

Single Technology Appraisal

**Durvalumab with gemcitabine and
cisplatin before surgery (neoadjuvant)
then alone after surgery (adjuvant) for
treating muscle-invasive bladder cancer
[ID6168]**

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the [NICE website](#).

- 1. Company submission** from AstraZeneca:
 - a. Full submission
 - b. Summary of Information for Patients (SIP)
- 2. Clarification questions and company responses**
 - a. Clarification response
 - b. Clarification appendix
- 3. Patient group, professional group, and NHS organisation submission** from:
 - a. Action Bladder Cancer
 - b. Fight Bladder Cancer
 - c. British Uro-Oncology Group
- 4. Expert personal perspectives** from:
 - a. Professor Syed Hussain – clinical expert, nominated by AstraZeneca
 - b. Professor Robert Huddart – clinical expert, nominated by British Uro-Oncology Group
 - c. Anne Wass – patient expert, nominated by Fight Bladder Cancer
 - d. Melanie Costin – patient expert, nominated by Fight Bladder Cancer
- 5. External Assessment Report** prepared by Centre for Reviews and Dissemination and Centre for Health Economics, University of York
- 6. External Assessment Group response to factual accuracy check of EAR**
- 7. Company addendum** from AstraZeneca
- 8. External Assessment Group critique of the company addendum**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Durvalumab with gemcitabine and cisplatin
before surgery (neoadjuvant) then alone after
surgery (adjuvant) for treating muscle-invasive
bladder cancer**

ID6168

Company evidence submission

June 2025

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Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Contents

Contents.....	2
Tables and figures	2
List of abbreviations	7
1 Decision problem, description of the technology and clinical care pathway	10
1.1 Decision problem	10
1.2 Description of the technology being evaluated	16
1.3 Health condition and position of the technology in the treatment pathway.....	17
1.4 Equality considerations.....	28
2 Clinical effectiveness.....	30
2.1 Identification and selection of relevant studies	31
2.2 List of relevant clinical effectiveness evidence	31
2.3 Summary of methodology of the relevant clinical effectiveness evidence.....	33
2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence.....	42
2.5 Critical appraisal of NIAGARA trial	48
2.6 Clinical effectiveness results of the relevant studies	48
2.7 Subgroup analysis	67
2.8 Meta-analysis	71
2.9 Indirect Treatment Comparison	71
2.10 Adverse reactions	89
2.11 Ongoing studies	92
2.12 Interpretation of clinical effectiveness and safety evidence	93
3 Cost effectiveness.....	100
3.1 Published cost effectiveness studies	101
3.2 Economic analysis.....	104
3.3 Clinical parameters and variables	109
3.4 Measurement and valuation of health effects	127
3.5 Cost and healthcare resource use identification, measurement, and valuation ...	134
3.6 Severity.....	139
3.7 Uncertainty	140
3.8 Managed access proposal.....	140
3.9 Summary of base-case inputs and assumptions	140
3.10 Base-case results	144
3.11 Exploring uncertainty	145
3.12 Subgroup analysis	154
3.13 Benefits not captured in the QALY calculation.....	154
3.14 Validation	156
3.15 Interpretation and conclusions of economic evidence	157
4 References.....	161

Tables and figures

List of Tables

Table 1: The decision problem.....	12
Table 2: Technology being evaluated	16
Table 3: Clinical effectiveness evidence	32
Table 4: Summary of trial methodology: NIAGARA trial	34
Table 5: Key eligibility criteria for the NIAGARA trial	37
Table 6: Patient disposition in NIAGARA trial (DCO 29 April 2024)	38
Table 7: Patient demographic and baseline characteristics at study entry in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	40
Table 8: Definitions of the NIAGARA trials' analysis sets	43
Table 9: Summary of outcome variables and analysis populations	43
Table 10: NIAGARA trial objective and hypothesis testing	44
Table 11: NIAGARA trial analysis timepoints.....	44
Table 12: NIAGARA trial sample size and power calculation	47
Table 13: Quality assessment results for NIAGARA trial.....	48
Table 14: Dates of data cut off for endpoint analysis.....	49
Table 15: Analysis of dual-primary endpoint: EFS, per BICR or central pathology review, in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)	50
Table 16: pCR rate, based on central pathology, in NIAGARA trial (FAS [ITT population], Formal analysis DCO 14 January 2022, Re-analysis DCO 29 April 2024).....	52
Table 17: Analysis of overall survival in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	54
Table 18: Analysis of OS at five years in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	56
Table 19: Analysis of MFS in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024)	58
Table 20: Analysis of DSS in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)....	60
Table 21: Analysis of DFS in NIAGARA trial (Cystectomy population, DCO 29 April 2024). 61	
Table 22: EORTC QLQ-C30 scores at baseline and over time (FAS [ITT population], DCO 29 April 2024).....	64
Table 23: Compliance and scores for EQ-5D-5L and scores for EQ-VAS by time and overall (FAS [ITT population], DCO 29 April 2024)	65
Table 24: Differences in analysis between the NIAGARA and CheckMate-274 trials	76
Table 25: Summary of goodness of fit and AF parameter estimates for the PD-L1 MIBC subgroup	79
Table 26: Summary of goodness of fit and AF parameter estimates for the PD-L1 MIBC subgroup	80
Table 27: Step 1: Acceleration factor calculation results for EFS and OS	80
Table 28: Hazard ratios and 95% Confidence intervals for EFS comparing versus G+C and G+C+N (log-logistic)	85
Table 29: Hazard ratios and 95% Confidence intervals for OS comparing versus G+C and G+C+N.....	87
Table 30: Summary of results D+G+C versus G+C+N	87

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Table 31: Overview of duration of exposure, AEs and treatment discontinuation in the SAS ^a (overall period, DCO 29 April 2024).....	90
Table 32: Most common AEs of any cause by preferred term (overall period, SAS, DCO 29 April 2024).....	91
Table 33: Characteristics of the <i>de novo</i> economic model	104
Table 34: Intervention and comparator included in the CEM.....	108
Table 35: Summary of endpoints in the model (DCO 29 April 2024).....	109
Table 36: Goodness of fit statistics for standard parametric models for EFS	112
Table 37: Goodness of fit statistics for standard parametric models for MFS.....	117
Table 38: Goodness of fit statistics for standard parametric models for OS	122
Table 39: Clinician overall survival survival curve recommendations for perioperative durvalumab and control arm	124
Table 40: External literature for OS in the control arm.....	125
Table 41: Base case curve selection for EFS, MFS and OS	127
Table 42: Scenario curve selection for EFS, MFS and OS	127
Table 43: Results of MMRM analysis for HSUs in the NIAGARA trial	130
Table 44: Estimated marginal means for HSUs from the disease-state only MMRM	131
Table 45: Adverse events disutilities used in the model	132
Table 46: Summary of HSUs used in the CEM.....	133
Table 47: Drug acquisition costs identified for the neoadjuvant and adjuvant treatment regimens	134
Table 48: Treatment administration cost inputs	135
Table 49: Proportion of patients receiving treatment in each cycle of the model.....	136
Table 50: Health care resource use by health state	136
Table 51: Radical cystectomy frequency	137
Table 52: Radical cystectomy costs.....	137
Table 53: Adverse event management costs.....	138
Table 54: Cost inputs for subsequent treatments	139
Table 55: End-of-life costs	139
Table 56: Base-case inputs	141
Table 57: List of assumptions for the base-case cost effectiveness analysis	143
Table 58: Pairwise incremental cost effectiveness results – Base case (deterministic)	144
Table 59: Pairwise incremental cost effectiveness results – Base case (probabilistic).....	145
Table 60: Top ten parameters based on the impact on ICER for perioperative durvalumab versus SoC	148
Table 61: List of scenario analyses.....	150
Table 62: Scenario analyses results	151
Table 63: Pairwise incremental cost effectiveness results – scenario analysis (deterministic)	152

List of Figures

Figure 1: Management of resectable MIBC in the UK according to European guidelines validated with the UK-based clinical experts.....	24
Figure 2: The UK resectable MIBC pathway of care, incorporating validated positioning for perioperative durvalumab in MIBC.....	27
Figure 3: NIAGARA trial design	33
Figure 4: Multiple testing procedure for controlling the type I error rate	45
Figure 5: KM plot of EFS per BICR or by central pathology in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	51
Figure 6: NIAGARA trial pCR rate (FAS [ITT population], Formal analysis DCO 14 January 2022, Re-analysis DCO 29 April 2024).....	53
Figure 7: KM plot of overall survival in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	55
Figure 8: KM plot of EFS, per investigator or local biopsy review, in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	57
Figure 9: KM plot of MFS in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	59
Figure 10: KM Plot of disease-specific survival in NIAGARA trial (FAS [ITT population], DCO 29 April 2024).....	60
Figure 11: KM plot of DFS in NIAGARA trial (Cystectomy population, DCO 29 April 2024). 62	
Figure 12: KM plot of time from randomisation to subsequent progression or recurrence post-EFS event (PFS-2) in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024) . 63	
Figure 13: Subgroup analysis forest plot for event-free survival (FAS [ITT population] DCO 29 April 2024).....	68
Figure 14: Subgroup analysis forest plot for overall survival (FAS [ITT population] DCO 29 April 2024).....	69
Figure 15: Representation of NIAGARA and CheckMate-274 trials	75
Figure 16: Schematic Overview of the Survival time-adjusted ITC Methodology	77
Figure 17: Kaplan-Meier plots for disease-free survival in the high-risk PD-L1 and non-high-risk groups in the control and counterfactual arm of the NIAGARA trial (log-logistic model with constant AF)	82
Figure 18: Kaplan-Meier plots for adjuvant-OS in the high risk and non-high-risk groups in the control and counterfactual arm of the NIAGARA trial	83
Figure 19: Kaplan-Meier plots for EFS comparing perioperative durvalumab (D+G+C) with G+C (control arm) and G+C+N (counterfactual arm) with and without re-censoring	84
Figure 20: Kaplan-Meier plots for OS comparing perioperative durvalumab (D+G+C) with G+C (control arm) and G+C+N (counterfactual arm) with and without re-censoring	86
Figure 21: Economic model structure	105
Figure 22: Illustration of partitioned survival model simulation technique for four-health states	107
Figure 23: Independent spline hazard curves for EFS.....	113
Figure 24: Independent spline normal curves for EFS.....	114
Figure 25: Independent spline odds curves for EFS	114
Figure 26: Base case curve selections for EFS	115
Figure 27: Independent spline hazard curves for MFS	118
Figure 28: Independent spline normal curves for MFS	118
Figure 29: Independent spline odds curves for MFS	119

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Figure 30: Base case curve selections for MFS	120
Figure 31: Independent standard parametric curves for OS	123
Figure 32: Independent standard parametric hazard rate plot for OS	124
Figure 33: Base case curve selections for OS	126
Figure 34: Cost effectiveness plane (Incremental costs and QALYs perioperative durvalumab versus SoC) – base-case	146
Figure 35: Cost effectiveness acceptability curve – base-case	146
Figure 36: Tornado diagram based on the impact on ICER for perioperative durvalumab vs. G+C	149
Figure 37: Cost effectiveness plane (Incremental costs and QALYs perioperative durvalumab versus adjuvant nivolumab)	153
Figure 38: Cost effectiveness acceptability curve (perioperative durvalumab versus adjuvant nivolumab)	153

List of abbreviations

Abbreviation	Definition
AE	Adverse events
AFT	Accelerated failure time
AIC	Akaike Information Criteria
AZ	AstraZeneca
BC	Bladder cancer
BIC	Bayesian Information Criteria
BICR	Blinded Independent Central Review
BNF	British National Formulary
CD80	Cluster of differentiation 80
CDA-AMC	Canada's Drug Agency
CEM	Cost effectiveness model
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CONSORT	Consolidated standards of reporting trials
CRD	Centre for Reviews and Dissemination
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCO	Data cut-off
DFS	Disease-free survival
DM	Distant metastasis
DSS	Disease-specific survival
DSU	Decision support unit
EAG	External assessment group
EAU	European Association of Urology
ECOG	Eastern cooperative oncology group
EF	Event-free
EFS	Event-free survival
EMA	European medicines agency
eMiT	Electronic market information tool
EOL	End-of-life
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D-5L	EuroQol 5-Dimension 5-Level
EQ-VAS	EuroQol-visual analogue scales
ESMO	European Society for Medical Oncology
EU	European union
FAS	Full analysis set

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

GFR	Glomerular filtration rate
GHS/QOL	Global health status/ Quality of life
HCRU	Healthcare resource utilisation
HR	Hazard ratio
HRQoL	Health-related quality of life
HSU	Health state utility
HTA	Health technology assessment
IA	Interim analysis
IA-1	First interim analysis
IA-2	Second interim analysis
ICD	International Classification of Diseases
ICER	Incremental cost effectiveness ratio
IgG1k	Immunoglobulin G1 kappa
ImAE	Immune-mediated adverse event
IO	Immuno-oncology
ITT	Intention-to-treat
IVRS	Interactive voice response system
KM	Kaplan-Meier
LABC	Life After Bladder Cancer
LR	Locoregional recurrence
LY	Life years
mBC	Metastatic bladder cancer
MFS	Metastasis-free survival
mg	Milligram
MHRA	Medicines and Healthcare products Regulatory Agency
MIBC	Muscle invasive bladder cancer
MMRM	Mixed effects repeated measures
MTP	Multiple testing procedure
N/A	Not applicable
NAC	Neoadjuvant chemotherapy
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMIBC	Non-muscle-invasive bladder cancer
ONS	Office of the National Statistics
OS	Overall survival
OS5	Overall survival at five years
OWSA	One-way sensitivity analysis
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
pCR	Pathological complete response

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

PD	Progressed disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PD-L2	Programmed death-ligand 2
PFS	Progression-free survival
PFS-2	Time from randomisation to subsequent progression or recurrence post-EFS event
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PH	Proportional hazards
PK	Pharmacokinetics
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ProBCI	Prospective Bladder Cancer Infrastructure
PRO-CTCAE	Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life years
QoL	Quality of life
QQ	Quantile-quantile
RC	Radical cystectomy
RCT	Randomised clinical trial
RD	Recurred disease
RECIST	Response evaluation criteria in solid tumours
RR	Response rate
SAE	Serious adverse event
SAS	Safety analysis set
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard-of-care
TCC	Transitional cell carcinoma
TNM	Tumour-node-metastasis
TSD	Technical support document
TTD	Time to deterioration
UK	United Kingdom
VAS	Visual analogue scale
WTP	Willingness-to-pay

1 Decision problem, description of the technology and clinical care pathway

1.1 Decision problem

The objective of the current evaluation is to determine the clinical and cost effectiveness of durvalumab (IMFINZI®) in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after radical cystectomy (RC), for the treatment of patients with resectable muscle invasive bladder cancer (MIBC) (1). The aforementioned regimen, hereinafter referred to as 'perioperative durvalumab', involves four cycles of durvalumab combined with gemcitabine and cisplatin as neoadjuvant therapy, followed by eight cycles of durvalumab as a single-agent adjuvant therapy (1). The marketing authorisation of perioperative durvalumab in MIBC is supported by the robust clinical evidence from the NIAGARA clinical trial (2).

MIBC poses a significant clinical challenge as it is associated with rapid progression, aggressive tumours, high recurrence rates, and limited effective treatment options (3). Standard treatments like RC and neoadjuvant chemotherapy (NAC) offer poor survival outcomes, with a five-year overall survival (OS) rate of less than 60% (4). Patients with MIBC continue to face high risk of disease recurrence and progression even after NAC and RC (5-8), profoundly impacting patients' quality of life (QoL) (9, 10). Although nivolumab is available as an adjuvant immuno-oncology (IO) therapy for MIBC, following NICE recommendation, it is used as a reactive intervention, only in patients at high risk of recurrence following RC with a programmed death-ligand 1 (PD-L1) expression $\geq 1\%$ and for whom adjuvant cisplatin-based chemotherapy is not suitable (11). There is an unmet need in the current treatment pathway for cisplatin-eligible patients with resectable MIBC for treatment regimens that can address the following:

- Increase long-term survival outcomes while reducing disease recurrence and progression rates.
- Utilise the potential of IO therapies in both neoadjuvant and adjuvant settings to enhance curative intent surgery outcomes.
- Facilitate the use of IO treatment for all patients, taking a proactive approach.

Addressing the highlighted unmet need is crucial, as MIBC represents the last opportunity to cure the patient before the disease advances to metastatic bladder cancer (mBC).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

A perioperative regimen deploying the same IO therapy before and after surgery, has the potential to improve patient outcomes by priming anti-tumour immunity before surgery and sustaining immunosurveillance to eliminate micro-metastatic disease after surgery, thereby enhancing the likelihood of long-term disease control (12).

The NIAGARA trial is the first Phase III study of perioperative IO in MIBC to demonstrate significantly improved OS for patients receiving perioperative durvalumab as compared to NAC alone (hazard ratio [HR]=0.75; 95% confidence interval [CI] 0.594, 0.934; p=0.0106) (2). The NIAGARA trial also showed a statistically significant improvement in event-free survival (EFS) in favour of perioperative durvalumab, versus NAC alone without compromising the ability of patients to undergo RC (HR=0.68; 95% CI: 0.558, 0.817; p<0.0001) (2). The survival benefits demonstrated confirm that perioperative durvalumab effectively addresses the unmet need of cisplatin-eligible resectable MIBC and therefore it is poised to become the new standard of care in this population.

The decision problem addressed in the current appraisal is broadly consistent with the final scope published by NICE, with any deviations detailed in Table 1 (13).

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final scope issued by NICE
Population	Adults with resectable MIBC who are eligible to receive gemcitabine and cisplatin		The population aligns with the final scope and the expected license
Intervention	Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant)	Durvalumab (IMFINZI®) in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after RC	The intervention is in line with the final scope and the expected license
Comparator(s)	Established clinical management without durvalumab, including but not limited to: - As neoadjuvant (before surgery) treatment: - cisplatin-based chemotherapy - As adjuvant (after surgery) treatment: - nivolumab (for people whose tumours express PD-L1 at a level of 1% or more) - best supportive care	Established clinical management without durvalumab: - Cisplatin-based chemotherapy (gemcitabine + cisplatin) followed by RC and: - No treatment - or - Nivolumab (for patients whose tumours express PD-L1 ≥ 1% and present high-risk of recurrence (ypT2 to ypT4a or ypN+) after surgery)	The comparators considered in the current appraisal are aligned with current practice as validated through interviews with UK-based MIBC clinical experts (14). - Comparators have been aligned with the single treatment decision point for perioperative durvalumab, which is made before surgery and dictates both pre- and post- RC treatment. - Adjuvant treatments are captured as treatment following NAC and RC before recurrence: - Best supportive care or no treatment is captured by NIAGARA control arm (gemcitabine + cisplatin followed by no treatment after RC) - Adjuvant nivolumab -aligned with final scope population and TA817 positioning: patients at high risk of recurrence and with PD-L1 ≥ 1%, only when adjuvant cisplatin-based chemotherapy is unsuitable. Accordingly, for cisplatin-eligible patients, adjuvant nivolumab is appropriate only if the patient has already received NAC. While the company has made an effort to include the extensive list of proposed comparators for completeness, it is important to note—as detailed in section 2.9—that perioperative durvalumab and adjuvant nivolumab are two separate therapeutic strategies, that are not interchangeable, with one being a proactive therapeutic approach (perioperative durvalumab) while the other being considered escalation therapy (adjuvant nivolumab) after

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final scope issued by NICE
			insufficient response from NAC alone and RC. Decision on nivolumab treatment is only made after surgery and it represent a reactive intervention based on post-surgical assessment and PD-L1 expression status. The introduction of perioperative durvalumab is expected to displace the use of NAC alone, which in turn will reduce the use of subsequent treatments—given the restrictions on adjuvant nivolumab and the limited overlap between patient populations, this will most often result in no further treatment. As such, the company has included a comparison with adjuvant nivolumab as an additional scenario analysis.
Outcomes	The outcome measures to be considered include: • OS • EFS • PFS • DFS • RR • AE • HRQoL	The outcome measures to be considered include: • OS • EFS • pCR • MFS • DSS • DFS • PFS-2 • AE • HRQoL	The outcomes included in the appraisal provide detailed evidence of the efficacy of perioperative durvalumab in MIBC and are aligned with the outcomes measured in the NIAGARA clinical trial. Progression-free survival (PFS) was not an endpoint in the NIAGARA trial due to the limited utility of PFS for decision-making in perioperative regimens in comparison to OS and EFS. Additionally, the company has included the recently published results of Metastasis-free survival (MFS) and Disease-specific survival (DSS), as these secondary endpoints support decision-making by increasing certainty. MFS is a valuable endpoint, as the prevention of metastasis can significantly improve long-term outcomes (15-17). DSS, when considered alongside OS, strengthens the interpretation of survival outcomes specific to MIBC by isolating disease-related mortality and reducing confounding from unrelated causes of death. pCR has been included as it is co-primary endpoint in NIAGARA trial and serves to assess neoadjuvant treatment response rather than response rate (RR). Additionally, the proportion of patients undergoing RC and time to RC have been included. When introducing neoadjuvant or perioperative treatments, it is essential to ensure that the intervention does not delay, preclude, or compromise curative-intent surgery.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of	Cost effectiveness evidence has been provided for the full licensed patient population for NIAGARA trial -	N/A

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final scope issued by NICE
	incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after RC, for the treatment of patients with resectable MIBC. The cost effectiveness analysis conducted is aligned with the specifications requested in the final scope.	
Subgroups to be considered	If the evidence allows subgroups will be considered based on: PD-L1 status	Subgroup analyses from the NIAGARA trial have been presented in Section 2.7 to demonstrate the efficacy of perioperative durvalumab across prespecified subgroups, among other patient characteristics. Stratification factors included clinical tumour stage, renal function, and tumour PD-L1 expression level.	PD-L1 subgroup analysis was included as a stratification factor of the NIAGARA trial. However, the relevance of PD-L1 subgroup for decision-making is very limited (14). As the NIAGARA trial demonstrated consistent efficacy across subgroups and the lack of evidence supporting PD-L1 as a treatment effect modifier for MIBC (18), the primary focus of the appraisal is the ITT population.
Special considerations including issues related to equity or equality	N/A	AstraZeneca do not anticipate any equality issues to arise with the introduction of perioperative durvalumab in the UK clinical practice. However, evidence suggests that men are more likely to develop BC, while women often present with more advanced and high-	N/A

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final scope issued by NICE
		grade disease and have a worse prognosis due to longer diagnostic delays rather than differences in treatment patterns (19-21).	

Abbreviations: AE: adverse effects/events; BC: bladder cancer; BSC: best supportive care; DFS: disease-free survival; DSS: disease-specific survival; EAU: European Association of Urology; EFS: event-free survival; ESMO: European Society for Medical Oncology; HRQoL: health-related quality of life; ITT: intention-to-treat; MFS: metastasis-free survival; MIBC: muscle invasive bladder cancer; N/A: not applicable; NAC: neoadjuvant chemotherapy; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: overall survival; pCR: pathological complete response; PD-L1: programmed death-ligand 1; PFS: progression-free survival; PFS-2: time from randomisation to subsequent progression or recurrence post-EFS event; RC: radical cystectomy; RR: response rates; SoC: Standard-of-care; UK: United Kingdom.

Source: Durvalumab final scope [ID6168] (13).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

1.2 Description of the technology being evaluated

A description of the technology being evaluated is presented in Table 2. The summary of product characteristics (SmPC) for durvalumab is available in Appendix A.

Table 2: Technology being evaluated

UK approved name and brand name	Durvalumab (IMFINZI®)
Mechanism of action	Durvalumab is a fully human, high affinity, IgG1κ monoclonal antibody that selectively blocks the interaction of PD-L1 with PD-1 and CD80 (B7-1) while leaving PD-1/PD-L2 interaction intact. Durvalumab does not induce antibody dependent cell-mediated cytotoxicity. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances anti-tumour immune responses. These anti-tumour responses may result in tumour elimination (1).
Marketing authorisation/CE mark status	An application for the UK MHRA marketing authorisation in adults with resectable MIBC was made and is expected to be approved in [REDACTED] An application for EMA marketing authorisation for the same indication was made and type II variation was adopted by CHMP on the 22 nd May 2025.
Indications and any restriction(s) as described in the SmPC	Durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable MIBC (1).
Method of administration and dosage	1500 mg ^a in combination with chemotherapy every three weeks (21 days) for four cycles prior to surgery, followed by 1500 mg ^a every four weeks as monotherapy for up to eight cycles after surgery (1).
Additional tests or investigations	No additional tests or investigations are required for durvalumab
List price and average cost of a course of treatment	List price: £2,466.00. Overall cost of a course of treatment at list price: £88,776.00 Average cost of treatment cycle: £7,398.00
Patient access scheme (if applicable)	Confidential commercial access arrangement: [REDACTED] Overall cost of a course of treatment at net price: [REDACTED] Average cost of treatment cycle (Confidential commercial access arrangement): [REDACTED]

Notes: ^aPatients with a body weight of 30 kg or less must receive weight-based dosing of durvalumab at 20 mg/kg. In combination with chemotherapy, dose durvalumab at 20 mg/kg every three weeks (21 days) prior to surgery, followed by monotherapy at 20 mg/kg every four weeks after surgery until weight increases to greater than 30 kg.

Abbreviations: AZ: AstraZeneca; EMA: European Medicines Agency; IgG1κ: immunoglobulin G1 kappa; CD80: cluster of differentiation 80; CHMP: Committee for Medicinal Products for Human Use; MHRA: Medicines and Healthcare products Regulatory Agency; mg: milligram; MIBC: muscle-Invasive Bladder Cancer; PAS: Patient access scheme; PD-1: programmed death-1; PD-L1: programmed Death Ligand 1; PD-L2: programmed Death Ligand 2; SmPC: summary of product characteristics; UK: United Kingdom.

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1.3 Health condition and position of the technology in the treatment pathway

Summary of health condition and position of the technology in the treatment pathway

Disease overview

- Bladder cancer (BC) is the 9th most prevalent cancer globally; MIBC accounts for 25% of BC cases.
- MIBC is defined by invasion of the detrusor muscle and represents the last opportunity for curative treatment.
- **MIBC carries a high mortality risk: ~50% of patients relapse or progress to metastatic disease within five years despite standard treatment.**
- BC has the highest lifetime cost of any cancer, due to frequent recurrence, intensive monitoring, and substantial direct and indirect costs.

Standard of Care treatment in the UK

- **For eligible patients, European and UK guidelines recommend cisplatin-based NAC (gemcitabine and cisplatin) followed by RC**, with NAC offering only marginal survival benefits (~5% improvement).
- Most patients do not receive treatment after radical cystectomy; adjuvant nivolumab is only offered to a restricted subset of patients.
- Adjuvant nivolumab is positioned as a reactive intervention for high-risk, PD-L1 $\geq$ 1% patients who are unsuitable for adjuvant cisplatin, failing to address the unmet need of the larger MIBC patient population in the appraisal scope.

Unmet need

- There is a critical need for therapies that reduce recurrence and progression, especially in cisplatin-eligible patients, as **current options fail to deliver durable survival or disease control.**
- **There is a need of perioperative IO regimen**, deploying the same IO therapy before and after surgery, that can improve surgery outcomes by priming anti-tumour immunity before RC and sustain immunosurveillance to eliminate micro-metastatic disease after RC, thereby enhancing the likelihood of long-term disease control.

Proposed positioning of perioperative durvalumab

- Perioperative durvalumab regimen involves four cycles of durvalumab combined with gemcitabine and cisplatin as neoadjuvant therapy, followed by eight cycles of durvalumab as a single-agent adjuvant therapy.
- The addition of durvalumab to standard neoadjuvant therapy enhances the therapeutic efficacy through synergistic interaction with chemotherapy, and its continuation as adjuvant treatment maintains immunosurveillance after surgery, supporting the

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elimination of micro-metastatic disease

- **The NIAGARA trial is the first and only study of a perioperative IO regimen demonstrating a statistically significant improvement in OS and EFS.**
- Results show a 25% reduction in the risk of death and a 32% reduction in the risk of progression/recurrence or death compared to NAC followed by RC. The benefit was consistent across all patient subgroups.
- **These unprecedented results have led the EAU to update the clinical guidelines to incorporate perioperative durvalumab, even before formal approval by the EMA.**
- The proactive, single-decision point intervention, initiated at the start of the neoadjuvant setting, enables early and streamlined treatment planning, facilitates optimal scheduling of clinic visits, ensures clear and consistent communication with patients, and prevents the need for repeated evaluations for adjuvant therapy.
- Perioperative durvalumab minimises uncertainty and reduces the burden of ongoing treatment decisions – ultimately enhancing both clinical outcomes and patient experience, reducing economic burden on payers, and improving overall treatment care.
- **UK-based clinical experts consulted by the company unanimously agree that perioperative durvalumab will represent a paradigm shift and become standard of care for eligible patients.**
- **Perioperative durvalumab represents a transformative opportunity in the treatment of cisplatin-eligible resectable MIBC patients.**

1.3.1 Disease overview

BC is the most common malignancy of the urinary system that originates from the cells lining the urinary tract (22). It is particularly common among older adults, with risk factors including smoking, chemical exposure, and chronic bladder inflammation (23).

1.3.1.1 Disease classification, clinical presentation, diagnosis and staging of bladder cancer

Classification

The classification of BC is based on the extent of tumour invasion within the bladder walls (22). Non-muscle-invasive bladder cancer (NMIBC) is confined to the inner urothelial layers and does not penetrate the detrusor muscle. In contrast, MIBC, the focus of the appraisal, refers to high-grade tumours that have infiltrated the deep detrusor muscle layers (24-26). MIBC represents the final stage at which curative treatment remains a viable option for patients, with the primary goal of preventing progression to advanced or mBC involving distant organs and tissues (4).

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Clinical presentation

Most BC patients are symptomatic at diagnosis. Painless macroscopic haematuria is the most frequent initial symptom experienced by over 80% patients with MIBC (27, 28). Other presenting clinical signs and symptoms include microscopic haematuria, urinary urgency, dysuria, and in more advanced tumours, pelvic pain or symptoms related to urinary tract obstruction (24, 27). A small proportion of patients are asymptomatic and detected incidentally through imaging and cystoscopy (29, 30).

Diagnosis

The European Association of Urology (EAU) guidelines for MIBC diagnosis recommend a comprehensive approach incorporating clinical evaluation, imaging, and histopathological assessment (4). Cystoscopy remains the gold standard for confirming MIBC and urinary cytology can be recommended, particularly for high-grade tumours. In cases where tumour visualisation through imaging is unequivocal, patients may proceed directly to transurethral resection of the bladder tumour without the need for diagnostic cystoscopy. Bladder imaging modalities are also essential for assessing suspected bladder masses (4). Additional methods, such as photodynamic diagnosis for carcinoma *in situ* detection and assessments of prostatic urethra involvement in male patients, are recommended to enhance diagnostic precision, ensuring a more refined and targeted clinical evaluation (4).

The diagnostic recommendations for MIBC provided by the European Society for Medical Oncology (ESMO) are consistent with the guidelines established by the EAU (4, 31).

Staging

MIBC is staged using the eighth edition of the Tumour-Node-Metastasis (TNM) classification systems developed by the Union for International Cancer Control and the American Joint Committee on Cancer (32). Staging is determined by the extent of the primary tumour (T), regional lymph node involvement (N), and the presence of distant metastases (M) (32). Clinical staging is based on imaging, physical examination, and biopsy results, while pathological staging is determined after surgical removal of the tumour, providing a more definitive assessment of the disease extent (33, 34).

Clinically and pathologically, MIBC tumours are staged as T2, T3, and T4 based on their depth of invasion, ranging from muscle invasion (T2) to invasion of surrounding tissues or nearby organs (T4), while the nodal involvement is staged as N0, N1, N2, and N3 based on the number and location of regional lymph nodes affected by metastasis, ranging from no regional lymph node

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metastasis (N0) to metastasis in common iliac lymph node(s) (N3) (33-35). The clinical stage of MIBC and the focus of the current appraisal is represented as T2N0/1M0-T4aN0/1M0 (32).

Accurate staging is challenging, and several studies have reported the risk of mis-staging in BC, with patients clinically staged as T2N0 often found to be >T2N0 after RC, leading to inequities in treatment access and impacting overall outcomes (36-39).

1.3.1.2 Epidemiology

Prevalence

BC is the ninth most prevalent cancer globally. In the United Kingdom (UK), BC is the eleventh most common cancer, with a five-year prevalence of 79,763 per 100,000 individuals in 2022 (40). In England, BC was the seventh most common cancer, with a five-year prevalence rate of 108.22 per 100,000 individuals in 2021 (41). Malignant BC cases (International Classification of Diseases [ICD] 10 code: C67 [Malignant neoplasm of bladder]) were 41.99 per 100,000 individuals (41).

Gender disparities in BC are evident in the UK, with men accounting for over three times higher prevalence rate than in females (41), making it the seventh most common cancer among males in the UK as of 2022 (42). The higher prevalence of BC in males is attributed to increased likelihood of males being smokers and working in industries associated with exposure to carcinogenic substances (43-45).

Incidence

In the UK, the annual incidence rate of BC is 0.04%, translating to approximately 17,544 new cases each year (41). Of these, 90% cases are diagnosed as urothelial carcinoma, the most common histological subtype, accounting for 15,790 cases (23).

MIBC accounts for approximately 25% of BC cases (46).

1.3.1.3 Burden of disease

1.3.1.3.1 Clinical burden

Mortality

In 2022, BC ranked as the thirteenth leading cause of cancer deaths globally, with 220,596 deaths recorded (47), and an age-standardised mortality rate of 2.9 per 100,000 individuals (40). A systematic literature review (SLR) found that MIBC mortality rates in the UK range from 53.9% to 60.4%, with variations influenced by the timing of outcome measurements and the scheduling of

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the treatment in relation to the RC, as delays or suboptimal timing may impact disease progression and long-term survival outcomes (16, 48).

Recurrence/progression

BC imposes a significant burden on patients and the National Health Service (NHS) due to high recurrence rate (34, 42). MIBC is particularly aggressive, with nearly 50% of patients undergoing curative-intent treatment eventually relapsing and developing metastatic disease, most commonly within the first five years (24, 49).

MIBC represents the final stage before progression to mBC, and hence preventing recurrence and reducing progression rates become highly critical as treatment goals. Current data highlight an unmet need for new treatments that can reduce or prevent disease progression and improve OS in the MIBC population.

1.3.1.3.2 Humanistic burden

Patients with BC report worse experiences than patients with any other pelvic cancers, as shown by data from the 2011/2012 English Cancer Patient Experience Survey conducted within NHS hospitals (50). Frequent urinary dysfunction, pain, fatigue and reduced mobility can severely impact patients' daily life and routine function (27). These physical burdens are compounded by psychological distress, including heightened anxiety and depression due to the uncertainty of disease trajectory, which collectively impair emotional and social health (51). Furthermore, disease recurrence and progression in BC significantly diminish patients' overall well-being, intensifying both the physical and emotional burdens they face. Caregivers also face considerable strain, managing complex care needs and coping with emotional challenges, particularly during advanced stages of the disease (52).

Although the current standard of care (SoC) treatments for MIBC (NAC followed by RC) offer potential for disease control to a certain extent, they fall short in providing long-term survival benefits and are associated with high recurrence rates (4). As a result, patients and associated caregivers often continue to experience significant psychological stress (53). There is an unmet need in patients with MIBC for a novel therapy that can not only prolong survival but also reduce or prevent disease recurrence and progression, thereby alleviating their emotional burden associated with the fear of relapse.

1.3.1.3.3 Economic burden

Direct costs

A study conducted in 2012 estimated that the healthcare expenses of BC including primary care, outpatient and inpatient services, accident and emergency care, and medication, accounted for 59% of the total cost and represent 5% of all cancer-related healthcare expenses (54). BC has the highest lifetime treatment costs per patient among all cancers, driven by high recurrence rates and the need for ongoing invasive monitoring (55). BC management remains suboptimal, as reflected by NHS England data showing 52,437 hospital admissions and 30,679 day cases due to malignant neoplasms of the bladder (ICD-10 code: C67) between 2020 and 2021 (56). In the UK, the total direct healthcare costs of BC were estimated at €286 million in 2012, with inpatient care alone accounting for €153 million (54). Additionally, disease progression to mBC necessitates greater healthcare resource utilisation (HCRU) than earlier stages, including frequent hospitalisations, advanced imaging, and additional therapeutic interventions (34).

Indirect costs

Beyond direct medical expenditures, BC is associated with high indirect costs, including lost productivity due to illness, workplace absenteeism, disability, and premature death (57). According to a study conducted in 2012, the indirect costs comprising of productivity losses due to morbidity and mortality, as well as informal care costs amounted to approximately €257 million in the UK (54).

A substantial economic burden is highlighted by the direct and indirect costs associated with the treatment of BC, driven by high recurrence rates and the need for long-term monitoring, resulting in the highest lifetime treatment costs among all cancers. The financial strain on healthcare systems and society underscores an urgent need for more effective and economically sustainable treatment options that can reduce recurrence rates and disease progression, thereby alleviating the economic burden of payers.

1.3.2 Clinical pathway of care

1.3.2.1 Current treatment pathway – established/recommended treatments

1.3.2.1.1 Standard of Care treatment in the UK

EAU and ESMO therapeutic guidelines emphasise the importance of a multidisciplinary approach for treating MIBC patients. In the context of the scope of this appraisal, for MIBC patients with cT2-T4a N0-1 M0 disease, clinical guidelines recommend RC with pelvic lymph node dissection. Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

as the standard treatment (4, 31). Additionally, for patients eligible for cisplatin-based chemotherapy, which is the target population of the appraisal, clinical guidelines recommend the use of cisplatin-based chemotherapy as neoadjuvant therapy prior to RC, as it has shown to improve survival outcomes compared to RC alone (4).

External clinical validation interviews for the purpose of this appraisal were conducted with several leading urologists and oncologists who manage patients with MIBC in routine clinical practice in the UK (hereafter referred to as the UK-based clinical experts). The UK-based clinical experts corroborated the adoption of the EAU and ESMO guidelines within their practice and confirmed that gemcitabine plus cisplatin is the standard NAC regimen in the UK (14).

Current cisplatin eligibility criteria include an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, adequate renal function (glomerular filtration rate [GFR] of 60 mL/min/1.73 m² or above), and no significant hearing loss, peripheral neuropathy, or cardiac dysfunction (4, 31). Additionally, the UK-based clinical experts have noted that a lower GFR threshold (40-<60 mL/min/1.73) may be considered in their practice when using a split-dose regimen (14). The population included in the NIAGARA trial is aligned with the cisplatin eligibility criteria (2).

1.3.2.1.2 Additional therapeutic options

In addition to the current SoC (NAC followed by RC) treatment guidelines include adjuvant treatments, such as adjuvant nivolumab (4, 31), that are aimed at eliminating residual disease, reducing the risk of recurrence, and improving long-term outcomes by targeting micro-metastases (4).

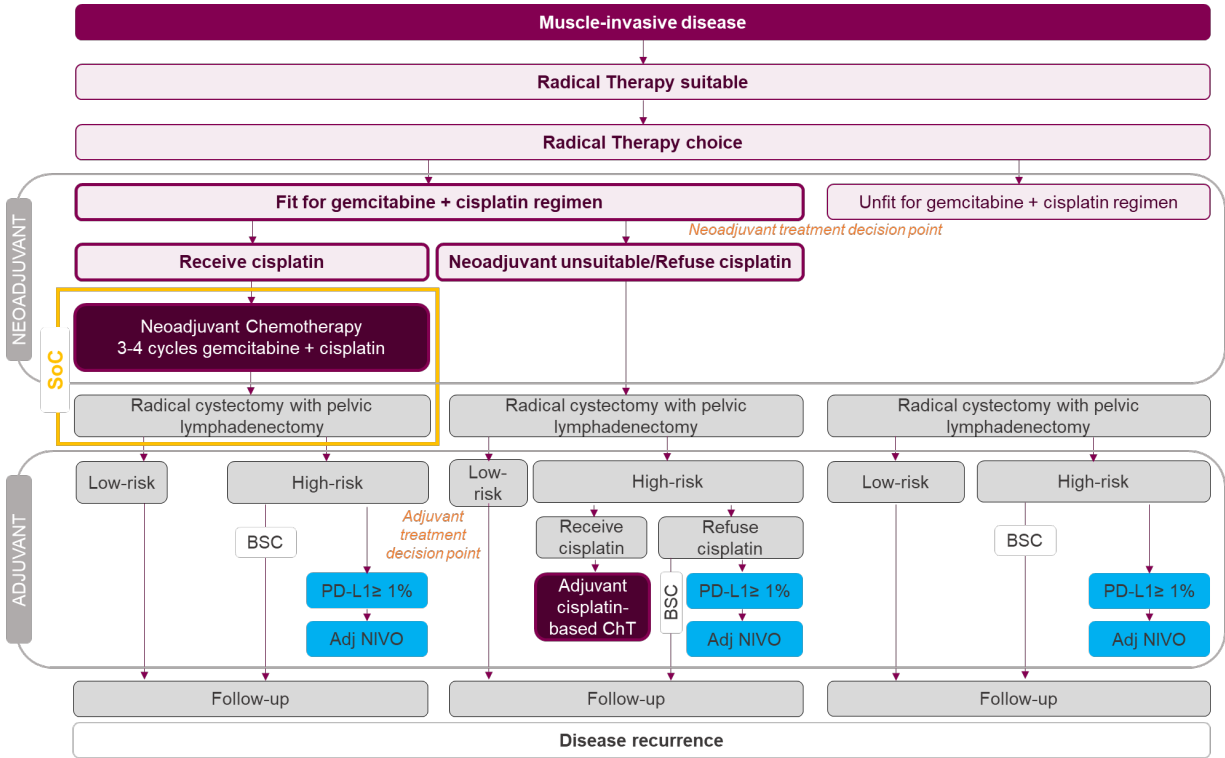
Adjuvant nivolumab

In 2022, NICE approved adjuvant nivolumab for patients at high risk of recurrence following RC, specifically for those with PD-L1 expression $\geq 1\%$ and for whom cisplatin-based adjuvant chemotherapy is not suitable (11). In the case of cis-eligible patients adjuvant nivolumab eligibility criteria includes pathological stage of the resected tumour ypT2-ypT4a or any ypN+ stage, PD-L1 expression on $\geq 1\%$ of tumour cells as determined by an approved and validated PD-L1 assay and adjuvant platinum-based chemotherapy being unsuitable due to prior neoadjuvant chemotherapy (11). Adjuvant nivolumab serves as a reactive approach in MIBC, guided by the postoperative risk of recurrence of the patient and PD-L1 expression (11). The duration of the treatment is one year (i.e., 13 cycles every 4-weeks)

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The clinical care pathway for the management of resectable MIBC, as recommended by EAU and ESMO, and validated with the UK-based clinical experts is illustrated in Figure 1.

Figure 1: Management of resectable MIBC in the UK according to European guidelines validated with the UK-based clinical experts



Notes: Figure adapted from: Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer and AstraZeneca internal clinical experts. The restriction on the use of nivolumab to patients with PD-L1 expression $\geq 1\%$ and for whom cisplatin is not a suitable option is aligned with the NICE recommendation (11). Abbreviations: Adj: adjuvant; BSC: best supportive care; ChT: chemotherapy; EAU: European Association of Urology; ESMO: European Society for Medical Oncology; MIBC: muscle invasive bladder cancer; NICE: National Institute for Health and Care Excellence; NIVO: nivolumab; PD-L1: programmed death-ligand 1; SoC: standard-of-care; UK: United Kingdom. Sources: EAU 2025 (4); ESMO (31); NICE 2022 (11)

1.3.2.2 Unmet need within the current treatment pathway

Overview

RC is used with curative intent in resectable MIBC. However, for many patients, it is associated with high recurrence rates and does not provide long-term survival benefits. It is estimated that up to 50% of MIBC patients will progress within five years, with either local recurrence or distant progression, even after undergoing RC (4). When the disease spreads to distant organs and tissues, causing metastasis, managing the condition becomes considerably more challenging, patient outcomes are notably poorer, and the possibility of curative-intent treatment is lost. Furthermore, the associated cost of managing metastatic disease increases substantially (4).

Among the other available treatment regimens for MIBC:

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

- In neoadjuvant setting, clinical experts have confirmed that gemcitabine-cisplatin is the standard in the UK, which offers only a modest survival benefit and is associated with high recurrence and progression rate (4),
- In adjuvant setting, active treatment is use as reactive approach based on high-risk of recurrence after RC and it is furthermore limited to PD-L1 $\geq 1\%$ patients for whom cisplatin is not a suitable treatment option, thereby restricting its potential benefit in a wide range of MIBC patients (14).

The limitations of the current treatments highlight an unmet need for an effective treatment option in both neoadjuvant and adjuvant settings (4). Emerging evidence from the NIAGARA trial demonstrates that IO perioperative treatment approach offers a promising solution by mitigating recurrence and progression risks, while demonstrating long-term survival benefits (2).

Standard of care – NAC followed by RC

Surgical resection remains the cornerstone of curative intent; however, its prognostic outcomes are suboptimal, with a five-year survival rate of around 50% (4). Following RC, up to 15% MIBC patients experience local pelvic recurrence, while distant recurrence affects nearly 50% (4).

