6.02 DURVALUMAB, Solution concentrate for I.V. infusion, 120 mg in 2.4 mL, Solution concentrate for I.V. infusion, 500 mg in 10 mL, Imfinizi®, AstraZeneca Pty Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a Section 100 (Efficient Funding of Chemotherapy [EFC] Program) listing for durvalumab for the perioperative treatment (i.e. both before and after surgery) of patients with muscle-invasive bladder cancer (MIBC) who are planning to undergo radical cystectomy (RC) and are eligible for cisplatin-based neoadjuvant chemotherapy (NAC)[1].

1.2 Listing was requested on the basis of a cost-utility analysis of:

- Perioperative durvalumab: neoadjuvant durvalumab in combination with NAC [and RC] followed by adjuvant durvalumab monotherapy, versus
- Standard of care (SoC): NAC [and RC] followed by
  - adjuvant nivolumab for patients with high risk of recurrence

    OR
  - post-surgery active surveillance for all other patients.

1.3 A summary of the key components of the clinical issue addressed by the submission is presented in Table 1.

[1] Clinical criteria for cisplatin eligibility: (1) ECOG performance status <2; (2) creatinine clearance ≥60 mL/min; (3) no significant hearing loss (measured at audiometry of 25 dB at 2 contiguous frequencies); (4) less than Grade 2 peripheral neuropathy, and (5) no clinical evidence of New York Heart Association class III or greater heart failure (Galsky MD et al. 2011).

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

Component	Description
Population	Patients with MIBC who are planning to undergo radical cystectomy and are eligible for cisplatin-based NAC.
Intervention	Neoadjuvant: Durvalumab (1500 mg IV) every 3 weeks in combination with gemcitabine plus cisplatin for four cycles (12 weeks), followed by: Adjuvant: Durvalumab (1500 mg IV) every four weeks as monotherapy for up to 8 cycles (32 weeks).
Comparator	Main comparator: Standard of care (SoC) comprising GC NAC followed by active surveillance post-radical cystectomy. Relevant comparator: SoC which includes a subgroup of eligible patients who receive GC NAC followed by adjuvant nivolumab.
Outcomes	EFS, pCR, OS, DFS, MFS, HRQoL, safety
Clinical claim	Main: Compared to standard of care, perioperative durvalumab plus GC NAC has superior comparative efficacy and inferior safety. Supplementary: Compared to standard of care in which some patients receive adjuvant nivolumab, perioperative durvalumab plus GC NAC has superior comparative efficacy and non-inferior safety.

Source: Table 1-1, p16 of the submission.

DFS = disease-free survival; EFS = event free survival; GC = gemcitabine plus cisplatin; HRQoL = health-related quality of life; IV = intravenous; MFS = metastasis-free survival; MIBC muscle-invasive bladder cancer; NAC = neoadjuvant chemotherapy; OS = overall survival; pCR = pathologic complete response; SoC = standard of care.

Note: Clinical criteria for cisplatin eligibility: (1) ECOG performance status < 2; (2) creatinine clearance ≥60 mL/min; (3) no significant hearing loss (measured at audiometry of 25 dB at 2 contiguous frequencies); (4) less than Grade 2 peripheral neuropathy, and (5) no clinical evidence of NYHA class III or greater heart failure (Galsky MD et al. 2011).

2 Background

Registration status

2.1 The submission was made under the TGA/PBAC Parallel Process. The proposed TGA indication is:

> IMFINZI® (durvalumab) in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI® as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adult patients with muscle-invasive bladder cancer (MIBC).

2.2 At the time of PBAC consideration, the Delegate's Overview was available. The Delegate stated an intention to approve the registration of durvalumab for the above-mentioned indication, with an additional condition for the sponsor to submit the final analysis of overall survival (OS) in the pivotal NIAGARA study (5 years after final enrolment) for TGA evaluation. The PBAC noted that this condition of registration will not reduce the key uncertainty regarding the comparison of perioperative durvalumab to adjuvant nivolumab in patients at high risk of recurrence (see paragraph 6.36 below).

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

3 Requested listing

3.1 The requested listing is presented below. Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Essential elements of the requested listing for each of initial and continuing treatment

Name, restriction, manner of administration and form	Max Quantity (units)	Number of repeats	DPMQ		Proprietary name and manufacturer
			Public hospital	Private hospital	
Durvalumab 500 mg/10 mL; 10 mL vial Durvalumab 120 mg/2.4 mL; 10 mL vial	1500 mg	3	Published: $[redacted] Effective: $[redacted] with SPA	Published: $[redacted] Effective: $[redacted]	IMFINZI® AstraZeneca Pty Ltd

Source: Tables 1-8 and 1-9, p28 of the submission
DPMQ = dispensed price for maximum quantity; mg = milligram; mL = millilitre; SPA = special pricing arrangement

Requested restriction for durvalumab – initial treatment

Restriction Summary NEW / Treatment of Concept: NEW
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED) [new]
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Condition: ~~Muscle-invasive bladder cancer~~ *Urothelial Carcinoma*
Indication: ~~Muscle-invasive bladder cancer~~ *Urothelial Carcinoma*
Treatment Phase: Initial *treatment – neoadjuvant setting*
Population criteria:
Patient must be initiating treatment with this drug for this condition; or
Patient must be transitioning from ~~existing~~ non-PBS to PBS subsidised *treatment with this drug for this condition* ~~supply of this drug~~
Clinical criteria:
The condition must not have previously been treated with systemic therapy for muscle-invasive bladder cancer *at the time this drug was initiated for this condition*
AND
Clinical criteria:
The condition must be of muscle-invasive type disease ~~(T2-T4a)~~ *with a clinical tumour stage of either T2, T3 or T4a*
AND
Clinical criteria:
The treatment must be for ~~the purpose of~~ neoadjuvant use in a patient preparing for radical cystectomy
AND
Clinical criteria:
Patient must have/have had at the time of initiating treatment with this drug, a WHO performance status no higher than 1
AND
Clinical criteria:

~~The treatment must be initiated in combination with gemcitabine and cisplatin~~ *The treatment must be/have been initiated with both: (i) gemcitabine, (ii) cisplatin (refer to Product Information of gemcitabine and cisplatin for dosing information).*
AND
Treatment criteria:
Patient must not be undergoing PBS subsidised treatment where this prescription extends treatment beyond whichever comes first: (i) 4 cycles 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.
~~**Administration advice:** The prescribing dose is 1500 mg administered every 3 weeks~~
Prescribing Instruction: *Patients with a body weight of 30 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg as per the TGA approved Product Information*

Requested restriction for durvalumab – continuing treatment

Restriction Summary NEW / Treatment of Concept: NEW
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (STREAMLINED) [new]
Administrative Advice: No increase in the maximum quantity or number of units may be authorised
Administrative Advice: No increase in the maximum number of repeats may be authorised
Administrative Advice: Special Pricing Arrangements apply
Condition: ~~Muscle-invasive bladder cancer~~ *Urothelial Carcinoma*
Indication: ~~Muscle-invasive bladder cancer~~ *Urothelial Carcinoma*
Treatment Phase: Continuing treatment – adjuvant setting
Population criteria:
Patient must have previously received PBS subsidised neoadjuvant treatment with this drug for this condition; or
Patient must be both: (i) transitioning from existing non-PBS to PBS subsidised *treatment with* ~~supply of~~ this drug *for this condition*, (ii) treated *in combination* with ~~combined therapy with~~ durvalumab, ~~and~~ cisplatin and gemcitabine as neoadjuvant treatment for this condition.
Clinical criteria:
Patient must have undergone radical cystectomy within 70 days from the final dose of neoadjuvant therapy with this drug for this condition
AND
Clinical criteria:
The treatment must be for adjuvant therapy that is/was initiated within *42 to* 120 days of radical cystectomy for this condition
Clinical criteria:
~~The treatment must be as monotherapy~~ *The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication*
AND
Clinical criteria:
Patient must have received prior neoadjuvant chemotherapy with gemcitabine plus cisplatin for this condition
AND
Treatment criteria:
Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) maximum of 8 ~~months~~ *cycles* for this condition from the first administered dose following radical cystectomy, (iii) unacceptable toxicity; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
~~**Administration advice:** The prescribing dose is 1500 mg administered every 4 weeks~~

Prescribing Instruction: *Patients with a body weight of 30 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg as per the TGA approved Product Information*
Prescribing Instruction: *Treatment with this drug for this condition must not exceed 12 treatment cycles (neoadjuvant and adjuvant) in a lifetime*

3.2 The submission requested a Special Pricing Arrangement (SPA). The requested effective ex-manufacturer price is $[redacted] per 500 mg vial.

3.3 The PBAC agreed with the submission that a flow-on change to the existing PBS items for adjuvant nivolumab for MIBC would be appropriate if/when durvalumab is listed. This was proposed in order to reflect the once-per-lifetime use of immunotherapy, which is consistent with other PBS listings for locally advanced and metastatic urothelial carcinoma.

PBS items	Additional clinical criteria:
14231B 14260M	*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.*

Source: Table 1-12; p31 of the submission

3.4 A separate grandfathering listing was not requested in the submission. The PBAC acknowledged that proposed restrictions for initial and continuing treatment with durvalumab were worded to allow grandfathered patients from the planned patient access program to transition to PBS subsidised therapy. Durvalumab was anticipated to be provided via an Early Access Program for patients with MIBC following the drug's registration.

3.5 The requested restriction did not propose a timeframe between patients receiving neoadjuvant durvalumab and undergoing surgery. The NIAGARA trial specified RC should be performed as soon as possible after completion of, and recovery from, neoadjuvant therapy and was recommended to occur within 56 days after the last dose of neoadjuvant chemotherapy. RC was not recommended earlier than 14 days after the last dose of neoadjuvant therapy. Delays up to 70 days (the outer limit supported by guidelines) due to medical reasons were permitted. The PBAC agreed with the ESC in considering that a timeframe between patients receiving neoadjuvant durvalumab and undergoing surgery would not be needed in the restriction because it may preclude a small number of patients whose surgery was delayed and who may benefit from treatment.

3.6 The proposed PBS restriction for continuing use of durvalumab required patients to commence adjuvant therapy within 120 days of undergoing a RC. This is broadly in line with the treatment scheme of the NIAGARA trial (42−120 days) and with the PBS restriction for the use of nivolumab as adjuvant therapy for patients with MIBC who are at high risk of disease recurrence. The PBAC agreed with the ESC that it may be appropriate to specify "within 6 months" in the criteria to allow for flexibility in clinical practice.

3.7 With regard to the nodal involvement and disease metastasis in the proposed population, the submission's proposed restriction (MIBC clinical stage T2 to T4a) does

not limit the use of perioperative durvalumab to patients who would reflect the NIAGARA trial population (stage N0 or N1, and stage M0). Therefore, patients with stage IIIb [T2-T4a, N2 or N3] and more advanced disease would also be eligible according to the proposed restriction. The evaluation noted that there is limited clinical evidence to support the efficacy and safety of perioperative durvalumab in patients with MIBC who have nodal involvement beyond stage N1 or with metastatic disease. Of note, the trial population represents patients with MIBC who do not have nodal involvement because the vast majority of the patients (94.5%) had stage N0 MIBC. The Pre-Sub-Committee Response (PSCR) stated that this issue could be addressed by specifying stage N0/1 in the restriction criteria, which the ESC and the PBAC agreed with. The ESC and the PBAC noted that it is not necessary to specify M0, as durvalumab would be restricted to those patients planned for RC and would thus have no detectable distant metastases.

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

4 Population and disease

4.1 Bladder cancer is the eleventh most diagnosed cancer in Australia. In 2024, 3,319 new cases of the disease were estimated (compared to 3,017 in 2020, and 2,012 in 2005[2]). Bladder cancer affects more males than females and mainly affects older people. The median age of patients with primary muscle-invasive or metastatic urothelial cancer in the BLADDA registry[3] who had a surgery with perioperative chemotherapy was 68 years. Smoking has been known as the major risk factor, as well as other environmental factors and occupational exposures in industries such as dye manufacturing, rubber production, and aluminium processing. More recently, western diet, imbalanced microbiome, gene-external risk factor interactions, diesel exhaust emission exposure, and pelvic radiotherapy are considered risk factors of bladder cancer[4].

4.2 Bladder cancer typically presents with intermittent, painless haematuria (grossly visible or microscopic). Irritative voiding symptoms (frequency, urgency, dysuria) can also be the initial clinical presentations. Advanced cases of bladder cancer may present with symptoms like flank pain due to ureteric obstruction, causing hydronephrosis or declining renal function. The extent of invasion of the tumour into deeper layers of the bladder and surrounding tissues is the most important element in the pathologic staging of bladder cancer and has major implications for both prognosis and treatment[5]. Bladder cancer is typically confirmed by cystoscopy with

[2] Australian Bureau of Statistics. Yearbook Australia 2009-10. Canberra, ABS, 2010.
[3] BLADDA (Bladder cancer). URL: https://figshare.unimelb.edu.au/articles/dataset/BLADDA_Bladder_Cancer_/12495617
[4] Jubber I et al. Epidemiology of bladder cancer in 2023: A systematic review of risk factors. *European Urology* 2023; 84(2): 176-190.
[5] Magi-Galluzzi C, Zhou M. Pathology of bladder neoplasms. *UptoDate* 2024. URL: https://www.uptodate.com/contents/pathology-of-bladder-

transurethral resection of bladder tumour, together with imaging assessment of the extent of disease (i.e., nodal involvement and distant metastases). Bladder cancer of clinical stage T2 to stage T4 (defined by the 8th Edition of the American Joint Committee on Cancer [AJCC] Tumour-Node-Metastasis [TNM] staging system) are included in the category of MIBC. The target population in the submission is patients with clinical stages T2 to T4a (i.e., without tumour invasion of the pelvic or abdominal wall).

4.3 In current clinical practice, NAC with gemcitabine plus cisplatin (GC) followed by RC is the primary treatment recommended by the National Comprehensive Cancer Network (NCCN) for MIBC patients with T2N0M0 disease (i.e., stage II MIBC) to T3-T4aN0/N1M0 disease (i.e., Stage IIIa MIBC). Following RC, patients who are considered high risk for disease recurrence (defined by a pathologic staging of ypT2[6] to ypT4a or ypN+[7] of the tumour tissue obtained from the surgery) commence adjuvant nivolumab as monotherapy within 120 days if there is no evidence of disease recurrence. Nivolumab is given for a maximum duration of 1 year. For patients who are not at high risk for disease recurrence following RC, post-surgery active surveillance is required. For patients who have MIBC but are not candidates for RC, avelumab is an option for first-line immunotherapy after a platinum-based chemotherapy if there is no evidence of disease progression. In Australia, both GC and dose dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) are available options for neoadjuvant NAC in MIBC management (refer to paragraph 5.5 below).

4.4 Durvalumab is a human monoclonal antibody of the IgG1 kappa subclass that acts as a programmed cell death ligand 1 (PD-L1) receptor inhibitor. PD-L1 blockade by durvalumab can lead to increased T-cell activation and decreased tumour size. Durvalumab is proposed to be as a neoadjuvant therapy in combination with GC, followed by RC, then as a monotherapy in the adjuvant setting.

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

5 Comparator

5.1 The submission nominated SoC (GC NAC and RC followed by post-surgery active surveillance) as the main comparator. While the evaluation considered that SoC is appropriate as the main comparator, SoC as described by the submission did not incorporate adjuvant nivolumab (see next paragraph) and therefore may not reflect current practice in the Australian setting.

5.2 The submission also described adjuvant nivolumab as a relevant comparator, specifically for MIBC patients with a high risk of disease recurrence who have received GC NAC. Nivolumab is currently listed on the PBS as an adjuvant immunotherapy for

neoplasms?sectionName=CLASSIFICATION&search=bladder%20cancer&topicRef=2989&anchor=H2&source=see_link#H4

[6] ypT refers to: y=post neoadjuvant therapy; p=pathologic staging; T=size and extend of the primary tumour.

[7] The "yp" prefix indicates that this pathologic staging is made after a neoadjuvant therapy.

this patient group. The evaluation noted that if perioperative durvalumab is PBS-listed, it will replace adjuvant nivolumab in patients at high risk of recurrence and thus it is reasonable to consider adjuvant nivolumab as a relevant comparator for a proportion of patients. However, at the time the key trial (NIAGARA) was designed, adjuvant nivolumab was not yet available in clinical practice and was therefore not included in the comparator arm in the trial.

5.3 Incorporating both the neoadjuvant and adjuvant treatment stages, the evaluation considered that the most relevant comparator could be described as:

- GC NAC and RC, followed by
  - adjuvant nivolumab for patients with high risk of recurrence
    OR
  - post-surgery active surveillance for all other patients.

Given that nivolumab is likely to be used in the adjuvant setting for high risk patients in line with its PBS listing, the ESC considered that it is likely that the mixed comparator described above should have been defined as the main comparator in the submission. The Pre-PBAC response accepted the description of the comparators as proposed by the evaluation and the ESC, and agreed that it accurately reflects the comparison presented in the submission since adjuvant nivolumab was addressed in the clinical section and accounted for in the economic and financial models.

5.4 With respect to the proportion of patients at high risk of recurrence, the submission reported that 27.6% of patients in the SoC arm of NIAGARA had residual T2+ and/or node positive disease after neoadjuvant chemotherapy and an RC, and would have satisfied the PBS eligibility criteria to receive adjuvant nivolumab.[8] The ESC considered this proportion to be consistent with studies of neoadjuvant chemotherapy and clinical experience, although noted that some comorbid patients would not proceed to any adjuvant immunotherapy after RC, regardless of their risk status.

5.5 In current Australian clinical practice, ddMVAC is also used as NAC for patients with MIBC but is used slightly less frequently compared with GC (41% vs 45%, according to the BLADDA registry data[9]). Thus, ddMVAC may be replaced by durvalumab, in combination with GC, in the neoadjuvant setting for some patients. ddMVAC has been shown to have improved progression-free survival over GC (hazard ratio [HR]: 0.68; 95% confidence interval [CI]: 0.50, 0.93) and improved OS over GC (HR: 0.71; 95% CI:

[8] The derivation of the proportion of patients (27.6%) (i) at high risk of recurrence and (ii) would have satisfied the PBS eligibility criteria to receive adjuvant nivolumab, was described in the submission in Table 2-31 and text on p85. The Pre-PBAC response clarified (p3) that the analysis/derivation was not pre-specified and therefore did not appear in the NIAGARA Clinical Study Report [noting that treatment with adjuvant nivolumab for patients at high risk of recurrence was not part of the SoC arm of the NIAGARA trial (see paragraph 6.5 below)].

[9] BLADDA (Bladder cancer). URL: https://figshare.unimelb.edu.au/articles/dataset/BLADDA_Bladder_Cancer_/12495617

0.52, 0.97) in the neoadjuvant setting in the VESPER trial, but had increased treatment-related toxicity[10,11].

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from 3 organisations via the Consumer Comments facility on the PBS website. One individual also provided input expressing support for the PBS listing of durvalumab, but specially in relation to endometrial cancer, not MIBC.

6.3 The Medical Oncology Group Australia (MOGA) indicated their strong support for the PBS listing of durvalumab to be extended to perioperative treatment of patients with MIBC. The MOGA categorised durvalumab as one of the therapies of 'highest priority for PBS listing' on the basis of the NIAGARA trial. The PBAC noted that the MOGA classified durvalumab with a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) grade 'A', categorising it as a new treatment with substantial benefit in the curative setting.[12]

6.4 Similarly, two consumer groups (Rare Cancers Australia and BEAT Bladder Cancer Australia) expressed their support for durvalumab for the treatment of MIBC. Rare Cancers Australia discussed how access to perioperative treatment will reduce the risk of metastases that cannot always be eliminated by surgery alone and that reported side effects can be managed with the support of general practitioners. BEAT Bladder Cancer Australia discussed the currently available treatments for MIBC, including adjuvant nivolumab as a welcome recent option, but noted that there is still a high chance of the cancer returning as metastatic disease. It stated that the advantage of patient access to perioperative durvalumab is reflected by the survival advantage demonstrated in the NIAGARA trial.

