An addendum to this Public Summary Document has been included at the end of the document.

5.18 TORIPALIMAB, Solution concentrate for I.V. infusion 240 mg in 6 mL (40 mg per mL), Zytorvi®, Dr Reddy's Laboratories Australia 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 the treatment of recurrent or metastatic nasopharyngeal carcinoma (RM-NPC).

1.2 Listing was requested on the basis of a cost-effectiveness analysis versus standard of care, defined as a platinum-containing chemotherapy doublet, specifically, cisplatin and gemcitabine (Cis+Gem). The submission presented a cost-effectiveness analysis for first-line (1L) treatment of RM-NPC, only; no economic evaluation for the second-line (2L) treatment of RM-NPC was presented.

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

Component	Description
Population	First-line treatment of adults with metastatic or with recurrent, locally advanced NPC. Second-line treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.
Intervention	First-line treatment: Toripalimab 240 mg once every three weeks, intravenous infusion administration in combination with gemcitabine (1000 mg/m^2) and cisplatin (80 mg/m^2) for six cycles, followed by toripalimab 240 mg monotherapy every three weeks for up to 24 months. Second-line treatment: Toripalimab monotherapy 3 mg/kg once every two weeks for a treatment cycle of 4 weeks, intravenous infusion administration.
Comparator	First-line treatment: Platinum-containing chemotherapy doublet (cisplatin-gemcitabine; SoC). Second-line treatment: Other chemotherapy regimens.
Outcomes	Efficacy: Overall survival, progression-free survival, objective response rate, duration of response Safety: treatment-emergent and treatment-related adverse events.
Clinical claim	In patients with RM-NPC with no prior systemic therapy, toripalimab in combination with chemotherapy is superior in terms of effectiveness and non-inferior in terms of safety compared to SoC chemotherapy. In patients with RM-NPC who have previously progressed while on chemotherapy, toripalimab provides a clinically meaningful treatment response and duration of response, while demonstrating a manageable safety profile.

Source: Table 1-1, pp 25 of the submission.
NPC, nasopharyngeal carcinoma; SoC, standard of care

2 Background

Registration status

2.1 Toripalimab was approved for registration by the Therapeutic Goods Administration (TGA) on 16 January 2025 for the following indications:

- in combination with cisplatin and gemcitabine, for the first-line treatment of adults with metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NPC).
- as a single agent, for the treatment of adults with recurrent unresectable or metastatic NPC with disease progression on or after a platinum-containing chemotherapy.

3 Requested listing

MEDICINAL PRODUCT Form	Dispensed Price Max Amt	Max. Amount	№.of Rpts
TORIPALIMAB 240 mg/6ml vial	$ (public) $ (private)	1 [a]	8
Available brands			
Zytorvi®. Dr Reddy's Laboratories Australia			

Source: Table1-4 of the submission, of the submission.
a: this was presented as a maximum amount of one pack/vial, or 240 mg

Category / program: **Section 100—Efficient Funding of Chemotherapy Public/Private hospitals.**
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives.
Restriction Type—assessment time by Services Australia—Method of obtaining authority approval (if Authority Required) ☒Authority Required—Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia; retrospective audit of patient records possible))
Episodicity: N/A.
Severity: Recurrent or metastatic.
Condition: Nasopharyngeal carcinoma.
Indication: Recurrent or metastatic nasopharyngeal carcinoma.
Treatment Phase: Initial and continuing.
Clinical criteria:
Patient must not have received prior systemic therapy for this condition, with the exception of neoadjuvant/adjuvant chemotherapy,
AND
Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
Treatment criteria:
Patient must be undergoing combination therapy consisting of: (i) toripalimab, (ii) chemotherapy; OR Patient must be undergoing monotherapy with this drug after receiving no longer than 6 cycles of chemotherapy; OR Patient must be undergoing monotherapy with this drug due to a contraindication/intolerance to chemotherapy, requiring temporary/permanent discontinuation; document the details in the patient's medical records;
AND
Patient must not be undergoing treatment with this drug beyond 24 months from the first administered dose,
AND
Patient must be undergoing treatment with this drug for the first time; OR Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Administrative Advice: No increase in the maximum amount or number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Category / program: Section 100—Efficient Funding of Chemotherapy Public/Private hospitals.
Prescriber type: ☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives.
Restriction Type—assessment time by Services Australia—Method of obtaining authority approval (if Authority Required) ☒Authority Required—Streamlined [new/existing code] (specification of 4-digit code by prescriber to certify that they have read the PBS restriction; no prior assessment by Services Australia; retrospective audit of patient records possible)
Episodicity: N/A.
Severity: Recurrent or metastatic.
Condition: Nasopharyngeal carcinoma.
Indication: Recurrent or metastatic nasopharyngeal carcinoma.
Treatment Phase: Initial and continuing.
Clinical criteria:
Patient must have received prior systemic therapy for this condition.
AND
Patient must not have experienced disease progression having received a PD-(L)1 inhibitor in a prior line of treatment.
AND
Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug.
Treatment criteria:
Must be the only PBS subsidised treatment.

AND
Patient must not be undergoing treatment with this drug beyond 24 months from the first administered dose,
AND
Patient must be undergoing treatment with this drug for the first time; OR Patient must be undergoing continuing treatment with this drug, with each of the following being true: (i) all other PBS eligibility criteria in this restriction are met, (ii) disease progression is absent.
Administrative Advice: At the time of the authority application, medical practitioners should request the appropriate number of vials for a single dose based on the patient's weight, as per the approved Product Information.
Administrative Advice: No increase in the maximum number of repeats may be authorised.

3.1 The submission did not propose an effective price, stating that "The list price is used in the model as the effective price is to be confirmed following a positive recommendation". It was therefore unclear during the evaluation as to what the requested price was and whether there was an effective price. The pre-PBAC response stated that the effective ex-manufacturer price (EMP) requested had been reduced from $ to $ per 240 mg vial.

3.2 The proposed dosage of toripalimab is 240 mg administered every 3 weeks in combination with chemotherapy in the 1L setting. The proposed maximum quantity of one vial of toripalimab (240 mg) provides sufficient treatment for 21 days at the recommended dose in the 1L setting for both combination (with chemotherapy) or maintenance therapy.

3.3 The proposed dosage of toripalimab is 3 mg/kg every 2 weeks when administered as monotherapy in the 2L setting. For patients receiving toripalimab monotherapy in the 2L setting, the submission stated that medical practitioners should request the appropriate number of vials for a single dose, based on the patient's weight.

3.4 The requested restriction included the statement: "Patient must have/have had a WHO performance status score of no greater than 2 at treatment initiation with this drug." However, the JUPITER-02 trial and the POLARIS-02 study included only patients with Eastern Cooperative Oncology Group (ECOG) performance status scores of 0 or 1.

3.5 The 1L requested restriction did not restrict use of toripalimab to patients who were not amenable to salvage surgery or re-irradiation. However, patients enrolled in JUPITER-02 must have had RM-NPC that is not amenable for local regional treatment or curative treatment.

3.6 The PBAC noted no grandfathering provisions were requested.

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

4 Population and disease

4.1 NPC is an epithelial carcinoma that arises from the nasopharyngeal mucosal lining, and is often observed in the pharyngeal recess. Although it originates from similar tissue lineages as other head and neck epithelial tumours, NPC is distinct in terms of its epidemiology, histology, natural history, and treatment response.

4.2 NPC is classified histologically into four main pathological subtypes. The keratinising subtype of NPC (type I), which accounts for less than 20% of cases worldwide, is primarily seen in Western countries, including Australia. In contrast, in NPC-endemic regions with high-incidence rates, such as Southern China, Southeast Asia, the Middle East, and North Africa, patients predominantly present with undifferentiated non-keratinising carcinoma (type III), which constitutes around 95% of NPC cases in these jurisdictions. The remaining cases are primarily differentiated non-keratinising carcinoma (type II). A further, rare subtype is basaloid squamous cell carcinoma. Both non-keratinising subtypes (types II and III) are associated with latent Epstein-Barr virus (EBV) infection and are more responsive to radiation therapy.

4.3 Non-keratinising subtypes also tend to have better survival outcomes compared to the keratinising subtype. A number of studies have reported this relationship, some examples include:

- Murakami 2020[1] reported on the outcomes of 59 consecutive patients who were referred to a single department from May 2009 to September 2017 for chemoradiation therapy for locally advanced NPC. Fifty-one patients (47 non-keratinising and four keratinising) were analysed. Three-year progression-free survival (PFS) for patients with keratinising and non-keratinising squamous cell carcinoma (SCC) were 25.0% and 60.5%, respectively (p=0.033, hazard ratio [HR] 4.851 (95% CI: 1.321, 17.814)).
- Reddy 1995[2] reported the survival outcomes of 50 NPC patients (17 with keratinising, 33 with non-keratinising) treated over a period of 15 years (1971-1986) with high-dose megavoltage irradiation with curative intent. Most patients (62%) had advanced disease with the remaining patients having early-stage tumours. The 5-year survival rates were 35% for all patients, 6% for those with keratinising squamous-cell cancers (KSCCs), and 51% for non-keratinising (p=0.001).
- Numerous studies have been published analysing Surveillance, Epidemiology and End-Results (SEER) data. One of the largest was reported by Wu 2019[3] that analysed data from non-metastatic NPC patients between 2004 and 2014. The study included 2,845 patients (1,218 (42.8%), 849 (29.8%), and 778 (27.3%)) with KSCCs,

[1] Murakami N, Mori T, Kubo Y, Yoshimoto S, Ito K, Honma Y, Ueno T, Kobayashi K, Okamoto H, Boku N, Takahashi K, Inaba K, Okuma K, Igaki H, Nakayama Y, Itami J. Prognostic impact of immunohistopathologic features in definitive radiation therapy for nasopharyngeal cancer patients. *J Radiat Res*. 2020 Jan 23;61(1):161-168. doi: 10.1093/jrr/rrz071. PMID: 31822892; PMCID: PMC6976734.

[2] Reddy SP, Raslan WF, Gooneratne S, Kathuria S, Marks JE. Prognostic significance of keratinization in nasopharyngeal carcinoma. *Am J Otolaryngol*. 1995 Mar-Apr;16(2):103-8. doi: 10.1016/0196-0709(95)90040-3. PMID: 7540805.

[3] Wu SG, Lian CL, Wang J, Zhang WW, Sun JY, Lin Q, He ZY. The effect of histological subtypes on survival outcome in nasopharyngeal carcinoma after extensive follow up. *Ann Transl Med*. 2019 Dec;7(23):768. doi: 10.21037/atm.2019.11.75. PMID: 32042784; PMCID: PMC6989997.

differentiated non-keratinising carcinoma (DNKC), and undifferentiated non-keratinising carcinoma (UNKC), respectively). The authors reported there was comparable distribution of tumour-node-metastasis (TNM) stage among the three histological subtypes (p=0.191). The median follow-up time was 45 months (range, 0–143 months). Multivariate Cox regression analysis, adjusted by age, race/ethnicity, tumour stage, nodal stage, and chemotherapy indicated that those with KSCC had poorer NPC-specific survival than those with UNKC (HR 2.323, 95% CI: 1.636–3.297, p<0.001).

4.4 The pre-PBAC response acknowledged that a higher proportion of patients in Western countries such as Australia are expected to be diagnosed with the keratinising subtype of NPC, which typically has a worse prognosis, but stated that a substantial proportion of patients in Australia are still expected to have non-keratinising NPC.

