

## 6.07 NIVOLUMAB,

**Injection concentrate for I.V. infusion 40 mg in 4 mL,  
Injection concentrate for I.V. Infusion 100 mg in  
10 mL,  
Opdivo<sup>®</sup>,  
BRISTOL-MYERS SQUIBB AUSTRALIA PTY LTD.**

### 1 Purpose of submission

- 1.1 The Category 2 submission requested Section 100 (Efficient Funding of Chemotherapy Program), Authority Required (Telephone/ Online) listing for nivolumab (NIVO) for the first-line (1L) treatment of cisplatin-eligible adult patients with unresectable or metastatic urothelial carcinoma (u/mUC).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis of NIVO plus standard of care (SoC) - consisting of gemcitabine-cisplatin chemotherapy (GC) – versus SoC.

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

Component	Description
Population	Cisplatin-eligible adult patients with unresectable or metastatic urothelial carcinoma
Intervention	NIVO in combination with GC followed by NIVO monotherapy
Comparator	Main comparator: SoC as GC chemotherapy Supplementary comparator: GC followed by AVEL maintenance for those patients who do not progress after the GC component.
Outcomes	OS, PFS by BICR and ORR per BICR
Clinical claim	Main: NIVO+SoC, has superior efficacy and inferior <sup>a</sup> safety compared to SoC.  Supplementary: NIVO monotherapy has non-inferior efficacy and non-inferior safety compared to AVEL maintenance therapy in patients who remain progression free after GC.

Source: Table 1, p17 of the submission.

AVEL = avelumab; BICR = blinded independent central review; GC = gemcitabine-cisplatin chemotherapy; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; ORR = objective response rate; SoC = standard of care.

<sup>a</sup> Non-inferior safety is stated in Table 1, p17 of the submission but the therapeutic conclusion of the submission states that NIVO is inferior in terms of safety.

## 2 Background

### Registration status

- 2.1 The submission for NIVO, in combination with cisplatin-based chemotherapy, as a first line treatment for u/mUC was made under the TGA/PBAC Parallel Process. At the time of PBAC consideration the Delegate's overview and the TGA Notice of decisions to register the new indication were available. The TGA Delegate advised of the decision to approve the registration of NIVO, in combination with cisplatin and gemcitabine, for the first-line treatment of patients with u/mUC.

2.2 NIVO is currently TGA approved as a treatment for several other types of cancer. The current indications of relevance to urothelial cancer are:

- NIVO, as monotherapy, is indicated for the adjuvant treatment of patients with muscle invasive urothelial carcinoma (MIUC) who are at high risk of recurrence after undergoing radical resection of MIUC.
- NIVO, as monotherapy, is indicated for the treatment of patients with locally advanced unresectable or metastatic urothelial carcinoma after prior platinum-containing therapy. The approval of this indication is based on objective response rate and duration of response in a single arm study.

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

### 3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max Amt	Max. Amount	No. of Rpts
NIVOLUMAB Injection	NEW (Public) NEW (Private)	Published prices: \$7,333.85 (Private Hospital) \$7,191.12 (Public Hospital) Effective prices: \$ [REDACTED] (Private Hospital) \$ [REDACTED] (Public Hospital)	360mg	5
<b>Available brands</b>				
Opdivo (Nivolumab 40 mg/4 mL injection, 4 mL vial)				
Opdivo (Nivolumab 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/Private hospitals		
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
		<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)		
		<b>Administrative Advice:</b> <i>No increase in the maximum amount or number of units may be authorised.</i>		
		<b>Administrative Advice:</b> <i>No increase in the maximum number of repeats may be authorised.</i>		
		<b>Administrative Advice:</b> <i>Special Pricing Arrangements apply.</i>		
		<b>Administrative Advice:</b> <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a>) or by telephone by contacting Services Australia on 1800 888 333.</i>		
		<b>Episodicity:</b> n/a		
		<b>Severity:</b> Unresectable or metastatic		
		<b>Condition:</b> Urothelial carcinoma		
		<b>Indication:</b> Unresectable or metastatic urothelial carcinoma		
		<b>Treatment Phase:</b> Initial treatment		
		<b>Clinical criteria:</b>		

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	The condition must not have previously been treated with systemic therapy for unresectable or metastatic urothelial carcinoma
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be initiated in combination with cisplatin-based chemotherapy and gemcitabine
	<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>Clinical criteria:</b>
	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
	<b>Treatment criteria:</b>
	<del>Patient must not have developed disease progression while receiving PBS-subsidised treatment with this drug for this PBS indication.</del>
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
	<b>Prescribing instruction:</b> Patient must only receive up to a maximum 6 doses of PBS-subsidised combined therapy with nivolumab and cisplatin-based chemotherapy under this PBS listing, once in a lifetime.
	<del><b>Administrative Advice:</b> An increase in repeat prescriptions, up to a value of 11, may only be sought where the prescribed dosing is 240 mg administered fortnightly.</del>

MEDICINAL PRODUCT Form	PBS item code	Dispensed Price Max Amt	Max. Amount	No. of Rpts
NIVOLUMAB Injection	NEW (Public) NEW (Private)	Published prices: \$9,734.47 (Private Hospital) \$9,558.60 (Public Hospital) Effective prices: \$ [REDACTED] (Private Hospital) \$ [REDACTED] (Public Hospital)	480mg	5
<b>Available brands</b>				
Opdivo (Nivolumab 40 mg/4 mL injection, 4 mL vial)				
Opdivo (Nivolumab 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/Private hospitals		
		<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
		<b>Restriction type:</b> <input type="checkbox"/> Authority Required (telephone/online PBS Authorities system)		
		<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>Administrative Advice:</b> Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.		

	<b>Episodicity:</b> n/a
	<b>Severity:</b> Unresectable or metastatic
	<b>Condition:</b> Urothelial carcinoma
	<b>Indication:</b> Unresectable or metastatic urothelial carcinoma
	<b>Treatment Phase:</b> Continuing treatment
	<b>Clinical criteria:</b>
	Patient must have previously received of up to maximum 6 doses of PBS-subsidised combined therapy with nivolumab and cisplatin-based chemotherapy and gemcitabine as initial treatment for this condition,
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be as monotherapy for this condition.
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information,
	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must not be undergoing continuing PBS-subsidised treatment where this prescription extends treatment beyond whichever comes first: (i) 24 months from treatment initiation, irrespective of whether initial treatment was PBS subsidised/non-PBS subsidised, (ii) disease progression recurrence despite treatment with this drug, (iii) unacceptable toxicity; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.
	<b>Prescribing Instructions: Administrative Advice:</b> An increase in repeat prescriptions, up to a value of 11, may only be sought where the prescribed dosing is 240 mg administered fortnightly.

- 3.2 The requested listing includes two maximum amounts: 360 mg for initial treatment and 480 mg for continuing treatment. Initial dosing consists of 360 mg every 3 weeks in combination with up to 6 cycles of cisplatin-based chemotherapy. According to the proposed restriction, continuing monotherapy dosing can be either 240 mg every 2 weeks or 480 mg every 4 weeks after the completion of up to 6 cycles of cisplatin-based chemotherapy. As the draft TGA PI does not specify fortnightly dosing as part of the initial treatment regimen the administrative advice allowing an increase in the number of repeats up to 11 may not be required.
- 3.3 The sponsor requested a special pricing arrangement (SPA). The submission requested an ex-manufacturer price of \$[REDACTED] for the 100 mg vial and \$[REDACTED] for the 40 mg vial. The Pre-Sub-Committee Response (PSCR) proposed a reduced ex-manufacturer price of \$[REDACTED] for the 100 mg vial and \$[REDACTED] for the 40 mg vial. The pre-PBAC response stated that the sponsor agreed in principle to a subsequent price reduction to reduce the ICER to under \$55,000 to < \$75,000 per QALY gained as outlined in paragraph 6.69.
- 3.4 The requested restrictions for initial treatment do not align with the key CM-901 substudy. Patients in the CM-901 substudy all received cisplatin and gemcitabine, while the requested restriction only requires that NIVO be initiated in combination with cisplatin-based chemotherapy. The PSCR noted the TGA Delegates Overview advice that the indication should specify NIVO use in combination with cisplatin and gemcitabine, rather than the broader cisplatin-based chemotherapy. As such, the PSCR accepted the Secretariat recommendation to amend the restriction clinical

criteria to specify cisplatin and gemcitabine, rather than cisplatin-based chemotherapy.

- 3.5 The pre-PBAC response requested minor amendments to the restriction to allow grandfathered patients from the sponsors planned patient access program to transition to PBS subsidised therapy.

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

## 4 Population and disease

- 4.1 Urothelial carcinomas are cancers which originate from the urothelial cells lining the bladder, ureters, urethra, and renal pelvis<sup>1</sup>. Based on staging, bladder cancer and urothelial carcinoma are clinically classified as non-muscle invasive, resectable muscle invasive, locally advanced/unresectable muscle invasive, or metastatic. Locally advanced/unresectable muscle invasive disease includes cancer that has extended beyond the primary site to nearby tissues such as the pelvic or abdominal wall or lymph nodes. While in the metastatic stage, it has spread to distant parts of the body, such as the lungs, liver, or bones<sup>2</sup>. It is particularly challenging to manage due to its aggressive progression and resistance to conventional treatments<sup>3</sup>.
- 4.2 Bladder cancer, primarily urothelial carcinoma, is the ninth most common cancer in Australia. Each year, around 3,000 new cases are diagnosed, with the disease predominantly affecting older adults, particularly those over the age of 65<sup>45</sup>. The incidence is significantly higher in men, with a male-to-female ratio of approximately 3:1. Risk factors include smoking (the most significant risk factor), exposure to certain chemicals (such as those used in the dye and rubber industries), and chronic bladder inflammation<sup>6</sup>. Although the incidence of bladder cancer has been stable or slightly decreasing, the prognosis for those with u/mUC remains poor.
- 4.3 For patients with localised urothelial cancer (confined to the bladder), the five-year survival rate is relatively favourable, typically exceeding 70-80%. However, survival rates with locally advanced or unresectable disease are around 30-50% and patients with metastatic disease have a 5-year survival rate of approximately 5-15%<sup>7</sup>.

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<sup>1</sup> Abou El-Ghar ME, Badawy MA, El-Diasty TA (2018). Bladder and Upper Urinary Tract Urothelial Cancer. In: Akata D, Papanikolaou N, editors. Diffusion Weighted Imaging of the Genitourinary System: Techniques and Clinical Applications. Cham: Springer International Publishing; p. 73-104.

<sup>2</sup> Kobayashi T. (2016). Understanding the biology of urothelial cancer metastasis. *Asian J Urol.* Oct;3(4):211-22.

<sup>3</sup> Stecca C, Abdeljalil O, Sridhar SS. (2021). Metastatic Urothelial Cancer: a rapidly changing treatment landscape. *Ther Adv Med Oncol*;13:17588359211047352.

<sup>4</sup>Cancer Australia (2024). <https://www.canceraustralia.gov.au/cancer-types/bladder-cancer/statistics>.

<sup>5</sup> Australian Institute of Health; Welfare (2024). Cancer data in Australia. Canberra: AIHW2024.

<sup>6</sup> Shadab R, Nerli RB, Bidi SR, Ghagane SC. (2023). Risk Factors for Bladder Cancer: Results of a Survey of Hospital Patients. *J Cancer Allied Spec.* 9(1):485

<sup>7</sup> Ripoll J, Ramos M, Montañó J, Pons J, Amejjide A, Franch P. (2021). Cancer-specific survival by stage of bladder cancer and factors collected by Mallorca Cancer Registry associated to survival. *BMC Cancer*;21(1):676.

- 4.4 The clinical management algorithm proposed in the submission would place NIVO+SoC as a 1L treatment for patients with u/mUC. The use of NIVO+SoC would be contingent upon patients being cisplatin eligible. As such, patients who are cisplatin-ineligible but carboplatin-eligible would still receive carboplatin with gemcitabine without NIVO and patients who are platinum-ineligible would receive immunotherapy or best supportive care. Additionally, patients who receive carboplatin + gemcitabine and who do not have disease progression would be eligible for avelumab. The inclusion of NIVO+SoC with NIVO maintenance therapy is proposed to replace avelumab maintenance therapy for cisplatin-eligible patients. The ESC noted the NCCN Clinical Practice Guidelines<sup>8</sup> include NIVO+SoC and SoC followed by maintenance avelumab as “other recommended” regimens for cisplatin eligible patients.
- 4.5 NIVO is a monoclonal antibody which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2<sup>9</sup>. PD-1 is an immune checkpoint receptor that limits the activity of T lymphocytes in peripheral tissues. The PD-1 pathway can be used by cancer cells to inhibit T-cell immune surveillance<sup>10</sup>. By inhibiting the PD-1 receptor, NIVO reactivates tumour-specific cytotoxic T-cells, allowing for anti-tumour immune responses.

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

## 5 Comparator

- 5.1 The submission nominated SoC consisting of GC as the main comparator. The main arguments provided in support of this nomination were that GC is the recommended SoC for the first line treatment of u/mUC in Australia. As the requested listing would restrict the use of NIVO to patients who are cisplatin-eligible, it was reasonable to not include carboplatin as a comparator.
- 5.2 The submission also nominated avelumab maintenance therapy as a supplementary comparator for the use of NIVO monotherapy as maintenance therapy. Both of these maintenance therapies are contingent upon patients not progressing while receiving GC. This was reasonable as the listing of NIVO would replace the use of avelumab maintenance therapy in the nominated population.
- 5.3 Enfortumab vedotin in combination with pembrolizumab (EV+PEM) was identified as a near market comparator. EV+PEM was considered by the PBAC at the November 2024 PBAC meeting for the first line treatment of locally advanced or metastatic urothelial cancer (la/mUC). The submission included an indirect treatment

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<sup>8</sup> National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 4.2024 (May 9, 2024).

<sup>9</sup> van der Heijden MS, Sonpavde G, Powles T, Necchi A, Burotto M, Schenker M, et al. (2023) Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma. *N Engl J Med*. Nov 9;389(19):1778-89.

<sup>10</sup> Pardoll DM. (2012) The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. Mar 22;12(4):252-64.

comparison (ITC) of the EV-302 trial (EV+PEM) with the CM-901 substudy. The ESC advised that if EV-PEM were to be recommended by the PBAC, it is likely that this would become the new SoC.

*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 organisations (3) via the Consumer Comments facility on the PBS website. The comments from Rare Cancers Australia described the impact of urothelial carcinoma on patients quality of life and the need for more treatment options. The comments from BEAT Bladder Cancer Australia described the impact on the quality of life of patients and their family to live with, or support someone with, advanced/metastatic bladder cancer. The comments describe an unmet clinical need for improved first-line treatment options other than SoC. The comments also describe the benefits of treatment with NIVO as patients living longer, and stating that in many cases, patients have a partial or complete response. The comments also state that from a patient perspective, there are no disadvantages to a new treatment that provides strong clinical data with a proven, well understood safety profile.

6.3 The Medical Oncology Group of Australia (MOGA) also expressed its support for the NIVO submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for NIVO, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>11</sup>, based on a comparison with SoC.

### ***Clinical studies***

6.4 The submission was based on a substudy of one head-to-head trial comparing NIVO+SoC to SoC in u/mUC patients (n=608); the CM-901 substudy. The CM-901 study was a phase III open-label, randomised trial investigating the efficacy and safety of NIVO combined with ipilimumab or NIVO+SoC versus SoC alone, where SoC consisted of GC. The CM-901 substudy consisted of just the NIVO+SoC versus SoC alone arms of the CM- 901 study.

6.5 Two additional trials, JAVELIN Bladder 100 (JB-100) and EV-302, were selected to provide efficacy and safety data for ITCs with the supplementary and near market comparators.

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<sup>11</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

- JB-100 (n=700) was a phase III open-label trial that randomised patients with u/mUC who did not have disease progression with first-line chemotherapy to receive best supportive care (BSC) with or without avelumab. This trial was used to inform the ITC of NIVO+SoC followed by NIVO monotherapy to avelumab.
- EV-302 (n=886) was a phase III, open-label randomised trial comparing EV+PEM to gemcitabine plus platinum-based chemotherapy (Plat+Gem) in patients with previously untreated la/mUC. EV-302 was used to inform the ITC between NIVO+SoC and EV+PEM. A clinical claim was not made against EV+PEM.

6.6 The submission stated that the purpose of the NIVO versus avelumab ITC was that the use of avelumab in the CM-901 substudy SoC arm does not accurately reflect the use of avelumab in the Australian clinical setting. An advisory board survey conducted by the Sponsor (provided with submission) indicated that 80.9% of patients who respond to first line chemotherapy receive avelumab in Australia. In the SoC arm of the CM-901 substudy, 20.5% of patients who received subsequent systemic therapy received avelumab (equivalent to 10.5% of all patients randomised to SoC). Accurate data regarding the extent of avelumab maintenance use in Australia was not available at the time of evaluation. The ESC agreed with the evaluation that the use of avelumab in the CM-901 substudy was likely an underestimation of its use in the Australian clinical setting.

6.7 Table 2 details key subsequent systemic therapies in the CM-901 substudy. More patients in the SoC arm, compared to the NIVO+SoC arm, received any subsequent systemic therapy (51.3% vs 35.5%). Of note, more patients in the SoC arm received PEM (17.8% vs 4.6%) and avelumab (10.5% vs 1.0%) compared to the NIVO+SoC arm, while similar proportions of patients in each arm received EV (3.3% for NIVO+SoC vs 3.0% for SoC).

