispensed prices and assumed 69% private hospital use. Pricing agreements are made by Government under the *National Health Act 1953* at the ex-manufacturer level and, as such, the prices would be agreed on this basis. It is not usually the case that pharmacy and wholesaler mark-ups are considered for the purpose of cost-minimisation as they do not relate to the cost of the medicine.
- 6.34 The results of the base case CMA as presented in the submission are presented in Table 12. The estimates of dose intensity could not be confirmed from the published data for nivolumab and therefore the resulting cost per cycle estimate may favour tislelizumab. The PSCR stated that given the similar safety profile and similarity of mechanism of action between the therapies, it would be reasonable to assume similar dose intensity between tislelizumab and nivolumab. The ESC considered this was reasonable.

**Table 12: Results of the cost-minimisation approach presented in the submission**

Measurement	Tislelizumab	Nivolumab
AEMP per 100 mg	\$3,551.24	\$1,972.91
AEMP per mg	\$35.51	\$19.73
mg per cycle	200	360
Dispensed drug cost per cycle (3-weekly)	\$7,291.87	\$7,291.87
Time on treatment (weeks)	38.3	38.3
Time on treatment cycles (3-weekly)	11.7	11.7
Drug cost per treatment course	\$85,654.70	\$85,654.70
Administration costs per treatment course	\$1,445.42	\$1,445.42
Total cost immunotherapy per treatment course	\$87,100.12	\$87,100.12
Total cost of chemotherapy per treatment course	\$0.00	\$0.00
Total cost per treatment course	\$87,100.12	\$87,100.12

Source: Table 3.4, p 91 of the submission. Abbreviations: AEMP: Approved ex-manufacturer price; mg: milligram

- 6.35 The PBAC noted it had previously considered that pembrolizumab’s cost-effectiveness (as a first-line treatment for gastro-oesophageal cancers) would be acceptable at the same or lower cost per 3-weekly treatment cycle as for nivolumab (Paragraph 11.2, Pembrolizumab PSD, May 2022 PBAC Meeting), and considered that similarly tislelizumab’s cost-effectiveness would also be acceptable at the same or lower cost per 3-weekly treatment cycle as for nivolumab.

### ***Drug cost per patient per course***

- 6.36 The submission estimated the cost per patient per course of treatment over 38.3 weeks to be \$87,100.12, using the published price of nivolumab as the basis for the price of tislelizumab as calculated in the CMA presented in the submission (Table 12).

### ***Estimated PBS usage & financial implications***

- 6.37 This submission was not considered by DUSC.

6.38 The submission appropriately presented a market share approach to estimate use and financial impact. The key inputs used in the estimates are shown in Table 13.

6.39 The number of grandfathered patients was not included in the estimates.

**Table 13: Key inputs for financial estimates**

Data	Value	Source	Comment
Utilisation of nivolumab in 2023	12,322	Medicare Statistics PBS item reports for 13117J and 13117N	Appropriate as nivolumab was listed in October 2022
Estimated annual rate of growth	Yr 1: 20% Yr 2: 10% Yr 3: 5% Yr 4: 5% Yr 5: 5% Yr 6: 5%	Estimated based on current annual growth	
Proportion applicable to indication	16%	Estimate based on 40% of gastro-oesophageal cancers being oesophageal. Of those, 40% are squamous subtype. Therefore 16% of total nivolumab indications are OSCC related.	Equals population 2 in restrictions for nivolumab.
Tislelizumab share of nivolumab market	Up to 60%	Sponsor estimate. Note that proportion of market share is different for the Q2W and Q3W nivolumab market and also depends on approval of Q2W tislelizumab in 2025	Assumptions may or may not be reasonable given different markets for different dosage regimens as well as depending on TGA approval of additional dosage regimen for tislelizumab; application yet to be submitted at the time of the evaluation.
Script equivalence	1.5 nivolumab Q2W = 1 Q3W = 1 Q3W tislelizumab	Assumes that utilisation is split 80:20 Q2W: Q3W, adjusts equivalence by this weighting =1.4	Consistent with PBS data.
MBS items - infusion administration costs	MBS item 13950, \$123.05	MBS Schedule	The MBS item cost for administration was reasonable. However, the submission used 100% of the MBS fee rather than 80% (as recommended in the PBAC Guidelines).  Base case that the current split of 2-weekly vs 3-weekly dosing for nivolumab will continue. This assumes that the 3-weekly regimen is used for the same indication as the 2-weekly regimen. Assumption tested in sensitivity analysis.

Source: Tables 4.1, 4.11, p93, 102 and associated text of the submission. Abbreviations: OSCC= oesophageal squamous cell carcinoma; Q2W= every 2 weeks; Q3W= every 3 weeks.