[10] Pfister C et al. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: results of the GETUG-AFU V05 VESPER trial. *Journal of Clinical Oncology* 2022; 40 (18): 2013-2022.

[11] Pfister C et al. Perioperative dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin in muscle-invasive bladder cancer (VESPER): survival endpoints at 5 years in an open-label, randomised, phase 3 study. *Lancet Oncology* 2023; 25: 255-264.

[12] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Clinical trials

6.5 The submission was based on one head-to-head trial (NIAGARA) comparing:

- neoadjuvant durvalumab in combination with GC followed by RC and adjuvant durvalumab as a monotherapy (durvalumab + GC arm)

  with

- cisplatin-based NAC followed by RC and post-surgery active surveillance (GC arm).

The trial population comprised patients with MIBC of stage T2 to T4a, N0 or N1, and M0 (i.e., stage II to stage IIIa) (N = 1,063).

6.6 The submission also performed an ITC involving the NIAGARA trial and the Checkmate 274 (CM274) trial. The CM274 trial compared:

- [Possible NAC, followed by] RC and adjuvant nivolumab

  with

- [Possible NAC, followed by] RC and adjuvant placebo.

The trial population comprised patients with high-risk muscle-invasive urothelial carcinoma (MIUC). Almost half the patients (43%) in the CM274 trial received cisplatin-based NAC compared to all of the patients in the NIAGARA trial.

6.7 Details of the NIAGARA and CM274 trials presented in the submission are provided in Table 2.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
NIAGARA NCT03732677	NIAGARA CSR - DCO: 29 April, 2024 Clinical Study Protocol v5: June 1, 2021 Statistical analysis plan v2: November 30, 2021	
	Powles, T., Catto, J. W. F., Galsky, M. D., et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer	NEJM 2024; 391(19), 1773-1786.
	Galsky, M. D., Van Der Heijden, M. S., Catto, et al. Additional efficacy and safety outcomes and an exploratory analysis of the impact of pathological complete response (pCR) on long-term outcomes from NIAGARA.	Journal of Clinical Oncology 2025; 43.
	Powles, T. B., van der Heijden, M. S., Galsky, M. D., et al. LBA5 A randomized phase III trial of neoadjuvant durvalumab plus chemotherapy followed by radical cystectomy and adjuvant durvalumab in muscle-invasive bladder cancer (NIAGARA).	Annals of Oncology 2024; 35, S1271.
	Powles, T., Meeks, J. J., Galsky, M. D., et al. A phase III, randomized, open-label, multicenter, global study of efficacy and safety of durvalumab in combination with gemcitabine+cisplatin (GC) for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in muscle-invasive bladder cancer (MIBC) (NIAGARA).	Journal of Clinical Oncology 2019; 37.
	Powles, T., Meeks, J. J., Galsky, M. D., et al. A phase III, randomized, open-label, multicenter, global study of efficacy and safety of durvalumab in combination with gemcitabine plus cisplatin for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in muscle-invasive bladder cancer (NIAGARA).	Journal of Clinical Oncology 2021; 39(6 SUPPL).
	Kubler, H. R., Powles, T., Meeks, J. J., et al. A Phase 3, randomized, open-label, multicenter, global study of efficacy and safety of durvalumab in combination with gemcitabine+cisplatin (GC) for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in muscle-invasive bladder cancer (MIBC) (NIAGARA)	Oncology Research and Treatment 2020; 43 (Suppl. 1): 82.
Checkmate 274 NCT02632409	Bajorin, D.F., Witjes, J. A., Gschwend, J.E., et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma.	NEJM 2021; 384 (22), 2102-2114.

Source: Table 2-3, pp38-39 of the submission
CSR = Clinical study report; DCO = Data cut-off; EUCTR = EU Clinical Trials Register; GC = Gemcitabine plus cisplatin; MIBC = Muscle-invasive bladder cancer

Head-to-head trial (NIAGARA) of perioperative durvalumab versus neoadjuvant chemotherapy

6.8 The key features of the NIAGARA and CM274 trials are summarised in Table 3. For brevity in the tables below, "DURVA + GC" refers to neoadjuvant durvalumab in combination with GC followed by RC and adjuvant durvalumab as a monotherapy, and "GC" refers to cisplatin-based NAC followed by RC and post-surgery active surveillance.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
DURVA + GC vs GC (SoC) (perioperative treatment setting)						
NIAGARA	1,063	R, MC, OL Median follow-up: DURVA + GC: 42.3 mths GC: 39.6 mths	Varied depending on the subjectivity of the outcome[c]	Patients with Stage T2-T4a, N0 or N1, M0 MIBC	Primary (dual): EFS by BICR, pCR by CPR Secondary: OS, DFS (by BICR)[e], MFS, % of patients who achieved < P2[f], % of patients who underwent cystectomy, HRQoL, and AEs	EFS, DFS
Nivolumab vs placebo (proxy for watchful waiting) (adjuvant treatment setting)						
CM274	709[a]	R, MC, DB 36.1 mths[b]	Low[d]	Patients with MIUC who had undergone radical surgical resection	Primary: DFS Secondary: NUTRFS, OS, and DSS Exploratory: DMFS	HR for DFS with nivolumab versus active surveillance

Source: Information provided in Section 2.3, pp31-43 of the submission.

AEs = Adverse Events; BICR = Blinded independent central review; DB = double-blind; DFS = Disease-free survival; DMFS = distant metastasis-free survival; DSS = disease-specific survival; DURVA = durvalumab; EFS = Event free survival; HR = hazard ratio; HRQoL = Health related quality of life; M = stage of metastasis; MC = Multicentre; MFS = Metastasis-free survival; MIBC = Muscle-invasive bladder cancer; MIUC = muscle-invasive urothelial carcinoma; mths = months; N = stage of lymph node involvement; NUTRFS = non upper tract recurrence free survival; OL = open label; OS = overall survival; R = randomised; SoC = standard of care; T = tumour.

[a] In the CM274 trial, 353 patients were randomly assigned to the nivolumab arm and 356 to the placebo arm. In the trial, 560 patients (279 in the nivolumab arm and 281 in the placebo arm) had the original tumour in the bladder.

[b] According to the extended follow-up results from the CM274 trial (Galsky MD et al.), duration of median follow-up for the nivolumab arm was 37.4 months and 33.9 months for the placebo arm.

[c] Low risk of bias for assessment of EFS, pCR, OS, DFS, and MFS. Moderate-to-high risk of bias for assessment of patient-reported outcomes and AE outcomes

[d] Based on Table 5 of the nivolumab Public Summary Document, November 2023 PBAC Meeting with March 2024 Addendum.

[e] DFS data was reported for patients who underwent radical cystectomy which included 64.8% of randomised patients.

[f] Assessed by local pathology review.

6.9 Blinded independent central review (BICR) and central pathological review (CPR) were used to reduce the risk of bias for the assessment of event-free survival (EFS) and pathological complete response (pCR) in the NIAGARA trial. However, due to the open-label study design, the assessment of health-related quality of life (HRQoL) and safety outcomes was subject to a moderate-to-high risk of bias.

6.10 In the NIAGARA trial, patients in the durvalumab + GC arm received both neoadjuvant and adjuvant durvalumab, regardless of individual risk profiles. The design of the trial did not allow the effect of the neoadjuvant and adjuvant durvalumab to be distinguished from each other and therefore the most effective use of the immunotherapy (neoadjuvant vs adjuvant setting) in treating MIBC could not be determined. The PSCR acknowledged that the NIAGARA trial was not designed to demonstrate contribution by phase of treatment but noted that the exposure of patients to perioperative durvalumab (in the NIAGARA trial) is similar to exposure to adjuvant nivolumab (in the CM274 trial) in terms of total number of cycles, indicating no difference in overall exposure to immunotherapy with either regimen. The PSCR noted that perioperative durvalumab has been shown to provide statistically

significant OS benefits in MIBC, while adjuvant nivolumab is yet to demonstrate statistical significance for OS.

6.11 NIAGARA is an ongoing trial. The results presented in the submission were from the Interim Analysis-2 (IA-2). At the data cutoff (DCO) of IA-2, among patients who received post-discontinuation anti-cancer therapies (including radiotherapy, immunotherapy, chemotherapy, targeted therapy and others) in the SoC arm, 62/93 (66.7%) of patients received subsequent immunotherapy[13]. While the evaluation noted that this proportion may be different in Australia given the availability of multiple options of immunotherapy in the subsequent line setting for MIBC treatment, the ESC considered the proportion was unlikely to be significantly higher in clinical practice given the age of patients and comorbidities.

Indirect treatment comparison based on NIAGARA and CM274 subgroups and construction of a counterfactual arm

6.12 As part of the ITC, the submission estimated 'counterfactual' survival times for the control arm of the NIAGARA trial. Its purpose was to adjust the outcomes in the control arm to account for patients at high risk of recurrence receiving adjuvant nivolumab after RC (as per the CM274 trial), instead of active surveillance (as per the NIAGARA trial). The creation of the counterfactual arm was to represent the mixed SoC comparator as outlined in paragraph 5.3 (27.6% of patients at high risk of recurrence and, inversely, 72.4% of patients not at high risk).

6.13 The ITC was performed using a method that consisted of three stages:

- An acceleration factor (AF; the amount by which an individual's expected survival time is increased by treatment) was estimated for adjuvant nivolumab vs placebo from the CM274 trial.
- A counterfactual arm was constructed by applying the AF from stage one to the comparator arm of NIAGARA. The AF was applied to the 'adjuvant phase' survival times of patients who were eligible for adjuvant nivolumab. The aim was to estimate their 'counterfactual survival times' if they had received treatment. The survival times of eligible patients up to the adjuvant phase, as well as the total survival times of patients who were ineligible for adjuvant nivolumab, remained unchanged from their observed outcomes.
- The ITC comparing perioperative durvalumab vs the counterfactual arm created in stage two was conducted.

For safety, an unanchored unadjusted ITC was presented in the submission.

6.14 The ESC noted a technical report of the ITC was attached to the submission and that the methodology described in the report uses established techniques originally developed for adjusting survival times for the impact of crossover or treatment

[13] The evaluation noted that this proportion reduced to 62/161 (38.5%) when the number of patients alive with disease progression or recurrence after cystectomy was used as the denominator for the calculation.

switching (Latimer et al 2016[14]). The ESC noted these existing methods were adapted to capture the effect of including a new therapy (i.e., adjuvant nivolumab) in the pathway. The ESC noted and agreed with the following limitations summarised in the report:

- Assumption of generalisability of effect:

  It was necessary to assume that the relative effects of nivolumab in the MIBC subgroups of CM274 are generalisable to the corresponding NIAGARA population. Where possible, data that closely resembled the NIAGARA cohort were used.

- Double counting:

  Four patients in the NIAGARA trial received adjuvant nivolumab during study follow-up. The effect of nivolumab was applied to the entire eligible population, including those treated during follow-up, leading to double counting and overestimating the impact of nivolumab. Since the double counting favoured nivolumab over durvalumab, no further adjustment was made.

6.15 The ESC noted there were a number of key differences identified across the NIAGARA and CM274 trials by the evaluation:

- Regarding study populations:
  - The majority of the NIAGARA population (94.5%) had stage N0 at baseline. However, in the CM274 population, 24.7% of patients had stage N0, 20.2% had stage N1, 21.3% had stage N2, and 5.6% had stage N3 disease. The Pre-PBAC response noted that the nivolumab benefit is applied only to the subgroup of patients in the NIAGARA control arm known to meet the PBS-specified eligibility criteria for adjuvant nivolumab (those at high risk of recurrence, i.e. pathological stage of ypT2 to ypT4a or ypN+ after NAC and RC). Thus, the Pre-PBAC response stated that the differences across the CM274 and NIAGARA trials do not affect the transitivity assumption of the ITC with respect to baseline clinical staging.
  - The NIAGARA population had a higher proportion of patients with high PD-L1 expression (53.8% of study population had tumour cell [TC] ≥1% and 73% had high expression[15]) compared to the CM274 population (approximately 40% had TC ≥1%)
- At the adjuvant baseline in the trials:
  - 100% of patients in NIAGARA received GC NAC vs approximately 43% in CM274. The Pre-PBAC response noted that only data from CM274's prior-NAC subgroup are used to inform the ITC and thus the applied benefit from adjuvant

[14] Latimer, N.R., Et Al., Treatment Switching: Statistical and Decision-Making Challenges and Approaches. Int J Technol Assess Health Care, 2016. 32(3): P. 160-6.

[15] High PD-L1 expression in NIAGARA was defined as ≥ 25% tumour cells or immune cells stained positive for PD-L1 in an IHC assay.

nivolumab reflects prior NAC use in 100% of patients, consistent with both the NIAGARA trial and the nivolumab PBS restriction. Therefore, the Pre-PBAC response stated that the differences across the CM274 and NIAGARA trials do not affect the transitivity assumption of the ITC with respect to prior NAC.

- 100% of patients in CM274 were at high-risk for disease recurrence (i.e., tumour with pathological stage of ypT2 to ypT4a or ypN+) versus 27.6% of high-risk patients in NIAGARA. The Pre-PBAC response stated that the differences across the CM274 and NIAGARA trials do not affect the transitivity assumption of the ITC with respect to clinical staging because only the subgroup of patients in the NIAGARA control arm known to be at high risk of recurrence was included in the ITC (as described in the dot point above), and it is applied only at the time they become eligible (i.e., following RC at the adjuvant baseline).

- Regarding endpoint definitions:
  - In NIAGARA, EFS was defined as time from randomisation to the first recurrence of disease after RC, the time of first documented progression in patients who were medically precluded from a RC, or time of expected surgery in patients who refused to undergo a RC or failure to undergo a RC in participants with residual disease, or the time of death due to any cause, whichever occurred first. In CM274, disease-free survival (DFS) was defined as the time between the date of randomisation and the date of first recurrence (local recurrence in the urothelial tract, local recurrence outside the urothelial tract, or distant recurrence), or death. The Pre-PBAC response stated that the definition of an EFS event in NIAGARA (recurrence or death) is identical to the definition of DFS in CM274. Consequently, applying the DFS benefit for nivolumab to the EFS curve from adjuvant baseline does not affect the transitivity assumption of the ITC with respect to EFS/DFS.

- Regarding duration of follow-up:
  - NIAGARA had a longer median duration of follow-up compared to CM274. In NIAGARA, the median duration of follow-up for EFS was 34.7 months for the durvalumab + GC arm and 27.7 months for the GC arm. In CM274, the median duration of follow-up for DFS was 20.9 months for the nivolumab arm and 19.5 months for the placebo arm. The ESC noted it is difficult to compare median follow up between the two trials given patients were randomised at different stages of treatment.

Comparative effectiveness

Head-to-head trial (NIAGARA) of perioperative durvalumab vs neoadjuvant chemotherapy

6.16 Results of the dual primary endpoint of EFS by BICR as per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) and pCR (based on central pathology review)

in the FAS[16] population of NIAGARA are presented in Table 4 and Table 5, respectively. The EFS Kaplan-Meier (KM) curves are presented in Figure 1.

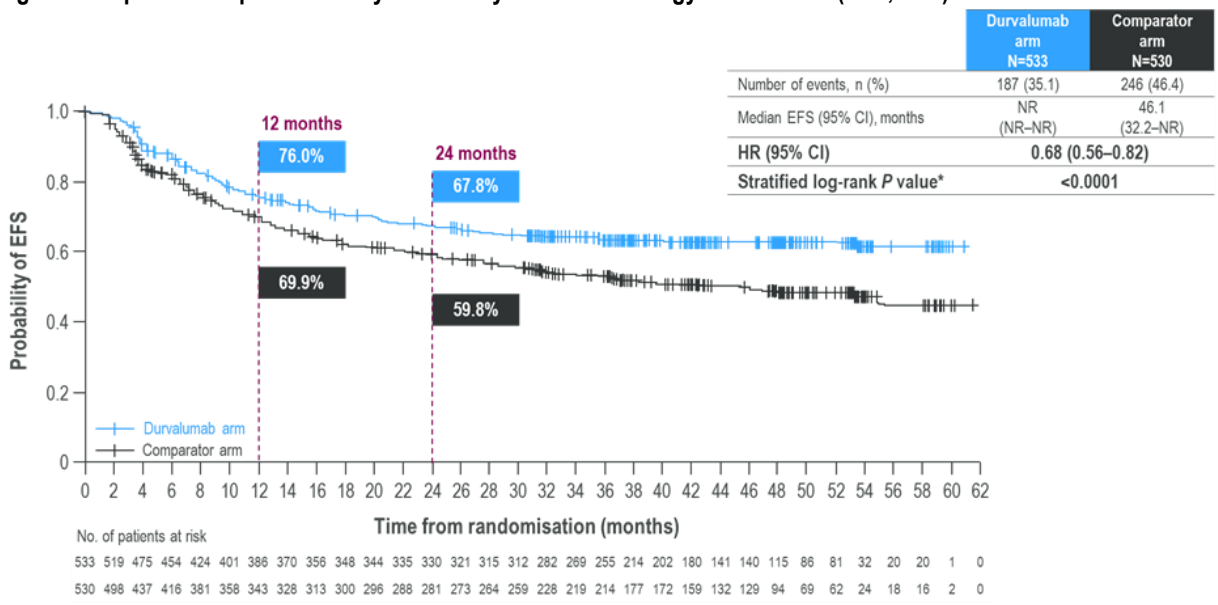
Table 4: Results of EFS by BICR or by Central Pathology in NIAGARA (IA-2, FAS)

	DURVA + GC N = 533	GC N = 530
Number of events (%)	187 (35.1)	246 (46.4)
Progression in patients precluding RC	9 (1.7)	9 (1.7)
Refused or failed to undergo RC in patients with residual disease	40 (7.5)	60 (11.3)
Recurrence of disease after RC	69 (12.9)	87 (16.4)
Death in the absence of other EFS events	67 (12.6)	85 (16.0)
Partial cystectomy medically not justified	1 (0.2)	5 (0.9)
Failure to undergo delayed cystectomy	1 (0.2)	0
Number censored (%)	346 (64.9)	284 (53.6)
Event-free at time of analysis	337 (63.2)	265 (50.0)
Withdrawal by patient	6 (1.1)	16 (3.0)
No neo-adjuvant baseline data	3 (0.6)	3 (0.6)
Lost to follow-up	0	0
Median EFS (months)	NR	46.1
Hazard ratio (95% CI)[a,b]	**0.68 (0.558 - 0.817)**	
p-value[c]	**< 0.0001**	
EFS rate, % (95% CI)[d]		
At month 6	87.7 (84.5 - 90.2)	82.4 (78.8 - 85.4)
At month 12	76.0 (72.0 - 79.4)	69.9 (65.7 - 73.7)
At month 24	67.8 (63.6 - 71.7)	59.8 (55.4 - 64.0)
At month 36	63.7 (59.3 - 67.7)	53.6 (49.0 - 57.9)

Source: Table 2-16, p60 of the submission; Table 21, pp97-98 of the NIAGARA Clinical Study Report
BICR = blinded independent central review; CI = confidence interval; DURVA = durvalumab; EFS = event-free survival; FAS = full analysis set; IA = interim analysis; NR = not reached; RC = radical cystectomy.
[a] Based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per interactive voice response system, with ties handled by the Efron approach.
[b] A hazard ratio < 1 favors DURVA + GC and is associated with a longer EFS than GC.
[c] Calculated using a stratified log-rank test, and the stratification factors are the same as the ones indicated in [a]
[d] Calculated using the Kaplan-Meier technique.
Note: Median EFS was not reached in the DURVA + GC arm; data cutoff: 29 April 2024.