Neoadjuvant treatment with cisplatin-based chemotherapy improves survival outcomes as compared to RC alone and is, therefore, considered a SoC treatment for MIBC (58). Studies have reported an extended five-year survival of 5% in patients receiving NAC followed by RC (4). Despite the survival improvement, the overall five-year OS rate still remains below 60% (4). Furthermore, the recurrence rates for MIBC following cisplatin-based NAC and RC still remains high (exceeding 50%) (4), highlighting the limited effectiveness of the current SoC.

The aforementioned data highlights that the current SoC, NAC followed by RC, offers limited survival benefits and is associated with high recurrence rates, necessitating the need for a more effective treatment.

Adjuvant IO therapy

Nivolumab (an adjuvant IO therapy) has demonstrated benefits in MIBC patients at high-risk of disease recurrence post-surgery, with PD-L1 expression $\geq 1\%$, as shown in the CheckMate-274 trial (59). The treatment was restricted to patients with PD-L1 expression $\geq 1\%$, due to uncertainty of benefit in PD-L1 negative, failing to address the needs of the larger MIBC patient population (11, 14). Therefore, adjuvant nivolumab represents a reactive intervention limited to a narrow patient cohort, restricting the opportunity for early, proactive treatment planning and depriving patients of the potential benefits of immune priming with neoadjuvant immunotherapy.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Patients in the scope of this appraisal are not only deprived of IO treatment in the neoadjuvant setting, but a large proportion of them will also be unable to receive IO as adjuvant treatment due to the restricted use of nivolumab (4).

The high likelihood of recurrence, combined with the substantial burden of disease progression to the metastatic stage, places a continuous clinical and economic burden on both patients and the payers.

Need for perioperative IO therapy

The limitations of the current neoadjuvant and adjuvant therapies to prevent early-stage recurrence and provide long-term survival in cisplatin-eligible resectable MIBC patients leave a critical gap in the treatment landscape – particularly in utilising the potential of IO therapies earlier in the disease course.

A perioperative regimen, deploying the same IO therapy before and after surgery, has the potential to improve surgery outcomes by priming anti-tumour immunity before surgery (neoadjuvant setting) and sustaining immunosurveillance to eliminate micro-metastatic disease after surgery (adjuvant setting), thereby enhancing the likelihood of long-term disease control, both of which are associated with a high risk of recurrence (12).

Adopting perioperative regimens that establish both pre- and post-surgical treatment decisions at a single, early point in the disease course provides greater certainty in treatment planning, enabling proactive management to reduce the risk of recurrence and facilitate timely interventions.

UK-based clinical experts emphasised the importance of effective treatments for resectable MIBC, highlighting the need to minimise the risk of relapse across a broader spectrum of patients. (14).

Preclinical and early clinical evidence support the synergistic potential of combining IOs with chemotherapy, providing a strong rationale for perioperative strategies that integrate neoadjuvant gemcitabine and cisplatin with IO therapies (60). The efficacy results of the NIAGARA trial demonstrate that perioperative durvalumab offers a meaningful advance in curative-intent strategies for cisplatin-eligible patients with resectable MIBC (1).

1.3.2.3 Proposed positioning of perioperative durvalumab

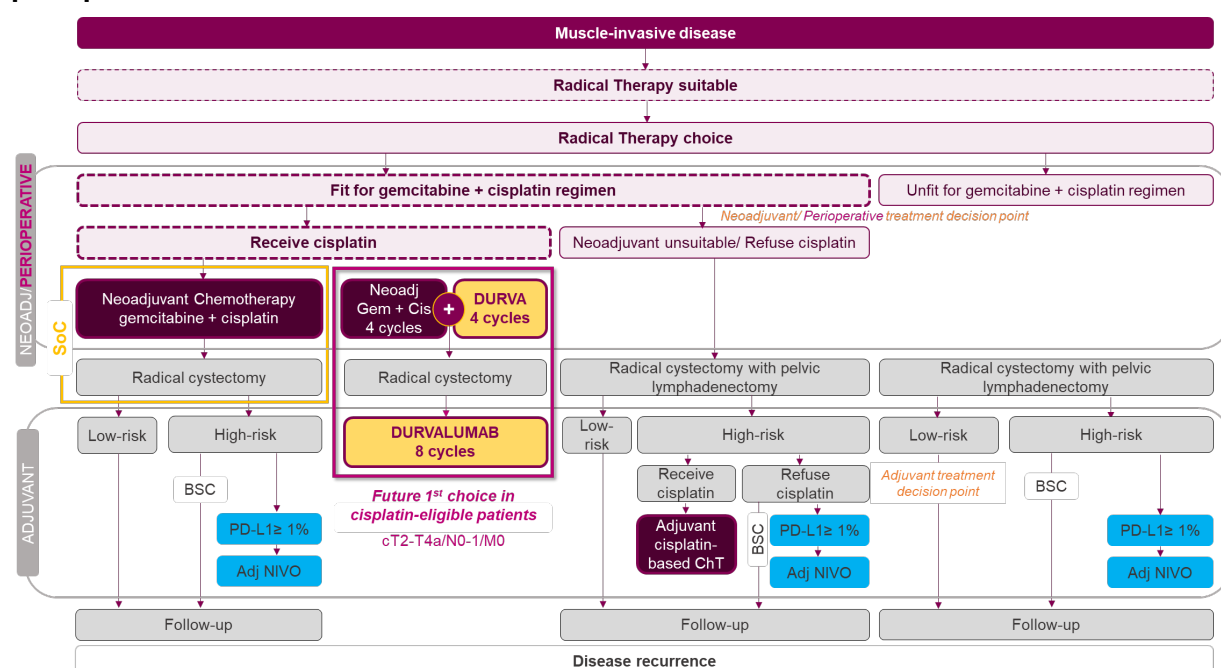
Perioperative durvalumab is the first perioperative immune checkpoint inhibitor regimen to show benefit in survival for the treatment of resectable MIBC patients who are cisplatin eligible. The proposed positioning of durvalumab as a perioperative treatment in resectable MIBC was

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

validated with the UK-based clinical experts, who unanimously concluded that perioperative durvalumab would become the preferred first choice treatment for eligible patients, marking a significant shift in the therapeutic paradigm toward more durable, recurrence-preventive strategies (14). The clinical experts also unanimously agreed that the eligibility criteria that will be adopted in clinical practice for perioperative durvalumab aligns with the inclusion criteria used in the NIAGARA trial (14).

Figure 2 shows the validated positioning of perioperative durvalumab in the current pathway of care for MIBC in the UK.

Figure 2: The UK resectable MIBC pathway of care, incorporating validated positioning for perioperative durvalumab in MIBC



Notes: Figure adapted from: Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up, EAU Guidelines on Muscle-Invasive and Metastatic Bladder Cancer and AstraZeneca internal clinical experts

The restriction on the use of nivolumab to patients with PD-L1 expression $\geq 1\%$ and for whom cisplatin is not a suitable option is aligned with the NICE recommendation (11).

Abbreviations: Adj: adjuvant; BSC: best supportive care; ChT: chemotherapy; Cis: cisplatin; cT2-T4a/N0-1/M0: cisplatin-eligible patients with resectable muscle-invasive bladder cancer; DURVA: durvalumab; EAU: European Association of Urology; ESMO: European Society for Medical Oncology; Gem: gemcitabine; MIBC: muscle invasive bladder cancer; NICE: National Institute for Health and Care Excellence; Neoadj: neoadjuvant; NIVO: nivolumab; PD-L1: programmed death-ligand 1; SoC: standard-of-care; UK: United Kingdom. Sources: EAU 2025 (4); ESMO (31); NICE 2022 (11)

The NIAGARA trial is the first and only study demonstrating a statistically significant improvement in OS and EFS for all resectable MIBC cisplatin-eligible patients, treated with perioperative durvalumab combined with gemcitabine and cisplatin. Preliminary results show a 25% reduction in the risk of death and a 32% reduction in the risk of progression/recurrence or death compared to NAC (2, 61). The OS and EFS benefit with perioperative durvalumab plus NAC was consistent across patient subgroups (62, 63). Importantly, the regimen did not compromise patients' ability

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

to undergo surgery and the safety profile was consistent with the known effects of durvalumab, with no new safety concerns and no increase in discontinuation rates due to adverse events (AEs) (2).

These unprecedented results have led the EAU to update the clinical guidelines to incorporate perioperative durvalumab, even before formal approval by the European Medicines Agency (EMA) (1, 4). The proactive action taken by EAU is reflective of the strong clinical momentum and growing appetite for integrating perioperative IO as a potential solution to the high unmet need in the management of MIBC (14).

Perioperative durvalumab offers a streamlined and fixed-duration regimen which is associated with a predictable budget impact and cost offsets due to reduced risk of recurrence (2, 61). By delivering clinically proven survival benefits, delaying disease progression, reducing the risk of disease recurrence, and not compromising the ability of patients to undergo surgery, perioperative durvalumab offers substantial value across the entire treatment pathway.

Perioperative durvalumab, represents a transformative opportunity in the treatment of cisplatin-eligible resectable MIBC patients. The proactive, single-decision point intervention, initiated at the start of the neoadjuvant setting, enables early and streamlined treatment planning, facilitates optimal scheduling of clinic visits, ensures clear and consistent communication with patients, and prevents the need for repeated evaluations for adjuvant therapy. Perioperative durvalumab can also minimise uncertainty around efficacy and duration of the treatment before and after surgery, and reduce the burden of ongoing treatment decisions – ultimately enhancing both clinical outcomes and patient experience, reducing post-recurrence clinical and economic burden on payers, and improving overall treatment care (14).

1.4 Equality considerations

AstraZeneca do not anticipate any equality issues to arise with the introduction of the technology presented in the current appraisal within clinical practice.

However, the bladder cancer burden is unequal, with persistent outcome gaps among different populations.

Women: Although men are more likely to develop BC, women often present with more advanced disease and have worse prognosis (19). The latter is explained by a longer diagnostic delay in women and not by treatment patterns (20, 21). Women showed lower survival rates only within the first two years after diagnosis, partly due to a higher T stage at initial diagnosis (64).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

People with a lower socioeconomic status: Factors such as lifestyle and occupation contribute to higher rates of BC, and these can often be attributed to lower-paid work and socioeconomic status. For example, globally, 33.72% of deaths caused by BC could be attributed to smoking and around 10% of BC arise following occupational exposure to carcinogen in jobs such as steel, foundry, metal, engineering and transport industries (65, 66).

2 Clinical effectiveness

Summary of direct clinical effectiveness

NIAGARA clinical trial

- The efficacy and safety of perioperative durvalumab was determined in the NIAGARA trial: an ongoing, **Phase III, randomised, open label, multicentre, international study**.
- Neoadjuvant durvalumab in combination with gemcitabine and cisplatin (G+C) every three weeks for four cycles prior to RC, followed by adjuvant durvalumab monotherapy every four weeks until recurrence, unacceptable toxicity or a maximum of eight cycles after surgery (perioperative durvalumab arm) is **compared to neoadjuvant G+C followed by RC alone with no adjuvant treatment** (control arm).
- **Baseline characteristics and control arm were considered reflective of UK population and standard practice by UK-based clinical experts.**

Summary of efficacy results

- Perioperative durvalumab **reduced the risk of an EFS event by 32%** when compared to the SoC (HR 0.68 [95% CI: 0.558, 0.817]).
- An approximate **10% increase in pCR rate** was observed in the perioperative durvalumab arm compared to the control arm (37.3% versus 27.5%).
- EFS benefit translated in **statistically significant and clinically meaningful improvement in OS**. Perioperative durvalumab **reduced the risk of death by 25%** compared to the SoC (HR 0.75 (95% CI: 0.594, 0.934))
- The **certainty in the efficacy** benefit attributable to perioperative durvalumab is further strengthened by the **multidimensional assessment**. Perioperative durvalumab demonstrated a **33% reduction in the risk of metastasis and 31% reduction in the risk of death due to bladder cancer**.
- The early and sustained separation of survival curves observed across multiple endpoints highlights the unique value of a perioperative intervention.
- Perioperative durvalumab arm reported **no decrement in HRQoL** of patients as compared to the control arm; no additional burden is conferred upon patients with the addition of perioperative durvalumab to the current SoC.
- **Subgroup analyses demonstrated consistency** between the ITT population and subgroups outcomes. Results across PD-L1 subgroups indicate that **PD-L1 level of expression is not influencing** the efficacy of perioperative durvalumab regimen.

Summary of safety results

- Adding durvalumab to G+C **did not negatively impact achieving surgery**. No delays in surgery were observed. A higher proportion of patients in the perioperative durvalumab arm underwent RC as planned.
- The safety data for the perioperative durvalumab demonstrated a **well-tolerated and manageable safety profile** that aligned with the individual safety profiles of durvalumab

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

monotherapy as well as G+C components.

Conclusion

- The **high level of certainty** in the efficacy outcomes delivered by perioperative durvalumab in the NIAGARA trial—providing **early and sustained survival benefits** without compromising patients' quality of life—together with a well-tolerated and manageable safety profile, has led **UK-based clinical experts to conclude that perioperative durvalumab will become the future standard of care**, addressing the significant unmet need that persists for cis-eligible resectable MIBC patients under current treatment options.

2.1 Identification and selection of relevant studies

A *de novo* SLR was conducted to identify published clinical efficacy and safety evidence to contextualise the clinical data collected for durvalumab in the perioperative setting for the treatment of patients with MIBC (67). MEDLINE®, Embase® and Cochrane databases were searched to identify published literature relevant to the research question. Key eligibility criteria for the SLR included adult patients (≥18 years old) with MIBC, receiving neoadjuvant or adjuvant therapy (if patient previously received neoadjuvant therapy) (67). The SLR included a broader scope in terms of comparators, but the population eligibility criteria were in alignment with the NICE final scope (13, 67).

In summary, the SLR adhered to the guidelines published by the University of York Centre for Reviews and Dissemination (CRD), the Cochrane Handbook for Systematic Reviews of Interventions and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (68-70). The SLR research question was specified using the Population, Intervention, Comparator, Outcome, and Study type (PICOS) framework and was aligned with the intended patient population of perioperative durvalumab (67).

The methods used to identify the relevant clinical evidence and a full list of studies that were included and excluded during the SLR are described in Appendix B.

2.2 List of relevant clinical effectiveness evidence

The SLR identified one pivotal Phase III trial (NIAGARA) of durvalumab in the population of interest for the current appraisal (67). NIAGARA (NCT03732677) is an ongoing Phase III, randomised, open-label, multicentre, international trial evaluating the efficacy and safety of perioperative durvalumab (neoadjuvant durvalumab in combination with gemcitabine and cisplatin prior to RC, followed by adjuvant durvalumab monotherapy), compared to neoadjuvant gemcitabine and cisplatin followed by RC alone with no adjuvant treatment, in patients with resectable MIBC (Table 3) (2). The NIAGARA trial was considered relevant for the current Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

appraisal and is the primary source of clinical evidence for the economic model. The NIAGARA trial is described in full in Section 2.3.

Table 3: Clinical effectiveness evidence

Study	NIAGARA (NCT03732677)	
Study design	NIAGARA is an ongoing, Phase III, randomised, open label, multicentre, international trial	
Population	Adult patients (≥18 years) with histologically or cytologically documented, resectable MIBC (i.e., T2N0/1M0-T4aNO/1M0) ^a who are cisplatin-eligible and candidates for RC and have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC.	
Intervention(s)	Neoadjuvant durvalumab (1500 mg IV) in combination with gemcitabine (Day 1 and Day 8 at dose 1000mg/m ²) and cisplatin (Day 1 at dose 70 mg/m ²) for four cycles Q3W prior to RC followed by adjuvant durvalumab monotherapy (1500 mg IV) post-surgery up to eight cycles Q4W.	
Comparator(s)	Neoadjuvant gemcitabine (Day 1 and Day 8 at dose 1000mg/m ²) in combination with cisplatin (Day 1 at dose 70 mg/m ²) for four cycles Q3W followed by RC alone.	
Indicate if study supports application for marketing authorisation	Yes	
Indicate if study used in the economic model	Yes	
Reported outcomes specified in the decision problem^b	Primary	- EFS (central review)^c - pCR (central review)
	Secondary	- OS^d, OS5 - EFS (local review), EFS24* - MFS - DSS - DFS^e - PFS-2 - Proportion undergoing RC - Proportion of patients who achieve <P2 (local review)* - EORTC QLQ-C30
	Safety	AEs
	Exploratory	EQ-5D-5L

^a Including those with divergent differentiation or histologic subtypes i.e., TCC (transitional cell and mixed transitional/non-transitional cell histology).

^b Non-exhaustive.

^c EFS is defined as the time from randomisation to the first recurrence of disease after RC, the time of first documented progression in patients who are precluded from RC, time of documented residual disease in patients who refuse to undergo a RC, or the time of death due to any cause, whichever occurs first.

^d OS is defined as the time from randomisation until death due to any cause.

^e DFS is defined as the time from the date of RC to the first recurrence of disease post RC, or death due to any cause, whichever occurs first.

* Detailed in Appendix J

Abbreviations: AEs: Adverse Events; DFS: Disease-Free Survival; DSS: Disease-Specific Survival; EFS: Event-Free Survival; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-5L: EuroQol 5-Dimension 5-Level; IV: Intravenous; MFS: Metastasis-Free Survival; OS: Overall Survival; OS5: Overall Survival at five years; pCR: Pathological Complete Response; PFS-2: Progression-free survival after second-line therapy; Q3W: every three weeks; Q4W: every four weeks; RC: Radical Cystectomy; TCC: transitional cell carcinoma.

Source: AZ NIAGARA trial Clinical Study Report (CSR) (71)

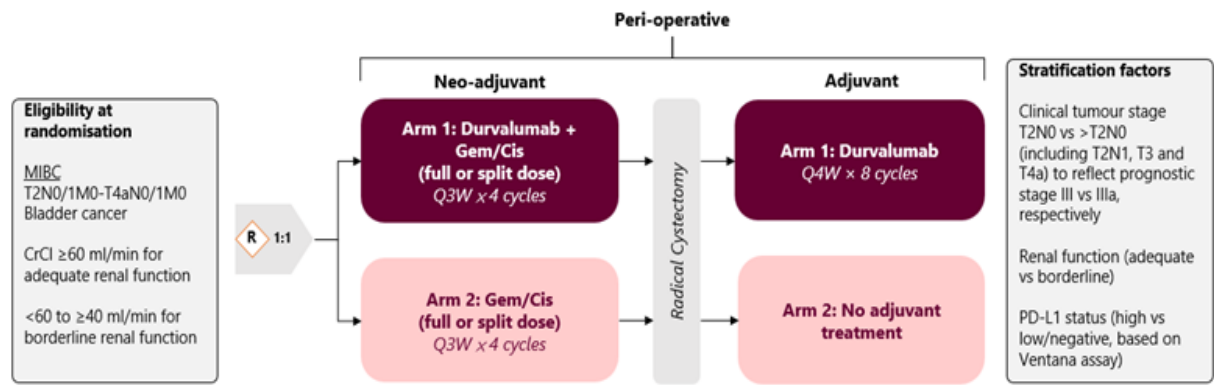
Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

2.3 Summary of methodology of the relevant clinical effectiveness evidence

2.3.1 Summary of trial methodology

NIAGARA (NCT03732677) is an ongoing, Phase III, randomised, open label, multicentre, international study to examine the efficacy and safety of neoadjuvant durvalumab in combination with gemcitabine and cisplatin every three weeks for four cycles prior to RC, followed by adjuvant durvalumab monotherapy every four weeks until recurrence, unacceptable toxicity or a maximum of eight cycles after surgery (perioperative durvalumab arm). Perioperative durvalumab is compared to neoadjuvant gemcitabine and cisplatin followed by RC alone with no adjuvant treatment (current SoC in the UK, hereafter referred to as the control arm). Perioperative durvalumab is being investigated for the treatment of adult (≥18 years) cisplatin-eligible patients with resectable MIBC (T2N0/1M0-T4aN0/1M0) including those with divergent differentiation or histologic subtypes (2). A schematic representation of the design for the NIAGARA trial is presented in Figure 3.

Figure 3: NIAGARA trial design



Abbreviations: Cis: Cisplatin; CrCl: Creatinine Clearance; Gem: Gemcitabine; MIBC: Muscle-Invasive Bladder Cancer; PD-L1: Programmed Death-Ligand 1; Q3W: Every three weeks; Q4W: Every four weeks; vs: versus; R: Randomisation.
Source: Powles *et al.* (2024) (2)

Table 4 below presents the full methods of NIAGARA trial, with inclusion and exclusion criteria described in Table 5.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Table 4: Summary of trial methodology: NIAGARA trial

Study	NIAGARA trial (NCT03732677)
Settings and location	168 sites in 22 countries across Europe, Asia-Pacific, North America, and South America. The trial included four sites based in the UK: London, Sheffield, Wirral and Edinburgh.
Trial design	NIAGARA is an ongoing, Phase III, randomised, open label, multicentre, international study.
Eligibility criteria for participants	Age ≥ 18 years with histologically or cytologically documented resectable MIBC, with clinical tumour staging (T2N0/1M0-T4aN0/1M0) and transitional cell and mixed transitional/non-transitional cell histologies (adenocarcinoma, squamous cell)/variant transitional (eg, micropapillary, plasmacytoid, sarcomatoid, nested variant, lymphoepithelioid, nested variant) histologies. Patients must be planning to undergo a RC. Patients who have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC. ECOG performance status of 0 or 1. The detailed inclusion and exclusion criteria of NIAGARA trial are summarised in Table 5.
Sample size	Based on a 2-sided overall alpha level of 0.1% allocated to the pCR endpoint, a study with approximately 1,050 eligible patients with 525 patients in each arm, was assumed to have at least 95% power to demonstrate a statistically significant difference at a 2-sided alpha level of 0.1%. It was assumed that the pCR for patients in control arm was 35% (72). Under the alternative hypothesis, pCR was assumed to be 50% for perioperative durvalumab arm. Assuming a pCR rate of 35% in control arm, the smallest pCR rate that could be observed as being statistically significant at the time of pCR analysis was a 10-percentage point increase to 45% in perioperative durvalumab. An estimated 451 EFS events (43% maturity) were expected to be observed at 45 months after the date of the last patient randomised. With 451 EFS events, the study would have at least 90% power to demonstrate a statistically significant difference at a 2-sided overall alpha level of 4.90%, allowing two interim analyses to be conducted at approximately 67% and 91% of the target events. The smallest treatment difference that could be statistically significant would be an average HR of 0.82. The actual number of randomised patients in the FAS (ITT population) is 1,063 with: • n=533 in the perioperative durvalumab arm • n=530 in the control arm
Planned analysis	pCR and EFS In order to strongly control the type I error at the 5% 2-sided alpha level, a MTP with gatekeeping strategy was used across the dual-primary endpoints (EFS and pCR). Hypotheses were tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (73). Using the specified approach, hypothesis were tested in a pre-defined order by first splitting the 5% alpha into 0.1% and 4.9% for pCR and EFS for control arm versus perioperative durvalumab arm, respectively, in the FAS (ITT population) as outlined in Figure 4. Planned analyses included one interim and one final for pCR, and two interim and one final for EFS.^b OS OS was analysed using stratified log-rank tests, using the same methodology as described for the primary EFS endpoint. The first interim analysis of OS was planned to be conducted at the time of the final EFS analysis. The final analysis was planned to be conducted when approximately 428 OS events had occurred (41% maturity, 428/1,050) across control arm and perioperative durvalumab arm, which was expected to be approximately 60 months after the last participant was randomised to the study and would provide at least 80% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 4.9%, allowing for two interim analyses (only formerly tested if EFS was positive per the MTP) to be conducted at approximately 67% and 74% of the target events. The smallest treatment difference that could be statistically significant was an HR of 0.82.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Study	NIAGARA trial (NCT03732677)
Trial drugs	Perioperative durvalumab arm Durvalumab 1500 mg IV Q3W with gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and adjuvant Durvalumab 1500 mg IV Q4W for up to eight 28-day cycles (32 weeks, eight months). Control arm (Current SoC in the UK) Neoadjuvant gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and no adjuvant treatment. Gemcitabine and cisplatin was dosed at 1000 mg/m² IV on Days 1 and 8 Q3W (gemcitabine) and 70 mg/m² IV on Day 1 Q3W (cisplatin) for patients with adequate renal function (CrCl ≥ 60 mL/min) and at 1000 mg/m² IV on Days 1 and 8 Q3W (gemcitabine) and 35 mg/m² IV on Days 1 and 8 Q3W (cisplatin) for patients with borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min) for both arms.
Prior and concomitant medication	Allowed concomitant medications Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) was acceptable. Disallowed concomitant medications Any concurrent chemotherapy, investigational product (IP), biologic, or hormonal therapy for cancer treatment. Prior pelvic radiotherapy treatment within two years of randomisation to study. Prior exposure to immune-mediated therapy (with exclusion of BCG), including but not limited to other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies. Current or prior use of immunosuppressive medication within 14 days before the first dose of IP. The following are exceptions to the criterion: • Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection). • Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent. • Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication). • Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. • Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. • Prior pelvic radiotherapy treatment within 2 years of randomisation to study.
Method of randomisation and blinding	Since NIAGARA is an open-label trial, there was no blinding at sites, but the company was blinded to the study drug allocation. Patients were centrally randomised 1:1 to the study arms. Randomisation was stratified by clinical tumour stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative).
Primary outcomes	The NIAGARA trial had two co-primary endpoints: • EFS, defined as the time from randomisation to the first recurrence of disease after RC, the time of first documented progression in patients who are medically precluded from a RC, or time of expected surgery in patients who refuse 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 occurs first as evaluated by BICR • pCR, defined as the proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via RC following the neoadjuvant treatment evaluated by BCPR.
Major secondary outcomes (definition and inclusion in NICE)	Secondary • OS • OS5 • EFS per investigator or local biopsy review • EFS24*

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Study	NIAGARA trial (NCT03732677)
scope/economic model)	• MFS per investigator assessment or local biopsy review • DSS per investigator assessment or local biopsy review • DFS • PFS-2 • Proportion undergoing RC • Proportion of patients who achieve <P2 per local pathology review* • EORTC QLQ-C30 (global health status/quality of life, physical functioning, fatigue, and pain) Exploratory • EQ-5D-5L/EQ-5D-5L VAS Safety • Safety and Tolerability as evaluated by adverse events occurring throughout the study
Pre-planned subgroups	Subgroup analyses were conducted comparing pCR/EFS/OS between arms in the following subgroups of patients in the FAS (ITT population) including, but not limited to: • Age at randomisation (<65 years versus ≥65 years) • Sex (male versus female) • Race (white versus non-white) • Geographic region (Asia, Europe, North America and Australia, South America) • Histologic type at baseline (Urothelial carcinoma versus Urothelial carcinoma with divergent differentiation or histologic subtypes) • Prior BCG therapy (Yes versus No) • Regional lymph node stage at baseline (N0 versus N1) • Tumour stage (T2N0 versus >T2N0) at baseline per IVRS • Creatinine clearance at baseline (≥60 ml/min/1.73 m² versus 40 to <60ml/min/1.73m²) • PD-L1 expression level at baseline (high, low/negative) per IVRS

^a An exponential model was assumed for EFS such that in patients who are assigned to the control arm, the overall median EFS is 38.0 months and the EFS rate at 24 months is 64.5%. For perioperative durvalumab, an exponential model was assumed for EFS such that patients who are assigned to perioperative durvalumab arm, the overall median EFS is 27.8 months and the EFS rate at 24 months is 55%.

^b NIAGARA is an ongoing trial and per the MTP, OS will be formally assessed at subsequent final analyses. EFS efficacy data continues to be collected.

* Located in Appendix J.

Abbreviations: BCG: Bacillus Calmette-Guerin; BCPR: Blinded Central Pathology Review; BICR: Blinded Independent Central Review; CT: Computed Tomography; CTLA-4: Cytotoxic T-Lymphocyte-Associated Protein 4; CrCl: Creatinine Clearance; DFS: Disease-Free Survival; DSS: Disease Specific Survival; ECOG: Eastern Cooperative Oncology Group; EFS: Event-Free Survival; EFS24: Event-Free Survival at 24 months; EQ-5D-5L: EuroQol 5-Dimension 5-Level; EQ-5D-5L VAS: EuroQol 5-Dimension 5-Level Visual Analogue Scale; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FAS: Full Analysis Set; HR: Hazard Ratio; IP: Investigational Product; ITT: Intention-To-Treat; IV: Intravenous; IVRS: Interactive Voice Response System; MFS: Metastasis-Free Survival; MIBC: Muscle-Invasive Bladder Cancer; MTP: Multiple Testing Procedure; OS: Overall Survival; OS5: Overall Survival at 5 years; pCR: Pathological Complete Response; PD-1: Programmed Death-1; PD-L1: Programmed Death-Ligand 1; PD-L2: Programmed Death-Ligand 2; PFS-2: Progression-free survival after second-line therapy; Q3W: Every three weeks; Q4W: Every four weeks; RC: Radical Cystectomy; UK: United Kingdom.

Sources: AZ NIAGARA trial CSR (71), Burman *et al.* (2009) (73), Grossman *et al.* (2003) (72)

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Table 5: Key eligibility criteria for the NIAGARA trial

Study	NIAGARA trial (NCT03732677)
Inclusion criteria	• Age ≥18 years • Histologically or cytologically documented muscle-invasive TCC/UC of the bladder - Transitional cell and mixed transitional/non-transitional cell/variant transitional histologies - Clinical tumour stage T2N0/1M0-T4aN0/1M0 - Medically fit for treatment with neoadjuvant therapy prior to RC. - Medically fit to undergo a RC. - No prior systemic chemotherapy or immunotherapy for MIBC • ECOG PS of 0 or 1 at enrolment • Known tumour PD-L1 status prior to randomisation. • Adequate organ and marrow function as defined by: - Haemoglobin ≥ 9.0 g/dL - Absolute neutrophil count ≥ 1.5×10⁹/L - Platelet count ≥ 100×10⁹/L - Serum bilirubin ≤ 1.5 × ULN^a - ALT and AST ≤ 2.5×ULN - CrCl calculated by Cockcroft-Gault equation or measured by 24-hour urine collection for determination. CrCl for Borderline Renal Function arm: ≥40 mL/min to <60 mL/min. CrCl for Adequate Renal Function arm: ≥60 mL/min
Exclusion criteria	• Specific medical conditions including, but not limited to: - Evidence of lymph node (N2-3) or metastatic TCC/UC (M1), extravesical TCC/UC - Inoperable tumour(s) with fixation to the pelvic wall on clinical exam - Certain comorbidities (e.g. autoimmune/inflammatory disorders) - History of a MI six months prior to randomisation - NYHA Class III or IV heart failure - Contraindication to platinum (cisplatin)-based doublet chemotherapy • Specific prior/concomitant therapy including but not limited to: - Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment - Prior exposure to immune-mediated therapy, live vaccine, major surgery, radiotherapy or immunosuppressants • Prior/concurrent clinical study experience

Abbreviations: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CrCl: Creatinine Clearance; ECOG PS: Eastern Cooperative Oncology Group Performance Status; IP: Investigational Product; MI: Myocardial Infarction; MIBC: Muscle-Invasive Bladder Cancer; NYHA: New York Heart Association; PD-L1: Programmed Death-Ligand 1; RC: Radical Cystectomy; TCC: Transitional Cell Carcinoma; UC: Urothelial Carcinoma; ULN: Upper Limit of Normal.

Source: AZ NIAGARA trial CSR (71)

2.3.2 Patient disposition

Patients were randomised between 16 November 2018 and 23 August 2021 (71). At the timepoint of the second interim analysis (IA) of EFS (EFS IA-2) and the first IA of OS (OS IA-1) (Data Cut-Off [DCO] 29 April 2024) (Section 2.4.2.2), 1,063 patients had been randomised to the full analysis set (FAS) (intention-to-treat [ITT] population) (71). Among 1,063 patients included in the FAS (ITT population), patients were assigned to either the perioperative durvalumab arm (N=533) or the control arm (N=530) in a 1:1 ratio. Of these, all except seven patients (three in the perioperative durvalumab arm and four in the control arm) received study

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

treatment. Of the patients who received treatment, 417 (78.7%) patients in the perioperative durvalumab arm and 389 (74.0%) patients in the control arm completed neoadjuvant treatment. A total of 470 (88.2%) patients in the perioperative durvalumab arm and 446 (84.2%) patients in the control arm underwent cystectomy, and six of the patients in the perioperative durvalumab arm entered the non-cystectomy phase. A total of 383 (72.3%) patients in the perioperative durvalumab arm started adjuvant durvalumab monotherapy treatment, and 287 (53.8%) patients completed eight cycles. As of EFS IA-2 (DCO 29 April 2024), 379 (71.1%) patients and 333 (62.8%) patients in the perioperative durvalumab arm and control arm, respectively, were ongoing in the study in survival follow-up. There were no major imbalances in patient disposition between study arms (Table 6) (71).

Table 6: Patient disposition in NIAGARA trial (DCO 29 April 2024)

Characteristic	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Patients randomised, n (%)	533 (100.0)	530 (100.0)
Full analysis set (FAS) ^a , n (%)	533 (100.0)	530 (100.0)
Patients who received study treatment ^a , n (%)	530 (99.4)	526 (99.2)
Patients who completed neoadjuvant treatment ^{b,c,d} , n (%)	417 (78.7)	389 (74.0)
Patients who discontinued neoadjuvant treatment ^{b,d,e} , n (%)	113 (21.3)	137 (26.0)
Patient decision, n (%)	10 (1.9)	30 (5.7)
AE, n (%)	82 (15.5)	80 (15.2)
Condition under investigation worsened, n (%)	2 (0.4)	4 (0.8)
Lack of therapeutic response, n (%)	1 (0.2)	0
Due to COVID-19 pandemic, n (%)	2 (0.4)	3 (0.6)
Other, n (%)	16 (3.0)	20 (3.8)
Patients who entered non-cystectomy extension phase ^b	6 (1.1)	0
Patients who underwent cystectomy prior to DCO ^a	470 (88.2)	446 (84.2)
RC	469 (88.0)	441 (83.2)
Partial cystectomy	1 (0.2)	5 (0.9)
Patients who did not undergo cystectomy as planned ^a	63 (11.8)	84 (15.8)
Patient decision	32 (6.0)	36 (6.8)
Disease progression	9 (1.7)	9 (1.7)
Unfit for surgery (e.g., Performance status decline)	2 (0.4)	6 (1.1)
AE	6 (1.1)	7 (1.3)
Death	5 (0.9)	8 (1.5)
Study discontinuation	3 (0.6)	12 (2.3)
Investigator decision to not perform surgery	5 (0.9)	6 (1.1)
Abandoned procedure (intra-operative)	1 (0.2)	0
Randomisation to cystectomy (days), Median (min, max)	112.0 (42, 221)	112.0 (29, 404)
Last dose of neoadjuvant therapy to cystectomy (days), Median (min, max)	39.0 (8, 118)	38.0 (12, 333)
Patients who started adjuvant treatment ^b	383 (72.3)	0
Patients who completed adjuvant treatment ^{b,f} , n (%)	287 (53.8)	0

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Characteristic	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Patients who discontinued adjuvant treatment ^b , n (%)	95 (17.9)	0
Patient decision, n (%)	15 (2.8)	0
Adverse event, n (%)	34 (6.4)	0
Development of study specific discontinuation criteria, n (%)	1 (0.2)	0
Patient lost to follow-up, n (%)	2 (0.4)	0
Disease relapse, n (%)	34 (6.4)	0
Other, n (%)	9 (1.7)	0
Patients who terminated study ^{g,h} , n (%)	154 (28.9)	197 (37.2)
Death n (%)	134 (25.1)	165 (31.1)
Withdrawal by patient, n (%)	20 (3.8)	32 (6.0)

^a Percentages are calculated from the number of patients randomised. In NIAGARA trial, full analysis set includes all randomised patients.

^b Percentages are calculated from the number of patients who received treatment.

^c Neoadjuvant treatment includes non-cystectomy extension phase.

^d Obtained from the patients who discontinued due to maximum cycle reached for all of the neoadjuvant treatments.

^e Patients who discontinued at least one of the neoadjuvant treatments for reasons other than reaching the maximum number of cycles are classified as having discontinued study treatment.

^f Patients that completed all eight cycles of adjuvant durvalumab.

^g Withdrawal by patient includes withdrawal by parent/guardian.

^h Percentages are calculated from the number of patients randomised. In NIAGARA trial, full analysis set includes all randomised patients.

Abbreviations: AE: adverse event; C: cisplatin; COVID-19: coronavirus disease of 2019; D: durvalumab; DCO: data cut-off; FAS: Full analysis set; G: gemcitabine; min: minimum; max: maximum; RC: Radical Cystectomy.

Source: AZ NIAGARA trial CSR (71)

2.3.2.1 Patients who undergo cystectomy

In the NIAGARA trial, a higher percentage of patients in the perioperative durvalumab arm (88.0%) underwent RC, as planned, compared to the control arm (83.2%) (Table 6). Notably, there were no delays in surgery for the perioperative durvalumab arm compared to the control arm, with the median time from the last dose of neoadjuvant therapy to cystectomy being 39.0 days in the perioperative durvalumab arm and 38.0 days in the control arm (71). Among the patients who did not undergo cystectomy, patient decision was the most common reason in each group (6.0% and 6.8% patients in the perioperative durvalumab arm and the control arm, respectively) (71). Furthermore, a greater number of patients did not proceed with surgery in the control arm due to factors that can be associated with increased morbidity and mortality, such as study discontinuation (0.6% in the perioperative durvalumab arm versus 2.3% in the control arm), being unfit for surgery (0.4% in the perioperative durvalumab arm versus 1.1% in the control arm), and death (0.9% in the perioperative durvalumab arm and 1.5% in the control arm) (Table 6) (71).

The above evidence highlights that adding durvalumab to the current neoadjuvant SoC did not preclude or delay patients from undergoing surgery.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

The flow of participants through the NIAGARA trial is summarised in a consolidated standards of reporting trials (CONSORT) diagram in Section 1.2 of Appendix B.

2.3.3 Demographics and baseline characteristics

The patient demographics and baseline disease characteristics of patients in the NIAGARA trial are presented for the FAS (ITT population) at the EFS IA-2 (N=1,063) in Table 7 (71).

The patient demographics and disease characteristics were representative of the target population of patients with resectable MIBC, focus of this appraisal, and were well-balanced between treatment arms (71). The NIAGARA trial included four sites located in the UK, and the UK-based clinical experts confirmed that the baseline patient characteristics of patients in the NIAGARA trial are reflective of the real-world patients with resectable MIBC in the UK (14). The NIAGARA trial population is representative across most demographics (median age of patients, smoking status and renal function), while UK-based clinical experts acknowledged that some minor differences in patient population characteristics of the trial can exist as compared to the clinical practice, none of the factors were considered a cause for uncertainty or bias (14).

Table 7: Patient demographic and baseline characteristics at study entry in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

Characteristic	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1,063)
Age, years			
N	533	530	1,063
Mean (SD)	64.1 (8.93)	64.6 (8.94)	64.4 (8.94)
Median (Min, Max)	65.0 (34, 84)	66.0 (32, 83)	65.0 (32, 84)
Age group (years), n (%)			
<50	33 (6.2)	35 (6.6)	68 (6.4)
≥50 - <65	225 (42.2)	206 (38.9)	431 (40.5)
≥65 - <75	217 (40.7)	226 (42.6)	443 (41.7)
≥75	58 (10.9)	63 (11.9)	121 (11.4)
Total	533 (100.0)	530 (100.0)	1,063 (100.0)
Sex, n (%)			
Male	437 (82.0)	433 (81.7)	870 (81.8)
Female	96 (18.0)	97 (18.3)	193 (18.2)
Total	533 (100.0)	530 (100.0)	1,063 (100.0)
Race, n (%)			
White	354 (66.4)	358 (67.5)	712 (67.0)
Black or African American	6 (1.1)	4 (0.8)	10 (0.9)
Asian	152 (28.5)	145 (27.4)	297 (27.9)
Other	7 (1.3)	1 (0.2)	8 (0.8)
Missing	14 (2.6)	22 (4.2)	36 (3.4)

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Characteristic	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1,063)
Total	533 (100.0)	530 (100.0)	1,063 (100.0)
Ethnic group, n (%)			
Hispanic or Latino	44 (8.3)	41 (7.7)	85 (8.0)
Not Hispanic or Latino	483 (90.6)	477 (90.0)	960 (90.3)
Missing	6 (1.1)	12 (2.3)	18 (1.7)
Total	533 (100.0)	530 (100.0)	1,063 (100.0)
Weight (kg)			
Mean (SD)	77.6 (17.02)	76.6 (16.01)	77.1 (16.53)
Median (min, max)	76.0 (38, 157)	75.0 (35, 125)	75.7 (35, 157)
Weight group (kg), n (%)			
< 70	193 (36.2)	180 (34.0)	373 (35.1)
≥ 70 - < 90	210 (39.4)	251 (47.4)	461 (43.4)
≥ 90	130 (24.4)	99 (18.7)	229 (21.5)
Smoking status, n (%)			
Non-smoker	144 (27.0)	120 (22.6)	264 (24.8)
Smoker	377 (70.7)	399 (75.3)	776 (73.0)
Ex-smoker	255 (47.8)	269 (50.8)	524 (49.3)
Current smoker	122 (22.9)	130 (24.5)	252 (23.7)
Missing	12 (2.3)	11 (2.1)	23 (2.2)
Region, n (%)			
Asia	151 (28.3)	143 (27.0)	294 (27.7)
Europe	265 (49.7)	287 (54.2)	552 (51.9)
North America and Australia	66 (12.4)	62 (11.7)	128 (12.0)
South America	51 (9.6)	38 (7.2)	89 (8.4)
WHO/ECOG performance status			
Normal activity (ECOG 0)	418 (78.4)	415 (78.3)	833 (78.4)
Restricted activity (ECOG 1)	115 (21.6)	115 (21.7)	230 (21.6)
Tumour stage (per IVRS)			
T2N0	215 (40.3)	213 (40.2)	428 (40.3)
> T2N0	318 (59.7)	317 (59.8)	635 (59.7)
Renal function (per IVRS)^a			
Adequate renal function	432 (81.1)	430 (81.1)	862 (81.1)
Borderline renal function	101 (18.9)	100 (18.9)	201 (18.9)
PD-L1 status (per IVRS)^b			
High ^c	389 (73.0)	388 (73.2)	777 (73.1)
Low/Negative ^d	144 (27.0)	142 (26.8)	286 (26.9)
Renal function (per eCRF)			
Adequate renal function (CrCl ≥ 60 mL/min)	431 (80.9)	431 (81.3)	862 (81.1)
Borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min)	102 (19.1)	99 (18.7)	201 (18.9)
PD-L1 status (per laboratory data)			
High ^c	388 (72.8)	388 (73.2)	776 (73.0)
Low/Negative ^d	145 (27.2)	142 (26.8)	287 (27.0)

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Characteristic	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1,063)
TC1 (per laboratory data)^e			
TC ≥ 1%	291 (54.6)	281 (53.0)	572 (53.8)
TC < 1%	242 (45.4)	249 (47.0)	491 (46.2)
TC25 (per laboratory data)^f			
TC ≥ 25%	152 (28.5)	153 (28.9)	305 (28.7)
TC < 25%	381 (71.5)	377 (71.1)	758 (71.3)
Primary tumour location			
Bladder	533 (100.0)	530 (100.0)	1,063 (100.0)
Histology type			
Urothelial (transitional cell) carcinoma	457 (85.7)	441 (83.2)	898 (84.5)
Urothelial (transitional cell) carcinoma with squamous differentiation	38 (7.1)	49 (9.2)	87 (8.2)
Urothelial (transitional cell) carcinoma with glandular differentiation	10 (1.9)	15 (2.8)	25 (2.4)
Urothelial (transitional cell) carcinoma with variant histology	28 (5.3)	25 (4.7)	53 (5.0)
Regional lymph nodes			
N0	505 (94.7)	500 (94.3)	1,005 (94.5)
N1	28 (5.3)	30 (5.7)	58 (5.5)
Distant metastasis			
M0	533 (100.0)	530 (100.0)	1,063 (100.0)

^a One patient in the perioperative durvalumab arm was mis-stratified to adequate renal function and one patient in the control arm was mis-stratified to borderline renal function per IVRS.

^b One patient in the perioperative durvalumab arm was mis-stratified to the PD-L1 high group according to IVRS and should belong to PD-L1 low group per central laboratory data.

^c PD-L1 high status was considered high if any of the following are met: ≥ 25% of tumour cells exhibit membrane staining; Immune cells present (ICP) > 1% and IC+ ≥ 25%; ICP = 1% and IC+ = 100%.

^d PD-L1 low/negative status was considered low/negative if: none of the criteria for PD-L1 high status are met.

^e TC1 was defined as TC ≥ 1% versus TC < 1%.

^f TC25 was defined as TC ≥ 25% versus TC < 25%.

Abbreviations: C: cisplatin; CrCl: creatinine clearance; D: durvalumab; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; eCRF: Electronic case report form; G: gemcitabine; IA-2: Second interim analysis; ICP: Immune cells present; IVRS: interactive voice response; ITT: Intention-To-Treat; kg: kilogram; Max: maximum; Min: minimum; PD-L1: Programmed death-ligand 1; SD: standard deviation; T: tumour; TC: Tumour cell; WHO: World Health Organisation.