**Table 2: Key subsequent systemic therapies in the CM-901 substudy.**

Therapy	CM-901 substudy	
	NIVO+SoC N=304	SoC N=304
Any subsequent systemic therapy	108 (35.5%)	156 (51.3%)
Anti-PD1	22 (7.2%)	72 (23.7%)
nivolumab	6 (2.0%)	5 (1.6%)
pembrolizumab	14 (4.6%)	54 (17.8%)
Anti-PDL1	3 (1.0%)	52 (17.1%)
avelumab	3 (1.0%)	32 (10.5%)
atezolizumab	0 (0%)	13 (4.3%)
durvalumab	0 (0%)	7 (2.3%)
Platinum-based chemotherapy	25 (8.2%)	26 (8.6%)
carboplatin	12 (3.9%)	7 (2.3%)
cisplatin	11 (3.6%)	18 (5.9%)
Enfortumab vedotin	10 (3.3%)	9 (3.0%)

Source: Table 6.5.4-1, pp82-83 of the CM-901 CSR.

PD1 = programmed death protein 1; PDL1 = programmed death ligand 1.

6.8 Details of the studies presented in the submission are provided in Table 3.

**Table 3: Studies and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
CheckMate 901 (CM-901) NCT03036098	Van Der Heijden, M. S., Sonpavde, G., Powles, T., Necchi, A., Burotto, M., Schenker, M., Sade, J. P., Bamias, A., Beuzeboc, P., Bedke, J., Oldenburg, J., Chatta, G., Ürün, Y., Ye, D., He, Z., Valderrama, B. P., Ku, J. H., Tomita, Y., Filian, J., Wang, L., Purcea, D., Patel, M. Y., Nasroulah, F., & Galsky, M. D. Nivolumab plus Gemcitabine-Cisplatin in Advanced Urothelial Carcinoma	<i>New England Journal of Medicine</i> 2023; 389(19): 1778-1789.
	Bedke, J., Van der Heijden, M. S., Sonpavde, G., Powles, T., Necchi, A., Burotto, M., Schenker, M., Sade, J. P., Bamias, A., Beuzeboc, P., Oldenburg, J., Urun, Y., Ye, D., He, Z., Valderrama, B. P., Tomita, Y., Filian, J., Purcea, D., Nasroulah, F., & Galsky, M. Nivolumab (NIVO) + gemcitabine-cisplatin (GC) vs GC alone for previously untreated unresectable or metastatic urothelial carcinoma (mUC): results from the phase 3 CheckMate 901 trial.	<i>Oncology Research and Treatment</i> 2024; 47, 230: <a href="https://doi.org/10.1159/000535363">https://doi.org/10.1159/000535363</a>
	Galsky, M. D., Powles, T., Li, S., Hennicken, D., & Sonpavde, G. A phase 3, open-label, randomised study of nivolumab plus ipilimumab or standard of care (SoC) vs SoC alone in patients (pts) with previously untreated unresectable or metastatic urothelial carcinoma (mUC; CheckMate 901).	<i>Journal of Clinical Oncology</i> 2018; 36(15): <a href="https://doi.org/10.1200/jco.2018.36.15_suppl.tps4588">https://doi.org/10.1200/jco.2018.36.15_suppl.tps4588</a>
	Galsky, M. D., Powles, T., Li, S., Hennicken, D., & Sonpavde, G. A phase 3, open-label, randomised study of nivolumab plus ipilimumab or standard of care (SoC) versus SoC alone in patients (PTS) with previously untreated unresectable or metastatic UROTHELIAL CARCINOMA (mUC; CheckMate 901)	<i>Journal of Clinical Oncology</i> 2018; 36(6): <a href="https://doi.org/10.1200/JCO.2018.36.6_suppl.TPS539">https://doi.org/10.1200/JCO.2018.36.6_suppl.TPS539</a>
	van der Heijden, M. S., Sonpavde, G. P., Powles, T. B., Necchi, A., Burotto, M., Schenker, M., Sade, J. P., Bamias, A., Beuzeboc, P., Bedke, J., Oldenburg, J., Urun, Y., Ye, D., He, Z., Perez Valderrama, B., Tomita, Y., Filian, J., Purcea, D., Nasroulah, F., & Galsky, M. D. LBA7 Nivolumab plus gemcitabine-cisplatin versus gemcitabine-cisplatin alone for previously untreated unresectable or metastatic urothelial carcinoma: Results from the phase III CheckMate 901 trial.	<i>Annals of Oncology</i> 2023; 34, S1341: <a href="https://doi.org/10.1016/j.anonc.2023.10.107">https://doi.org/10.1016/j.anonc.2023.10.107</a>
	Waller, C. F., Galsky, M. D., Powles, T., Van Der Heijden, M. S., Li, S., Hennicken, D., & Sonpavde, G. A phase 3, open-label, randomised study of nivolumab plus ipilimumab or standard of care (SoC) vs SoC alone in patients with previously untreated unresectable or metastatic urothelial carcinoma (CheckMate 901)	<i>Oncology Research and Treatment</i> 2018; 41, 324-325: <a href="https://doi.org/10.1159/000492737">https://doi.org/10.1159/000492737</a>
JAVELIN Bladder 100	Powles T., Park S.H., Voog E., Caserta C., Valderrama B.P., Gurney H., Kalofonos H., Radulović S., Demey W., Ullén A., Loriot Y., Sridhar S.S., Tsuchiya N., Kopyltsov E., Sternberg C.N., Bellmunt J., AragonChing J.B., Petrylak D.P., Laliberte R., Wang J., Huang B., Davis C., Fowst C., Costa N., Blake-Haskins J.A., di Pietro A., and Grivas P. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma.	<i>The New England Journal of Medicine</i> 2020; 383(13), 1218-1230.
EV-302	Powles T., Valderrama B.P., Gupta S., Bedke J., Kikuchi E., Hoffman-Censits J., Iyer G., Vulsteke C., Park S.H., Shin S.J., Castellano D., Fornarini G., Li J.-R., Gümüş M., Mar N., Loriot Y., Fléchon A., Duran I., Drakaki A., Narayanan S., Yu X., Gorla S., Homet Moreno B., and van der Heijden M.S. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer	<i>The New England Journal of Medicine</i> 2024; 390(10), 875-888

Source: Table 17, pp49-51 of the submission.

**6.9 The key features of the included evidence are summarised in Table 4.**

**Table 4: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Nivolumab + GC vs. GC (SoC)</b>						
Checkmate 901 substudy	608	R, OL, MC	Low	Previously untreated unresectable or metastatic UC	OS PFS PRO ORR Safety	OS PFS Safety

Source: Table 18, pp52-53, Table 19, pp55-56, and Table 21, p59 of the submission.

GC = gemcitabine and cisplatin; MC = multi-centre; OL = open label; OS = overall survival; ORR = objective response rate; PFS = progression-free survival; PRO = patient reported outcomes; R = randomised; SoC = standard of care UC = urothelial carcinoma.

- 6.10 Overall, the risk of bias was considered low in the CM-901 substudy except for outcomes with subjective elements such as patient reported outcomes (PROs) and patient reported adverse events (AEs) due to the trial being open label.
- 6.11 Progression-free survival (PFS) and objective response rate (ORR) are used as surrogate endpoints for OS. However, recent literature investigating the validity of these endpoints as surrogates for OS in metastatic urothelial cancer has found a moderate correlation between PFS and OS, and a poor correlation between ORR and OS<sup>12</sup>.
- 6.12 For the ITC comparing NIVO+SoC followed by NIVO monotherapy to avelumab maintenance, the common comparator arm was SoC in CM-901 and BSC in JB-100. In the JB-100 trial, BSC included antibiotic agents, nutritional support, hydration, and pain management. Other systemic antitumour therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable. In the CM-901 substudy, patients in the SoC arm were allowed to receive subsequent anti-cancer therapy after GC. This included avelumab and pembrolizumab. The risk of bias for this ITC was high, given these, and other, transitivity concerns.
- 6.13 For the ITC comparing NIVO+SoC to EV+PEM, the common comparator arm was SoC. In EV-302, the SoC arm was Plat+Gem which included either cisplatin or carboplatin. In contrast, the SoC arm in the CM-901 substudy only included patients who were eligible for cisplatin. The risk of bias for this ITC was high, given these, and other, transitivity concerns.

<sup>12</sup> Ghali F, Zhao Y, Patel D, Jewell T, Yu EY, Grivas P, et al. (2023) Surrogate Endpoints as Predictors of Overall Survival in Metastatic Urothelial Cancer: A Trial-level Analysis. *Eur Urol Open Sci.* Jan;47:58-64.

**Table 5: Key features of the included evidence for the supplementary and near market comparator – indirect comparison**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
<b>Avelumab vs. BSC (common reference)</b>						
JAVELIN Bladder 100	700	R, OL, MC	Low	Locally advanced or metastatic urothelial carcinoma and progression free after 1L chemotherapy.	OS, PFS, ORR, Safety	Not used
<b>EV+PEM vs. Plat+Gem (common reference)</b>						
EV-302	886	R, OL, MC	Low	Previously untreated locally advanced or metastatic urothelial carcinoma	PFS, OS, ORR, DOR, PRO, safety	Not used

Source: Figure 18, p103, Figure 19, p104, and Table 35, p107 of the submission.

1L = first line; BSC = best supportive care; EV+PEM = enfortumab vedotin with pembrolizumab; DOR = duration of response; MC = multi-centre; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; Plat+Gem = platinum-based chemotherapy with gemcitabine; R = randomised, SoC = standard of care.

### **Comparative effectiveness**

- 6.14 In the CM-901 substudy, the primary efficacy outcomes were OS and PFS by blinded independent central review (BICR) in the intention-to-treat population (ITT). At the 9 May 2023 data cut-off (DCO) the median duration of follow-up was 33.61 months for the NIVO+SoC arm and 33.53 months for the SoC arm.
- 6.15 Table 6 summarises the survival outcomes in the CM-901 substudy. Figure 1 shows the Kaplan-Meier (KM) plots for OS and Figure 2 shows the KM plots for PFS by BICR.

**Table 6: Summary of survival outcomes in CM-901 substudy**

	NIVO+SoC n/N (%)	SoC n/N (%)	Absolute difference	HR (95% CI)
<b>Overall survival</b>				
Deaths, n/N (%)	172/304 (56.6%)	193/304 (63.5%)	-	<b>0.78 (0.63, 0.96)</b> <b>p=0.0171</b>
Median months OS (95% CI)	21.72 (18.63, 26.38)	18.86 (14.72, 22.44)	2.86	
6-month OS rates % (95% CI)	88.1 (83.8, 91.2)	83.9 (79.2, 87.7)	4.2% <sup>a</sup>	-
12-month OS rates % (95% CI)	70.2 (64.6, 75.1)	62.7 (56.8, 68.1)	7.5% <sup>a</sup>	-
18-month OS rates % (95% CI)	57.5 (51.5, 63.0)	51.7 (45.5, 57.4)	5.8% <sup>a</sup>	-
24-month OS rates % (95% CI)	46.9 (40.7, 52.8)	40.7 (34.6, 46.7)	6.2% <sup>a</sup>	-
<b>Progression-free survival by BICR</b>				
Events, n/N (%)	211/304 (69.4%)	191/304 (62.8%)	-	<b>0.72 (0.59, 0.88)</b> <b>p=0.0012</b>
Median months PFS (95% CI)	7.92 (7.62, 9.49)	7.56 (6.05, 7.75)	0.36	
6-month PFS rates % (95% CI)	65.5 (59.6, 70.7)	58.1 (51.6, 64.1)	7.4% <sup>a</sup>	-
12-month PFS rates % (95% CI)	34.2 (28.6, 40.0)	21.8 (16.1, 27.9)	12.4% <sup>a</sup>	-
18-month PFS rates % (95% CI)	27.6 (22.2, 33.2)	12.7 (8.1, 18.4)	14.9% <sup>a</sup>	-
24-month PFS rates % (95% CI)	23.5 (18.3, 29.0)	9.6 (5.6, 15.0)	13.9% <sup>a</sup>	-

Source: Table 29, p82, and Table 30, p83 of the submission.

BICR = blinded independent central review; CI = confidence interval; HR = hazard ratio; n = number of participants reporting data; N = total participants in group; NIVO = nivolumab; OS = overall survival; PFS = progression-free survival; SoC = standard of care.

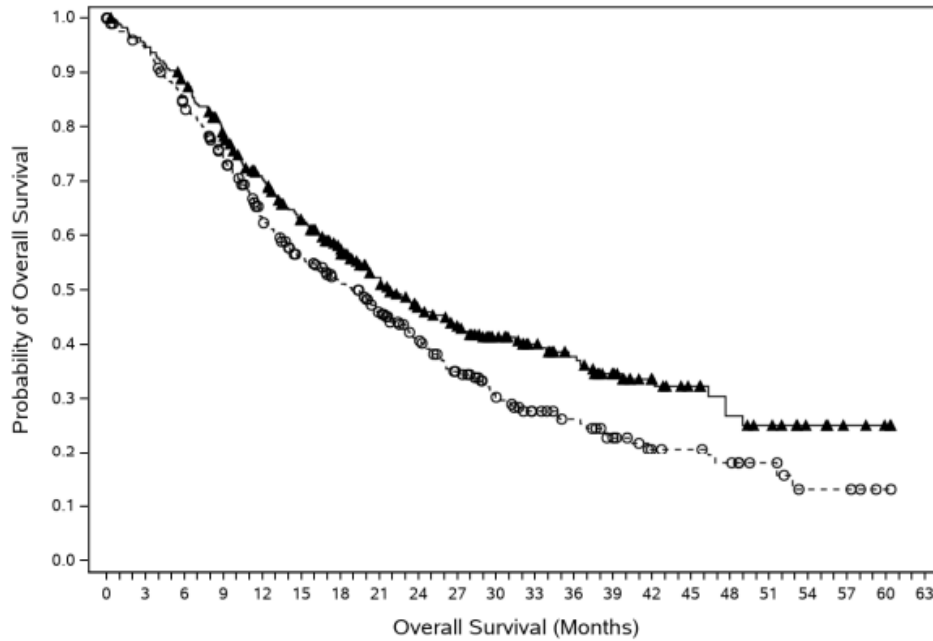
**Bold** = statistically significant results.

<sup>a</sup> calculated during the evaluation.

- 6.16 NIVO+SoC demonstrated a statistically significant improvement in OS against SoC in the ITT population, with a hazard ratio (HR) for death of 0.78 (95% confidence interval [CI]: 0.63, 0.96) corresponding to a 22% risk reduction for death in the NIVO+SoC arm. The median OS in the NIVO+SoC arm was 21.72 months compared to 18.86 months in the GC (SoC) arm, resulting in an incremental median OS benefit of 2.86 months. The KM curves for OS (Figure 1) began to separate after 9 months, favouring NIVO+SoC, and remained separated. The ESC noted the statistically significant improvement in OS against SoC and advised that the benefit reported in the trial may be overestimated compared to the proposed PBS population due to differences in use of avelumab (see paragraph 6.6).
- 6.17 NIVO+SoC also resulted in a statistically significant improvement in PFS by BICR when compared to SoC in the ITT population, with a HR for progression or death of 0.72 (95% CI: 0.59, 0.88). The KM curves for PFS by BICR separated at approximately 9 months, favouring NIVO+SoC, and remained separated (Figure 2). The ESC noted that the incremental median PFS benefit reported for NIVO+SoC is unlikely to be clinically

meaningful, noting that PFS can be difficult to interpret for immune checkpoint inhibitors.

Figure 1: KM plot of OS - ITT population.



Number of Subjects at Risk

Nivo + SOC

304 286 264 228 196 167 142 119 97 84 69 58 48 36 25 20 15 12 7 4 2 0

SOC

304 277 242 208 166 140 122 102 82 65 49 39 33 24 17 16 13 9 4 4 1 0

—▲— Nivo + SOC (events: 172/304), median and 95% CI: 21.72 (18.63, 26.38)

--○-- SOC (events: 193/304), median and 95% CI: 18.86 (14.72, 22.44)

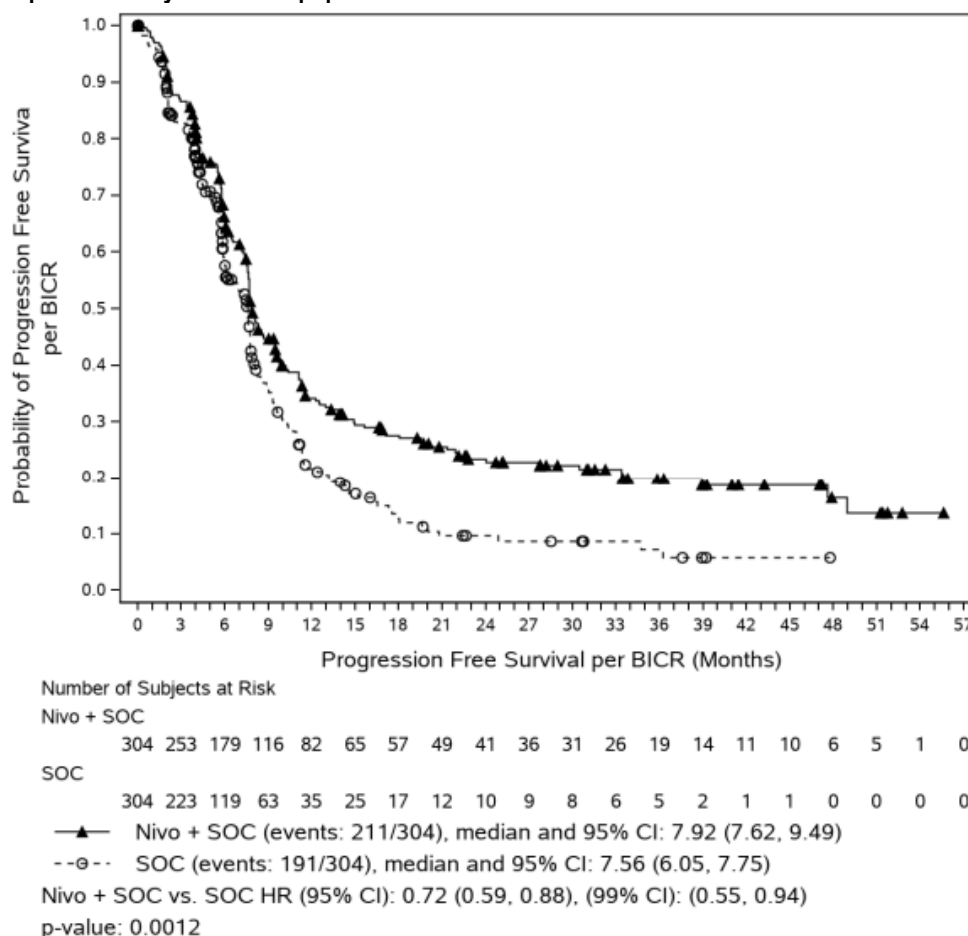
Nivo + SOC vs. SOC HR (95% CI): 0.78 (0.63, 0.96), (95.59% CI): (0.63, 0.96).

p-value: 0.0171

Source: Figure 9, p82 of the submission.