[16] Full analysis set (FAS) in the NIAGARA trial included all randomised patients. Patients who were randomised but did not subsequently receive treatment were included in the FAS in the treatment arm to which they were randomised. The analysis of data using the FAS follows the principles of intention to treat.

Figure 1: Kaplan-Meier plot of EFS by BICR or by Central Pathology in NIAGARA (FAS, IA-2)



Source: Figure 2-3, p61 of the submission; Figure 6, p98 of the NIAGARA Clinical Study Report
BICR = blinded independent central review; CI = confidence interval; EFS = event-free survival; FAS = full analysis set; HR = hazard ratio; IA = interim analysis; NR = not reached
Data cutoff: 29 April 2024

6.17 The median duration of follow-up for all patients for EFS in the durvalumab + GC arm was 34.7 months and 27.7 months in the GC arm. At IA-2, there was a statistically significant reduction in the risk of an EFS event for patients in the durvalumab + GC arm compared with the GC arm (HR 0.68 [95% CI: 0.558, 0.817], p <0.0001). Median EFS was not reached in the durvalumab + GC arm compared with 46.1 months in the GC arm. The EFS KM curves of the two treatment arms separated from approximately Month 2 and remained separated throughout the evaluation period when there were reasonable numbers of patients remaining at risk.

Table 5: pCR based on central pathology review in NIAGARA (FAS)

	Primary analysis		Updated analysis (Jan 2022)	
	DURVA + GC N = 533	**GC N = 530**	**DURVA + GC N = 533**	**GC N = 530**
Patients with pCR, n (%)	180 (33.8)	137 (25.8)	199 (37.3)	146 (27.5)
95% CI (%)[a]	29.8, 38.0	22.2, 29.8	33.2, 41.6	23.8, 31.6
Odds ratio[b]	1.49		1.60	
95% CI for odds ratio[b]	1.138, 1.958		1.227, 2.084	
2-sided p-value[b]	0.0038[c]		**0.0005[d]**	

Source: Table 2-15, p59 of the submission; Table 18 and Table 20, pp88 and 92 of the NIAGARA Clinical Study Report
CI = confidence interval; DURVA = durvalumab; FAS = final analysis set; GC = gemcitabine + cisplatin; pCR, pathological complete response; N = number of patients.
[a] 95% CIs are calculated using the Clopper Pearson method.
[b] Odds ratio and the corresponding CI, and p-value are obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs borderline], tumour stage [T2N0 vs > T2N0] and PD-L1 status [high vs low/negative] per interactive voice response system)
[c] Threshold for significance, p = 0.001.
[d] This was an updated analysis of the primary endpoint and as such was an exploratory analysis with a nominal p-value.
Note: an odds ratio > 1 indicates a result favouring DURVA + GC; Data cutoff: 14 January 2022.

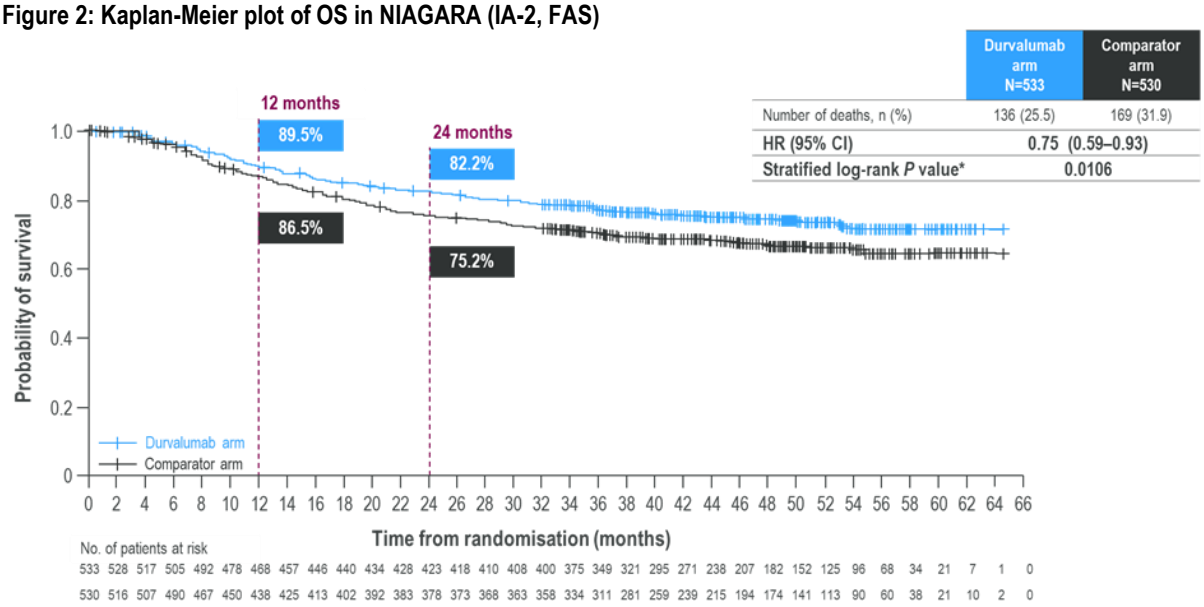
6.18 OS results in the FAS population of NIAGARA are summarised in Table 6, with the corresponding KM plot presented in Figure 2.

Table 6: Results of OS in NIAGARA (IA-2, FAS)

	DURVA + GC N = 533	**GC N = 530**
Number of events, n (%)	136 (25.5)	169 (31.9)
Censored patients, n (%)	397 (74.5%)	361 (68.1%)
Kaplan-Meier estimates (months)		
Median (95% CI)	NR	NR[a]
Hazard ratio (95% CI)[b,c]	**0.75 (0.594 - 0.934)**	
2-sided p-value[d]	**0.0106**	
OS rate, % (95% CI)[e]		
At month 12	96.2 (94.2 - 97.5)	95.6 (93.4 - 97.0)
At month 24	89.5 (86.6 - 91.9)	86.5 (83.3 - 89.2)
At month 36	82.2 (78.7 - 85.2)	75.2 (71.3 - 78.8)
At month 48	76.6 (72.7 - 80.0)	69.8 (65.5 - 73.6)
At month 60	71.1 (66.3 - 75.3)	63.9 (58.9 - 68.5)

Source: Table 2-17, p62 of the submission; Table 24, p111 of the NIAGARA Clinical Study Report (CSR)
CI = confidence interval; DURVA = durvalumab; FAS = final analysis set; GC = gemcitabine + cisplatin; IA = interim analysis; NR = not reached; OS = overall survival; N = number of patients.
[a] Data based on Table 24, p111 of the NIAGARA CSR. In the submission, the median OS in the GC arm was written as '46.1 months' which is incorrect and is inconsistent with the data presented in the KM curve of OS for the GC arm.
[b] Based on stratified Cox PH model; the stratification factors were renal function (adequate vs borderline), tumor stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per interactive voice response system, with ties handled by the Efron approach.
[c] A hazard ratio < 1 favors durvalumab + GC and was associated with a longer OS than GC.
[d] Based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in [b]
[e] Calculated using the Kaplan-Meier technique.
Data cutoff: 29 April 2024

Figure 2: Kaplan-Meier plot of OS in NIAGARA (IA-2, FAS)



Source: Figure 2-4, p62 of the submission; Figure 9, p112 of the NIAGARA Clinical Study Report
CI = confidence interval; HR = hazard ratio; IA = interim analysis; OS = overall survival
Data cutoff: 29 April 2024

6.19 The OS data were immature at the IA-2 data cut off (DCO) and median OS was not reached for either treatment arm. The OS KM curves of the two treatment arms separated from approximately Month 7 and remained separated throughout the evaluation period when there were reasonable number of patients remaining at risk.

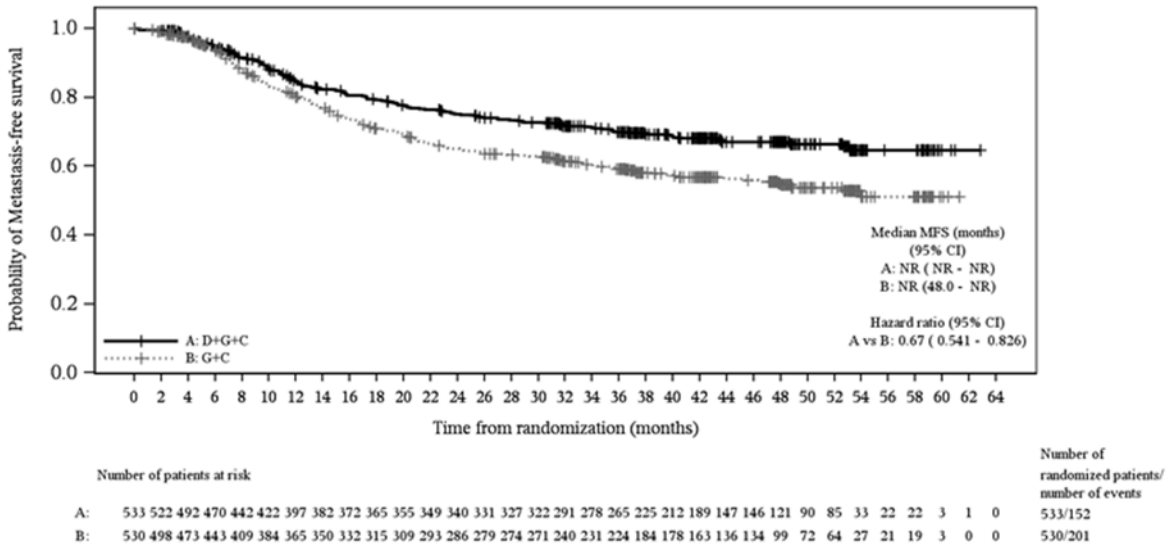
6.20 Metastasis-free survival (MFS) results in the FAS population of NIAGARA are summarised in Table 7 with corresponding KM plots presented in Figure 3. The MFS endpoint was not included in the multiple testing procedure and therefore, the findings are considered descriptive.

Table 7: Results of MFS in NIAGARA (IA-2, FAS)

	DURVA + GC N = 533	GC N = 530
Number of events, n (%) Distant metastasis Death in the absence of distant metastasis	152 (28.5) 54 (10.1) 98 (18.4)	201 (37.9) 77 (14.5) 124 (23.4)
Censored patients, n (%)	381 (71.5)	329 (62.1)
Kaplan-Meier estimates (months) Median (95% CI)	NR	NR
Hazard ratio (95% CI)[a,b] 2-sided p-value[c]	**0. 67 (0.541, 0.826)** 0.0002	
MFS rate, % (95% CI)[d] At month 6 At month 12 At month 24 At month 36	 95.1 (92.8, 96.6) 84.5 (80.9, 87.4) 75.1 (71.0, 78.8) 69.9 (65.5, 73.9)	 93.9 (91.3, 95.7) 80.1 (76.1, 83.4) 65.1 (60.6, 69.3) 59.3 (54.6, 63.7)

Source: Table 2-19, p64 of the submission; Table 26, p118 of the NIAGARA Clinical Study Report
CI = confidence interval; MFS = metastasis-free survival; DURVA = durvalumab; FAS = final analysis set; GC = gemcitabine + cisplatin; IA = interim analysis; N = number of patients; NR = not reached.
[a] Based on stratified Cox PH model; the stratification factors were renal function (adequate vs borderline), tumour stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per interactive voice response system, with ties handled by the Efron approach.
[b] A hazard ratio < 1 favours durvalumab + GC to be associated with a longer OS than GC.
[c] Based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in footnote a. The p-value is nominal as this endpoint is not included in the multiple testing procedure in the trial.
[d] Calculated using the Kaplan-Meier technique, data cutoff: 29 April 2024.

Figure 3: KM plot of MFS in NIAGARA (IA-2, FAS)



Source: Figure 2-6, p65 of the submission; Figure 11, p118 of the NIAGARA Clinical Study Report
CI = confidence interval; MFS = metastasis-free survival; HR = hazard ratio; IA = interim analysis; NR = not reached
Data cutoff: 29 April 2024

6.21 In NIAGARA, health related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life (EORTC QLQ-C30) (global health status (GHS)/QoL, physical functioning, fatigue, and pain scores). Results of time to definitive clinical meaningful deterioration (TTD) showed a slightly lower number of total TTD events in the durvalumab + GC arm

compared to the GC arm (for GHS/QoL: 127 [23.8%] vs 142 [26.8%]; for physical functioning: 134 [25.1%] vs 156 [29.4%]; for pain: 106 [19.9%] vs 125 [23.6%]). For the fatigue domain, the number of total TTD events in the two arms were similar (178 [33.4%] in durvalumab + GC vs 177 [33.4%] in the GC). The evaluation considered that no conclusions could be drawn regarding the impact of the addition of perioperative durvalumab on treated patients' HRQoL compared to chemotherapy alone. HRQoL data from the trial were not used in the economic model.

Indirect treatment comparison based on NIAGARA and CM274 subgroups and construction of a counterfactual arm

6.22 The results of the ITCs of the efficacy endpoints for perioperative durvalumab vs adjuvant nivolumab are presented in Table 8. KM curves of EFS and OS comparing perioperative durvalumab + GC, GC, and GC + adjuvant nivolumab (counterfactual arm) (with re-censoring) are presented in Figure 4 and Figure 5.

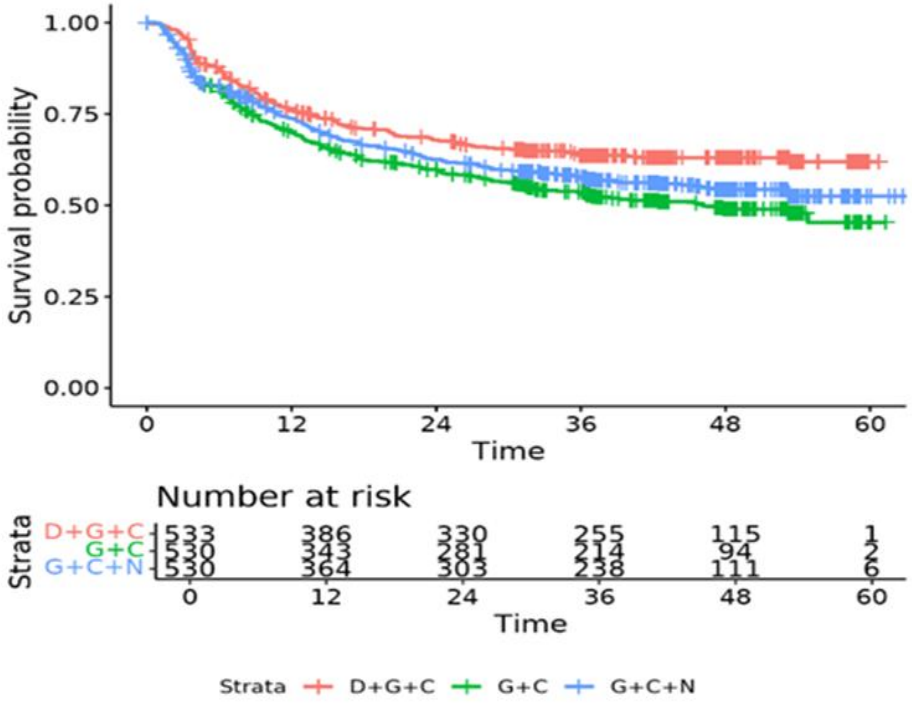
Table 8: Results for the survival time-adjusted ITC of perioperative durvalumab + GC versus GC + adjuvant nivolumab in high-risk MIBC

Scenario	Perioperative durvalumab + GC NAC vs GC NAC + nivolumab		
	Endpoint	HR	95% CI
With re-censoring	EFS	0.781	0.642 - 0.958
	OS	0.793	0.628 - 0.982
Without re-censoring	EFS	0.778	0.639 - 0.947
	OS	0.781	0.623 - 0.962

Source: Table 2-32, p88 of the submission

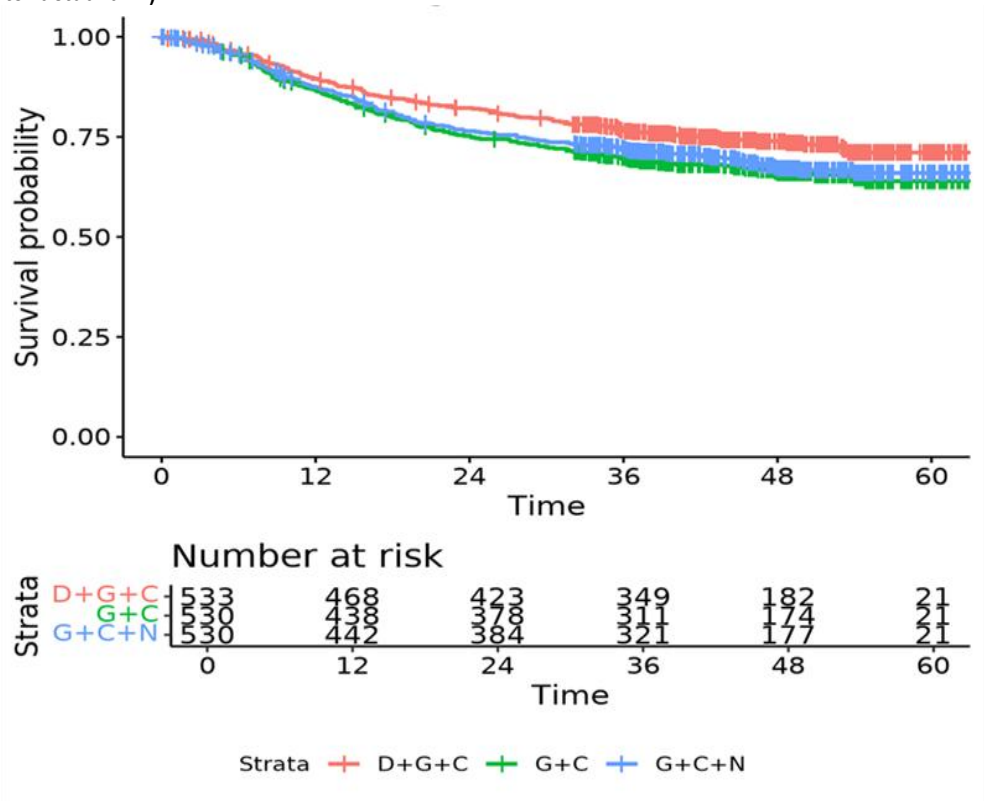
CI = confidence interval; DURVA = durvalumab; EFS = event-free survival; GC = gemcitabine + cisplatin; HR = hazard ratio; NIVO = nivolumab; OS = overall survival.