Source: AZ NIAGARA trial CSR (71)

2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

2.4.1 Definition of study groups

Analysis sets in the NIAGARA trial are defined in Table 8 below (71, 74). At the DCO of 29 April 2024, both treatment arms had similar numbers of patients in the analysis sets (71).

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Table 8: Definitions of the NIAGARA trials' analysis sets

Population/ Analysis set	Description	Number (%) of patients		
		Perioperative durvalumab arm (D+G+C)	Control arm (G+C)	Total
Enrolled	All patients who signed the ICF.	-	-	1,530
FAS (ITT population)	All randomised patients. Patients who were randomised but did not subsequently receive treatment were included in the FAS (ITT population) in the treatment arm to which they were randomised.	533 (100%) ^a	530 (100%) ^a	1,063 (100%) ^a
SAS	All randomised patients who received at least one dose of study treatment. Safety data were not formally analysed but summarised according to actual treatment received.	530 (99.4%)	526 (99.2%)	1,056 (99.3%)
Cystectomy population	All patients in FAS (ITT population) who underwent RC and were disease free at adjuvant baseline. Treatment arms were compared on the basis of randomised study treatment, regardless of the treatment actually received. This analysis set was used for DFS only.	352 (66.0%)	337 (63.6%)	689 (64.8%)

^a Patient percentages are calculated with FAS (ITT population) patient numbers as the denominator.

Abbreviations: D+G+C: durvalumab plus gemcitabine plus cisplatin; DFS: Disease Free Survival; FAS: Full Analysis Set; G+C: gemcitabine plus cisplatin; ICF: Informed Consent Form; IP: Investigational Product; ITT: Intention-to-treat; IVRS: Interactive Voice Response System; RC: Radical Cystectomy; SAS: Safety Analysis Set.

Source: AZ NIAGARA trial CSR (71)

Description of the analysis and corresponding analysis sets for which each outcome variable was analysed in the NIAGARA trial is provided in Table 9.

Table 9: Summary of outcome variables and analysis populations

Endpoint	Analysis	Populations
Dual-Primary endpoints		
pCR ^a	Logistic regression adjusted for the stratification factors, odds ratio and the corresponding CI	FAS (ITT population)
EFS ^a	Stratified log-rank test to obtain the p-value, stratified Cox PH model to obtain the HR and the corresponding CI	FAS (ITT population)
Secondary endpoints		
OS ^a and OS5 ^a	The KM estimate of OS after randomisation. Stratified log-rank test for OS. KM estimates of survival rate at five years	FAS (ITT population)
EFS24*	Kaplan-Meier estimates of EFS rate at 24 months by treatment	FAS (ITT population)
MFS	Stratified log-rank test	FAS (ITT population)
DSS	Stratified log-rank test	FAS (ITT population)
DFS	Stratified log-rank test	Cystectomy population
PFS-2	Stratified log-rank test	FAS (ITT population)
Proportion of patients achieving <P2*	Logistic regression adjusted for the stratification factors	FAS (ITT population)
Proportion of patients who undergo cystectomy	Point estimate and 95% CI	FAS (ITT population)
QLQ-C30	Stratified log-rank test. Average change from baseline using a MMRM analysis	FAS (ITT population)
Exploratory Endpoints		
PROs	Descriptive statistics	FAS (ITT population)

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Endpoint	Analysis	Populations
Demography	Descriptive statistics	FAS (ITT population)
Safety Endpoints		
Exposure	Descriptive statistics	SAS
AEs	Descriptive statistics	SAS
ECOG PS	Descriptive statistics	SAS
Laboratory measurements	Descriptive statistics	SAS
Vital signs	Descriptive statistics	SAS

^a Alpha controlled within a multiple testing procedure.

* Detailed in Appendix J.

Abbreviations: AE: adverse event; DFS: Disease-free survival; DSS: Disease-specific survival; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EFS: Event-free survival; EFS24: Proportion of patients alive and event-free at 24 months; FAS: Full analysis set; ITT: Intention-to-treat; KM: Kaplan-Meier; MFS: Metastasis-free survival; MMRM: Mixed effects repeated measures; OS5: Proportion of patients alive at five years; pCR: Pathologic complete response; PFS-2: Time from the date of randomisation to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PH: proportional hazards; PRO: Patient-reported outcome.

Source: AZ NIAGARA trial CSR (71)

2.4.2 Statistical analysis

2.4.2.1. Hypothesis objective

The objective of the NIAGARA trial as well as the hypothesis testing performed is described in Table 10.

Table 10: NIAGARA trial objective and hypothesis testing

Objective of the NIAGARA trial	Hypothesis testing
To demonstrate superiority of the perioperative durvalumab arm versus the control arm, in terms of pCR and EFS, in patients with resectable muscle-invasive bladder cancer in the FAS (ITT population)*.	Testing for significant differences between the two treatment arms, with H0: no difference between the perioperative durvalumab arm and control arm, and H1: difference between the perioperative durvalumab arm and control arm.
The study was considered to have a positive outcome if either of the two endpoints, pCR or EFS in the FAS (ITT population), showed a significant improvement in the perioperative durvalumab arm compared to the control arm (11).	

*The populations on which the different analyses for efficacy (primary, secondary and dual-primary endpoints) and safety were performed are described in Table 9.

Abbreviations: EFS: Event-free survival; FAS: Full analysis set; ITT: Intention-to-treat; pCR: Pathologic complete response

Source: AZ NIAGARA trial CSR (71)

2.4.2.2. Analysis timepoints

The analysis timepoints for the NIAGARA trial are described in Table 11.

Table 11: NIAGARA trial analysis timepoints

Analysis	Timepoint	DCO
Final analysis of dual-primary endpoint pCR	Performed approximately six months after the last patient was randomised to the study and after all patients had undergone surgery.	14 January 2022
First IA of dual-primary endpoint EFS	Performed at the time of the final pCR analysis. At the time of analysis, 301/1,050 EFS events had occurred across the two treatment arms in the full analysis set FAS (ITT population) (28.7% maturity) and the threshold for statistical significance was not met.	14 January 2022

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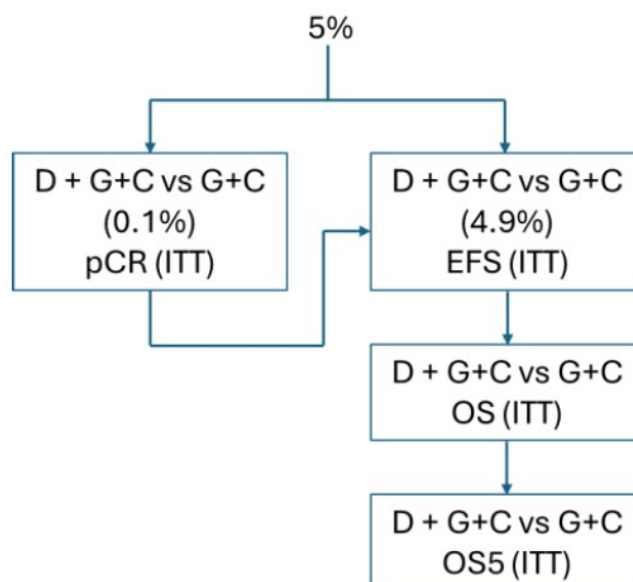
Analysis	Timepoint	DCO
Second IA of dual-primary endpoint EFS and first IA of key secondary endpoint OS	The analysis was event driven and at the time of analysis, there were 433 EFS events (40.7% maturity) across the two arms in the FAS (ITT population). EFS showed a statistically significant benefit at the second IA.	29 April 2024
Final analysis of dual-primary endpoint EFS and second IA of key secondary endpoint OS	Planned to be conducted when approximately 451 EFS events in the FAS (ITT population) have occurred across the two arms (43% maturity, 451/1,050)	Not yet reached
Final analysis of key secondary endpoint OS	Planned to be conducted when approximately 428 OS events have occurred (41% maturity, 428/1050) across both arms, which is expected to be approximately 60 months after the last patient was randomised.	Not yet reached

Abbreviations: DCO: data cut-off; EFS: Event-free survival; FAS: Full analysis set; IA: Interim analysis; ITT: Intention-to-treat; OS: overall survival; pCR: Pathologic complete response
Source: AZ NIAGARA trial CSR (71)

2.4.2.3. Testing for multiplicity

To control the type I error at the 5% 2-sided alpha level, a multiple testing procedure (MTP) with a gatekeeping strategy was chosen for the dual-primary endpoints (pCR and EFS) and key secondary endpoint (OS) (Figure 4) (71, 74). Initially, the 5% alpha was split into 0.1% for pCR and 4.9% for EFS in the FAS (ITT population). The study was considered positive if either of the dual-primary endpoint was met (75). Rejected hypotheses' test mass was recycled to secondary hypotheses. The alpha level for pCR and EFS was controlled at interim and final timepoints using the Lan-DeMets spending function, approximating an O'Brien-Fleming approach (74, 76).

Figure 4: Multiple testing procedure for controlling the type I error rate



Abbreviations: C: Cisplatin; D: Durvalumab; EFS: Event-Free Survival; G: Gemcitabine; ITT: Intention-To-Treat; OS: Overall Survival; OS5: Overall Survival at five years; pCR: Pathological Complete Response.
Source: NIAGARA trial Clinical Study Protocol (74)

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2.4.2.4. Sample size and power calculation

The trial planned to enroll and screen approximately 1,400 patients in order to randomise approximately 1,050 eligible patients in a 1:1 ratio to the NIAGARA regimen perioperative durvalumab arm or control arm (71). The trial was sized to characterise the pCR rate and EFS benefit of the perioperative durvalumab arm versus the control arm in patients with resectable MIBC who had not received prior systemic chemotherapy. Statistical assumptions were made using a pCR rate of 50% and 35% for patients enrolled on the perioperative durvalumab arm and control arm, respectively, for the FAS (ITT population) Non-uniform accrual of patients (with $k=2$) was assumed when estimating the analysis times (71). The statistical analysis undertaken in the NIAGARA trial is presented in Table 12.

Table 12: NIAGARA trial sample size and power calculation

Analyses	Description
pCR	It was assumed that the pCR for patients (FAS [ITT population]) in the control arm was 35% (72). Under the alternative hypothesis, pCR was assumed to be 50% for the perioperative durvalumab arm. With 525 patients in each arm, the study would have at least 95% power to demonstrate a statistically significant difference at a 2-sided alpha level of 0.1%. Assuming a pCR rate of 35% in the control arm, the smallest pCR rate that could be observed as being statistically significant at the time of pCR analysis was a 10% increase to 45% in the perioperative durvalumab arm. Using the specified approach translated to an increase of approximately 10% from that in the control arm, where pCR was assumed to be 35%.
EFS	Under the alternative hypothesis, the assumed EFS treatment effect was represented by an average HR of 0.733 for the perioperative durvalumab arm versus the control arm. The estimate was based on the following assumptions: - For the perioperative durvalumab arm, an exponential model was assumed for EFS such that in patients who were assigned to the perioperative durvalumab arm, the overall median EFS was 38.0 months and the EFS rate at 24 months was 64.5%. - For the control arm, an exponential model was assumed for EFS such that in patients who were assigned to the control arm, the overall median EFS was 27.8 months and the EFS rate at 24 months was 55%. Based on a blinded event prediction an estimated 451 EFS events (43% maturity) were expected to be observed at 45 months after the date of the last patient randomised. With 451 EFS events, the study would have at least 90% power to demonstrate a statistically significant difference at a 2-sided overall alpha level of 4.90%, allowing two interim analyses to be conducted at approximately 67% and 91% of the target events. The smallest treatment difference that could be statistically significant would be an average HR of 0.82.
OS	Under the alternative hypothesis, the assumed OS treatment effect was represented by an average HR of 0.76 for the perioperative durvalumab arm versus the control arm. The estimate was based on the following assumptions: - For the perioperative durvalumab arm, an exponential model was assumed for OS such that in all patients who were assigned to the perioperative durvalumab arm, the overall median OS was 8.6 years (103 months), and the OS rate at five years was 66.8%. - For the control arm, an exponential model was assumed for OS such that in all patients who were assigned to the control arm, the overall median OS was 6.5 years (78 months) and the OS rate at five years was 58.7%. The final analysis of OS based on approximately 428 OS events for the comparison of the perioperative durvalumab arm versus the control arm (41% maturity, 428/1,050), from the FAS (ITT population), was expected to occur five years (60 months) after the last patient was randomised to the study and would provide at least 80% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 4.9%, allowing for two interim analyses (only formerly tested if EFS was positive per MTP) to be conducted at approximately 67% and 74% of the target events. The smallest treatment difference that could be statistically significant was an HR of 0.82.
OS5	The statistical model assumptions for OS5 in the FAS (ITT population) of each arm are stated above. The analysis of OS5 at the time of the final analysis of OS would provide at least 77% power to demonstrate a statistically significant difference in OS5 at a 2-sided alpha level of 4.9%.

Abbreviations: EFS: Event-Free Survival; FAS: Full analysis set; HR: Hazard Ratio; ITT: Intention-to-treat; MTP: Multiple Testing Procedure; OS: Overall Survival; OS5: Overall Survival at five years; pCR: Pathologic Complete Response.

Source: AZ NIAGARA trial CSR (71)

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2.4.2.5. Data management and patient withdrawals

The quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. AstraZeneca's quality assurance and quality control procedures provide reassurance that the clinical study program was carried out in accordance with the Good Clinical Practice guidelines (77). Patients could discontinue treatment with the investigational products and assessments at any time, or at the discretion of the Investigator(s), reasons for discontinuation can be found in Table 6. Patients were also free to withdraw from the study at any time, without prejudice to further treatment.

2.5 Critical appraisal of NIAGARA trial

A summary of quality assessment for NIAGARA trial is presented in Table 13.

Table 13: Quality assessment results for NIAGARA trial

	Grade	Details
Was randomisation carried out appropriately?	Yes	Block randomisation stratified by clinical tumour stage T2N0 versus > T2N0, renal function and PD-L1 status.
Was the concealment of treatment allocation adequate?	Yes	Assigned via interactive voice/web recognition system.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Baseline characteristics were similar between both treatment arms.
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes	NIAGARA is an open label trial. The Sponsor remained blinded during the study, including at the time of interim analysis. The primary endpoint analyses were reviewed by the IDMC, with the Sponsor remaining blinded. The Sponsor was only unblinded after the IDMC had determined that the threshold for statistical significance had been met for the EFS endpoint at EFS IA-2.
Were there any unexpected imbalances in drop-outs between groups?	No	There were no imbalances or unexpected drop-outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	All outcomes were reported for data which were available.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	NIAGARA trial included an ITT analysis, which was performed in the FAS.

Abbreviations: EFS: Event-Free Survival; FAS: Full analysis set; IA-2: Interim Analysis 2; IDMC: Independent Data Monitoring Committee; ITT: Intention-To-Treat; PD-L1: Programmed Death-Ligand 1
Source: AZ NIAGARA trial CSR (71)

2.6 Clinical effectiveness results of the relevant studies

The following sections present results for the FAS (ITT population) based on a DCO of 14 January 2022 for the formal analysis of pCR, and a DCO of 29 April 2024 for the EFS IA-2 (Table 14) (71).

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Table 14: Dates of data cut off for endpoint analysis

Endpoints	DCO	
	14 January 2022	29 April 2024
pCR	Formal analysis	Re-analysis
EFS	First interim analysis (EFS IA-1)	Second interim analysis (EFS IA-2)
OS	-	First interim analysis (OS IA-1)

Abbreviations: DCO: Data cut-off; EFS: Event-Free Survival; IA-1: First interim analysis; IA-2: Second interim analysis; OS: Overall Survival; OS5: Overall Survival at five years; pCR: Pathologic Complete Response.

2.6.1 Dual-primary endpoint: EFS and pCR

The NIAGARA trial evaluated EFS and pCR as dual-primary endpoints, capturing both the immediate and longer-term benefits of perioperative treatment. The aim of the neoadjuvant setting is to remove the primary tumour and reduce the risk of subsequent recurrence, while adjuvant setting aims to sustain immunosurveillance to eliminate micro-metastatic disease after surgery, thereby enhancing the likelihood of long-term disease control (31).

In the NIAGARA trial, EFS is defined as the time from randomisation to the first recurrence of disease after RC, the time of first documented progression in patients who are medically precluded from RC, or time of expected surgery in patients who refuse to undergo RC or failure to undergo RC in patients with residual disease, or the time of death due to any cause, whichever occurs first (2). The definition implies that EFS considers the occurrence of multiple patient-relevant events, provides a direct measure of treatment efficacy across both neoadjuvant and adjuvant treatment periods with surgery as a curative intent therapeutic strategy, and is not confounded by subsequent therapy following progression or recurrence. The EFS definition in the NIAGARA trial aligns with the therapeutic goals of the perioperative setting and evaluates the success or failure of neoadjuvant followed by adjuvant therapy.

In addition to the strength of EFS as a direct measure of efficacy, there is strong association between EFS and OS in the perioperative MIBC setting (78). The correlation between EFS and OS in NIAGARA trial has been demonstrated in the first interim analysis of OS, as will be discussed in Section 2.6.2.1.

The inclusion of pCR as a dual-primary endpoint addresses the discordant complexities between clinical and pathologic stages, which are typical of response assessments incorporating information from both pre- and post-neoadjuvant chemotherapy.

The objective of neoadjuvant therapy in the treatment pathway of MIBC is to decrease primary tumour burden before consolidative local therapy. Achieving pCR following neoadjuvant treatment has been associated with a marked improvement in outcomes in patients with resectable MIBC (72, 79).

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In the NIAGARA trial, pCR was defined as the proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via RC following the neoadjuvant treatment evaluated by blinded central pathology review (2).

2.6.1.1 EFS per BICR or central pathology review (FAS [ITT population], DCO 29 April 2024)

At EFS IA-2 (DCO 29 April 2024), the NIAGARA trial met the primary objective of EFS per BICR or central pathology review in the FAS (ITT population) (71). The median duration of follow-up for EFS was similar between the perioperative durvalumab arm (34.7 months) and the control arm (27.7 months).

There was a statistically significant and clinically meaningful improvement in the perioperative durvalumab arm compared to control arm, with a HR of 0.68 (95% CI: 0.558, 0.817; p<0.0001), indicating a 32% reduction in the risk of an EFS event arm (Table 15) (71).

The KM curves for EFS began to separate in favour of the perioperative durvalumab arm at approximately two months, prior to the planned timing of the first response evaluation criteria in solid tumours (RECIST) scan after randomisation (~12 weeks) (71). Curve separation prior to the timepoint of the first RECIST scan implies a noticeable benefit of durvalumab compared to SoC within the neoadjuvant period of the perioperative durvalumab regimen where anti-tumour immunity is primed prior to surgery (2).

The clear and sustained separation of the curve thereafter, reinforces the benefits of perioperative regimen wherein deploying durvalumab as the same IO therapy before and after surgery improves the surgery outcomes by priming anti-tumour immunity before surgery (neoadjuvant setting) and supporting immunosurveillance to eliminate micro-metastatic disease after surgery (adjuvant setting), thereby enhancing the likelihood of long-term disease control (Figure 5) (71).

Table 15: Analysis of dual-primary endpoint: EFS, per BICR or central pathology review, in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

EFS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Total EFS events, n (%)	187 (35.1)	246 (46.4)
Median EFS (months) ^a	NR	46.1
95% CI for median EFS (months)	NR, NR	32.2, NR
EFS rate at six months (%) ^a	87.7	82.4
95% CI for EFS rate at six months (%) ^a	84.5, 90.2	78.8, 85.4
EFS rate at 12 months (%) ^a	76.0	69.9
95% CI for EFS rate at 12 months (%) ^a	72.0, 79.4	65.7, 73.7
EFS rate at 24 months (%) ^a	67.8	59.8

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EFS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
95% CI for EFS rate at 24 months (%) ^a	63.6, 71.7	55.4, 64.0
EFS rate at 36 months (%)	63.7	53.6
95% CI for EFS rate at 36 months (%) ^a	59.3, 67.7	49.0, 57.9
Hazard ratio ^{c,d}	0.68	
95% CI for hazard ratio ^b	0.558, 0.817	
Two-sided p-value ^e	<0.0001	

^a Calculated using the KM technique.

^b Based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^c A hazard ratio < 1 favours the perioperative durvalumab arm to be associated with a longer EFS than control arm.

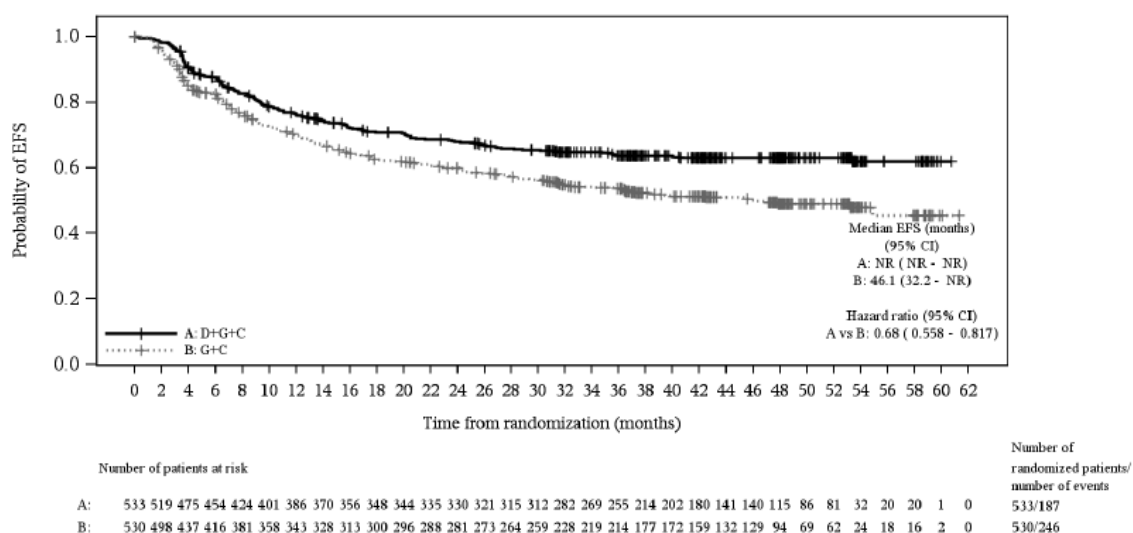
^d p-value calculated using a stratified log-rank test, and the stratification factors are the same as the ones indicated in b.

^e Based on a Lan-DeMets alpha spending function with O'Brien Fleming boundary with the observed number of events; the boundaries for declaring statistical significance are 0.04123 for a 4.9% overall alpha.

Abbreviations: BICR: blinded independent central review; C: cisplatin; CI: confidence interval; CSR: clinical study report; D: durvalumab; DCO: data cut-off; EFS: event-free survival; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response system; ITT: Intention-To-Treat; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards; RC: radical cystectomy.

Source: AZ NIAGARA trial CSR (71)

Figure 5: KM plot of EFS per BICR or by central pathology in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



Notes: Median EFS calculated using the KM technique. HR based on stratified Cox proportional hazard model and including TC25 as a categorical covariate in the model; the stratification factors are tumour stage [T2N0 versus >T2N0] and renal function [adequate versus borderline], with ties handled by the Efron approach. A hazard ratio < 1 favours the perioperative durvalumab arm to be associated with a longer EFS than the control arm.

Abbreviations: BICR: blinded independent central review; C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; G: gemcitabine; EFS: event-free survival; FAS: full analysis set; HR: hazard ratio; IA-2: second interim analysis; KM: Kaplan-Meier; IVRS: interactive voice response system; ITT: Intention-To-Treat; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (71)

Perioperative durvalumab addresses the high unmet need in the cisplatin-eligible patients with resectable MIBC by reducing the risk of an EFS event by 32% when compared to the SoC (control arm). The UK-based clinical experts emphasised the urgent need for effective treatments in MIBC, particularly those aimed at minimising the risk of relapse, recognising that MIBC represents the last opportunity to prevent the progression of patients to mBC. Therefore, Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

the addition of durvalumab to the current SoC in the UK offers a promising advance in curative-intent strategies by reducing the risk of recurrence and preventing the progression of disease in cisplatin-eligible patients with resectable MIBC (14).

2.6.1.2 **pCR rate based on central pathology review (FAS [ITT population], DCO 14 January 2022)**

At the time of the final pCR analysis (DCO 14 January 2022), due to a programming error the DCO date was applied to the date of central assessment rather than the date of surgery. As a result, 59 evaluable samples were omitted and 28 of them were incorrectly considered non-responders for the pCR calculation. Consequently, the final analysis for pCR at the 14 January 2022 DCO was not statistically significant, even though results indicated a numerical improvement favouring perioperative durvalumab (71). pCR was achieved in 33.8% (95% CI: 29.8, 38.0) patients in the perioperative durvalumab arm and in 25.8% (95% CI: 22.2, 29.8) patients in the control arm (risk ratio [RR]: 1.30; 95% CI: 1.09, 1.56; $p=0.004$) (Table 16) (2, 71).

At the time of EFS IA-2 (DCO 29 April 2024) an updated pCR analysis (re-analysis) was conducted, which showed a nominally significant improvement in the pCR rate (per central pathology review), with approximately a 10% increase in the perioperative durvalumab arm (37.3%) compared to the control arm (27.5%) ($p=0.0005$) (Table 16 and Figure 6) (2, 78).

Table 16: pCR rate, based on central pathology, in NIAGARA trial (FAS [ITT population], Formal analysis DCO 14 January 2022, Re-analysis DCO 29 April 2024)

pCR by central pathology	Formal analysis (14 January 2022 DCO)		Re-analysis (29 April 2024 DCO)	
	Perioperative durvalumab arm (D+G+C) (N=533)	7Control arm (G+C) (N=530)	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (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	
Risk ratio	1.30		1.34	
95% CI for the risk ratio	1.09, 1.56		1.13, 1.60	
Two-sided p-value ^b	0.0038 ^c		0.0005 ^c	

^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 versus borderline], tumour stage [T2N0 versus > T2N0] and PD-L1 status [high versus low/negative] per IVRS). An odds ratio > 1 favours perioperative durvalumab over control.

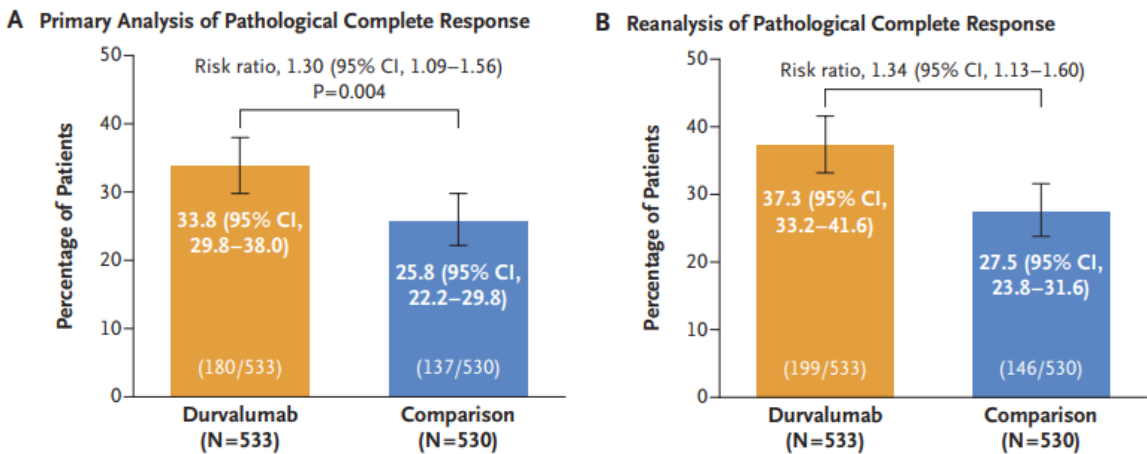
^c Threshold for significance, $p=0.001$.

Abbreviations: C: Cisplatin; CI: Confidence interval; D: durvalumab; DCO: Data cut-off; FAS: Full analysis set; G: Gemcitabine; ITT: Intention-To-Treat; pCR: Pathologic complete response.

Source: Powles *et al.* (2024) (2), AZ NIAGARA trial CSR (71)

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Figure 6: NIAGARA trial pCR rate (FAS [ITT population], Formal analysis DCO 14 January 2022, Re-analysis DCO 29 April 2024)



Abbreviations: CI: confidence interval; DCO: data cut-off; FAS: Full analysis set; ITT: Intention-To-Treat; N: number; pCR: pathologic complete response.
Source: Powles *et al.* 2024 (2)

Perioperative durvalumab shows a significant numerical improvement in pCR rate, and in combination with the early separation of EFS KM curves, suggests that the addition of durvalumab to SoC in the neoadjuvant treatment phase primes the tumour for radical cystectomy, allowing patients a greater chance of curative therapy and improved long term survival outcomes (2).

2.6.2 Secondary endpoints

2.6.2.1 Overall survival (FAS [ITT population], DCO 29 April 2024)

The OS IA-1 was conducted at the same timepoint as the EFS IA-2 (DCO 29 April 2024), after 305 death events had occurred (28.7% maturity for OS overall). The median duration of follow-up for OS was 42.3 months (0.26 to 64.62) and 39.6 months (0.03 to 64.66) in the perioperative durvalumab arm and control arm, respectively.

The results from the OS IA-1 in the FAS (ITT population) demonstrated a statistically significant and clinically meaningful improvement in OS for the perioperative durvalumab arm as compared to the control arm (71). The HR was 0.75 (95% CI: 0.594, 0.934; p=0.0106) indicating a 25% overall reduction in the risk of death compared to the SoC.

The results of the OS analysis are detailed in Table 17 and the KM curve is illustrated in Figure 7 (71).

Table 17: Analysis of overall survival in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

OS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Death, n (%)	136 (25.5)	169 (31.9)
Censored patients, n (%)	397 (74.5)	361 (68.1)
Still in survival follow-up ^a	379 (71.1)	333 (62.8)
Terminated prior to death ^{b,c}	18 (3.4)	28 (5.3)
Withdrawal by patient	18 (3.4)	28 (5.3)
Lost to follow-up	0	0
Other	0	0
25 th percentile OS (months) ^d	41.9	24.1
Median OS (months) ^d	NR	NR
75 th percentile OS (months) ^d	NR	NR
Survival rate at six months (%) ^d	96.2	95.6
95% CI for OS rate at six months (%) ^d	94.2, 97.5	93.4, 97.0
Survival rate at 12 months (%) ^d	89.5	86.5
95% CI for OS rate at 12 months (%) ^d	86.6, 91.9	83.3, 89.2
Survival rate at 24 months (%) ^d	82.2	75.2
95% CI for OS rate at 24 months (%) ^d	78.7, 85.2	71.3, 78.8
Survival rate at 36 months (%) ^d	76.6	69.8
95% CI for OS rate at 36 months (%) ^d	72.7, 80.0	65.5, 73.6
Hazard ratio (perioperative durvalumab versus control) ^{e,f}	0.75	
95% CI for hazard ratio ^e	0.594, 0.934	
Two-sided p-value ^g	0.0106 ^h	

^a Includes patients known to be alive at DCO.

^b Includes patients with unknown survival status or patients who were lost to follow-up.

^c Withdrawal by patient includes withdrawal by parent/guardian.

^d Calculated using the KM technique.

^e Based on stratified Cox PH model; the stratification factors were renal function (adequate versus borderline), tumour stage (T2N0 versus > T2N0), and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^f A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer OS than control.

^g Based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in e.

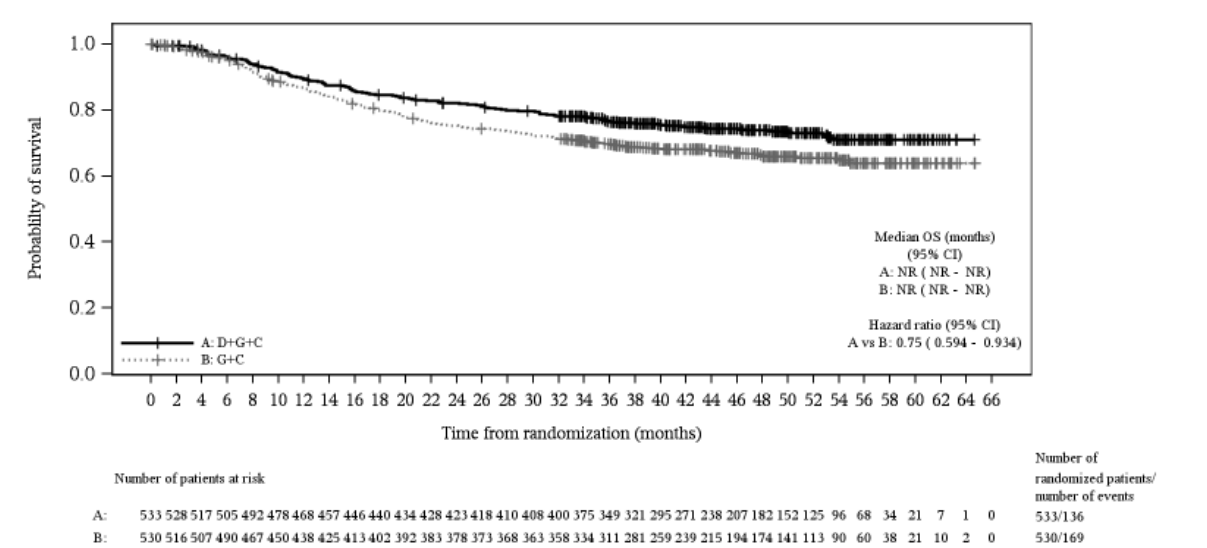
^h The threshold for statistical significance was p=0.0154.

Abbreviations: AE: adverse event; C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; G: gemcitabine; IA-2: second interim analysis; ITT: Intention-To-Treat; NR: not reached; OS: overall survival; PH: proportional hazard

Source: AZ NIAGARA trial CSR (71)

The OS KM curves began to separate at approximately six months in favour of perioperative durvalumab compared to the control and there was a clear and sustained separation thereafter (71).

Figure 7: KM plot of overall survival in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



Notes: Overall survival is defined as the time from the date of randomisation until death due to any cause regardless of whether the patient withdraws from randomised therapy or receives another anticancer therapy (i.e., date of death or censoring – date of randomisation + 1).

Median OS calculated using the KM technique.

HR based on stratified Cox PH model; the stratification factors were tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach. A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer OS than control.

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response system; ITT: Intention-To-Treat; KM: Kaplan-Meier; NR: not reached; OS: overall survival; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (71)

Perioperative durvalumab offers a statistically significant and clinically meaningful improvement in survival outcomes for patients with resectable MIBC, reducing the risk of death by 25% (2). **The finding that improvement in EFS translates into a benefit in OS—the gold standard endpoint in oncology—provides robust evidence of the effectiveness of perioperative durvalumab (80).** The correlation between OS and additional clinically relevant endpoints, which further reinforces the certainty regarding the efficacy of perioperative durvalumab, will be explored in subsequent sections. Notably, this marks the first time that a perioperative IO regimen has shown statistically significant superiority over standard of care in both EFS and OS.

2.6.2.2 Overall survival at five years (FAS [ITT population], DCO 29 April 2024)

Although OS rate at five years (OS5) will be formally tested at the final analysis (per the MTP), a descriptive analysis of OS5 was conducted at EFS IA-2 (DCO 29 April 2024). The OS5 was higher in the perioperative durvalumab arm (XX%) than the control arm (XX%) (xx x.xx [xx% xx: x.xx – x.xx], x=x.xxx) (Table 18) (71).

Table 18: Analysis of OS at five years in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

OS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Survival rate at 60 months (%) ^a		
95% CI for survival rate at 60 months (%) ^a		
Hazard ratio (perioperative durvalumab versus control) ^{b, c}		
95% CI for hazard ratio		
Two-sided p-valued		

^a Calculated using the KM technique.

^b HR and CI were obtained using KM estimator of OS5 using Klein approach (Klein *et al.* 2007).

^c A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer overall survival than control.

^d P-value is based on a chi-squared test with one degree of freedom.

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; G: gemcitabine; HR: hazard ratio; IA-2: second interim analysis; ITT: Intention-To-Treat; OS: overall survival.

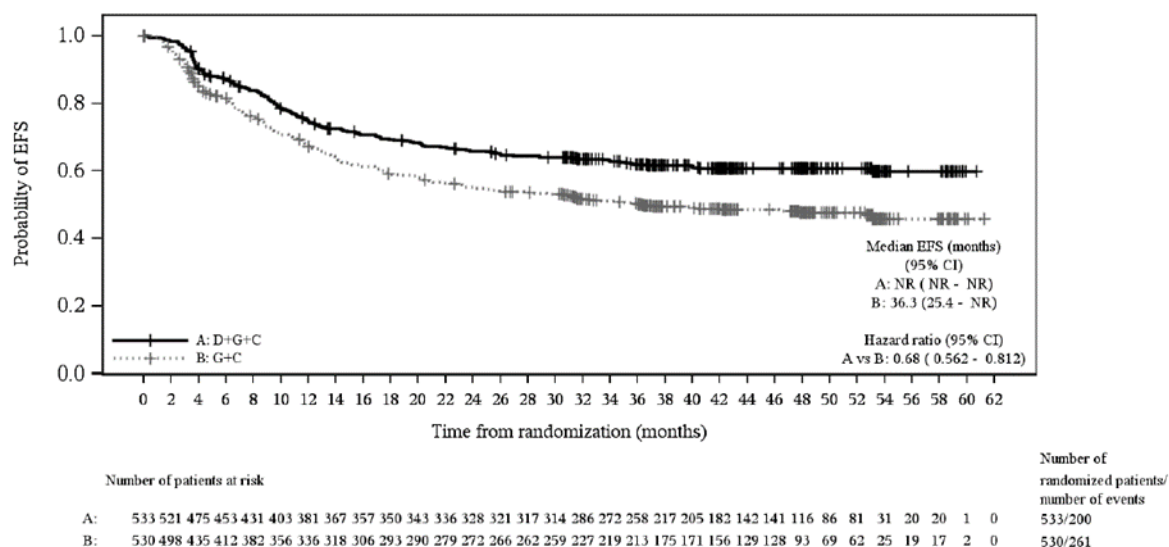
Source: AZ NIAGARA trial CSR (71)

A sensitivity analysis undertaken to assess potential attrition bias revealed no difference between the KM curves. The results indicated that censoring was comparable between treatment arms (71). Additionally, post-hoc subgroup analyses of OS were undertaken to assess the consistency of the treatment effect. The OS treatment effect was consistent across all subgroups when compared to the FAS (ITT population) (71). For further details, please refer to Appendix C.

2.6.2.3 EFS per investigator or local biopsy review (FAS [ITT population], DCO 29 April 2024)

There was a clinically meaningful improvement in EFS (per Investigator or local biopsy review) for the perioperative durvalumab arm as compared to the control arm in the FAS (ITT population) at IA-2 (DCO 29 April 2024) (71). The HR was 0.68 (95% CI: 0.562, 0.812, 2-sided p-value <0.001) indicating a 32% overall reduction in the risk of an EFS event (Figure 8). The results are aligned with the primary analysis for EFS by BICR or central pathology assessment (71). Further information on EFS status as per local pathology review can be found in Appendix J. The KM curves for EFS (per investigator or local biopsy review) began to separate at approximately two months in favour of perioperative durvalumab compared to the control, and there was a clear and sustained separation thereafter (Figure 8) (71).

Figure 8: KM plot of EFS, per investigator or local biopsy review, in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



^a EFS analysis based on assessments per Investigator or by local pathology review if a biopsy is required for a suspected new lesion.

^b Median EFS calculated using the KM technique.

^c HR based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^d A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer EFS than control.

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; G: gemcitabine; EFS: event-free survival; FAS: full-analysis set; HR: hazard ratio; IA-2: second interim analysis; IVRS: interactive voice response system; ITT: Intention-To-Treat; KM: Kaplan-Meier; N: Node; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards; T: tumour. Source: AZ NIAGARA trial CSR (71)

EFS results per investigator or local biopsy review followed a similar trend to those assessed per BICR or central review, demonstrating same overall 32% reduction in the risk of an EFS event. This consistency across assessment methodology and results reinforces the robustness of the EFS results and supports the clinical value of perioperative durvalumab in patients with MIBC (2).

2.6.2.4 Metastasis-free survival (FAS [ITT population], DCO 29 April 2024)

MFS was defined as the time from date of randomisation until the first recognition of distant metastases or death, whichever occurs first. In addition to more established endpoints, such as EFS and OS, MFS constitutes an informative endpoint, especially in early-stage cancer, when preventing metastasis can significantly improve long-term outcomes, associated costs and overall survival (81).

MFS data also supports the development of a cost effectiveness model as it enables local recurrence and distant metastases health states to be distinguished, aligning with the health states found in clinical practice, as described in Section 3.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

In the FAS (ITT population), at IA-2 DCO (29 April 2024), the perioperative durvalumab arm demonstrated a clinically meaningful improvement in MFS as compared to the control arm. The HR was 0.67 (95% CI: 0.541, 0.826; p=0.0002) indicating a 33% overall reduction in the risk of experiencing distant metastases or death (Table 19) (71).

The KM curves of MFS began to separate in favour of the perioperative durvalumab arm at approximately six months, and there was a clear and sustained separation thereafter (Figure 9) (71).

Table 19: Analysis of MFS in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

MFS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Total MFS events, n (%)	152 (28.5)	201 (37.9)
Distant metastasis	54 (10.1)	77 (14.5)
Death in the absence of distant metastasis	98 (18.4)	124 (23.4)
Censored patients, n (%)	381 (71.5)	329 (62.1)
Metastasis-free at time of analysis ^a	363 (68.1)	303 (57.2)
Lost to follow-up	0	0
Withdrawn consent	18 (3.4)	26 (4.9)
Other	0	0
25th percentile MFS (months) ^b	24.2	15.0
MFS survival (months) ^b	NR	NR
75th percentile MFS (months) ^b	NR	NR
MFS rate at six months (%) ^b	95.1	93.9
95% CI for MFS at six months ^b	92.8, 96.6	91.3, 95.7
MFS rate at 12 months (%) ^b	84.5	80.1
95% CI for MFS at 12 months ^b	80.9, 87.4	76.1, 83.4
MFS rate at 24 months (%) ^b	75.1	65.1
95% CI for MFS at 24 months ^b	71.0, 78.8	60.6, 69.3
MFS rate at 36 months (%) ^b	69.9	59.3
95% CI for MFS at 36 months ^b	65.5, 73.9	54.6, 63.7
Hazard ratio ^{c,d}	0.67	
95% CI for hazard ratio	0.541, 0.826	
Two-sided p-value ^e	0.0002	

^a Includes patients who do not have distant metastasis at DCO.

^b Calculated using the KM technique.

^c Based on stratified Cox PH model; the stratification factors are renal function (adequate versus borderline), tumour stage (T2N0 versus > T2N0), and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^d A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer MFS than control.

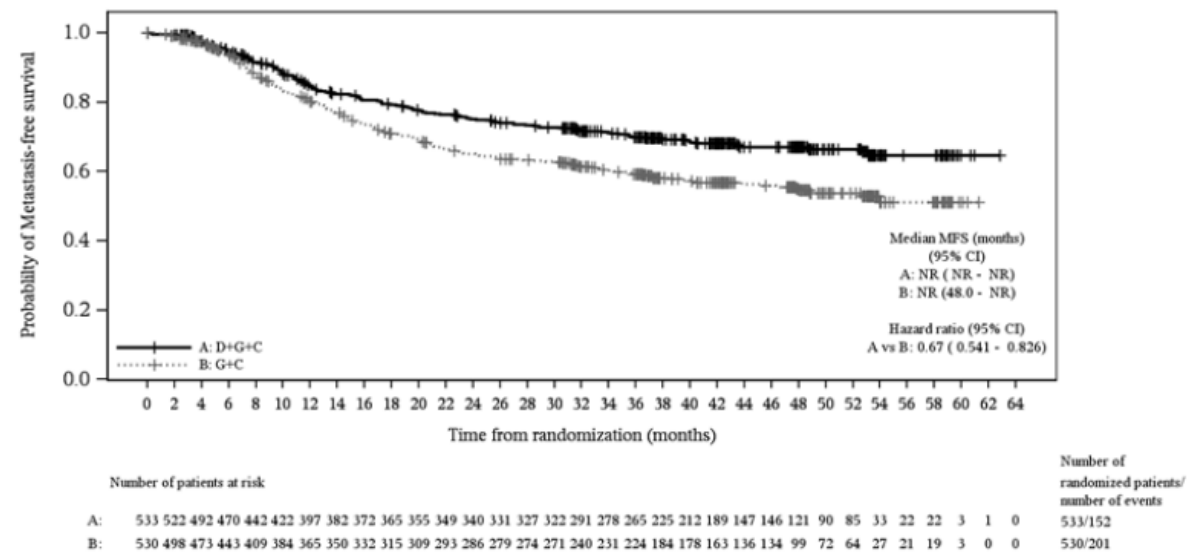
^e p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in c. p-value is nominal as MFS is not included in the MTP.