4.5 The ESC noted that as an epithelial carcinoma, it can take a while to progress and that patients diagnosed with NPC typically present quite late.

4.6 The ESC noted that use of toripalimab in 1L and 2L RM-NPC is supported by a Category 1 recommendation in the National Comprehensive Cancer Network guidelines (National Comprehensive Cancer Network (NCCN), 2025). The ESC noted that the 2L recommendation is for use as monotherapy following disease progression on or after platinum-containing therapy.

4.7 Toripalimab is a humanised IgG_{4k} (gamma 4, kappa) monoclonal antibody specific for programmed cell death protein 1 (PD-1), a co-inhibitory receptor expressed on T-cells. Toripalimab has a high affinity and blocks interaction between PD-1 and its ligand, programmed cell death ligand 1 (PD-L1; B7-H1 or CD274).

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

5 Comparator

5.1 The ESC noted that there are no TGA approved therapies specifically for NPC and that in clinical practice, patients are treated with chemotherapy combinations that have been in use for more than 20 years.

5.2 The ESC agreed that the submission reasonably nominated standard of care chemotherapy as the main comparator in the 1L setting, specifically cisplatin-gemcitabine (Cis+Gem).

5.3 In the 2L setting, single-agent chemotherapy was nominated as the comparator on the basis that treatment in 2L is extremely limited and involves gemcitabine as a single-agent and the only PBS-listed therapy available.

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

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician presented an overview of

the current treatment of RM-NPC in Australia and discussed the results of the JUPITER-02 trial, stating that there is an unmet need for new treatment options that will improve survival, where the typical patient is young and otherwise well.

Consumer comments

6.2 The PBAC noted and welcomed the input from Rare Cancers Australia and the Medical Oncology Group of Australia via the Consumer Comments facility on the PBS website. Rare Cancers Australia highlighted that patients with NPC have a poor prognosis, that there is significant morbidity associated with the condition and that patients face significant financial burden. The Medical Oncology Group of Australia (MOGA) expressed its strong support for the toripalimab submission, categorising it as one of the therapies of "high priority for PBS listing" on the basis of the JUPITER-02 and POLARIS-02 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for toripalimab, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[4], based on a comparison with placebo (in combination with cisplatin and gemcitabine). The PBAC also noted there was input from one individual who provided contact details but no comments.

Clinical studies/trials

6.3 The submission was based on one head-to-head trial comparing 3-weekly (Q3W) toripalimab 240 mg in combination with Cis+Gem for up to 6 cycles followed by toripalimab 240 mg monotherapy (n=146) versus 3-weekly placebo in combination with Cis+Gem for up to 6 cycles followed by placebo monotherapy (n=143) as a 1L treatment for patients with RM-NPC (JUPITER-02).

6.4 The submission also presented a single-arm, multicentre phase II study investigating the use of toripalimab 3 mg/kg via infusion every 2 weeks in 190 patients with previously treated RM-NPC who were refractory to at least one line of SOC chemotherapy (POLARIS-02).

6.5 Details of the studies presented in the submission are provided in Table 2.

[4] 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: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
JUPITER-02	A Phase III, Randomized, Placebo Controlled, Multicenter, Double-Blind Study Comparing Toripalimab Injection (JS001) Combined with Chemotherapy Versus Placebo Combined with Chemotherapy for Recurrent or Metastatic Nasopharyngeal Cancer	15 January 2021 22 November 2021 (Addendum 1) 2 September 2022 (Addendum 2; V1.0) 13 October 2022 (Addendum 2; V1.1)
	Mai, H. Q., Chen, Q. Y., Chen, D., Hu, C., Yang, K., Wen, J., Li, J., Shi, Y., Jin, F., Xu, R., Pan, J., Qu, S., Li, P., Hu, C., Liu, Y. C., Jiang, Y., He, X., Wang, H. M., Lim, W. T.,. .. Xu, R. H. 2023, Toripalimab Plus Chemotherapy for Recurrent or Metastatic Nasopharyngeal Carcinoma: The JUPITER-02 Randomised Clinical Trial [Clinical Trial, Phase III Comparative Study Multicentre Study Randomised Controlled Trial Research Support, Non-U.S. Gov't]	JAMA 2023, 330(20), 1961-1970.
	Mai, H. Q., Chen, Q. Y., Chen, D., Hu, C., Yang, K., Wen, J., Li, J., Shi, Y. R., Jin, F., Xu, R., Pan, J., Qu, S., Li, P., Hu, C., Liu, Y. C., Jiang, Y., He, X., Wang, H. M., Lim, W. T., Xu, R. H. 2021, Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicentre randomised phase 3 trial [Clinical Trial, Phase III Multicentre Study Randomised Controlled Trial Research Support, Non-U.S. Gov't].	Nature Medicine 2021, 27(9), 1536-1543.
POLARIS-02	A Multicenter, Open-label Phase Ib/II Clinical Study of JS001 in Treatment of Advanced Gastric Adenocarcinoma, Esophageal Squamous Cell Carcinoma, Nasopharyngeal Carcinoma, and Head and Neck Squamous Cell Carcinoma - Cohort 3 Nasopharyngeal Carcinoma	7 April 2020
	Wang, F.H., Wei, X.L., Feng,J.,Li, Q., Xu, N., Hu, X,C.,; Liao, W;,Jiang, Y., Lin, X,Y., Zhang,Q, Y., Yuan, X, L.,; Huang, H, X.,Chen, Y., Dai, G, H., Shi, J, H., Shen,L., Yang,S, J., Shu, Y, Q., Liu, Y, P., Wang, W.,Wu, H., Feng, H., Yao, S., and Xu, R, H. 2021, Efficacy, Safety, and Correlative Biomarkers of Toripalimab in Previously Treated Recurrent or Metastatic Nasopharyngeal Carcinoma: A Phase II Clinical Trial (POLARIS-02).	Journal of Clinical Oncology 2021, 39, 404-712.

Source: Table 2-2, p43 of the submission.

6.6 The key features of the direct randomised trial and the clinical study are summarised in Table 3.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
JUPITER-02	289	R, DB 36.7 months[a]	Low	1L RM-NPC	PFS, OS, ORR	PFS, OS
POLARIS-02	190	SA 3.7 months[a]	High[b]	2L+ RM-NPC	ORR, PFS, OS	Not used

Source: compiled during the evaluation.
DB, double blind; N/A, not applicable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; R, randomised, RM-NPC = recurrent or metastatic nasopharyngeal carcinoma; SA = single-arm.
a: median follow-up
b: considered to be a 'fair' quality study by assessment with National Heart, Lung and Blood Institute (NHLBI) Quality Assessment Tool for Case Series Studies. Single arm nature results in 'high' risk of bias categorisation

6.7 The JUPITER-02 trial had two phases:

- a chemotherapy phase where patients were treated with toripalimab or placebo (in combination with Cis+Gem) for a maximum of six cycles; and
- a post-chemotherapy phase where patients who did not have progressive disease or were responding/stabilised, continued to receive randomised treatment (toripalimab or placebo) as maintenance therapy until any of the following occurred: excessive toxicity, disease progression, withdrawal of consent, the investigator's judgment that the patient was no longer receiving benefit, or a maximum of two years of treatment.

Cross-over was not permitted in the trial.

6.8 The ESC noted that the submission presented results of the POLARIS-02 study to support a request for use of toripalimab 2L. The ESC noted that the trial enrolled patients with predominantly (95.8%) non-keratinising NPC, and that the median duration of response as assessed by the independent review committee (IRC) was 14.9 months. While the submission claimed that toripalimab provides a clinically meaningful treatment response and duration of response to patients, and demonstrates a manageable safety profile, as the submission presented only the single-arm POLARIS-02 study to inform the assessment of toripalimab in the 2L setting, the comparative benefit/harms and magnitude of effect could not be determined. The PBAC noted the ORR was 20.5% with a median PFS of 1.9 months and median OS of 17.4 months.

Comparative effectiveness

6.9 The primary outcome of the JUPITER-02 trial was PFS as assessed with RECIST version 1.1 by IRC; see Table 4 for results at data cutoff 1 (DCO1) and data cutoff 2 (DCO2). Figure 1 and Figure 2 present the associated Kaplan-Meier (KM) curves.

6.10 Although DCO1 was an interim analysis, the stopping boundary for the trial was crossed and this analysis is considered the final PFS analysis. Patients who remained on the study drug in the investigational arm continued to receive toripalimab and patients in the control arm discontinued placebo following the Independent Data

Monitoring Committee's review of the interim analysis. Results at DCO2 include longer follow-up and have been provided for descriptive purposes.

6.11 The results indicate that treatment with toripalimab in combination with Cis+Gem resulted in statistically significantly improved PFS compared with placebo in combination with Cis+Gem, reducing the risk of progression or death by 48% at DCO1 (HR=0.52; 95% CI: 0.359, 0.740; p=0.0003) and DCO2 (HR=0.52; 95% CI: 0.374, 0.726; nominal p<0.0001). The ESC noted that median PFS for toripalimab treated patients was 11.7 months at DCO1 and 21.4 months at DCO2 (see Table 4) compared to 8.0 months at DCO1 and 8.2 months at DCO2 in the placebo arm and considered the improvement in median PFS to be clinically meaningful.

Table 4: PFS results in JUPITER-02: IRC assessed per RECIST v1.1 and per irRECIST (ITT Analysis Set; stratified by (i) ECOG performance status (0 versus 1) and (ii) disease stage (recurrent versus metastatic))

	Toripalimab + Cis+Gem N=146	**Placebo + Cis+Gem N=143**
PFS analysis (DCO1): median follow-up 10.68 months		
Per RECIST		
Events of progressive disease or death, n (%)	49 (33.6)	79 (55.2)
Stratified analysis HR[a] (95% CI); p value[b]	0.52 (0.359, 0.740); p=0.0003	
Median PFS, months (95% CI)	11.7 (11.04, NE)	8.0 (6.97, 9.53)
PFS rate (%) at 1 year (95% CI)	49.4 (36.41, 61.09)	27.9 (18.00, 38.75)
Difference of 1-year PFS rate (95% CI)	21.4 (5.1, 37.8)	
Per irRECIST		
Stratified analysis HR[a] (95% CI); p value[b]	0.48 (0.334, 0.705); p<0.0001	
PFS analysis (DCO2): median follow-up 21.82 months		
Per RECIST		
Events of progressive disease or death, n (%)	63 (43.2)	87 (60.8)
Censored, n (%)	83 (56.8)	56 (39.2)
No post-baseline tumour assessment, n (%)	2 (1.4)	5 (3.5)
No disease progression or death, n (%)	47 (32.2)	14 (9.8)
Missing ≥2 tumour assessments, n (%)	14 (9.6)	7 (4.9)
Started new anti-cancer therapy, n (%)	20 (13.7)	30 (31.0)
Stratified analysis HR[a] (95% CI); nominal p value[b]	0.52 (0.374, 0.726); p<0.0001	
Median PFS, months (95% CI)	21.4 (11.73, NE)	8.2 (7.03, 9.79)
1-year PFS rate (%) (95% CI)	59.0 (49.72, 67.16)	32.9 (24.55, 41.53)
Difference of 1-year PFS rate (95% CI)	26.1 (13.8, 38.3)	
2-year PFS rate (%) (95% CI)	44.8 (34.39, 54.71)	25.4 (16.95, 34.81)
Difference of 2-year PFS rate (95% CI)	19.4 (5.7, 33.1)	
Per irRECIST		
Stratified analysis HR[a] (95% CI); nominal p value[b]	0.49 (0.346, 0.686); p<0.0001	