Figure 4: Kaplan-Meier curves for EFS comparing perioperative durvalumab + GC, GC, and GC + adjuvant nivolumab (counterfactual arm)



Source: Figure 2-7, p87 of the submission
D = durvalumab; EFS = event-free survival; GC = gemcitabine + cisplatin; N = nivolumab

Figure 5: Kaplan-Meier curves for OS comparing perioperative durvalumab + GC, GC, and GC + adjuvant nivolumab (counterfactual arm)



Source: Figure 2-8, p89 of the submission
D = durvalumab; GC = gemcitabine + cisplatin; N = nivolumab; OS = overall survival

Comparative harms

Head-to-head trial (NIAGARA) of perioperative durvalumab vs neoadjuvant chemotherapy

6.23 The overall AEs reported in NIAGARA are summarised in Table 9.

Table 9: Summary of overall AEs in NIAGARA (Safety analysis Set)

	Neoadjuvant treatment period		Adjuvant treatment period	
	DURVA + GC n (%) N = 530	GC n (%) N = 526	DURVA + GC n (%) N = 383	GC[g] n (%) N = 383
Any AE	520 (98.1)	515 (97.9)	331 (86.4)	273 (71.3)
Any treatment[a] -related AE[b]	493 (93.0)	487 (92.6)	156 (40.7)	23 (6.0)
Any DURVA-related AE[b]	248 (46.8)	NA	148 (38.6)	NA
Grade ≥3, n (%)	249 (47.0)	271 (51.5)	119 (31.1)	91 (23.8)
Treatment[a]-related Grade ≥3[b]	201 (37.9)	213 (40.5)	21 (5.5)	3 (0.8)
DURVA-related Grade ≥3[b]	41 (7.7)	NA	17 (4.4)	NA
Serious AEs	125 (23.6)	118 (22.4)	101 (26.4)	85 (22.2)
Treatment [a]-related SAEs[b]	70 (13.2)	61 (11.6)	14 (3.7)	1 (0.3)
DURVA-related SAEs[b]	19 (3.6)	NA	12 (3.1)	NA
AEs leading to death	6 (1.1)	10 (1.9)	7 (1.8)	6 (1.6)
Study treatment [a] -related AEs leading to death[b]	3 (0.6)	2 (0.4)	0	0
DURVA-related AEs leading to death[b]	1 (0.2)	NA	0	NA
AEs leading to discontinuation of study treatment [a]	79 (14.9)	80 (15.2)	30 (7.8)	0
AEs Leading to discontinuation of DURVA	50 (9.4)	NA	30 (7.8)	NA
DURVA-related AEs leading to discontinuation of DURVA[b]	19 (3.6)	NA	19 (5.0)	NA
AEs leading to surgery not done[c]	6 (1.1)	7 (1.3)	NA	NA
AEs leading to a delay in surgery[c,d]	9 (1.7)	6 (1.1)	NA	NA
Any AESI[e]	262 (49.4)	222 (42.2)	208 (54.3)	84 (21.9)
AESIs related to DURVA	148 (27.9)	NA	124 (32.4)	NA
AESIs leading to discontinuation of DURVA	18 (3.4)	NA	17 (4.4)	NA
AESIs leading to a delay in surgery	1 (0.2)	0	NA	NA
Immune-mediated AEs[b]	161 (30.4)	0	127 (33.2)	0

Source: Table 2-23, pp71-72 of the submission; Table 44, pp156-158 of the NIAGARA Clinical Study Report

AE = adverse events; AESI = adverse event of special interest; CI = confidence interval; DURVA = durvalumab; GC = gemcitabine + cisplatin; N = number of patients; NA = not applicable; NC = not calculable; RR = relative risk; SAE = serious adverse events

[a] Study treatment refers to durvalumab/gemcitabine/cisplatin and does not include surgery.

[b] As assessed by the Investigator. Missing responses are counted as related.

[c] Taken from SURG module.

[d] > 56 days after last dose of study treatment in neoadjuvant period.

[e] An AESI is of scientific and medical interest to the study treatment. An AESI may be serious or non-serious.

[f] RRs were calculated during the evaluation, using Stata 15.

[g] Although the arm is labelled GC for simplicity, it is actually active surveillance (not GC) in the adjuvant treatment period.

Note: Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.

6.24 Grade ≥3 durvalumab-related imAEs occurred in 3.0% of patients in the overall period, in 2.1% in the neoadjuvant period, and in 1.0% in the adjuvant period. Durvalumab was discontinued due to imAEs in 4.3% of patients in the overall period, in 2.3% in the neoadjuvant period, and in 2.9% in the adjuvant period. In the neoadjuvant period, one death as a result of imAE occurred in the GC arm but none in the durvalumab + GC arm. In the adjuvant period, no deaths that were considered associated with an imAE occurred in either arm.

6.25 The most commonly reported imAEs in NIAGARA were thyroid events. Serious renal events occurred in 5 (0.9%) patients, and 6 patients (1.1%) in the durvalumab + GC

arm discontinued treatment due this AE. Serious diarrhoea or colitis occurred in 4 (0.8%) patients in the durvalumab + GC arm and all discontinued treatment due this AE. Serious pneumonitis occurred in 3 (0.6%) patients in durvalumab + GC and 1 (0.2%) in GC and resulted in one patient's death in the neoadjuvant period (GC arm).

6.26 Overall, death as an outcome of AEs was similar in the two treatment arms. In the durvalumab + GC arm, there were 27 deaths (5.1%) with 6 (1.1%) occurring in the neoadjuvant period, 15 (3.2%) in the post-surgery period, and 7 (1.8%) in the adjuvant period. In the GC arm, there were 29 deaths (5.5%) with 10 (1.9%) in the neoadjuvant period, 13 (2.9%) in the post-surgery period, and 6 (1.6%) in the adjuvant period. The most commonly reported AEs leading to death in the durvalumab + GC arm were sepsis (4 patients), cardio-respiratory arrest (3 patients), COVID-19 (2 patients), and pulmonary embolism (2 patients), compared to septic shock (3 patients), sepsis (2 patients), and multiple organ dysfunction syndrome (2 patients) in the GC arm.

6.27 The safety outcomes of perioperative durvalumab therapy in NIAGARA appeared to be similar to the known safety profile of the drug. The addition of durvalumab in the neoadjuvant period did not increase the number of failed planned surgeries, compared to GC alone in the trial. Beyond the neoadjuvant period, the association between the treatment received and the AEs reported became unclear. Given NIAGARA has an open-label study design, Investigators and patients were not blinded to the treatment allocation. There is therefore a risk of bias for the results of AEs.

Indirect comparison of perioperative durvalumab (NIAGARA) versus adjuvant nivolumab (CM274)

6.28 Overall AEs and study-drug related AEs in NIAGARA and CM274 in patients who had received NAC are summarised in Table 10 and Table 11. Since NIAGARA was an open-label study (compared with the double-blind study design of CM274), there is potential for bias in the identification and reporting of AEs in NIAGARA because the investigator and patients were not blinded. This has impacted the robustness of the results of AEs in CM274, particularly uncommon AEs.

Table 10: Overall AEs in NIAGARA versus CM274 in patients who had received NAC

	NIAGARA		CM274 (prior NAC)	
	DURVA + GC (N = 530)	GC (N = 526)	Nivolumab (N=155)	PBO (N=156)
AEs (any grade), n (%)	527 (99.4)	525 (99.8)	153 (98.7)	149 (95.5)
Grade ≥ 3 AEs, n (%)	368 (69.4)	355 (67.5)	64 (41.3)	58 (37.2)
Serious AEs (any grade), n (%)	326 (61.5)	287 (54.6)	47 (30.3)	50 (32.1)
Discontinuation of study treatment due to AEs, n (%)	112 (21.1)	80 (15.2)	28 (18.1)	17 (10.9)
Death, n (%)	6 (1.1)	10 (1.9)	95 (27.1)	107 (30.7)

Source: Table 2-34, p91 of the submission; Table 44, pp156-158 of the NIAGARA Clinical Study Report; Table 9, p23 of the nivolumab PSD (November 2023 PBAC Meeting with March 2024 Addendum)

AE = adverse event; DURVA = durvalumab; GC = gemcitabine + cisplatin; N = number of patients; NAC = neoadjuvant chemotherapy; PBO = placebo; PSD = public summary document.

Table 11: Study drug-related AEs in NIAGARA versus CM274 in patients who had received NAC

	Durvalumab + GC		CM274
	Overall N = 530	Adjuvant durvalumab N = 383	Adjuvant nivolumab N = 155
AEs (any grade), n (%)	328 (61.9)	148 (38.6)	127 (81.9)
Grade ≥ 3 AEs, n (%)	61 (11.5)	17 (4.4)	23 (14.8)
Serious AEs (any grade), n (%)	35 (6.6)	12 (3.1)	11 (7.1)
Discontinuation of study treatment due to AEs, n (%)	42 (7.9)	19 (5.0)	18 (11.6)
AEs leading to death, n (%)	1 (0.2)	0	NA[a]

Source: developed during evaluation; Table 2-35, p92 of the submission; Table 44, pp156-158 of the NIAGARA CSR; Table 9, p23 of the nivolumab PSD (November 2023 PBAC Meeting with March 2024 Addendum)
AE = adverse event; CSR = clinical study report; GC = gemcitabine + cisplatin; N = number of patients; NA = not available; NAC = neoadjuvant chemotherapy; PSD = public summary document
[a] Data for nivolumab-related AEs leading to death in patients who had received NAC in CM274 is not available. In the nivolumab arm (including patients not receiving prior NAC, N = 351) in CM274, two treatment-related deaths due to pneumonitis and one treatment-related death due to bowel perforation were reported.

Benefits/harms

6.29 A summary of the comparative benefits and harms for perioperative durvalumab + GC compared to GC in the NIAGARA trial is presented in Table 12.

Table 12: Summary of comparative benefits and harms for perioperative DURVA + GC vs GC[a]

Benefits (FAS population)				
	DURVA + GC	**GC**	**Absolute difference**	**HR (95% CI)**
EFS				
EFS events, n/N (%)	187/533 (35.1%)	246/530 (46.4%)	–	0.68 (0.558 - 0.817) P < 0.0001
Median EFS, months	NR	46.1	–	
EFS rate at 12 months, % (95% CI)	76.0 (72.0, 79.4)	69.9 (65.7, 73.7)	6.1	
EFS rate at 24 months, % (95% CI)	67.8 (63.6, 71.7)	59.8 (55.4, 64.0)	8.0	
EFS rate at 36 months, % (95% CI)	63.7 (59.3, 67.7)	53.6 (49.0, 57.9)	10.4	
OS				
Deaths, n/N (%)	136/533 (25.5%)	169/530 (31.9%)	–	0.75 (0.594 - 0.934) 0.0106
Median OS, months	NR	NR	NE	
Alive at 24 months, % (95% CI)	89.5 (86.6 - 91.9)	86.5 (83.3 - 89.2)	3.0	
Alive at 36 months, % (95% CI)	82.2 (78.7 - 85.2)	75.2 (71.3 - 78.8)	7.0	
Alice at 48 months, % (95% CI)	76.6 (72.7 - 80.0)	69.8 (65.5 - 73.6)	6.8	
Alive at 60 months, % (95% CI)	71.1 (66.3, 75.3)	63.9 (58.9, 68.5)	7.2	

Harms (SAS population)						
	DURVA + GC n/N	**GC n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				DURVA + GC	**GC**	
SAEs	326/530	287/526	1.13 (1.02, 1.25)	61.5	54.6	0.07 (0.01, 0.13)
AEs leading to discontinuation	112/530	50/526	2.22 (1.63, 3.03)	21.1	9.5	0.12 (0.07, 0.16)
AESI	377/530	284/526	1.32 (1.20, 1.45)	71.1	54	0.17 (0.11, 0.23)

Source: Table 2-16, p60, Table 2-17, p62, Table 2-23, pp71-72, and Table 44, pp156-158 of the Durvalumab Clinical Study Report
AESI = Adverse event of special interest; AEs = Adverse Events; CI = Confidence interval; DURVA = durvalumab; EFS = Event free survival; FAS = Full analysis set; GC = Gemcitabine plus cisplatin; HR = Hazard ratio; NAC = Neoadjuvant chemotherapy; NR = Not reached; OS = Overall survival; PFS = Progression free survival; SAS = Safety analysis set.
[a] Efficacy and safety data were from the NIAGARA trial at IA-2, with a median follow-up of 34.7 months in durvalumab + GC and 27.7 months in GC for EFS, and a median follow-up of 42.3 months in durvalumab + GC and 39.6 months in GC for OS.

6.30 On the basis of direct evidence presented by the submission, for every 100 patients treated with neoadjuvant durvalumab in combination with NAC followed by RC and adjuvant durvalumab monotherapy, in comparison with NAC followed by RC, over a median follow-up of 42.3 months:

- Approximately 10 additional patients will remain free of disease progression, recurrence, or death at 3 years.
- Approximately 7 additional patients will remain alive at 5 years.
- Approximately 7 additional patients will experience a SAE.

Clinical claim

Head-to-head trial (NIAGARA) of perioperative durvalumab vs neoadjuvant chemotherapy

6.31 The submission described perioperative durvalumab in combination with GC NAC as superior in terms of effectiveness compared to GC NAC.

6.32 It was noted by the evaluation that nivolumab, as adjuvant treatment for patients with high-risk of disease recurrence, was not accommodated as part of the SoC comparator arm. While it is noted that adjuvant therapy with nivolumab was not available in clinical practice at the time NIAGARA was designed, SoC adjuvant management in Australia now comprises patients at high risk of recurrence who receive nivolumab[17] and all other patients who receive post-surgery active surveillance (consistent with the comparator accepted by ESC/PBAC and the Pre-PBAC response, paragraph 5.3). Therefore, the NIAGARA trial results may show a bigger incremental benefit for durvalumab than would be seen in Australian clinical practice.

6.33 The ESC made the following comments:

- It agreed with the evaluation that the SoC comparator is best represented in Australia by NAC [and RC] followed by post-surgery active surveillance OR adjuvant nivolumab in patients at high risk of recurrence.
- It considered that superior efficacy of perioperative durvalumab arm over the control arm of the NIAGARA trial (NAC [and RC] followed by post-surgery active surveillance) was supported based on the trial results. The PBAC agreed with this conclusion and thus considered that the clinical claim of superiority of perioperative durvalumab over SoC could be supported for the majority of patients (i.e., those not at high risk of recurrent disease, which applies to over 70% of patients).

[17] Nivolumab was recommended for PBS listing in March 2024. Paragraph 9.1 of the PSD (addendum to the November 2023 PSD) states: The PBAC recommended the Section 100 (Efficient Funding of Chemotherapy) Authority Required (telephone/online) listing of nivolumab for the adjuvant treatment of high-risk muscle invasive urothelial carcinoma in patients who have received prior neoadjuvant platinum-based chemotherapy (NAC). The PBAC is satisfied that nivolumab provides, for some patients, a significant improvement in efficacy over watchful waiting.

- It noted that the control arm of the NIAGRA trial does not represent SoC, as it did not include treatment with adjuvant nivolumab for the proportion of patients at high risk of recurrence.

6.34 The submission described perioperative durvalumab in combination with GC NAC as inferior in terms of safety compared to SoC (defined as GC NAC in the NIAGARA trial). The PBAC agreed with both the ESC and the evaluation, that this claim is appropriate based on the evidence presented in the submission; both committees noted that the safety profile of durvalumab is as expected for this class of drug.

Indirect treatment comparison based on NIAGARA and CM274 subgroups and construction of a counterfactual arm

6.35 The submission also described perioperative durvalumab in combination with GC NAC as superior in terms of effectiveness compared to SoC, noting that post-surgery SoC includes the subgroup of patients with high risk of disease recurrence who would be eligible for nivolumab (paragraph 5.3). The ITC approach was based on subgroups from the two trials (NIAGARA and CM274) and the construction of a 'counterfactual' survival time for the control arm of the NIAGARA trial (paragraphs 6.12 to 6.14).

6.36 The evaluation identified key differences across the NIAGARA and CM274 trials with respect to MIBC disease staging, PD-L1 expression, use of prior NAC, proportion of patients at high risk of recurrence, endpoint definitions, and duration of follow up (paragraph 6.15).

6.37 The Pre-PBAC response stated that by matching the NIAGARA and CM274 trials on pathological high-risk status at the adjuvant baseline, restricting efficacy inputs to CM274's prior-NAC subgroup, applying the nivolumab benefit only to patients that meet the eligibility criteria for high risk of recurrence, and reflecting the interchangeability of the EFS/DFS definitions post-surgery, the potential transitivity and generalisability issues do not apply.

6.38 The ESC considered that the superior efficacy of perioperative durvalumab over SoC could be supported but the magnitude of effect is uncertain. The PBAC considered that the data matching performed by the submission ameliorated the differences across the trials and further acknowledged that, as stated in the PSCR, perioperative durvalumab is the first immunotherapy to achieve a statistically significant and clinically meaningful OS benefit in the curative treatment setting for cisplatin-eligible MIBC, noting that the PBAC recommendation for adjuvant nivolumab was based on a subgroup analysis based on only DFS without any OS data. However, the PBAC considered that it would be impossible to completely address all the potential transitivity issues arising from differences in the NIAGARA and CM274 trials and considered that the comparative benefit using this method could not be robustly demonstrated. Overall, the PBAC considered that the evidence does not support superiority for those patients who otherwise might have received adjuvant nivolumab, noting that while perioperative durvalumab could possibly be similar to adjuvant nivolumab, even a claim of non-inferiority would be uncertain.

6.39 The submission described perioperative durvalumab in combination with GC NAC as non-inferior in terms of safety compared adjuvant nivolumab in the subgroup of MIBC patients with high risk of disease recurrence. The evaluation considered that this claim was not adequately supported by the evidence presented in the submission. The key issues included the moderate-to-high risk of bias associated with the safety outcomes in the NIAGARA trial due to its open-label study design and the safety results from a small patient subgroup in the CM274 trial for comparison. The PBAC agreed with the ESC that non-inferior safety is likely reasonable but difficult to accurately assess in a side-by-side comparison.

Economic analysis

6.40 The submission presented cost-effectiveness and cost-utility analyses based on the Phase 3 randomised controlled NIAGARA trial in MIBC, which compared neoadjuvant durvalumab with GC followed by RC and adjuvant durvalumab, versus NAC with GC followed by RC and post-surgery active surveillance. Adjuvant nivolumab is reimbursed for high-risk MIBC patients who have had prior NAC, while avelumab is reimbursed for those with locally advanced or metastatic urothelial cancer not previously treated with immunotherapy. Patients in the GC arm of the NIAGARA trial received post-surgery active surveillance, not nivolumab or avelumab. In contrast, patients in the GC arm of the economic model could receive either drug (but not both) because this is aligned with current clinical practice in Australia.

6.41 The model measured outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained. The key components of the cost utility analysis are presented in Table 13.

Table 13: Summary of model structure, key inputs and rationale

Component	Summary
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years gained
Time horizon	20 years in the model base case vs. a median follow-up of 34.7 months in the durvalumab+GC arm and 27.7 months in the GC arm in the key trial (NIAGARA).
Methods used to generate results	Markov cohort model
Health states	Five core health states: event-free survival (EFS), locoregional recurrence (LR), distant recurrence (DR), cured and death.
Cycle length	One month
Transition probabilities	Probability of disease recurrence in the neoadjuvant setting was based on the NIAGARA trial for each arm. Probability of death post recurrence and the probability of cure after 5 years was based on the inputs used for the economic model for adjuvant nivolumab (Tables 11 and 16, nivolumab PSD, March 2024). Health outcomes associated with adjuvant therapy or treatments for metastatic MIBC were estimated based on the previous PBAC submissions of nivolumab and avelumab in the SoC arm (Table 6, avelumab PSD, March 2021 PBAC meeting and Table 16, nivolumab PSD, March 2024). The transition probabilities for EF to health states LR, DR and death were based on a fixed proportion of events observed in the NIAGARA trial in each treatment arm. A background mortality risk—1.8 times higher than the general population—was applied to bladder cancer patients in the adjuvant EFS health state, based on Australian life tables and previous consideration of adjuvant nivolumab (nivolumab PSD, March 2024).
Extrapolation method	KM data were used until 48 months for EFS. Independent parametric models were fitted to the observed data. Lognormal models were selected for the base case for both the high and low risk subgroups and the Gompertz model was selected for the remaining of the EFS curves. 93% of the incremental LYs (undiscounted) were gained in the extrapolated period.
Health related quality of life	The utility weights from the PBAC consideration of adjuvant nivolumab were used – pre recurrence: 0.83; locoregional recurrence: 0.746; distant recurrence: 0.727. Health state utility was not assumed to vary by treatment arm. A one-off disutility of 0.00423 related to adverse events was applied to the patients receiving durvalumab or nivolumab, based on estimates from previous PBAC submissions for nivolumab.
Costs	Direct treatment costs, costs for disease management (event free and post recurrence), costs for subsequent treatments (nivolumab, avelumab and PBC induction), costs for treatment of AEs were applied. The evaluation considered that the modelled costs for perioperative durvalumab and neoadjuvant GC were appropriate, but the actual price and duration of subsequent nivolumab and avelumab treatments remain uncertain due to reliance on external trial data from PSDs.