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; ITT: Intention-To-Treat; MFS: metastases-free survival; MTP: multiple testing procedure; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (71)

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Figure 9: KM plot of MFS in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



Notes: Median MFS is calculated using the KM technique.
HR based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.
A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer MFS than control.
Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; ITT: Intention-To-Treat; KM: Kaplan-Meier; MFS: metastasis-free survival; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards.
Source: AZ NIAGARA trial CSR (71)

MFS validates long-term consistency in the survival outcomes and supports the findings of the EFS primary endpoint. Perioperative durvalumab demonstrated a 33% reduction in the risk of metastasis, reinforcing the long-term value of perioperative durvalumab in reducing the risk of disease progression for patients with resectable MIBC (2).

2.6.2.5 Disease-specific survival (FAS [ITT population], DCO 29 April 2024)

In the NIAGARA trial, DSS was defined as the time from randomisation to death specifically due to bladder cancer. DSS provides a targeted assessment of survival outcomes related to MIBC by isolating mortality attributable to the disease, and thereby minimising the confounding impact of deaths unrelated to cancer that can obscure the treatment effect (90). This distinction is particularly valuable in older or comorbid populations, where non-cancer-related deaths are more frequent (91). DSS complements OS by providing disease-specific context, and the use of both endpoints together effectively reduces uncertainty in survival outcomes for patients with resectable MIBC (82).

In the FAS (ITT population), at EFS IA-2 (DCO 29 April 2024), perioperative durvalumab demonstrated a clinically meaningful improvement in DSS as compared to the control arm. The HR was 0.69 (95% CI: 0.516, 0.907; p=0.0081) indicating a 31% overall reduction in the risk of death due to bladder cancer (Table 20) (71).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

The benefit in DSS is observed after six to eight months of follow-up, after which the separation of the curves is clear and sustained (Figure 10) (71).

Table 20: Analysis of DSS in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)

DSS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Total DSS events, n (%)	85 (15.9)	114 (21.5)
Hazard ratio ^{b,c}	0.69	
95% CI for hazard ratio	0.516, 0.907	
Two-sided p-value ^d	0.0081	

^a Calculated using the KM technique.

^b Based on stratified Cox PH model; the stratification factors are renal function (adequate versus borderline), tumour stage (T2N0 versus > T2N0), and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

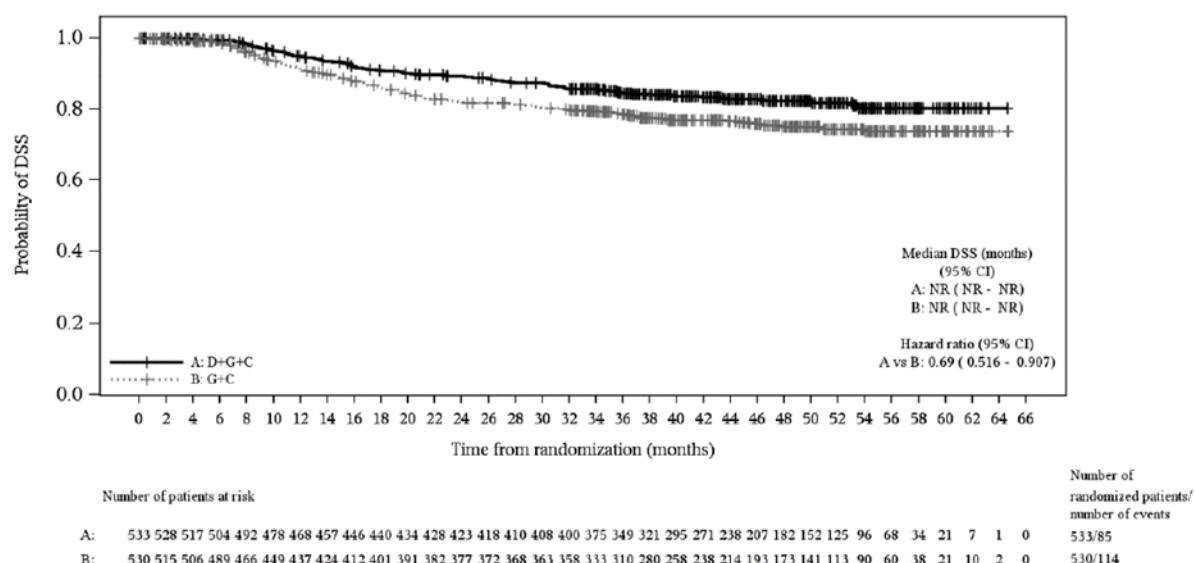
^c A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer DSS than control.

^d p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in b. p-value is nominal as DSS is not included in the MTP.

Abbreviations: C: cisplatin; CI: confidence interval; DCO: data cut-off; DSS: disease-specific survival; D: durvalumab; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; ITT: Intention-To-Treat; KM: Kaplan-Meier; MTP: multiple testing procedure; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (71)

Figure 10: KM Plot of disease-specific survival in NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



Notes: Median DSS calculated using the KM technique.

HR based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

A hazard ratio < 1 favours perioperative durvalumab over control.

Abbreviations: C: cisplatin; CI: confidence interval; DCO: data cut-off; DSS: disease-specific survival; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; ITT: Intention-To-Treat; KM: Kaplan-Meier; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (71)

The DSS benefit, in conjunction with the limited use of targeted IO as subsequent therapy after discontinuation of either treatment arm, suggests that the statistical significance of the OS benefit can be directly attributed to perioperative durvalumab treatment (2).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

2.6.2.6 Disease-free survival (Cystectomy population, DCO 29 April 2024)

DFS is used as a clinical endpoint for adjuvant treatments after definitive surgery or radiotherapy. In the NIAGARA trial, DFS was assessed in cystectomy population – patients who underwent RC and were disease-free at adjuvant baseline visit per BICR assessment. The cystectomy population included 352 patients in the perioperative durvalumab arm and 337 patients in the control arm (71).

DFS was defined as the time from the date of RC to the first recurrence of disease post RC, or death due to any cause, whichever occurs first.

The HR was 0.69 (95% CI: 0.514, 0.930; p=0.0143) indicating a 31% overall reduction in the risk of experiencing recurrence of disease or death post RC (Table 21) (71).

Table 21: Analysis of DFS in NIAGARA trial (Cystectomy population, DCO 29 April 2024)

DFS status	Perioperative durvalumab arm (D+G+C) (N=352)	Control arm (G+C) (N=337)
Total DFS events, n (%)	78 (22.2)	102 (30.3)
Disease recurrence	46 (13.1)	60 (17.8)
Death	32 (9.1)	42 (12.5)
Censored patients, n (%)	274 (77.8)	235 (69.7)
Disease-free at time of analysis	273 (77.6)	230 (68.2)
Lost to follow-up	0	0
Withdrawn consent	1 (0.3)	5 (1.5)
Other	0	0
25 th percentile DFS (months) ^a	NR	26.7
Median DFS (months) ^a	NR	NR
75 th percentile DFS (months) ^a	NR	NR
Hazard ratio ^{b,c}	0.69	
95% CI for hazard ratio	0.514, 0.930	
Two-sided p-value ^d	0.0143	

^a Calculated using the KM technique.

^b Based on stratified Cox PH model; the stratification factors are renal function (adequate versus borderline), tumour stage (T2N0 versus > T2N0), and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^c A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer DFS than control.

^d p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in b. p-value is nominal as DFS is not included in the MTP.

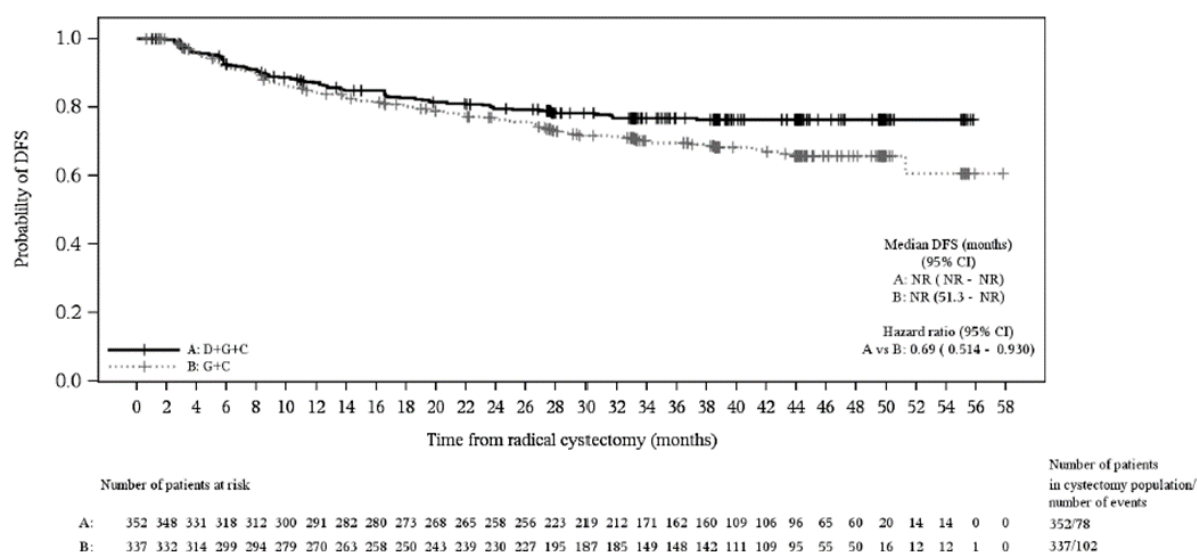
Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; DFS: disease-free survival; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; MTP: multiple testing procedure; PD-L1: programmed death-ligand 1; PH: proportional hazards; T: tumour.

Source: AZ NIAGARA trial CSR (71)

The DFS KM curves began to separate in favour of perioperative durvalumab at approximately eight months after cystectomy, and there was a clear and sustained separation thereafter (Figure 11).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Figure 11: KM plot of DFS in NIAGARA trial (Cystectomy population, DCO 29 April 2024)



Notes: DFS refers to the time from the date of RC to the first recurrence of disease post RC, or death due to any cause, whichever occurred first. DFS was assessed in patients who underwent RC and were disease free at adjuvant baseline visit per BICR assessment. Median DFS calculated using the KM technique.

HR based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer DFS than control.

Abbreviations: BICR: blinded independent central review; C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; DFS: disease-free survival; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; KM: Kaplan-Meier; PD-L1: programmed death-ligand 1; PH: proportional hazards; RC: radical cystectomy; T: tumour.

Source: AZ NIAGARA trial CSR (71)

The above data shows that perioperative durvalumab reduces the risk of disease recurrence or death as compared to the SoC. DFS data from the NIAGARA trial is still being monitored and will continue to provide valuable insights into the long-term benefits of perioperative durvalumab over SoC (2).

2.6.2.7 Time from randomisation to subsequent progression or recurrence post-EFS event (PFS-2) (FAS [ITT population], DCO 29 April 2024)

PFS-2 is a particularly valuable endpoint in the perioperative setting, where treatment strategies involve multiple phases and long-term outcomes are influenced by both initial and subsequent therapies (83). PFS-2 reflects the durability of treatment benefit beyond the first event. As such, it provides a more comprehensive measure of long-term disease control and is increasingly recognised as a meaningful surrogate for OS in trials involving immune checkpoint inhibitors (83, 84).

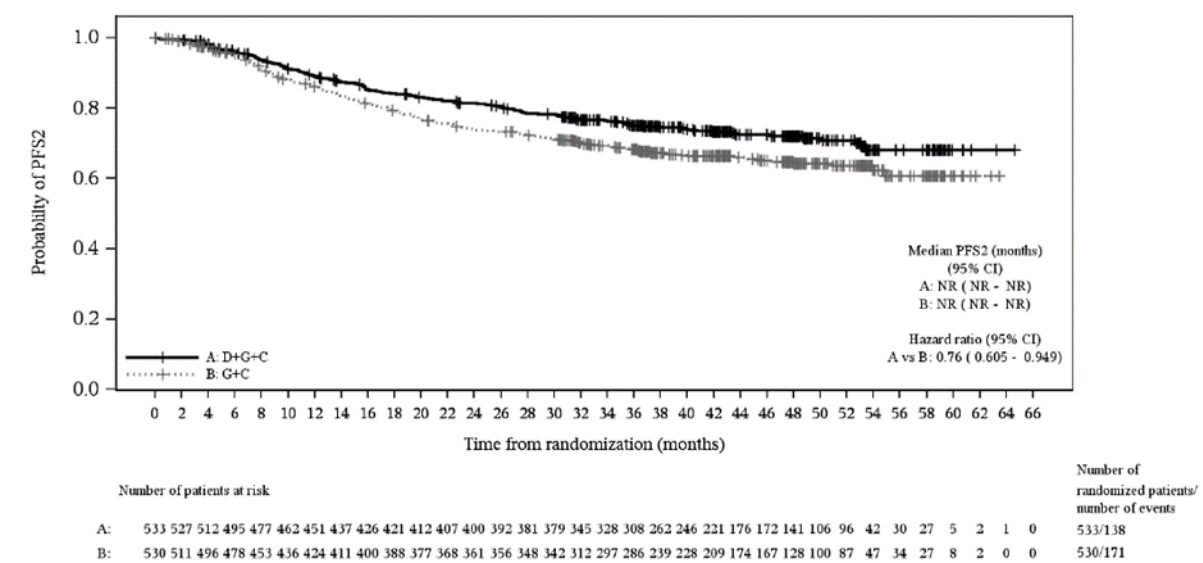
In the FAS (ITT population), at EFS IA-2 (DCO 29 April 2024), patients in the perioperative durvalumab arm had a clinically meaningful improvement in PFS-2 compared with those in the control arm. **The HR was 0.76 (95% CI: 0.605, 0.949); p=0.0155, indicating a 24% overall reduction in the risk of having a PFS-2 event.** Most of the PFS-2 events were

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deaths (71). The PFS-2 KM curves were similar until approximately six months, after which there was a clear and sustained separation (Figure 12) (71).

The observed 24% improvement, coupled with the sustained separation of KM curves beyond six months, highlights the durable clinical benefit of perioperative durvalumab treatment.

Figure 12: KM plot of time from randomisation to subsequent progression or recurrence post-EFS event (PFS-2) in the NIAGARA trial (FAS [ITT population], DCO 29 April 2024)



Notes: Median time to subsequent progression calculated using the KM technique.
HR based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 versus > T2N0), renal function (adequate versus borderline) and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.
A hazard ratio < 1 favours the perioperative arm to be associated with a longer time to subsequent progression than the control arm.
Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; EFS: event-free survival; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response system; ITT: intention-to-treat; KM: Kaplan-Meier; NR: not reached; PFS-2: Time from the date of randomisation to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PH: proportional hazard.
Source: AZ NIAGARA trial CSR (71)

2.6.2.8 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (FAS [ITT population], DCO 29 April 2024)

In the NIAGARA trial, adjusted mean change from baseline and time to deterioration (TTD) in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scales were secondary endpoints. Prioritised subscales of the EORTC QLQ-C30 consisted of global health status (GHS)/quality of life (QoL), physical functioning, fatigue, and pain. However, separate analyses were also conducted for each subscale (71, 74).

The HRQoL analysis was conducted using a data set that included baseline questionnaires completed prior to the initiation of study drug. Baseline questionnaires obtained at a date and

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time after treatment initiation were excluded. However, a number of patients were not included in the HRQoL analyses presented in the clinical study report (CSR) because their first PRO assessment, while conducted on the day of first dosing, was recorded in the database with a time stamp after treatment had started. This resulted in a programmatically-defined missing baseline assessment. AstraZeneca has become aware that there is some uncertainty in the time stamp in the database because the PRO devices were set up with an option to select a local time zone, but the time zone was not recorded in the database. In order to maximise the number of patients for analysis, the neoadjuvant baseline was re-defined as the last PRO assessment completed before or on the day of first dose of neoadjuvant treatment irrespective of the timing of the PRO assessment relative to first dose.

The post-hoc analysis results, presented below, align with the primary trial analysis, supporting the findings of the planned analysis. Full results of the post-hoc analysis are available in the addendum to the CSR (85), while the primary analysis results are available in the CSR (71).

In the post-hoc analysis, no differences were observed between treatment arms in the prioritised (GHS/QoL, physical functioning, fatigue, and pain) and non-prioritised EORTC QLQ-C30 scales (85).

In the FAS (ITT population), at the EFS IA-2 (DCO 29 April 2024), baseline compliance with the EORTC QLQ-C30 was 73.1% and 71.7% in the perioperative durvalumab arm and the control arm, respectively, and baseline mean GHS/QoL, physical functioning, fatigue, and pain scores were similar between treatment arms, reflecting the mild restricted activity as shown in the Eastern Cooperative Oncology Group Performance Status at baseline (Table 22) (85).

Table 22: EORTC QLQ-C30 scores at baseline and over time (FAS [ITT population], DCO 29 April 2024)

	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
GHS/QoL absolute score, mean (SD)		
Baseline	73.1 (18.50)	71.7 (18.70)
Week 25	63.3 (20.88)	60.6 (20.58)
Adjuvant week 29	73.3 (15.85)	73.0 (18.70)
Follow-up 33	41.7 (NC)	NC (NC)
Physical functioning absolute score, mean (SD)		
Baseline	87.8 (14.67)	88.3 (13.49)
Week 25	75.0 (20.83)	68.8 (23.72)
Adjuvant week 29	85.4 (16.97)	86.8 (16.64)
Follow-up 33	86.7 (NC)	NC (NC)
Fatigue absolute score, mean (SD)		
Baseline	18.6 (18.31)	20.0 (18.16)
Week 25	34.6 (22.83)	38.8 (25.62)
Adjuvant week 29	22.3 (19.29)	20.3 (20.97)
Follow-up 33	22.2 (NC)	NC (NC)
Pain absolute score, mean (SD)		

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	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Baseline	15.6 (20.51)	15.7 (20.98)
Week 25	23.1 (22.97)	24.6 (25.56)
Adjuvant week 29	13.5 (20.95)	12.3 (19.30)
Follow-up 33	0.0 (NC)	NC (NC)

Notes: Higher scores on the global health status and function scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

Abbreviations: C: cisplatin; D: durvalumab, DCO: data cut-off; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; FAS: full analysis set; G: gemcitabine; GHS: global health status; IA-2: interim analysis 2; ITT: intention-to-treat; NC: not calculated; QoL: quality of life; SD: standard deviation.

Source: AZ NIAGARA trial CSR addendum (85)

Perioperative durvalumab arm reported no decrement in the health-related quality of life (HRQoL) of patients as compared to the control arm, thereby concluding that no additional burden is conferred upon patients with the addition of perioperative durvalumab to the current SoC (85).

2.6.3 Exploratory endpoints

2.6.3.1 *EuroQoL 5-Dimension 5-Level (EQ-5D-5L) Questionnaire (FAS [ITT population], DCO 29 April 2024)*

As described in section 2.6.2.8, due to a programming error, a post-hoc analysis of the HRQoL outcomes was conducted. In this post-hoc analysis, the baseline compliance rate for EQ-5D-5L at baseline was 78.2% in the perioperative durvalumab arm and 81.1% in the control arm. Compliance decreased in both arms throughout the study (Table 23) (71).

At baseline, mean EQ-5D-5L index utility was slightly higher in the perioperative durvalumab arm (0.88) as compared to the control arm (0.84) while mean visual analogue scale (VAS) was comparable between treatment arms. Subsequently, both EQ-5D-5L index utility and EQ-VAS scores decreased by similar and small amounts in each treatment arm throughout the study (Table 23) (71).

Table 23: Compliance and scores for EQ-5D-5L and scores for EQ-VAS by time and overall (FAS [ITT population], DCO 29 April 2024)

	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Baseline		
Compliance rate (%) ^a	78.20	81.10
EQ-5D index score, mean (SD)	0.88 (0.43)	0.84 (0.14)
EQ-VAS score, mean (SD)	77.30 (15.93)	74.90 (16.85)
Week 25		
Compliance rate (%) ^a	50.90	43.20
EQ-5D index score, mean (SD)	0.73 (0.29)	0.71 (1.19)
EQ-VAS score, mean (SD)	70.90 (19.03)	66.10 (19.74)
Adjuvant Week 29		

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	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Compliance rate (%) ^a	72.70	69.50
EQ-5D index score, mean (SD)	0.84 (0.34)	0.85 (0.18)
EQ-VAS score, mean (SD)	77.10 (16.46)	77.20 (15.55)
Follow-up 33		
Compliance rate (%) ^a	50.00	NC
EQ-5D index score, mean (SD)	0.91 (NC)	NC (NC)
EQ-VAS score, mean (SD)	55.00 (NC)	NC (NC)
Overall		
Compliance rate (%) ^a	73.40	71.70
EQ-5D index score, mean (SD)	N/A	N/A
EQ-VAS score, mean (SD)	N/A	N/A

^a Compliance rate = Evaluable/Expected * 100%, Completion rate = Completed/Received *100%, Evaluability rate = Evaluable/Received *100%

Abbreviations: C: cisplatin; D: durvalumab, DCO: data cut-off; EQ-5D-5L: EuroQoL five dimensions, five level health state utility index; EQ-VAS: EuroQoL-visual analogue scales; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; ITT: intention-to-treat; N/A: not applicable; NC: not calculated; SD: standard deviation.

Source: AZ NIAGARA trial CSR (71)

The addition of perioperative durvalumab to SoC resulted in EQ-5D index scores that were comparable to those observed in the control arm (71). This finding is particularly important, as combination therapies—especially those involving immunotherapy—can increase the humanistic burden on patients (51). **The maintenance of similar extent of HRQoL demonstrates that the clinical benefits of perioperative durvalumab were achieved without compromising patients' overall well-being, reinforcing its suitability for patients with resectable MIBC (71).**

Other exploratory endpoints (Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events [PRO-CTCAE], Patient Global Impression of Change [PGIC] and Patient Global Impression of Severity [PGIS]) are presented in Appendix J.

2.6.4 Summary of clinical effectiveness results

NIAGARA is the first trial of a perioperative IO regimen to provide results in MIBC. Perioperative durvalumab has demonstrated a statistically significant and clinically meaningful benefit in EFS, reducing the risk of recurrence by 32% (HR 0.68 95% CI: 0.558, 0.817). These findings are further reinforced by a statistically significant and clinically meaningful improvement in OS (the gold standard endpoint in oncology (86)) with perioperative durvalumab reducing the risk of death by 25% (HR 0.75 95% CI: 0.594, 0.934) compared to the current UK SoC (80). Correlation with additional endpoints included in the trial as part of the multidimensional assessment, further strengthens the certainty in the benefit attributable to perioperative durvalumab, with demonstrated reductions in the risk of metastasis by 33% (MFS HR 0.67 95% CI: 0.541, 0.826) and death due to bladder cancer by 31% (DSS HR was 0.69 95% CI: 0.516, 0.907).

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The early and sustained separation of survival curves observed across multiple endpoints highlights the unique value of a perioperative intervention. In the NIAGARA trial, EFS curves began to separate in favour of perioperative durvalumab as early as two months, with this benefit maintained over time. Similarly, OS, MFS, and DSS curves showed clear and maintained separation starting at approximately six months post-treatment, further reinforcing the sustained impact of perioperative durvalumab. This pattern reflects the underlying mechanism of action, where the same IO therapy administered both before and after surgery primes anti-tumour immunity in the neoadjuvant setting and sustains immunosurveillance in the adjuvant setting, thereby reducing early recurrence and supporting long-term disease control. Collectively, these results emphasise the value of perioperative immunotherapy in delivering early and enduring clinical benefits for patients with resectable MIBC.

This unprecedented direct evidence versus UK standard of care, alongside with the existing unmet medical need, has led UK-based clinical experts to conclude that perioperative durvalumab is poised to become the new standard of care for cis-eligible patients with resectable MIBC.

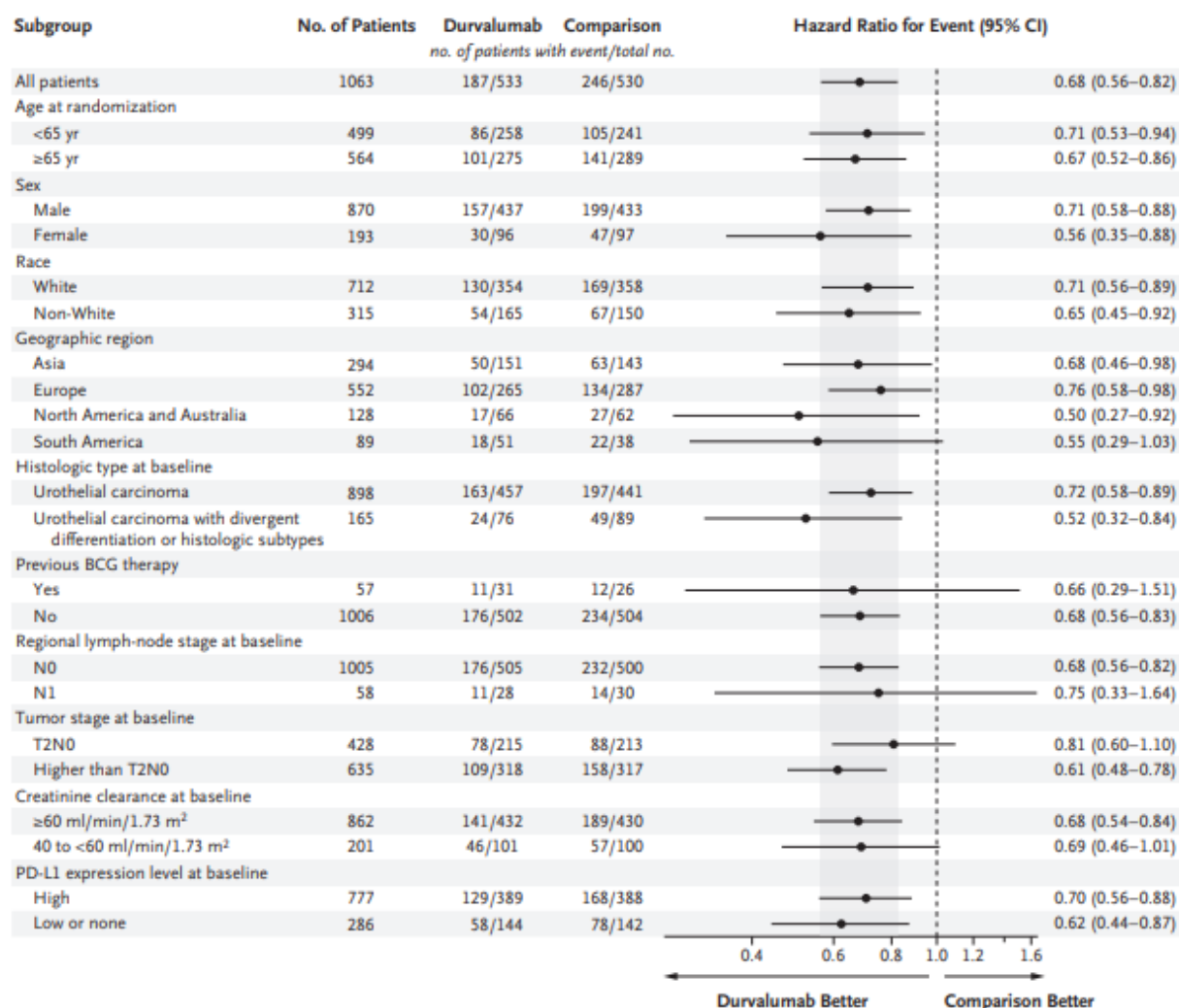
2.7 Subgroup analysis

In the NIAGARA trial, in order to mitigate any potential imbalances across treatment arms concerning pivotal tumour characteristics, the randomisation process was stratified according to tumour stage, baseline PD-L1 expression, and renal function (71). Analyses were conducted for several prespecified subgroups in addition to the stratification factors, including but not limited to age, sex, histology, prior Bacillus Calmette Guérin (BCG) therapy, lymph node involvement, race and region (71).

2.7.1 EFS and OS

Observed treatment effect was broadly consistent for EFS and OS across all prespecified subgroups as seen in Figure 13 and Figure 14 below (71).

Figure 13: Subgroup analysis forest plot for event-free survival (FAS [ITT population] DCO 29 April 2024)

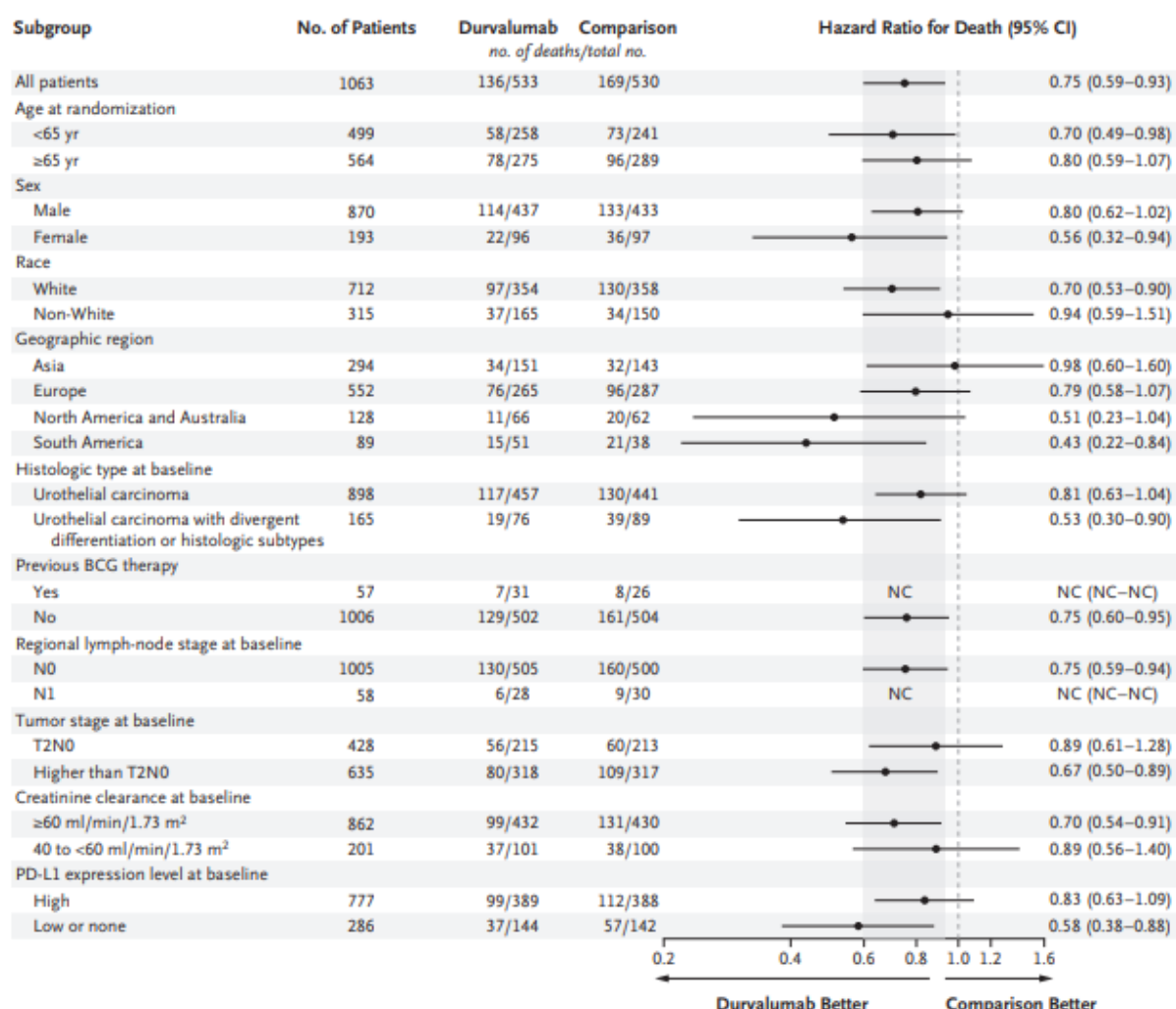


Notes: The gray shading indicates the 95% confidence interval for the hazard ratio for an event in the FAS (ITT population). Prespecified subgroup analyses were performed with the use of an unstratified Cox proportional hazards model with treatment as the only covariate and the use of Efron's approach for handling ties.

Abbreviations: BCG: Bacillus Calmette-Guérin; CI: Confidence Interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; FAS: Full analysis set; ITT: intention-to-treat; No.: Number; PD-L1: Programmed Death-Ligand 1

Source: AZ NIAGARA trial CSR (71)

Figure 14: Subgroup analysis forest plot for overall survival (FAS [ITT population] DCO 29 April 2024)



Notes: The gray shading indicates the 95% confidence interval for the hazard ratio for an event in the FAS (ITT population). Prespecified subgroup analyses were performed with the use of an unstratified Cox proportional hazards model with treatment as the only covariate and the use of Efron's approach for handling ties.

Abbreviations: BCG: Bacillus Calmette-Guérin; CI: Confidence Interval; DCO: data cut-off; ECOG: Eastern Cooperative Oncology Group; FAS: Full analysis set; ITT: Intention-to-treat; No.: Number; NC: Not calculated; PD-L1: Programmed Death-Ligand 1

Source: AZ NIAGARA trial CSR (71)

The observed treatment effect for EFS and OS across all subgroups is consistent with the results for the FAS (ITT population). Subgroup analyses can introduce inherent uncertainties, with lower numbers of patients and events across individual subgroups leading to greater uncertainty in point estimates and wider CIs, which can warrant caution while interpreting the results. **In the case of the NIAGARA trial, broad alignment is seen between the FAS (ITT population) and subgroups, providing an additional layer of validity to the results obtained in the FAS (ITT population).**

2.7.2 pCR

The results from all the subgroup analyses undertaken for the NIAGARA trial should be interpreted with caution as the study was not powered for any of the individual subgroup Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

evaluations and there was a low number of patients and events across the individual subgroups. Subgroup analyses for both the primary analysis and reanalysis of pCR (per central pathology review) were consistent with those observed in the overall FAS (ITT population) analysis (71). Please refer to Appendix C for more details on the pCR subgroup analyses.

2.7.3 PD-L1 subgroups

As outlined in the final scope published by NICE, and for completeness, the NIAGARA trial assessed the benefit of perioperative durvalumab across different levels of PD-L1 expression (13, 71). However, the UK-based clinical experts consulted by the company unanimously confirmed that the value of PD-L1 in BC is uncertain and would not guide the use of perioperative durvalumab in their clinical practice (14).

Several studies have evaluated the marker with mixed results, which may, partially, be related to the use of different antibodies and scoring methods (4). The variability, especially given the notable number of PD-L1-negative patients who still respond to immune checkpoint blockade, suggests that PD-L1 does not drive treatment decisions in MIBC, or BC in general, outside of patient selection for drugs that are restricted to a specific level of PD-L1 expression in the label as evidenced by the EAU and ESMO clinical guidelines (4, 31).

The CheckMate-274 trial reported HR values for the PD-L1 negative subgroup within the MIBC patient population for the primary endpoint of DFS, which were not statistically significant. This finding led to regulatory and reimbursement restrictions limiting use to patients with PD-L1 $\geq$ 1%, as reflected in the NICE recommendation for TA817, aligned with the EMA license (95, 96).

In contrast, the NIAGARA trial demonstrated that subgroup analyses of EFS and OS endpoints by PD-L1 expression were consistent with the results observed in the FAS (ITT population) (71). The HRs for both endpoints (EFS HR 0.68, OS HR 0.75) in the FAS (ITT population) fell between those observed in the PD-L1-high (EFS HR 0.70, OS HR 0.83) and PD-L1-low (EFS HR 0.62, OS HR 0.53) subgroups, and were within the respective CIs, supporting consistency across subgroups. These results indicate that PD-L1 is not influencing the efficacy of perioperative durvalumab regimen in the NIAGARA trial (2).

Given the consistency between PD-L1 subgroups and the FAS (ITT population) in the NIAGARA trial and the lack of evidence supporting PD-L1 as a treatment effect modifier in MIBC, PD-L1 expression holds no relevance for the UK clinical practice in the context of this appraisal. Therefore, it should focus exclusively on the FAS (ITT population), as also validated by the UK-based clinical experts who confirmed that the relevance of PD-L1 subgroup is quite

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minor in MIBC and affirmed that perioperative durvalumab is expected to provide benefit across all patients, independent of the PD-L1 status, providing a broad application for the regimen (14).

2.8 Meta-analysis

Only one trial (NIAGARA) evaluating perioperative durvalumab for the treatment of cisplatin-eligible patients with resectable MIBC was identified in the SLR, thus a meta-analysis could not be conducted. Further information can be founded in section 2.1 and section 2.9.

2.9 Indirect Treatment Comparison

Summary of indirect treatment comparison

Trials identified for ITC

- An SLR was conducted to identify and summarise all published evidence from RCTs on the clinical efficacy and safety of treatments for adult patients with MIBC, with the aim of conducting an ITC feasibility assessment. In line with the scope of the appraisal, **only one RCT (CheckMate-274) was considered relevant for the UK treatment landscape.**
- The overlap between patients eligible for perioperative durvalumab and those eligible for adjuvant nivolumab among cis-eligible resectable MIBC patients is minimal. An estimated **xx.x%** of patients in the NIAGARA control arm would be eligible for adjuvant nivolumab when aligning populations to CheckMate-274 and TA817. These are patients who had undergone RC, were disease free at adjuvant baseline visit, whose tumours express PD-L1 $\geq$ 1% and considered at high-risk of recurrence after surgery.
- An ITC versus adjuvant nivolumab has been included for completeness, as the expected reduction in the use of NAC alone if perioperative durvalumab is reimbursed—resulting from the superiority demonstrated in the NIAGARA trial—will consequently decrease the use of adjuvant nivolumab in an already restricted number of eligible patients.
- It is important to emphasise that **the two treatments are not interchangeable**, with one being a **proactive therapeutic approach (perioperative durvalumab)** while the other is considered **reactive intervention (adjuvant nivolumab)** after insufficient response from NAC alone and RC. **No patient initiated on perioperative durvalumab would be eligible to receive adjuvant nivolumab, and any patient receiving NAC alone would not be eligible to receive durvalumab as an adjuvant only therapy.**

ITC feasibility assessment

- **Standard ITC methods were unsuitable for comparing CheckMate-274 and NIAGARA ITT cohorts** due to differences in the control arms, the timing of randomisation and the inclusion criteria.
- **Comparing only the adjuvant phases of the NIAGARA and CheckMate-274 trials was deemed infeasible with existing ITC methods** due to several sources of bias, such as endpoints definition, differences in baseline risk of recurrence and in potential effect modifiers across the adjuvant phases of the studies, including prior IO use in the durvalumab arm during the neoadjuvant phase of NIAGARA.

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Survival Time-Adjusted ITC

Objective

- As standard ITC methods were not considered suitable and address key questions for decision making, an alternative **'survival-time adjusted ITC' approach has been proposed**
- Survival times were estimated for the control arm of the NIAGARA trial, simulating a scenario where eligible high-risk PD-L1 $\geq 1\%$ patients received adjuvant nivolumab instead of no treatment after neoadjuvant chemotherapy followed by radical cystectomy.

Method

- The analysis was performed on the endpoints of EFS and OS, using the IA-2 (DCO 29 April 2024) of the NIAGARA trial and the latest 3-year extended follow-up of CheckMate-274 trial.
- The analysis consisted of three steps:
 1. **Estimate the acceleration factor (AF)** – extent of survival increase associated with adjuvant nivolumab
 2. **Create the counterfactual survival times** for EFS and OS applying the AF to the 'adjuvant phase' survival times of eligible patients in the NIAGARA trial control arm (G+C+N)
 3. **Conduct the ITC by comparing perioperative durvalumab with G+C+N**

Summary of Survival Time-Adjusted ITC Results

- **Perioperative durvalumab led to a statistically significant improvement in EFS versus G+C+N with an HR of 0.742 (0.610, 0.8990).**
- **Perioperative durvalumab is associated with a statistically significant improvement in OS versus G+C+N with an HR of 0.800 (0.633, 0.994).**

Conclusions of Survival Time-Adjusted ITC

- **Strengths: the analysis addresses a key decision-maker question** and provides robust comparative results by capturing all relevant outcomes arising from the decision to use perioperative durvalumab. **Comprehensive data utilisation** and the application of bootstrapping methods appropriately **captured uncertainty** and further strengthened these findings.
- **The key limitations** of the analysis are relying of PD-L1 subgroup results with different testing assays across studies and the lack of safety and tolerability evaluation, since the ITC focused on the key efficacy endpoints of EFS and OS.
- The Survival Time-Adjusted ITC results show that perioperative durvalumab significantly improves EFS and OS compared to a regimen of neoadjuvant chemotherapy followed by either no treatment or adjuvant nivolumab in eligible patients with MIBC (G+C+N).
- **The observed results are consistent with the mechanism of action and value of perioperative IO regimens, demonstrating how a proactive approach can improve survival and address the main unmet medical need in a broader cis-eligible resectable MIBC population. These findings answer a key decision-making question and further strengthen the position of perioperative durvalumab as the new SoC in cis-eligible resectable MIBC.**

An SLR was conducted on the 22 July 2024 and updated on 25 April 2025 to identify and summarise all published evidence from randomised clinical trials (RCTs) on the clinical efficacy and safety of treatments for adult patients with MIBC, with the aim of conducting an indirect treatment comparison (ITC) feasibility assessment. Evidence connectivity was assessed by grouping RCTs based on treatment setting and cisplatin eligibility.

The ITC feasibility assessment aimed to determine if an ITC was suitable to compare the efficacy of perioperative durvalumab to approved neoadjuvant and adjuvant therapies. Adjuvant therapies were included to provide a broader perspective of the therapeutic landscape, acknowledging that the introduction of a perioperative regimen—with a single treatment decision point encompassing both pre- and post-surgical phases—will ultimately replace interventions prescribed at the same decision point (pre-surgery). The decision to initiate perioperative durvalumab precludes patients from receiving any adjuvant therapy other than durvalumab monotherapy, including adjuvant nivolumab.

Feasibility was assessed by evaluating differences in trial design and in effect modifiers (EMs) between the NIAGARA trial and RCTs of neoadjuvant/perioperative (randomised before radical cystectomy) and adjuvant regimens (randomised after radical cystectomy). Potential EMs and prognostic factors were identified through targeted reviews and consultation with clinical experts. Heterogeneity in study designs, patient populations, interventions and outcome definitions and assessments was explored qualitatively.

The evidence base summary comprised 53 RCTs reporting efficacy and/or safety endpoints of interest (52 SLR-identified studies plus the NIAGARA trial). This ITC assessment, initially conducted at a global level, was subsequently adapted to align with the final scope of this appraisal and UK clinical practice. Consequently, none of the neoadjuvant studies and only one of the adjuvant studies was considered relevant (CheckMate-274 trial).

The overlap between patients that are eligible for perioperative durvalumab and for adjuvant nivolumab is minimal. Adjuvant nivolumab is used for cisplatin-eligible or -ineligible patients who cannot receive adjuvant cisplatin, present PD-L1 positive tumours, and are at high risk of recurrence after RC, regardless of prior NAC (see Figure 2, Section 1.3). Of these, only cisplatin-eligible patients who receive NAC may be considered for perioperative durvalumab, regardless of PD-L1 status and risk of recurrence. As high-risk recurrence criteria for adjuvant nivolumab are assessed post-surgery, while perioperative durvalumab eligibility is determined pre-surgery, the exact overlap cannot be prospectively quantified. The expected decrease in adjuvant nivolumab use with the availability of perioperative durvalumab is primarily due to a reduction in the use of NAC alone, in favour of NAC plus durvalumab - followed by durvalumab

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after surgery- given the superior outcomes shown with perioperative durvalumab in the NIAGARA trial.

Comparison of perioperative durvalumab to adjuvant nivolumab

Common ITC methods relying on either a network of evidence anchored by a shared control arm (“anchored comparisons”) or the cross-trial comparison of absolute outcomes in overlapping populations (“unanchored comparisons”) are not suitable for comparing the ITT cohorts of the CheckMate-274 and the NIAGARA. Furthermore, comparing adjuvant-only phases of NIAGARA to CheckMate-274 trials was deemed infeasible with existing ITC methods. The main reasons why these comparisons cannot be made, and an alternative methodology is proposed are:

- **Differences in the primary endpoint used and secondary endpoints definition -**

In CheckMate-274 trial, the primary endpoint was DFS measured since randomisation, which was defined at start of the adjuvant phase. Secondary endpoints included OS defined as time to death from randomisation (at the adjuvant baseline). In NIAGARA trial, the dual primary endpoint was EFS, which included outcomes in both the neoadjuvant and adjuvant phases. Secondary endpoints included DFS, which was measured post-randomisation from the baseline adjuvant visit in NIAGARA, and OS, which was measured since randomisation (at neoadjuvant baseline).

EFS covers different aspects of disease to DFS and cannot therefore be compared across studies. Similarly, OS endpoints are measured from different points in the treatment pathway (neoadjuvant baseline in NIAGARA versus adjuvant baseline in CheckMate-274), capturing death events pre- and post-surgery in NIAGARA and only post-surgery in CheckMate-274.

DFS endpoints are measured from an approximately consistent time point, however, the comparison of these endpoints is not considered appropriate, because of differences in inclusion criteria discussed below.