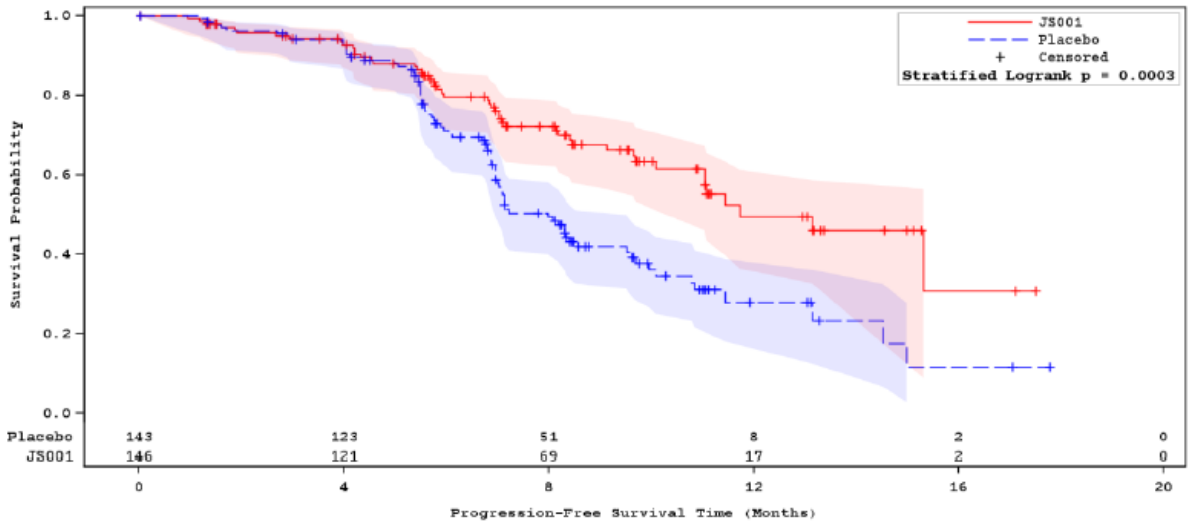
Source: Table 2-12, p59 and Table 2-13, p61 of the submission; Table 4, pp12-13 JUPITER-02 CSR Addendum 1 Final PFS (Attachment 2.3 to the submission.

CI, confidence interval; Cis+Gem, cisplatin and gemcitabine; DCO, data cutoff; HR, hazard ratio; IRC, independent review committee; irRECIST, Immune-Related Response Evaluation Criteria in Solid Tumours; ITT, intent-to-treat; NE, not estimable; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours;

a: the hazard ratio was estimated with the use of the Cox proportional hazards model. Efron's method was used to handle ties

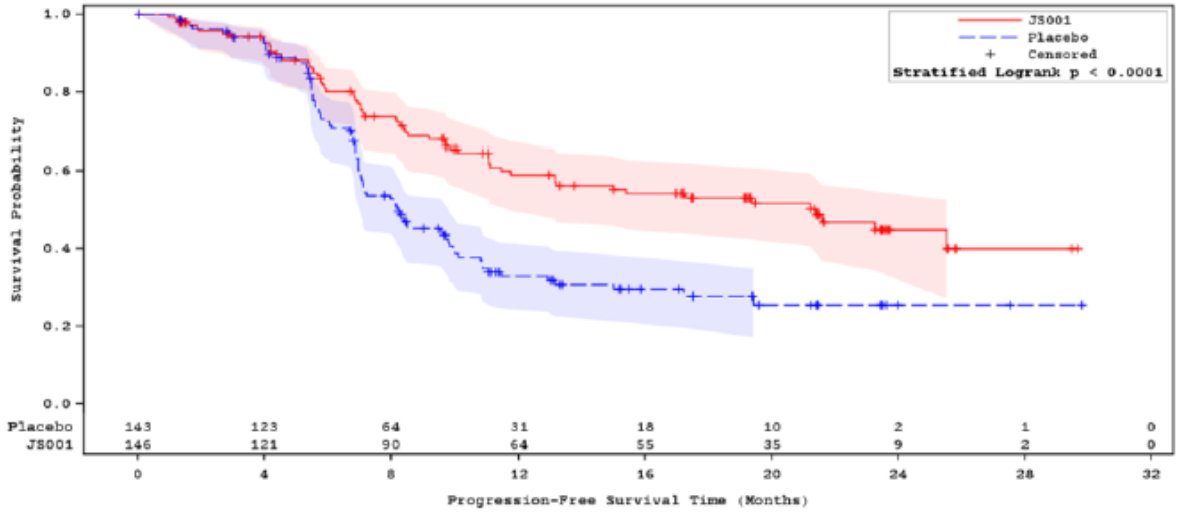
b: calculated using two-sided log-rank test. The p value threshold for statistical significance is 0.05

Figure 1: **Kaplan-Meier estimates of IRC-assessed PFS (DCO1) (ITT Population)**



Source: Figure 2-4, p 60 of the submission.
IRC, independent review committee; ITT, intent-to-treat; JS001, toripalimab

Figure 2: **Kaplan-Meier estimates of IRC-assessed PFS (DCO2) (ITT Population)**



Source: Figure 2-5, p61 of the submission.
IRC, independent review committee; ITT, intent-to-treat; JS001, toripalimab

6.12 The ESC noted that the submission presented the results of subgroup analyses of IRC-assessed PFS from DCO1, showing that the treatment effect of toripalimab with chemotherapy was favourable (although not necessarily statistically significant) across all pre-specified subgroups including baseline disease stage, EBV copy number, and PD-L1 expression status.

6.13 Overall survival was a key secondary outcome in the JUPITER-02 trial, however no multiplicity adjustments were made in the statistical analysis to account for multiple looks at the data, thus the estimate of statistical significance of the hazard ratio is uncertain. The results for the final analysis of OS in the ITT population at DCO4 (median

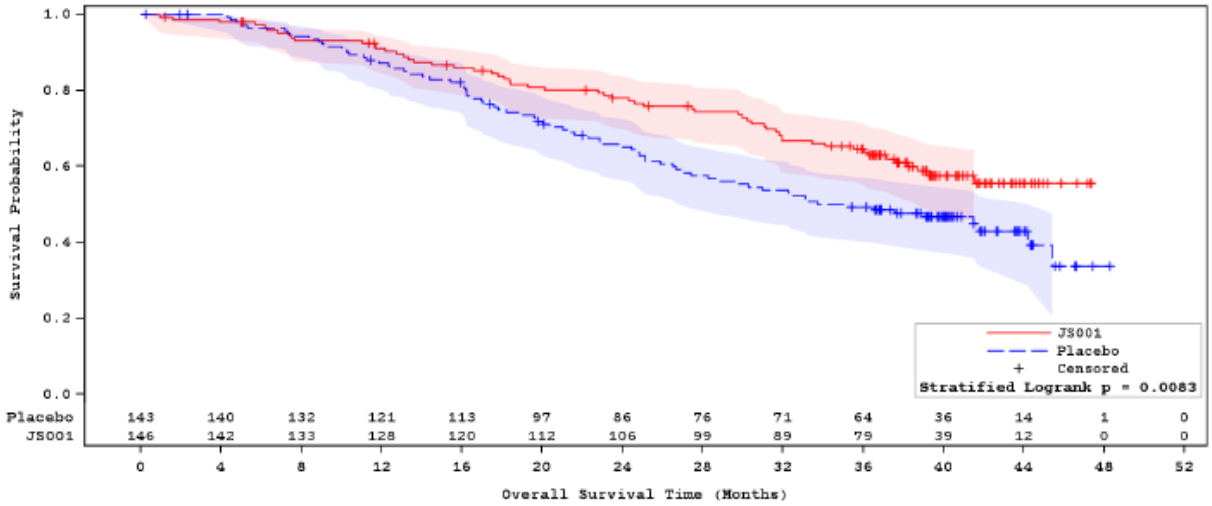
follow-up of 36.7 and 31.0 months in the toripalimab and placebo arms, respectively) are presented in Table 5 and Figure 3.

Table 5: Summary of OS in JUPITER-02

	Toripalimab + Cis+Gem N=146	Placebo + Cis+Gem N =143	Absolute difference	HR[b] (95% CI)
Number of deaths, n (%)	57 (39.0)	76 (53.1)	NR	NR
Median[a] OS months (95% CI)	NE (38.7, NE)	33.7 (27.01, 44.19)	NR	0.63 (0.446, 0.891) p = 0.0083
1-year OS rate (%) (95% CI)	90.9 (84.87, 94.62)	87.1 (80.36, 91.69)	3.8 (-3.5. 11.1)	NR
2-year OS rate (%) (95% CI)	78.0 (70.18, 83.97)	65.1 (56.50, 72.44)	12.9 (2.3, 23.4)	NR
3-year OS rate (%) (95% CI)	64.5 (55.86, 71.87)	49.2 (40.53, 57.32)	15.3 (3.6, 26.9)	NR

Source: Table 2-14, p64 of the submission.
CI, confidence interval; Cis+Gem, cisplatin and gemcitabine; HR, hazard ratio; NE, not estimable; NR, not reported; OS, overall survival
a: the stratified analyses used ECOG performance status (0 vs 1), and disease stage (recurrent vs metastatic) as recorded in the IWRS;
b: the hazard ratio was estimated with the use of the Cox proportional hazards model. Efron's method was used to handle ties.

Figure 3: Kaplan-Meier estimates of OS in JUPITER-02 (DCO4) (ITT Analysis set)



Source: Fig 2-8, p64 of the submission
ITT, intent-to-treat; JS001, toripalimab

6.14 The results suggest a benefit for toripalimab compared to placebo in terms of OS. Toripalimab resulted in a 37% reduction in the risk of death (HR=0.63; 95% CI: 0.446, 0.891; p=0.0083). Median OS was not reached in the toripalimab group, while the median OS in the placebo group was 33.7 months.