6.40 The estimated use and financial implications of listing tislelizumab, based on the published prices of nivolumab, and the cost-minimised price of tislelizumab as estimated in Table 12 are shown in Table 14.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts dispensed	1	2	2	2	2	2
<b>Estimated financial implications of tislelizumab</b>						
Cost to PBS/RPBS less copayments	3	3	3	3	3	4
<b>Estimated financial implications for nivolumab</b>						
Cost to PBS/RPBS less copayments	5	5	5	5	5	5
<b>Net financial implications</b>						
Net cost to PBS/RPBS	5	5	5	5	5	5
Net cost to PBS/RPBS/MBS/Services Australia	5	5	5	5	5	5

Source: Tables 4.3, 4.6, 4.7, 4.12 pp96, 99, 100, 102-103 of the submission

The redacted values correspond to the following ranges:

1 < 500

2 500 to < 5,000

3 \$0 to < \$10 million

4 \$10 million to < \$20 million

5 net cost saving

6.41 The submission estimated the total cost to the PBS/RPBS of listing tislelizumab to be \$10 million to < \$20 million in Year 6, based on the published price, with a net cost saving -(accounting for reduced use of nivolumab). The cost saving is driven by substitution of tislelizumab for nivolumab administered 2-weekly at a lower script cost given that the cost-minimised price for tislelizumab did not include cost offsets associated with 3-weekly vs 2-weekly administration of nivolumab.

### Financial Management – Risk Sharing Arrangements

6.42 The submission stated that ‘it is expected that tislelizumab will join existing risk sharing arrangements for nivolumab, so this and other uncertainties arising from utilisation will be addressed through this mechanism and thus tislelizumab listing will remain cost neutral.’ The ESC considered this was appropriate.

*For more detail on PBAC’s view, see section 7 PBAC outcome.*

## 7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (streamlined) listing of tislelizumab under the Section 100 (Efficient Funding of Chemotherapy) Program for the treatment of advanced or metastatic gastro-oesophageal cancer. The PBAC’s recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of tislelizumab in this population would be acceptable if it were cost minimised to nivolumab. The PBAC considered the equi-effective doses to be tislelizumab 200 mg 3-weekly is equi-effective to nivolumab 360 mg 3-weekly. The PBAC considered it was appropriate for tislelizumab to be included in the risk sharing arrangement currently in place for gastro-oesophageal cancers without an increase in the expenditure caps.

- 7.2 The PBAC noted that the listing requested in the submission was for the first-line treatment of patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC). The proposed listing criteria were revised in the pre-PBAC response to be consistent with the current PBS listing for nivolumab as outlined in paragraph 3.6.
- 7.3 The PBAC recalled it had previously recommended nivolumab for advanced or metastatic gastro-oesophageal cancers as specified in the 'Indications' section of the approved Australian Product Information (paragraph 14.1, nivolumab PSD, OOS, November 2021 – March 2022). Nivolumab was listed on the PBS on 1 October 2022 for this indication. At its July 2023 meeting, the PBAC recommended the PBS listing be amended to remove reference to the approved Product information and to specify concomitant therapy, line-of-therapy and HER2 status for each relevant population (i.e., Population 1, Population 2 and Population 3), without reference to PD-L1 status. Noting the TGA registered indication for nivolumab for OSCC is for patients with PD-L1 status  $\geq 1\%$ , this change would allow the small group of patients with PD-L1 status  $< 1\%$  to access nivolumab on the PBS. In July 2023, the sponsor advised it was unable to proceed with a listing that was silent on PD-L1 status, line of therapy, concomitant therapy and HER2 status without first undertaking an assessment of its impact on utilisation. The PBAC stated a future application for HER2-positive patients would be welcomed.
- 7.4 The PBAC considered a listing for tislelizumab for 'advanced or metastatic gastro-oesophageal cancers' without reference to the TGA approved indication that is silent on PD-L1 status, line of therapy, concomitant therapy and HER2 status would be appropriate and consistent with the nivolumab restriction. The PBAC noted this restriction would provide access to patients with HER2 positive disease, patients with MSI-H/dMMR tumours and for the second line treatment of gastro-oesophageal cancers other than OSCC for which there is some clinical evidence supporting the use of PD-(L)1 inhibitors. The PBAC noted this population is excluded from the current nivolumab restriction.
- 7.5 The PBAC considered it would be reasonable for the nivolumab listing to be amended to 'advanced or metastatic gastro-oesophageal cancers' as outlined in paragraph 7.4. Additionally, the change could also apply to pembrolizumab should it progress to a PBS listing.
- 7.6 The PBAC considered it would be preferable, and clinically appropriate for the listings for tislelizumab and nivolumab to not be restricted to the advanced and metastatic settings but to include all stages of the disease with a listing for 'gastro-oesophageal cancers'. However, financial estimates would be required to support this listing change, and as such the PBAC requested sponsors provide these estimates to facilitate the broader listing.
- 7.7 The PBAC considered that while the submission requested a maximum quantity of 200 mg with 6 repeats for initial and continuing scripts (providing 21 weeks of