- **Differences in the inclusion criteria -** In the CheckMate-274 trial, all patients had to be sufficiently fit and willing to undergo RC and had to achieve disease-free status within four weeks prior to randomisation. Conversely, in the NIAGARA trial, patients entered the study as medically fit to undergo radical cystectomy, however a proportion of patients became ineligible or refused surgery during the neoadjuvant phase or fail to achieve disease-free status post-surgery (59). The exclusion of patients with these unfavourable prognostic characteristics from enrolment in the CheckMate-274 trial could introduce selection bias. Other differences in the inclusion criteria include receipt

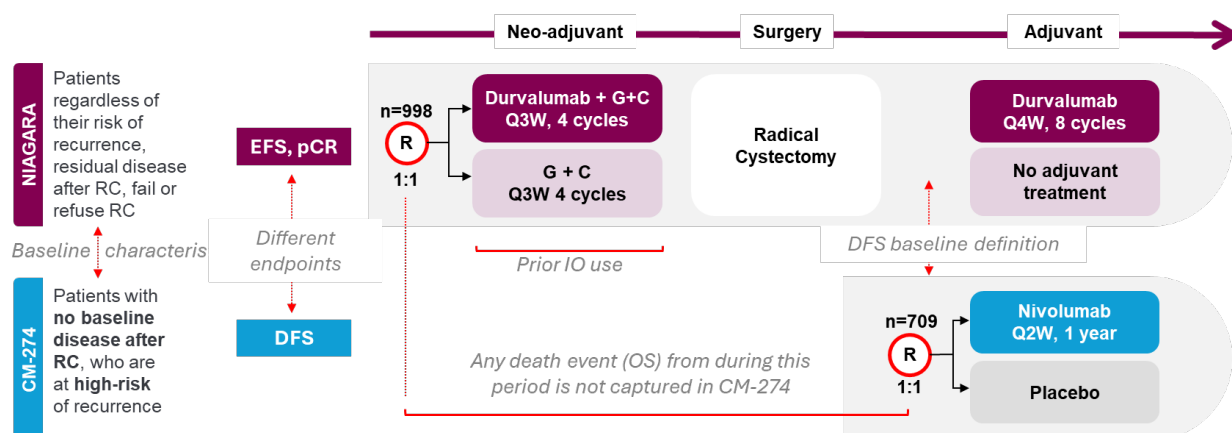
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of prior IO in the neoadjuvant phase of the NIAGARA trial, and risk of recurrence at adjuvant baseline.

- **Differences in the control arms** – Placebo in CheckMate-274 trial and neoadjuvant gemcitabine-cisplatin followed by RC in NIAGARA trial

A representation of both trials and the source of bias is represented in Figure 15.

Figure 15: Representation of NIAGARA and CheckMate-274 trials



Notes: Figure adapted by the company based on NIAGARA (2) and CheckMate-274 trials (15) designs.

Abbreviations: C: cisplatin; CM: CheckMate; DFS: disease-free survival; EFS: event free survival; G: gemcitabine; OS: overall survival; pCR: pathological complete response; Q2W: every two weeks; Q3W: every three weeks; Q4W: every four weeks; RC: radical cystectomy; R: randomisation.

Comparison of perioperative durvalumab to neoadjuvant gemcitabine-cisplatin followed by RC with or without adjuvant nivolumab

To overcome traditional ITC method's challenges, an alternative 'survival-time adjusted ITC' approach has been proposed. This approach allows a more appropriate comparison of outcomes between perioperative durvalumab, and NAC followed by no treatment or adjuvant nivolumab in PD-L1 $\geq$ 1% high-risk MIBC patients after surgery. Whilst the ITT population CheckMate-274 trial does not specify PD-L1 $\geq$ 1%, this is aligned to the NICE recommendation of nivolumab in this setting (TA817).

In addition to avoiding the bias that renders typical ITC methods unfeasible, this approach:

- Represents the treatment decision points of clinical practice in the neoadjuvant and perioperative space: patients treated with perioperative durvalumab only have one treatment decision point before surgery, that dictates treatment pre- and post-RC.
- Aligns with current treatment landscape for patients in the scope (cis-eligible resectable MIBC) where patients will be treated with adjuvant nivolumab only if they have received NAC and therefore are ineligible for adjuvant cisplatin.

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- Current treatment displacement of nivolumab by durvalumab will occur only in those patients who received NAC followed by RC and would have met adjuvant nivolumab eligibility criteria, reflecting a limited overlap.

The proposed survival-time adjusted ITC approach uses counterfactual survival time methods to estimate the outcomes of neoadjuvant chemotherapy followed by no treatment or adjuvant nivolumab in high-risk patients PD-L1 $\geq$ 1%, where counterfactual survival time represents the survival time that would have been observed for an individual under a different treatment or condition than the one they actually experienced. The methodology uses established techniques originally developed for adjusting survival times for the impact of crossover or treatment switching (87). These existing methods have been adapted to capture the effect of including a new therapy (i.e., adjuvant nivolumab) in the pathway. In this analysis, survival times were estimated for the control arm of the NIAGARA trial, simulating a scenario where eligible high-risk PD-L1 $\geq$ 1% patients received adjuvant nivolumab instead of no treatment after NAC and RC.

2.9.1 Population and endpoints

The survival time adjusted ITC used data from the full ITT population of the NIAGARA trial and was performed as a scenario where adjuvant nivolumab is used aligned with NICE positioning, namely in high-risk PD-L1 $\geq$ 1% patients (11).

Given this approach attempts to estimate the relative efficacy of NAC followed by RC with or without adjuvant nivolumab, using the prior NAC subgroup from the CheckMate-274 trial could be considered.

The analysis was performed on the endpoints of EFS and OS, using the IA-2 (DCO 29 April 2024) of the NIAGARA trial and the 3-year extended follow-up of the CheckMate-274 trial (88) (Table 24).

Table 24: Differences in analysis between the NIAGARA and CheckMate-274 trials

NIAGARA	CheckMate-274
• EFS, OS: ITT cohort • Second planned interim superiority analysis • Data Cut off: 29 April 2024	• DFS, OS: Subgroup of patients with high-risk MIBC and tumour PD-L1 $\geq$ 1% (n=113 for nivolumab, n=117 for placebo) • Extended 3-year follow-up • Data cut off: not reported

Abbreviations: DFS: Disease-free survival; EFS: Event-free survival; ITT: Intention-to-treat; OS: Overall Survival; PD-L1: Programmed Death Ligand-1.

Source: AZ NIAGARA trial CSR (71), 3-year extended follow-up of the CheckMate-274 trial (88).

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2.9.2 Methods

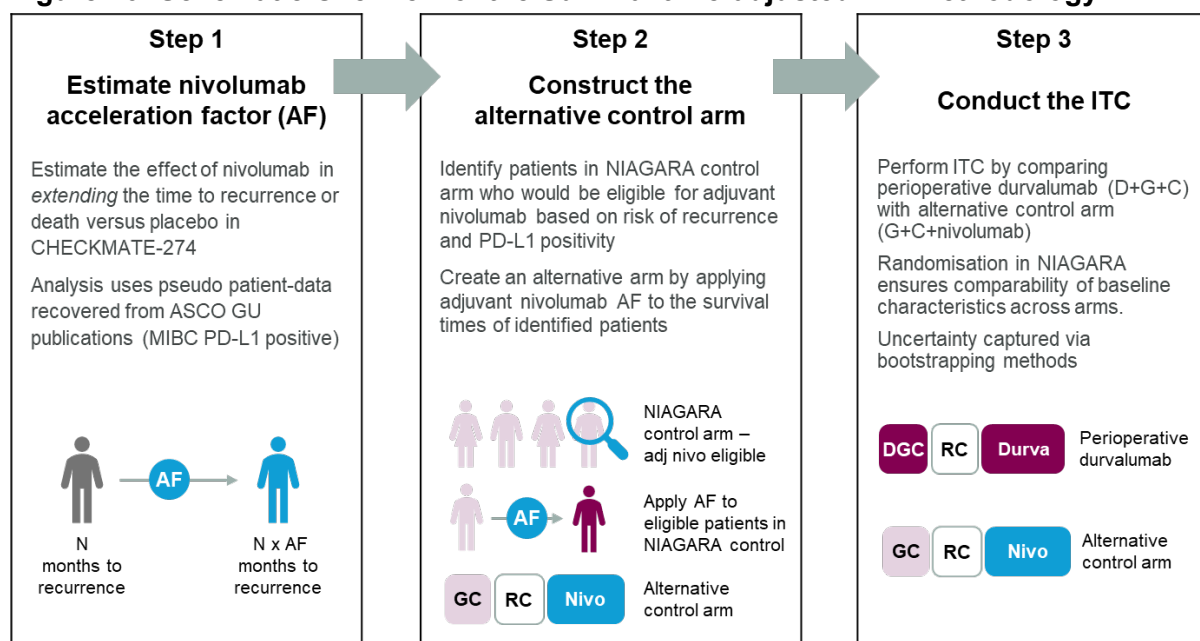
The analysis consisted of three steps:

1. **Estimate the acceleration factor (AF)** – the amount by which an individual's expected survival time is increased by treatment - for adjuvant nivolumab versus placebo from the MIBC and PD-L1>1% subgroup of the CheckMate-274 trial (15).
2. **Create the counterfactual survival times** by applying the AF from step one to the control arm of the NIAGARA trial. The AF was applied to the 'adjuvant phase' survival times from the control arm for patients who identified as eligible for adjuvant nivolumab. 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 the observed outcomes in the NIAGARA trial.
3. **Conduct the ITC** comparing perioperative durvalumab versus the counterfactual control arm created in step two. Randomisation in the NIAGARA trial ensured comparable baseline characteristics across all arms in the ITC and population adjustment was not required.

Following treatment switching guidelines, the counterfactual survival analysis was performed with and without re-censoring (87).

A simplified illustration of the methodology is presented in Figure 16.

Figure 16: Schematic Overview of the Survival time-adjusted ITC Methodology



Abbreviations: AF: acceleration factor; ASCO: American Society of Clinical Oncology; Durva: durvalumab; D+G+C: durvalumab plus gemcitabine plus cisplatin; G+C: gemcitabine cisplatin; ITC: indirect treatment comparison; RC: Radical cystectomy; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; Nivo: nivolumab; PD-L1: programmed death-ligand 1.

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Step 1: Estimate the effect (AF) of adjuvant nivolumab in the CheckMate-274 trial

The effect of nivolumab was estimated using pseudo patient-level data reconstructed from the CheckMate-274 trial KM curves for the subgroup of patients with high-risk MIBC and tumour PD-L1 $\geq 1\%$. Pseudo patient data were recovered from published KM plots using the Guyot *et al.* algorithm ref (89).

The AF for nivolumab versus placebo was estimated by fitting a series of accelerated failure time (AFT) models (log-normal, Weibull, generalised gamma, log-logistic, and gamma) to a data set containing both arms of the CheckMate-274 trial with a covariate representing treatment. The treatment covariate in each model estimates the effect of nivolumab in the form of a constant AF, representing a multiplicative factor by which an individual's expected survival time is increased by nivolumab when compared with placebo.

Model selection was based on visual fit to the CheckMate-274 trial KM curves and goodness of fit statistics (AIC and BIC) (15). Where standard AFT models did not fit well, flexible parametric models with time-varying treatment effects, such as Royston-Parmar cubic spline models, were considered. The spline analysis used an odds link function, which is an extension of the log-logistic AFT model. To incorporate time-varying treatment effects for nivolumab, the treatment covariate was applied to all spline parameters, yielding survival outcomes equivalent to fitting independent models to each arm. Models with up to 4-knots were considered, and the model with the best AIC score was used to predict the time-varying AFs for nivolumab.

Time-varying AFs were derived from the mathematical relationship between AF and quantile survival times. In a standard AFT model, the treatment effect (i.e., the AF) is modeled as a constant multiplicative shift in the outcome distribution across all survival quantiles (90). The time-varying AF adopts this principle but allows the ratio of quantiles (and hence AFs) to vary over quantile (and hence time).

The time-varying AFs were calculated via a multi-step process. First, the quantile survival times (ranging from 0.01 to 0.99) for each arm were estimated using the best-fitting model and the predict function from the flexure package. In the second step, the AFs were calculated as the ratio of quantile survival times for nivolumab and placebo. To apply these AFs to the NIAGARA trial, a generalised additive model (GAM) with a cubic spline term was then fitted to the AFs, with quantile value for the placebo arm included as an independent variable. The observed survival times of each eligible patient in the NIAGARA trial was mapped to the quantile scale using KM estimates (i.e., the quantile was 1 minus the survival probability at time X). The GAM was then used to predict the AF for nivolumab based on each individual's

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quantile value. This approach assumes that nivolumab's effect (multiplicative effect on survival time) is consistent for patients at corresponding quantiles in both studies.

Calculating the DFS AF for adjuvant nivolumab

The KM curve for DFS in the PD-L1 MIBC subgroup of the CheckMate-274 trial, produced using the recovered patient data is presented in Appendix B.4 Section 4.2.1.1, alongside details of the corresponding landmark and median survival times, as well as the hazard ratio for nivolumab versus placebo.

The results of the AFT models fit to this data are provided in Appendix B.4. This covariate represents the effect of nivolumab in decelerating the time to an event compared to placebo. Appendix B.4, Figure 5 shows the visual fit of the AFT models to the KM curves. To better capture the effect of nivolumab in the PD-L1 subgroup, a series of flexible parametric survival models with time-varying treatment effects was fitted to the CheckMate-274 trial data. These are provided in the Appendix B.4. A summary of goodness of fit and AF parameter estimates for the PD-L1 MIBC subgroup is included in Table 25. According to goodness of fit statistics, the best fitting model was generalised gamma. However, based on visual fit, this model failed to adequately predict the trial data as it systematically underestimated survival in the nivolumab arm and overestimated survival in the placebo arm. The log-logistic AFT yielded the most optimistic estimate of the effect of nivolumab [REDACTED], and therefore was considered to provide the most conservative scenario for the ITC. Accordingly, the ITC base case was performed using the log-logistic constant AF.

Table 25: Summary of goodness of fit and AF parameter estimates for the PD-L1 MIBC subgroup

Model	GOF AIC	GOF BIC	Estimate	Standard error	Lower 95% CI	Upper 95% CI
Generalised gamma	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Log-normal	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Log-logistic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Weibull	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: AF: acceleration factor; AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; CI: Confidence interval; GOF: goodness of fit; MIBC: muscle-invasive bladder cancer; PD-L1: programmed death-ligand 1

The 3-knot spline odd's time-varying AF was used in sensitivity analysis as this was the best fitting spline and provided a good fit to the PD-L1 subgroup data.

Calculating the OS AF for adjuvant nivolumab

The KM curve for OS in the PD-L1 MIBC subgroup of the CheckMate-274 trial, produced using the recovered patient data is presented in Appendix B.4, alongside details of the corresponding landmark and median survival times, as well as the hazard ratio for nivolumab versus placebo.

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The results of the AFT models fit to this data are provided in Table 26. The visual fit of the AFT models to the KM curves is provided in Appendix B.4.

The best fitting model according to AIC and BIC, and visual fit to the KM curve was the log-normal model. The AF for nivolumab versus placebo from this model was [REDACTED]. Across all fitted models, the mean AF ranged from [REDACTED]. The standard AFT models yielded a sufficient fit to the trial data and splines were not explored for this endpoint.

Table 26: Summary of goodness of fit and AF parameter estimates for the PD-L1 MIBC subgroup

Model	GOF AIC	GOF BIC	Estimate	Standard error	Lower 95% CI	Upper 95% CI
Log-normal	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Log-logistic	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Generalised gamma	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
Weibull	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Abbreviations: AF: acceleration factor; AIC: Akaike Information Criteria; BIC: Bayesian Information Criteria; CI: Confidence interval; GOF: goodness of fit; MIBC: muscle-invasive bladder cancer; PD-L1: programmed death-ligand 1

To summarise, Table 27 presents the base case adjuvant nivolumab AF for each endpoint as result of Step 1.

Table 27: Step 1: Acceleration factor calculation results for EFS and OS

Endpoint	Model selected	AF
EFS	Log-logistic	[REDACTED]
OS	Log-normal	[REDACTED]

Abbreviation: AF: Acceleration ~Factor; EFS: Event-free survival; OS: Overall Survival

Step 2: Estimate the counterfactual control arm survival times in the NIAGARA trial for adjuvant nivolumab eligible patients

Identification of eligible patients for adjuvant nivolumab in the NIAGARA trial population

A counterfactual control arm representing treatment with NAC and RC followed by no treatment or adjuvant nivolumab in eligible patients was created from the NIAGARA trial control arm, using the AF estimates from Step 1 to predict counterfactual survival times in those eligible for adjuvant nivolumab in the UK:

- Patients who underwent cystectomy and were disease-free (eligible for DFS measurement in the NIAGARA and CheckMate-274 trials) and
- are determined high-risk MIBC based on staging criteria in the CheckMate-274 trial (15) and
- have PD-L1 tumour expression of at least 1%.

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In total, [REDACTED] from the NIAGARA trial control arm fulfilled these criteria and were considered eligible for adjuvant nivolumab. A detailed breakdown of the exact numbers eligible for each criterion is provided in the Appendix B.4.

Construction of the counterfactual arm by applying adjuvant nivolumab AF to eligible patients in the NIAGARA trial

The DFS AF for nivolumab was applied to the DFS times in the NIAGARA trial, i.e., time from adjuvant therapy to recurrence or death, and the OS AF(s) for nivolumab was applied to the ‘adjuvant OS’ times, i.e., time from adjuvant therapy to death. The time from randomisation to adjuvant therapy (start of DFS and ‘adjuvant OS’) remained unchanged in the study. Similarly, the EFS and OS times of patients who were ineligible for nivolumab remained the same as observed in the study.

A summary of the calculation is provided below:

Eligible patients:

$$T_{CF} = T_{Neoadj} + T_{DFS/adj} \times \phi$$

Ineligible patients:

$$T_{CF} = T_{Neoadj} + T_{DFS/adj} = T_{EFS}$$

Where T is the survival time and ϕ is the AF from the fitted AFT model(s) from the CheckMate-274 trial.

Guidelines for treatment switching analysis recommend consideration of the use of re-censoring when applying counterfactual survival time methods. This helps to guard against informative censoring bias in the counterfactual data set which may occur through the adjustment of survival times of eligible ‘high-risk’ patients but not for ineligible patients in the NIAGARA trial. These include patients who did not have surgery, those who had residual disease after surgery and those considered at a low risk of recurrence. Details on handling re-censoring of counterfactual survival times in the analysis have been provided in Appendix B.4.

Results of the counterfactual arm: EFS for NAC and RC followed by no treatment or adjuvant nivolumab

KM curves presenting DFS according to high-risk with PD-L1 and low risk/high-risk non-PD-L1 groups in the control arm of the NIAGARA trial are included in Appendix B.4, as well as details on baseline characteristics.

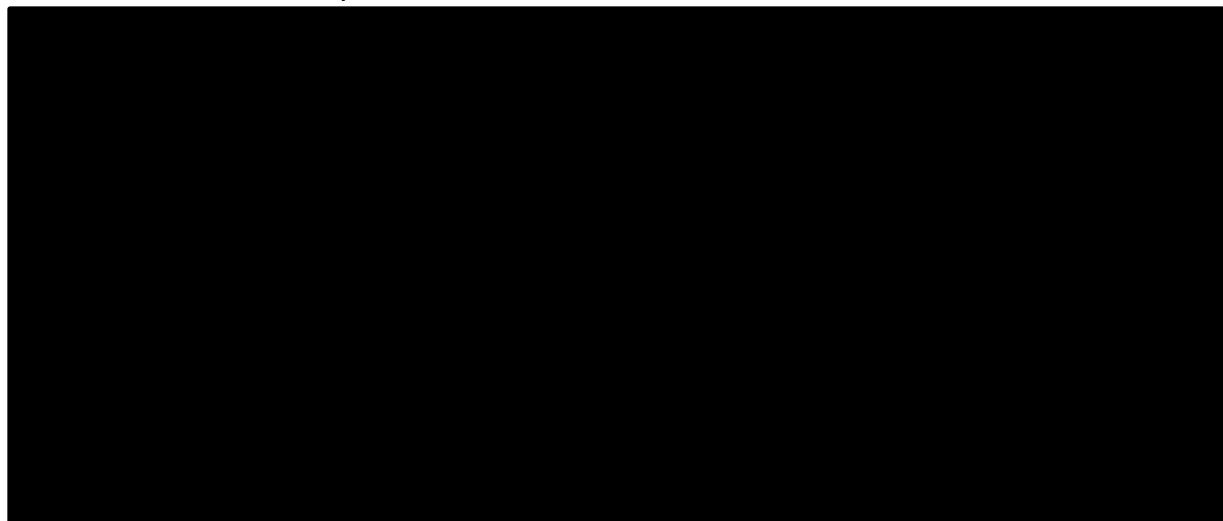
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Figure 17 presents the KM curves for DFS for the control and counterfactual arms in the high-risk PD-L1 and low risk/high-risk non-PD-L1 groups using the constant AF from the log-logistic model.

As expected, the application of the AF for nivolumab to DFS in the eligible 'high-risk' PD-L1 cohort of the NIAGARA trial led to improved outcomes, with adjuvant nivolumab increasing the time to recurrence compared to G+C followed by no treatment (left panel). Patients with low risk/high-risk non-PD-L1 MIBC, and who are ineligible for adjuvant nivolumab, had the same outcomes across arms. The Cox regression analysis comparing adjuvant nivolumab with no treatment in the PD-L1 positive high-risk subgroup of the NIAGARA trial yielded a hazard ratio of [REDACTED], which is comparable to the magnitude of the benefit observed in CheckMate-274 (DFS HR 0.44, 95% CI 0.30 to 0.63), further supporting the robustness of this estimate.

The counterfactual arm using the spline-based approach are included in Appendix B.4.

Figure 17: Kaplan-Meier plots for disease-free survival in the high-risk PD-L1 and non-high-risk groups in the control and counterfactual arm of the NIAGARA trial (log-logistic model with constant AF)



Abbreviation: AF: acceleration factor; DFS: Disease-free survival; G+C: gemcitabine-cisplatin followed by no treatment; G+C+N: gemcitabine-cisplatin followed by nivolumab; PD-L1: programmed death-ligand 1.

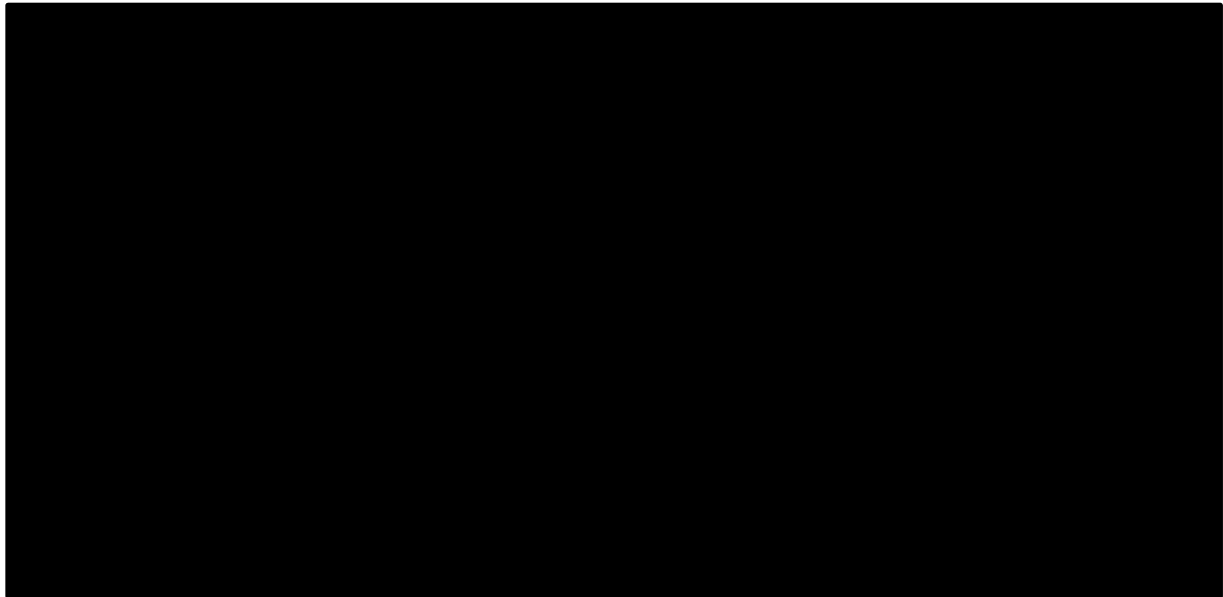
Counterfactual arm: OS for NAC and RC followed by no treatment or adjuvant nivolumab

KM curves presenting OS according to high-risk PD-L1 and low-risk or non-PD-L1 MIBC in the control arm of the NIAGARA trial are included in Appendix B.4, as well as details on baseline characteristics.

Figure 18 presents the KM curves for adjuvant-OS for the control arm and counterfactual arm in the high PD-L1 and non-high PDL1 groups.

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Figure 18: Kaplan-Meier plots for adjuvant-OS in the high risk and non-high-risk groups in the control and counterfactual arm of the NIAGARA trial



Abbreviations: D+G+C: Durvalumab, gemcitabine, cisplatin; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab; OS: Overall survival

The application of the AF for nivolumab to adjuvant-OS in the eligible ‘high-risk’ PD-L1 positive cohort of the NIAGARA trial led to improved outcomes, with adjuvant nivolumab extending the time to death. The Cox regression analysis comparing adjuvant nivolumab with no treatment in the high-risk subgroup yielded a hazard ratio of [REDACTED] which is close to the magnitude of the benefit observed in CheckMate-274 (OS HR 0.48, 95% CI: 0.29 – 0.77) further supporting the robustness of this estimate.

Step 3: Conduct the ITC

The final stage in the analysis involved comparing the EFS and OS of the perioperative durvalumab (active) and G+C+N (counterfactual) arms of the NIAGARA trial to estimate the ITC of perioperative durvalumab versus adjuvant nivolumab.

The ITC was estimated using a stratified Cox-regression analysis fitted to a dataset containing the original perioperative durvalumab and G+C arms of the NIAGARA trial and the G+C+N arm (i.e., equivalent to a 3-arm study). As per the planned analysis, stratification factors were tumour stage, renal function and PD-L1 status. The regression analysis was repeated for scenarios with G+C (original control arm) as the reference treatment and with G+C+N (counterfactual control arm), as reference. Additional analyses comparing G+C+N with G+C over the first 6 months and post-6-month periods were estimated to support extrapolations in economic models.

It is important to note that the hazard ratios for perioperative durvalumab versus G+C will differ slightly (+/-0.01 decimal places) to the clinical study results for several reasons. Firstly, the

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hazard ratios reported here are based on a Cox regression model fitted to 3-arms as opposed to the 2-arm comparisons used in the study report. This can lead to small differences in the fit of the Cox regression model, and to small differences in results. Secondly, the confidence intervals presented in this report are estimated via bootstrapping, whereas the intervals in the clinical study report are obtained directly from the fitted model.

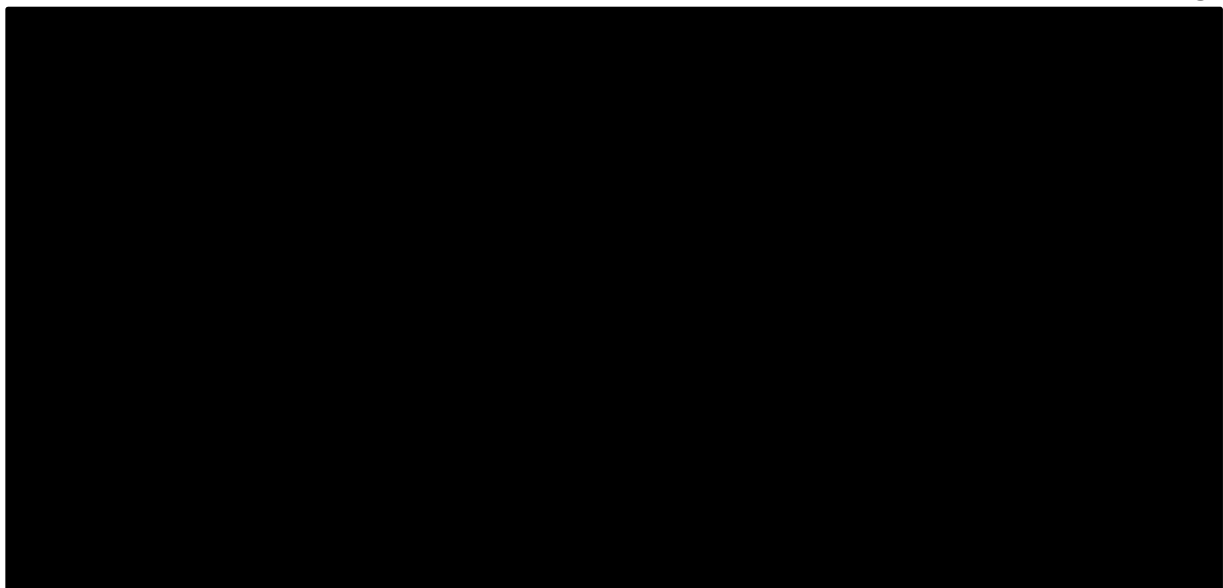
Results of the ITC in terms of EFS and OS are presented in the following section.

2.9.3 ITC Results

2.9.3.1 *EFS ITC results*

Figure 19 presents the KM plots of EFS for the perioperative durvalumab (D+G+C, active), G+C (control) and G+C+N (counterfactual) arms of the NIAGARA trial, with and without the application of re-censoring, and assuming a constant AF for nivolumab.

Figure 19: Kaplan-Meier plots for EFS comparing perioperative durvalumab (D+G+C) with G+C (control arm) and G+C+N (counterfactual arm) with and without re-censoring



Abbreviations: D+G+C: Durvalumab, gemcitabine, cisplatin; EFS: Event-free survival; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab.

Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of the NIAGARA trial, due to the effect of nivolumab in extending (by a factor of [REDACTED]) survival times in the counterfactual arm. The application of re-censoring leads to similar follow-up across arms.

Perioperative durvalumab (D+G+C) led to improved EFS versus both G+C (control) and G+C+N (counterfactual control) arms, with the curves separating early and favouring perioperative durvalumab throughout study follow-up. In the neoadjuvant phase, there was no difference in EFS between control and counterfactual control arm, as a result of both arms

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having the same neoadjuvant treatment. At approximately months 4-6, in line with the start of adjuvant treatment, the EFS for the alternative control arm was improved versus the control arm, due to the effects of adjuvant nivolumab. Despite this improvement, the EFS for perioperative durvalumab was superior compared to the G+C+N arm.

Perioperative durvalumab is associated with significant improvement in EFS [REDACTED] compared to neoadjuvant G+C followed by adjuvant nivolumab in eligible patients.

Table 28 resents the hazard ratios for EFS comparing to the G+C and G+C+N arms. The HR excluding re-censoring are presented in Appendix B.4.

Table 28: Hazard ratios and 95% Confidence intervals for EFS comparing versus G+C and G+C+N (log-logistic)

	HR vs G+C (‘Control arm’)			HR vs G+C+N (‘Counterfactual control arm’)		
	HR	Lower 95% CI*	Upper 95% CI*	HR	Lower 95% CI*	Upper 95% CI*
With re-censoring						
G+C	-	-	-	[REDACTED]	[REDACTED]	[REDACTED]
D+G+C	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
G+C+N	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-
With re-censoring, piecewise (for use in economic models)						
G+C+N 0-6 months	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-
G+C+N 6 months plus	[REDACTED]	[REDACTED]	[REDACTED]	-	-	-

Notes: *Confidence Interval estimated by bootstrapping
Abbreviations: CI: Confidence interval; D+G+C: perioperative durvalumab; EFS: Event-free survival; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab; HR: Hazard ratio; OS: Overall survival

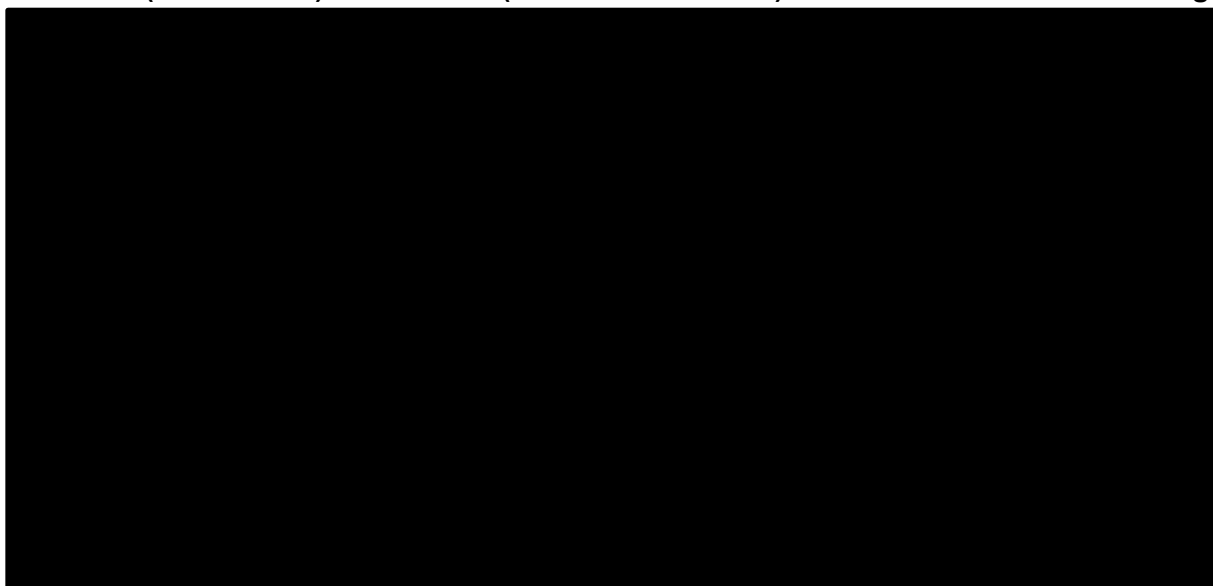
Sensitivity analyses

The results of the sensitivity analyses using time-varying AF support the base case analysis in showing that perioperative durvalumab is consistently associated with a significant improvement in EFS when compared with G+C and G+C+N, and can be found in Appendix B, Section B.4.2.1.1.

2.9.3.2 OS ITC results

Figure 20 presents the KM plots of OS for the perioperative durvalumab, G+C and G+C+N arms of the NIAGARA trial, with and without the application of re-censoring.

Figure 20: Kaplan-Meier plots for OS comparing perioperative durvalumab (D+G+C) with G+C (control arm) and G+C+N (counterfactual arm) with and without re-censoring



Abbreviations: D+G+C: perioperative durvalumab; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab; OS: Overall survival

Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of the NIAGARA trial, due to the effect of nivolumab in extending (by a factor of [REDACTED]) OS times in the counterfactual arm. The application of re-censoring leads to similar follow-up across arms.

The comparison between perioperative durvalumab, G+C (control) and G+C+N (counterfactual control) was conducted with and without the application of re-censoring, and assuming a constant AF for nivolumab. In both analyses, perioperative durvalumab led to improved OS versus both control and alternative control arms, with the curves separating early and favouring perioperative durvalumab throughout study follow-up.

Perioperative durvalumab was associated with a significant improvement in OS [REDACTED] [REDACTED] compared to neoadjuvant G+C followed by adjuvant nivolumab.

Table 29 presents the hazard ratios for EFS comparing to both alternative control arms, the G+C (control arm) and G+C+N (counterfactual arm). The HR excluding re-censoring are presented in the Appendix B.4.

Table 29: Hazard ratios and 95% Confidence intervals for OS comparing versus G+C and G+C+N

	HR vs G+C (‘Control arm’)			HR vs G+C+N (‘Counterfactual control arm’)		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
With re-censoring						
G+C	-	-	-	■	■	■
D+G+C	■	■	■	■	■	■
G+C+N	■	■	■	-	-	-
With re-censoring, piecewise (for use in economic models)						
G+C+N, 0-6 months	■	■	■	-	-	-
G+C+N, 6 months plus	■	■	■	-	-	-

Abbreviations: CI: Confidence interval; D+G+C: Perioperative Durvalumab; EFS: Event-free survival; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab; HR: Hazard ratio; OS: Overall survival

2.9.4 Discussion

The ITC results suggest that perioperative durvalumab significantly improves EFS and OS versus a regimen of neoadjuvant chemotherapy followed by no treatment (G+C) or adjuvant nivolumab in patients with PD-L1 > 1% high-risk MIBC (G+C+N).

The main objective of the Survival-Time Adjusted ITC was to address the question of which strategy provides a greater survival benefit—perioperative durvalumab or NAC followed by adjuvant nivolumab after RC—for eligible patients (high-risk and PD-L1 ≥ 1%). Table 30 presents a summary of the EFS and OS results for this comparison.

Table 30: Summary of results D+G+C versus G+C+N

HR	EFS (95% CI)	OS (95% CI)
D+G+C (control arm) versus G+C+N (counterfactual arm)	■	■

Abbreviations: CI: Confidence interval; D+G+C: Perioperative durvalumab; EFS: Event-free survival; G+C: gemcitabine, cisplatin; G+C+N: gemcitabine, cisplatin, nivolumab; HR: Hazard ratio; OS: Overall survival

The outcomes of perioperative durvalumab versus NAC followed by no treatment after RC are included in Table 28 and Table 29 and are also considered to be addressed by the results of the NIAGARA trial.

The key strengths of this analyses are:

- **Addresses the key question for decision makers:** Through a counterfactual framework aligned with the scope of this appraisal, the ITC enabled the comparison of perioperative durvalumab plus neoadjuvant chemotherapy with a treatment strategy of neoadjuvant chemotherapy followed by adjuvant nivolumab. By including the neoadjuvant phase, the ITC captures all relevant outcomes arising from the decision

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to use perioperative durvalumab. The comparison of adjuvant phases only would yield biased results given population differences across trials, whilst failing to appropriately capture the outcomes of treating with neoadjuvant durvalumab. A decision to treat with perioperative durvalumab will therefore lead to improvements in outcomes during both the neoadjuvant and adjuvant phases. To fully evaluate the impact of treatment, it is important to capture both phases.

- **Comprehensive data utilisation:** The analysis leverages all available relevant data from the NIAGARA and CheckMate-274 trials to compare strategies between perioperative durvalumab and adjuvant nivolumab.
- **Uncertainty capture:** Bootstrapping methods were employed to capture uncertainty across all aspects of the comparison, including the effect of nivolumab in the CheckMate-274 trial.

The limitations of the analysis include:

- **Assumption of Generalisability of Effect:** It was necessary to assume that the relative effects of nivolumab in the MIBC subgroups of the CheckMate-274 trial are generalisable to the corresponding NIAGARA trial population. Where possible, we used data that closely resembled the NIAGARA trial cohort. To align the CheckMate-274 trial data with the positioning of adjuvant nivolumab in the UK we needed to rely on PD-L1 > 1% subgroup analysis, including those with and without prior NAC.
- **PD-L1 Subgroup Considerations:** the effect of nivolumab in the PD-L1 >1% tumour expression subgroup from the CheckMate-274 trial was applied to the corresponding PD-L1 >1% cohort of the NIAGARA trial. Different testing assays across studies could impact the number of patients eligible for nivolumab and its effect within the NIAGARA trial PD-L1 subgroup.
- **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 treatment's impact. Since this is a conservative assumption favouring nivolumab's addition, no further adjustment was made.
- **Lack of safety and tolerability evaluation:** It is important to note that the ITC focused on the key efficacy endpoints of EFS and OS. The ITC did not evaluate the safety and/or tolerability of D+G+C versus G+C+N. These endpoints are typically evaluated in terms of risk (ratios or differences) and/or odds (ratios) and are reported in terms of the number of patients with an event. Without Kaplan-Meier plots, it is not possible to

utilise the survival-time adjusted method to predict safety outcomes with adjuvant nivolumab in NIAGARA. The comparison of safety outcomes across adjuvant phases is at the same risks of bias as the efficacy analysis, such as the impact of prior immunotherapy.

Conclusion

The survival time-adjusted ITC provides a comparison that evaluates all relevant patient outcomes, including recurrence during both periods, before and after surgery. This approach maintains the comparator list as inclusive as specified in the final scope, offering an additional layer of evidence that enhances certainty for decision makers.

Perioperative durvalumab has demonstrated improved EFS and OS outcomes compared to NAC followed by either no treatment or adjuvant nivolumab for eligible patients, thus showing superiority over current clinical practice in the UK.

These findings are consistent with the mechanism of action of perioperative IO regimens and support its ability to address the unmet medical need, as discussed in Section 1.3.2.2. By priming anti-tumour immunity in the neoadjuvant phase and sustaining immunosurveillance in the adjuvant phase, perioperative durvalumab addresses a critical gap in the current treatment landscape. The results observed against G+C+N further reinforce the validity of perioperative durvalumab's positioning as the new SoC in cisplatin-eligible resectable MIBC, as already endorsed by EAU guidelines and confirmed by UK-based clinical experts.

Although it is important to emphasise that perioperative durvalumab and adjuvant nivolumab are not interchangeable treatments for the differences raised in section 2.9, with one being a proactive therapeutic approach (perioperative durvalumab) while the other is considered reactive therapy (adjuvant nivolumab) after insufficient response from NAC alone and RC. The company has nevertheless included a cost-effectiveness scenario based on the ITC results comparing perioperative durvalumab to NAC and RC followed by no treatment or adjuvant nivolumab in PD-L1 $\geq 1\%$ high-risk patients ('G+C+N'), as conducted in response to the final scope issued by NICE. Results of this comparison are available in section 3.11.3.1 where perioperative durvalumab demonstrated to be a cost-effective treatment regimen.

2.10 Adverse reactions

The safety data for the perioperative durvalumab demonstrated a well-tolerated and manageable safety profile that aligned with the individual safety profiles of durvalumab monotherapy as well as gemcitabine and cisplatin components (2).

In the safety analysis set (SAS), at the EFS IA-2 (DCO 29 April 2024), the median total duration of exposure to durvalumab for the overall period in the perioperative durvalumab arm was 44.0 Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

weeks (range: 1 to 84) (Table 31). Median exposure during neoadjuvant and adjuvant periods was 12.1 weeks (range: 1 to 84), and 32.0 weeks (range: 2 to 50), respectively, aligned with the study treatment plan (71).

In the context of perioperative or neoadjuvant treatments combined with the standard curative-intent treatment, it is crucial to assess the absence of a negative impact on the standard treatment, such as by delaying or complicating surgery, or by adding toxicity that reduces the likelihood of completing the full neoadjuvant treatment regimen.

Combining durvalumab with gemcitabine-cisplatin chemotherapy did not prevent patients from receiving four cycles of chemotherapy in the neoadjuvant phase as recommended per clinical guidelines (71). Adding durvalumab to gemcitabine and cisplatin did not negatively impact achieving surgery and also resulted in a higher proportion of patients undergoing RC in the perioperative durvalumab arm compared to the control arm (88.0% versus 83.2%). There were no delays in surgery, with the time from the last dose of neoadjuvant therapy to cystectomy being similar in both arms (39 days versus 38 days, respectively) (71).

Safety Profile

Most patients experienced at least one AE during the overall study period (99.4% in the perioperative durvalumab arm versus 99.8% in the control arm). More patients in the perioperative durvalumab arm experienced serious adverse events (SAEs) (61.5%) and AEs leading to discontinuation of any study treatment (21.1%) compared to patients in the control arm (SAEs 54.6%, AE leading to discontinuation 15.2%) (71). However, a similar proportion of patients in both treatment arms experienced AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 (69.4% and 67.5% in the perioperative durvalumab and control arms, respectively) (Table 31) (71).

Table 31: Overview of duration of exposure, AEs and treatment discontinuation in the SAS^a (overall period, DCO 29 April 2024)

	Perioperative durvalumab arm (D+G+C) (N=530)	Control arm (G+C) (N=526)
Duration of exposure to durvalumab (weeks)		
Mean (SD)	33.5 (16.33)	11.6 (3.12)
Median (min, max)	44.0 (1, 84)	12.0 (1, 27)
AEs of any cause		
Event of any grade, n (%)	527 (99.4)	525 (99.8)
Event of grade 3 or 4 ^b , n (%)	368 (69.4)	355 (67.5)
SAE, n (%)	326 (61.5)	287 (54.6)
Event leading to death (%)	27 (5.1)	29 (5.5)
Event leading to discontinuation of trial treatment ^c , n (%)	112 (21.1)	80 (15.2)
Event leading to discontinuation of durvalumab, n (%)	86 (16.2)	-
Event leading to discontinuation of chemotherapy, n (%)	72 (13.6)	80 (15.2)
Event leading to cancellation of surgery ^d , n (%)	6 (1.1)	7 (1.3)
Event leading to a delay in surgery ^d , n (%)	9 (1.7)	6 (1.1)

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

	Perioperative durvalumab arm (D+G+C) (N=530)	Control arm (G+C) (N=526)
Treatment-related adverse events^e		
Event of any grade, n (%)	502 (94.7)	487 (92.6)
Event of grade 3 or 4 ^{b,c} , n (%)	215 (40.6)	215 (40.9)
SAE, n (%)	86 (16.2)	63 (12.0)
Event leading to death ^f , n (%)	3 (0.6)	3 (0.6)
Durvalumab-related event leading to discontinuation, n (%)	42 (7.9)	-
Chemotherapy-related event leading to discontinuation, n (%)	55 (10.4)	64 (12.2)

^a The safety analysis set included patients who received at least one dose of neoadjuvant treatment. Safety data are shown for the overall trial period, which included the time from the first dose of trial treatment and the earliest of 90 days after the last dose of trial treatment or surgery (in the perioperative durvalumab arm); 90 days after the last neoadjuvant treatment, surgery, or last visit during the adjuvant phase (in the comparison group); the date of the first dose of subsequent anticancer therapy (in both groups); or the date of DCO (in both groups). Patients with multiple events in the same category are counted only once in that category.