Comparative harms

6.15 Select adverse events reported in the JUPTER-02 trial are presented in Table 6.

Table 6: Summary of key adverse events in the JUPITER-02 trial

Adverse event	Toripalimab + Cis+Gem N=146; n (%)	Placebo + Cis+Gem N=143; n (%)	RD (95% CI)
Any TEAE	146 (100.0)	143 (100.0)	0.0 (0.0, 0.0)
Any TEAE leading to withdrawal of study drug	17 (11.6)	7 (4.9)	6.7 (0.5, 13.0)
Any TEAE leading to withdrawal of study drug, SAE	14 (9.6)	5 (3.5)	6.1 (0.4, 11.7)
TEAE, Grade ≥3	131 (89.7)	129 (90.2)	-0.5 (-7.4, 6.4)
TEAE, Any irAE	79 (54.1)	31 (21.7)	32.4 (21.9, 43.0)
TEAE, Any irAE with Grade ≥3	14 (9.6)	2 (1.4)	8.2 (3.0, 13.3)
Any SAE	64 (43.8)	62 (43.4)	0.5 (-11.0, 11.9)
Any SAE which is life-threatening	5 (3.4)	6 (4.2)	-0.8 (-5.2, 3.6)
Any study drug related SAE	56 (38.4)	52 (36.4)	2.0 (-9.2, 13.1)
Specific SAEs			
Neutropenia	15 (10.3)	9 (6.3)	4.0 (-2.4, 10.3)
Bone marrow failure	2 (1.4)	5 (3.5)	-2.1 (-5.7, 1.4)
Pneumonia	14 (9.6)	5 (3.5)	6.1 (0.4, 11.7)
Pulmonary tuberculosis	2 (1.4)	0	1.4 (-0.5, 3.3)
Hypokalaemia	1 (0.7)	3 (2.1)	-1.4 (-4.1, 1.3)

Source: Table 2-17, p69 and Table 2-18, p71 of the submission.
CI, confidence interval; irAE, immune-related adverse event; n, number of participants reporting data; N, total participants in group; RD, risk difference; SAE, serious adverse event; TEAE, treatment emergent adverse event

6.16 The evaluation noted there was a higher incidence of any and serious treatment-emergent adverse event (TEAE) leading to withdrawal of study drug, any and ≥Grade 3 immune-related adverse events, and cases of pneumonia in those treated with toripalimab (Cis+Gem) compared to placebo (Cis+Gem) in the JUPITER-02 trial.

6.17 The ESC noted that investigator-assessed immune-related adverse events (irAEs), were significantly higher in the toripalimab group than the placebo group with common immune-related AEs including hypothyroidism (23.3% vs. 8.4%), rash (14.4% vs. 6.3%), and pruritus (8.2% vs. 4.2%), that the incidence of Grade 3 or higher immune-related AEs were also higher in the toripalimab group (9.6%) compared to the placebo group (1.4%), and that while nausea and vomiting occurred in more than 67% of patients, the events were fairly well controlled. The ESC considered there were no new safety signals raised and that the adverse events reported were in line with what would be expected for PD-L1 inhibitors.

Benefits/harms

6.18 A summary of the comparative benefits and harms for toripalimab versus placebo is presented in Table 7.

Table 7: Summary of comparative benefits and harms for toripalimab and placebo

Event	Toripalimab + Cis+Gem	Placebo + Cis+Gem	Absolute Difference	HR (95% CI)
Progression free survival (median duration of follow up 21.82 months)				
Progressed, n (%)	63/146 (43.2%)	87/143 (60.8%)	-	0.52 (0.374, 0.726) p<0.0001
Median PFS, months (95% CI)	21.4 (11.73, NE)	8.2 (7.03, 9.79)	13.2 months	
% not progressed at 24 months (95% CI)	44.8 (34.39, 54.71)	25.4 (16.95, 34.81)	19.4 (5.7, 33.1)	
Overall survival (median duration of follow up 36.04 months)				
Deaths, n/N (%)	57/146 (39.0%)	76/143 (53.1%)	-	0.63 (0.446, 0.891) p = 0.0083
Median OS, months (95% CI)	NE (38.7, NE)	33.7 (27.01, 44.19)	NR	
% Alive at 12 months (95% CI)	90.9 (84.87, 94.62)	87.1 (80.36, 91.69)	3.8 (-3.5. 11.1)	
% Alive at 24 months (95% CI)	78.0 (70.18, 83.97)	65.1 (56.50, 72.44)	12.9 (2.3, 23.4)	
% Alive at 36 months (95% CI)	64.5 (55.86, 71.87)	49.2 (40.53, 57.32)	15.3 (3.6, 26.9)	
Adverse events				
TEAE, Any irAE	79 (54.1)	31 (21.7)	32.4 (21.9, 43.0)	-
TEAE, Any irAE with Grade ≥3	14 (9.6)	2 (1.4)	8.2 (3.0, 13.3)	-
Any TEAE leading to withdrawal of study drug	17 (11.6)	7 (4.9)	6.7 (0.5, 13.0)	-
Pneumonia	14 (9.6)	5 (3.5)	6.1 (0.4, 11.7)	-

Source: complied during the evaluation.
CI, confidence interval; Cis+Gem, cisplatin and gemcitabine; HR, hazard ratio; irAE, immune-related adverse event; n, number of participants reporting data; N, total participants in group; OS, overall survival; PFS, progression-free survival; RD, risk difference; TEAE, treatment emergent adverse event

6.19 On the basis of direct evidence presented by the submission, for every 100 patients treated with toripalimab in combination with Cis+Gem followed by toripalimab maintenance therapy in comparison with placebo in combination with Cis+Gem followed by placebo maintenance therapy:

- Approximately 19 additional patients will remain progression-free after two years (median follow-up of 21.82 months),
- Approximately 15 additional patients will be alive after three years (median follow-up of 36.04 months),
- Approximately 32 additional patients will experience any immune-related adverse event,
- Approximately 8 additional patients will experience a Grade ≥3 immune-related adverse event,
- Approximately 7 additional patients will experience a treatment-emergent adverse event leading to withdrawal of the drug,
- Approximately 6 additional patients will experience pneumonia.

Clinical claim

6.20 The submission described toripalimab in combination with Cis+Gem followed by toripalimab maintenance therapy as superior in terms of effectiveness compared to

placebo in combination with Cis+Gem followed by placebo maintenance therapy. The claim was adequately supported by the trial data but the magnitude of the effect in the Australian population was uncertain. The evaluation considered the key issue was uncertainty about the generalisability of the JUPITER-02 results to the proposed PBS population and Australian care setting based on differences in (i) ethnicity; (ii) histologic subtype of NPC with varying survival outcomes; and (iii) overall performance status. The ESC noted that the Pre-Sub-Committee Response (PSCR) (p1) highlighted that differences in ethnicity are not expected to substantially impact the comparative efficacy results from JUPITER-02 given that monoclonal antibodies do not undergo traditional drug related metabolism like liver and gut metabolism, properties that make them less likely to be affected by ethnic differences. The ESC noted that toripalimab has predominantly been studied in Asian cohorts with endemic NPC of the non-keratinising squamous cell variant. While the ESC noted that the keratinising squamous cell variant is more common in Australia (~25%) than in JUPITER-02 (<3%) and that this variant is associated with poorer survival outcomes, the ESC considered specific data on the efficacy of toripalimab in patients with this subtype is unlikely to be forthcoming given the difficultly of enrolling a sufficient number of patients in a trial over a reasonably defined period of time.

6.21 The submission described toripalimab in combination with Cis+Gem followed by toripalimab maintenance therapy as non-inferior in terms of safety compared to placebo in combination with Cis+Gem followed by placebo maintenance therapy. This claim was not adequately supported as a greater number of patients in the toripalimab arm of the JUPITER-02 trial experienced any immune-related adverse event, a Grade ≥3 immune-related adverse event, any treatment-emergent adverse event leading to withdrawal of study drug and pneumonia. The ESC considered that the safety profile of toripalimab was similar to that of other PDL1-inhibitors.

6.22 The ESC considered that the clinical data submitted supported the clinical effectiveness claim.

6.23 For patients with RM-NPC with no prior systemic therapy, the PBAC considered that the claim that toripalimab in combination with chemotherapy has superior comparative effectiveness compared to standard of care chemotherapy to be supported in a population with predominantly non-keratinising NPC. However, the PBAC considered the magnitude of clinical benefit in a population where a higher proportion of patients have keratinised NPC, to be unclear.

6.24 For patients with RM-NPC who have previously progressed while on chemotherapy, the PBAC considered that the clinical claim that toripalimab provides a clinically meaningful treatment response and duration of response to be reasonable.

6.25 The PBAC considered the claim of non-inferior safety of toripalimab versus standard of care chemotherapy in the first-line RM-NPC setting was not adequately supported by the data presented.

Economic analysis

6.26 The submission presented a cost-utility analysis comparing toripalimab in combination with Cis+Gem followed by toripalimab maintenance therapy and placebo in combination with Cis+Gem followed by placebo maintenance therapy for 1L treatment of RM-NPC. This was consistent with a claim of superior effectiveness.

6.27 The submission did not present an economic evaluation for second-line use of toripalimab. The PSCR stated that second-line use is likely to be low and that there was precedent for a line-agnostic listing (para 7.15, selpercatinib Public Summary Document (PSD), July 2024 PBAC meeting), particularly since the 2025 version of the National Comprehensive Cancer Network Guidelines for head and neck cancer lists toripalimab used in combination with cisplatin and gemcitabine as the preferred first-line treatment.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Toripalimab in combination with chemotherapy for up to six cycles followed by toripalimab monotherapy for up to two years versus placebo in combination with chemotherapy for up to six cycles followed by placebo monotherapy for up to two years
Time horizon	35 years in the model base case versus median follow-up of 21.82 months (DCO2) for PFS and 36.7 months (DCO4) for OS in the toripalimab arm of the trial
Outcomes	LYG and QALYs
Methods used to generate results	Partitioned survival model
Health states	PFS, PD, death
Cycle length	1 month
Extrapolation method	Parametric model fitted to each treatment arm with log-normal selected in base case for toripalimab and placebo OS (and log-normal and log-logistic for toripalimab and placebo PFS, respectively) based on goodness of fit/ based on statistical fit, visual fit and clinical plausibility. Switch from KM to extrapolation occurred at 20 months for OS and PFS in both arms. No convergence was assumed to occur within the modelled time horizon.
Health related quality of life	Progression-free = 0.79; Progressed = 0.71

Source: compiled during the evaluation.
DCO, data cutoff; KM, Kaplan-Meier; LYG, life year gained; OS, overall survival; PFS, progression-free survival; QALYs, quality adjusted life years.

6.28 The evaluation and the ESC noted that the submission inappropriately applied a half cycle correction to drug acquisition costs. As these costs will be accrued at the beginning of the cycle regardless of when a patient stops taking them (toripalimab is expected to be dispensed on 21-day intervals), this was inappropriate. During the evaluation, the half cycle correction was removed for drug acquisition costs. This increased the base case incremental cost-effectiveness ratio (ICER) from $155,000 to < $255,000/quality adjusted life year (QALY) gained to $155,000 to < $255,000/QALY gained. All presented results below are reflective of these corrections.

6.29 The submission assumed a time horizon of 35 years, noting that median survival among subjects in JUPITER-02 who were treated with toripalimab was not reached

(median follow up 36.7 months). The evaluation considered that a 35-year time horizon was optimistic and uncertain. The ESC noted that the baseline age for patients entering the model was 47 years and considered that a time horizon of 35 years was too long in the context of a non-curative treatment. The ESC noted the ICER was sensitive to the time horizon and that with a time horizon of 10 years, the base case ICER increased to $255,000 to < $355,000 (Table 11).