CI = confidence interval; HR = hazard ratio; ITT = intention to treat population; KM = Kaplan-Meier; Nivo = nivolumab; OS = overall survival; SOC = standard of care.

Figure 2: KM plot of PFS by BICR – ITT population.



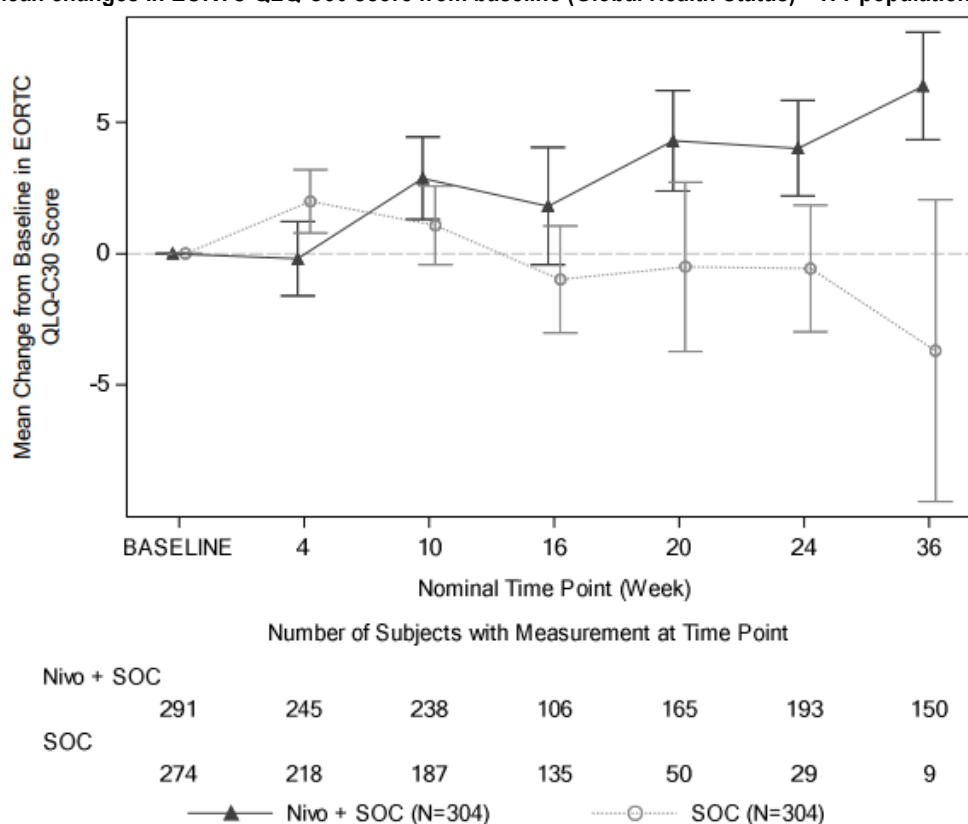
Source: Figure 10, p84 of the submission.

BICR = Blinded independent central review; CI = confidence interval; HR = hazard ratio; ITT = intention to treat population; KM = Kaplan-Meier; Nivo = nivolumab; PFS = progression-free survival; SOC = standard of care.

- 6.18 OS and PFS by BICR in patients with tumour expression of PD-L1  $\geq 1\%$  were also included in the submission. In patients with PD-L1  $\geq 1\%$ , both endpoints favoured NIVO+SoC and demonstrated an improvement against SoC. The OS HR was 0.74 (95% CI: 0.52, 1.04) and the PFS HR was 0.58 (95% CI: 0.41, 0.81) indicating that the risk of disease progression or death was reduced in those patients with tumours with PD-L1  $\geq 1\%$  who received NIVO+SoC. In patients with PD-L1  $< 1\%$ , NIVO+SoC, compared to SoC, demonstrated an OS HR of 0.82 (95% CI: 0.63, 1.05) and a PFS HR of 0.80 (95% CI: 0.62, 1.02) which indicating a reduced risk of disease progression or death in PD-L1  $< 1\%$  patients who received NIVO+SoC. This result was not statistically significant.
- 6.19 Median OS was longer in NIVO+SoC than SoC in subjects with PD-L1 expression  $\geq 1\%$  (25.10 months vs 15.34 months). In the PD-L1  $< 1\%$  subgroup, median OS in the NIVO+SoC arm was 21.06 months compared to 20.76 months in the SoC arm. OS and PFS by PD-L1  $< 1\%$  was not a pre-specified analysis in the CM-901 substudy.
- 6.20 The percentage of patients in the ITT population that completed the European Organisation for the Research and Treatment of Cancer core 30 quality of life

questionnaire (EORTC QLQ-C30) at baseline was 95.7% in the NIVO+SoC arm and 91.1% in the SoC arm. At baseline, mean EORTC QLQ-C30 summary scores for all domains were comparable between treatment arms (Figure 3). No statistical tests were performed on change from baseline scores between treatment arms. The submission considered a difference of 10 points on a 100-point scale between the two treatment arms to be a better indicator than statistical significance of clinically meaningful differences. This threshold was derived from Osoba et al., 1998<sup>13</sup> and is recommended by the EORTC for interpreting group differences and changes in the EORTC QLQ-C30<sup>14</sup>. No mean EORTC QLQ-C30 score reached a 10-point difference from baseline and therefore no clinically important changes in quality of life were identified between treatment arms.

Figure 3: Mean changes in EORTC QLQ-C30 score from baseline (Global Health Status) – ITT population



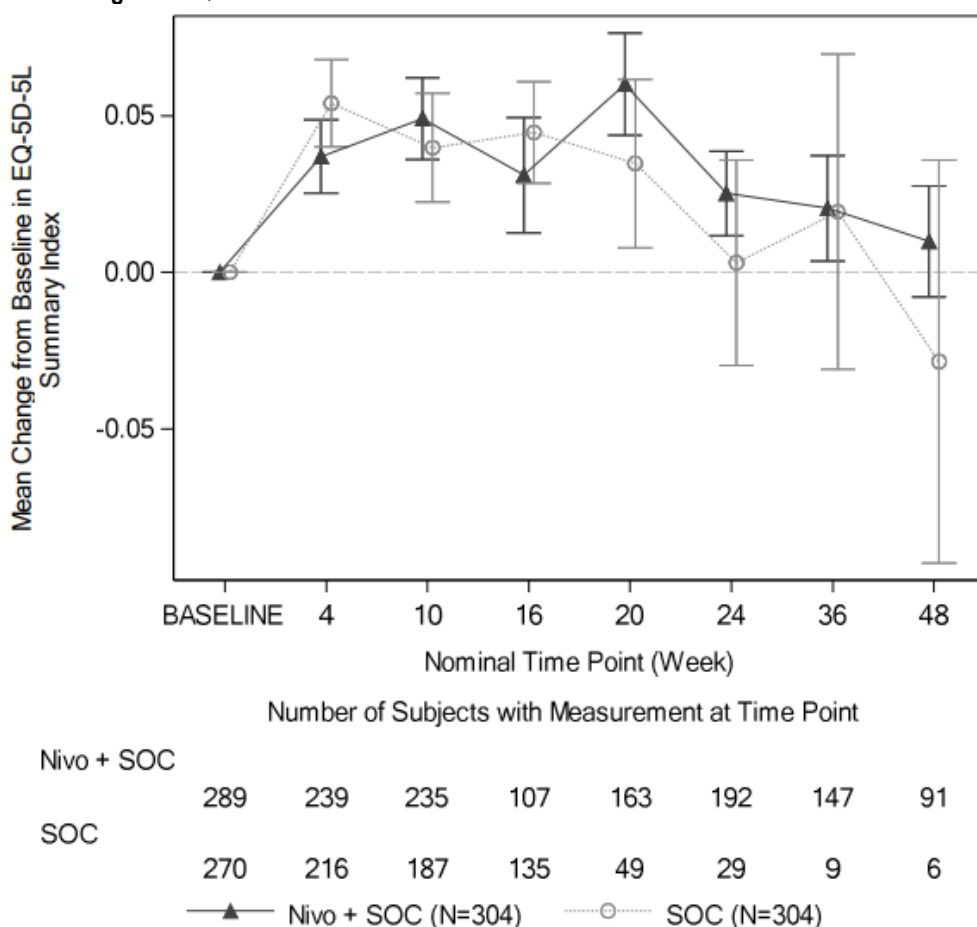
Source: Figure 12, p88 of the submission.  
 EORTC QLQ-C30 = European Organisation for the Research and Treatment of Cancer core 30 quality of life questionnaire; ITT = intention to treat; Nivo = nivolumab; SOC = standard of care.  
 Notes: Error bars represent standard error of the mean. Minimal clinically important difference considered to be a change of  $\geq 10$  points from baseline. Only timepoints where data available for  $\geq 5$  subjects in each treatment group are plotted.

<sup>13</sup> Osoba D, Rodrigues G, Myles J, Zee B, Pater J. (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol.* Jan;16(1):139-44.

<sup>14</sup> [How do I interpret QOL scores? | EORTC – Quality of Life](#)

6.21 The percentage of patients in the ITT population that completed the EuroQol 5-dimensional 5-level (EQ-5D-5L) questionnaire at baseline was 95.1% in the NIVO+SoC arm and 88.8% in the SoC arm. At baseline, mean EQ-5D-5L utility index and EQ-5D visual analogue scale (VAS) scores were comparable between treatment arms. No statistical tests were performed on change from baseline scores between treatment arms, but a mean change score from baseline of 0.08 for the utility score and of 7 for the VAS were considered as MCIDs based on the work of Pickard *et al.*, 2007<sup>15</sup>. Quality of life as measured by EQ-5D utility index and VAS scores were generally stable between treatment arms, with no mean change scores considered clinically important. This has implications for the choice of utilities and utility gain estimated in the economic evaluation.

Figure 4: Mean changes in EQ-5D-5L from baseline: index score



Source: Figure 13, p89 of the submission.  
EQ-5D-5L = EuroQol 5-dimensional 5-level index; ITT = intention to treat; Nivo = nivolumab; SoC = standard of care

<sup>15</sup> Pickard AS, Wilke CT, Lin HW, Lloyd A. (2007) Health utilities using the EQ-5D in studies of cancer. *Pharmacoeconomics*. 25(5):365-84.

Indirect comparisons

- 6.22 An ITC was conducted between NIVO monotherapy and avelumab using the results from the CM-901 substudy (NIVO) and the JB-100 trial (avelumab). The ITC was carried out using the Bucher single pairwise method. The data from CM-901 used to inform the ITC was restricted to patients who were progression-free and continued NIVO monotherapy after 18 weeks in the NIVO+SoC arm and who were progression free after 18 weeks in the SoC arm. This was done to align the CM-901 population with the inclusion criteria of JB-100, which required patients to be progression-free after chemotherapy. For PFS, this population included 224/304 (73.7%) of patients randomised to NIVO+SoC, and 180/304 (59.2%) of patients randomised to SoC. For OS, this population included 239/304 (78.6%) of patients randomised to NIVO+SoC, and 218/304 (71.7%) of patients of patients randomised to SoC. It was not explained why the two outcomes have different patient numbers.
- 6.23 Table 7 presents the results of the ITC based on the Bucher method for NIVO vs. avelumab, via SoC as the common reference, for PFS and OS. The result of the main indirect analysis on PFS shows no statistically significant difference between NIVO and avelumab (HR = 1.22, 95% CI: 0.91, 1.64). The results for the analysis of OS produced an HR of 0.97 (95% CI: 0.72, 1.32) indicating no difference between NIVO and avelumab with respect to OS.

**Table 7: Indirect treatment comparison results for OS and PFS: NIVO vs. AVEL via SoC for patients' progression free after 18 weeks**

Outcome	Direct HR (95% CI) Result <1 favors active intervention		Indirect HR (95% CI; p-value) Result <1 favors NIVO
	NIVO vs SoC	AVEL vs SoC	NIVO vs AVEL
OS	0.74 (0.58, 0.95)	0.76 (0.63, 0.91)	0.97 (0.72, 1.32)
PFS	0.66 (0.52, 0.84)	0.54 (0.46, 0.64)	1.22 (0.91, 1.64)

Source: Table 40, p116 of the submission.

AVEL = Avelumab; HR = hazard ratio; NIVO = Nivolumab; OS = overall survival; PFS = progression-free survival; SoC = standard of care

- 6.24 The submission identified several transitivity issues that are likely to have introduced bias into the indirect comparison. These were:
- 1L chemotherapy differences. More patients in the JB-100 trial received carboplatin in their 1L chemotherapy regimen, this may have had an impact on the outcomes. The PSCR stated that subgroup analyses of JB-100 reported little difference in treatment efficacy for those receiving gemcitabine + cisplatin or gemcitabine + carboplatin. As such, the PSCR argued that the 1L chemotherapy received is unlikely to be a significant effect modifier.
  - Baseline demographics. The data from CM-901 was derived from the subgroup of patients who were progression-free and continued NIVO monotherapy after 18 weeks. Selection of this subgroup resulted in a loss of randomisation.
  - Subsequent therapies. More patients in JB-100 received subsequent therapies than in the CM-901 substudy. Additionally, patients in the control arm of CM-901

were able to receive avelumab. The PSCR noted that patients were censored at initiation of subsequent cancer therapies. The PSCR stated that although the use of subsequent therapies may influence the results of the OS ITC, they would have minimal impact on the results of the PFS ITC.

- Event rates in common reference arm. In the CM-901 substudy the median OS for the SoC arm was 19.7 months and the median PFS was 4.1 months in the subgroup of patients selected for the ITC. In comparison, the median OS in the SoC arm of the JB-100 trial was 15 months and the median PFS was 2.1 months.

The ESC agreed with the evaluation that due to the transitivity issues detailed above, the results of the ITC were not informative.

6.25 The submission also included an indirect comparison of NIVO+SoC versus the near market comparator EV+PEM. The results are summarized in Table 8.

**Table 8: Indirect comparison results: NIVO+SoC vs. PEM+EV via SoC**

Analysis	Direct HR (95% CI) Result <1 favour treatment		Indirect HR (95% CI; p-value) Result <1 favours NIVO+SoC
	NIVO+SoC vs. SoC	EV + PEM vs. SoC	
OS	0.78 (0.63, 0.96)	0.47 (0.38, 0.58)	1.66 [1.23, 2.24] (p = 0.0009)
PFS	0.72 (0.59, 0.88)	0.45 (0.38, 0.54)	1.6 [1.23, 2.09] (p = 0.0005)

Source: Table 2, p5 of attachment 7 to the submission.

EV = enfortumab vedotin; HR= hazard ratio; NIVO= Nivolumab; OS= overall survival; PEM = pembrolizumab; PFS= progression-free survival; SoC= standard of care.

6.26 The ITC between NIVO+SoC (where SoC comprised of GC only) and EV+PEM based on the ITT population produced an OS HR of 1.66 (95% CI: 1.23, 2.24; p=0.0009) and a PFS HR of 1.60 (95% CI: 1.23, 2.09; p=0.0005), indicating that NIVO+SoC was inferior to EV+PEM with respect to efficacy.

6.27 An important difference between the two trials is that the inclusion criteria of the EV-302 trial allowed the enrolment of both cisplatin eligible (54%) and ineligible (46%) patients, while CM-901 only enrolled cisplatin eligible patients (15% of patients did however switch to carboplatin during the trial). Given that cisplatin is generally considered to be less tolerable than carboplatin in mUC, although with similar efficacy, patients in CM-901 may have been fitter than those in EV-302, and this is supported by the median age in EV-302 being older than in CM-901 (69 vs. 65). The ESC agreed with the evaluation that this suggests that the magnitude of benefit of EV+PEM over NIVO+SoC may be larger than observed in the ITC.

### **Comparative harms**

6.28 A summary of the safety results of the CM-901 substudy is presented in Table 9. Analyses of safety were conducted on all patients who received study treatment. The submission made a claim of inferior safety for NIVO+SoC compared to SoC.