^b The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events, version 5.0. For patients with multiple episodes of the same adverse event, only the episode with the highest grade is included.

^c Trial treatment is defined as durvalumab and gemcitabine–cisplatin and does not include surgery.

^d Delayed surgery was defined as surgery that occurred more than 56 days after the last dose of trial treatment during the neoadjuvant period.

^e Data are for adverse events considered by the investigator to be related to the trial treatment. Adverse events with missing data were considered to be related to the trial treatment.

^f Treatment-related adverse events leading to death were cardiorespiratory arrest, myocardial infarction, and pulmonary embolism in one patient each in the perioperative durvalumab arm and cardiorespiratory arrest and pneumonitis in one patient each in the comparison group. The cause of death was unknown in one patient in the comparison group.

Abbreviations: AE: adverse event; C: cisplatin; D: durvalumab; DCO: data cut-off; G: gemcitabine; IA-2: second interim analysis; SAE: serious adverse event; SD: standard deviation; Min: minimum; Max: maximum.

Source: Powles *et al.* 2024 (2), AZ NIAGARA trial CSR (71)

In both treatment arms, the most common AEs of any cause were nausea, anaemia, and constipation (Table 32) (2).

Table 32: Most common AEs of any cause by preferred term (overall period, SAS, DCO 29 April 2024)

AE	Perioperative durvalumab arm (D+G+C) (N=530)		Control arm (G+C) (N=526)	
	Any Grade ^a	Grade 3 or 4 ^b	Any Grade ^a	Grade 3 or 4 ^b
	Number of patients (%)			
Nausea	284 (53.6)	8 (1.5)	255 (48.5)	5 (1.0)
Anaemia	205 (38.7)	73 (13.8)	213 (40.5)	79 (15.0)
Constipation	205 (38.7)	4 (0.8)	203 (38.6)	4 (0.8)
Fatigue	191 (36.0)	8 (1.5)	169 (32.1)	10 (1.9)
Urinary tract infection	159 (30.0)	75 (14.2)	153 (29.1)	70 (13.3)
Decreased appetite	141 (26.6)	3 (0.6)	131 (24.9)	3 (0.6)
Neutropenia	137 (25.8)	76 (14.3)	165 (31.4)	89 (16.9)
Pyrexia	110 (20.8)	1 (0.2)	87 (16.5)	0
Diarrhoea	109 (20.6)	8 (1.5)	74 (14.1)	2 (0.4)
Vomiting	102 (19.2)	5 (0.9)	97 (18.4)	1 (0.2)
Blood creatinine increase	98 (18.5)	12 (2.3)	77 (14.6)	4 (0.8)
Asthenia	93 (17.5)	4 (0.8)	96 (18.3)	6 (1.1)
Neutrophil count decreased	81 (15.3)	37 (7.0)	74 (14.1)	35 (6.7)
Pruritus	80 (15.1)	0	38 (7.2)	0

^a Participants with multiple events in the same category were counted only once in that category.

^b Patients with multiple adverse events of maximum Common Terminology Criteria for Adverse Events (version 5.0) of grade 3 or 4 are counted once for each preferred term.

Notes: Adverse events that were reported in the overall period and occurred in at least 15% of the patients in either group are shown

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

2.10.1 Immune-mediated adverse events

Although a higher frequency of immune-mediated AEs (imAEs), SAEs and AEs leading to discontinuation of any study treatment occurred in the perioperative durvalumab arm, the nature of these events was consistent with the individual interventions (71).

In the neoadjuvant period, both treatment arms had a comparable safety profile that predominantly reflected known chemotherapy-related adverse drug reactions (71).

The safety profile of the perioperative durvalumab arm during the adjuvant period also aligned with the known profile for durvalumab (71).

While the majority of imAEs were reported in the perioperative durvalumab arm, the observation aligns with the mechanism of action of durvalumab and may be partly attributed to the open-label design of NIAGARA trial. Most imAEs were of low grade and manageable, with hypothyroid events being the most prevalent (71).

Overall, no new safety concerns were identified with perioperative durvalumab, and the combination demonstrated a well-tolerated and manageable safety profile consistent with the known safety profile of the individual agents (71). There was no increased frequency or severity of toxicities associated with gemcitabine and cisplatin and no new adverse drug reactions were attributable to the combination therapy.

The safety profile of adjuvant durvalumab aligned with its established profile, with most imAEs being low grade and manageable (71). Further details on adverse reactions can be found in Appendix D.

2.11 Ongoing studies

The NIAGARA trial is currently ongoing and has an estimated completion date of June 2026 (74). Additional analyses for EFS are scheduled at approximately 50% data maturity (final analysis). Per the MTP, OS will be tested when a significant result for DFS is reached in subsequent analyses (74).

2.12 Interpretation of clinical effectiveness and safety evidence

2.12.1 Critical review of the NIAGARA trial

Rationale for the study

Standard treatment for cisplatin-eligible patients with resectable MIBC involves cisplatin-based NAC followed by RC with pelvic-lymph-node dissection (4, 31). However, the overall five-year OS rate for patients treated with NAC followed by RC remains below 60% and approximately 50% patients experience recurrence within five years (91, 92). As previously described in section 1.3.2, adjuvant nivolumab is available for cis-eligible resectable MIBC patients who had received NAC, however, the decision point for considering this treatment is different to NIAGARA (requiring a reactive intervention post-surgery) and the eligible population is restricted to those at high risk of recurrence and PD-L1 positive (11).

The limitations of the currently available therapies have created a critical gap in the treatment landscape of cisplatin-eligible resectable MIBC, as more efficient therapies that can be used more broadly and earlier in the treatment pathway, are needed to minimise recurrence and provide long term survival. Preclinical and early clinical evidence support the synergistic potential of combining IOs with chemotherapy, providing a strong rationale for perioperative strategies that integrate neoadjuvant gemcitabine and cisplatin with IO therapies (60).

This dual-phase strategy has the potential to improve long-term disease control in patients with resectable MIBC and prevent their progression to mBC (12).

Overview of the NIAGARA trial

The NIAGARA trial is a Phase III, randomised, open-label, multicentre, international that constitutes a landmark study for the treatment of resectable MIBC, establishing perioperative durvalumab as the first and only perioperative IO regimen to successfully achieve statistically significant positive EFS and OS outcomes on a direct comparison with the current SoC in the UK (NAC followed by RC) (2). In addition, no delays in surgery or increases in surgical complications were observed with the introduction of perioperative durvalumab regimen, indicating that the improved efficacy outcomes were achieved without compromising the ability of patients to undergo curative-intent surgical treatment (5).

This robust evidence base supports a warranted change in standard practice, positioning perioperative durvalumab as the preferred future SoC for cisplatin-eligible patients with resectable MIBC. The UK-based clinical experts have reaffirmed the medical need for perioperative durvalumab in clinical practice and validated the positioning in the current treatment pathway as the new SoC for eligible patients in the UK (14).

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In the following section, the Company will explore the strengths and limitations of the NIAGARA clinical trial.

2.12.2 Strengths of the evidence base

Large sample size and robust statistical analysis

NIAGARA is the largest Phase III trial ever conducted in bladder cancer, with 1,050 patients enrolled, providing sufficient statistical power to detect clinically meaningful differences between treatment arms with high confidence (2). The substantial sample size minimises the risk of Type I errors and strengthens the reliability of the observed treatment effects. The statistical design of the trial, including its predefined hierarchical testing strategy for multiple endpoints, further reinforces the validity of its findings (2).

The NIAGARA trial represents the highest level of clinical evidence available in the therapeutic area under consideration, addressing a significant evidence gap for cisplatin-eligible patients with resectable MIBC and establishing a new benchmark for evaluating perioperative immunotherapy strategies (14).

Head-to-head comparison with current SoC

The NIAGARA trial provides a pivotal head-to-head comparison with the current SoC in the UK, representing a key divergence from other IO trials in oncology that compare novel agents to placebo or best supportive care (2). For example, in the CheckMate 274 trial, adjuvant nivolumab was compared only against placebo, which allowed a comparison to best supportive care but required an indirect comparison to adjuvant chemotherapy, and was identified as a key concern by the External Assessment Group (EAG) during the TA817 appraisal (11).

The direct comparison in the NIAGARA trial enhances the certainty of the benefit provided by perioperative durvalumab, supporting both its evaluation by NICE and its adoption in the resectable MIBC treatment pathway as the new preferred option for cisplatin-eligible patients.

Strong evidence and correlation in survival outcomes (EFS, OS)

Efficacy evidence from the NIAGARA trial establishes a robust clinical profile for perioperative durvalumab. EFS and OS results from EFS IA-2 (DCO 29 April 2024) of the NIAGARA trial show an unprecedented benefit in resectable MIBC for a perioperative immunotherapy regimen (2). Perioperative durvalumab has demonstrated a statistically significant benefit in EFS compared to the SoC, with a HR of 0.68 (95% CI: 0.558, 0.817; $p < 0.0001$), reducing the risk of an EFS event by 32% (2). The EFS benefit translated into a statistically significant

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improvement in OS, the gold standard in oncology endpoints, reducing the risk of death by 25% with perioperative durvalumab treatment compared to SoC, with an HR of 0.75 (95% CI: 0.594, 0.934; $p=0.0106$) (2, 93). The correlation between EFS and OS supports the perioperative setting of durvalumab, where the same IO therapy administered both before and after surgery primes anti-tumour immunity in the neoadjuvant setting and sustains immunosurveillance in the adjuvant setting, thereby reducing early recurrence and supporting long-term disease control.

Multidimensional evidence base (pCR, MFS, DSS, PFS-2, safety, HRQoL)

The NIAGARA trial evaluated a wide range of clinically relevant endpoints, including pCR, MFS, DSS, PFS-2, safety and HRQoL providing a multidimensional assessment of the benefit of perioperative durvalumab in patients with resectable MIBC (2). Benefits shown in these endpoints complement those already observed in EFS and OS, offering greater certainty on the value of perioperative durvalumab.

Patients treated with durvalumab had 60% greater odds of achieving pCR (odds ratio: 1.60 [95% CI: 1.227, 2.084]; nominal $p=0.0005$), pCR is an important prognostic marker for OS, with prior studies reporting OS5 rates of 80-85% in patients who achieve pCR following NAC (72).

Treatment with perioperative durvalumab was associated with a 33% reduction in the risk of metastasis or death HR was (HR: 0.67 [95% CI: 0.541, 0.826]; $p=0.0002$), as measured by MFS, underscoring its benefit to delay progression from early-stage to invasive metastatic disease, a stage associated with poor clinical outcomes (2).

DSS results showed that durvalumab was associated with a 31% improvement in patient survival outcomes that are directly related to MIBC (HR: 0.69 [95% CI: 0.516, 0.907]; $p=0.0081$), mitigating the confounding influence of unrelated causes of death (2), a distinction is particularly valuable in older or comorbid populations, where non-cancer-related deaths are more frequent (91). DSS complements OS by providing disease-specific context, and the use of both endpoints together effectively reduces uncertainty in survival outcomes for patients with resectable MIBC

Patients treated with durvalumab experienced a 24% reduction in the time to subsequent progression or recurrence post-EFS event (PFS-2) as compared to SoC (HR: 0.76 [95% CI: 0.605, 0.949]; $p=0.0155$), underscoring the durable clinical benefits of perioperative durvalumab.

Safety and HRQoL results showed that perioperative durvalumab was associated with a well-tolerated safety profile and did not present any detriment in HRQoL as compared to SoC,

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implying that the addition of durvalumab to routine clinical practice is not expected to impose additional burden on patients, payers or society (2).

Consistent evidence across subgroups

The treatment effect observed for EFS and OS in the FAS (ITT population) of the NIAGARA trial was aligned with all prespecified subgroups (2). The company validated these findings in an advisory board with the UK-based clinical experts who agreed that the subgroup results are consistent with the results in FAS (ITT population) from the NIAGARA trial (14).

Generalisability to the UK clinical practice

The NIAGARA trial is considered generalisable to the UK clinical practice. The trial included four centres in the UK and enrolled patients with baseline characteristics that are considered representative of the UK MIBC population (2). The feedback received from the UK-based clinical experts indicate consensus that the NIAGARA trial population is representative of the standard NHS practice (14). Therefore, the results of the NIAGARA trial are also relevant and generalisable to the UK clinical practice, representing a paradigm shift in the treatment pathway for patients with resectable MIBC in the UK.

2.12.3 Limitations of the evidence base

Certain limitations of the evidence base should be acknowledged while contextualising their impact on the overall evaluation of perioperative durvalumab in MIBC.

Open label design

The NIAGARA trial was limited by the open-label design. Concerns were mitigated by adopting careful consideration in study design, including clearly defined objective endpoints, use of rigorous data collection methods, following BICR approach for imaging data to ensure objective evaluation of patient tumour assessments, and blinding of the sponsor to the trial-group assignments and patient-level efficacy data (71).

pCR re-analysis (due to programming error)

In the initial analysis of pCR in the NIAGARA trial, a programming error occurred wherein the DCO date (14 January 2022) was applied to the date of central assessment rather than the date of surgery, meaning 59 patients were considered non-responders for the pCR calculation, leading to a result which was not statistically significant (71).

An updated analysis was conducted at the EFS IAS-2 timepoint (DCO 29 April 2024), in which correct dates were applied for the 59 non-responders, leading to 28 patients being correctly confirmed for achieving pCR (71). Notably, pCR rates in the updated analysis conducted on Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

the FAS (ITT population) indicated a statistically significant ~10% increase in favour of perioperative durvalumab (37.3% versus 27.5%) (2). The numerical between-group difference in the reported percentage and the early separation of the KM curves for EFS shows that the addition of durvalumab to chemotherapy improves efficacy outcomes, supporting the perioperative approach (2).

Use of pCR as a primary endpoint

pCR is an important indicator of long-term survival outcomes, with patients who achieve pCR demonstrating an OS5 rate of 80–85% (72). Therefore, pCR alone is not considered a valuable standalone endpoint in MIBC for evaluating perioperative regimens. To mitigate this, pCR was included alongside other key endpoints such as EFS and OS providing an additional layer of validation for the benefits observed with perioperative durvalumab. pCR captures the complexities underlying response mechanisms between clinical and pathological stages, particularly with IO combinations, and thereby offers important prognostic insights that complement EFS. Collectively, these endpoints enable a more comprehensive assessment of clinical benefit in the perioperative setting.

The limitations detailed above do not undermine the statistically significant improvements in EFS and OS, nor do they invalidate the overall favourable benefit-risk assessment for perioperative durvalumab in cisplatin-eligible patients with resectable MIBC. Consultation with the UK-based clinical experts suggest that the limitations identified are not considered impactful and would not preclude treatment in the eligible patient population (14). The evidence is considered unprecedented and supports healthcare decision making, facilitating the assessment of the current appraisal.

2.12.4 Conclusions on clinical effectiveness and safety

The results from the NIAGARA trial have established perioperative durvalumab regimen as a landmark advancement in the management of MIBC, validating the hypothesis that perioperative IO therapies can redefine the treatment paradigm of MIBC (2). **The NIAGARA trial demonstrated that perioperative durvalumab provides statistically significant and clinically meaningful benefits in both EFS and OS compared to the current SoC (2).** These survival benefits are particularly noteworthy as they were achieved in a direct comparison against the current SoC rather than placebo, underscoring the additional value that perioperative durvalumab brings to the established treatment approach (2).

The robust evidence base from the NIAGARA trial supports the positioning of perioperative durvalumab as a superior therapeutic strategy as compared to the current SoC for cisplatin-eligible patients with resectable MIBC. The clinical significance of the Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

findings from the NIAGARA trial has been recognised by both the UK-based clinical experts and international guidelines. The EAU clinical guidelines have been updated to incorporate perioperative durvalumab, even before formal approval by the EMA, underscoring its practice-changing outcomes (4). The UK-based clinical experts confirmed that the results from the NIAGARA trial are generalisable to the UK clinical practice. They also unanimously confirmed that perioperative durvalumab will become the preferred first choice for treatment of patients with resectable MIBC in the UK (14).

In addition to demonstrating statistically significant and clinically meaningful benefits in EFS and OS, the perioperative durvalumab regimen consistently conferred survival benefits and reduced rates of recurrence, progression or death, as evidenced by secondary outcomes (MFS, DSS, DFS, and PFS-2). **The results from the multidimensional secondary outcomes underscore the certainty regarding the efficacy of perioperative durvalumab in reducing recurrence, sustaining long-term survival, and delaying progression to mBC** (2). The consistent improvements in OS, EFS and pCR across patient subgroups validate the robustness of the clinical efficacy outcomes of perioperative durvalumab (2).

Treatment with perioperative durvalumab delivers substantial clinical efficacy benefits while maintaining the feasibility and safety to undergo the surgical component of treatment (2). The higher rates of patients proceeding to RC without any delays or any increase in surgical complications in the perioperative durvalumab arm as compared to the control arm validates the practicality of incorporating durvalumab into the perioperative setting. The preservation of surgical outcomes is particularly significant in MIBC, where timely and successful surgical intervention remains a cornerstone of curative intent treatment (2).

Perioperative durvalumab demonstrated a well-characterised and manageable safety profile, consistent with established knowledge of the individual components of immune checkpoint inhibition (2). The predominantly low grade and manageable nature of imAEs provides reassurance regarding the tolerability of perioperative durvalumab regimen. There was no detriment observed in the HRQoL of patients receiving perioperative durvalumab treatment as compared to the SoC. **The safety and HRQoL data, thus, indicate that the addition of durvalumab does not compromise the overall benefit-risk balance of the treatment approach** (2).

MIBC represents the final opportunity for curative intervention before progression to mBC. By delivering sustained survival benefits in both neoadjuvant and adjuvant settings, perioperative durvalumab addresses a critical unmet need. The regimen offers a unified treatment approach that reduces the burden of recurrence and the uncertainty surrounding treatment efficacy and prognosis, ultimately improving patient outcomes and experience (2).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Perioperative durvalumab is the first IO regimen to demonstrate transformative advancement in resectable MIBC, as supported by the comprehensive evidence base from the NIAGARA trial. **The evidence supports the consideration of perioperative durvalumab regimen as a new SoC for patients with resectable MIBC within NHS practice, as also confirmed by the UK-based clinical experts, particularly given the high unmet need related to poor survival outcomes, disease prognosis and limited efficacious treatments.** In neoadjuvant setting, modest survival benefits are observed with NAC, which typically show only a 5% improvement in survival outcomes as compared to RC alone (8). In adjuvant setting, the use of adjuvant IO is considered a reactive approach, reserved for patients at high risk of recurrence following RC with PD-L1 expression $\geq 1\%$ who are unsuitable for cisplatin-based adjuvant chemotherapy (11).

The adoption of perioperative durvalumab as a new SoC within NHS practice represents a significant step forward towards overcoming the limitations of the current treatment pathway. Perioperative durvalumab addresses the critical unmet need for effective treatment in MIBC by leveraging the synergies of sustained clinical outcomes across neoadjuvant and adjuvant settings, offering a comprehensive, durable, and patient-centered therapeutic solution.

3 Cost effectiveness

Summary of cost effectiveness analysis

Model structure and inputs

- A *de novo* **partitioned survival model** with four health states—event-free, locoregional recurrence, distant metastasis, and death—was developed. This approach was used to accurately reflect the **clinical progression** post-recurrence. Use of a PSM is also supported by a relatively long follow-up for **OS data** from the NIAGARA trial.
- The clinical inputs for the model were derived from the NIAGARA trial. Parametric models were used to extrapolate **long-term outcomes for EFS, MFS and OS**.
- Health state utilities were derived from EQ-5D-5L data in the NIAGARA trial and mapped to EQ-5D-3L using the Hernandez-Alava algorithm. The model comprehensively considered relevant costs and resources from an NHS and PSS perspective, in line with the NICE reference case.

Summary of cost effectiveness analysis results

- Perioperative durvalumab yielded **x.xx additional LYs** and **x.xx additional QALYs** compared to SoC, at an incremental cost of **£xx,xxx**, resulting in an ICER of **£14,048/QALY, substantially below the WTP threshold**.
- In the deterministic sensitivity analysis, the **percentage of patients undergoing RC in the durvalumab arm** was the most influential determinant on the ICER. Probabilistic sensitivity analyses showed that the probability of perioperative durvalumab **being cost effective versus SoC** at a WTP threshold of **£20,000/QALY and £30,000/QALY is 96.4% and 99.8%**, respectively.
- All tested scenarios (e.g., alternative survival curves, utility decrements, exclusion of IO rechallenge) **yielded ICERs below £20,000/QALY**, supporting the robustness of the base-case findings.
- A scenario comparing perioperative durvalumab to NAC and RC followed by no treatment or adjuvant nivolumab (in PD-L1 ≥1% high-risk patients) showed an **ICER of £13,723/QALY, demonstrating to be cost-effective at a WTP of £20,000/QALY threshold**.
- The model was **validated internally and externally** and was supported by experts.

Benefits beyond QALY

- The submission highlights **broader patient-centric benefits** not captured in QALY metrics, including **emotional reassurance, early treatment planning, reduced caregiver burden, and societal productivity gains**.

Conclusion

- The analysis concluded that perioperative durvalumab is a **highly cost-effective and clinically valuable treatment option** for MIBC in the UK.

3.1 Published cost effectiveness studies

3.1.1 Identification of studies

A *de novo* SLR was conducted in July 2024, with an update performed in February 2025, to identify published economic evaluations, HRQoL, and cost and healthcare resource use (HCRU) associated with the treatment of patients with MIBC relevant to the context of the current appraisal (94). The SLR was conducted adhering to the same guidelines and using the same methodology as the SLR described in section 2.1. A detailed description of the economic SLR is provided in Appendix E.

The economic SLR identified 24 unique studies presenting economic evaluations relevant to MIBC (Appendix E), including three studies conducted in the UK setting (11, 95, 96). All three UK-based studies evaluated the same intervention – adjuvant nivolumab in MIBC (11, 95, 96). Among the three studies, two were health technology assessment (HTA) submissions (NICE [TA817]) and Scottish Medicine Consortium [SMC2503]) and one was presented as a conference abstract (11, 95, 96). The models reported in all the three studies were structurally identical and based on the same underlying evidence (11, 95, 96).

In addition, a targeted search of previous appraisals published by NICE and two other cost effectiveness-driven HTA agencies (Pharmaceutical Benefits Advisory Committee [PBAC] and Canada's Drug Agency [CDA-AMC]) was conducted to compare commonly employed modelling approaches in cost effectiveness analyses conducted for therapies in MIBC and oncology therapies in the perioperative setting outside MIBC, with the aim of informing the model structure for the current appraisal. From the targeted search for therapies in MIBC, two more appraisals for adjuvant nivolumab in MIBC by PBAC and CDA-AMC (PC0272-000) were identified (97, 98). In the perioperative setting outside MIBC, two appraisals – one for triple-negative breast cancer (pembrolizumab; TA851) and one for non-small cell lung cancer (durvalumab; TA1030) were considered the most relevant for the decision problem of the current appraisal (99, 100).

3.1.2 Description of identified studies

All identified appraisals (TA817, SMC2503, TA851, TA1030 and the appraisals for adjuvant nivolumab in MIBC by PBAC and CDA [(PC0272-000)]) reported the use of semi-Markov or Markov models (with three to four health states) to assess the cost effectiveness of the intervention under consideration (11, 97, 98). The cycle length in these models ranged from one week to three months; all models incorporated long-term time horizons ranging from 20 years to lifetime. The comparators used in the appraisals included watchful waiting (PBAC appraisal for nivolumab) (98), best supportive care (TA817 and SMC2503) (11, 95),

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observation (no active treatment) and adjuvant chemotherapy (PC0272-000) (97), placebo (TA851) (99) and surgery alone (TA1030) (100).

The key critique points from the appraisals included:

In MIBC setting:

- The assessors for the NICE and SMC appraisals of nivolumab criticised the exclusion of an active treatment (cisplatin-based adjuvant chemotherapy) as a comparator from the cost effectiveness analysis (11, 95). Upon assessors' request the comparison against the requested comparator was provided by the manufacturer; however, nivolumab was not found to be superior and hence reimbursement was restricted to only patients who are cisplatin-ineligible, at high risk of relapse or present PD-L1 expression $\geq 1\%$.
- The assessors of the CDA and PBAC appraisals of nivolumab raised concerns around combining local and metastatic (distant) recurrences into a single recurred disease (RD) health state despite the heterogeneity in these patients in terms of the extent of disease progression during recurrence (97, 98).
- Other points of critique included uncertainty in clinical efficacy and extrapolation of survival outcomes over a longer time horizon, as well as uncertainty around the assumed timepoint of cure for long-term disease-free health state (11, 97, 98). Whilst the company base-case model assumes a cure point at 5 years in a disease-free survival state, the EAG provided an exploratory analysis using a 10-year cure point. The committee noted that there was uncertainty surrounding which of these points in time is the most accurate but, agreed that the exploratory analyses provided by the ERG had a minimal impact on the cost-effectiveness results.

In perioperative setting outside MIBC:

- In the pembrolizumab appraisal (TA851), the assessors outlined that placebo alone may not be the best available comparator in the adjuvant phase (99)
- In the durvalumab appraisal (TA1030), the assessors questioned the rationale of using surgery alone as the only relevant form of active monitoring; and the omission of a comparator based on clinical opinion alone (rather than objective data) (100).

The following themes were identified from the review of previous models:

- **Model state structures:**

- Splitting disease recurrence into locoregional and distant metastasis was considered appropriate to better reflect clinical distinctions, as patients in

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locoregional state have better prognosis than patients in distant metastasis state (101). Including separate health states may enhance the clinical validity of the model, as demonstrated by a study on the conceptualisation of economic model structures in MIBC by Teitsson *et al.* (102). The granularity in post-recurrence health states also captures meaningful differences in quality of life between these states, further justifying their separation.

- The use of semi-Markov state transition modelling was motivated by the lack of OS data available at the time of previous submissions for nivolumab (TA817) and pembrolizumab (TA851).
- **Comparator:** Use of active treatments as comparators in the economic analysis was encouraged, while watchful waiting/observation, placebo and best supportive care were deemed as unsuitable comparators.
- **Time horizon:** Longer time horizons ranging up to lifetime are generally used for therapies in perioperative setting to capture long term outcomes and costs.

Conclusion

The review of previous appraisals highlights several methodological and clinical concerns raised by HTA assessors, including the exclusion of relevant comparators, oversimplified health state modelling, and uncertainties in long-term efficacy projections. These insights underscore the importance of robust, transparent modelling and clinically relevant comparators in demonstrating the full value of new therapies in the MIBC setting.

Therefore, two key considerations were prioritised for the development of cost effectiveness model (CEM) for the current appraisal – the selection of health states for post-recurrence survival and the appropriate modelling methodology. More granularity is preferred in the modelling of post-recurrence survival (to reflect the differentiated prognosis and quality of life associated with the different states based on the extent of metastasis), through the inclusion of locoregional and distant metastatic states (100). The increased granularity is expected to improve the clinical validity of the model and provide more accurate assessments on survival (100). Splitting the recurrence stage into locoregional and distant metastasis in the current appraisal was deemed appropriate to accurately reflect the distinct prognostic profiles associated with each state (103), thereby enabling a more differentiated and clinically valid estimation of survival outcomes.

Whilst the use of semi-Markov state transition modelling was motivated by the lack of OS data available at the time of previous submissions for nivolumab (TA817), unlike the CheckMate-274 trial, OS data are available from the NIAGARA trial with a median follow-up in censored

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patients of 46-47 months across arms and a maximum follow-up that extends beyond five years (71). Teitsson *et al.* noted that partitioned survival modelling may be a viable option where there is mature OS data available (10). Therefore, a partitioned survival model (PSM) was considered a viable option for this setting.

3.2 Economic analysis

A *de novo* CEM was developed in Microsoft Excel® to address the decision problem of the current appraisal, as outlined in the final NICE scope (13). The model structure is a four-state PSM comprising health states for event-free (EF), locoregional recurrence (LR), distant metastatic disease (DM) and death. This was informed by the NIAGARA trial design and relevant treatment guidelines (4, 31, 71, 104-108). The PSM approach was preferred to alternative methods, such as Markov state transition modelling, for the following reasons:

- The PSM is widely used and accepted for reimbursement decision making in HTA, especially in oncology, where it has been employed in 73% of all oncology submissions, as per the NICE Technical Support Document (TSD) 19 (109). PSMs are well-understood due to their intuitive structure and the ease of interpreting outcomes, which are usually linked to key trial endpoints, such as EFS and OS.
- The PSM involves direct modelling of key trial endpoints such as EFS and OS, ensuring accurate replication of trial data (109). In contrast to the previous submissions (e.g., TA817 and TA851), where limited OS data necessitated semi-Markov modelling, the availability of mature OS data in the current appraisal supports the use of PSM (71). Therefore, use of a PSM structure in the current CEM effectively facilitates the integration of the trial data directly into the model.

The key characteristics of the CEM are presented in Table 33.

Table 33: Characteristics of the *de novo* economic model

Aspect	Details	Justification
Model structure	PSM with four health states: EF, LR, DM, and Death	The approach is in line with the clinical pathway for patients with MIBC.
Perspective	UK NHS and PSS	In line with the NICE reference case (110).
Time horizon	Lifetime horizon - 36 years	Based on the time from the baseline average age of 64 years in the NIAGARA trial to 100 years old, as per NICE reference case (110).
Comparator	Gemcitabine in combination with cisplatin	In line with the NIAGARA trial, treatment guidelines and clinical experts' opinion (4, 14, 31, 71)
Cycle length	30.44 days per cycle	This cycle length is consistent with the frequency of administration for adjuvant durvalumab, and the expected shortest period between follow-up visits (365.25 days divided by 12 calendar months).
Half-cycle correction	Applied in the base-case analysis	Half-cycle correction was implemented in accordance with standard practices in health

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Aspect	Details	Justification
		economic models to mitigate potential bias from events that could occur at different points throughout the model cycle.
Discounting	Future costs and outcomes are discounted at an annual rate of 3.5%	In line with the NICE reference case (110).
Clinical effectiveness – EF, LR and DM	Informed from the EFS, MFS and OS outcomes from the NIAGARA trial	The NIAGARA trial served as the primary source of clinical data for most clinical inputs to the CEM (71)
Treatment and healthcare resource use costs	NHS reference costs; BNF; eMIT; PSSRU; resource utilisation and costs accepted in previous NICE submissions	Widely used and accepted sources of cost and resource use data in UK HTAs (110).
Health-related quality of life	NIAGARA trial (NIAGARA EQ-5D-5L mapped to UK EQ-5D-3L value set via the Hernandez Alava DSU algorithm) (111)	HRQoL was assessed in the NIAGARA trial using the EQ-5D-5L questionnaire (71). Mapping to EQ-5D-3L was performed as per the NICE reference case.
AE rates and costs	AE rates: NIAGARA trial (Grade 3-4 with incidence $\geq 5\%$ in any treatment arm) AE costs: Unit costs for AE management were sourced from the NHS reference costs 2023-24 (112)	The inclusion of AEs experienced during neoadjuvant/ adjuvant treatment period only, as well as the criteria for AE grade and incidence are in line with previous submissions (11, 99, 113).

Abbreviations: BNF: British National Formulary; CEM: Cost effectiveness Model; DM: distant metastatic disease; EF: Event-Free; eMIT: electronic market information tool; EQ-5D-3L: EuroQol 5-Dimension 3-Level; EQ-5D-5L: EuroQol 5-Dimension 5-Level; HRQoL: Health-Related Quality of Life; HTA: Health Technology Assessment; LR: Locoregional recurrence; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSM: Partition survival model; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; RC: radical cystectomy; UK: United Kingdom.

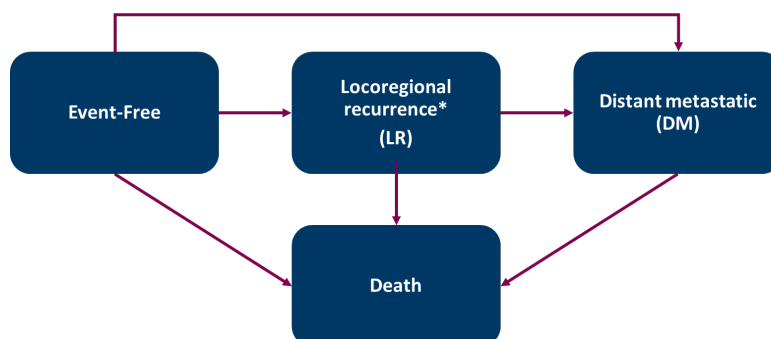
3.2.1 Patient population

The patient population used to inform the primary clinical data in the CEM is based on the ITT population of the NIAGARA trial and comprised of cisplatin-eligible patients with resectable MIBC (71). Table 7 in Section 2.3.3 provides a summary of the baseline characteristics of the patient population used in the CEM.

3.2.2 Model structure

The CEM comprised of four-state PSM including health states for EF, LR, DM, and death. An illustration of the model structure is provided in Figure 21.

Figure 21: Economic model structure



Note: *Depending on EFS definition, the state may include patients who had refused or failed surgery

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Abbreviations: DM: Distant metastatic; LR: Locoregional recurrence.

Patients enter the model in the EF state and begin NAC, with or without perioperative durvalumab, followed by RC, if suitable. The EF state represents the pre-recurrence phase, including patients who progress before surgery or decline or are unfit for surgery. From EF state, patients may transition to LR, DM or death states. LR includes recurrence in MIBC patients, including those who did not undergo surgery. DM can arise from either EF or LR and is associated with poorer survival and lower HRQoL compared to EF and LR. Death is the absorbing state, capturing all-cause mortality.

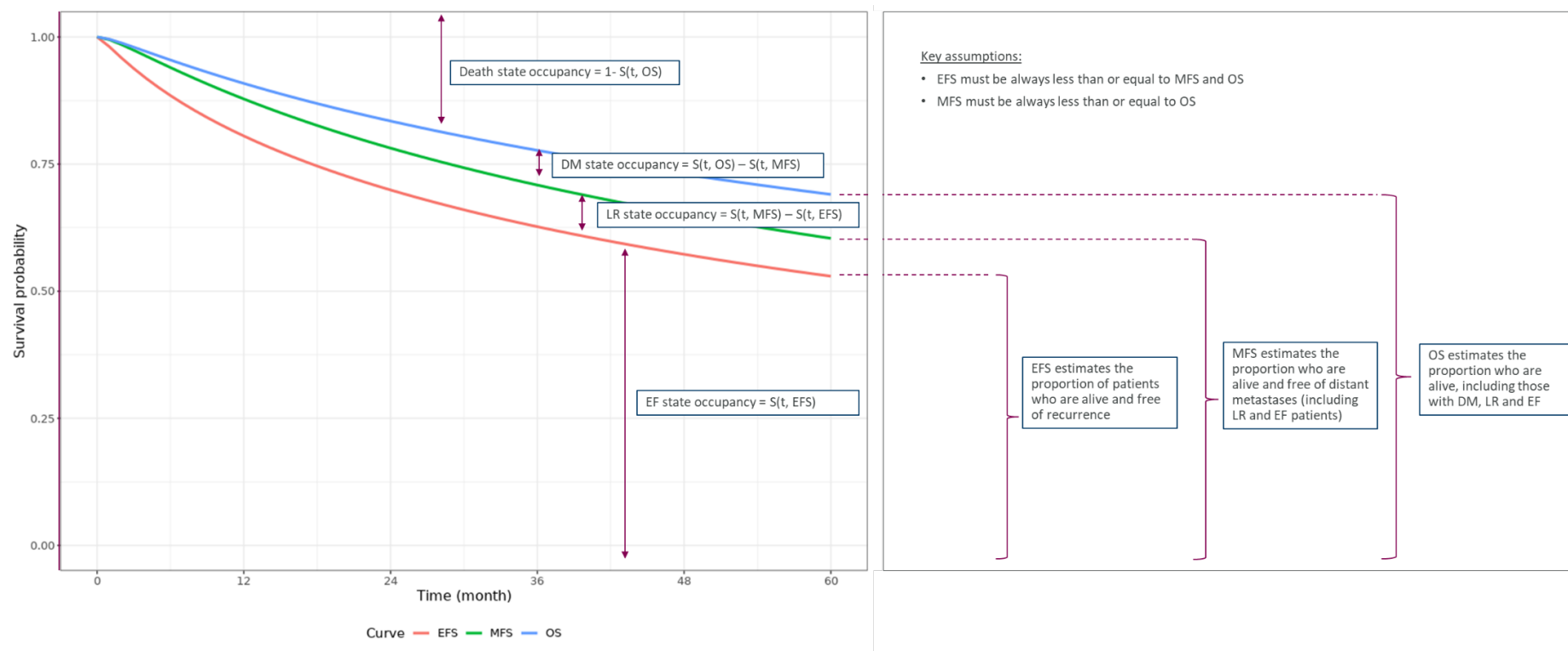
The model estimates treatment duration for NAC and durvalumab using data from the NIAGARA trial, based on the proportion of patients receiving treatment in each cycle (71). Since all patients had completed treatment at DCO 29 April 2024, no extrapolation, or censoring adjustments (e.g., KM) were needed. Treatment costs are modeled independently of health states to reflect discontinuations due to AEs or withdrawal.

An illustration of the PSM simulation technique for four-health states is provided in Figure 22, with further details outlined below.

The proportion of patients alive over time is estimated directly from the OS curve. Using the MFS curve, OS is then partitioned into the proportion of patients who are alive with DM (OS minus MFS) and proportion of patients who are alive without DM (MFS). The EFS curve further partitions MFS into proportion of patients who are EF, based on the cumulative survival probabilities of EFS, and those with a non-metastatic recurrence who occupy the LR state (MFS minus EFS). The LR state comprised of patients who failed or refused surgery or experienced non-metastatic recurrence (details on these patients from the NIAGARA trial are provided in Table 6 and CONSORT diagram in Section 1.2 of Appendix B). Finally, the death state is estimated as one minus the cumulative survival probabilities for OS.

To avoid negative state membership, EFS is constrained to values that are less than or equal to MFS and MFS is constrained to values that are less than or equal to OS, over the lifetime of the model. The hazard for death is also constrained to values that are greater than or equal to the background all-cause mortality rate from the general population matched on age and gender, to avoid cases where survivorship in the cohort exceeds that of the general population (114). Survival curves (EFS, MFS, OS) are extrapolated beyond trial follow-up using parametric models (Section 3.3.2).

Figure 22: Illustration of partitioned survival model simulation technique for four-health states



Abbreviations: DM: distant metastasis; EF: event-free; EFS: event-free survival; LR: locoregional recurrence; MFS: metastasis-free survival; OS: overall survival

3.2.3 Intervention technology and comparators

The intervention technology included perioperative durvalumab, as assessed in the NIAGARA trial (71).

The comparator included was cisplatin-based NAC, followed by RC, with no adjuvant treatment. The choice of comparator is aligned with the recommendations of the European clinical guidelines for MIBC and the NICE scope and rationale as presented in section 1.1 (Table 1) (4, 31). Furthermore, as stated in section 1.3.2, the UK-based clinical experts also confirmed that the comparator included in the current appraisal is reflective of the UK clinical practice (14).

The intervention and comparator included in the CEM are presented in Table 34.

Table 34: Intervention and comparator included in the CEM

Treatment	Dosage and duration	Administration type
Perioperative durvalumab	Durvalumab 1500 mg Q3W with gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and adjuvant durvalumab 1500 mg Q4W for up to eight 28-day cycles (32 weeks, eight months).	IV
Gemcitabine and cisplatin	Neoadjuvant gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and no adjuvant treatment. Gemcitabine and cisplatin was dosed at 1000 mg/m ² on Days 1 and 8 Q3W (gemcitabine) and 70 mg/m ² on Day 1 Q3W (cisplatin) for patients with adequate renal function (CrCl ≥ 60 mL/min) and at 1000 mg/m ² on Days 1 and 8 Q3W (gemcitabine) and 35 mg/m ² on Days 1 and 8 Q3W (cisplatin) for patients with borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min) for both arms.	IV

Abbreviations: CEM: cost effectiveness model; CrCl: creatinine clearance; IV: intravenous; mg: milligram; Q3W: every three weeks; Q4W: every four weeks; RC: radical cystectomy
Source: AZ NIAGARA trial CSR (71)

As mentioned in Section 1.3.2, the use of nivolumab as adjuvant treatment is limited to patients at high risk of recurrence (assessed after surgery) and whose tumours express PD-L1 at a level of 1% (11). This means that the overlap between patients eligible for perioperative durvalumab and adjuvant nivolumab is minimal. Whilst we acknowledge that adjuvant nivolumab is part of the current treatment landscape for MIBC in the UK, the relevance of nivolumab as a comparator for cost effectiveness decision-making in a perioperative setting is uncertain. Adjuvant nivolumab and perioperative durvalumab occupy distinct points in the treatment pathway and target different populations: nivolumab as adjuvant therapy constitutes a reactive or salvage intervention in response to a post-surgical assessment where risk of disease recurrence has been deemed to be high; in contrast, the perioperative approach is a proactive strategy suitable for all eligible patients.

As described in Section 2.9, there are challenges with conducting comparisons between adjuvant and perioperative settings. However, we have attempted this comparison in response to the NICE final scope using a novel survival time-adjusted ITC approach. In this approach, Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

the comparison is made to a counterfactual control arm representing treatment with NAC and RC followed by no treatment or adjuvant nivolumab in high-risk patients was created from the NIAGARA control arm in those eligible for adjuvant nivolumab in the UK, that is patients who:

- underwent cystectomy and were disease-free (eligible for DFS in NIAGARA and CheckMate-274)
- are determined as high risk MIBC based on staging criteria in CheckMate-274
- have a PD-L1 tumour expression of at least 1%.

This counterfactual arm includes [REDACTED] of patients who receive nivolumab, as calculated from the NIAGARA trial (see Section 2.9.2).

We maintain that the relevance of nivolumab as a comparator for cost effectiveness decision-making in a perioperative setting is uncertain due to the limitations of this comparison (outlined in Section 2.9). Nevertheless, we have included the results from the ITC in the cost effectiveness analysis as a scenario.

All methodology and inputs related specifically to adjuvant nivolumab have been included in Appendix K. The results of this scenario are included in Section 3.11.3.1.

3.3 Clinical parameters and variables

3.3.1 Data sources and survival endpoints

The primary source of clinical inputs for the CEM is the patient-level data collected at IA-2 (DCO 29 April 2024) of the NIAGARA trial. The results of the NIAGARA trial were considered representative of the outcomes of treatment in UK clinical practice (as described in section 2.12) (71).

The model constrains age and gender-adjusted mortality using UK life table data from the Office of the National Statistics (ONS), ensuring death risk remains at or above background levels by age (114).

The data sources used for each endpoint in the model are detailed in Table 35.

Table 35: Summary of endpoints in the model (DCO 29 April 2024)

Transitions/ endpoint	Notes/ definition of statistical endpoint	Numbers at risk	Numbers of events
EFS (Blinded independent central review) (Table 15)	Time from randomisation to: • the time of first recurrence of disease after RC; • the time of first documented progression in patients who are medically precluded from RC;	Control arm: 530 Perioperative durvalumab arm: 533	Control arm: 246 (46.4%) Perioperative durvalumab arm: 187 (35.1%)

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Transitions/ endpoint	Notes/ definition of statistical endpoint	Numbers at risk	Numbers of events
	- the time of expected surgery in patients who refuse to undergo RC or failure to undergo RC in patients with residual disease; or, - the time of death due to any cause		
MFS (investigator only) (Table 19)	Time from randomisation to distant metastases or death in the absence of metastases	Control arm: 530 Perioperative durvalumab arm: 533	Control arm: 201 (37.9%) Perioperative durvalumab arm: 152 (28.5%)
OS (Table 17)	Time from randomisation to death of any cause	Control arm: 530 Perioperative durvalumab arm: 533	Control arm: 169 (31.9%) Perioperative durvalumab arm: 136 (25.5%)

Abbreviations: DCO: Data-cut off; EFS: event-free survival; EF: event-free; MFS: Metastasis-free survival; OS: overall survival; RC: radical cystectomy.

Source: AZ NIAGARA trial CSR (DCO 29 April 2024) (71)

3.3.2 Parametric survival analysis methods

The survival modelling for EFS, MFS and OS was conducted in line with the NICE Decision Support Unit (DSU) TSD 14 and TSD 21 (115, 116). The approach included:

- An assessment of the proportional hazards (PH) and accelerated failure time (AFT) assumption to determine the suitability of using independent models fitted to each arm or joint models that are fitted to a data set containing both arms with a covariate for treatment group
 - PH were assessed using log-cumulative hazard plots, Schoenfeld residuals, and the Grambsch-Therneau test. Proportionality can be supported by parallel log-hazard lines, flat Schoenfeld plots, and test p-values<0.05.
 - For AFT models (e.g., log-normal, log-logistic), treatment effects were evaluated on survival time using quantile-quantile (QQ) plots. A linear relationship between treatment arms would support the AFT assumption.
- Generation of statistical goodness of fit measures such as Akaike- and Bayesian information criteria (AIC and BIC)
- Visual inspection of model fit to the trial data (both to the KM curves and the observed hazards)
- An assessment of the clinical plausibility of extrapolation.