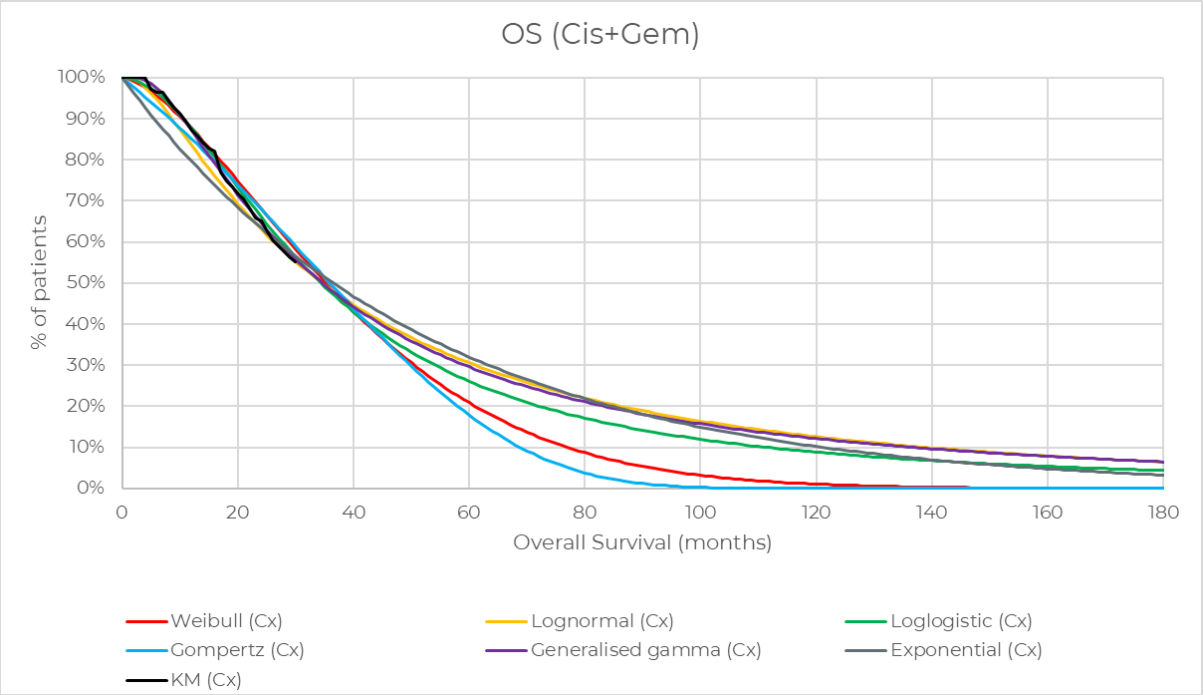
6.30 The evaluation and the ESC noted that the PBAC recommended cetuximab and pembrolizumab on the basis of time horizons of 5 years for recurrent or metastatic (R/M) head and neck squamous cell carcinoma (SCCHN) (para 7.8, cetuximab PSD, March 2018 PBAC Meeting and para 7.13, pembrolizumab PSD, November 2021 PBAC meeting). The pre-PBAC response acknowledged that the time horizon presented in the base case economic model (35 years) may be optimistic; however, asserted that a comparison to the time horizon considered in SCCHN is inappropriate given the vastly different prognosis of the two diseases. The pre-PBAC response noted that based on results from the JUPITER-02 trial, median OS in toripalimab treated patients was not yet reached after median follow up of over 36 months compared to the median OS of 13 months in pembrolizumab treated patients with SCCHN in the Keynote 048 trial (Table 8, pembrolizumab PSD, November 2021 PBAC Meeting). The PBAC noted the pre-PBAC response presented a comparison of outcomes for a population with largely non-keratinising NPC and SCCHN. The PBAC noted more patients in an Australian population would have keratinising NPC which has a similar prognosis to SCCHN.

6.31 The timepoint of the switch from Kaplan-Meier (KM) to extrapolation was 20 months for PFS and OS in both arms. The submission fitted the extrapolation in each treatment arm with log-normal extrapolation selected in the base case for OS in both arms, and log-normal and log-logistic for toripalimab and placebo PFS, respectively. The submission fitted the distributions separately for each treatment arm. The appropriateness of fitting separate curves was unclear as the submission did not provide an analysis assessing whether the proportional hazard assumption was violated. The ESC noted more KM data could have been used for OS before switching to extrapolation with 36/143 and 39/146 patients at risk at 40 months in the placebo and toripalimab arms, respectively (see Figure 3). The ESC noted the ICER increased by % if KM data to 40 months was used.

6.32 The ESC considered the submission's choice of log-normal extrapolation of PFS for the toripalimab arm and log-logistic extrapolation for the placebo arm to be reasonable, noting that these were the best fitting curves based on average AIC and BIC and the model was not sensitive to choice of extrapolation function.

6.33 The ESC considered the submission's choice of the log-normal distribution for placebo for OS (Figure 4) to be reasonable and consistent with the AIC and BIC criteria.

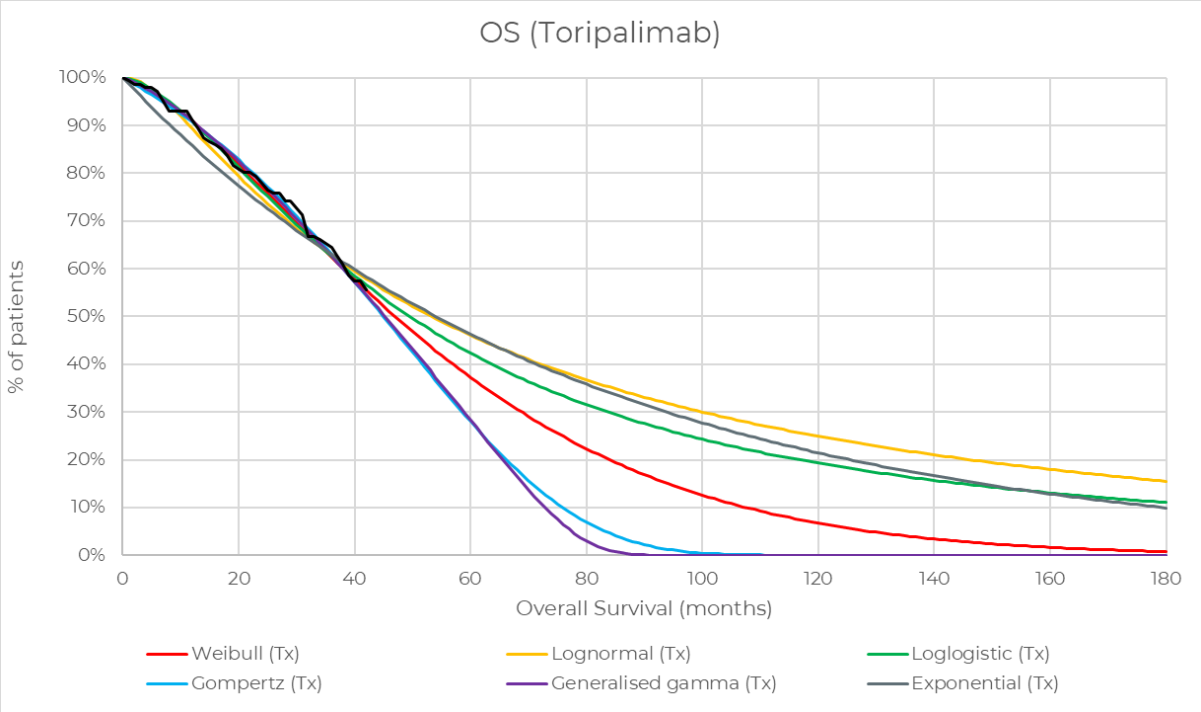
Figure 4: Overall survival parametric curves for placebo (Cis+Gem alone)



Source: Figure 3-3, p 87 of the submission

6.34 In relation to the choice of extrapolation function for OS for toripalimab, the ESC noted that this was not based on statistical fit, but a mix of statistical fit, visual fit and clinical plausibility. The ESC noted that the submission acknowledged that the best statistical fit for OS in the toripalimab arm was the Gompertz model but stated that it was not used due to concerns about clinical plausibility, as it predicted lower survival in the toripalimab compared to the placebo arm, which did not align with the observed data from JUPITER-02 (Figure 5).

Figure 5: Overall survival parametric curves for toripalimab (in combination with Cis+Gem)



Source: Figure 3-2, p 86 of the submission.

6.35 The ESC noted using a log-logistic function in both arms, which had a better AIC/BIC than the log-normal function for toripalimab and appeared to fit the data reasonably well, increased the ICER by |%. The ESC noted that the model was highly sensitive to using different extrapolation functions for OS, with the ICER increasing by +|% with Gompertz and by +|% with Weibull.

6.36 Despite the long time horizon, no convergence of OS was assumed by the submission.

6.37 Time on Treatment (ToT) was sourced from the JUPITER-02 trial, and observed data was used until the point where they could potentially become unreliable. Given that the treatments (toripalimab and Cis+Gem) have a time-limited duration - a maximum of two years for toripalimab and six cycles for Cis+Gem - the submission asserted that the observed KM data was sufficient for modelling ToT. The mean (and median) duration of treatment for the JUPITER-02 trial was taken from exposure at DCO3 (reported in JUPITER-02 CSR Addendum 2 Updated Safety; Attachment 2.4 to the submission). It is likely that treatment durations for cisplatin and gemcitabine are

representative of full treatment exposure (given they were used for a maximum of six cycles at the beginning of the trial), however, exposure to toripalimab in particular, may be underestimated given there was a further median six months of follow-up to DCO4 from these reported durations and 52 patients completed two years of treatment. No extent of exposure was reported in the final addendum CSR for JUPITER-02 (JUPITER-02 CSR Addendum 3 Final OS; Attachment 2.5 to the submission). The model presented shows that the median treatment duration falls between 15 to 16 months (mean of 15.53 months) for toripalimab and 8 to 9 (mean of 10.2 months) months for the comparator arm. The evaluation and the ESC considered this to be reasonable based on available data from JUPITER-02.

6.38 Utility values for the PF and PD health states in the base case were 0.79 and 0.71, respectively. These were sourced from the recent Pembrolizumab SCCHN PSD (pembrolizumab SCCHN PSD, November 2021 PBAC meeting) as although EQ-5D, QLQ-C30, and QLQ-H&N35 questionnaires were used in the JUPITER-02 trial, the submission stated that these questionnaires could not be aligned with Australian-specific utility values. The ESC noted that the utilities were higher than in previously published data and that sensitivity analyses using alternative utilities from Nie (2024; PF = 0.76; PD = 0.35) and Zhu (2022; PF = 0.65 and PD = 0.52) resulted in increases to the ICER of +% and +%. The PBAC noted it would have been informative to present utilities from the JUPITER-02 trial.

6.39 Disutilities for adverse events were also accounted for, but assuming no disutility applied had negligible effects on the ICER.

6.40 Post-discontinuation of study treatment, patients were assumed to have subsequent therapy (representing second- and subsequent-lines). Subsequent therapy was assumed to be a weighted average (based on reported use in the JUPITER-02 trial) of capecitabine, paclitaxel and cisplatin + fluorouracil. The proportion of patients assumed to undergo subsequent treatment with cisplatin + fluorouracil relates to the proportion of those undergoing treatment with cisplatin in JUPITER-02. The proportions were also based on a total of 32 (29.1%) and 64 (44.8%) patients randomised to toripalimab and placebo, respectively having had subsequent therapy at DCO1. At DCO4, 82 (56.2%) and 106 (74.1%) patients randomised to toripalimab and placebo, respectively had subsequent therapy where cytotoxic systemic therapy continued to be most widely used in both groups, followed by PD-L1 inhibitors.

6.41 In the base case, 10% of the time spent in the progressive disease (PD) health state was assumed to be the duration of treatment with subsequent therapies. This corresponded to 5.71 months on subsequent treatment for toripalimab and 4.70 months for placebo. Assuming 20% of the time in PD or excluding these costs assumption had little impact on the ICER, with changes of % and +%, respectively.