6.29 The submission performed *post hoc* statistical analyses for selected AEs. The presented relative risks (RR) and risk differences (RD) highlight areas of interest.

6.30 In the NIVO+SoC arm, 99.7% of patients experienced all-cause AEs of any grade compared to 98.6% in the SoC arm. More patients in the NIVO+SoC arm compared to SoC experienced all-cause severe AEs (72.4% vs 64.9%), serious adverse events (SAEs) (46.7% vs 36.5%), and severe SAEs (37.2% vs 27.4%). Additionally, a greater proportion of patients in the NIVO+SoC arm compared to SoC experienced treatment-related: AEs of any grade (97.4% vs 92.7%), severe AEs (61.7% vs 51.4%), SAEs (24.7% vs 16.7%) and severe SAEs (20.1% vs 12.9%).

**Table 9: Summary of key adverse events in the CM-901 substudy**

Category	NIVO+SoC (N=304)	SoC (N=288)	RR [95% CI]	RD [95% CI]
	n/N (%)	n/N (%)	< 1 favours NIVO+SoC	< 0 favours NIVO+SoC
<b>All cause</b>				
AE (any grade)	303/304 (99.67%)	284/288 (98.61%)	1.01 [1.00, 1.03]	0.01 [0.00, 0.03]
Severe AE (grade 3 or 4)	220/304 (72.37%)	187/288 (64.93%)	<b>1.11 [1.00, 1.24]</b>	0.07 [0.00, 0.15]
SAE (any grade)	142/304 (46.71%)	105/288 (36.46%)	<b>1.28 [1.06, 1.56]</b>	<b>0.10 [0.02, 0.18]</b>
Severe SAE (grade 3 or 4)	113/304 (37.17%)	79/288 (27.43%)	<b>1.36 [1.07, 1.72]</b>	<b>0.10 [0.02, 0.17]</b>
Discontinuation due to AEs (any grade)	90/304 (29.61%)	69/288 (23.96%)	1.24 [0.94, 1.62]	0.06 [-0.01, 0.13]
Discontinuation due to Severe AEs (grade 3 or 4)	50/304 (16.45%)	38/288 (13.19%)	1.25 [0.84, 1.84]	0.03 [-0.02, 0.09]
Death	172/304 (56.58%)	186/288 (64.58%)	0.88 [0.77, 1.00]	-0.08 [-0.16, 0.00]
<b>Study-drug related</b>				
AE (any grade)	296/304 (97.37%)	267/288 (92.71%)	<b>1.05 [1.01, 1.09]</b>	<b>0.05 [0.01, 0.08]</b>
Severe AE (grade 3 or 4)	187/304 (61.51%)	148/288 (51.39%)	<b>1.20 [1.04, 1.38]</b>	<b>0.10 [0.02, 0.18]</b>
SAE (any grade)	75/304 (24.67%)	48/288 (16.67%)	<b>1.48 [1.07, 2.05]</b>	<b>0.08 [0.01, 0.15]</b>
Severe SAE (grade 3 or 4)	61/304 (20.07%)	37/288 (12.85%)	<b>1.56 [1.07, 2.27]</b>	<b>0.07 [0.01, 0.13]</b>
Discontinuation due to AEs (any grade)	64/304 (21.05%)	50/288 (17.36%)	1.21 [0.87, 1.69]	0.04 [-0.03, 0.10]
Discontinuation due to Severe AEs (grade 3 or 4)	33/304 (10.86%)	22/288 (7.64%)	1.42 [0.85, 2.38]	0.03 [-0.01, 0.08]
Death	2/304 (0.66%)	1/288 (0.35%)	1.89 [0.17, 20.78]	0.00 [-0.01, 0.01]

Source: Table 33, p91 of the submission.

AE = adverse event; CI = confidence intervals; CM-901 = CheckMate 901; n = number of participants with event; N = total number of participants in treatment arm; NIVO = nivolumab; RD = risk difference; RR = relative risk; SAE = serious adverse event; SoC = standard of care.

**Bold** = statistically significant

6.31 Table 10 presents a summary of any grade severity study drug-related AEs and grade 3-4 severity study drug-related AEs reported in ≥ 10% of patients in the NIVO+SoC arm.

6.32 The most common study drug-related AEs with severity of any grade, that occurred in ≥ 10% of patients in the NIVO+SoC arm, were anaemia (57.2%), nausea (46.7%), and neutropenia (30.6%). The only grade 3 or 4 severity drug-related AEs that occurred in ≥ 5% of patients in the NIVO+SoC arm were anaemia (22.0%), neutropenia (18.8%), and a decrease in neutrophil count (14.5%). A grade 5 treatment-related adverse event (sepsis) occurred in 1 patient in the NIVO+SoC group and in 1 patient (acute kidney injury) in the SoC group.

Table 10: Overview of most frequently reported study drug-related AEs - all-treated population

Category	NIVO+SoC (N=304)	SoC (N=288)	RR [95% CI]	RD [95% CI]
	n/N (%)	n/N (%)	< 1 favours NIVO+SoC	< 0 favours NIVO+SoC
<b>Study-drug related AEs – any grade<sup>a</sup></b>				
Total patients	296/304 (97.37%)	267/288 (92.71%)	<b>1.05 [1.01, 1.09]</b>	<b>0.05 [0.01, 0.08]</b>
Blood and lymphatic system disorders	218/304 (71.71%)	188/288 (65.28%)	1.10 [0.98, 1.23]	0.06 [-0.01, 0.14]
Anaemia	174/304 (57.24%)	137/288 (47.57%)	<b>1.20 [1.03, 1.41]</b>	<b>0.10 [0.02, 0.18]</b>
Neutropenia	93/304 (30.59%)	86/288 (29.86%)	1.02 [0.80, 1.31]	0.01 [-0.07, 0.08]
Thrombocytopenia	45/304 (14.80%)	35/288 (12.15%)	1.22 [0.81, 1.84]	0.03 [-0.03, 0.08]
Leukopenia	38/304 (12.50%)	33/288 (11.46%)	1.09 [0.70, 1.69]	0.01 [-0.04, 0.06]
Gastrointestinal disorders	201/304 (66.12%)	175/288 (60.76%)	1.09 [0.96, 1.23]	0.05 [-0.02, 0.13]
Nausea	142/304 (46.71%)	138/288 (47.92%)	0.97 [0.82, 1.16]	-0.01 [-0.09, 0.07]
Vomiting	55/304 (18.09%)	48/288 (16.67%)	1.09 [0.76, 1.54]	0.01 [-0.05, 0.08]
Constipation	44/304 (14.47%)	40/288 (13.89%)	1.04 [0.70, 1.55]	0.01 [-0.05, 0.06]
Diarrhoea	40/304 (13.16%)	25/288 (8.68%)	1.52 [0.94, 2.43]	0.04 [-0.01, 0.10]
Investigations	170/304 (55.92%)	132/288 (45.83%)	<b>1.22 [1.04, 1.43]</b>	<b>0.10 [0.02, 0.18]</b>
Neutrophil count decreased	75/304 (24.67%)	60/288 (20.83%)	1.18 [0.88, 1.60]	0.04 [-0.03, 0.11]
Platelet count decreased	66/304 (21.71%)	43/288 (14.93%)	<b>1.45 [1.03, 2.06]</b>	<b>0.07 [0.01, 0.13]</b>
White blood cell count decreased	64/304 (21.05%)	40/288 (13.89%)	<b>1.52 [1.06, 2.17]</b>	<b>0.07 [0.01, 0.13]</b>
Blood creatinine increased	39/304 (12.83%)	35/288 (12.15%)	1.06 [0.69, 1.62]	0.01 [-0.05, 0.06]
General disorders and administration site conditions	151/304 (49.67%)	131/288 (45.49%)	1.09 [0.92, 1.29]	0.04 [-0.04, 0.12]
Fatigue	74/304 (24.34%)	69/288 (23.96%)	1.02 [0.76, 1.35]	0.00 [-0.07, 0.07]
Asthenia	47/304 (15.46%)	46/288 (15.97%)	0.97 [0.67, 1.41]	-0.01 [-0.06, 0.05]
Skin and subcutaneous tissue disorders	111/304 (36.51%)	45/288 (15.63%)	<b>2.34 [1.72, 3.18]</b>	<b>0.21 [0.14, 0.28]</b>
Pruritis	44/304 (14.47%)	8/288 (2.78%)	<b>5.21 [2.50, 10.88]</b>	<b>0.12 [0.07, 0.16]</b>
Rash	41/304 (13.49%)	10/288 (3.47%)	<b>3.88 [1.98, 7.61]</b>	<b>0.10 [0.05, 0.15]</b>
Metabolism and nutrition disorders	107/304 (35.20%)	71/288 (24.65%)	<b>1.43 [1.11, 1.84]</b>	<b>0.11 [0.03, 0.18]</b>
Decreased appetite	68/304 (22.37%)	45/288 (15.63%)	<b>1.43 [1.02, 2.01]</b>	0.07 [0.00, 0.13]
Endocrine disorders	56/304 (18.42%)	0/288 (0.00%)	NE	<b>0.18 [0.14, 0.23]</b>
Hypothyroidism	40/304 (13.16%)	0/288 (0.00%)	NE	<b>0.13 [0.09, 0.17]</b>
<b>Study-drug related AEs - severe (grade 3 or 4)</b>				
Total patients	187/304 (61.51%)	148/288 (51.39%)	<b>1.20 [1.04, 1.38]</b>	<b>0.10 [0.02, 0.18]</b>
Blood and lymphatic system disorders	111/304 (36.51%)	96/288 (33.33%)	1.10 [0.88, 1.37]	0.03 [-0.05, 0.11]
Anaemia	67/304 (22.04%)	51/288 (17.71%)	1.24 [0.90, 1.73]	0.04 [-0.02, 0.11]
Neutropenia	57/304 (18.75%)	44/288 (15.28%)	1.23 [0.86, 1.76]	0.03 [-0.03, 0.10]
Investigations	75/304 (24.67%)	132/288 (45.83%)	<b>0.54 [0.43, 0.68]</b>	<b>-0.21 [-0.29, -0.13]</b>
Neutrophil count decreased	44/304 (14.47%)	60/288 (20.83%)	<b>0.69 [0.49, 0.99]</b>	-0.06 [-0.12, 0.00]

Source: Table 34, p93 of the submission.

AE = adverse event; CI = confidence intervals; n = number of participants with event; N = total number of participants in treatment arm; NIVO = nivolumab; RD = risk difference; RR = risk ratio; SoC = standard of care.

a. Shown are events that occurred in ≥ 10% of patients in the NIVO+SoC treatment arm

**Bold** = statistically significant

### Indirect comparisons

- 6.33 Safety data were not available for the CM-901 substudy subgroup of patients who did not progress within the first 18 weeks, which are the patients used to assess efficacy in the ITC. As such, an anchored ITC for safety was not possible and so a unanchored indirect comparison of NIVO+SoC versus avelumab was presented in the submission.
- 6.34 The unanchored indirect comparison of safety indicated that avelumab, in comparison to NIVO+SoC, may be associated with fewer Grade  $\geq 3$  AEs (53.8% vs. 76.6%), Grade  $\geq 3$  treatment related adverse events (TRAEs) (19.5% vs. 61.8%), SAEs (30.5% vs. 46.7%), AEs leading to discontinuation (14.2% vs. 29.6%) and TRAEs leading to discontinuation (11.6% vs. 21.1%).
- 6.35 The submission noted that the AEs recorded for the CM-901 substudy patients included both the induction and maintenance phase whereas the JB-100 study only included the maintenance phase, likely biasing the comparison in favour of avelumab. This is in addition to the transitivity issues detailed in paragraph 6.24. Due to these issues, the unanchored indirect comparison of safety between NIVO and avelumab should be interpreted with caution.
- 6.36 The submission presented an unanchored indirect comparison of safety for NIVO+SoC vs. EV+PEM.
- 6.37 The unanchored safety comparison reported that individuals in both trials experienced similar rates of Grade  $\geq 3$  treatment emergent adverse events (TEAEs) (NIVO+SoC 76.6% vs. EV+PEM 73.0%), Grade  $\geq 3$  TRAEs (61.8% vs. 55.9%), and serious TEAEs (46.7% vs. 50.0%), inferring that NIVO+SoC followed by NIVO monotherapy may be non-inferior to EV+PEM on safety outcomes. However, as with the efficacy indirect comparison, differences in chemotherapy and median age between the two trials suggest that patients in the NIVO+SoC may have been fitter and so AEs in this arm may underestimate what would be expected in a comparison between EV+PEM and NIVO+SoC in the target PBS population.

### **Benefits/harms**

- 6.38 A summary of the comparative benefits and harms for NIVO+SoC versus SoC is presented in Table 11.
- 6.39 A benefits and harms table is not presented for NIVO+SoC versus avelumab as the submission made a claim of non-inferiority. Additionally, the unanchored indirect comparison of safety did not allow for a meaningful comparison.

**Table 11: Summary of comparative benefits and harms for NIVO+SoC vs. SoC**

<b>Progression-free survival (median duration of follow up 33.6 months)</b>						
<b>Event</b>	<b>NIVO+SoC</b>		<b>SoC</b>		<b>Absolute Difference</b>	<b>HR (95% CI)</b>
Events, n/N (%)	211/304 (69.4%)		191/304 (62.8%)		-	<b>0.72 (0.59, 0.88)</b> <b>p=0.0012</b>
Median months PFS (95% CI)	7.92 (7.62, 9.49)		7.56 (6.05, 7.75)		0.36	
6-month PFS rates, % (95% CI)	65.5 (59.6, 70.7)		58.1 (51.6, 64.1)		7.4%	
12-month PFS rates, % (95% CI)	34.2 (28.6, 40.0)		21.8 (16.1, 27.9)		12.4%	
18-month PFS rates, % (95% CI)	27.6 (22.2, 33.2)		12.7 (8.1, 18.4)		14.9%	
24-month PFS rates, % (95% CI)	23.5 (18.3, 29.0)		9.6 (5.6, 15.0)		13.9%	
<b>Overall survival (median duration of follow up 33.6 months)</b>						
Deaths, n/N (%)	172/304 (56.6%)		193/304 (63.5%)		-	<b>0.78 (0.63, 0.96)</b> <b>p=0.0171</b>
Median months OS (95% CI)	21.72 (18.63, 26.38)		18.86 (14.72, 22.44)		2.86	
6-month OS rates, % (95% CI)	88.1 (83.8, 91.2)		83.9 (79.2, 87.7)		4.2%	
12-month OS rates, % (95% CI)	70.2 (64.6, 75.1)		62.7 (56.8, 68.1)		7.5%	
18-month OS rates, % (95% CI)	57.5 (51.5, 63.0)		51.7 (45.5, 57.4)		5.8%	
24-month OS rates, % (95% CI)	46.9 (40.7, 52.8)		40.7 (34.6, 46.7)		6.2%	
<b>Harms</b>						
	<b>NIVO+SoC n/N</b>	<b>SoC n/N</b>	<b>RR (95% CI)</b>	<b>Event rate/100 patients*</b>		<b>RD (95% CI)</b>
				<b>NIVO+SoC</b>	<b>SoC</b>	
Anaemia	174/304	137/288	<b>1.20 (1.03, 1.41)</b>	57.2	47.6	<b>0.10 (0.02, 0.18)</b>
White blood cell count decrease	64/304	40/288	<b>1.52 (1.06, 2.17)</b>	21.1	13.9	<b>0.07 (0.01, 0.13)</b>
Pruritis	44/304	8/288	<b>5.21 (2.50, 10.88)</b>	14.5	2.8	<b>0.12 (0.07, 0.16)</b>

Source: Table 29, p82, Table 30, p83, and Table 32, pp93-94 of the submission.

CI = confidence interval; HR = hazard ratio; Nivo = nivolumab; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = risk ratio; SoC = standard of care.

\* Median duration of follow-up: 33.6 months.

**Bold** = statistically significant.

6.40 On the basis of the direct evidence presented by the submission, for every 100 patients treated with NIVO+SoC in comparison with SoC over a median duration of follow-up of 33.6 months:

- Approximately 6 fewer patients would have died at 18 months.
- Approximately 10 additional patients would experience anaemia.
- Approximately 7 additional patients would experience a decrease in white blood cell count.
- Approximately 12 additional patients would experience pruritis (itchy skin).

### **Clinical claim**

6.41 The submission described NIVO+SoC as superior in terms of effectiveness compared to SoC. The ESC agreed with the evaluation that this claim was adequately supported. NIVO+SoC demonstrated a statistically significant improvement in OS in the ITT population compared to SoC, with an HR for death of 0.78 (95% CI: 0.62, 0.96) and an incremental OS gain of 2.86 months.