Standard parametric models (e.g., exponential, Weibull, Gompertz, log-normal, log-logistic, Gamma) were fitted to the NIAGARA trial data (71). Where hazards were complex or non-Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

monotonic, flexible Royston-Parmar spline models (1–3-knots, various link functions) were also considered (117). Flexible spline models are commonly used in the economic evaluations of IO therapies because they can accommodate non-PH and complex hazard functions, which are frequently observed in IO treatments due to delayed treatment effects and long-term survival plateaus (117).

Model selection was based on statistical fit and clinical plausibility. The extrapolated survival probabilities were validated against clinical expert opinion (118), and literature estimates from registry studies, identified from targeted searches. In validation interviews conducted with UK-based clinical experts (N=4), clinical experts were shown results for EFS, MFS and OS from the NIAGARA trial, and the corresponding long-term extrapolation using statistically parametric survival models (118).

3.3.2.1 *Survival modelling of EFS*

At DCO 29 April 2024 of the NIAGARA trial, the estimated EFS at 24 months was 67.8% in the perioperative durvalumab arm and 59.8% in the control arm (HR for EFS, 0.75; 95% CI, 0.62 to 0.90; $p < 0.01$ by stratified log-rank test) (2). The KM plot for EFS is shown in Figure 8.

The hazard profiles for each arm exhibits different patterns. In the control arm, the hazard rate is initially high and decreases over time until around month 36, after which it becomes approximately constant. In contrast, the hazard rate in the perioperative durvalumab arm is initially low, increasing to a peak at approximately month 5, and then declines over time. The declining hazard profile for perioperative durvalumab may reflect the longer-term benefit of immunotherapy, such as sustained immune activation or delayed relapse, which are characteristic of IO therapies (119). The hazard profiles of both arms are shown in Appendix L.

The non-monotonic hazard pattern seen in the control arm, characterised by its rapid decline and stabilisation, suggests that flexible models may be more appropriate. The perioperative durvalumab arm also has hazards that may be more suited to splines. As a result, both standard and flexible parameter survival models were considered for both arms.

Assessment of PH and AFT assumption

The Schoenfeld plot in Appendix L shows a concave arc trend line. Initially, the log-hazard ratio is low (and positive), before increasing slightly and then decreasing over the long-term. The trend indicates an improving effect of treatment throughout the period of the study. Although the test statistic for PH was non-significant ($p = 0.6985$), supporting the null

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hypothesis that treatment effect is constant, the absence of a horizontal line on the Schoenfeld plot suggests that the PH assumption may not hold.

These findings are supported by the patterns seen in the KM and log-cumulative hazards plot. The KM and log-cumulative hazard plots (Appendix L) provide some evidence of non-PH in the form of delayed separation and evidence of crossing curves at the very early phases of study follow-up. Together, these findings indicate that a joint model assuming PH may not accurately capture the outcomes of treatment.

For joint AFT models such as log-logistic and log-normal, the effect of treatment is assumed to have a constant multiplicative effect on survival time. To evaluate this assumption, a QQ plot was constructed, as shown in Appendix L. This indicates that the AFT assumption is unlikely to hold. Therefore, dependent AFT models may not be appropriate to extrapolate EFS.

In the absence of clear evidence supporting either PH or AFT assumption, the modelling of EFS was performed using independent parametric survival models fitted to patient-level data from each arm of NIAGARA study.

Goodness of fit

The statistical goodness of fit was reported in terms of the AIC and BIC scores, where a lower score indicates a more parsimonious fit to the trial data (Table 36). For the perioperative durvalumab arm, the 1-knot spline odds model demonstrates the best fit according to both AIC and BIC criteria. The generalised gamma had the best statistical fit to the control arm, but the normal spline family also demonstrated a good statistical fit.

Table 36: Goodness of fit statistics for standard parametric models for EFS

Model	Akaike Information Criterion		Bayesian Information Criterion	
	Control arm	Perioperative durvalumab arm	Control arm	Perioperative durvalumab arm
Scale=hazard (1-knot)	2380.6	1922.4	2393.4	1935.2
Scale=hazard (2-knots)	2372.7	1923.9	2389.8	1941.0
Scale=hazard (3-knots)	2370.3	1925.9	2391.6	1947.3
Scale=normal (1-knot)	2371.7	1927.8	2384.5	1940.6
Scale=normal (2-knots)	2369.0	1926.8	2386.1	1943.9
Scale=normal (3-knots)	2368.8	1927.7	2390.2	1949.1
Scale=odds (1-knot)	2379.0	1922.2	2391.8	1935.0
Scale=odds (2-knots)	2372.1	1923.9	2389.2	1941.1
Scale=odds (3-knots)	2370.1	1925.9	2391.4	1947.3
Exponential	2483.3	2040.1	2487.6	2044.4
Weibull	2447.4	2006.5	2456.0	2015.1
Log-normal	2405.6	1972.7	2414.2	1981.2
Log-logistic	2426.7	1992.0	2435.2	2000.5

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Model	Akaike Information Criterion		Bayesian Information Criterion	
	Control arm	Perioperative durvalumab arm	Control arm	Perioperative durvalumab arm
Gompertz	2405.4	1947.0	2413.9	1955.6
Generalised gamma	2365.8	1943.9	2378.6	1956.7
Gamma	2455.9	2013.4	2464.4	2021.9

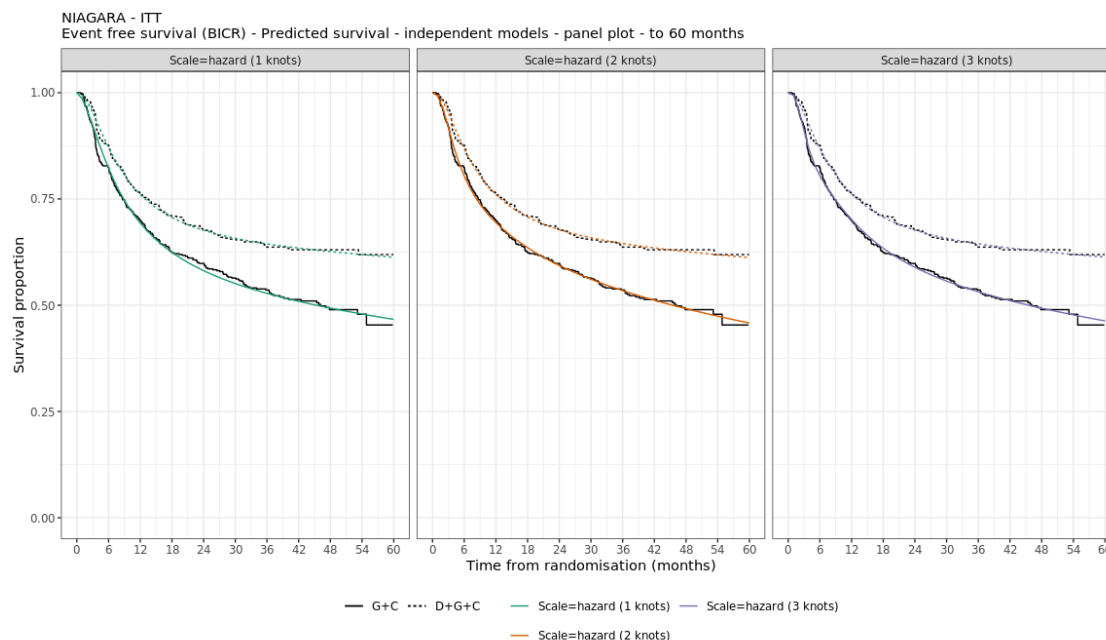
Abbreviations: EFS: event-free survival

Visual fit

For both arms, all spline-based models provided a good visual fit to the KM curve. Similarly, a visual assessment of the hazards showed that all spline-based models approximated the observed hazards well. All curves were within 1-2 percentiles of each other at the end of follow-up in both arms (Figure 23, Figure 24 and Figure 25). Plots of the observed versus modelled hazard are included in Appendix L.

This contrasts with the standard models. In the perioperative durvalumab arm, only the generalised gamma model provided a sufficient visual fit to the KM curve and the hazard over time. In the control arm, whilst the Gompertz and generalised gamma models provided a sufficient visual fit to the KM curve, the fit to the observed hazards was poor across all models (Appendix L).

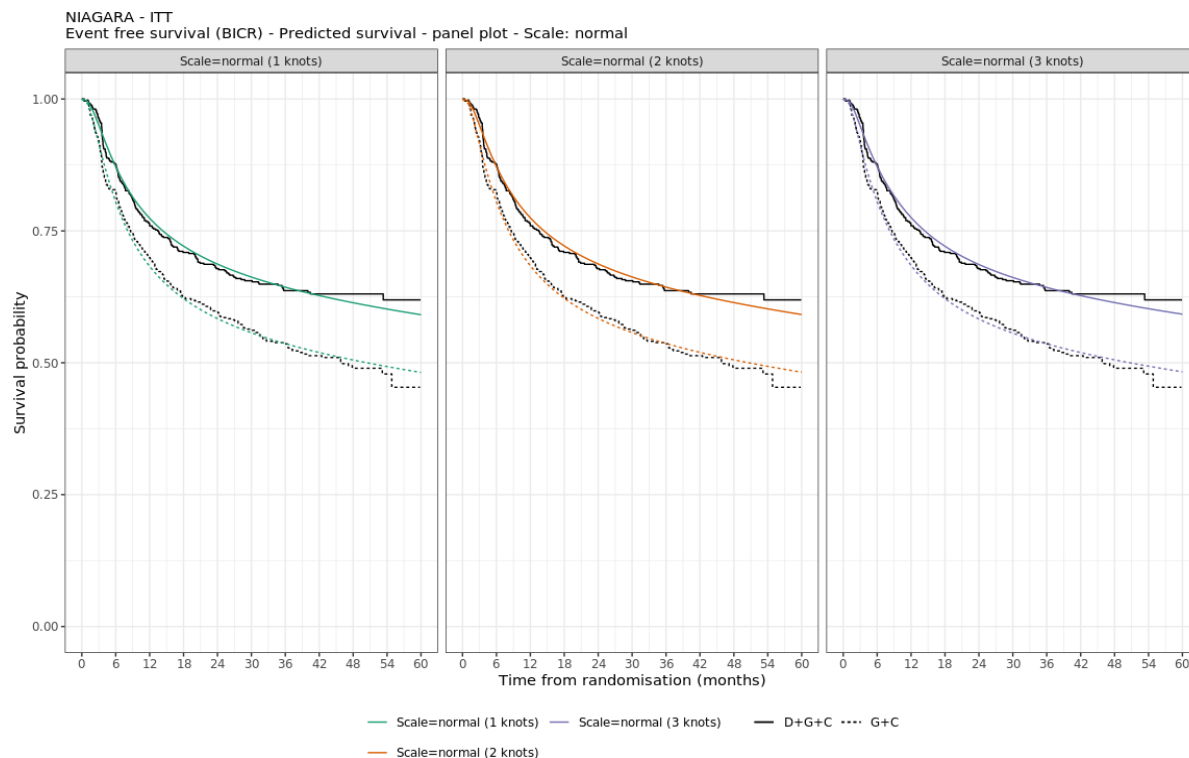
Figure 23: Independent spline hazard curves for EFS



Abbreviations: BICR: blinded independent central review; C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat

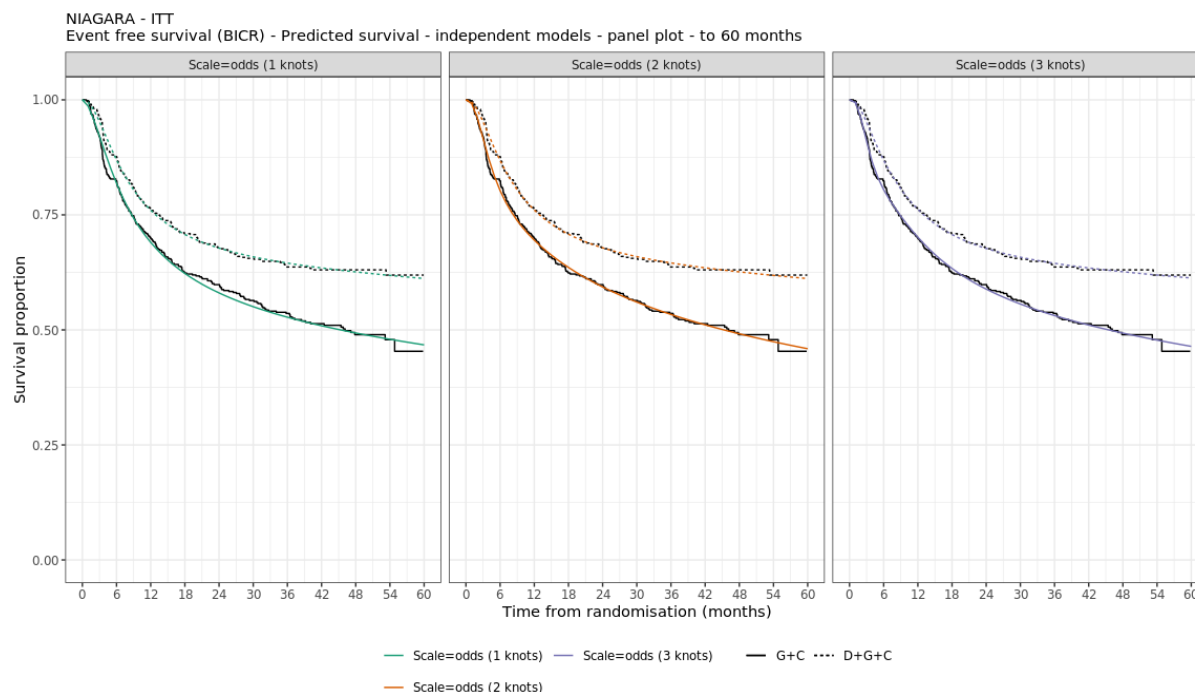
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Figure 24: Independent spline normal curves for EFS



Abbreviations: BICR: blinded independent central review; C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat

Figure 25: Independent spline odds curves for EFS



Abbreviations: BICR: blinded independent central review; C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat

Clinical experts' validation

All UK-based clinical experts considered the spline-based curves presented to them as being the same or similar and any curve was considered acceptable (118). One clinician explicitly mentioned the spline 2-knot odds model and spline 2-knot hazard model being the most plausible for the perioperative durvalumab and control arm, respectively (118).

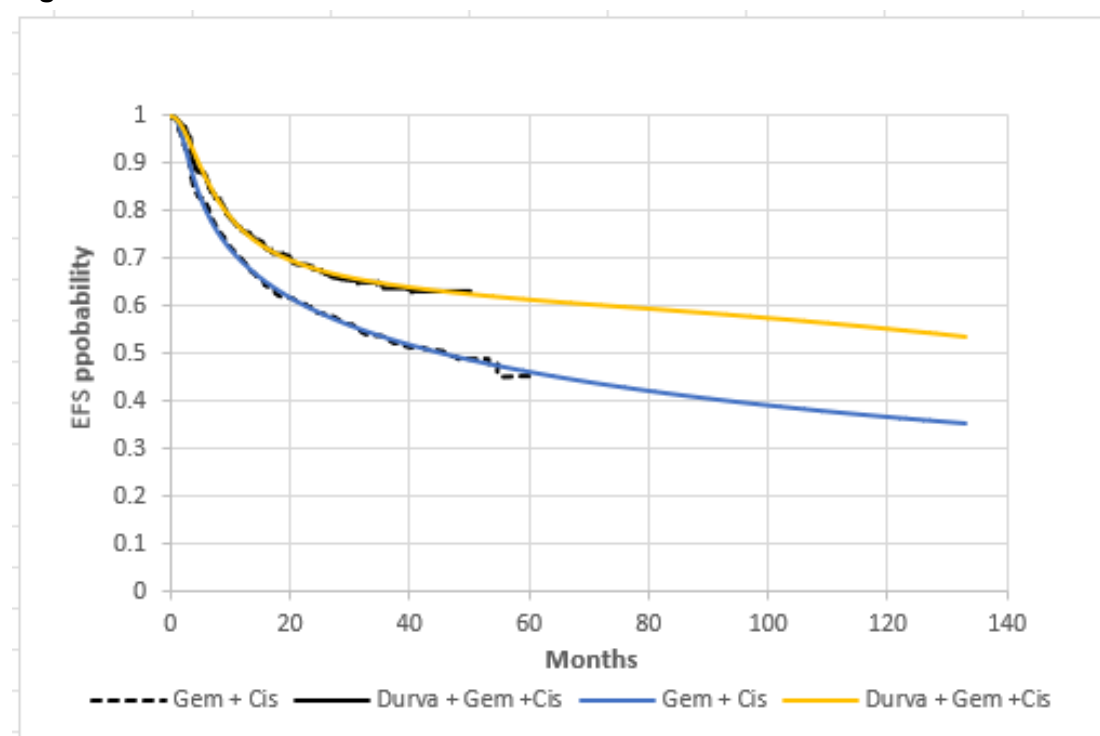
Literature estimates:

No relevant external papers were identified for the EFS endpoint.

Conclusion

Given the poor visual fit of the KM curves to the standard models, the standard models were excluded from consideration. From the spline-based models, as all models provided a good visual fit to the data and clinical experts agreed that all curves presented could be plausible, the best fitting spline-based model was selected for each arm: for perioperative durvalumab this was 1-knot spline odds, and for the control arm this was 2-knot spline normal. The base case curve selection for each arm is presented Figure 26.

Figure 26: Base case curve selections for EFS



Note: EFS was adjusted to ensure that risk of death is above general population mortality.

Abbreviations: C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine

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For the scenario analyses, an alternative model was tested for each arm. This was informed by the clinician who explicitly called out the spline 2-knot odds model for perioperative durvalumab and the spline 2-knot hazard model for the control arm (118).

3.3.2.2 *Survival modelling of MFS*

At DCO 29 April 2024 of the NIAGARA trial, MFS events occurred in 152 (28.5%) patients in the perioperative durvalumab arm and 201 (37.9%) patients in the control arm (71). The estimated MFS at 36 months was 69.9% (95% CI, 65.5 to 59.3) in the perioperative durvalumab group and 59.3% (95% CI, 54.6 to 63.7) in the control arm (HR for death, 0.67; 95% CI, 0.54 to 0.83; $p=0.01$ by stratified log-rank test) (71).

The KM plot (shown in Figure 9) shows similar survival across arms until approximately six months, after which there was clear and sustained separation favouring perioperative durvalumab. The associated hazard profiles (shown in Appendix L) are broadly similar across arms with rates initially increasing to a peak before declining towards zero over the remaining follow-up. Similar to EFS, the survival modelling of MFS considered both standard and flexible parametric models, to ensure an adequate fit to the observed hazard profiles.

Assessment of PH and AFT assumption

The Schoenfeld plot in Appendix L shows a generally constant and horizontal trend line for the log-hazard ratio. The test statistic for PH was non-significant suggesting that the PH assumption may hold. In contrast, the KM and log-cumulative hazard plots (Appendix L) provide some evidence of non-PH in the form of delayed separation and evidence of crossing curves at the very early phases of study follow-up. The QQ plot for MFS shown in Appendix L indicates that the AFT assumption is unlikely to hold.

In the absence of clear evidence supporting either PH or AFT assumptions, the modelling of MFS was performed using independent parametric survival models fitted to patient-level data from each arm of the NIAGARA trial.

Goodness of fit

The statistical goodness of fit for MFS reported in terms of the AIC and BIC scores is presented in Table 37.

For perioperative durvalumab arm, the 3-knot spline normal model has the best fit according to AIC score, while the 1-knot hazard model performs best according to BIC score. The BIC applies a greater penalty for model complexity than AIC, indicating that the additional knots in the 3-knot versus the 1- and 2-knot spline models may not be justified. For control arm, the 1-knot hazard model has the best fit according to both AIC and BIC scores.

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Table 37: Goodness of fit statistics for standard parametric models for MFS

Model	Akaike Information Criterion		Bayesian Information Criterion	
	Control arm	Perioperative durvalumab arm	Control arm	Perioperative durvalumab arm
Scale=hazard (1-knot)	2076.7	1698.2	2089.5	1711.0
Scale=hazard (2-knots)	2078.7	1699.8	2095.8	1716.9
Scale=hazard (3-knots)	2080.1	1696.7	2101.5	1718.1
Scale=normal (1-knot)	2081.9	1706.9	2094.7	1719.7
Scale=normal (2-knots)	2079.4	1700.3	2096.5	1717.5
Scale=normal (3-knots)	2079.9	1695.7	2101.3	1717.1
Scale=odds (1-knot)	2076.8	1698.3	2089.7	1711.2
Scale=odds (2-knots)	2078.6	1699.4	2095.7	1716.6
Scale=odds (3-knots)	2080.0	1696.4	2101.4	1717.8
Exponential	2128.3	1732.4	2132.6	1736.7
Weibull	2129.3	1732.0	2137.8	1740.6
Log-normal	2098.5	1713.5	2107.1	1722.0
Log-logistic	2113.9	1724.4	2122.4	1733.0
Gompertz	2112.6	1717.0	2121.2	1725.5
Generalised gamma	2086.9	1711.0	2099.7	1723.8
Gamma	2130.2	1733.1	2138.7	1741.7

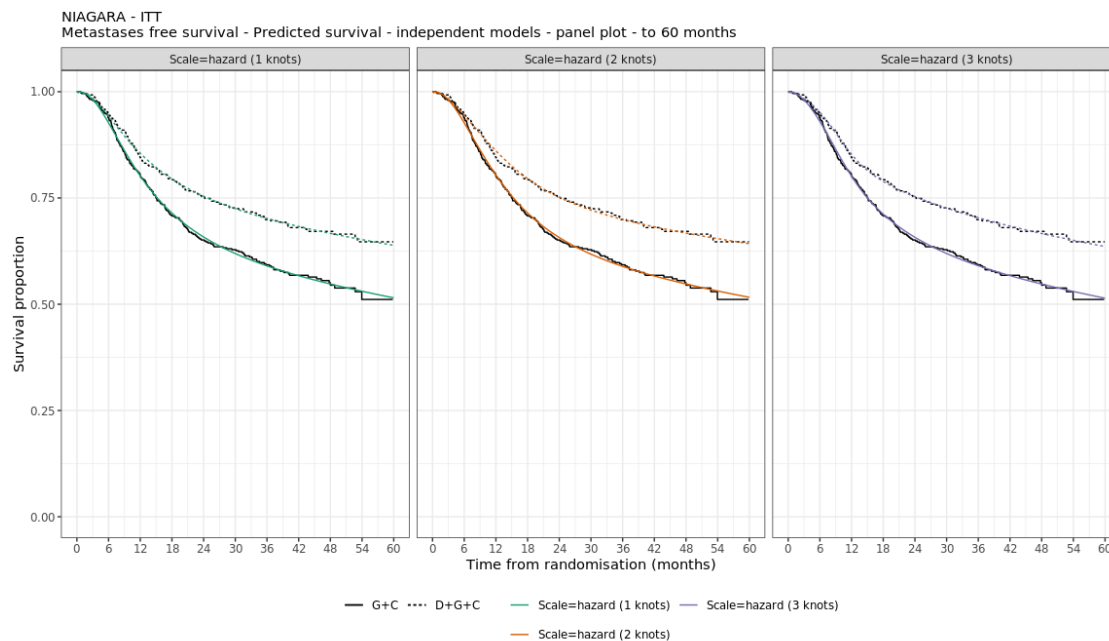
Abbreviations: MFS: metastasis-free survival

Visual fit

For both arms, all spline-based models provided a good visual fit to the KM curve (Figure 27, Figure 28 and Figure 29). Similarly, a visual assessment of the hazards showed that all spline-based models approximated the observed hazards well. All curves were within 1-2 percentiles of each other at the end of follow-up in both arms.

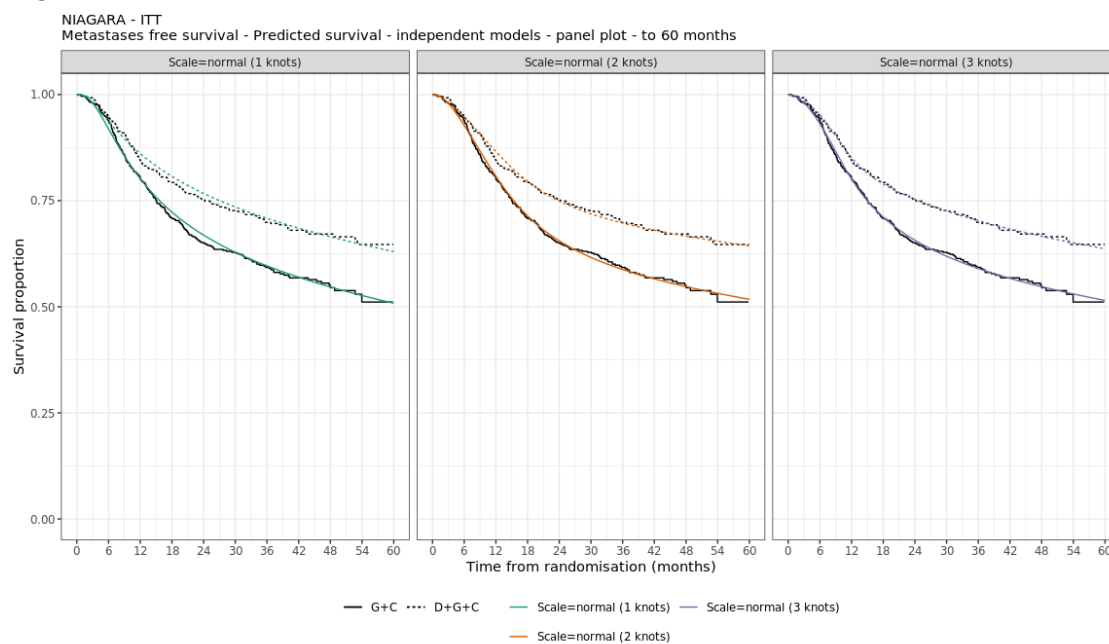
This is in contrast to the standard models, where all models provided a poor visual fit to the observed data (Appendix L).

Figure 27: Independent spline hazard curves for MFS



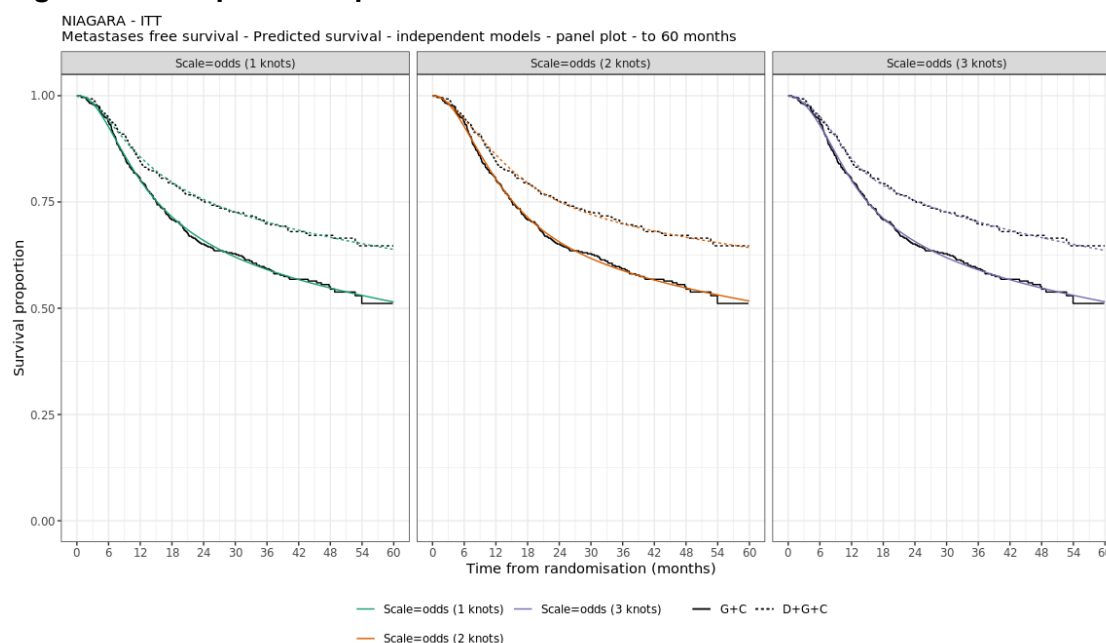
Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; ITT: intention-to-treat; MFS: metastasis-free survival

Figure 28: Independent spline normal curves for MFS



Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; ITT: intention-to-treat; MFS: metastasis-free survival

Figure 29: Independent spline odds curves for MFS



Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; ITT: intention-to-treat; MFS: metastasis-free survival

Clinical expert validation

All UK-based clinical experts considered the spline-based curves presented to them as being the same or similar and any curve was considered acceptable (118).

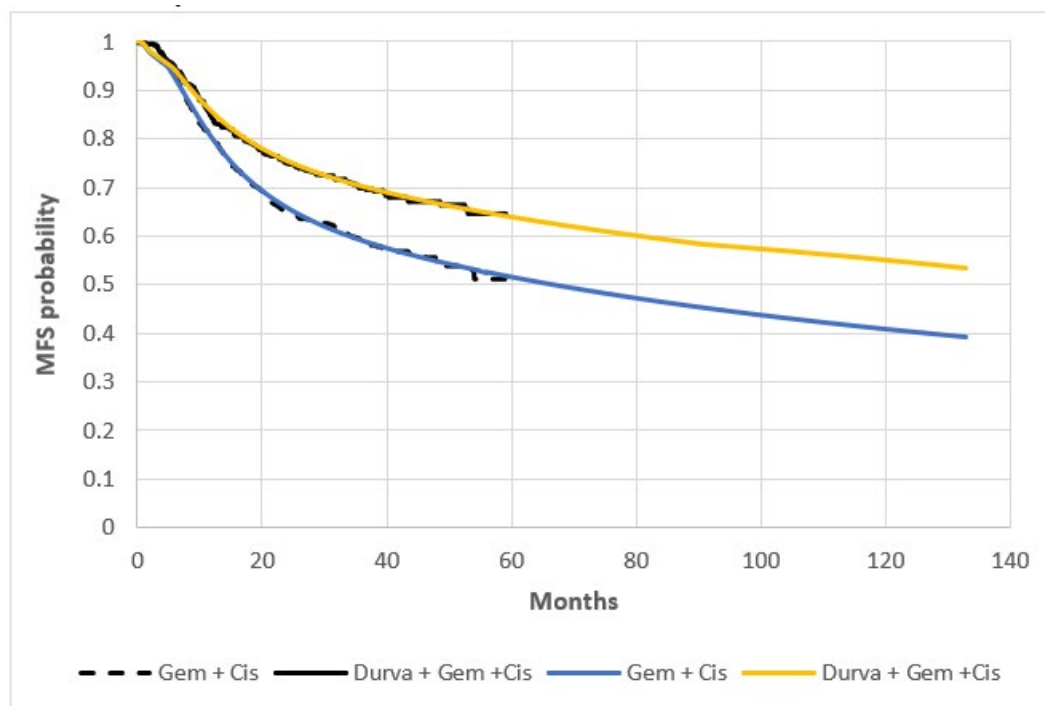
Literature estimates:

No relevant external papers were identified for the MFS endpoint.

Conclusion

Given the poor visual fit of the KM curves to the standard models, the standard models were excluded from consideration. From the spline-based models, as all models provided a good visual fit to the data and clinical experts agreed that all curves presented could be plausible, the best fitting spline-based model was selected for each arm; for both arms 1-knot spline hazard was selected. The base case curve selection for each arm is presented in Figure 30.

Figure 30: Base case curve selections for MFS



Note: MFS was adjusted to ensure that risk of death is above general population mortality.

Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; MFS: metastasis-free survival

For the scenario analyses, an alternative model was tested for each arm. The spline 3-knots normal and spline 2-knots normal curves were tested for the perioperative durvalumab and control arms, respectively (118).

3.3.2.3 *Survival modelling of OS*

At DCO 29 April 2024 of the NIAGARA trial, death occurred in 136 (25.5%) patients in the perioperative durvalumab arm and 169 (31.9%) patients in the control arm (2). The estimated OS at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the perioperative durvalumab arm and 75.2% (95% CI, 71.3 to 78.8) in the control arm (HR for death, 0.75; 95% CI, 0.59 to 0.93; $p=0.01$ by stratified log-rank test) (2).

The KM plot (presented in Figure 7) shows similar survival across arms until approximately six months, after which a sustained separation favouring perioperative durvalumab emerged. Throughout follow-up, perioperative durvalumab consistently showed lower mortality, indicating a durable survival benefit. The hazard profiles (shown in Appendix L) were considered to be well-captured by standard parametric models. Flexible survival models were not considered for OS given the relatively simple hazard pattern.

Assessment of PH and AFT assumption

The Schoenfeld plot in Appendix L shows a generally constant and horizontal trend line for the log-hazard ratio. The test statistic for PH was non-significant ($p=0.7425$) suggesting that there is no significant evidence that the PH assumption does not hold. In contrast, the KM and log-cumulative hazard plots (Appendix L) provide some evidence of non-PH in the form of delayed separation and crossing curves at the very early phases of study follow-up. The QQ plot for OS is shown in Appendix L indicates that the AFT assumption is unlikely to hold.

Without clear evidence supporting either PH or AFT assumptions (shown in Appendix L), the modelling of OS was performed using independent parametric survival models fitted to patient-level data from each arm of NIAGARA trial.

Goodness of fit

The statistical goodness of fit for OS reported in terms of the AIC and BIC scores is presented in Table 38. According to the AIC and BIC scores, the generalised gamma and log-normal are the best-fitting models for the control and perioperative durvalumab arm, respectively.

Table 38: Goodness of fit statistics for standard parametric models for OS

Model	Akaike Information Criterion				Bayesian Information Criterion			
	Control arm	Ranking	Perioperative durvalumab arm	Ranking	Control arm	Ranking	Perioperative durvalumab arm	Ranking
Exponential	1935.1	6	1638.7	6	1939.4	5	1643.0	4
Weibull	1933.9	5	1638.5	5	1942.5	6	1647.0	6
Log-normal	1913.4	2	1627.1	1	1922.0	2	1635.7	1
Log-logistic	1925.7	4	1634.4	4	1934.3	4	1643.0	4
Gompertz	1917.6	3	1629.2	3	1926.2	3	1637.7	2
Generalised gamma	1905.9	1	1627.5	2	1918.7	1	1640.3	3
Gamma	1935.3	7	1639.2	7	1943.8	7	1647.8	7

Note: The best-fit curves as determined by Akaike Information Criterion and Bayesian Information Criterion criteria are indicated in bold.

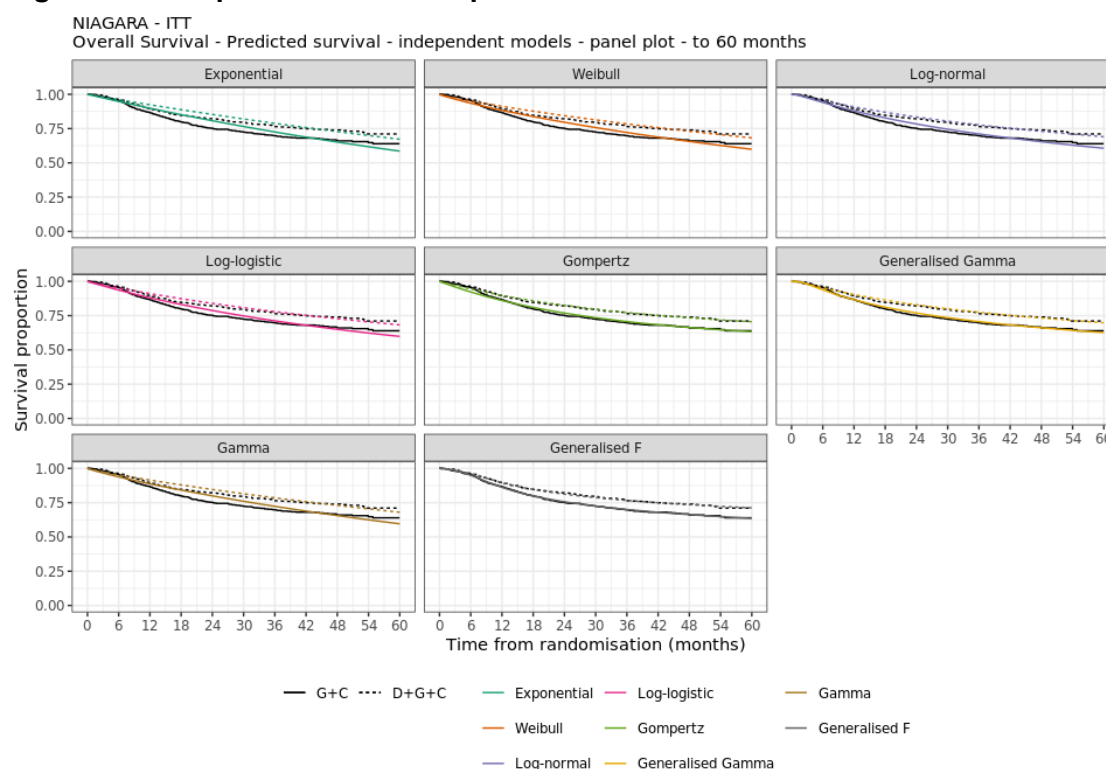
Abbreviations: OS: overall survival

Visual fit

The fit of the models to the KM plot for OS and the corresponding hazard rates for both arms, are presented in Figure 31 and Figure 32, respectively.

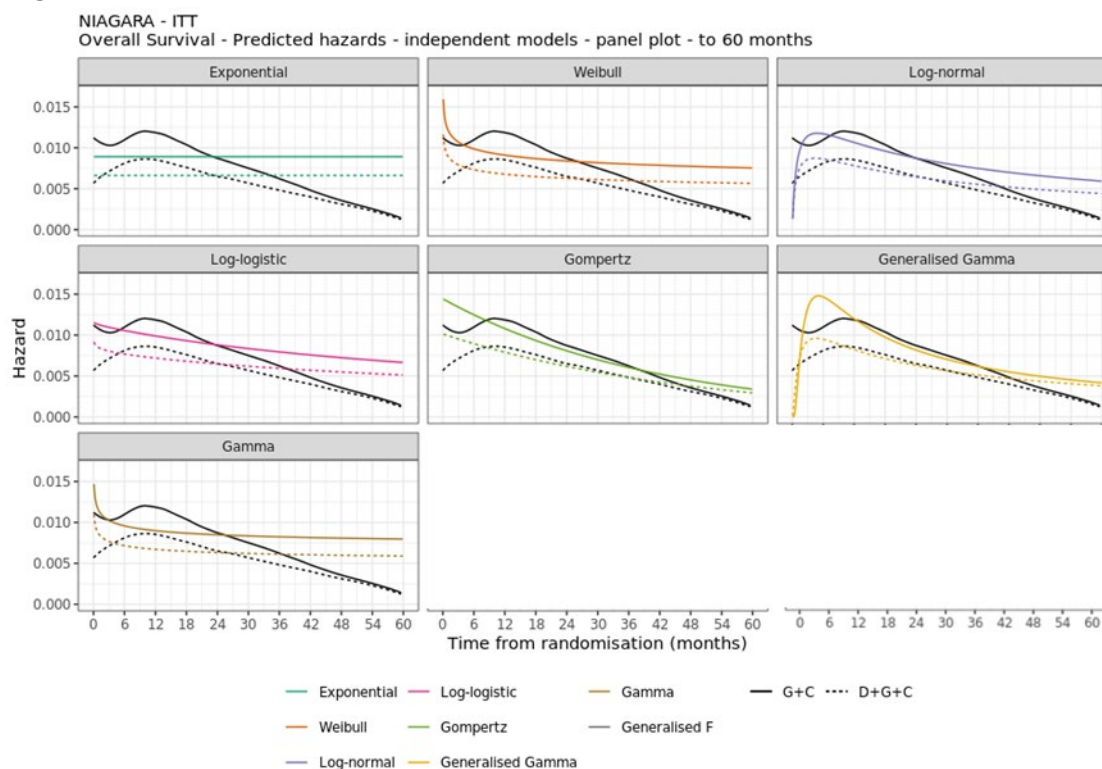
For perioperative durvalumab, both the Gompertz and generalised gamma models provide a sufficiently good visual fit to the KM curve. For the control arm, the Gompertz and generalised gamma models seem to also provide the best visual fit to the KM curve. For both arms the observed hazards from the NIAGARA trial seem to increase initially and then decrease. This decrease happens slightly earlier in the perioperative durvalumab arm (~9 months vs. ~12 months in the perioperative durvalumab and control arm, respectively). This seems best captured by the Gompertz model for perioperative durvalumab, and Gompertz and generalised gamma for the control arm.

Figure 31: Independent standard parametric curves for OS



Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; ITT: intention-to-treat; OS: overall survival

Figure 32: Independent standard parametric hazard rate plot for OS



Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; ITT: intention-to-treat; OS: overall survival

Clinical expert validation

Clinical experts were shown the four best-fitting distributions for each arm (log-normal, generalised gamma, Gompertz and log-logistic). The recommendations for OS survival curves by the clinical experts for the control and perioperative durvalumab arm are presented in Table 39 (118).

Table 39: Clinician overall survival curve recommendations for perioperative durvalumab and control arm

Clinician number	Clinician's preferred curves.	
	Control arm	Perioperative durvalumab arm
Clinician 1	Gompertz	All plausible, Gompertz preferred
Clinician 2	Log-logistic	Log-normal
Clinician 3	- Log-logistic preferred. - Generalised gamma and Gompertz not plausible.	All plausible, log-logistic preferred
Clinician 4	Log-normal	Gompertz

Literature estimates

Evidence available from other randomised trials in MIBC were not considered owing to the fact that the duration of follow-up of these studies was up to approximately 5 years [VESPER, 5.3 years (120); SWOG S1314 53 months (121)]. This timeframe was not considered sufficient

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to support the validation of long-term extrapolations beyond NIAGARA, given that the median follow-up in NIAGARA is 42.3 months, and the maximum follow-up is 61.3 months (2).

Four studies were identified that reported long-term OS outcomes for patients with MIBC. Two studies were considering bladder-salvage treatment (122, 123), and two studies considered survival after RC (124, 125). Mahoney *et al.* (2025) report outcomes from a retrospective chart review of NAC followed CRT bladder sparing approaches for 57 patients over a median follow-up of 74.4 months (9.7-142.1). Faraj *et al.* (2021) compare outcomes for patients with MIBC receiving cisplatin-based NAC with those not receiving NAC (125). Mak *et al.* (2014) report outcomes from a pooled analysis of six RTOG bladder-preservation studies for 468 patients over a median follow-up of 51.6 months among all patients and 93.6 months among survivors (n= 205). Vlaming *et al.* (2020) report survival outcomes from a retrospective chart review of 431 patients with MIBC after RC, differentiated by *de novo* and progressive MIBC, with 10-year OS reported.

Table 40 presents evidence from these studies alongside the observed NIAGARA data and the extrapolations for the three distributions that were considered clinically plausible by the UK-based clinical experts for the control arm (Table 39). At 5-years, Gompertz is most aligned to NIAGARA and two identified external studies, whilst at 10-years the Gompertz distribution may overestimate survival, and the log-logistic distribution may offer a more accurate extrapolation compared with identified external study data. Published baseline characteristics are broadly comparable across studies. However, we recognise the differences in patient selection and treatment intent, and notably era of enrolment for the RTOG studies. Despite this, they are the best available external evidence identified.

Table 40: External literature for OS in the control arm

Study	OS at 5 years	OS at 10 years
Mahoney <i>et al.</i> 2025 (122)	65% (50.7-75.5%)	Not available
Faraj <i>et al.</i> 2021 (125)	53.2%	42.7%
Vlaming <i>et al.</i> 2020 (<i>de novo</i> MIBC) (124)	49%	39%
Mak <i>et al.</i> 2014 (all patients) (123)	57% (52-61%)	36% (31-42%)
Mak <i>et al.</i> 2014 (T2 only)	62%	41%
NIAGARA observed (control arm)	63.9%	Not available
Log-logistic fit to OS data from NIAGARA data control arm*	59.62%	42.67%
Log-normal fit to OS data from NIAGARA data control arm*	60.48%	45.20%
Gompertz fit to OS data from NIAGARA data control arm*	63.19%	55.47%

*Including adjustment for general population mortality; confidence intervals, where available, are presented in brackets.