6.42 Adverse event costs were applied as a one-off cost in the first cycle of the economic model, exclusion of these costs in a sensitivity analysis decreased the ICER by -%.

6.43 Terminal care cost derived from Goldsbury 2018, estimated at $[redacted] was assigned when patients transition to the 'death' health state. Sensitivity analysis halving this

cost increased the ICER by +[redacted]%, removing it completely increased the ICER by +[redacted]%. The ESC noted the model would be more sensitive to removing terminal care costs with a shorter time horizon as the impact depends on the difference in the proportion of patients alive at the end of the time horizon.

6.44 The key drivers of the model are presented in Table 9.

Table 9: Key drivers of the model

Description	Method/Value	Impact
Time horizon	35 years in the base case	High, favours toripalimab
Extrapolation	Treatment effect continued beyond median of 36.7 months follow-up in trial period for up to 35 years.	High, favours toripalimab
Utilities	Health state utility values sourced from a previous PBAC consideration (pembrolizumab SCCHN PSD, November 2021 PBAC meeting) were higher than others reported in the literature.	Moderate, favours toripalimab

Source: compiled during the evaluation.

6.45 The results of the stepped economic evaluation are presented in Table 10.

Table 10: Results of the stepped economic evaluation[1]

Step and component	Toripalimab + Cis+Gem	Placebo + Cis+Gem	Increment
Step 1: Cost per LY over 5-year trial horizon			
Costs	$[redacted]	$53,048	$[redacted]
LY	3.233	2.819	0.415
Incremental cost/extra LY gained			$[redacted][1]
Step 2: Cost per LY over a 35-year time horizon			
Costs	$[redacted]	$66,857	$[redacted]
LY	5.563	4.006	1.556
Incremental cost/extra LY gained			$[redacted][2]
Step 3: Cost per QALY over a 35-year time horizon (base case)			
Costs	$[redacted]	$66,857	$[redacted]
QALYs	4.147	2.927	1.220
Incremental cost/extra QALY gained			$[redacted][3]

Source: Table 3-21, p97 of the submission. Cis+Gem, cisplatin and gemcitabine; ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year

1, Adjusted for inappropriate half cycle correction of 'time on treatment'

The redacted values correspond to the following ranges

[1] $555,000 to < $655,000
[2] $135,000 to < $155,000
[3] $155,000 to < $255,000

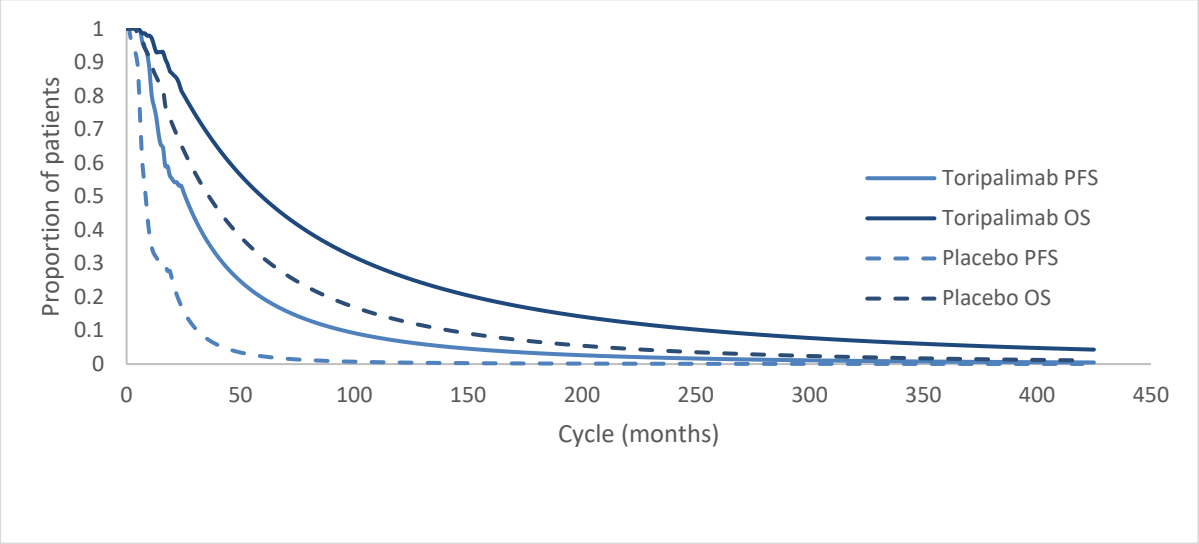
6.46 Over the 35-year time horizon, the model estimates 8.0 (3.2 PF and 4.8 PD) and 5.2 (1.2 PF and 3.9 PD) undiscounted life years gained for toripalimab and placebo, respectively, resulting in an incremental 2.8 (2.0 PF and 0.8 PD) undiscounted life years gained.

6.47 Traces of the base case model are presented in Figure 6.

6.48 Over the 35-year time horizon, the model estimates 8.0 (3.2 PF and 4.8 PD) and 5.2 (1.2 PF and 3.9 PD) undiscounted life years gained for toripalimab and placebo, respectively, resulting in an incremental 2.8 (2.0 PF and 0.8 PD) undiscounted life years gained.

6.49 Traces of the base case model are presented in Figure 6.

Figure 6: Model traces of the base case over a 35-year (420 months) time horizon



Source: Attachment 3.1 of the submission.

6.50 The results of key sensitivity analyses are summarised in Table 10.

Table 10: Sensitivity analyses

Analyses	Incremental cost ($)	Incremental QALY	ICER	% change to ICER
Base case	[redacted]	**1.220**	[redacted][1]	**-**
Time horizon (35 years in base case)				
7.5 years **#3**	[redacted]	0.575	[redacted][2]	+[redacted]%
5 years **#5**		0.366	[redacted][3]	+[redacted]%
10 years **#6**		0.738	[redacted][4]	+[redacted]%
Time point for OS extrapolation (base case: 20 months for both treatment arms)				
40 months **#1**	[redacted]	1.149	[redacted][1]	+[redacted]%
Toripalimab and placebo OS extrapolation (log-normal in base case; best fit AIC, BIC for placebo)				
Weibull	[redacted]	0.759	[redacted][4]	+[redacted]%
Log-logistic **#2**		1.115	[redacted][1]	+[redacted]%
Gompertz (best fit AIC, BIC for tori)		0.415	[redacted][5]	+[redacted]%
Health state utilities (PF 0.79 and PD 0.71 in base case)				
PF 0.76, PD 0.35 (Nie 2024)	[redacted]	1.138	[redacted][1]	+[redacted]%
PF 0.65, PD 0.52 (Zhu 2022)		0.996	[redacted][1]	+[redacted]%
Terminal care costs ($62,676 in base case)				
Exclude **#4**	[redacted]	1.220	[redacted][1]	+[redacted]%
Discounting (5% in base case)				
3.5%	[redacted]	1.418	[redacted][6]	-[redacted]%
0%		2.146	[redacted][7]	-[redacted]%
Multi-variate sensitivity analyses				
#1 and #2	[redacted]	1.027	[redacted][1]	+[redacted]%
#1 and #2 and #3		0.560	[redacted][2]	+[redacted]4%
#1 and #2 and #3 and #4		0.560	[redacted][2]	+[redacted]%
#1 and #2 and #5 and #4		0.373	[redacted][3]	+[redacted]%
#1 and #2 and #6 and #4		0.694	[redacted][4]	+[redacted]%

Source: Table 3-25 of the submission and sensitivity analysis performed during the evaluation.
AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion; ICER, incremental cost-effective ratio; OS, overall survival; PD, progressive disease; PF, progression-free; QALY, quality adjusted life year.
The redacted values correspond to the following ranges
[1] $155,000 to < $255,000
[2] $355,000 to < $455,000
[3] $555,000 to < $655,000
[4] $255,000 to < $355,000
[5] $455,000 to < $555,000
[6] $135,000 to < $155,000
[7] $95,000 to < $115,000

6.51 The ESC noted a multi-variate sensitivity analysis that (i) used more of the KM OS data (ii) applied log-logistic extrapolation function to OS for both arms (iii) used a 7.5-year time horizon and (iv) excluded terminal care costs resulted in an ICER of $355,000 to < $455,000 per QALY. The ESC noted that applying these steps above but using a 5-year and 10-year time horizon instead resulted in ICERs of $555,000 to < $655,000 and $255,000 to < $355,000 per QALY, respectively.

6.52 The ESC noted that in consideration of other cancers (e.g. pembrolizumab for head and neck squamous cell carcinoma in March 2022) acceptable ICERs were less than $55,000 to < $75,000 /QALY.

6.53 The PBAC noted the ICER using the economic model outlined in paragraph 6.51 with a 10 year time horizon and the price proposed in the pre-PBAC response (see paragraph 3.1) was $155,000 to < $255,000 per QALY gained.

Drug cost/patient

6.54 The drug cost per patient for toripalimab in the trial, model and financial estimates are presented in Table 11. As toripalimab is intended to be used as an add-on to standard of care chemotherapy, no comparator costs were presented.

Table 11: Drug cost per patient for toripalimab (using the price proposed in the submission)

	Trial dose and duration	Model	Financial estimates
Dose	240 mg Q3W	240 mg Q3W	240 mg Q3W
Mean duration	64.4 weeks[a]	15.53 months[b]	14.78 months[c]
Cost/patient/script[d]	$	$	$
Cost/patient/course	$[e]	$[g]	$[g]

Source: compiled during the evaluation.
Q3W, every 3 weeks
a: JUPITER-02 reported mean duration of treatment
b: using observed KM time on treatment from JUPITER-02, estimated by the model
c: assumed to be converted to months from mean weeks (see footnote 'a') reported in JUPITER-02
d: assuming a 33.14%:66.86% public:private split and 99.4% RDI
e: =64.4/3*$
f: =estimated by model
g: =14.78/12-365/21-$

Estimated PBS usage & financial implications

6.55 This submission was not considered by DUSC.

6.56 Table 12 presents the key inputs relied on in the financial estimates. The submission took an epidemiological approach to derive the financial estimates.

Table 12: Key inputs for financial estimates

Data	Values	Source	Comment
Eligible population			
Incident cases of RM-NPC cases	2017: 144 2018: 164 2019: 168 2020: 178 2021: 172 2022: 177 2023: 191 2024: 200	Source: AIHW 2023	The source was appropriate.
Growth rate	4.0%	Calculated based on differences in incident cases of RM-NPC annually as reported by the AIHW incidence data between 2017 and 2024	The submission claimed that the rate was calculated based on the AIHW incidence rate between 2017 and 2024. However, the rate of 4% was based on the average incident NPC diagnosed cases from 2020 to 2024 only. Sensitivity analysis, which considered the average from 2017 to 2024, resulted in a 5% growth rate. The PSCR revised growth to 5%.