- treatment) that 7 repeats would be more appropriate (providing for 24 weeks of treatment).
- 7.8 The PBAC considered that a grandfather restriction would not be required, noting that the proposed restriction allowed for patients who had commenced non-PBS subsidised treatment to be treated with tislelizumab on the PBS.
- 7.9 The submission nominated nivolumab plus chemotherapy as the comparator. The PBAC considered the nominated comparator was appropriate.
- 7.10 The submission was based on one randomised, double-blind trial (RATIONALE-306; N=649) comparing tislelizumab plus chemotherapy compared to placebo plus chemotherapy, in the first-line treatment of patients with unresectable advanced, recurrent, or metastatic oesophageal squamous cell carcinoma (OSCC), and one randomised, open-label trial (CheckMate-648; N=675) comparing nivolumab plus chemotherapy to chemotherapy alone. The PBAC noted there was a statistically significant benefit in terms of overall survival (OS) for tislelizumab (HR = 0.66, 95% CI: 0.54, 0.80) with the median OS increasing from 10.6 to 17.2 months, as well as an improvement in progression-free survival (PFS) (5.6 to 7.3 months, HR = 0.62, 95% CI: 0.52, 0.75). The PBAC noted that while there were differences in the outcomes of the trials and the populations studied, as detailed in paragraph 6.6, these were unlikely to substantially impact on the comparison. The PBAC noted that the indirect treatment comparison presented in the submission indicated that there were no statistically significant differences in OS (HR = 0.89, 95% CI: 0.68, 1.17) or PFS (HR = 0.76, 95% CI: 0.59, 1.00) between tislelizumab and nivolumab. The Committee considered the claim of non-inferior efficacy of tislelizumab compared to nivolumab was reasonable.
- 7.11 The PBAC noted the submission presented an indirect treatment comparison of the treatment related adverse events, and any grade 3 or 4 treatment related adverse events which suggested there were no differences between tislelizumab and nivolumab. The PBAC the claim of non-inferior safety of tislelizumab compared to nivolumab was reasonable.
- 7.12 The PBAC noted the submission presented a cost-minimisation approach (CMA) of tislelizumab compared to nivolumab. The PBAC considered that tislelizumab would be cost-effective at the same or lower cost per 3-weekly treatment cycle as for nivolumab, using the effective ex-manufacturer price of nivolumab. The PBAC considered that tislelizumab 200 mg 3-weekly is equi-effective to nivolumab 360 mg 3-weekly.
- 7.13 The PBAC noted that the financial estimates provided in the submission resulted in a small cost saving to the PBS/RPBS driven by substitution of nivolumab 2-weekly (as discussed in paragraph 6.41). The PBAC noted the revised listing is expected to increase the number of patients treated by approximately 12% per year.
- 7.14 The PBAC considered it was appropriate for tislelizumab to be included in the risk sharing arrangement currently in place for nivolumab for gastro-oesophageal cancer.

The PBAC considered any increase in utilisation was likely to be small and should be accommodated within the existing expenditure caps with no increase.

- 7.15 The PBAC recommended that tislelizumab should be treated as interchangeable with nivolumab and pembrolizumab for advanced or metastatic gastro-oesophageal cancers.
- 7.16 The PBAC advised that tislelizumab is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC recommended that the Early Supply Rule should not apply.
- 7.18 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because tislelizumab is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over nivolumab, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.
- 7.19 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. Amount	No. of Rpts
TISLELIZUMAB Injection	NEW (Public) NEW (Private)	200 mg (2 vials)	7
<b>Available brands</b>			
Tevimbra (tislelizumab 100 mg/10 mL injection, 10 mL vial)			
<b>Restriction Summary – NEW / Treatment of Concept: NEW</b>			
<b>Category / Program:</b> Section 100 – Efficient Funding of Chemotherapy - Public and Private Hospitals			
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners			
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required – STREAMLINED - [new code]			
<b>Administrative Advice:</b> No increase in the maximum amount or number of units may be authorised.			
<b>Administrative Advice:</b> No increase in the maximum number of repeats may be authorised.			
<b>Administrative Advice:</b> Special Pricing Arrangements apply.			
<b>Caution:</b> When administering tislelizumab in combination with chemotherapy, administer tislelizumab before chemotherapy when both are given on the same day.			
<b>Caution:</b> In the first few months after starting immunotherapy, a transient tumour flare may occur that may be mistaken as disease progression despite an overall positive response to treatment			
<b>Indication:</b> Advanced or metastatic gastro-oesophageal cancer			

	<b>Clinical criteria:</b>
	Patient must be untreated (up until initiating this drug) with programmed cell death-1/ligand-1 (PD-1/PD-L1) inhibitor therapy for gastro-oesophageal cancer
	<b>AND</b>
	<b>Clinical criteria:</b>
	Patient must have/have had, at the time of initiating treatment with this drug, a WHO performance status no higher than 1,
	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must not be undergoing treatment with this drug as a PBS benefit where the treatment duration extends beyond the following, whichever comes first: (i) disease progression despite treatment with this drug, (ii) 24 months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.

***This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.***

## 9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

## 10 Sponsor's Comment

BeiGene Aus Pty Ltd welcomes the PBAC's positive recommendation to include tislelizumab on the PBS for advanced or metastatic gastro-oesophageal cancer. We commend the PBAC's efforts to improve access to care for Australians living with these cancers. BeiGene is committed to ensuring patients have timely access to innovative treatments and looks forward to working with the Department of Health to implement this important PBS listing.