Source: Table 3-1, p108 of the submission.

AEs = adverse events; AIC = Akaike information criterion; BIC = Bayesian information criterion; DR = distant recurrence; EF = event free; EFS = event free survival; GC = gemcitabine plus cisplatin; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; LR = locoregional recurrence; LYs = life-years; MIBC = muscle-invasive bladder cancer; MIUC = muscle-invasive urothelial carcinoma; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBC = platinum-based chemotherapy; PSCR = Pre-Sub-Committee Response; PSD = Public Summary Document; QALY = quality-adjusted life year; SoC = standard of care.

6.42 The submission presented a decision analytic Markov cohort model that included five main health states: event-free survival (EFS), locoregional recurrence (LR), distant

recurrence (DR), cured, and death. This core structure is aligned with previous ESC and PBAC advice for the consideration of adjuvant nivolumab (paragraph 7.8, nivolumab Public Summary Document [PSD], July 2022).

6.43 Patients were further stratified according to treatment setting (neoadjuvant vs adjuvant), treatment (durvalumab+GC vs GC +/- nivolumab or avelumab), and subpopulations (RC vs non-RC). After five years, a cure assumption was applied, with cured patients assumed to have mortality rates similar to the general population, adjusted for prior bladder cancer diagnosis. The model distinguishes between RC and non-RC patients, tracking their transitions between health states after neoadjuvant and adjuvant treatments. RC patients cannot recur during early cycles and move to "event free" states based on treatment and risk. Non-RC patients face recurrence risk earlier and their outcomes were determined by treatment type, recurrence patterns, and eligibility for further therapies. The submission stated that the model structure, Markov cohort approach, and selected health states appropriately reflected key aspects of current and proposed clinical pathways for early MIBC and were consistent with a previous submission of adjuvant therapy presented to the PBAC (nivolumab PSD, March 2024). However, the evaluation considered that the chosen stratification introduced complexity and resulted in model validation issues that remain unresolved.

6.44 The PSCR stated that it was necessary to ensure the model was applicable to treatment practices in Australia by stratifying the trial data by treatment setting, treatment group and RC, and disagreed with the evaluation that the stratification was complex. It stated that the model uses subgroup data to populate the event risks in each of the stratum / health states, which allows the application of the treatment effect of adjuvant nivolumab on event risks in the high-risk population, and allows appropriate downstream treatment options to be implemented, such as patients with prior immunotherapy not receiving a second immunotherapy treatment, consistent with PBS restrictions. The ESC agreed with the PSCR that an advantage of the model's structure was its ability to incorporate the effect of downstream treatment options, however considered that the multiple stratifications for treatment setting, treatment group, and subpopulations led to unnecessary complexity and that reducing the level of stratification within health states may have improved model transparency and validity. The ESC also considered that modelling all OS transition probabilities directly from NIAGARA trial data, with adjustments for improved survival in high-risk patients receiving nivolumab or avelumab in the comparator arm, could allow for a more transparent testing of OS assumptions compared to the submission's approach.

6.45 The submission applied a time horizon of 20 years in the base case, based on a median follow-up of 34.7 months in the durvalumab + GC arm and 27.7 months in the GC arm in the key trial (NIAGARA trial). The ESC previously considered that a 15-year horizon was appropriate for the consideration of adjuvant nivolumab with patients with MIUC who have undergone resection surgery and at high risk of recurrence (paragraph 6.57, nivolumab PSD, March 2024), but given durvalumab's potential benefits in the neoadjuvant setting, which also includes lower risk patients, the evaluation noted that

a longer period may be justified. The ESC considered that 15 years would be a more reasonable time horizon, given the expected age and health status of this patient cohort. While the Pre-PBAC response maintained that a longer time period is justified given the OS benefit of durvalumab in a curative setting,[18] it agreed to reduce the time horizon from the base case of 20 years to 15 years to be consistent with previous PBAC decision-making for adjuvant nivolumab.

6.46 The NIAGARA trial data (durvalumab + NAC + RC vs NAC + RC) were used for transition probabilities for EF to health states LR, DR and death, while external trial data were applied for adjuvant nivolumab in the comparator arm (CM274), and OS was informed by an avelumab study (JAVELIN Bladder 100) in those who had progressed in the comparator arm. The PSCR stated that the submission's approach combines robust, high-quality randomised controlled trial data from NIAGARA for the initial treatment period, including the primary endpoint data in full, with PBAC-recommended external assumptions for all downstream treatments and long-term outcomes and provides a sound foundation for decision making. It stated that the methodology accounts for both the demonstrated clinical benefits from the NIAGARA trial and the need for real-world applicability as patients transition through treatment lines.

6.47 The EFS and disease-free survival (DFS) curves in the NIAGARA trial were used to derive risk of recurrence in the model. The model assumed that all patients who were disease-free yet at high risk of recurrence following NAC and RC (representing 27.6% of the overall SoC population) would receive nivolumab, which was incorporated into the economic model to reflect current clinical practice.

6.48 Conditional probability estimation and survival matched ITC were used to disaggregate EFS data into the required subgroups (based on surgery status, high-risk or low risk of recurrence) for analysis.

6.49 The NIAGARA trial data were used for transitions from the event free health state, while a HR from CM274 was applied to reflect adjuvant nivolumab efficacy in the comparator arm (HR = 0.54 applied to the high-risk EFS curve for GC; para 7.3, nivolumab PSD, March 2024). This effect was applied to the GC arm's high-risk subgroup, assuming proportional hazards—an assumption that is often violated with immunotherapies versus chemotherapy, potentially misrepresenting time-varying effects. Sensitivity analyses showed the ICER was highly sensitive to the assumed treatment effect of nivolumab, with greater efficacy increasing the ICER (see Table 18 below).

6.50 Observed KM EFS or DFS data were used until 48 months for risk of recurrence. Using Gebski criterion 2, the truncation point of the KM data could have been extended to 56 months for both durvalumab + GC (20 patients at risk, 61% survival) and GC (18 patients at risk, 43% survival), exceeding the base case's selected truncation point of

[18] However, the quoted OS benefit is from the NIAGARA trial, which does not include treatment with adjuvant nivolumab in the control arm for patients at high risk of recurrence.

48 months. The EFS curves were mostly flat after 32 and 34 months for durvalumab + GC and DC, respectively, which may have been influenced by high levels of censoring. Earlier truncation points tended to reduce the incremental LYs generated in the model.

6.51 Independent parametric models were fitted to the disaggregated observed EFS data. The lognormal models were selected for the base case for both high and low risk subgroups and the Gompertz model was selected for the remaining of the EFS curves. The evaluation considered that the Weibull function would also be clinically plausible for extrapolating all the EFS curves in the submission's base case.[19] This increased the ICER by 7% (evaluation's re-specified base case). The Pre-PBAC response stated that given a cure is a reasonable assumption after 5 years, the Weibull function is not appropriate as it allows patients to continue to recur beyond this period. The response maintained that the submission's base case used the most appropriate and best-fitting curves.

6.52 Recurrence events in the Markov model were assigned using fixed transition probabilities from the NIAGARA trial data, distinguishing fatal, locoregional, and distant recurrences according to neoadjuvant or adjuvant phases. Recurrences were assumed to occur for up to 5 years, after which cure was assumed and only locoregional progression to distant metastasis was modelled. The cured assumption was applied to all patients who were event free after 5 years. A cure assumption at five years in MIUC was previously considered likely reasonable by the PBAC (paragraph 6.49, nivolumab PSD, July 2022) and the ESC (paragraph 6.57, nivolumab PSD, March 2024). The evaluation noted that the submission did not justify applying the same cut-off time for a cure across the model arms. It may not be reasonable to assume that remaining event free at 5 years in the absence of immunotherapy represents the same likelihood of cure as having received immunotherapy in the neoadjuvant and adjuvant setting. Where the addition of durvalumab results in tumour suppression, an event that otherwise may have occurred close to 5 years may be time-shifted to beyond 5 years. When the cure assumption for the durvalumab treatment arm was postponed by 6 months, the ICERs increased by 16%.

6.53 Transition probability from LR to DR health state (0.2811 per month) was estimated using data from the JAVELIN Bladder 100 trial, applying a median time to progression of 2.1 months for both treatment arms.

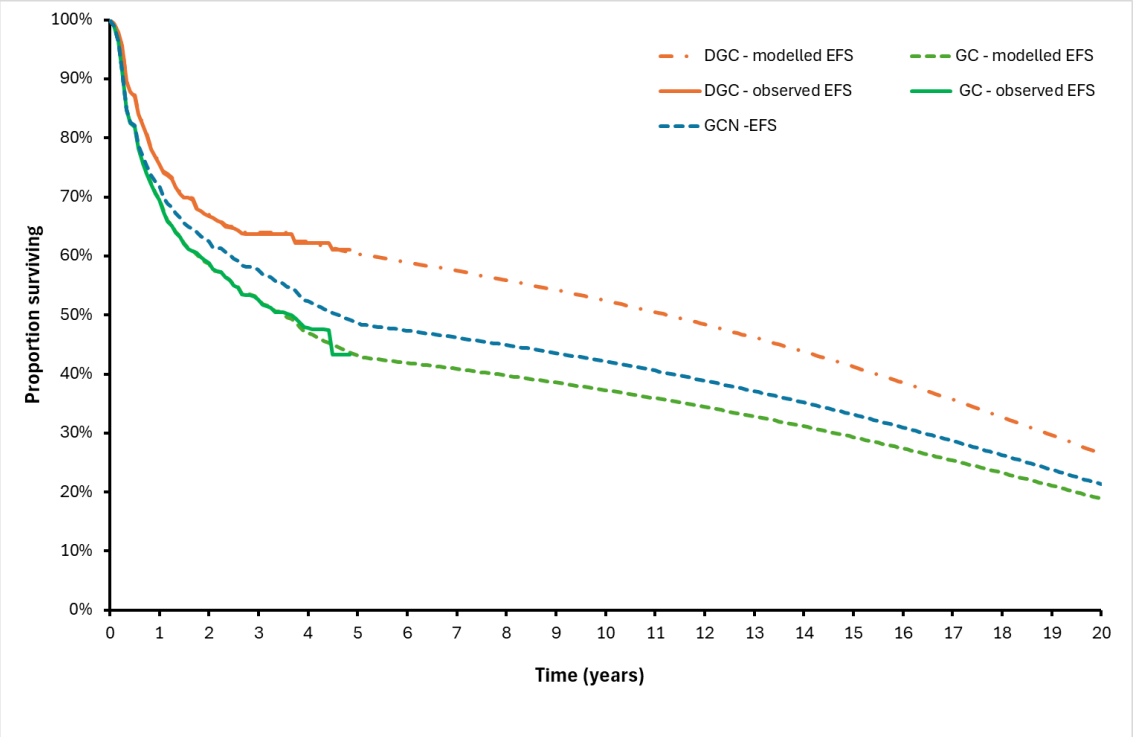
6.54 The DR survival estimates were based on median OS of 24.9 months and 16.3 months for patients who were and were not treated with avelumab (43% uptake assumed) in the metastatic setting, respectively, based on previously accepted estimates (Table

[19] Initially, the evaluation considered that the submission had incorrectly ranked the Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC) values for parametric models in descending order and therefore selected the worst fitting models for extrapolating the EFS curves. The PSCR clarified that the submission had neglected to notate the AIC and BIC values as negative and noted that the best fitting models and base case selection from the submission is accurate.

16, nivolumab PSD, March 2024). The evaluation noted that using a single median ignores the full distribution of survival (the tail of the curve is critical in immunotherapy, where long-term survivors exist).

6.55 Comparisons of the observed KM EFS and OS data to the modelled curves for both arms are presented in Figure 6 and Figure 7 for both treatment arms. From the figure it is evident that patients treated with durvalumab + GC spend a longer time in the EFS/cured health state compared to those treated with SoC.

Figure 6: Modelled versus observed EFS curves (submission base case)



Source: constructed during the evaluation using Attachment 3.2 'Model_Inputs_workbook_Jul25.xls' provided with the submission
DGC = durvalumab + GC; EFS = event free survival; GC = gemcitabine plus cisplatin; GCN = GC arm with the addition of avelumab and nivolumab in eligible patients.

6.56 The treatment of resectable MIBC in the Australian setting involves the use of nivolumab in the adjuvant setting and avelumab in the recurrent setting. The ESC noted that as the treatments received in the NIAGARA study do not include nivolumab or avelumab, the submission's economic evaluation has sought to structure the model to permit the inclusion of these treatments. The model is informed by the EFS/DFS curves, high risk status (to determine eligibility for nivolumab in the comparator arm) and distributions across LR, DR and death in the absence of recurrence directly from the NIAGARA study. The model traces appear to reasonably reflect the EFS/DFS curves in the NIAGARA study, and the evaluation considered that this is appropriate. After including the use of adjuvant nivolumab, the EFS/DFS curve for the comparator arm is slightly above the trial comparator arm. The ESC considered this to be reasonable but noted that the magnitude of this benefit is difficult to validate given the uncertainty associated with the ITC (paragraph 6.38).

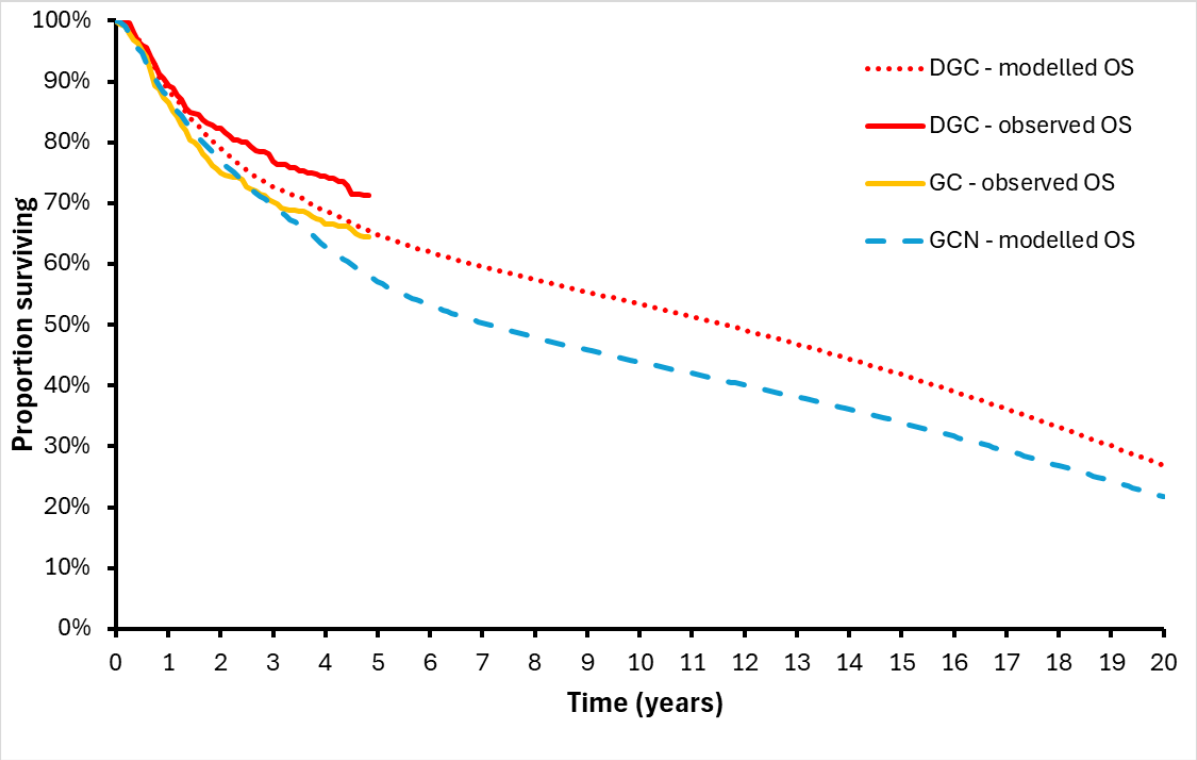
6.57 The modelled OS appears to underestimate the trial OS data after the second and or third year following durvalumab + GC and GC treatment, respectively. The underestimate is more noticeable in the GC arm. The modelled OS was not consistent with internal (NIAGARA KM curves) or external benchmarks (Australian BLADDA registry), which showed higher OS estimates for resected MIBC than produced by the model. The PSCR stated that the underestimation of OS in the durvalumab model is a direct consequence of the conservative assumptions used by the PBAC for the [adjuvant] nivolumab model, reflecting the lack of OS data provided in the nivolumab submission. The PSCR stated that this approach is biased against durvalumab because the model uses the same assumptions used in the nivolumab assessment despite perioperative durvalumab showing an OS benefit where nivolumab did not. However, the model may favour the treatment group if it undervalues later treatments' effectiveness.