Data	Values	Source	Comment
Projected incident patients	2025: 207 2026: 215 2027: 223 2028: 231 2029: 239 2030: 248	Source: Calculated by extrapolating from projected 2024 incidence as reported by AIHW 2023 and the 4% annual growth rate.	The calculation of the projected incident patient numbers appears reasonable.
Predicted prevalent patients	2025: 200 2026: 207 2027: 215 2028: 223 2029: 231 2030: 239	Based on number of incident cases in previous year as projected above	Implicitly, this assumed that patients have a life expectancy of just one year (e.g. there are no remaining prevalent patients diagnosed in 2025 in 2027), which may not be reasonable given the median survival of chemotherapy patients in JUPITER-02 was 33.7 months. This may lead to an underestimate of the prevalent population and consequently underestimate second (and subsequent) line use of toripalimab.
RM-NPC stage distribution			
Diagnosed metastatic	12.0%	Metastatic at time of diagnosis: Source: Qu 2020, which reported pattern and prognosis of distant metastasis in NPC from the US Surveillance, Epidemiology and End Results (SEER) program between 2010 and 2016.	The SEER cohort enrolled in Qu 2020 included a racial distribution of 43% White and 43% Others. While this may have potential applicability issues to the findings to the Australian population, the racial distribution in the Australian population was unknown.
Progress to RM-NPC	15.0%	Progress to recurrent or metastatic stage post-diagnosis: Source: Lee 2015, which was a review article of management in NPC.	Lee 2015 stated "Even with the best available treatment in modern practice, retrospective reports of patients treated with IMRT over the last decade have revealed the stark reality that 5% to 15% of patients will develop local failure, and 15% to 30% will experience failure at distant sites". While sources were cited by Lee 2015, a review of the sources did not reveal where these estimates were derived from. It was unclear if these were lifetime risks, or over a fixed (but unclear) time period.
Treatment utilisation			
Uptake rate	1L Year 1: [redacted]% Year 2: [redacted]% Year 3: [redacted]% Year 4: [redacted]% Year 5: [redacted]% Year 6: [redacted]% 2L Year 1: [redacted]% Year 2: [redacted]% Year 3: [redacted]%	Sponsor assumption. For 2L, assumed that by year 4 of listing of toripalimab in the 1L setting, patients who do not receive toripalimab as 1L treatment would not uptake 2L toripalimab monotherapy	Assumption for 1L uptake may be plausible given the lack of alternatives. Logic behind restriction to only three years of 2L uptake may be optimistic and a more conservative approach would be to assume uptake to be consistent beyond year 4, with the increase in uptake in 1L toripalimab naturally leading to a decrease in number of patients eligible for 2L. Patients are only assumed to be eligible for uptake in the year of progression which may not be reasonable and may underestimate uptake rate and utilisation in the 2L.
WHO/ECOG Performance Status	Not included explicitly	Assumed 100%	The submission did not explicitly account for the requirement that patients must have a WHO performance status score of no greater than 2 at treatment initiation. Information on WHO/ECOG performance status in the proposed population was not provided. The PSCR revised to 97.2

Data	Values	Source	Comment
Mean time on treatment with toripalimab	1L: 14.78 months 2L: 16 weeks	Based on results of the cost-effectiveness model for 1L and median treatment duration in POLARIS-02 for 2L	The value of 14.78 months for 1L treatment appears to be a conversion from a mean duration of 64.4 weeks in JUPITER-02, expressed as months. This compared with 15.53 months in the base case economic model presented, based on KM ToT data from JUPITER-02. The PSCR revised treatment duration to 15.53 months. Duration of therapy in 2L consistent with median duration of treatment in POLARIS-02 and was reasonable.
Proportion progressing in first year	67.10%	1-year Progression-Free Survival rate in control arm of JUPITER-02	The 67.1% progression rate was applied only for the first year, and the financial estimates assumed that patients who progress within the first year are considered for 2L therapy.
Treatment beyond 2L	Not included	Not applicable	Given the requested restriction, it was possible that toripalimab may be used in later line settings, but this was not considered in the financial estimates. The PBAC considered this was reasonable and would likely be a very small number of patients.
Number treated	1L Year 1: [redacted]1 Year 2: [redacted]1 Year 3: [redacted]1 Year 4: [redacted]1 Year 5: [redacted]1 Year 6: [redacted]1 2L Year 1: [redacted]1 Year 2: [redacted]1 Year 3: [redacted]1	1L treatment based on proportion diagnosed at stage IV (12%) and proportion who progressed to RM-NPC (15%) multiplied by incident population of that year 2L treatment based on estimated prevalent patients, adjusted for patients who did not have 1L toripalimab in previous year, multiplied by uptake rate.	Utilisation in 2L may be underestimated due to assumption that incident patients will not contribute to the prevalent pool after one year (despite a median OS of 33.7 months in the chemotherapy arm of JUPITER-02), the assumption that there will be no uptake after year 3.
Scripts dispensed	2025: [redacted]2 2026: [redacted]2 2027: [redacted]2 2028: [redacted]2 2029: [redacted]2 2030: [redacted]2	Assuming 21.43 scripts per patient in 1L, based on a duration of 14.78 months and three weekly administration and a 99.4% compliance (based on compliance in JUPITER-02) Assuming 7.95 scripts per patient in 2L, based on a duration of 16 weeks and fortnightly administration and a 99.4% compliance (based on compliance in JUPITER-02)	It was unclear if it was appropriate to use the compliance rate from JUPITER-02, which was in the 1L setting, to inform compliance in the 2L setting. Nonetheless given the high compliance rate this was likely to be reasonable.
Costs			

Data	Values	Source	Comment
Toripalimab	AEMP: $[redacted] DPMQ (public): $[redacted] DPMQ (private): $[redacted]	Proposed pricing	
Patient copayment	PBS: $19.02 RPBS: $6.57	Based on utilisation of cisplatin (PBS item 4319H and 7224F) and gemcitabine (PBS items 4439P and 7246J) Between Jan-Dec 2024	Listing for cisplatin and gemcitabine were not specific for RM-NPC so there may be some uncertainty in the distribution of beneficiary types in RM-NPC. However given the relative high cost of toripalimab compared to the copayment amounts, this was unlikely to lead to a tangible difference.
MBS costs	$123.05 per administration of toripalimab	MBS item 13950, with 80% rebate assumed in the base case.	Applied to each toripalimab script with no offsets. However, given that toripalimab would be administered with chemotherapy for six cycles in 1L, the MBS costs were overestimated in the submission. This was corrected in the revised estimates provided in the PSCR.

Source: Table 4-1, of the submission; Excel workbook 'Attachment 4.1- Toripalimab budget impact model';
AEMP, Approved ex-manufacturer price; AIHW, Australian Institute of Health and Welfare; DPMQ, dispensed price for maximum quantity; ECOG, Eastern Cooperative Oncology Group; OS, overall survival; RM-NPC: recurrent or metastatic nasopharyngeal carcinoma; WHO: World Health Organization; 1L, first-line; 2L: second-line; ToT:, time on treatment; OS, overall survival; KM, Kaplan Meier, MBS, Medicare Benefits Schedule

The redacted values correspond to the following ranges

[1] < 500

[2] 500 to < 5,000

6.57 The estimated net financial impact of toripalimab is presented in Table 13.

Table 13: Estimated use and financial implications (using price proposed in the submission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated 1L	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of patients treated 2L	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Number of scripts dispensed	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications of toripalimab						
Cost to PBS/RPBS less copayments	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net financial implications						
Net cost to PBS/RPBS	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]
Net cost to MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net cost to PBS/RPBS/MBS	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]	[redacted][4]

Source: compiled during the evaluation.
PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Schedule of Pharmaceutical Benefits, MBS, Medicare Benefits Schedule
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

6.58 The total cost to the PBS/RPBS of listing toripalimab was estimated to be $10 million to < $20 million in Year 6, and a total of $70 million to < $80 million over the first six years of listing.

6.59 The financial estimates were overall uncertain, as:

- The number of prevalent patients was likely underestimated as the prevalent population of patients are not included in the prevalent pool after one year which will underestimate the number of treated 2L patients. The PBAC agreed with the evaluation that the number of prevalent patients was likely underestimated but considered it was not likely to have a large impact on the utilisation as the number of patients appropriate for second line treatment with toripalimab was likely to be small and reducing over time.
- The Surveillance, Epidemiology and End Results (SEER) data from Qu 2020 which was relied upon to inform the proportion diagnosed with metastatic disease was based on a US cohort and may not be directly applicable to Australia; and
- The assumption that 15% of incident NPC patients have recurrent or metastatic disease within 12 months was based on Lee 2015 and was uncertain as the source could not be verified.

6.60 The evaluation also noted the financial estimates were uncertain due to the following factors, which were corrected in the PSCR: duration of 1L therapy lower than in the economic model, no adjustment for WHO/ECOG performance status, no cost offset included for infusion costs for patients on 1L chemotherapy.

6.61 Revised financial estimates based on a 5% annual growth rate, a duration of treatment consistent with the economic model (15.53 months), removing the double counting of administration costs for 6 cycles with toripalimab as discussed in Table 13 and para 6.52, and an ECOG status of 0-2 for 97.2% of patients were presented in the PSCR, with the sponsor agreeing that changes proposed in the evaluation to these parameters were reasonable. This increased the net cost to the PBS/RPBS by approximately 10% to $10 million to < $20 million in Year 6 and a total of $70 million to < $80 million over the first six years of listing.

Quality Use of Medicines

6.62 The sponsor stated that they were committed to achieving optimal outcomes for patients with RM-NPC treated with toripalimab, actively involved in educational activities and post-marketing surveillance.

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 toripalimab for the treatment of recurrent or metastatic nasopharyngeal carcinoma (RM-NPC) on the basis that it should be available only under special arrangements under Section 100 (Efficient Funding of Chemotherapy Program (EFC)). The PBAC considered it reasonable for toripalimab to be available for patients in the first- and second-line setting. The PBAC recognised there was a high clinical need for additional treatment options for patients with this condition. The PBAC considered the evidence presented

demonstrated a progression-free and overall survival (OS) benefit for toripalimab given in combination with cisplatin and gemcitabine (Cis+Gem) over the comparator (Cis+Gem alone) but that the magnitude of benefit in the Australian population likely to be treated was uncertain. The PBAC considered toripalimab would be cost-effective with an incremental cost-effectiveness ratio (ICER) in the range of $55,000 to < $75,000 to $55,000 to < $75,000 per quality adjusted life year (QALY) gained.

7.2 The PBAC considered there was a high clinical need for an additional treatment for patients with RM-NPC and noted the consumer comments from two organisations, including the Medical Oncology Group of Australia who were supportive of the listing, designating the listing of toripalimab as high priority.

7.3 The PBAC noted that toripalimab in combination with Cis+Gem was listed as a preferred first-line (1L) regimen for patients with recurrent, unresectable, oligometastatic or metastatic cancer of the nasopharynx that was not amenable to surgery or radiotherapy, in the National Comprehensive Cancer Network (NCCN) guidelines version 2.2025, and as a subsequent second-line (2L) therapy for patients who experienced disease progression on or after platinum-containing therapy.