- 6.42 The submission described NIVO+SoC as inferior in terms of safety compared to SoC. The ESC agreed with the evaluation that this claim was reasonable. More patients in the NIVO+SoC arm than in the SoC arm experienced all-cause severe AEs (72.4% vs 64.9%), SAEs (46.7% vs 36.5%), and severe SAEs (37.2% vs 27.4%).
- 6.43 The submission additionally made a claim of non-inferior efficacy and non-inferior safety of NIVO+SoC followed by NIVO monotherapy compared to avelumab. To support this claim, the submission presented an anchored indirect comparison of efficacy which reported no statistically significant differences between NIVO+SoC and avelumab for PFS (HR=1.22, 95% CI: 0.91, 1.64) and no statistically significant differences between NIVO+SoC and avelumab for OS (HR=0.97 95%, CI:0.72, 1.32). The submission presented a unanchored indirect comparison of safety which indicated that avelumab, in comparison to NIVO+SoC, may be associated with fewer Grade  $\geq 3$  AEs (67.7% vs. 76.6%), Grade  $\geq 3$  TRAEs (51.7% vs. 61.8%), SAEs (36.5% vs. 46.7%), AEs leading to discontinuation (14.2% vs. 29.6%) and TRAEs leading to discontinuation (11.6% vs. 21.1%). However, numerous transitivity issues exist between the two studies such as differences in 1L chemotherapy, differences in baseline demographics, and differences in event rates in the common reference arms. The ESC agreed with the evaluation that these issues result in both the anchored ITC and unanchored ITC being uninformative. As such, the claim of non-inferior efficacy and non-inferior safety was not adequately supported.
- 6.44 The PBAC and the ESC noted the submission did not make a clinical claim for NIVO+SoC versus EV+PEM, although an ITC was presented.
- 6.45 The PBAC considered that the claim of superior comparative effectiveness versus SoC was reasonable.
- 6.46 The PBAC considered that the claim of inferior comparative safety versus SoC was reasonable.
- 6.47 The PBAC agreed with the ESC that the claim of non-inferior comparative effectiveness and non-inferior safety versus avelumab was not adequately supported due to the transitivity issues associated with the anchored ITC and unanchored ITC (see paragraph 6.43).

### ***Economic analysis***

- 6.48 The submission presented a stepped economic evaluation, based on the CM-901 substudy, that compared the 1L use of NIVO+SoC with SoC only in u/mUCs.

**Table 12: Summary of model structure, key inputs and rationale**

Component	Summary
Treatments	NIVO+SoC versus SoC only
Time horizon	10 years in the base case (vs. a median follow-up for OS of 33.53-33.61 months from the CM-901 substudy). The PBAC previously noted that a time horizon of 7.5 years may be more appropriate for this population (paragraph 7.10, avelumab PSD, PBAC March 2021 meeting). The ESC noted patients entering the model had an average age of 64 years.
Outcomes	LYs; QALYs
Methods used to generate results	Partitioned survival model
Health states	PF, PD and death
Cycle length	1 week
Allocation to health states	Derived from PFS and OS KM curves from the CM-901 substudy
Extrapolation method	KM data was used until a pooled truncation time points (i.e. same truncation point for both arms) of 12 months and 27 months for PFS and OS, respectively. Dependent parametric models, based on goodness of fit (AIC/BIC values and visual analysis), were fitted to the observed data based on the proportional hazards assumption. The 2-spline hazard model was fitted to the observed data for both PFS and OS across treatment arms. The choice of the spline 2-knot hazard model in the base case resulted in 8% of patients still alive at 10 years in the NIVO+SoC arm and 4% of patients still alive in the SoC arm. This may not be clinically plausible. Alternate parametric models were identified during the evaluation based on clinical plausibility and visual inspection. These had a moderate impact on the ICER.  82% of the incremental LYs were gained in the extrapolated period.
Health related quality of life	Utility values derived from the CM-901 substudy (PF = 0.888, PD = 0.843)
Subsequent treatment	35.5% and 51.3% of patients in the NIVO+SoC and SoC arms received subsequent treatment, respectively, based on observed use in the CM-901 substudy. Given that the trial was ongoing, subsequent treatment data may not be complete. Costs for subsequent treatment with PDC (63.9%) and EV (36.1%) were included in the NIVO+SoC arm while costs for treatment with avelumab (33.3%), pembrolizumab (47.4%), PDC (13.5%) and EV (5.8%) were included in the SoC arm. The costs applied in the economic model did not reflect the use observed in the CM-901 substudy. The use of PDC in the NIVO+SoC arm and use of pembrolizumab and other anti PD-1/PD-L1 therapies in the SoC arm were lower in the CM-901 substudy compared to that applied in the economic model.
Costs	Direct treatment costs, costs for disease management (PF and PD), costs for subsequent treatments, costs for treatment of AEs and terminal care costs were applied. While the costs included in the economic model were appropriate, it may not be reasonable to include terminal care costs as the patients modelled in both arms have advanced disease. Further, the fees for MBS items and mark-up fees for PBS medicines have been updated since the submission.

Source: Table 49, p133 of the submission and the "Attachment 13 – Economic Model 1L mUC" workbook provided in the submission. AEs = Adverse Events; AIC = Akaike information criteria; BIC = Bayesian information criteria; EV = enfortumab vedotin; KM = Kaplan-Meier; LYs = Life-years; MBS = Medicare benefits schedule; NIVO = Nivolumab; OS = Overall survival; PBS = Pharmaceutical benefits scheme; PD = Progressive disease; PDC = Platinum-doublet chemotherapy; PF = Progression-free; PFS = Progression-free survival; PSD = Public summary document; QALYs = Quality-adjusted life years; SoC = Standard of care

6.49 The submission employed a partitioned survival model and modelled three health states: progression-free (PF), progressed disease (PF) and death. Allocation to the three health states was based on the OS and PFS curves for the NIVO+SoC and SoC arms of the CM-901 substudy. A two-year stopping rule was applied to NIVO monotherapy in the base case analysis. The evaluation considered the structure of the economic model was reasonable.

- 6.50 A time horizon of 10 years, based on a median follow-up for OS of 33.53-33.61 months, was nominated in the submission’s base case. The PBAC and ESC have previously noted that a time horizon of 7.5 years is likely to be more appropriate in this population (paragraphs 6.45 and 7.10, avelumab Public summary document (PSD), March 2021 PBAC meeting). In the base case analysis, the spline 2-knot hazard model predicts that 13% and 7% of patients remain alive at 7.5 years and 8% and 4% of patients remain alive at 10 years, in the NIVO+SoC and SoC arms, respectively. Thus, a time horizon of 10 years may be necessary to adequately capture patient survival if the spline 2-knot hazard model is fitted to the KM OS data. Of note, alternate choices for parametric model extrapolation, which are more clinically plausible for the target population, may yield survival estimates more consistent with PBAC and ESC advice on the time horizon in this population (e.g. the use of either a gamma or Weibull model predicts 5% and 2% of patients remaining alive at 7.5 years, in the NIVO+SoC and SoC arms, respectively). The PSCR accepted that, consistent with avelumab, a 7.5 year time horizon may be more appropriate. The ESC agreed with the PSCR that the time horizon should be reduced to 7.5 years. The ESC also advised that the use of gamma extrapolations for OS would be appropriate based on clinical plausibility.
- 6.51 Health state membership was determined based on the PFS and OS curves from the CM-901 substudy data. KM data were used until 12 months for PFS and 27 months for OS. No justification was provided for the selection of these time points in the submission. Given that the PBAC guidelines v5.0 recommend that observed data should be utilised until the data becomes unreliable due to a small number of patients remaining event free, it may have been more appropriate to use treatment-specific truncation time points as, for example, in the NIVO+SoC arm, at 27 months, 84 patients were still at risk of death (Figure 1). However, 58 and 48 patients (n = 304) were still at risk of death at months 33 and 36 months, respectively. Extending the truncation time point in both treatment arms reduced the ICER. The ESC advised that the use of the approach outlined in GebSKI et al (2018) would provide a more rigorous approach for determining truncation points.<sup>16</sup> The ESC considered that based on GebSKI et al., a minimum n satisfying ‘Criterion 2’, which tests whether one extra event would not decrease the estimated survival to below its full information of a one-sided 95% confidence boundary at time t, could be calculated (Table 13).

**Table 13: Truncation time points based on the GebSKI (2018) approach, Criterion 2**

	<b>NIVO+SoC</b>	<b>SoC</b>
PFS	51 months	36 months
OS	54 months	57 months

Source: constructed during the preparation of the ESC advice

NIVO = Nivolumab; OS = Overall survival; PFS = Progression-free survival; SoC = Standard of care

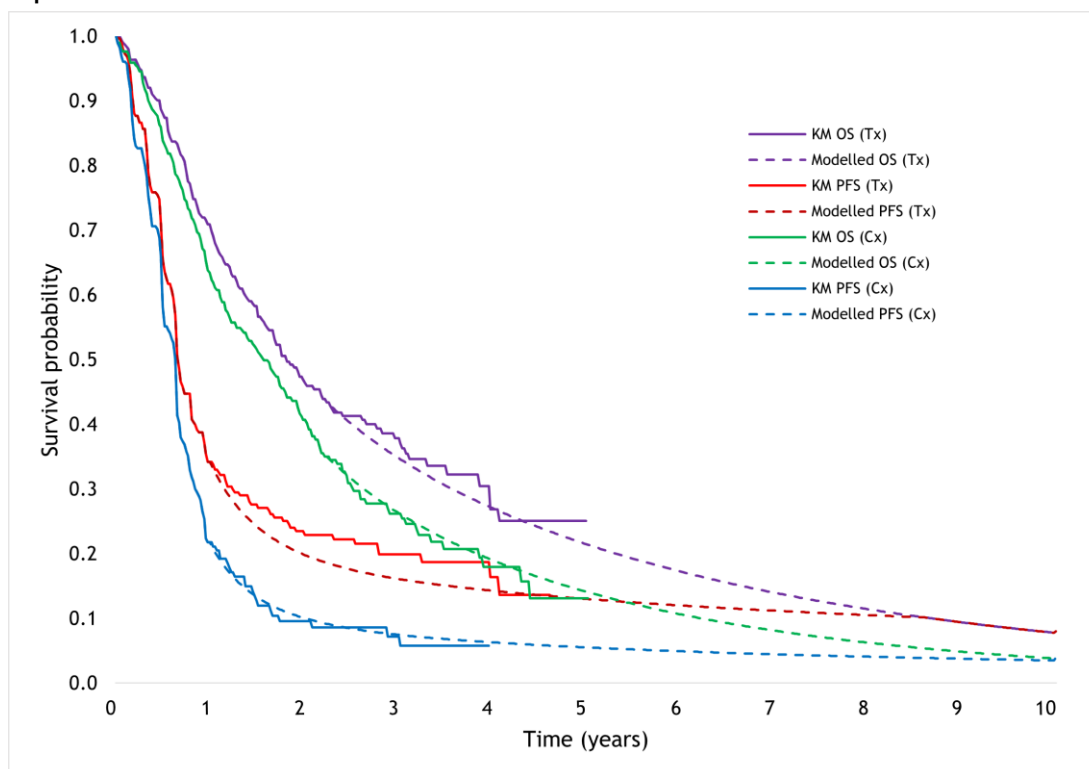
- 6.52 Dependent parametric models, based on the claim that the proportional hazards (PH) assumption held for both PFS and OS, were fitted to the KM data from the CM-901

<sup>16</sup> GebSKI V, Garès V, Gibbs E, Byth K. Data maturity and follow-up in time-to-event analyses. *Int J Epidemiol.* 2018 Jun 1;47(3):850-9.

substudy. Based on visual assessment of the log-cumulative hazard plots, the Schoenfeld residuals plots and the quantile-quantile plots, for both PFS and OS, the claim of PH was reasonable. For both PFS and OS, 2-spline hazard models were fitted to the observed data based on goodness of fit assessed by AIC/BIC values and visual inspection. As described in para 6.50, the model chosen in the base case may overestimate survival at 7.5 years. Alternate parametric models, based on goodness of fit (using AIC/BIC values and visual analysis) and clinical plausibility were explored during the evaluation. For OS, the spline 1-knot hazard, gamma and Weibull models were identified as alternate extrapolation approaches, noting that only the gamma and Weibull models generated plausible extrapolations for a time horizon of 7.5 years. For PFS, all models fit the data considerably well until month 16. Of note, the choice of extrapolation had a moderate impact on the ICER only when the gamma model was chosen. The alternate parametric extrapolations identified during the evaluation had a moderate (spline 1-knot hazard model for OS; gamma model for PFS) to high (gamma and Weibull models for OS) impact on the ICER.

6.53 Comparisons of the observed KM PFS and OS data to the modelled curves for both arms are presented in Figure 5 for both treatment arms. The modelled SoC data appeared to fit the observed data reasonably well, however the modelled estimates appeared to underestimate NIVO +SoC OS and PFS.

Figure 5: Kaplan-Meier and modelled curves for PFS and OS



Source: constructed during evaluation from the "Attachment 13 – Nivolumab 1L mUC" workbook provided in the submission.  
 Cx = Comparator arm; NIVO Nivolumab; OS = Overall survival; PFS = Progression-free survival; SoC = Standard of care; Tx = Treatment arm

- 6.54 The submission applied utility weights of 0.888 to patients in the PF health state and 0.843 in the PD state, which were derived from the Health-related quality of life (HRQoL) assessments of the CM-901 substudy using the EQ-5D-5L (and mapped using the Australian value set)<sup>17</sup>. The utility weights applied appeared to be clinically implausible, given that a recent study in a representative sample of the general Australian population (n = 9,958) reported an average utility of 0.86 using the EQ-5D-5L.<sup>18</sup> Further, the utility weight applied in the PD health was based on a small number of HRQoL assessments (162 in the NIVO+SoC arm and 34 in the SoC arm). The utility weights were also noted to be higher than estimates previously considered by the PBAC in 1L treatment of urothelial carcinomas, i.e., 0.772 and 0.698 for PF and PD health states, respectively (Table 12, avelumab PSD, March 2021 PBAC meeting). In addition, the trial-based measurement of differences in HRQoL in CM-901 indicated that there were no clinically important differences in between trial arms. The ICER was highly sensitive to the utility weights applied, especially in the PD state (increasing to \$75,000 to < \$95,000/quality-adjusted life year (QALY) when the previously considered values were used). The PSCR concurred with the evaluation that the utility values seem high relative to Australian population norms. The PSCR) proposed a scenario analysis that adjusted the trial based utility values against the Australian mean EQ-5D-5L values which resulted in utility values of 0.855 for PF and 0.810 for PD health states. The ESC considered that it was not appropriate to derive utility weights for patients with u/mUC using the Australian-population utility weights as patients with u/mUC are likely to have worse quality of life compared to the Australian population. The ESC advised that the utility weights previously considered by the PBAC for avelumab are likely to be reasonable for patients with u/mUC.
- 6.55 The treatment costs were estimated based on the mean number of doses of NIVO+SoC from the CM-901 substudy and on a fixed number of doses for SoC. For initial treatment (referred to as part 1 of treatment) with NIVO+SoC, the mean number of doses was 5.17 doses. For continuing treatment (referred to as part 2 of treatment) with NIVO (maintenance therapy), a mean number of doses of 7.06 was applied. This was reasonable as it allows for accurate estimation of initial and continuing treatment costs of NIVO+SoC therapy (which is followed by NIVO maintenance therapy). However, the submission applied the same number of doses for NIVO, cisplatin and gemcitabine (5.17 x 2) during initial treatment. This differed from the CM-901 substudy in which the mean number of doses for cisplatin and gemcitabine were 4.70

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<sup>17</sup> Norman R, Mulhern B, Lancsar E, Lorgelly P, Ratcliffe J, Street D, Viney R. The Use of a Discrete Choice Experiment Including Both Duration and Dead for the Development of an EQ-5D-5L Value Set for Australia. *Pharmacoeconomics*. 2023 Apr;41(4):427-38.

<sup>18</sup> Redwood L, Currow D, Kochovska S, Thomas SJ. Australian population norms for health-related quality of life measured using the EQ-5D-5L, and relationships with sociodemographic characteristics. *Qual Life Res*. 2024 Mar;33(3):721-33.

and 9.80, respectively. Of note, use of the mean number of doses had a minimal impact on the ICER (reduces to \$75,000 to < \$95,000/QALY).

- 6.56 For both arms, subsequent treatment costs were included based on usage from the CM-901 substudy. 35.5% and 51.3% of patients received subsequent systemic therapy in the NIVO+SoC and SoC arms, respectively. Given that the trial was ongoing, subsequent treatment data may not be complete and so this may not be appropriate. The ESC noted that assuming the proportion of patients receiving subsequent treatment was equal in both arms had a minimal impact on the ICER (an increase of 3%).
- 6.57 Of those that receive subsequent treatment, in the NIVO+SoC arm, the submission assumed 36.1% would receive treatment with EV (as monotherapy) while the remaining 63.9% would be rechallenged with PDC. This was not reasonable as the use of PDC as subsequent treatment in the NIVO+SoC arm of the CM-901 substudy was only 23%. Further, international guidelines recommend rechallenge only after a treatment free interval of at least 12 months since initial treatment with PDC. It is expected that if NIVO+SoC is listed, a majority of patients who progress and receive subsequent treatment will receive EV in the later line. Thus, the costs for EV treatment in the NIVO+SoC arm have been largely underestimated. The submission also incorrectly calculated the costs of subsequent treatment with EV as it assumed that only 1 dose of EV is given every 28 days. However, the recommended dose of EV is 1.25 mg/kg on days 1, 8 and 15 of every 28-day cycle. The ESC noted that when this is corrected, the ICER increased to \$75,000 to < \$95,000/QALY.
- 6.58 In the SoC arm, the cost of avelumab was applied in 33.3% of all patients. This does not reflect the use of avelumab in the SoC arm of the CM-901 substudy in which 20.5% of patients who received subsequent treatment received avelumab. While the costs applied are likely to reflect the expected use of avelumab<sup>19</sup> in the Australian setting, the survival benefits associated with avelumab maintenance therapy cannot be accurately adjusted for in the economic model. Thus, the incremental benefits associated with NIVO+SoC treatment should be interpreted with caution as the benefits accrued in the SoC arm, based on 20.5% use of avelumab in the CM-901 substudy, are likely under representative of the benefits accrued in clinical practice. Further, the costs for 2L treatment with pembrolizumab was applied to 47.4% of patients that received subsequent treatment in the SoC arm. However, in the CM-901 substudy, about 60% of patients received subsequent treatment with pembrolizumab and other anti PD-L1/PD-1 therapies. Thus, the split between pembrolizumab and avelumab use in the SoC arm remains largely uncertain. Sensitivity analyses results,

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<sup>19</sup> Kearney M, Mahmoudpour H, Ike C, Modh A, Monzon S, Fragkogianni M, Carson K. Real-world treatment patterns and sequencing in patients with locally advanced or metastatic urothelial cancer (la/mUC) in the US. *Journal of Clinical Oncology*. 2023;41(6\_suppl):572-.

for varying use of avelumab and pembrolizumab in the SoC arm (but maintaining an overall combined use of 80%), have been presented in Table 17.