6.58 The submission presented a sensitivity analysis calibrating modelled post progression survival to match modelled OS with observed OS at 48 months (Figure 7). To enable accurate prediction of outcomes from the NIAGARA trial, calibration factors were applied to the transition from DR to death in both treatment arms. The purpose of this calibration was to adjust these values so that the model would precisely replicate the proportion of patients alive at 48 months in each arm of the NIAGARA trial (74.5% for durvalumab + GC and 66.5% for GC). This analysis identified calibration factors of 2.07 and 2.05 to be applied to median OS used to estimate transitions from DR health state to dead for the durvalumab + GC arm and GC arm, respectively. The submission argued that the calibrated version of the model could be considered biased against durvalumab + GC because it inflates the survival benefits of avelumab in the comparator arm of the model from 8.6 months (24.9-16.3) to 18.5 months (54.0-35.5). The ESC noted this analysis increased the ICER by 16% (Table 18)

6.59 Figure 8 shows the modelled and observed OS curves for the SoC treatment arm, illustrating the effects of applying a calibration factor to align the modelled data with the observed OS KM data for the GC arm, as well as the influence of nivolumab and avelumab on the OS curve. The ESC noted the limitations of this calibration raised by the evaluation, that survival post recurrence is not the only driver for the predicted mortality in the model. The model also used treatment based fixed proportions from the NIAGARA trial to allocate patients to fatal (dead) and non-fatal recurrence health states (LR and DR), ignoring time-dependent hazard rates. Since recurrence risk changes over time, and the type of recurrence may also change over time, the use of static proportions moving from event free to death, LR and DR may skew predicted OS. However, the ESC also acknowledged that more robust data are unlikely to be available to inform downstream transitions required and it may be a pragmatic approach to refine downstream transitions to calibrate the OS curves in the model to those observed in the NIAGARA study. The Pre-PBAC response maintained that an 18.5 month OS gain from 10 months of avelumab treatment in the metastatic setting is clinically implausible and would inappropriately penalise durvalumab given that the

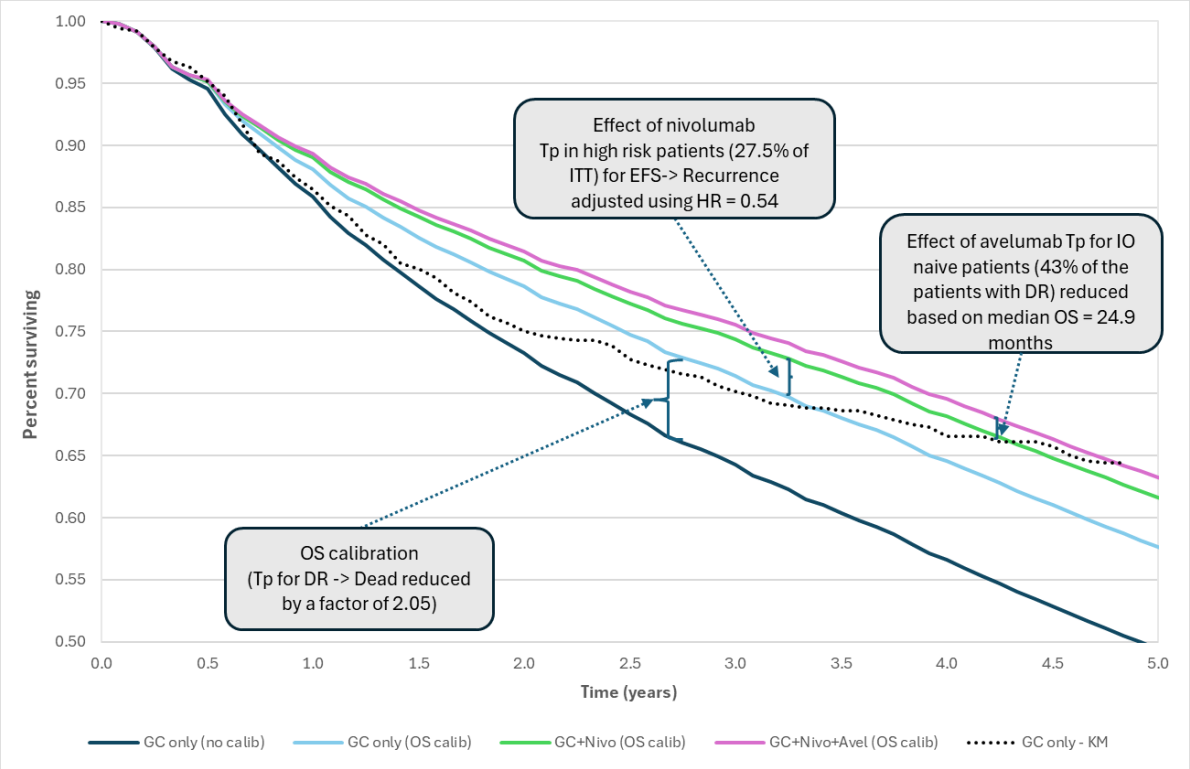
NIAGARA trial provides OS data. The response stated that it would be appropriate to use the same downstream survival assumptions as the adjuvant nivolumab model (and not apply the OS calibrations), and this approach would be consistent with previous PBAC decision-making.

Figure 7: Modelled versus observed OS curves



Source: constructed during the evaluation using Attachment 3.2 'Model_Inputs_workbook_Jul25.xls' provided with the submission
DGC = durvalumab + GC; GC = gemcitabine plus cisplatin; GCN = GC arm with the addition of avelumab and nivolumab in eligible patients; OS = overall survival.

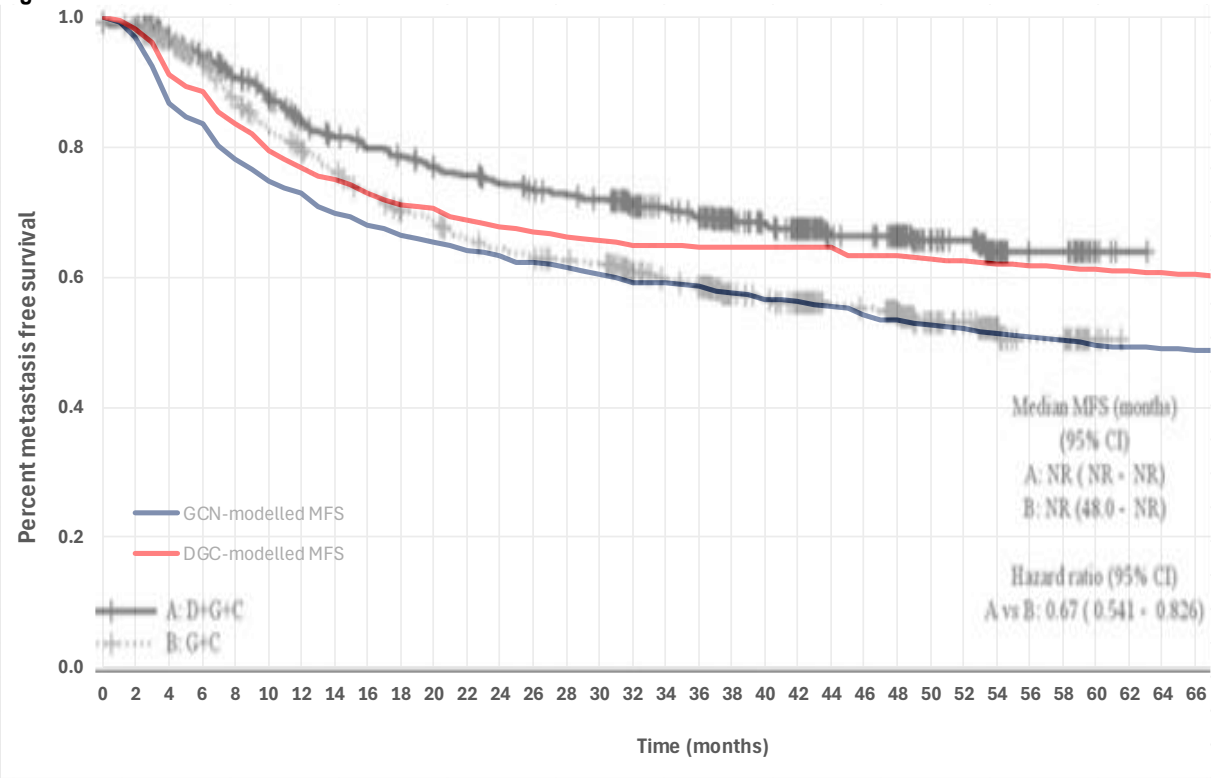
Figure 8: Modelled versus observed KM OS curves for SoC showing modelled incremental benefits of additional therapies



Source: constructed during the evaluation using Attachment 3.2 'Model_Inputs_workbook_Jul25.xls' provided with the submission
DR = distant recurrence; EFS = event free survival; GC = gemcitabine plus cisplatin; GC +Nivolumab = GC arm with the addition of nivolumab in eligible patients; GC+Nivolumab+Avel = GC arm with the addition of avelumab and nivolumab in eligible patients; OS = overall survival; SoC = standard of care; Tp = transition probability.
Respecified base case included better fitting Weibull parametric functions for extrapolating all EFs curves and had the cure function, that was incorrectly applied in the submission's base case to the second cycle of recurrence, switched off in the locoregional and distant recurrence health sates.

6.60 Additional validation was conducted during the evaluation comparing the modelled distant recurrence-free survival (DRFS) curves with observed metastasis-free survival (MFS) from the NIAGARA trial (Figure 9). The model appears to underestimate DRFS compared to trial data early in the model because it used fixed distribution for recurrence events. This caused differences between what the model predicted and what was seen in the trial. As a result, the evaluation noted that the model may favour the treatment group if it underestimates how effective later treatments are. Use of fixed distributions breaks internal consistency between EFS, OS and post-recurrence health states. The split for recurrence events should be calibrated so that the total events and deaths match trial KM data.

Figure 9: Observed versus modelled metastasis or distant recurrence free survival



Source: constructed during the evaluation using Figure 11, NIAGARA CSR and "Attachment 3.2 Model_Inputs_Workbook_Jul25.xlsx" provided with the submission.
DGC = durvalumab + GC; GC = gemcitabine plus cisplatin; GCN = GC arm with the addition of avelumab and nivolumab in eligible patients.

6.61 The submission applied the utility weights from the PBAC consideration of adjuvant nivolumab (pre recurrence: 0.83; LR: 0.746; DR: 0.727) arguing that relatively higher utility weights collected from the NIAGARA trial (baseline: 0.93, pre-regression: 0.92; post-regression: 0.89) were likely implausible. The ICER was not found to be sensitive to the alternate utility estimates for event free, pre-regression and post-regression when tested in a sensitivity analysis. The submission claimed that nivolumab and durvalumab have similar safety profiles and applied similar disutility for treatment associated AE (0.00423). The evaluation considered that this was reasonable.

6.62 The treatment costs were estimated based on the mean number of doses of durvalumab (8.8) and GC (3.8 cycles with durvalumab and 3.6 cycles in the comparator arm) from the NIAGARA trial. No patients remained on durvalumab treatment at the time of the data cut. Therefore, the evaluation considered that the use of the trial reported mean duration of treatment was reasonable.

6.63 The model included subsequent use of nivolumab in the high-risk patients post-RC in the comparator arm (usage: 27.6%). The economic model priced nivolumab (480 mg; published prices) at $9,739.06 (private hospital) and $9,560.79 (public hospital), with patients receiving an average of 8.9 cycles every four weeks as consistent with nivolumab evaluation (Table 17, nivolumab PSD, March 2024). A total treatment cost

of $[redacted] per patient was estimated after applying a hypothetical [redacted]% discount (to account for the undisclosed special pricing arrangement).

6.64 A proportion of patients with metastatic recurrence and without prior use of nivolumab were eligible for avelumab in the SoC arm of the model. The base case assumes uptake of 43% (nivolumab PSD, March 2024). The dispensed prices for avelumab (800 mg, published prices) were $5,367.06 in the private sector and $5,249.19 in the public sector. The model used a public/private treatment split and a hypothetical discount of [redacted]% (to account for the undisclosed special pricing arrangement) to estimate the cost per dose of avelumab, $[redacted]. A total treatment cost of $[redacted] per patient was estimated based on a mean treatment duration of 10 months (over 21.67 cycles).

6.65 Key model drivers are presented in Table 14.

Table 14: Key drivers of the model

Description	Method/Value	Impact Base case: $[redacted][1]/QALY gained.
Time horizon	20 years in the model base case vs. a median follow-up of 34.7 months in the durvalumab +GC arm and 27.7 months in the GC arm in the key trial (NIAGARA trial).	High, favours durvalumab + GC. Use of time horizon of 15 years increased the ICER to $[redacted][1]/QALY gained.
OS projections	The modelled OS was not consistent with internal (NIAGARA KM curves) or external benchmarks (Australian BLADDA registry) and was likely underestimated.	Moderate, favours durvalumab + GC. Calibrating modelled OS curves to match observed OS, increased the ICER to $[redacted][1]/QALY gained
Nivolumab effectiveness	Values for lower (HR: 0.41) and upper confidence limit (HR:0.72) used for effectiveness of adjuvant nivolumab (HR:0.54 applied in the base case).	Moderate. Increasing effectiveness of nivolumab (HR: 0.41) increased the ICER to $[redacted][1]/QALY gained

Source: Table ES 12, pp11-12 of the submission.
GC = Gemcitabine plus cisplatin; HR = Hazard ratio; ICER = incremental cost-effectiveness ratio; MIUC = Muscle-invasive urothelial carcinoma; OS = Overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PSD = Public Summary Document; QALY = Quality-adjusted life year; SoC = Standard of care; SPA = Special pricing arrangement
The redacted values correspond to the following range:
[1] *$35,000 to < $45,000*

6.66 The submission provided an economic evaluation in 13 steps, which included OS calibration to the NIAGARA trial through to step 8. The submission incorrectly applied cure in the LR and DR health states within the model to the second cycle of recurrence rather than after surviving five years in these health states. The evaluation performed a more concise stepped analysis starting with the trial-based time horizon and progressing to a fully modelled evaluation. The Weibull function was selected for extrapolation and the assumption of cure in LR and DR was removed in the stepped analysis. Step 1 describes a modelled evaluation for a 48-month time horizon matched to trial period. Results for stepped analysis are presented in Table 15.

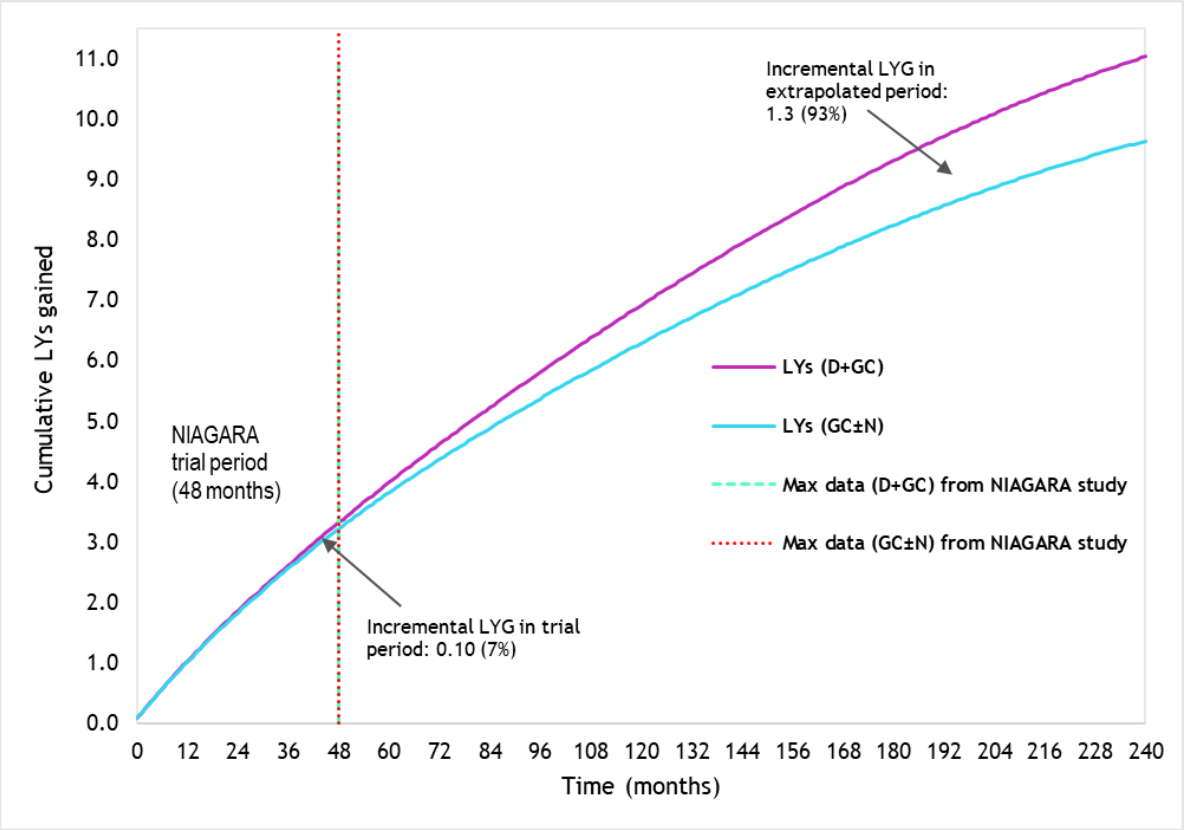
Table 15: Results of the stepped economic evaluation, conducted during the evaluation

Step and component	Durva + GC	SoC	Increment[a]
Step 1: Costs and outcomes for study drugs only (trial based 48-month time horizon)			
Costs	$[redacted]	$2,609	$[redacted]
LYG	2.9651	2.7646	0.2005
Incremental cost/extra LYG gained			$[redacted][1]
Step 2: Include cost of RC, adverse events and disease monitoring			
Costs	$[redacted]	$24,266	$[redacted]
LYG	2.9651	2.7646	0.2005
Incremental cost/extra LYG gained			$[redacted][1]
Step 3: Include adjuvant nivolumab outcomes and costs			
Costs	$[redacted]	$36,562	$[redacted]
LYG	2.9651	2.8437	0.1214
Incremental cost/extra LYG gained			$[redacted][2]
Step 4: Include LR and DR downstream treatment costs including avelumab use for DR			
Costs	$[redacted]	$44,925	$[redacted]
LYG	2.9651	2.8786	0.0865
Incremental cost/extra LYG gained			$[redacted][2]
Step 5: Time horizon extended to 20 years (using better fitting Weibull function)			
Costs	$[redacted]	$58,141	$[redacted]
LYG	6.8105	5.8622	0.9484
Incremental cost/extra LYG gained			$[redacted][3]
Step 6: Allow cure in all event free after 5 years			
Costs	$[redacted]	$48,202	$[redacted]
LYG	7.3870	6.5977	0.7894
Incremental cost/extra LYG gained			$[redacted][3]
Step 7: Transformation to QALYs			
Costs	$[redacted]	$48,202	$[redacted]
QALYs	6.0801	5.4054	0.6747
Incremental cost/extra QALY gained (respecified base case) [b]			$[redacted][4]

Source: Constructed during the evaluation from the Attachment 3.1 TreeAgeModel_Jul25.trex provided with the submission.
DR = Distant recurrence; GC = Gemcitabine plus cisplatin; LR = Locoregional recurrence; QALYs = Quality-adjusted life years; SoC = Standard of care.
[a] Uses the published prices of nivolumab and avelumab with a hypothetical [redacted]% discount
[b] Respecified base case included Weibull parametric functions for extrapolating all EFs curves and had the cure function, that was incorrectly applied in the submission's base case to the second cycle of recurrence, switched off in the locoregional and distant recurrence health sates.
The redacted values correspond to the following ranges:
[1] *$155,000 to < $255,000*
[2] *$255,000 to < $355,000*
[3] *$25,000 to < $35,000*
[4] *$35,000 to < $45,000*

6.67 Figure 10 depicts life years gained over the time horizon. The base case economic evaluation indicates that 93% of incremental LYs are accrued during the extrapolated period.

Figure 10: Cumulative LYs gained over the time horizon, undiscounted



Source: Constructed during the evaluation using the Attachment 3.1 'TreeAgeModel_Jul25.trex' provided with the submission.
C = cisplatin; D = durvalumab; G = gemcitabine; GC±N = GC arm with the addition of avelumab and nivolumab in eligible patients; LYG = life years gained; LYs = life years.

6.68 The disaggregated summary for costs and health outcomes is presented in Table 16. Costs associated with durvalumab acquisition account for most of the incremental costs between the two groups. Most cost savings are due to nivolumab and avelumab drug costs. The estimates for nivolumab and avelumab are based on published prices with a [redacted]% discount applied (to account for the undisclosed special pricing arrangement). Variability in the treatment duration for nivolumab and avelumab influences the total incremental cost.

Table 16: Disaggregated summary of cost impacts and health outcomes for respecified base case [a] (discounted)

Resource item	Durva + GC	SoC	Increment	% of total increment
Costs				
Durvalumab	$[redacted]	$0	$[redacted]	[redacted]%
GC	$1,796	$1,701	$95	[redacted]%
Administration of infusion	$1,588	$907	$680	[redacted]%
Hospital cost (RC)	$11,855	$11,210	$645	[redacted]%
Subsequent treatment with administration cost				
–Adjuvant nivolumab	$0	$[redacted] [b]	–$[redacted] [b]	–[redacted]%
–GC induction for LR or DR	$1,282	$2,045	–$763	–[redacted]%
–Avelumab for DR	$0	$[redacted] [b]	–$[redacted] [b]	–[redacted]%
Disease management	$13,117	$13,554	–$437	–[redacted]%
Management of AEs	$657	$178	$479	[redacted]%
Total cost	**$[redacted]**	**$48,202** [b]	**$[redacted]** [b]	
Outcomes				
Event free LYs	6.9286	5.9202	1.0084	127.74%
LR LYs	0.0154	0.0145	0.0009	0.12%
DR LYs	0.4430	0.6629	-0.2199	-27.86%
Total LYs	**7.3870**	**6.5977**	**0.7894**	
Event free QALYs	5.6935	4.8204	0.8731	129.42%
LR QALYs	0.0123	0.0115	0.0008	0.12%
DR QALYs	0.3742	0.5735	-0.1993	-29.54%
Total QALYs	**6.0801**	**5.4054**	**0.6747**	

Source: Table 3-26 and Table 3-27, p170 of the submission regenerated with respecified base case results using Attachment 3.1 'TreeAgeModel_Jul25.trex' provided with the submission.