7.4 With regards to the requested restriction, the PBAC considered that:

- a streamlined authority listing would be reasonable and consistent with the listing for other PD-1/PD-L1 inhibitors,
- a line agnostic listing would be reasonable, noting that the TGA had approved registration of toripalimab for patients in the first- and second-line setting (see paragraph 2.1), and that it would be appropriate to combine the listings to cover first- and second-line use in the one restriction,
- seven repeats would be appropriate, noting that this would provide a sufficient quantity for 24 weeks of treatment in the 1L setting and 16 weeks of treatment in the 2L setting at the recommended doses,
- while patients weighing more than 80 kg would require a dose of more than the maximum amount of 240 mg of toripalimab in the 2L setting, the administrative advice that the sponsor proposed, which stated that prescribers should request the appropriate number of vials for a single dose based on the patient's weight in the 2L setting, would not be required. The PBAC noted that due to the EFC algorithm, prescribers are expected to prescribe the dose in mg according to the patient's weight and pharmacists upon dispensing would be directed to the specific number of vials required to make up the final dose. The PBAC further noted that a prescriber instruction has been added to clarify that prescribers can request an increase in the maximum amount if needed according to the patient's body weight in the 2L setting,
- it would be appropriate to add the clinical criterion that the condition must not be amenable to salvage surgery or radiotherapy, noting that this was in line with the enrolment criteria in the key JUPITER-02 trial and in line with the NCCN guidelines

version 2.2025,

- it would be reasonable for the clinical criteria to allow patients with a WHO performance status score of no higher than 2 to access toripalimab as requested,
- the clinical criteria should include a statement to preclude patients who received prior treatment with a PD-1/PD-L1 inhibitor for this condition from receiving treatment with toripalimab,
- it would not be necessary to specify the chemotherapy agents that would need to be used ('in combination with platinum-based chemotherapy') for first-line use,
- it would be appropriate to simplify the stopping rule criteria (noting that the recommended treatment duration is until disease progression, unacceptable toxicity or up to 24 months) by including the following wording, "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 cumulative months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs",
- and the restriction should include an administrative advice to reflect that toripalimab will be listed with a Special Pricing Arrangement.

7.5 The PBAC considered the nominated comparator, platinum-containing doublet chemotherapy (represented in the clinical trial evidence by Cis+Gem) was an appropriate comparator in the first-line setting. The PBAC noted that while in the second-line setting, single-agent chemotherapy was nominated as the comparator, the submission did not present comparative clinical evidence that enabled the efficacy and safety of toripalimab against single-agent chemotherapy to be determined.

7.6 In the first-line setting where patients had not had prior systemic therapy, the PBAC noted that the submission was based on the JUPITER-02 trial, a randomised double-blind phase III trial comparing toripalimab 240 mg every 3 weeks (N=146) to placebo (N=143), in combination with Cis+Gem for up to 6 cycles and then as monotherapy in patients with RM-NPC. The PBAC noted that toripalimab reduced the risk of progression or death by 48% at the first data cutoff point (DCO1) when the trial was unblinded (HR=0.52; 95% CI: 0.359, 0.740; p=0.0003), with median PFS being higher in patients treated with toripalimab (11.7 months) compared to placebo (8.2 months). The PBAC noted that median PFS increased to 21.4 months at data cutoff 2 for patients who remained on toripalimab and considered the improvement to be clinically meaningful. The PBAC noted that the results for OS suggested a benefit for toripalimab, with the risk of death being reduced by 37% (HR=0.63; 95% CI: 0.446, 0.891), with median OS not being reached in patients treated with toripalimab compared to 33.7 months for the placebo arm. The PBAC considered that the claim that toripalimab in combination with chemotherapy has superior comparative

effectiveness compared to standard of care chemotherapy to be supported in population with predominantly non-keratinising NPC.

7.7 The PBAC noted that JUPITER-02 was conducted in China, Taiwan and Singapore, and that >97% of patients had non-keratinising RM-NPC. The PBAC noted that in Western countries such as Australia, the incidence of the keratinising squamous cell variant is higher than in JUPITER-02 (~25% vs <3%). The PBAC considered that as the prognosis is worse for patients with keratinising NPC (see paragraph 4.3) the magnitude of the clinical benefit in a population where more patients have keratinising NPC to be unclear, and thus the magnitude of the clinical benefit in an Australian population to be uncertain.

7.8 In the 2L setting, the PBAC noted that the submission presented data on patients treated with toripalimab at a dose of 3 mg/kg every 2 weeks from POLARIS-02, a phase II single arm study that enrolled patients (N=192) with predominantly (95.8%) non-keratinising refractory (second-line or second-line plus) RM-NPC. The PBAC noted the objective response rate was 20.5% with a median duration of response of 14.9 months. The PBAC considered that, while uncertain, the clinical claim that toripalimab provided a clinically meaningful treatment response and duration of response in patients who have previously progressed on chemotherapy was likely to be reasonable, noting the high clinical need for additional treatment options in this population. The PBAC considered that the number of patients who would be eligible for 2L toripalimab would be low and would decline over time, noting the high expected uptake in the 1L treatment setting and retreatment would not be permitted (see paragraph 7.4).

7.9 The PBAC considered the claim of non-inferior safety of toripalimab versus standard of care chemotherapy in the first-line RM-NPC setting was not adequately supported. The PBAC noted that patients in the toripalimab arm of JUPITER-02 experienced over twice as many immune related adverse events (irAEs) and a higher number of treatment emergent adverse events (TEAEs) that led to treatment discontinuation compared to the placebo arm. The PBAC noted the safety profile of toripalimab was similar to that of other PD-(L) inhibitors.

7.10 The submission presented a cost-utility analysis to support the cost-effectiveness of toripalimab commenced in combination with platinum-doublet chemotherapy versus platinum-doublet chemotherapy alone in the first-line treatment of patients with RM-NPC. The PBAC noted that the economic model reported an ICER of $155,000 to < $255,000 per QALY gained. The PBAC noted the base case model assumed a time horizon of 35 years and agreed with the evaluation that this was optimistic and uncertain in the context of the prognosis of this population and the length of follow up of JUPITER-02 (median 36.7 months for OS). The PBAC considered a respecified model as outlined by the ESC in paragraph 6.51 with a 10-year time horizon would provide a reasonable basis to consider the cost-effectiveness of toripalimab. The PBAC noted the ICER using the respecified model was $255,000 to < $355,000 per QALY using the price proposed in the submission and $155,000 to < $255,000 per QALY using

the price proposed in the pre-PBAC response (see paragraph 3.1). The PBAC considered toripalimab would be cost-effective with an ICER of between $55,000 to < $75,000 and $55,000 to < $75,000 per QALY consistent with other similar considerations.

7.11 The PBAC noted the submission had used an epidemiological approach to estimate the net cost of listing toripalimab on the PBS/RPBS/MBS and that the financial estimates were based on the published price of toripalimab. The PBAC noted there were some outstanding uncertainties regarding the financial estimates (as outlined in paragraph 6.59) but considered that, on balance, the estimated financial implications of listing toripalimab would be reasonable with the following amendments:

- An annual growth rate in incident cases of 5% as proposed in the PSCR;
- Assuming 90% of patients would have a WHO performance status of no greater than 2;
- Correction to the MBS administration offsets as proposed in the PSCR;
- Revised treatment duration to be consistent with the economic model as proposed in the PSCR; and
- Revised price as required in paragraph 7.10.

7.12 The PBAC recommended that toripalimab should not be treated as interchangeable with any other drugs.

7.13 The PBAC advised that toripalimab is not suitable for prescribing by nurse practitioners.

7.14 The PBAC advised that the Early Supply Rule should not apply.

7.15 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for toripalimab:

a) The treatment is expected to provide a substantial improvement in OS and PFS compared to Cis+Gem in an Asian population, however the magnitude of benefit in a non-Asian population with a high proportion of keratinised NPC is unclear;

b) The treatment is not expected to address an urgent clinical need because alternative therapies (Cis-Gem) are PBS listed;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.16 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:

MEDICINAL PRODUCT Form		PBS item code	Max. Amount	№.of Rpts
TORIPALIMAB Injection		NEW (Public) NEW (Private)	240 mg	7
Available brands				
Zytorvi toripalimab 240 mg/6 mL injection, 6 mL vial				
Concept ID		**Category / Program:** ☒Section 100 – Efficient Funding of Chemotherapy – Public / Private		
		Prescriber type: ☒Medical Practitioners		
		Benefit type: ☒Authority Required (Streamlined) [new code]		
Prescribing rule level:		**Administrative Advice:** No increase in the maximum number of repeats may be authorised.		
		Administrative Advice: Special Pricing Arrangements apply.		
		Restriction Summary [new1] / Treatment of Concept: [new1A]		
		Indication: Recurrent or metastatic nasopharyngeal carcinoma		
		Clinical criteria:		
		Patient must have a WHO performance status of no higher than 2.		
		AND		
		Clinical criteria:		
		The condition must not be amenable to salvage surgery or radiotherapy.		
		AND		
		Clinical criteria:		
		Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition.		
		Treatment criteria:		
		The treatment must be commenced in combination with platinum-based chemotherapy (PBC) where the patient has not previously received systemic therapy for this condition in the metastatic setting, (i.e. used in combination with PBC for 6 cycles in the first line setting unless intolerance/contraindication is confirmed) **OR**		
		The treatment must be the sole PBS subsidised therapy at the time of treatment initiation where the condition has progressed following treatment with PBC, (i.e. used as monotherapy in the second line setting).		
		AND		
		Treatment criteria:		
		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 cumulative months from treatment initiation; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.		

	Prescribing instructions: An increase above the listed maximum amount may only be requested when a dose of 3 mg/kg every two weeks is prescribed in the second line setting.

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

Dr Reddy's Laboratories Australia welcomes the positive recommendation made by PBAC and the acknowledgement of high clinical unmet need for RM-NPC. Dr Reddy's Laboratories Australia looks forward to working with PBAC and the Department of Health to help facilitate access to Toripalimab on the PBS at the earliest available opportunity.

July Addendum to the March 2025 PBAC PSD:

3.01 TORIPALIMAB, Solution concentrate for I.V. infusion 240 mg in 6 mL (40 mg per mL), Zytorvi®, Dr Reddy's Laboratories Australia Pty Ltd

11 Background

11.1 At its March 2025 meeting, the PBAC recommended the Authority Required (STREAMLINED) listing of toripalimab for the treatment of recurrent or metastatic nasopharyngeal carcinoma (RM-NPC). The PBAC considered toripalimab given in combination with cisplatin and gemcitabine (Cis+Gem) would be cost-effective with an incremental cost-effectiveness ratio (ICER) in the range of $55,000 to < $75,000 to

$55,000 to < $75,000 per quality adjusted life year (QALY) gained over the comparator (Cis+Gem alone) (paragraph **Error! Reference source not found.**).

11.2 Following the March 2025 recommendation, the sponsor indicated it could not proceed with a listing at the price required to achieve the outlined ICER range. The sponsor alternatively proposed an effective price of $[redacted] per vial (resulting in an ICER of $75,000 to < $95,000 per QALY) and asked the PBAC to reconsider the ICER in the context of high clinical need and the value of toripalimab compared to other therapies for rare cancers. The proposed price was [redacted]% lower than the price offered in the March 2025 pre-PBAC response.

12 PBAC Outcome

12.1 The PBAC noted it had previously recommended an ICER in the range of $55,000 to < $75,000 to $55,000 to < $75,000 per QALY and the sponsor proposed a price that resulted in an ICER of $75,000 to < $95,000 per QALY.

12.2 In the context of the high clinical need and noting the value and cost of other immunotherapy agents for similar cancer types, the PBAC considered toripalimab would be acceptably cost effective at the proposed price.

Outcome:

Recommended

13 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.

14 Sponsor's Comment

The sponsor had no comment.