6.59 Costs for treatment monitoring, disease management and terminal care<sup>20</sup> were also included in the base case. As resources assumed for treatment monitoring were the same as those applied for disease management and since these would occur in a similar frequency, treatment monitoring costs have likely been overestimated in the analysis. Exclusion of disease management costs for the PF health state while patients are still on treatment led to an increase of < [REDACTED] % in the ICER. The ESC considered it was reasonable to exclude terminal care costs as all patients will transition to the death health state. Exclusion of terminal care costs increased the ICER by [REDACTED] %.

6.60 The key drivers of the economic model are summarised in Table 14.

**Table 14: Key drivers of the model**

Description	Method/Value	Impact (Revised base case ICER: \$ [REDACTED] /QALY gained)
Extrapolation of OS	The spline 2-knot hazard model was fitted to the trial KM OS data in the base-case analysis.	High, favours NIVO+SoC. When the spline 1-knot hazard model is fitted to the observed data, the ICER increased to \$ [REDACTED] /QALY.
Utilities	The utility values for model health states were derived from the CM-901 substudy.	High, favours NIVO+SoC Applying lower and previously accepted utility values, increased the ICER to \$ [REDACTED] /QALY.
Time horizon	10 years	High, favours NIVO+SoC Decreases in the time horizon led to substantial increased in the ICER (\$ [REDACTED] /QALY for a time horizon of 7.5 years).
Distribution of subsequent treatment (NIVO+SoC arm)	PDC: 63.9% EV: 36.1%	Moderate, favours NIVO+SoC Increasing the use of EV to about 60% and reducing the use of PDC to 23% (as observed in the CM-901 substudy) resulted in an ICER of \$ [REDACTED] /QALY.
Distribution of subsequent treatment (SoC arm)	Pembrolizumab: 47.4% Avelumab: 33.3% PDC: 13.5% EV: 5.8%	Moderate, favours NIVO+SoC If the use of avelumab and pembrolizumab in the economic model is adjusted to reflect the use in the CM-901 substudy (20.5% and 59%), the ICER increases to \$ [REDACTED] /QALY.

Source: tabulated during the evaluation from the "Attachment 12 – Economic Model 1L mUC" workbook provided in the submission.  
KM = Kaplan-Meier; NIVO = Nivolumab; OS = Overall survival; PDC = Platinum-doublet chemotherapy; QALY = Quality-adjusted life year ; SoC = Standard of care

The redacted values correspond to the following ranges:  
1 \$75,000 to < \$95,000

6.61 The results of the stepped economic evaluation for the trial population are presented in Table 15. The submission applied rebates of [REDACTED] % to the published prices of avelumab, pembrolizumab and EV as special pricing arrangements apply for these drugs. The costs for all drugs included in the model were applied at the approved ex-

<sup>20</sup> Based on Langton 2016 and inflated to 2024 costs; \$29,092.00

Langton JM, Reeve R, Srasuebkul P, Haas M, Viney R, Currow D, Pearson SA. Health service use and costs in the last 6 months of life in elderly decedents with a history of cancer: a comprehensive analysis from a health payer perspective. *Br J Cancer*. 2016 May 24;114(11):1293-302.

manufacturer price (AEMPs) level, which was not appropriate. Further, the fees for MBS items were updated on 1 July 2024. Thus, the ICER was revised during the evaluation to utilise the dispensed price for maximum amounts for all drugs and the updated MBS item fees.

**Table 15: Results of the stepped economic evaluation <sup>a</sup>**

Step and component	NIVO+SoC	SoC	Increment
<b>Step 1: trial-based costs and outcomes (60 months)</b>			
Costs	\$ [redacted]	\$61,135	\$ [redacted]
LYG	2.26	1.96	0.30
Incremental cost/extra LYG			[redacted] <sup>1</sup>
<b>Step 2: time horizon extended to 10 years</b>			
Costs	\$ [redacted]	\$64,862	\$ [redacted]
LYG	2.75	2.25	0.50
Incremental cost/extra LYG			\$ [redacted] <sup>2</sup>
<b>Step 3: transformation into QALYs</b>			
Costs	\$ [redacted]	\$64,862	\$ [redacted]
QALYs	2.39	1.95	0.45
Incremental cost/extra QALY gained			\$ [redacted] <sup>3</sup>

Source: Tables 78 and 79, pp181-183 of the submission.

NIVO = Nivolumab; QALY = Quality-adjusted life year ; QALYs = Quality-adjusted life years; SoC = Standard of care

<sup>a</sup> Revised estimates are based on updated DPMA's and MBS item fees.

The redacted values correspond to the following ranges:

1 \$95,000 to < \$115,000

2 \$55,000 to < \$75,000

3 \$75,000 to < \$95,000

6.62 The submission presented trial-based outcomes in the stepped economic evaluation for up to 60 months. However, observed data was only used till 27 months in the base case. This is not reasonable. Majority of the costs and outcomes were accrued in the first 5 years of the model. The disaggregated costs and outcomes for the economic analysis in the trial population are presented in Table 16.

**Table 16: Disaggregated summary of costs and health outcomes (discounted)**

Resource item	NIVO+SoC	SoC	Increment	% of total increment
<b>Costs <sup>a</sup></b>				
Drug costs	\$ █████	\$4,358	\$ █████	█████%
Monitoring costs	\$3,002	\$1,095	\$1,097	5.4%
Subsequent treatments	\$2,485	\$20,593	-\$18,108	-51.3%
Disease management	\$8,764	\$8,101	\$662	1.9%
Management of AEs	\$3,914	\$2,745	\$1,169	3.3%
Terminal care	\$26,608	\$27,970	-\$1,161	-3.3%
<b>Total cost</b>	<b>\$ █████</b>	<b>\$64,862</b>	<b>\$ █████</b>	<b>█████%</b>
<b>Outcomes</b>				
Progression-free LYs	1.72	1.01	0.62	123.8%
Progressed LYs	1.03	1.15	-0.12	-23.8%
<b>Total LYs</b>	<b>2.75</b>	<b>2.25</b>	<b>0.50</b>	<b>100%</b>
Progression-free QALYs	1.52	0.98	0.55	122.4%
Progressed QALYs	0.87	0.97	-0.1	-22.4%
Disutility due to AEs	-0.0005	-0.0004	-0.0001	-0.02%
<b>Total QALYs</b>	<b>2.39</b>	<b>1.95</b>	<b>0.45</b>	<b>100%</b>

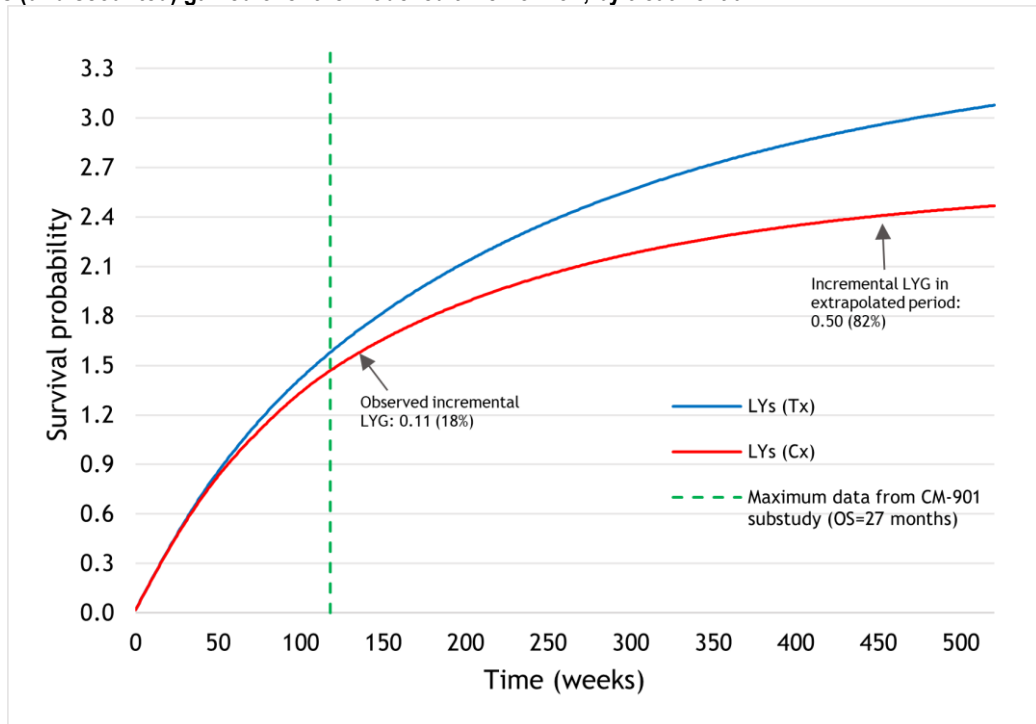
Source: Table 79, pp182-183 of the submission.

AEs = Adverse Events; LYs = Life-years; NIVO = Nivolumab; QALYs = Quality-adjusted life years; SoC = Standard of care

<sup>a</sup> Revised estimates based on calculated weighted DMPAs and updated MBS item fees.

- 6.63 NIVO+SoC, compared with SoC only, was associated with a 0.45 QALY gained, at an additional cost of \$35,000 to < \$45,000 resulting in an ICER of \$75,000 to < \$95,000 per QALY gained. The main driver of the costs was the cost of NIVO+SoC treatment, with monitoring costs, disease management and management of adverse events being minor contributors. The majority of the costs were offset by the costs of subsequent treatments in the SoC arm. As noted previously, the costs associated with subsequent treatments in both arms are largely uncertain due to the uncertainty regarding the distribution of subsequent treatments following 1L treatment in both arms. Changing the distribution of subsequent treatments to reflect that observed in the CM-901 substudy in both treatment arms, increased the ICER.
- 6.64 The life years (LYs) (undiscounted) gained over the model time horizon for the NIVO+SoC and SoC arms are presented in Figure 6.

Figure 6: LYs (undiscounted) gained over the modelled time horizon, by treatment arm.



Source: constructed during evaluation from the "Attachment 13 – Nivolumab 1L mUC" workbook provided in the submission. Cx = Comparator arm; LYG = Life-years gained; LYs = Life-years; OS = Overall survival; Tx = Treatment arm

6.65 The results of key sensitivity analyses are summarised in Table 17.

Table 17: Results of key sensitivity analyses

Analyses	Incremental cost (\$)	Incremental QALY	ICER	% change from baseline
<b>Revised base case <sup>a</sup></b>	█	0.45	█ <sup>1</sup>	-
<b>Time horizon (base case: 10 years)</b>				
7.5 years (#1)	█	0.38	█ <sup>1</sup>	█%
15 years	█	0.52	█ <sup>2</sup>	█%
<b>Discount rate (base case: 5%)</b>				
0%	█	0.55	█ <sup>2</sup>	█%
3.5%	█	0.47	█ <sup>2</sup>	█%
<b>Utilities (base case: PF = 0.888; PD = 0.843)</b>				
PF = 0.772; PD = 0.698 (#3) <sup>b</sup>	█	0.39	█ <sup>1</sup>	█%
<b>OS truncation time point (base case: OS = 27 months)</b>				
30 months (NIVO+SoC)	█	0.47	█ <sup>2</sup>	█%
33 months (NIVO+SoC)	█	0.51	█ <sup>2</sup>	█%
30 months (SoC)	█	0.46	█ <sup>1</sup>	█%
33 months (SoC)	█	0.47	█ <sup>1</sup>	█%
<b>OS and PFS truncation time point (base case: OS = 27 months, PFS = 12 months)</b>				
OS: 54 months (NIVO+SoC) and 57 months (SoC) <sup>d</sup>	█	0.55	█ <sup>2</sup>	█%
PFS: 51 months (NIVO+SoC) and 36 months (SoC) (#2) <sup>d</sup>	█			█%
<b>Extrapolation (base case: 2-spline hazard model for both PFS and OS)</b>				
OS: 1-spline hazard	█	0.41	█ <sup>1</sup>	█%
OS: Gamma (#4)	█	0.36	█ <sup>3</sup>	█%
OS: Weibull	█	0.37	█ <sup>3</sup>	█%
OS: log-logistic	█	0.35	█ <sup>3</sup>	█%
PFS: Gamma (#5)	█	0.43	█ <sup>1</sup>	█%
<b>Duration of treatment (base case: NIVO+SoC, mean dose; SoC: fixed number of doses)</b>				
Using ToT curve (both arms)	█	0.45	█ <sup>1</sup>	█%
Using ToT curve (SoC arm only)	█	0.45	█ <sup>1</sup>	█%
<b>Costs</b>				
Exclude terminal care costs (#7)	█	0.45	█ <sup>1</sup>	█%
Costs for 3 doses of EV in each 28-day cycle (#6)	█	0.45	█ <sup>1</sup>	█%
<b>Proportion of patients receiving subsequent treatment (base case: 35.5% in NIVO+SoC arm; 51.3% in SoC arm)</b>				
51.3% in both arms	█	0.45	█ <sup>1</sup>	█%
<b>Distribution of subsequent therapy (base case: 36.1% EV, 63.9% PDC in NIVO+SoC arm; 47.4% PEM use and 33.3% avelumab in the SoC arm)</b>				
60% EV; 23% PDC	█	0.45	█ <sup>1</sup>	█%
77% EV; 23% PDC	█	0.45	█ <sup>3</sup>	█%
20.5% avelumab, 59% pembrolizumab	█	0.45	█ <sup>1</sup>	█%
<b>Multivariate sensitivity analyses <sup>d</sup></b>				
#1 + #2	█	0.46	█ <sup>2</sup>	█%
#1 + #2 + #3	█	0.41	█ <sup>1</sup>	█%
#1 + #2 + #3 + #4 + #5	█	0.37	█ <sup>1</sup>	█%
#1 + #2 + #3 + #4 + #5 + #6	█	0.37	█ <sup>3</sup>	█%
#1 + #2 + #3 + #4 + #5 + #6 + #7	█	0.37	█ <sup>3</sup>	█%
#1 + #2 + #3 + #4 + #5 + #6 + #7 + revised ex-manufacture price offered in PSCR <sup>c</sup>	█	0.37	█ <sup>1</sup>	█%

Source: tabulated during evaluation from the "Attachment 13 – Nivolumab 1L mUC" workbook provided in the submission.

NIVO = Nivolumab; OS = Overall survival; PD = Progressive disease; PDC = Platinum-doublet chemotherapy; PEM = Pembrolizumab ; PF = Progression-free; PFS = Progression-free survival; QALY = Quality-adjusted life year ; SoC = Standard of care

<sup>a</sup> Revised estimates based on weighted DPMA for nivolumab, comparator and subsequent treatment drugs; and updated MBS item fees.

<sup>b</sup> Table 12, avelumab PSD, March 2021 PBAC meeting

<sup>c</sup> The PSCR offered a reduced ex-manufacturer price of \$█ for the 100 mg vial and \$█ for the 40 mg vial

<sup>d</sup> Tabulated during the preparation of the ESC advice

The redacted values correspond to the following ranges:

- 1 \$75,000 to < \$95,000
- 2 \$55,000 to < \$75,000
- 3 \$95,000 to < \$115,000

- 6.66 The ICER was sensitive to the choice of time horizon, utility weights, truncation time points for KM data and choice of extrapolation for OS in both treatment arms. The distribution of use of subsequent therapies in both arms had a moderate impact on the ICER.
- 6.67 The submission did not present any multivariate sensitivity analyses. Thus, multivariate sensitivity analyses were conducted around areas of key concern identified during the evaluation.
- 6.68 The PSCR) presented a revised base case model with a time horizon of 7.5 years , Australian population norm-adjusted utility values and a [REDACTED] % price reduction (see paragraph 3.3), resulting in an ICER of \$55,000 to < \$75,000 per QALY. The ESC did not accept the revised base case presented in the PSCR. Instead, the ESC advised that a respecified base case incorporating the following inputs would be appropriate:
- 7.5 year time horizon;
  - Amended OS and PFS truncation time points based on the GebSKI (2018) approach, Criterion 2 (see Table 13);
  - Utility values of 0.772 and 0.698 for the PF and PD health states (see paragraph 6.54);
  - Gamma extrapolation functions for both OS and PFS based on clinical plausibility; and
  - Corrected costs for EV in each 28 day cycle (see paragraph 6.58).
  - Removal of terminal care costs (see paragraph 6.59).

The ESC noted that incorporating these inputs increased the base case ICER from \$75,000 to < \$95,000/QALY to \$95,000 to < \$115,000 /QALY. The ESC noted that when the reduced price offered in the PSCR was incorporated the respecified base case ICER was \$75,000 to < \$95,000/QALY. The ESC noted that the use of effective prices for subsequent therapies would further impact the ICER.