AEs = Adverse Events; DR = Distant recurrence; GC = Gemcitabine plus cisplatin; LR = Locoregional recurrence; LYs = Life-years; QALYs = Quality-adjusted life years; SoC = Standard of care.

[a] Respecified base case included better fitting Weibull parametric functions for extrapolating all EFs curves and had the cure function, that was incorrectly applied in the submission's base case to the second cycle of recurrence, switched off in the locoregional and distant recurrence health sates.

[b] Uses the published prices of nivolumab and avelumab with a hypothetical [redacted]% discount.

6.69 The results of the Markov model reflect a mixture of immunotherapy options for the treatment of MIBC in the SoC arm, of which nivolumab was used in around 27.6% of ITT patients in the adjuvant setting and avelumab in around 11.3% of the ITT patients in the distant recurrence setting. No other subsequent therapies were modelled for the durvalumab + GC arm. Table 17 presents the health and outcomes, and modelled cost-effectiveness associated with each subsequent treatment option in the SoC arm. These figures assume a [redacted]% discount for avelumab and nivolumab from their published prices.

Table 17: Incremental cost-effectiveness of modelled subsequent therapies in the SoC arm (using respecified base case) [a,b]

	Durva + GC	SoC	Increment
(A) Include only costs and outcomes related to study drugs only Assuming no use of subsequent immunotherapies in the SoC arm.			
Costs	$ [redacted]	$28,939	$ [redacted]
QALYs	6.0801	4.9383	1.1418
Incremental cost/extra QALY gained			$ [redacted] [1]
(B) Include only nivolumab costs and outcomes in the SoC arm Assuming 27.6% patients with high risk of recurrence would receive adjuvant nivolumab in the SoC arm compared to no other subsequent therapy in the durvalumab + GC arm.			
Costs	$ [redacted]	$41,006	$ [redacted]
QALYs	6.0801	5.3400	0.7401
Incremental cost/extra QALY gained			$ [redacted] [1]
(C) Include only avelumab costs and outcomes in the SoC arm Assuming no prior exposure to immunotherapy in the SoC arm, 43% of the patients with distant recurrence will receive avelumab.			
Costs	$ [redacted]	$38,644	$ [redacted]
QALYs	6.0801	5.0266	1.0535
Incremental cost/extra QALY gained			$ [redacted] [2]
(D) Include both nivolumab and avelumab costs and outcomes in the SoC arm Assuming 27.6% patients with high risk of recurrence would receive adjuvant nivolumab, and 43% of the patients with no prior exposure to nivolumab will receive avelumab on distant recurrence in the SoC arm.			
Costs	$ [redacted]	$48,202	$ [redacted]
QALYs	6.0801	5.4054	0.6747
Incremental cost/extra QALY gained			$ [redacted] [1]

Source: analyses performed during the evaluation using Attachment 3.1 'TreeAgeModel_Jul25.trex' provided with the submission.
GC = Gemcitabine plus cisplatin; QALY = Quality-adjusted life year; QALYs = Quality-adjusted life years; SoC = Standard of care.
[a] Respecified base case included better fitting Weibull parametric functions for extrapolating all EFs curves and had the cure function, that was incorrectly applied in the submission's base case to the second cycle of recurrence, switched off in the locoregional and distant recurrence health states.
[b] Uses the published prices of nivolumab and avelumab with a hypothetical [redacted]% discount
The redacted values correspond to the following ranges:
[1] *$35,000 to < $45,000*
[2] *$25,000 to < $35,000*

6.70 The results of key sensitivity analyses are summarised in Table 18.

Table 18: Sensitivity analyses (evaluation respecified base case) [a,b]

	Incremental cost	Incremental QALY	ICER	% change
Respecified base case [a]	**$[redacted]**	**0.6747**	**$[redacted][1]**	**–**
Discount rate (base case: 5%)				
• 0%	$[redacted]	1.1076	$[redacted][2]	–[redacted]%
• 3.50%	$[redacted]	0.7764	$[redacted][3]	–[redacted]%
Time horizon (base case: 20 years)				
• 15 years **(#1)**	$[redacted]	0.5653	$[redacted][1]	[redacted]%
• 25 years	$[redacted]	0.7226	$[redacted][3]	–[redacted]%
Adjustment to cure function (base case: cured function applied after 5 years in both arms)[c]				
• Cured function applied after 5.5 years for durvalumab + GC and after 5 years for SoC treatment [c]	$[redacted]	0.6106	$[redacted][1]	[redacted]%
Effectiveness of adjuvant nivolumab (base case HR: 0.54)				
• 0.41 (lower 95% CI)	$[redacted]	0.5287	$[redacted][4]	[redacted]%
• 0.72 (upper 95% CI)	$[redacted]	0.8514	$[redacted][3]	–[redacted]%
Uptake of adjuvant nivolumab in the patients with high risk of recurrence (base case: 100% uptake)				
• 0%	$[redacted]	1.0535	$[redacted][3]	–[redacted]%
• 25%	$[redacted]	0.9588	$[redacted][3]	–[redacted]%
• 50%	$[redacted]	0.7694	$[redacted][1]	–[redacted]%
Avelumab uptake in DR (base case: 43%)				
• 30%	$[redacted]	0.6945	$[redacted][1]	[redacted]%
• 65%	$[redacted]	0.6412	$[redacted][1]	–[redacted]%
Incremental effectiveness of avelumab, DR setting (base case: 8.6 months)				
• 10 months	$[redacted]	0.6646	$[redacted][1]	[redacted]%
• 12 months	$[redacted]	0.6505	$[redacted][1]	[redacted]%
Adjustments to overall survival				
Use OS calibrations as suggested by the submission sensitivity analysis (base case: no calibrations) **(#2)**	$[redacted]	0.5582	$[redacted][1]	[redacted]%
Recurrence is fatal (base case: based on fixed proportion of deaths observed in trial)				
• Assumed no fatal recurrences in the model	$[redacted]	0.6021	$[redacted][3]	–[redacted]%
ESC suggested multivariate sensitivity analyses				
#1 and #2, and includes the evaluator's respecified base case [a]	$[redacted]	0.4606	$[redacted][4]	[redacted]%
#1 and #2, and removes the cure assumption and reverts to the parametric functions used in the submission's base case.	$[redacted]	0.4976	$[redacted][4]	[redacted]%

Source: constructed during the evaluation using respecified base case and Attachment 3.1 'TreeAgeModel_Jul25.trex' provided with the submission.

CI = Confidence interval; DR = Distant recurrence; GC = Gemcitabine plus cisplatin; HR = Hazard ratio; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = Overall survival; QALY = Quality-adjusted life year; SoC = Standard of care; SPA = Special pricing arrangement.

[a] Respecified base case included Weibull parametric functions for extrapolating all EFs curves and had the cure function, that was incorrectly applied in the submission's base case to the second cycle of recurrence, switched off in the locoregional and distant recurrence health sates.

[b] Uses the published prices of nivolumab and avelumab with a hypothetical [redacted]% discount

[c] Considering the addition of durvalumab results in tumour suppression, an event that otherwise may have occurred close to 5 years may be time-shifted to beyond 5 years. Sensitivity analysis assumes that cure is delayed by 6 months in the durvalumab + GC arm to capture delayed recurrences. Therefore, all patients who are event free after 5 years and 5.5 years are assumed to be cured for SoC and durvalumab + GC treatment arm, respectively.

The redacted values correspond to the following ranges:

[1] *$35,000 to < $45,000*

[2] *$15,000 to < $25,000*

[3] *$25,000 to < $35,000*

[4] *$45,000 to < $55,000*

6.71 The ESC considered the core-structure of the model was appropriate and consistent with previous recommendations in this setting (paragraph 7.8, nivolumab PSD, July 2022). However, the ESC considered that the model stratifications, primarily for RC vs non-RC subpopulations, likely led to unnecessary complexity. The ESC considered that a key issue related to the economic model was the underestimation of OS. However, the ESC considered that clinically plausible outcomes would likely be reflected by a revised base case using OS calibration in combination with a 15-year time horizon. The ESC noted the submission had included the best-fitting parametric functions for EFS, however the evaluator considered that the Weibull parametric functions had more plausible long-term projections. The ESC considered that the multivariate analysis, including the evaluator's respecified base case, within the current model structure, would result in a reliable estimate of the ICER (Table 18). The Pre-PBAC response commented that this approach would be inappropriate given that the NIAGARA trial provides robust OS evidence in a curative setting which supports a more favourable reimbursement outcome than adjuvant nivolumab.

6.72 The ESC noted that the ICER threshold previously considered cost-effective for adjuvant nivolumab was $30,000/QALY gained (paragraph 6.68, nivolumab PSD, March 2024).

Durvalumab cost/patient/course

6.73 Table 19 presents the cost per patient per course for durvalumab + GC and GC.

Table 19: Drug cost per patient for proposed and comparator drugs

	Durvalumab +GC			GC		
	NIAGARA	**Economic model**	**Financial estimates**	**NIAGARA**	**Economic model**	**Financial estimates**
Mean dose per administration (mg)	D: 1,500 (3 vials) G: 1,875 C: 131.25	D: 1,500 (3 vials) G: 1,875 C: 131.25	D: 1,500 (3 vials) GC: not modelled	G: 1,875 C: 131.25	G: 1,875 C: 131.25	GC: not modelled
Mean number of treatment cycles	D: 8.8 [a] GC: 3.8 [a]	D: 8.8 [a] GC: 3.8 [a]	D: 10.7 [b] GC: -	GC: 3.6	GC: 3.6	-
Cost/patient/treatment cycle	D: $[redacted] GC: $472.16	D: $[redacted] GC: $472.16	D: $[redacted] GC: -	GC: $472.16	GC: $472.16	-
Cost/patient/course	$[redacted]	$[redacted]	$[redacted]	GC: $1,701	GC: $1,701	-

Source: constructed during the evaluation using information provided in section 3.6 of the submission and the financial estimates from the submission: 2d. Patients - DTG, 3a. Scripts - proposed.

D = durvalumab; GC = Gemcitabine plus cisplatin; mg = milligram.

[a] Based on the overall safety analysis set (N = 530). Therefore, it includes patients not continuing to adjuvant therapy.

[b] Neoadjuvant treatment based on safety analysis set (N=530). Adjuvant, based only on those continuing to adjuvant treatment (N=383 / 72.3% of study population). Neoadjuvant treatment (11.4 weeks) and adjuvant treatment (27.6 weeks) resulting in 3.8 + 6.9 scripts per patient (10.7 scripts per course of treatment).

Estimated PBS usage & financial implications

6.74 This submission was not considered by DUSC.

6.75 The submission used an epidemiological approach to estimate the number of incident patients who would be eligible for durvalumab treatment. A summary of the data sources and parameter values used to estimate the utilisation and financial impacts associated with the proposed listing of durvalumab for the treatment of muscle invasive bladder cancer is shown in Table 20.

Table 20: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population – proposed medicine			
Incident patients	Increasing from 3,468 in Year 1 to 3,908 in Year 6	AIHW 2024 Book 1e	The population is patients with bladder cancer T1-4.
Proportion T2-T4	Constant at 53.47%	Reynolds 2021	The calculation, which is based on the proportions of the T1 and T2-4 populations in Reynolds 2021, could not be reproduced. The calculation was redone using the patient numbers presented in Reynolds. The revised value is 51.54%.
Proportion T1	Constant at 46.53%	Reynolds 2021	This calculation (T1) is the reciprocal of the previous (T2-T4) and hence is incorrect. The revised value is 48.46%.
Proportion T1-T4	Constant at 44.10%	Reynolds 2021	This calculation included bladder and upper tract urothelial carcinoma which is not appropriate. The revised value is 42.48%. The Pre-PBAC response agreed that the proportion should represent bladder cancer only.
Proportion Ta/Tis	Constant at 55.90%	Reynolds 2021	This calculation (Ta/Tis) is the reciprocal of the previous (T1-T4) and hence is incorrect. The revised value is 57.52%.
Incident patients	Increasing from 1,854 in Year 1 to 2,090 in Year 6	Calculation	
Progression from NMIBC to MIBC	Constant at 12%	BLADDA Registry, October 2024 interim report	
Progressing patients	Increasing from 721 in Year 1 to 813 in Year 6	Calculation	
Overall incident patients	Increasing from 2,575 in Year 1 to 2,902 in Year 6	Incident and progressing patients	
Patients receiving RC	Constant at 65%	BLADDA Registry, October 2024 interim report, Table 5	

Data	Value	Source	Comment
RC patients receiving NAC	Increasing from 60.50% in Year 1 to 67.40% in Year 6	Hiong et al, 2022	The method used to extrapolate across the listing period is unclear. The rate decreases uniformly across time, except for the last year which increases by nearly double the rate of the prior year which is not appropriate.
Adjustment for patients who initiate NAC but do not progress to RC	Constant at 113.65%	Sponsor calculation	The sponsor applied an adjustment based on the number of patients who underwent RC (469) in the durvalumab + gemcitabine/cisplatin arm (533) of the NIAGARA trial.
WHO Performance Status 0-1	Constant at 100%	Sponsor assumption	The sponsor assumed that all patients would have a WHO PS of 0-1, due to their eligibility for RC and NAC. However, in the nivolumab MIUC submission only 97% of patients have this status. The Pre-PBAC response stated that this adjustment is not required because the nivolumab MIUC population represents a cohort that is post-NAC and RC, which is not the NIAGARA population.
Eligible patients	Increasing from 1,151 in Year 1 to 1,445 in Year 6	Calculation	
Treatment utilisation			
Uptake – initial treatment	Increasing from [redacted]% in Year 1 to [redacted]% in Year 6	Expert opinion and sponsor assumption	Given the high recurrence rate and the lack of alternative treatment the evaluation considered that this appeared appropriate.
Initial patients	Increasing from [redacted][1] in Year 1 to [redacted][1] in Year 6	Calculation	
Uptake - continuing treatment based on initial patients	Constant at 72.26%	This was based on the number of patients in the NIAGARA trial who received adjuvant treatment following RC surgery (383/530).	This is consistent with the economic model.
Continuing patients	Increasing from [redacted][1] in Year 1 to [redacted][1] in Year 6	Calculation	
Treatment duration (days)	Initial: 79.80 Continuing: 193.20	Initial: 3.8 cycles x 3 weeks x 7 days = 79.80 days Continuing: 6.9 cycles x 4 weeks x 7 days = 193.20 days	This is consistent with the economic model.
Durvalumab scripts initial treatment	3.8, based on 11.4 weeks of treatment, assuming 100% compliance	Calculation	This is consistent with the treatment duration presented in the economic model.

Data	Value	Source	Comment
Durvalumab scripts continuing treatment	6.9, based on 27.6 weeks of treatment, assuming 100% compliance	Calculation	While 6.9 scripts are inconsistent with the treatment duration presented in the economic model (5 scripts), the treatment duration for the financials includes only those patients continuing to adjuvant therapy (72.26% of the total), whereas the economics estimate includes patients not continuing to adjuvant therapy.
Eligible population – proposed medicine			
Grandfathered patients	[redacted][1]	Sponsor assumption	These patients will be drawn from the sponsor's proposed PFP.
MBS Items - proposed and affected medicines			
Parenteral administration of one or more antineoplastic agents	$123.05	MBS item 13950	

Source: The financial estimates from the submission: 10. Registry population, 2a. Patients - incident, 2d. Patients - DTG, 3a. Scripts - proposed, 2c. Patients - GF, 11. Persistent population, 3b. Impact - proposed (pub), 3c. Impact - proposed (eff), 2e. Scripts - market, 7. Net changes - MBS.

AEMP = approved ex-manufacturer price; AIHW = Australian Institute of Health and Welfare; CEA = cost effectiveness analysis; CPG = co-payment group; DPMA = dispensed price for maximum amount; MBS = Medicare Benefits Schedule; MIBC = muscle-invasive bladder cancer; MIUC = muscle-invasive urothelial carcinoma; NAC = neoadjuvant chemotherapy; NMIBC = non-muscle-invasive bladder cancer; PBS = Pharmaceutical Benefits scheme; PFP = patient familiarisation program; RC = radical cystectomy; RPBS = Repatriation Pharmaceutical Benefits Scheme; Ta/Tis = non-invasive papillary carcinoma /carcinoma in situ; UC = urothelial carcinoma; WHO = World Health Organisation.

The redacted value corresponds to the following range:

[1] *500 to < 5,000*

[2] *< 500*

6.76 The estimated use and financial impacts of listing durvalumab are shown in Table 21.

Table 21: Estimated use and financial impact of listing durvalumab (effective)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Patients						
Eligible patients	1,151	1,204	1,254	1,309	1,364	1,445
Uptake – initial (neoadjuvant) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neoadjuvant patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Uptake – continuing (adjuvant) (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adjuvant patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Grandfathered patients	[redacted][2]					
Scripts – proposed medicine						
Durvalumab - Initial	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Durvalumab - Continuing	[redacted][1]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Durvalumab GF - Initial	[redacted][1]					
Durvalumab GF - Continuing	[redacted][1]					
Total scripts	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][4]
Net financial impact of durvalumab						
PBS/RPBS less copayments ($)	[redacted][5]	[redacted][5]	[redacted][5]	[redacted][6]	[redacted][6]	[redacted][6]
Scripts – affected medicines						
Nivolumab – Q4W	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Nivolumab – Q2W	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][1]	-[redacted][1]	-[redacted][1]
Avelumab - Initial	-[redacted][1]	-[redacted][1]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Avelumab – Continuing	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]	-[redacted][2]
Total scripts	-[redacted][2]	-[redacted][2]	-[redacted][3]	-[redacted][3]	-[redacted][3]	-[redacted][3]
Net financial impact of affected medicines[a]						
PBS/RPBS less copayments ($)	-[redacted][7]	-[redacted][7]	-[redacted][7]	-[redacted][8]	-[redacted][8]	-[redacted][8]
Net financial impact						
Net PBS/RPBS[a] ($)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]
Evaluation revised net PBS/RPBS[a,b] ($)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]
Pre-PBAC response revised net PBS/RPBS[a,c] ($)	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]
MBS impact ($)	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]	[redacted][10]
Net impact (submission)[a]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]
Revised net impact[a]	[redacted][8]	[redacted][8]	[redacted][8]	[redacted][9]	[redacted][9]	[redacted][9]

Source: The financial estimates from the submission: 3a. Scripts - proposed, 3b. Impact - proposed (pub), 3c. Impact - proposed (eff), 4a. Scripts - affected, 4b. Impact - affected (pub), 4c. Impact - affected (eff), 5. Impact - net, 7. Net changes - MBS.
MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
[a] Uses the published prices of nivolumab and avelumab with a hypothetical [redacted]% discount.
[b] Evaluation-revised net PBS/RPBS impact shows the impact of the rate adjustments described in Table 20.
[c] Pre-PBAC response revised net PBS/RPBS impact shows (i) changes to the epidemiology rates to reflect bladder cancer incidence only; and (ii) duration of treatment for grandfathered patients adjusted to account for treatment already received prior to PBS-transition (since the patient access program is expected to start in early 2026, only the neoadjuvant period has been adjusted as patients are unlikely to have initiated adjuvant treatment at listing).
The redacted values correspond to the following ranges:
[1] *500 to < 5000*
[2] *< 500*
[3] *5,000 to < 10,000*
[4] *10,000 to < 20,000*
[5] *$40 million < $50 million*
[6] *$50million to < $60 million*
[7] *$10 million to < $20 million*
[8] *$20 million to < $30 million*
[9] *$30 million to < $40 million*
[10] *$0 to < $10 million*

6.77 The total PBS/RPBS impact of listing durvalumab was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing. A revised total PBS/RPBS impact of listing durvalumab was estimated to be $30 million to < $40 million in Year 6, and a total of $100 million to < $200 million in the first 6 years of listing, when the revisions proposed by the evaluation in Table 20 are applied. The PSCR acknowledged the financial revisions and described them as minor. The Pre-PBAC response applied revisions as proposed by the evaluation to bladder cancer incidence and further amended the duration of treatment for grandfathered patients, which are also shown in Table 20.

6.78 The incident patients presented in the financial model were drawn from two sources, patients diagnosed with MIBC and patients who progress from non-muscle-invasive bladder cancer (NMIBC) to MIBC. The base bladder cancer incidence was taken from the Australian Institute of Health and Welfare (AIHW) projections in Book 1e, providing projections from 2026 to 2031. The submission indicated that the AIHW data only includes patients that are stage T1-T4.

6.79 To determine the proportion of MIBC cases, the submission applied proportions from Reynolds et al (2021). Reynolds et al (2021) reported tumour staging data from 306 newly diagnosed patients with bladder urothelial carcinoma. The submission applied these proportions to the AIHW data to calculate the number of T2-T4 (MIBC) patients. However, the percentages presented in Reynolds et al (2021) could not be reproduced by the evaluation and were recalculated.

6.80 To determine the cases of NMIBC who could progress to MIBC, the submission used the proportions in Reynolds et al (2021) for Ta/Tis patients and the number of T1 patients. However, the Reynolds et al (2021) proportions include both bladder and upper tract urothelial carcinoma. The evaluation considered that this was inappropriate as the upper tract urothelial carcinomas are outside the proposed restriction. The Pre-PBAC response agreed that the proportion should represent bladder cancer only and adjusted the estimate (Table 21).

6.81 The submission proposed there would be < 500 grandfathered patients who will be included in the sponsor's patient access program. The ESC noted the treatment duration for GF patients did not account for treatment already received prior to transition to PBS-subsidised treatment. The Pre-PBAC response agreed that the duration of treatment in the neoadjuvant period should not include treatment already received prior to PBS-transition and adjusted the estimate (Table 21). The response stated that the patient access program is expected to start in early 2026 and so patients would be unlikely to have initiated adjuvant treatment at listing.

Quality Use of Medicines

6.82 The submission did not provide details of any specific quality use of medicines activities to be undertaken. The submission stated that the sponsor will work collaboratively with healthcare professionals to ensure that durvalumab is used appropriately and in line with the available clinical evidence and the TGA indication.

6.83 The submission indicated that several post-marketing surveillance studies for perioperative durvalumab in combination with neoadjuvant chemotherapy are planned internationally.

Financial Management – Risk Sharing Arrangements

6.84 The submission did not seek a risk share arrangement for the listing of durvalumab for MIBC. The ESC noted there is an RSA in place for nivolumab, avelumab and pembrolizumab (paragraph 9.10, nivolumab PSD, March 2024).

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

7 PBAC Outcome

7.1 The PBAC recommended a Section 100 (Efficient Funding of Chemotherapy Program) (STREAMLINED) listing of durvalumab for the perioperative treatment (i.e. both before and after surgery) of patients with muscle-invasive bladder cancer (MIBC) who are eligible for cisplatin-based neoadjuvant chemotherapy (NAC) and planning to undergo radical cystectomy (RC). The PBAC considered that, on balance, perioperative durvalumab improves event free survival (EFS) and overall survival (OS) in the MIBC patient population compared with standard of care (SoC). However, the magnitude of benefit is uncertain due to differences across the trials included in the indirect treatment comparison (ITC) and from clinical practice in Australia. The PBAC considered that durvalumab would be considered acceptably cost-effective with some revision to model inputs and a price reduction that resulted in an acceptable incremental cost-effectiveness ratio (ICER). The PBAC considered that the financial estimates were reasonable once minor adjustments were made to account for the overestimated patient population. The PBAC recommended the listing should join the existing risk sharing arrangement (RSA) in place for adjuvant nivolumab in patients at high risk of recurrence, with an increase in expenditure caps to account for the net cost of listing.

7.2 The PBAC noted the clinical need in MIBC as it is a challenging condition to treat with significant impacts on quality of life despite the current treatment options available. The PBS listing of durvalumab would move the clinical place of immunotherapy into the perioperative treatment phase (both neoadjuvant and adjuvant), for all patients who are eligible for NAC and are planning to undergo RC, whereas nivolumab is only available as adjuvant therapy for those MIBC patients at high risk of recurrence. The PBAC acknowledged the consumer support for perioperative durvalumab in this therapeutic area from two consumer groups, Rare Cancers Australia and BEAT Bladder Cancer Australia, and noted that the MOGA classification of durvalumab with an ESMO-MCBS grade 'A' categorised it as a new treatment with substantial benefit in the curative setting.

7.3 The PBAC made the following determinations regarding the proposed PBS restriction for durvalumab:

- The treatment phases should be amended to specify that initial treatment pertains to the neoadjuvant setting and continuing treatment pertains to the adjuvant setting, to provide additional clarity to prescribers;
- It is not necessary to include a Prescribing Instruction in the restriction to specify weight-based dosing in patients under 30 kg, as it is in the Product Information;
- A separate grandfathering restriction would not be required, as grandfathered patients can be accommodated by the initial/continuing phase restrictions;
- STREAMLINED initial and continuing restrictions would be appropriate, consistent with the current PBS listings for durvalumab in other indications;

Initiation:

- The restriction should include a clinical criterion stating that the "condition must not have previously been treated with systemic therapy for muscle-invasive bladder cancer at the time this drug was initiated for this condition";
- The restriction should include a clinical criterion that "The treatment must be once in a lifetime with this drug for this condition";
- The restriction should specify nodal involvement of stage N0 or N1 to reflect the NIAGARA trial population and there is no need to specify stage M0, which is implicit for patients undergoing surgery;
- The restriction should specify clinical tumour stage of either T2, T3 or T4a, to be consistent with the NIAGARA trial;

Continuation:

- It is not necessary to specify a timeframe that patients must have completed surgery within 70 days of their final neoadjuvant durvalumab dose, as flexibility may be required for patients experiencing delays;
- It is not necessary to require patients to commence adjuvant durvalumab therapy within 120 days of undergoing a RC and it would alternatively be appropriate to specify "within 6 months" in the restriction criteria to allow for flexibility in clinical practice;
- The Prescribing Instruction in the continuing restriction should refer to "8 cycles" rather than "8 months" for consistency in terminology across the initial and continuing treatment phases.

7.4 While the submission nominated SoC (GC NAC, RC, active surveillance) as the main comparator, the PBAC noted that the sponsor's Pre-PBAC response was aligned with a mixed comparator approach, supported by the evaluation and the ESC, as describing the comparator to be gemcitabine plus cisplatin (GC) NAC and RC, followed by either

(i) adjuvant nivolumab for patients with high risk of recurrence OR (ii) post-surgery active surveillance for all other patients. The PBAC accepted that the submission's estimate for the proportion of patients at high risk of recurrence (27.6%), derived from the disease profile of patients in the control arm of NIAGARA trial, likely reflects the proportion of Australian patients who would have been eligible to receive adjuvant nivolumab.

7.5 The PBAC noted that the clinical evidence presented in the submission was based on one direct, randomised controlled trial (NIAGARA, N = 1,063), comparing the effectiveness and safety of neoadjuvant durvalumab in combination with GC followed by RC and adjuvant durvalumab as a monotherapy (durvalumab + GC arm) versus cisplatin-based NAC followed by RC and post-surgery active surveillance (GC arm). The PBAC noted that there was a statistically significant reduction in the risk of an EFS event for patients in the durvalumab + GC arm compared with the GC arm (hazard ratio [HR] 0.68; 95% confidence interval [CI]: 0.56, 0.82, p <0.0001). With respect to OS, the PBAC noted that the hazard of death was reduced by 25% (HR: 0.75; 95% CI: 0.59, 0.93).

7.6 Overall, the PBAC considered that the clinical claim of superior effectiveness of perioperative durvalumab with NAC and RC versus NAC and RC with post-surgery active surveillance could be supported for the majority of patients (i.e., those not at high risk of recurrence, which applies to over 70% of patients) based on results from the NIAGARA trial. This was based on a statistically significant benefit for patients receiving perioperative durvalumab with respect to EFS and OS.

7.7 In terms of the applicability of the NIAGARA trial data to the Australian patient population, the PBAC observed that while the durvalumab intervention arm represents the MIBC patient population described by the requested restriction, the patients at high risk of recurrence in the SoC control arm did not receive adjuvant nivolumab as would occur in Australia. Thus, the comparator arm likely underperformed current clinical practice and the benefit of perioperative durvalumab may be overestimated. The PBAC considered that performing an ITC to account for the estimated 27.6% of patients who would be at high risk of recurrence was an acceptable approach albeit with challenges that compromised the reliability of the outcomes.

7.8 The PBAC noted the complexity of performing the ITC using subgroups from the NIAGARA and CM274 trials to construct a 'counterfactual' survival time for the control arm of the NIAGARA trial, in order to accommodate the 27.6% of patients at high risk of recurrence into the SoC arm. The PBAC acknowledged that the data matching performed by the submission ameliorated the differences across the trials with respect to: (i) pathological high-risk status at the adjuvant baseline, (ii) restricting efficacy inputs to CM274's prior-NAC subgroup, (iii) applying the nivolumab benefit only to patients that meet the eligibility criteria for high risk of recurrence, and (iv) reflecting the interchangeability of the EFS/DFS definitions post-surgery. It also acknowledged that perioperative durvalumab is the first immunotherapy to achieve a

statistically significant and clinically meaningful OS benefit in the curative treatment setting for cisplatin-eligible MIBC, noting that the PBAC recommendation for adjuvant nivolumab was based on a subgroup analysis. However, the PBAC considered that the ITC method could not robustly demonstrate the comparative benefit of perioperative durvalumab to support superiority in patients who might otherwise receive adjuvant nivolumab.

7.9 Despite its reservations about the ITC, the PBAC considered that, on balance, the evidence base for perioperative durvalumab supports that it is likely superior to SoC (as defined by the mixed comparator described in paragraph 7.4), although the magnitude of effect is uncertain. Overall, the PBAC considered that perioperative durvalumab in MIBC could translate into a clinically meaningful improvement in survival for patients in a therapeutic area where there is a clinical need for new therapies.

7.10 The PBAC agreed with the submission that the claim of inferior safety for perioperative durvalumab compared to the control arm of the NIAGARA trial was appropriate, given that durvalumab is additive to SoC. With respect to the ITC, the PBAC considered that it is possible that perioperative durvalumab is non-inferior in terms of safety compared adjuvant nivolumab in the subgroup of MIBC patients with high risk of disease recurrence, but it is difficult to assess from the data presented. The PBAC noted that the safety profile of durvalumab is as expected for this class of drug.

7.11 The PBAC considered that the submission's economic model was reasonable for decision-making and that the following parameters would be suitable to apply:

- A 15 year time horizon; the PBAC noted that this would be consistent with the time horizon accepted for adjuvant nivolumab in MIBC.
- Independent parametric models for disaggregated observed EFS data, as used in the submission. The lognormal models were selected for the base case for both high and low risk subgroups, and the Gompertz model was selected for the remaining of the EFS curves. The PBAC noted that the submission used the best fitting parametric functions.
- Calibration factors for modelled OS curves. The PBAC noted the limitations of this calibration raised by the evaluation and the Pre-PBAC Response. However, noted that the economic model appeared to underestimate OS and agreed with the ESC that these projections required recalibration. The PBAC considered that further data to better inform downstream transitions are unlikely to become available.

The PBAC agreed with the evaluation that the cure function should be switched off in the locoregional and distant recurrence health states due to it being incorrectly applied in the submission's base case to the second cycle of recurrence.

7.12 The PBAC considered that the multivariate analysis proposed by the ESC, that (i) uses a 15 year time horizon, (ii) uses OS calibrations, (iii) removes the cure assumption in

the locoregional and distant recurrence health states due to a model error, and (iv) applies the EFS parametric functions used in the submission's base case, is the most appropriate scenario to reflect the value of perioperative durvalumab and remains generally consistent with the adjuvant nivolumab consideration in MIBC. The ICER for this scenario using published prices of nivolumab and avelumab (with a hypothetical [redacted]% reduction) is $45,000 to < $55,000 per quality adjusted life year (QALY) gained. The PBAC considered that the ICER should not exceed $35,000 per QALY gained, using effective prices, noting that although it exceeds the PBAC recommendation for adjuvant nivolumab of $30,000 per QALY gained (paragraph 6.68, nivolumab PSD, March 2024), it is appropriate for perioperative durvalumab given the survival gain shown in the NIAGARA trial.

7.13 The PBAC considered that the methodology to calculate the utilisation estimates was reasonable once the minor issues identified by the evaluation that overestimated the patient population were addressed in the Pre-PBAC response (as described in Table 20). The PBAC recommended that perioperative durvalumab should join the RSA for adjuvant nivolumab, with an increase in patient numbers to include all eligible patients who will receive perioperative therapy with durvalumab, accounting for the reduction in use of adjuvant therapy with nivolumab which is listed for the patient group at high risk of recurrence only. The PBAC noted that a relatively high proportion (72%) of patients who receive initial neoadjuvant durvalumab treatment are expected to continue through to adjuvant durvalumab treatment. The PBAC noted that the RSA should manage the risk of patients inappropriately receiving more than one immunotherapy for MIBC per lifetime.

7.14 The PBAC noted the flow-on restriction changes to nivolumab for urothelial carcinoma at high risk of recurrence (item numbers 14231B and 14260M):

- A flow-on change should specify that adjuvant therapy is initiated within 6 months of radical cystectomy (rather than 120 days);
- A flow-on change should reflect the once-per-lifetime use of immunotherapy (as discussed in paragraph 3.3);
- A flow on change should specify STREAMLINED initial and continuing restrictions.

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

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy over standard of care, as while clinically meaningful improvements in OS were evident from the NIAGARA trial, the magnitude of effect generalisable to the Australian population is uncertain as patients at high risk of recurrence in the SoC control arm did not receive adjuvant nivolumab;

b) The treatment is not 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.

7.16 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Initial treatment

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
DURVALUMAB Injection	NEW (private) NEW (public)	1500mg	3
Available brands			
Imfinzi durvalumab 500mg/10 mL injection, 10 mL vial			
Imfinzi durvalumab 120mg/2.4 mL injection, 10 mL vial			
Restriction Summary NEW / Treatment of Concept: NEW			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [new]			
Administrative Advice: No increase in the maximum quantity or number of units may be authorised			
Administrative Advice: No increase in the maximum number of repeats may be authorised			
Administrative Advice: Special Pricing Arrangements apply			
Condition: Urothelial Carcinoma			
Indication: Urothelial Carcinoma			
Treatment Phase: Initial treatment – neoadjuvant setting			
Population criteria:			
Patient must be initiating treatment with this drug for this condition; or			
Patient must be transitioning from non-PBS to PBS subsidised treatment with this drug for this condition			
Clinical criteria:			
The condition must not have previously been treated with systemic therapy for muscle-invasive bladder cancer at the time this drug was initiated for this condition			
AND			
Clinical criteria:			
The treatment must be once in a lifetime with this drug for this condition			
AND			
Clinical criteria:			
The condition must be of muscle-invasive type disease with both (i) clinical tumour stage of either T2, T3 or T4a (ii) nodal status of up to stage N1.			
AND			

Clinical criteria:
The treatment must be for neoadjuvant use in a patient preparing for radical cystectomy
AND
Clinical criteria:
Patient must have/have had at the time of initiating treatment with this drug, a WHO performance status no higher than 1
AND
Clinical criteria:
The treatment must be/have been initiated with both: (i) gemcitabine, (ii) cisplatin (refer to Product Information of gemcitabine and cisplatin for dosing information).
AND
Treatment criteria:
Patient must not be undergoing PBS subsidised treatment where this prescription extends treatment beyond whichever comes first: (i) 4 cycles 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.

Continuing treatment

MEDICINAL PRODUCT **Form**	**PBS item code**	**Max. Amount**	**№.of Rpts**
DURVALUMAB Injection	NEW (private) NEW (public)	1500mg	3
Available brands			
Imfinzi durvalumab 500mg/10 mL injection, 10 mL vial			
Imfinzi durvalumab 120mg/2.4 mL injection, 10 mL vial			
Restriction Summary NEW / Treatment of Concept: NEW			
Category / Program: Section 100 – Efficient Funding of Chemotherapy Public/Private hospitals			
Prescriber type: ☒Medical Practitioners			
Restriction type: ☒Authority Required (STREAMLINED) [new]			
Administrative Advice: No increase in the maximum quantity or number of units may be authorised			
Administrative Advice: No increase in the maximum number of repeats may be authorised			
Administrative Advice: Special Pricing Arrangements apply			
Condition: Urothelial Carcinoma			
Indication: Urothelial Carcinoma			
Treatment Phase: Continuing treatment – adjuvant setting			
Population criteria:			
Patient must have previously received PBS subsidised neoadjuvant treatment with this drug in combination with gemcitabine plus cisplatin for this condition; or			
Patient must be both: (i) transitioning from existing non-PBS to PBS subsidised treatment with this drug for this condition, (ii) previously treated in combination with cisplatin and gemcitabine as neoadjuvant treatment for this condition.			
Clinical criteria:			
Patient must have undergone radical cystectomy			
AND			
Clinical criteria:			
The treatment must be for adjuvant therapy that is/was initiated within 6 months of radical cystectomy for this condition			
Clinical criteria:			
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication			

AND
Treatment criteria:
Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) maximum of 8 cycles for this condition from the first administered dose following radical cystectomy, (iii) unacceptable toxicity; annotate any remaining repeat prescriptions with the word 'cancelled' where this occurs
Prescribing Instruction: Treatment with this drug for this condition must not exceed 12 treatment cycles (neoadjuvant and adjuvant) in a lifetime

Flow on changes to nivolumab (PBS items 14231B and 14260M)

Amend clinical criteria (concept 32188) to ensure adjuvant therapy is initiated within 6 months of radical cystectomy (rather than 120 days).

Clinical criteria:
The treatment must be for each of: (i) adjuvant therapy that is/was initiated within *6 months* ~~120 days~~ of radical surgical resection, (ii) muscle invasive type disease, (iii) disease considered to be at high risk of recurrence based on pathologic staging of radical surgery tissue (ypT2-ypT4a or ypN+), but yet to recur, (iv) use as the sole PBS-subsidised anti-cancer treatment for this condition

Addition of clinical criteria to reflect once-per-lifetime immunotherapy use in urothelial carcinoma.

Clinical criteria:
Patient must not have received prior treatment with a programmed cell death-1 (PD-1) inhibitor or a programmed cell death ligand-1 (PD-L1) inhibitor for this condition.

Remove Telephone/Online Administrative Note to accommodate a STREAMLINED listing

~~**Administrative Advice:**~~
~~Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.~~

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.