- 6.69 The pre-PBAC response accepted the revised base case parameters as specified by the ESC, but stated that the ICERs were unable to be exactly replicated. Noting that the effective prices of EV, pembrolizumab and avelumab still need to be incorporated, the pre-PBAC response agreed in principle to the revised base case and subsequent price reduction to reduce the ICER to under \$55,000 to < \$75,000 /QALY.

## Drug cost/patient/course

Table 18: Drug cost per patient for NIVO+SoC and SoC

	NIVO+SoC			SoC		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
<b>Mean dose</b>						
Nivolumab						
Part 1	360 mg	360 mg	360 mg	-	-	-
Part 2	480 mg	480 mg	240 mg, 480 mg			
Cisplatin	130.6 mg	130.6 mg	131 mg	130.6 mg	130.6 mg	131 mg
Gemcitabine	1,866 mg	1,866 mg	1,872 mg	1,866 mg	1,866 mg	1,872 mg
<b>Mean number of doses</b>						
Nivolumab						
Part 1	5.17	5.17	5.17	-	-	-
Part 2	7.06	7.06	7.06			
Cisplatin	4.70	5.17	4.70	4.50	6.0	4.50
Gemcitabine	9.80	10.34	9.80	9.60	12.0	9.60
<b>Cost/patient/course</b>	<b>NIVO:\$█ GC: \$2,323</b>	<b>NIVO:\$█ GC: \$2,483</b>	<b>NIVO:\$█ GC: \$2,268</b>	<b>\$2,161</b>	<b>\$4,358</b>	<b>\$2,161</b>

Source: tabulated during evaluation from the "Attachment 13 – Nivolumab 1L mUC" and "Attachment 14 – Nivolumab 1L mUC Utilisation and Cost Models" workbooks provided in the submission.

GC = Gemcitabine-cisplatin chemotherapy; NIVO = Nivolumab; SoC = Standard of care

- 6.70 The difference between the costs per patient per course in the economic model and financial analysis is due to the difference in the mean number of doses applied for cisplatin and gemcitabine treatment. For the NIVO+SoC arm, the submission applied a mean number of doses of 5.17 to nivolumab, cisplatin and gemcitabine (5.17 x 2) in the economic model. However, the mean number of doses for the NIVO+SoC arm from the CM-901 substudy were 5.17 for nivolumab, 4.70 for cisplatin and 9.80 for gemcitabine. Further, for the SoC arm, the submission applied a fixed number of doses of 6.0 for cisplatin and 12.0 for gemcitabine. This differed from the CM-901 substudy which observed lower mean number of doses for cisplatin (4.50) and gemcitabine (9.60). Of note, applying the mean number of doses from the CM-901 substudy in the economic model has a minimal impact on the ICER. Further, 10% of patients who received NIVO maintenance monotherapy, were assumed to be treated with the 240 mg dose of NIVO in the financial estimations
- 6.71 The PSCR offered a reduced ex-manufacturer price of \$█ for the 100 mg vial and \$█ for the 40 mg vial (see paragraph 3.3).
- 6.72 The pre-PBAC response) stated that the sponsor agreed in principle to a subsequent price reduction to reduce the ICER to under \$55,000 to < \$75,000 per QALY gained as outlined in paragraph 6.69.

### Estimated PBS usage & financial implications

- 6.73 This submission was not considered by DUSC. An epidemiological approach was used to estimate the extent of use and financial implications of listing NIVO+SoC on the PBS. The key inputs utilised in the financial analysis are summarised in Table 19.

**Table 19: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
Incidence	Incidence based on Australian institute of Health and Welfare cancer projections for bladder cancer and other urinary organs cancer <sup>21</sup> .	This was reasonable.
% that is urothelial carcinoma	90%; based on Urinary and Male Genital Tumours: WHO Classification of Tumours, Volume 8 <sup>22</sup>	This was reasonable. 93.7% has been accepted previously for avelumab (Table 15, avelumab Public Summary Document, March 2021 PBAC meeting).
% of patients with WHO status of 0 or 1	80.98%; BLADDA registry (Tran, Ben, 2023) <sup>23</sup>	This was reasonable.
% of patients who are eligible for first-line treatment	74.55%; Genitourinary Advisory Board 2024	The DUSC has previously considered that an eligibility of 70% for first-line treatment with PDC was reasonable while the PBAC noted that the upper end of the range of likely use of first-line treatment is about 90% (paragraphs 6.67 and 7.11, avelumab PSD, March 2021 PBAC meeting). Further, the proposed listing of NIVO+SoC is for patients with unresectable or mUC who are cisplatin-eligible. The submission did not account for patients who are cisplatin-eligible in the estimation of eligible patients. The PSCR stated that the eligibility criteria for cisplatin-based chemotherapy was included in the financial estimates with a value of 50% derived from the Genitourinary Advisory Board 2024. The ESC noted the 50% referred to by the PSCR was included in the financial model as the % of patients electing treatment. The ESC noted this approach effectively assumed 100% uptake of NIVO in cisplatin eligible patients, which may not be reasonable (see paragraph 6.74).
% of patients diagnosed with mUC	23.34%; BLADDA registry (Tran, Ben, 2023)	This input was largely uncertain with rates of 10-15% for patients with bladder cancer and rates of about 30% for upper tract urothelial carcinomas.
% of patients who develop mUC	35.62%; Kim et. Al, <sup>24</sup> Samnani et al, 2021 <sup>25</sup>	This was reasonable and in line with literature surrounding the progression of early-stage disease to metastatic disease.

<sup>21</sup> Australian Institute of Health and Welfare (AIHW). Cancer data in Australia 2024.

<sup>22</sup> WHO Classification of Tumours, 5th Edition, Volume 8: Urinary and Male Genital Tumours 2022.

<sup>23</sup> Melbourne Academic Centre for Health. BLADDA Registry.

<sup>24</sup> Kim KH, Lee HW, Ha HK, Seo HK. Perioperative systemic therapy in muscle invasive bladder cancer: Current standard method, biomarkers and emerging strategies. *Investig Clin Urol*. 2023 May;64(3):202-18.

<sup>25</sup> Samnani S, Veitch ZWN, Kaiser J, Stecca C, Alqaisi H, North SA, et al. Trends over time in survival in patients with urothelial carcinoma in the real-world: A multicenter analysis. *Journal of Clinical Oncology*. 2021;39(6\_suppl):412-.

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Parameter	Value applied and source	Comment
% electing treatment	50%; Genitourinary Advisory Board 2024	The ESC noted the input of 50% was intended to reflect eligibility for cisplatin-based chemotherapy with a separate uptake rate not applied in the financial estimates (see paragraph 6.74).
Duration of NIVO+SoC treatment	5.17, 9.70 and 4.60 doses for initial treatment with nivolumab, gemcitabine and cisplatin; 7.06 doses for NIVO monotherapy; from the CM-901 substudy.	This was reasonable.
Duration of SoC treatment	4.5 doses for cisplatin and 9.6 doses for gemcitabine.	This was sourced from the SoC arm of the CM-901 substudy and was reasonable.
Nivolumab costs	240 mg: \$■■■■; 360 mg: \$■■■■; 480 mg: \$■■■■; proposed DPMA based AEMPs of \$■■■■ and \$■■■■ for the 40 mg and 100 mg vials, respectively, and weighted based on the split between public and private use.	As proposed in the submission.
Gemcitabine-cisplatin cost	Gemcitabine: \$157.01, cisplatin: \$147.88; weighted DPMA for the average dose.	The DPMA was revised during the evaluation as the mark-up fees for drugs was updated on 1 July 2024.
MBS costs	MBS item 13950, for intravenous administration of chemotherapy drugs.	This was reasonable. However, the submission incorrectly calculated the MBS costs associated with the listing of NIVO+SoC as it applied the MBS fee to each prescription of the proposed medicines. NIVO and cisplatin are administered on day 1 of each 3-week cycle and gemcitabine is administered on days 1 and 8 of each 3-week cycle. Thus, only 2 MBS services per cycle would apply. Further, the fee for MBS item 13950 was updated to \$123.05 on 1 July 2024. The ESC noted that this was corrected during the evaluation (see Table 21).

Source: Table 81, p189 of the submission

1L = First-line; DUSC = Drug Utilisation Sub Committee; MBS = Medicare benefits schedule; mUC = Metastatic urothelial carcinomas; NIVO = Nivolumab; PBAC = Pharmaceutical Benefits Advisory Committee; PDC = Platinum-doublet chemotherapy; PSD = Public summary document; SoC = Standard of care

6.74 The submission estimated the total number of patients eligible for treatment with NIVO+SoC based on the inputs presented in Table 19. Australian Institute of Health and Welfare (AIHW) cancer incidence projections (based on years 2001 – 2023) for bladder cancer and cancer of other urinary organs was utilised to estimate the number of eligible patients. Of all incident patients, it was assumed that 90% would have urothelial carcinomas with 80.98% of patients with a WHO performance status of 0 or 1. Of these patients, it was assumed that 74.55% would be eligible for first-line treatment with platinum-doublet chemotherapy (PDC). However, the submission did not account for patients who are ineligible for cisplatin-based chemotherapy. Published literature reports a 50/50 split between cisplatin-based and

carboplatin-based chemotherapy for urothelial cancers<sup>26, 27</sup>. Thus, the number of patients eligible for treatment with NIVO+SoC has been overestimated in the submission. The PSCR stated that eligibility for cisplatin-based chemotherapy was included in the financial estimates as part of sheet '2a. Patient – incident' rows 45 & 83 with the value of 50% derived from the Genitourinary Advisory Board 2024. The ESC noted that the rows referred to sheet '2a. Patient – incident' relate to proportion of patients electing treatment. Based the published literature reporting a 50/50 split between cisplatin-based and carboplatin-based chemotherapy the ESC considered assuming 50% eligibility for cisplatin-based chemotherapy was reasonable. However, without applying an additional uptake rate the ESC considered this assumption effectively assumed 100% uptake of NIVO in cisplatin eligible patients, which may not be reasonable. As such, the ESC agreed with the evaluation that the number of patients eligible for treatment with NIVO+SoC was overestimated.

- 6.75 The submission estimated the number of eligible patients for treatment with NIVO+SoC based on two cohorts: patients who are diagnosed with mUC and patients diagnosed with early-stage disease who progress to mUC. It was assumed that 23.4% of all patients are diagnosed with mUC with 35.62% progressing to metastatic disease. Lower rates of metastatic disease at diagnosis and varying rates of progression to metastatic disease have been reported in published literature depending on the location of the cancer. As such, the inputs utilised to estimate these proportions of patients are associated with uncertainty.
- 6.76 The submission assumed that the listing of NIVO+SoC would impact the first-line use of PDC (due to a small difference in mean dosing between NIVO+SoC and SoC), avelumab maintenance therapy and second-line use of pembrolizumab. This was reasonable. However, the number of eligible patients for avelumab and pembrolizumab were estimated by applying the rates of progression-free disease (for avelumab) and for progressive disease (for pembrolizumab) to all eligible patients without first restricting eligible patients to those who receive first-line chemotherapy, i.e., eligible patients (67.27%) (see Table 20). The ESC noted that the total population treated with NIVO + SoC (625 in Year 1 increasing to 702 in Year 6) was used to determine the avelumab and pembrolizumab cost offsets. The ESC agreed with the evaluation that the cost offsets associated with a reduction in the use of avelumab and pembrolizumab were therefore overestimated in the submission due to the overestimation of patients who are likely to receive avelumab and pembrolizumab. Further, the submission applied avelumab offsets to 76.82% of patients who remained progression-free after 1L PDC. This is most likely an overestimation as the proportion

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<sup>26</sup> Alimohamed N, Grewal S, Wirtz HS, Hepp Z, Sauvageau S, Boyne DJ, et al. Understanding Treatment Patterns and Outcomes among Patients with De Novo Unresectable Locally Advanced or Metastatic Urothelial Cancer: A Population-Level Retrospective Analysis from Alberta, Canada. *Curr Oncol*. 2022 Oct 12;29(10):7587-97.

<sup>27</sup> Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. *New England Journal of Medicine*. 2020;383(13):1218-30.

of patients who were progression-free at 18 weeks was 59.2% in the SoC arm of the CM-901 substudy. The pre-PBAC response noted the data provided by the DUSC Secretariat indicated over 500 patients were treated with PEM or AVEL in 2023 (312 + 273, see Table 22). The pre-PBAC response noted this is higher than the number of patients which was used to calculate the cost offsets in Year 1 (< 500 + < 500 + < 500 = < 500 see Table 20). The PBAC noted the number of patients treated with PEM or AVEL provided by the DUSC Secretariat do not take into account cisplatin-eligibility. Assuming 50% of patients would have been cisplatin-eligible, reduces the patients treated with PEM or AVEL in 2023 to approximately <500 (<500 x 50%) which indicates the cost-offsets are overestimated.

- 6.77 The number of patients who are treated with NIVO+SoC and the reduction in the use of SoC drugs, avelumab and pembrolizumab is presented in Table 20. The evaluation noted the submission did not consider the increase in the use of EV as a subsequent treatment for patients treated with NIVO+SoC (as they will no longer be eligible for treatment with avelumab and pembrolizumab due to the restriction criteria limiting immunotherapy use to once per lifetime). The PSCR noted that EV is PBS listed for mUC for patients who have progressed on/following both platinum-based chemotherapy and PD-1/PD-L1 inhibitor therapy or following platinum-based chemotherapy, whilst PD-1/PD-L1 inhibitor therapy resulted in an intolerance that required treatment cessation. As such, the PSCR argued that the availability of NIVO+SoC would result in the same usage of EV as for chemotherapy followed by avelumab maintenance and hence there is no need to account for increased EV usage.

**Table 20: Estimation of the increase in use of NIVO+SoC and reduction in the use of SoC, avelumab and pembrolizumab**

			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimation of patients treated with NIVO+SoC</b>								
A	Incidence of bladder and other urinary organs cancer		█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
B	% of patients with urothelial cancer	A x 90%	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
C	% of patients with WHO status of 0 or 1	B x 80.98%	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Patients with mUC</b>								
D	% diagnosed with mUC	C x 23.34%	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
E	% of patients who are eligible for PDC	D x 74.55%	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
F	% electing treatment	E x 50%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Patients who progress to mUC</b>								
G	% who progress to mUC	B x 35.62%	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
H	% of patients who are eligible for PDC	G x 74.55%	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
I	% electing treatment	H x 50%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Total patients treated</b>		<b>F + I</b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Reduction in the use of comparator and subsequent therapies</b>								
J	Treated population		█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>PDC offset</b>								
K	% eligible	J x 67.27%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
L	% electing treatment	K x 54.55%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Avelumab offset</b>								
M	% progression-free after PDC	J x 76.82%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
N	% receiving avelumab	M x 80.91%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
O	% electing treatment	N x 50%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Pembrolizumab offset</b>								
P	% who develop progressive disease after PDC	J x 23.18%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
Q	% electing treatment	P x 76.36%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
R	% who remain progression-free after PDC	Q x 76.82%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
S	% who opt not to receive avelumab	R x 19.09%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
T	% of patients who progress	S x 90%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
U	% electing treatment	T x 76.36%	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>	█ <sup>2</sup>
<b>Total patients treated</b>		<b>L+O+Q+U</b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>

Source: tabulated during the evaluation from Table 82, p191 of the submission and Sheet '2a. Patients - incident' of the "Attachment 14 - Nivolumab 1L mUC Utilisation and Cost Model" workbook provided in the submission.

mUC = Metastatic urothelial carcinomas; NIVO = Nivolumab; PDC = Platinum-based chemotherapy; WHO = World Health Organization

The redacted values correspond to the following ranges:

1 500 to < 5,000

2 < 500

6.78 The total cost of listing NIVO+SoC on the PBS/RPBS was based on the number of eligible patients and the scripts/treatment for each drug. Treatment durations were based on the mean number of doses administered in the CM-901 substudy, i.e., 5.17, 9.70 and 4.80 for nivolumab, gemcitabine and cisplatin, respectively in the NIVO+SoC arm. For NIVO monotherapy, patients received 7.06 doses of the 480 mg dose or 14.12 doses of the 240 mg dose. In the SoC arm, the mean number of doses applied were 9.70 and 4.50 for gemcitabine and cisplatin, respectively. While this was reasonable,

the submission incorrectly estimated the associated copayments as the number of repeats for cisplatin and gemcitabine were interchanged. This was corrected in the evaluation.

- 6.79 The treatment durations for avelumab (assumed to be 10 months based on the financial stopping rule) and for pembrolizumab (6.84 months, sourced from KEYNOTE-045 trial) were used to estimate the change in use of comparator and subsequent therapies and the associated cost offsets.
- 6.80 The submission estimated an increase in the costs to the MBS based on MBS item 13950. While this was reasonable, the submission erroneously calculated the change in the number of MBS services during initial treatment. NIVO and cisplatin are administered only on day 1 of each 3-week cycle while gemcitabine is administered on days 1 and 8 of each 3-week cycle. Thus, only one MBS service would be required on day 1 for administration of NIVO and cisplatin and one MBS service would be required on day 8 for administration of gemcitabine. The revised estimates are presented in the table below.
- 6.81 The net financial implications of listing NIVO+SoC, based on the effective prices of all NIVO doses, are presented in Table 21. The ESC noted the PSCR provided revised financial estimates that included the reduced ex-manufacturer price for NIVO offered in the PSCR (see paragraph 3.3).

**Table 21: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total treated patients	1	1	1	1	1	1
ThNumber of scripts						
Nivolumab 240 mg	1	1	1	1	1	1
Nivolumab 360 mg	1	1	1	1	1	1
Nivolumab 480 mg	1	1	1	1	1	1
Gemcitabine	2	2	2	2	2	2
Cisplatin	1	1	1	1	1	1
Total NIVO+SoC scripts <sup>a</sup>	3	3	3	3	3	3
<b>Estimated financial implications of NIVO+SoC</b>						
Nivolumab	4	4	4	4	4	4
SoC	5	5	5	5	5	5
Cost to the PBS/RPBS less copayments <sup>b</sup>	4	4	4	4	4	4
<b>Comparator and subsequent treatments (cisplatin, gemcitabine, avelumab and pembrolizumab)</b>						
Total treated patients	1	1	1	1	1	1
Number of scripts						
Cisplatin	1	1	1	1	1	1
Gemcitabine	1	1	1	1	1	1
Avelumab	1	1	1	1	1	1
Pembrolizumab	1	1	1	1	1	1
Total reduction in scripts	2	2	2	2	3	3
<b>Estimated financial implications of comparators and subsequent treatments</b>						
PDC	5	5	5	5	5	5
Avelumab	6	6	6	6	6	6
Pembrolizumab	5	5	5	5	5	5
Cost to the PBS/RPBS less copayments <sup>c</sup>	6	6	6	6	6	6
<b>Net financial implications</b>						
Net cost to PBS/RPBS <sup>d</sup>	6	6	6	6	6	6
Net cost to MBS <sup>e</sup>	5	5	5	5	5	5
<b>Net cost to PBS/RPBS/MBS</b>	6	6	6	6	6	6
<b>Net cost to PBS/RPBS presented in PSCR<sup>f</sup></b>	6	6	6	6	6	6
<b>Net cost to PBS/RPBS presented in the pre-PBAC response<sup>f, g</sup></b>	6	6	6	6	6	6

Note: Costs to the PBS/RPBS are based on the effective prices of all nivolumab doses.

Source: tabulated during evaluation from the "Attachment 14 – Nivolumab 1L mUC Utilisation and Cost Model" workbook provided in the submission, Nivolumab 1L mUC Utilisation and Cost Model PSCR, Table 1 Nivolumab Pre-PBAC response

<sup>a</sup> The number of scripts was based on scripts/treatment of 5.17 scripts for 360 mg NIVO; 7.06 scripts for 480 mg NIVO; 14.12 scripts for 240 mg NIVO; 9.70 scripts for gemcitabine and 4.80 scripts for cisplatin.

<sup>b, c, d</sup> Revised estimates are based on weighted DPMA which utilise the updated mark-up fees and revised copayments for the correct number of repeats for cisplatin and gemcitabine scripts.

<sup>e</sup> Revised estimates are based on the correct number of MBS services required for initial treatment with NIVO+SoC

<sup>f</sup> Includes revisions based on weighted DPMA which utilise the updated mark-up fees and revised copayments for the correct number of repeats for cisplatin and gemcitabine scripts as per the evaluation along with a reduced ex-manufacturer price for nivolumab as outlined in paragraph 3.3.

<sup>g</sup> Addition of <500 grandfather patients in year 1

MBS = Medicare benefits schedule; NIVO = Nivolumab; PBS = Pharmaceutical benefits scheme; PDC = Platinum-doublet chemotherapy; RPBS = Repatriation pharmaceutical benefits scheme; SoC = Standard of care.

The redacted values correspond to the following ranges:

1 500 to < 5,000

- 2 5,000 to < 10,000
- 3 10,000 to < 20,000
- 4 \$30 million to < \$40 million
- 5 \$0 to < \$10 million
- 6 \$10 million to < \$20 million

- 6.82 The submission estimated a cost of \$10 million to < \$20 million in the first year of listing, increasing to \$10 million to < \$20 million in the sixth year of listing, and a cumulative cost of \$100 million to < \$200 million across the first 6 years of listing, to the PBS/RPBS. The revised financial estimates presented in the PSCR estimated a cost of \$10 million to < \$20 million in the first year of listing, increasing to \$10 million to < \$20 million in the sixth year of listing, and a cumulative cost of \$70 million to < \$80 million across the first 6 years of listing. The ESC agreed with the evaluation that the number of patients eligible for treatment with NIVO+SoC was overestimated (see paragraph 6.74). Further, the cost offsets estimated in the submission are also uncertain due to the uncertainty of the inputs utilised to estimate the number of patients who are likely to use all comparator and subsequent therapies. The ESC noted the revised financial estimates presented in the PSCR did not include amendments to address concerns regarding the approach taken in the estimation of eligible patients or regarding the cost offsets.
- 6.83 The pre-PBAC response stated the sponsor intends to open a patient access program and anticipates that up to <500 patients would be eligible for transfer to the PBS if NIVO recommended. The pre-PBAC response provided revised financial estimates that included an additional <500 grandfathered patients in the first year of listing (see Table 21). The revised financial estimates presented in the pre-PBAC response did not include amendments to address concerns regarding the approach taken in the estimation of eligible patients or regarding the cost offsets.
- 6.84 The ESC noted the number of patients treated with AVEL, PEM and EV was provided by the DUSC Secretariat (Table 22). Data was extracted to 31 August for PBS item codes 11632F, 11646Y, 13122P, 13123Q, 13126W, 13132E, 13634N and 13648H based on the date of supply.

**Table 22: Number of incident patients treated (as per data provided by DUSC Secretariat)**

	<b>Pembrolizumab</b>	<b>Avelumab</b>	<b>Enfortumab vedotin</b>
First PBS listed	1 March 2019	1 October 2022	1 October 2023
2019	485	-	-
2020	467	-	-
2021	438	-	-
2022	363	176	-
2023	312	273	-
2024	222 <sup>a</sup>	225 <sup>a</sup>	293 <sup>b</sup>

Source: Compiled during the preparation of the ESC advice

<sup>a</sup> To 31 August 2024

<sup>b</sup> 1 October 2023 to 21 August 2024

- 6.85 The PBAC noted assuming that < 500 patients (see paragraph 6.76) represented 58.9% ((< 500 +< 500 +< 500)/ 500 to < 5,000, from Table 20) of the population that would be treated with NIVO, resulted in an estimated number of patients of

< 500(< 500/58.9%). The PBAC noted that triangulation of the number of patients treated with avelumab and later line PEM indicated that the estimated number of patients likely to be treated with NIVO in Year 1 (500 to < 5,000) was substantially overestimated.

### **Quality Use of Medicines**

- 6.86 The submission noted that while the adverse events associated with NIVO treatment mirror those with other therapies, immune-related adverse reactions (irARs) require a specific course of management due to the difference in the underlying mechanism. In line with this, the sponsor outlined activities aimed at ensuring the availability of on-demand education for physicians, provision of additional education materials for awareness and management of irARs and development of a risk management plan which contains a description and analysis of the safety profile of nivolumab. Further, the sponsor noted that they continue to offer nursing and pharmacy in-services at all sites where NIVO is available. No other QUM issues were identified during the evaluation.

### **Risk sharing arrangements**

- 6.87 The sponsor stated that they would be willing to enter into a risk sharing arrangement (RSA) following a positive recommendation from the PBAC. The PBAC noted there are RSAs in place for PEM, EV and AVEL in this indication, with the RSAs for EV and AVEL designed to achieve cost-effective prices.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) Authority Required (STREAMLINED) listing of nivolumab (NIVO) for the first-line treatment of cisplatin-eligible adult patients with unresectable or metastatic urothelial carcinoma (u/mUC). The PBAC is satisfied that NIVO provides, for some patients, a small improvement in efficacy over standard of care (SoC) - consisting of gemcitabine-cisplatin chemotherapy (GC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of NIVO would be acceptable with a price reduction to achieve an incremental cost-effectiveness ratio (ICER) of around \$55,000 to < \$75,000 per QALY gained (using the ESC-respecified economic model) and with a risk sharing arrangement arrangement that accounts for expenditure on the use of first line and subsequent line therapies.
- 7.2 The PBAC noted the input from organisations that highlighted the lived experience of metastatic urothelial carcinoma and the need for more treatment options. The PBAC also noted the support for NIVO for this indication from the Medical Oncology Group of Australia (MOGA) as a "supporting application", based on an ESMO MCBS score of 2 out of 5 (where a score of 4 or 5 represents an intervention with high incremental clinical benefit). The PBAC acknowledged the high clinical need for more effective

therapies for u/mUC, noting that overall the current PBS-listed therapies are moderately effective.

- 7.3 With regard to the requested listing and restriction, the PBAC advised that:
- An Authority Required (STREAMLINED) listing, rather than the Authority Required (Telephone/online) listing requested by the submission, was appropriate.
  - As per the TGA indication, the clinical criteria for initial treatment should specify use must be in combination with cisplatin and gemcitabine.
  - The amendments to the restriction proposed in the pre-PBAC response to allow grandfathered patients access to PBS subsidised treatment were appropriate.
  - The initial treatment restriction administrative advice that allowed an increase in the number of repeats should be removed with the number of repeats instead set at a maximum of 5.
- 7.4 The PBAC considered that the proposed comparator of SoC, consisting of GC, was the appropriate main comparator. The PBAC noted that avelumab used as maintenance therapy was nominated as a supplementary comparator, however the PBAC considered this to be a less relevant comparator given the proposed listing for nivolumab was broader than maintenance therapy and only for cisplatin-eligible patients. The PBAC also noted that enfortumab vedotin in combination with pembrolizumab (EV+PEM) was identified as a near market comparator, and agreed with ESC that if EV-PEM were PBS listed, it would likely become the new SoC and be used in preference to NIVO.
- 7.5 The primary clinical evidence supporting the clinical claim for NIVO compared with SoC was the CM-901 substudy, which consisted of the NIVO+SoC and SoC alone arms of the CM-901 study. The PBAC noted that in the SoC alone arm, 20.5% of patients who received subsequent systemic therapy received avelumab (equivalent to 10.5% of all patients randomised to SoC). The PBAC agreed with the ESC that the use of avelumab in the CM-901 substudy was likely to be less than what is observed in the Australian clinical setting. The PBAC noted that NIVO+SoC demonstrated a small statistically significant improvement in overall survival (OS) compared to SoC, with a hazard ratio (HR) for death of 0.78 (95% CI: 0.62, 0.96), and an incremental median OS gain of 2.86 months. For progression-free survival (PFS) by blinded independent central review, the HR for progression or death was 0.72 (95% CI: 0.59, 0.88). The PBAC agreed with the ESC that the small improvement in OS reported in the CM-901 substudy may be overestimated compared to the proposed PBS population due to differences in use of avelumab. Overall, the PBAC considered the claim of superior comparative effectiveness versus SoC was reasonable based on the differences in OS.
- 7.6 The PBAC noted that in the CM-901 substudy, more patients in the NIVO+SoC arm than in the SoC arm experienced all-cause severe adverse events (AEs) (72.4% vs 64.9%), serious adverse events (SAEs) (46.7% vs 36.5%), and severe SAEs (37.2% vs

- 27.4%). Additionally, a greater proportion of patients in the NIVO+SoC arm compared to SoC experienced treatment-related AEs of any grade (97.4% vs 92.7%), severe AEs (61.7% vs 51.4%), SAEs (24.7% vs 16.7%) and severe SAEs (20.1% vs 12.9%). The PBAC considered that the claim of inferior comparative safety versus SoC was reasonable.
- 7.7 The submission presented a stepped economic evaluation, based on the CM-901 substudy, that compared the 1L use of NIVO+SoC with SoC only in u/mUCs. The PBAC noted the ESC advised that a respecified base case incorporating the inputs outlined in paragraph 6.68 would be appropriate. The PBAC further noted that the pre-PBAC response agreed in principle to the revised base case proposed by the ESC and a subsequent price reduction to reduce the ICER to under \$55,000 to < \$75,000 /QALY gained. The PBAC considered the respecified base case proposed by the ESC appropriate to determine the cost-effectiveness of NIVO. However, the Committee considered an ICER of \$75,000 to < \$95,000/QALY gained was too high and that an ICER of around \$55,000 to < \$75,000 per QALY gained (using the effective prices of avelumab and pembrolizumab) was appropriate and consistent with relevant previous considerations. The PBAC noted that a further price reduction would be required to achieve this ICER.
- 7.8 The PBAC noted the pre-PBAC response provided revised financial estimates that included an additional < 500 grandfathered patients in the first year of listing. While the PBAC considered the addition of grandfathered patients appropriate, the Committee noted the revised financial estimates presented in the pre-PBAC response did not include amendments to address concerns raised by the ESC regarding the approach taken in the estimation of eligible patients or regarding the cost offsets. The PBAC noted that the estimates effectively assumed 100% of uptake of NIVO in cisplatin eligible patients (see paragraph 6.75), and agreed with the ESC that as a result the number of patients eligible for treatment with NIVO was overestimated. The PBAC considered the financial estimates should be amended to assume an annual uptake rate of 90%. The PBAC also agreed with the ESC that the cost offsets associated with subsequent therapies were overestimated due to a reduction in use being assumed in all eligible patients instead of only those who had received first line platinum-doublet chemotherapy (see paragraph 6.76), and advised that this should be amended to account for this criteria. The PBAC considered that with these amendments the financial estimates would be acceptable as the basis for a risk sharing arrangement. However, the PBAC further noted that if EV + PEM was available on the PBS, the uptake of nivolumab should be substantially reduced to account for the likelihood that EV + PEM would become the preferred SoC (see paragraph 5.3).
- 7.9 The PBAC considered that a risk sharing arrangement would be appropriate to mitigate any remaining uncertainty regarding the cost-offsets. The PBAC noted that there are currently separate risk sharing arrangements for urothelial carcinoma treatments. The PBAC considered that a combined risk sharing arrangement for urothelial cancer treatments across first and subsequent lines would be preferred.
- 7.10 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 nivolumab:

- a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over SoC, as while clinically relevant the OS treatment benefit is not expected to be substantial;
- b) The treatment is expected to address a high and urgent unmet clinical need.
- 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.

7.11 The PBAC advised that this submission would not meet the criteria for an Independent Review as received a positive PBAC recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

8.1 Amend existing listing as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection	NEW (Public) NEW (Private)	360mg	5
<b>Available brands</b>			
Opdivo (Nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (Nivolumab 100 mg/10 mL injection, 10 mL vial)			
<b>Concept ID</b>	<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy – Public (HB)/ Private (HS)		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Benefit type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]		
<b>Prescribing rule level:</b>			
<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>Restriction Summary [new] / Treatment of Concept: [new]</b>			
<b>Episodicity:</b> n/a			
<b>Severity:</b> Unresectable or metastatic			
<b>Condition:</b> Urothelial carcinoma			
<b>Indication:</b> Unresectable or metastatic urothelial carcinoma			
<b>Treatment Phase:</b> Initial treatment			
<b>Clinical criteria:</b>			

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	The condition must not have previously been treated with PBS-subsidised systemic therapy for unresectable or metastatic urothelial carcinoma
	<b>AND</b>
	<b>Clinical criteria:</b>
	The treatment must be initiated in combination with cisplatin and gemcitabine
	<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>Clinical criteria:</b>
	Patient must not have received prior treatment with a PBS subsidised programmed cell death-1 (PD-1) inhibitor or programmed cell death ligand-1 (PD-L1) inhibitor for this condition
	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
	<b>Prescribing instruction:</b> Patient must only receive up to a maximum 6 doses of PBS-subsidised combined therapy with both (i) nivolumab (ii) cisplatin and gemcitabine, under this PBS listing, once in a lifetime.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. Amount	No. of Rpts
NIVOLUMAB Injection	NEW (Public) NEW (Private)	480mg	5
<b>Available brands</b>			
Opdivo (Nivolumab 40 mg/4 mL injection, 4 mL vial)			
Opdivo (Nivolumab 100 mg/10 mL injection, 10 mL vial)			
<b>Concept ID</b>	<b>Category / Program:</b> <input checked="" type="checkbox"/> Section 100 – Efficient Funding of Chemotherapy - Public (HB) / Private (HS)		
	<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners		
	<b>Benefit type:</b> <input checked="" type="checkbox"/> Authority Required (Streamlined) [new code]		
	<b>Prescribing rule level:</b>		
	<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>Restriction Summary [new] / Treatment of Concept: [new]</b>		
	<b>Episodicity:</b> n/a		
	<b>Severity:</b> Unresectable or metastatic		
	<b>Condition:</b> Urothelial carcinoma		
	<b>Indication:</b> Unresectable or metastatic urothelial carcinoma		
	<b>Treatment Phase:</b> Continuing treatment		
	<b>Clinical criteria:</b>		
	Patient must have previously received up to a maximum 6 doses of combined therapy with both (i) nivolumab (ii) cisplatin and gemcitabine, as initial treatment for this condition.		

	<b>AND</b>
	Clinical criteria:
	The treatment must be as monotherapy for this condition.
	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must be undergoing treatment with a dosing regimen as set out in the drug's approved Australian Product Information
	<b>AND</b>
	<b>Treatment criteria:</b>
	Patient must not be undergoing continuing PBS-subsidised treatment where this prescription extends treatment beyond whichever comes first: (i) 24 months from treatment initiation, irrespective of whether initial treatment was PBS subsidised/non-PBS subsidised, (ii) disease progression despite treatment with this drug, (iii) unacceptable toxicity; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs.
	<b>Prescribing Instructions:</b> An increase in repeat prescriptions, up to a value of 11, may only be sought where the prescribed dosing is 240 mg administered fortnightly.

***These restrictions 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

The sponsor had no comment.