Abbreviations: MIBC: muscle-invasive bladder cancer; OS: overall survival

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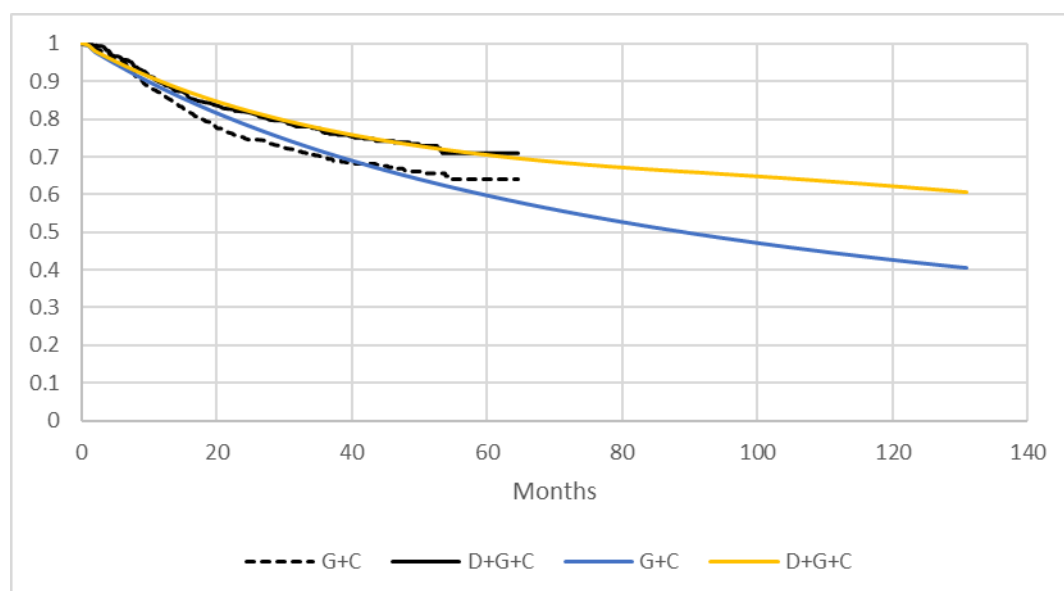
Conclusion

For perioperative durvalumab, whilst Gompertz is not the best fitting according to goodness-of-fit statistics, it does provide a good visual fit to the KM curve and observed declining hazards and was explicitly preferred by two out of four clinical experts. Gompertz was therefore selected in the base case. The log-normal distribution was tested in the scenario analyses as it is the statistically best-fitting distribution and was also highlighted by one clinician.

For the control arm, whilst log-logistic is the fourth best-fitting, this was considered to have the most plausible extrapolation in long-term by the two of the four clinical experts whom expert clinical input was sought. It also aligns closest to values reported in external studies. Two other distributions were tested in the scenario analyses for the control arm. Firstly, the log-normal distribution was explicitly mentioned by one clinical expert and still aligns with external literature. Secondly, the Gompertz distribution was tested as the hazard profiles between the two arms in the trial could be considered similar (declining over the trial period), however this scenario should be interpreted in the context of feedback provided by UK-based clinical experts and the external literature.

The OS base case curve selection for each arm is presented in Figure 33.

Figure 33: Base case curve selections for OS



Note: OS was adjusted to ensure that risk of death is above general population mortality; it was also adjusted that if EFS and OS curves crossed, OS was set equal to EFS.

Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; OS: overall survival

3.3.2.4 Cure

Where decreasing hazards have been observed in the NIAGARA trial, particularly for perioperative durvalumab EFS, this is indicative of the curative potential of this setting. In the nivolumab NICE technology appraisal (TA817), cure was explicitly modelled: the company assumed a cure point at 5 years, an assumption supported by clinical and patient experts. The EAG provided an exploratory analysis using a 10-year cure point and cited evidence from Sternberg *et al.* (2015). The committee concluded that it remains uncertain at what point it is reasonable to assume that people are cured, but that there is evidence that disease recurrence may take place after 5 years and mortality risks remain elevated (11).

In the current submission, the model does not include an explicit cure assumption, but models which capture the decreasing hazards observed in NIAGARA are considered in curve selection.

3.3.3 Summary of model selection

Based on the parametric survival analysis methods and UK-based clinical experts' opinions (described above), the curves selected as the most suitable for the survival modelling of EFS, MFS and OS in the base case of the current CEM are presented in Table 41. The distributions tested in the scenario analyses are presented in Table 42.

Table 41: Base case curve selection for EFS, MFS and OS

Treatment	Outcomes		
	EFS	MFS	OS
Perioperative durvalumab arm	Scale=odds (1-knot)	Scale=hazard (1-knot)	Gompertz
Control arm	Scale=normal (2-knots)	Scale=hazard (1-knot)	Log-logistic

Abbreviations: EFS: event-free survival; MFS: metastases-free survival; OS: overall survival

Table 42: Scenario curve selection for EFS, MFS and OS

Treatment	Outcomes		
	EFS	MFS	OS
Perioperative durvalumab arm	Scale=odds (2-knot)	Scale=normal (3-knot)	Log-normal
Control arm	Scale=hazard (2-knot)	Scale=normal (2-knot)	Log-normal and Gompertz

Abbreviations: EFS: event-free survival; MFS: metastases-free survival; OS: overall survival

3.4 Measurement and valuation of health effects

3.4.1 Health-related quality-of-life data from published studies

The SLR described in section 3.1 included identification of studies reporting HRQoL data in patients with MIBC. A detailed description of the SLR for HRQoL evaluations is provided in Appendix F.

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The SLR identified 24 studies; however, only one study (Broughton *et al.* (126)) reported EQ-5D-5L data, but did not provide utility values mapped to the EQ-5D-3L UK value set, which is required for the NICE reference case (111). The only publication providing relevant data for the CEM was the cost effectiveness study of adjuvant nivolumab by Brodtkorb *et al.* (127). This study reported health state utilities (HSUs) derived using a United States-based value set and summarised using a mixed effects repeated measures (MMRM) analysis of the CheckMate-274 trial data (59). Although aligned with the NIAGARA HSU analysis presented in Table 43 below, the results of Brodtkorb *et al.* (HSU mean values: EF: 0.863; LR: 0.793 and DM: 0.777) cannot be applied in the CEM of the current appraisal because the HSUs are based on a non-UK value set (127). While utility values relevant to the UK setting were used in the NICE appraisal of adjuvant nivolumab (TA817), the actual scores used in the assessment were commercial in confidence and redacted in the final reports (11).

3.4.2 Health-related quality-of-life data from the NIAGARA trial

HRQoL data in the CEM were informed based on a post-hoc analysis of the data collected in the NIAGARA trial (85) (Section 2.6.3.1). HRQoL was collected in the NIAGARA trial using the EQ-5D-5L (along with other patient-reported outcomes) (71). For the current model, HSUs were generated using the Hernandez-Alava *et al.* 5L to 3L mapping algorithm, following the NICE reference case (111). No other mapping analyses were performed.

The HSUs were summarised using a MMRM analysis. The primary aim of the MMRM analysis was to evaluate the associations between HSUs and randomised group and disease state, and to estimate HSU input parameters for the CEM. The results of an MMRM analysis provides inferences that account for the within-subject correlations from longitudinal measures and is appropriate when handling data that are missing at random (128).

In total, four MMRM analyses were performed with covariates for 'randomised group only', 'disease state only', and two models combining disease state and randomised group, with and without interaction terms. The relative performance of each model in predicting HSUs in the NIAGARA trial was assessed using the AIC score, with lower scores indicating a more parsimonious fit to the data (71). The analysis was conducted in R using the MMRM package version 0.3.14 (129).

The disease state assigned to each HSU was estimated using the event times for EFS and MFS from NIAGARA study. Since MFS was only available through investigator assessment and to maintain consistency across each subject's EFS and MFS times, the analysis was performed using study investigator-assessed EFS.

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Each EQ-5D-5L measure in NIAGARA study was assigned to a disease state according to the following rules:

- EQ-5D-5L measures obtained up to the date of investigator assessed EFS were assigned to the EF state.
- EQ-5D-5L measures obtained after metastatic disease, defined as an assessment occurring after an investigator-assessed metastases event per MFS, were assigned to the DM state.
- EQ-5D-5L measures obtained after EFS but before an MFS event were assigned to the LR state. Patients in this state had a documented recurrence of disease but were yet to be diagnosed with metastatic bladder cancer.

Any post-EFS measures observed after censoring for MFS were assigned to an additional state called 'recurrence with unknown status', since it was not possible to determine whether these patients had metastatic disease at the time of their assessment. Finally, any measures observed after censoring of both EFS and MFS were excluded from the data set (n=321 observations).

According to AIC score, the 'disease state only' model provides the best fit (rank 1), followed by the models with disease state and randomised group without (rank 2) and with (rank 3) interactions. Across all applicable models, there was no significant ($p>0.05$) or meaningful difference in HSUs across arms. In contrast, there was a consistent, meaningful and significant effect of disease state on HSUs across all models. As expected, the mean decrease in HSU associated with DM versus EF was larger than the decrement associated with LR. In the best fitting MMRM, the effect of DM versus EF was -0.106 and the effect of LR versus EF was -0.068. In summary, these results indicate that HSU is more closely related to disease state than treatment arm. The results of the MMRM analysis are detailed in Table 43.

Table 43: Results of MMRM analysis for HSUs in the NIAGARA trial

Parameter		Randomised group only	Disease state	Randomised group + disease state	
				Without interaction	With interaction
Intercept					
Randomised group	Perioperative durvalumab versus control				
Disease state	LR versus EF state	-			
	DM versus EF state	-			
	Recurrent with unknown metastatic status versus EF state	-			
Interaction between randomised group and disease state	Perioperative durvalumab: LR (interaction)	-	-	-	
	Perioperative durvalumab: DM state (interaction)	-	-	-	
	Perioperative durvalumab: Recurrent with unknown metastatic status (interaction)	-	-	-	
AIC score					
AIC rank					

Note: *Numerical difference due to rounding-off

The correlation of repeated measurements of HSUs within subjects was captured via the specification of a covariance structure. A series of covariance structures were considered in order of most to least flexible. The most flexible covariance structure that achieved convergence for all models was selected for the base case. The final covariance structure was autoregressive order 1 with heterogeneity. Prior to this, the unstructured and Toeplitz with heterogeneity structures failed to converge.

Abbreviations: AIC: Akaike Information Criterion; EF: event-free; DM: distant metastatic disease; HSU: health state utility; LR: locoregional recurrence; MMRM, mixed effects repeated measures; SE: standard error

The inputs for HSUs for EF, LR and DM in the CEM were derived from the ‘disease-state only’ MMRM analysis using the estimated marginal means (or least squares) method. The rationale of using the stated approach was to provide a model-based estimate of the mean HSU while appropriately accounting for the correlation between repeated measures of HSU data in NIAGARA trial (85).

The estimated marginal means by disease state from the ‘disease-state only’ MMRM analysis are detailed in Table 44.

Table 44: Estimated marginal means for HSUs from the disease-state only MMRM

Health state	Utility (95% CI)
EF	0.847 (0.837, 0.857)
LR	██████████
DM	██████████

Abbreviations: CI: confidence interval; DM: distant metastases health state; EF: event-free health state; HSU: health state utility; LR: local recurrence health state; MMRM, mixed effects repeated measures.

Source: NIAGARA trial CSR (71); Hernandez-Alava *et al.* 5L to 3L mapping algorithm (111)

3.4.3 Health related quality of life data from registries

In addition to the NIAGARA trial, HSUs were available from an unpublished analysis of the Prospective Bladder Cancer Infrastructure (ProBCI) registry. This registry collects prospective clinical and HRQoL data from patients with MIBC, non-muscle invasive and mBC, recruited from 22 hospitals in the Netherlands (130). AstraZeneca is a partner organisation to ProBCI, providing financial support for its research initiatives. As a partner, AstraZeneca can submit analysis requests to the ProBCI.

The results of the ProBCI analysis support the findings of the NIAGARA analysis, in demonstrating a significant and meaningful effect of recurrence on HSU. The change in HSU comparing pre- versus post-recurrence in ProBCI (██████████) is consistent with the NIAGARA trial results for DM MIBC (██████████), while the mean HSU for a pre-event state is similar to the mean HSU for EF in NIAGARA study (██████████ ProBCI versus 0.847 for NIAGARA study).

As the 5L Devlin *et al.* value set is no longer recommended by NICE in the UK (110, 131), and because the ProBCI analysis does not differentiate results based on LR or DM, the results of ProBCI were only used to validate the findings of the NIAGARA trial analysis.

3.4.4 Age-related health state utilities

The CEM included an adjustment for the impact of aging on HSUs (110). The HSU values in the modelled population were assumed to decline over time at a rate consistent with the change in HSUs in the age and gender-matched general population.

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The age-adjustment was modelled using the HSUs by age equations from Ara and Brazier (132), and was applied to each cycle for the duration of the time horizon, in line with the NICE reference case (110). Following ISPOR guidance, the age-related HSUs were applied as a “multiplier” to the HSUs assigned to each state (133).

3.4.5 Impact of adverse events and cystectomy on HSU

The impact of cystectomy and treatment-related AEs on HRQoL was incorporated in the CEM as a one-off quality-adjusted life years (QALY) adjustment applied to the proportion of patients who underwent cystectomy and the proportion of patients who experienced AEs. The one-off QALY adjustment was accrued at the start of the time horizon in the CEM because both cystectomy and treatment-related AEs are expected to have a temporary impact on HRQoL in the early phases of treatment, which is sufficiently captured by an initial one-off adjustment.

The impact of cystectomy on HRQoL was modelled using HSUs from the UK Life After Bladder Cancer (LABC) study, reporting a decline in mean EQ-5D-5L HSU of approximately 0.06 from baseline to the post-treatment phase (134). UK-based clinical experts consulted in validation interviews considered 5% - 10% to be an appropriate value for a one-off utility decrement for patients that underwent surgery (118). As a scenario analysis, this value was increased to 0.08.

The impact of AEs was calculated as the sum product of the disutility, duration, and frequency of each AE. The impact of AEs experienced by patients receiving subsequent treatment was not considered in the analysis as it was assumed that post-recurrence AEs would impact both arms of the model, and therefore have a minimal influence on incremental results. The frequency, duration, and disutility of the included AEs (Grade 3-4 with incidence $\geq 5\%$ in any treatment arm) are reported in Table 45.

Table 45: Adverse events disutilities used in the model

Adverse event	Disutility	Duration (days)	Frequency of AEs		Reference
			Perioperative durvalumab arm	Control arm	
Anaemia	-0.119	16.07	13.8%	15.0%	NICE TA306 (135)
Lipase level increase	-0.050	28.00	0.0%	0.0%	Assumption
Neutropenia	-0.007	15.09	14.3%	0.2%	NICE TA306 (135)
Neutrophil count decrease	-0.007	15.09	7.0%	16.9%	Assumed the same as neutropenia
Thrombocytopenia	-0.108	7.00	14.2%	6.7%	NICE TA1036 (136)
Urinary tract infection	-0.005	28.00	0.0%	13.3%	Sullivan <i>et al.</i> (2011) (137), NICE TA599 (138)

Abbreviations: AE: adverse event; NICE: National Institute for Health and Care Excellence; TA: technology appraisal.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

3.4.6 Summary of HSUs used in the cost effectiveness analysis

A summary of the HSUs used in the base-case of the CEM are presented in Table 46.

Table 46: Summary of HSUs used in the CEM

Analysis	Utility (95% CI)	Data source and rationale
EF	0.847 (0.837 - 0.857)	Consistent with the clinical input parameters in the model, the HSUs assigned to the EF, LR and DM states were based on the EQ-5D-5L data collected in the NIAGARA trial. Alternative data sources, including ProBCI (section 3.4.3) and the CheckMate-274 trial (59), had reported HSUs derived from value sets that are either not recommended by NICE or not aligned to the UK reference case. The decline in mean HSU associated with LR and DM in NIAGARA is consistent with, and hence supported by, the data from both ProBCI (section 3.4.3) and the CheckMate-274 trial (59), but these external values are not used in the model
LR	██████████ ██████████	
DM	██████████ ██████████	
Death	0	Standard assumption
RC	-0.06	Using UK-specific data from the LABC study (134). This is modelled as temporary disutility occurring during the first 6 months after surgery and modelled as a one-off QALY adjustment. Clinical experts consulted in validation interviews considered between 5% to 10% to be an appropriate value for a one-off utility decrement for patients that underwent surgery (118)

Note: The HSUs assigned to the EF, LR and DM states were consistent across all arms, and were therefore assumed to be treatment independent. This was based on the results of the MMRM analysis, which showed no difference in HSUs across arms of NIAGARA. Additionally, there was no evidence to suggest that HSUs would vary based on disease state and treatment, nor was there no clear rationale for why HSUs would differ by treatment.

Abbreviations: CEM: cost-effectiveness model; DM: distant metastases; EF: event Free, HSU: health state utility; QALY: quality-adjusted life years; LABC: Life After Bladder Cancer; LR: local recurrence; ProBCI: Prospective Bladder Cancer Infrastructure; RC: radical cystectomy; UK: United Kingdom

In validation interviews conducted with UK-based clinical experts, clinical experts considered the utility values, presented in Table 46, to be plausible, and highlighted the following points of consideration:

- DM is generally expected to have low utility values, given the poor prognosis associated with standard treatments, which typically offer a survival of only 8 to 15 months.
- The utility values for DM should be lower than those for LR, as most patients with DM are nearing the end of life and experience a substantially reduced quality of life. However, the clinical experts acknowledged that the difference in utility values between DM and EF from NIAGARA is relatively small (118). This indicates that the model may have included a conservative estimate of the DM utility.

3.5 Cost and healthcare resource use identification, measurement, and valuation

The SLR described in section 3.1 included identification of studies reporting cost and HCRU associated with the treatment patients with MIBC (94). A detailed description of the SLR for cost and HCRU evaluations is provided in Appendix G. Only one UK-based and one multi-country (which included the UK) study were identified but did not provide the required level of details and hence was deemed irrelevant for sourcing cost or HCRU inputs for the current appraisal (139, 140). Therefore, the inputs for costs and HCRU were sourced from the NHS reference costs 2023-24 (112), the Personal Social Services Research Unit (PSSRU) (141) and the nivolumab NICE appraisal (TA817) (11). Drug acquisition costs were sourced from the electronic market information tool (eMiT) (142) and the British National Formulary (BNF) (143).

3.5.1 Drug acquisition and administration cost

Treatment regimens for perioperative durvalumab arm and control arm were based on the NIAGARA trial (71). Due to differences in the treatment cycle length in modelled regimens (e.g., durvalumab treatment cycles are 21 days in the neoadjuvant setting and 28 days in the adjuvant setting), the costs of treatment were estimated as cost per administration multiplied by the monthly frequency of administration, starting with the first neoadjuvant treatment administration at cycle 0 (for dosing, please refer to section 2.3.1). Then the estimated acquisition and administration costs were redistributed to 30.44-day cycles. For the control arm, only the neoadjuvant setting was relevant.

A confidential PAS discount for durvalumab was included in the model as provided by AstraZeneca. The acquisition costs for generic drugs (gemcitabine and cisplatin) were sourced from the eMIT national database (2024) (142, 143). The drug acquisition costs used in the model are presented in Table 47.

Table 47: Drug acquisition costs identified for the neoadjuvant and adjuvant treatment regimens

	Treatment	Dose per admin	Admin frequency per cycle	Unit size	Units per pack	Cost per unit (£)	Acquisition cost per Tx cycle (£)
Neoadjuvant setting							
Perioperative durvalumab arm	Durvalumab	1500 mg	1.00	500 mg	1	██████	██████
	Gemcitabine	1000mg/m ²	2.00	1000 mg	1	16.40	65.59
	Cisplatin	70 mg/m ²	1.00	10 mg	1	3.67	51.40
Control arm	Gemcitabine	1000mg/m ²	2.00	1000 mg	1	16.40	65.59
	Cisplatin	70 mg/m ²	1.00	10 mg	1	3.67	51.40

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

	Treatment	Dose per admin	Admin frequency per cycle	Unit size	Units per pack	Cost per unit (£)	Acquisition cost per Tx cycle (£)
Adjuvant setting							
Perioperative durvalumab arm	Durvalumab	1500 mg	1.00	500 mg	1	████	████

Abbreviations: Admin: administration; mg: milligram; NA: not applicable; Tx: treatment.

Source: Cost acquisition costs are sourced from BNF and eMIT (142, 143).

Administration costs were applied for all IV therapies used in the model. It was assumed that separate drugs are administered at the same time if used in combination, thus incurring a single administration cost. The cost associated with the administration of each treatment is presented in Table 48.

Table 48: Treatment administration cost inputs

Treatment	Admin frequency per cycle	Treatment cycle length (days)	Cost per admin (£)
Neoadjuvant setting			
Perioperative durvalumab	1	21	394.17
Control	1	21	394.17
Adjuvant setting			
Durvalumab	1	28	394.17

Note: Unit cost per administration is £394.17.

Abbreviations: Admin: administration; mg: milligram

Source: NHS Reference costs 2023-24 (112); TA944 (113); TA817 (11)

3.5.2 Time on-treatment

Time on treatment (ToT) data for the neoadjuvant and adjuvant components of both arms was based on the observed proportions of patients who received each scheduled cycle in each arm of the NIAGARA trial (Table 49) (71). No patient remained on neoadjuvant or adjuvant treatment in the NIAGARA trial as of DCO 29 April 2024 (71). Therefore, the observed proportions of patients who received each neoadjuvant/adjuvant treatment cycle could be used directly, without the need for extrapolation beyond the observed trial period.

In the perioperative durvalumab arm, patients could receive up to four doses of neoadjuvant durvalumab (one administration per cycle), up to four cycles of neoadjuvant gemcitabine and cisplatin (two doses of gemcitabine and one dose of cisplatin per treatment cycle), and up to eight treatment cycles of adjuvant durvalumab. The first dose of adjuvant treatment was applied to the model cycle corresponding to the scheduled administration of the first cycle of adjuvant treatment (e.g., week 24 for adjuvant durvalumab), allowing to account for the treatment-free period pre- and post-RC observed in the NIAGARA trial (Table 49). The control arm only comprised of neoadjuvant phase (71).

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Table 49: Proportion of patients receiving treatment in each cycle of the model

Setting	Treatment cycle	Week*	Percentage of patients on treatment		
			Perioperative durvalumab arm		Control arm (G+C)
			Durvalumab	G+C	
Neoadjuvant	1	0	██████	██████	██████
	2	3	██████	██████	██████
	3	6	██████	██████	██████
	4	9	██████	██████	██████
Percentage of patients receiving adjuvant treatment					
Adjuvant	1	24	██████	NA	NA
	2	28	██████	NA	NA
	3	32	██████	NA	NA
	4	36	██████	NA	NA
	5	40	██████	NA	NA
	6	44	██████	NA	NA
	7	48	██████	NA	NA
	8	52	██████	NA	NA

*Weeks count for the comparator may not correspond to cycle due to the treatment cycle length differences.

Abbreviations: G+C: gemcitabine, cisplatin; NA; not applicable.

Source: Calculated based on the number of patients completing each number of treatment cycles.

3.5.3 Health state costs and resource use

HCRU associated with disease management was incorporated in the CEM to capture costs associated with medical resource use by patients in each health state. HCRU items were defined by the NIAGARA trial schedule of assessments, the NICE TA817, and EAU and ESMO guidelines (4, 11, 31, 71). Frequency of HCRU was informed by NICE TA817 on bladder cancer treatment in the adjuvant setting and validated with UK-based clinical experts (11, 118).

Unit costs for healthcare resources associated with disease management were sourced from NHS reference costs 2023-24 and PSSRU 2022-23 service costs (112, 141). The type of resource use, percentage of patients receiving care, and unit costs for disease management costs are presented in Table 50. The same disease management costs were applied to both treatment arms.

Table 50: Health care resource use by health state

Resource items	Unit cost (£)	Frequency (per model cycle)		
		Event-free	LR	DM
Oncologist consultation	235.46	0.13	1.09	1.09
Cystoscopy (in upper tract patients only; 21.2% of the modelled cohort)	327.45	0.10	0.20	0.20
CT scans	141.52	0.28	0.31	0.26
Glomerular filtration rate	2.79	0.56	0.97	1.02
Hepatic and renal function tests	1.10	0.46	0.97	1.02
Community nurse specialist visit	102.00	0.00	0.95	1.00

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Resource items	Unit cost (£)	Frequency (per model cycle)		
		Event-free	LR	DM
GP home consultation	29.00	0.00	0.95	1.00
Dietician	62.00	0.02	0.09	0.09
Health home visitor	57.00	0.00	0.70	0.70
Urologist consultation	235.46	0.13	0.04	0.04

Abbreviations: CT: computed tomography; DM: distant metastatic disease GP: general practitioner; LR: locoregional recurrence. Source: Resource use costs are sourced from nivolumab submission NICE TA817 (11), NHS reference costs (112), and PSSRU (141).

3.5.4 Cystectomy costs

The costs associated with cystectomy were calculated based on the proportion of patients undergoing surgery in the NIAGARA trial (71). In both arms of the NIAGARA trial, most patients who had surgery underwent RC (n=469 [88.0%] for perioperative durvalumab arm and n=441 [83.2%] for control arm), with only a few patients undergoing partial cystectomy (n=1 for perioperative durvalumab arm and n=5 for control arm) (Table 51) (71). Therefore, only the proportion of patients undergoing RC were considered in the current CEM.

The unit cost of RC was sourced from NHS reference costs 2023-24 and was calculated as a weighted average of service codes associated with cystectomy with urinary diversion and reconstruction using NHS activity as weights (Table 52) (112).

Table 51: Radical cystectomy frequency

Therapy	Radical cystectomy
Perioperative durvalumab	88.00%
Control	83.20%

Abbreviations: CSR: clinical study report
Source: NIAGARA CSR (71)

Table 52: Radical cystectomy costs

Component	Description	NHS activity	Unit cost (£)
Radical cystectomy	LB39C - Cystectomy with Urinary Diversion and Reconstruction, with CC Score 3+	223	18,548.00
	LB39D - Cystectomy with Urinary Diversion and Reconstruction, with CC Score 0-2	127	16,821.00
	Total, weighted average		17,921.35

Abbreviations: CC: complications and comorbidities; NHS: National Health Service
Source: NHS reference costs 2023-2024 (112).

3.5.5 AE management

The cost associated with AEs was calculated as the sum product of the unit cost, duration, and frequency, and was applied as a one-off event at the start of the time horizon. Unit costs for AE management were sourced from the NHS reference costs 2023-24 (112). Weighted average of service codes was calculated using service activity as weights in case multiple service codes were available (Table 53) (112). No AE costs were assumed for subsequent

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

therapies as it was assumed that post-recurrence AEs would impact both arms of the model, and therefore have a minimal influence on incremental results.

Table 53: Adverse event management costs

Adverse event	Description	Unit cost (£)
Anaemia	Iron Deficiency Anaemia (SA04G- SA04L)	1,533.30
Lipase level increase	Other Endocrine Disorders, with CC Score 0-4+ (KA08A-C); Non-elective short-stay; cited in TA950	1,819.86
Neutropenia	Assumed to be the same as Anemia, as Neutropenia is a type of disorder associated with Haematology	1,533.30
Neutrophil count decrease	Assumed to be the same as Anemia, as Neutropenia is a type of disorder associated with Haematology	1,533.30
Thrombocytopenia	Thrombocytopenia, with CC Score 0-8+, SA12G - K (Currency code), cited in TA716	2,440.46
Urinary tract infection	Kidney or Urinary Tract Infections (LA04H - LA04H)	2,472.27

Abbreviations: CC: complications and comorbidities; NHS: National Health Service; TA: technology appraisal

Source: NHS reference costs 2023-24 (112)

3.5.6 Subsequent treatments

In the NIAGARA trial, the proportion of patients who had received a subsequent anticancer therapy was ██████ however, a lower proportion of patients had received at least one anticancer therapy post-study treatment discontinuation in the perioperative arm ██████ as compared to the control arm ██████ Whilst many of the subsequent treatments received are commonly used in UK clinical practice, some of the proportions received are not reflective of the UK. Therefore, in order to align with UK clinical practice, the subsequent treatments within the model were informed by the opinion of the UK-based clinical experts (118). The percentages presented in Table 54 are derived as an average across the four clinical experts interviewed. These percentages are expressed as a proportion of all progressed patients, and they encompass all subsequent treatments that patients would receive – for this reason the percentages would not be expected to total 100% because some patients may receive multiple different therapies (either in combinations, or sequentially across multiple lines of treatment) , whilst others would receive none (118).

Additionally, UK-based clinical experts agreed that immunotherapy-based regimens are an important post-progression treatment options to be considered in the management of MIBC. Clinical experts reached a consensus that:

- IO rechallenge is used in clinical practice, but it would depend on the circumstances.
- IO rechallenge would follow a period of 12 months from last dose of IO treatment; if the relapse is earlier than that period, is considered that tumour is not IO sensitive.
- IO rechallenge before 12 months is not routinely done.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

The UK-based clinical experts highlighted that the treatment landscape post MIBC progression is also evolving, and the cost of managing progression is increasing, further underscoring the need for effective treatments in earlier stages of the disease.

The total cost per subsequent treatment regimen, the usage per treatment and duration of each subsequent treatment are presented in Table 54.

Table 54: Cost inputs for subsequent treatments

Subsequent treatment	Cost per administration (£)	Cost per month (£)	Duration of treatment (months)	Subsequent treatment use (%) ^a	
				Perioperative durvalumab arm	Control arm
Atezolizumab	3,807.69	5,518.88	2.10	5.40%	13.06%
Avelumab	3,072.00	6,678.86	5.80	4.59%	17.64%
Nivolumab	2,633.00	5,724.42	7.40	0.67% ^b	1.12% ^b
Carboplatin	17.16	24.87	3.20	9.91%	12.11%
Cisplatin	48.19	52.39	5.52	11.70%	15.72%
Gemcitabine	16.40	51.49	4.75	17.15%	19.48%
Paclitaxel	34.88	50.55	1.50	6.73%	6.34%
Erdaftinib	910.71	1,319.99	4.80	5.90%	12.80%

Notes: ^a As a percentage of patients experience a non-death EFS event; ^b Off-label use

Source: Drug acquisition costs were sourced from BNF and eMIT (142, 143).

3.5.7 End-of-life (EOL) costs

The cost of EOL or terminal care was modelled as a one-off cost applied to patients that enter the death state. In line with the NICE TA817, the cost of EOL care was calculated from a study by Georghiou and Bardsley, which estimated hospital and non-hospital costs for people in the last 90 days of life in the UK (144). These costs were inflated to a 2023 cost year using the latest health inflation indices from the PSSRU (141). The EOL costs used in the model are presented in Table 55.

Table 55: End-of-life costs

Care setting	Unit cost, 2022/23 (£)
Hospital care	7,211.55
Social care	543.62
Nurse community support	719.93
GP	446.90

Abbreviations: GBP: British pound sterling; GP: general practitioner; PSS: Personal Social Services

Source: Georghiou and Bardsley (144); unit costs inflated from 2014 to 2023 GBP, using the PSS Pay & Prices Index (141).

3.6 Severity

It is not anticipated that perioperative durvalumab would qualify for a severity modifier in this indication.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

3.7 Uncertainty

The model draws heavily on clinical input parameters from the NIAGARA trial of perioperative durvalumab in MIBC. At the second interim analysis, the NIAGARA trial had met the dual primary endpoint of EFS, with perioperative durvalumab demonstrating a significant and meaningful improvement in EFS versus chemotherapy. This translated to a significant and meaningful improvement in the alpha-controlled secondary endpoint of OS (2). Additionally, results from a multidimensional secondary outcomes such as DSS and MFS underscore the certainty regarding the efficacy of perioperative durvalumab in reducing recurrence, sustaining long-term survival, and delaying progression to mBC (2). There was no evidence that durvalumab led to a reduction in the percentage of patients undergoing cystectomy. The safety profile of perioperative durvalumab with neoadjuvant chemotherapy was consistent with individual safety profiles for durvalumab and gemcitabine–cisplatin.

The CEM model was developed following a review of previous CEMs in MIBC and was constructed to meet the requirements of the NICE reference case and other international guidelines. The model uses data from the key primary and secondary endpoints of EFS, MFS and OS in NIAGARA.

Based on the strength of the clinical trial informing the economic model and the model meeting NICE reference case requirements the company believes there is no aspect of the condition or technology presented in this submission that would impact the ability to generate high-quality evidence. Furthermore, the base case and all tested scenarios yielded ICERs below £20,000/QALY, supporting the robustness of this submission.

3.8 Managed access proposal

The current submission proposes perioperative durvalumab is commissioned for routine use in patients within its expected licensed population, supported by robust clinical evidence from the NIAGARA trial and cost-effectiveness analyses demonstrating that the base case and all tested scenarios resulted in ICERs below £20,000 per QALY, underscoring the strength and reliability of this submission (71).

3.9 Summary of base-case inputs and assumptions

3.9.1 Summary of base-case analysis inputs

A summary of variables applied in the economic analysis is presented in Table 56.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Table 56: Base-case inputs

Variable	Value	Justification	Reference to section in submission
Model settings			
Perspective	Payer (NHS and PSS)	Aligned with the NICE reference case (110)	3.2
Time horizon	36 years	Lifetime horizon: denoting an age at which 99% of the cohort has reached death	
Cycle length	1 month (30.44 days)	Consistent with the average time between visits in the adjuvant and long-term follow-up phases	
Discount rate for costs	3.5%	Aligned with the NICE reference case (110)	
Discount rate for benefits			
Half cycle correction	Yes	To avoid over- or underestimating costs	
Population characteristics			
Patients' age (mean)	64.4 years	Aligned with the NIAGARA trial (71)	3.2.1
Percentage male	81.8%		
Patients' average weight (both genders)	77.1 kg		
BSA (both genders)	1.9		
GFR (mL/min)	49		
Survival inputs			
Survival curve for EFS (perioperative durvalumab arm)	Spline odds (1-knot)	Appropriate fit chosen after considering AIC/BIC scores, visual fit, plausibility of extrapolation and clinical experts' opinion.	3.3.2.1
Survival curve for MFS (perioperative durvalumab arm)	Spline hazard (1-knot)		3.3.2.2
Survival curve for OS (perioperative durvalumab arm)	Gompertz		3.3.2.3
Survival curve for EFS (control arm)	Spline normal (2-knots)		3.3.2.1
Survival curve for MFS (control arm)	Spline hazard (1-knot)		3.3.2.2
Survival curve for OS (control arm)	Log-logistic		3.3.2.3
Health state utilities			
Utility EF	0.847	Aligned with the NIAGARA trial MMRM analysis (Investigator Assessed)	3.4.6
Utility LR	████		
Utility DM	████		
AE disutility	Calculated as the sum product of the disutility, duration, and frequency of each AE	Aligned with previous appraisals and publications [NICE TA306 (135); NICE TA1036 (136); Sullivan <i>et al.</i> (2011) (137), NICE TA599 (138)]	3.4.5
RC disutility	-0.06	Informed from Rogers <i>et al.</i> (134).	

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

Variable	Value	Justification	Reference to section in submission
Drug acquisition costs			
Durvalumab		Confidential commercial access arrangement	3.5.1
Gemcitabine	£16.40	eMIT national database (2024) for generics and BNF (2025) for branded drugs (142, 143)	
Cisplatin	£3.67	eMIT national database (2024) for generics and BNF (2025) for branded drugs (142, 143)	
Drug administration costs			
Durvalumab	£394.17	NHS Schedule Costs 2021/22 (112), NICE TA817 (11), NICE TA944 (113)	3.5.1
Gemcitabine	£788.33		
Cisplatin	£394.17		
Subsequent treatment costs			
Subsequent treatment costs	Applied as a one-off cost	Applies a one-off subsequent treatment cost once a patient progresses based on treatments received in the NIAGARA trial (71).	3.5.6
One-off subsequent treatment cost (perioperative durvalumab arm)	£2,327.31	The one-off cost considers the percentage use of all subsequent therapies, the duration of therapy and the drug acquisition and administration costs. Proportions were validated with clinical experts (118).	
One-off subsequent treatment cost (control arm)	£6,867.03		
Disease monitoring costs			
EF health state	£136.53	The inputs for resource use are sourced from nivolumab submission NICE TA817 (11), and costs are sourced from NHS reference costs (112), and PSSRU (141)	3.5.3
LR health state	£549.24		
DM health state	£548.91		
RC proportion (perioperative durvalumab)	88.00%	Aligned with the NIAGARA trial (71)	3.5.4
RC proportion (control)	83.20%		
Cost of RC	£17,921.35	NHS reference costs 2023-24 (LB39C, LB39D) (112).	
AE management costs			
AE costs	Calculated as the sum product of the unit cost, duration, and frequency, and applied as a one-off event	The frequency of AE events is sourced from the NIAGARA trial (71); costs are sourced from NHS reference costs 2023-24 (112)	3.5.5
End of life costs			
EOL cost	Included. Modelled as a one-off cost applied to patients that enter the death state	Georghiou and Bardsley (144); unit costs inflated from 2014 to 2023 GBP, using the PSS Pay & Prices Index (141)	3.5.7

Abbreviations: AE: Adverse Event; AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; BNF: British National Formulary; BSA: Body Surface Area; DM: Distant Metastasis; EFS: Event-Free Survival; EF: Event-Free; eMIT: electronic market information tool; EOL: End of Life; GBP: Great British Pound; GFR: Glomerular Filtration Rate; LR: Locoregional Recurrence; MMRM: Mixed Model for Repeated Measures; MFS: Metastasis-Free Survival; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: Overall Survival; PSS: Personal Social Services; PSSRU: Personal Social Services Research Unit; RC: Radical Cystectomy; TA: Technology Appraisal.

Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

3.9.2 Assumptions

A summary of modelling assumptions, divided by category, used in the CEM is provided in Table 57.

Table 57: List of assumptions for the base-case cost effectiveness analysis

Category	Assumption	Justification
Choice of comparators	Neoadjuvant chemotherapy (combination of gemcitabine and cisplatin)	- The control arm of NIAGARA represents the standard of care treatment at the time of study design. - The UK-based clinical experts validated that the comparator included in the current appraisal is reflective of the UK clinical practice (14). - A comparison to NAC and RC followed by no treatment or adjuvant nivolumab (in PD-L1 $\geq 1\%$ high-risk patients) was included as an exploratory analysis
Model structure	PSM	PSM is a well-established methodology for predicting the lifetime cost effectiveness of oncology interventions. It can accurately predict within-trial EFS, MFS ad OS and facilitates the modelling of trial outcomes directly into the model.
Post-recurrence health state split	The model comprises of four health states where the post-EFS period is split into LR and DM MIBC	- Separating the recurrence state into two states of LR and DM addresses past concerns regarding the limited modelling of post-recurrence survival, and the lack of differentiation in distant versus local recurrence. - The analysis of EQ-5D-5L HSUs in both the CheckMate-274 (US value set) and NIAGARA (UK value set) trials support the differentiation of LR and DM given observed differences in mean HSU between states.
Time horizon	Lifetime	A lifetime time horizon of 36 years reflects the age at which 99% of the cohort reached death.
Curative effect of therapy	Curative effect is not captured explicitly in the model. Survival extrapolation models of clinical outcomes were selected such that the hazards of disease recurrence and pre-recurrence death diminishes progressively after five years.	This approach was supported by clinical expert opinion that suggest patients with MIBC who remain event/disease-free for five years are deemed functionally cured and subsequently discharged from their care (118).
Treatment waning	No treatment waning effect is assumed in the model	As the follow-up of NIAGARA trial extends for several years beyond the completion of treatment (~12 months), it is expected that any waning effects are reflected in the long-term survival data and captured by the modelled survival curves.
HSU	HSUs are treatment-independent and vary by disease state only	- The analysis of EQ-5D-5L HSU in NIAGARA suggests that HRQoL is more closely aligned to disease state than treatment arm. - There was no significant difference in HSU across arms of the comparison, and no clear rationale to support differences in HSU by state and treatment arm

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Category	Assumption	Justification
HRQoL impact of cystectomy and treatment-related AEs	One-off QALY adjustments for cystectomy and treatment-related AEs	Both cystectomy and treatment-related AEs are expected to have a temporary impact on HRQoL in the early phases of treatment, which is best captured by a single one-off QALY adjustment at the start of the time horizon.
AEs costs	AEs related to subsequent treatment lines are excluded	The costs of AEs related to subsequent treatment lines are likely to be negligible and/or similar across arms, and hence not determine a material impact on the incremental cost effectiveness ratio.
Subsequent treatment costs	Subsequent treatment costs are accounted for all second line plus treatments that the patients may receive in the UK	The proportion of patients receiving subsequent therapies include all second line plus treatments and the percentages would not be expected to total 100% because some patients would receive multiple different therapies (either in combinations, or sequentially across multiple lines of treatment).
EOL costs	EOL costs assumed to represent palliative care received by patients shortly prior to death	As per TA817, patients experience higher medical costs shortly prior death (11).

Abbreviations: AE, adverse events; CEM: cost effectiveness model; DM: distant metastasis; EFS: event-free survival; EQ-5D-5L: EuroQol 5-Dimension 5-Level; EOL: end of life; HRQoL: health-related quality of life; HSU: health state utility; LR: locoregional recurrence; MIBC: muscle-invasive bladder cancer; MFS: metastasis-free survival; OS: overall survival; PSM: Partitioned survival model; QALY: quality-adjusted life years; TA: technology appraisal; UK: United Kingdom; US: United States.

3.10 Base-case results

3.10.1 Base-case incremental cost effectiveness analysis results

Results from the base-case analysis show that perioperative durvalumab is associated with higher LYs (█████ versus 8.32) and QALYs (█████ versus 6.56) as compared to the current SoC. This translated into an additional █████ LYs and █████ QALYs for perioperative durvalumab versus SoC. Total costs in the base-case analysis were higher with perioperative durvalumab versus SoC (█████ versus £51,704) with an incremental cost of █████.

The incremental results for cost and health effects indicate that, at the current patient access scheme (PAS) price, durvalumab was associated with an ICER of £14,048, demonstrating to be cost-effective at a willingness to pay (WTP) of £20,000/QALY threshold (110).

The deterministic base-case results of the pairwise comparison between perioperative durvalumab and SoC are presented in Table 58.

Table 58: Pairwise incremental cost effectiveness results – Base case (deterministic)

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	█████	51,704	█████
Total LYs	█████	8.32	█████
Total QALYs	█████	6.56	█████

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	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
ICER (£ per QALY)	-	-	14,048

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

The clinical outcomes and disaggregated results from the model are presented in Appendix H.

3.11 Exploring uncertainty

3.11.1 Probabilistic sensitivity analysis (PSA)

A PSA was conducted using a Monte Carlo simulation of 1,000 iterations. Table 59 presents the probabilistic incremental cost effectiveness results for perioperative durvalumab versus SoC. The results of the probabilistic analysis are consistent with the results of the deterministic base case analysis, showing that perioperative durvalumab is more effective and more costly than the current SoC, with an ICER of £14,081, demonstrating to be cost-effective at a WTP of £20,000/QALY threshold (110).

Table 59: Pairwise incremental cost effectiveness results – Base case (probabilistic)

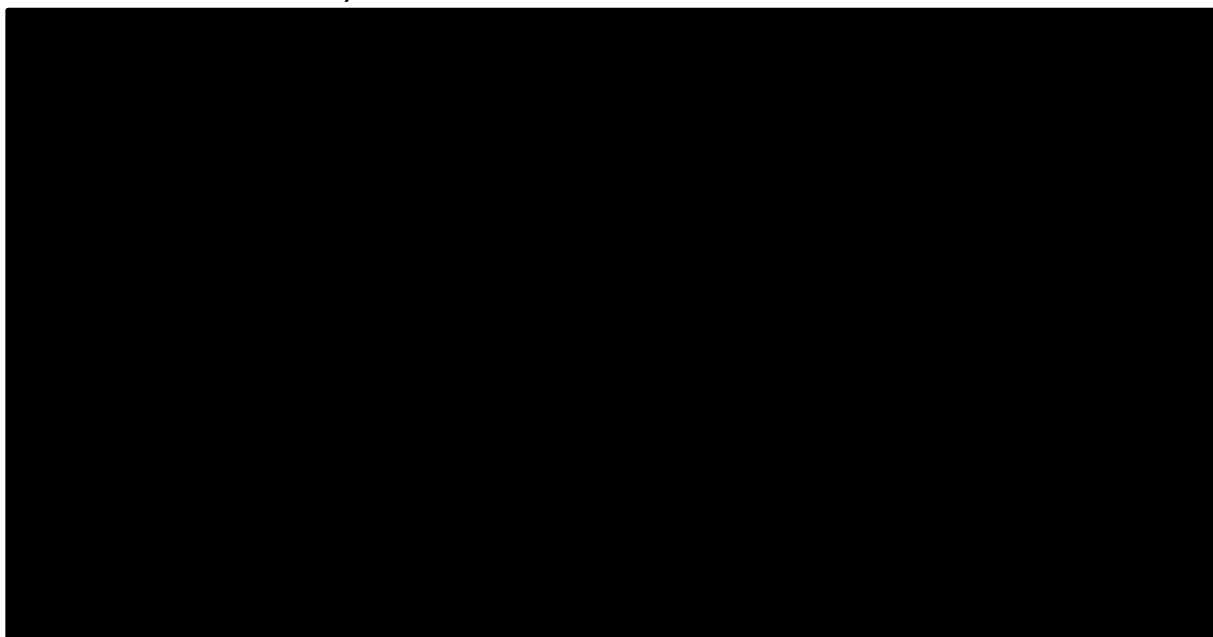
	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	■	50,909	■
Total LYs	■	8.32	■
Total QALYs	■	6.57	■
ICER (£ per QALY)	I	-	£14,081

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

A visual representation of the PSA results comparing perioperative durvalumab versus SoC is provided in the cost effectiveness plane (Figure 34). Each dot resembles one Monte Carlo simulation where the input parameters are sampled from the distributions in a total of 1,000 iterations. Figure 34 shows that all points lie in the north-east quadrant signifying that perioperative durvalumab provides higher QALYs than SoC at incremental cost.

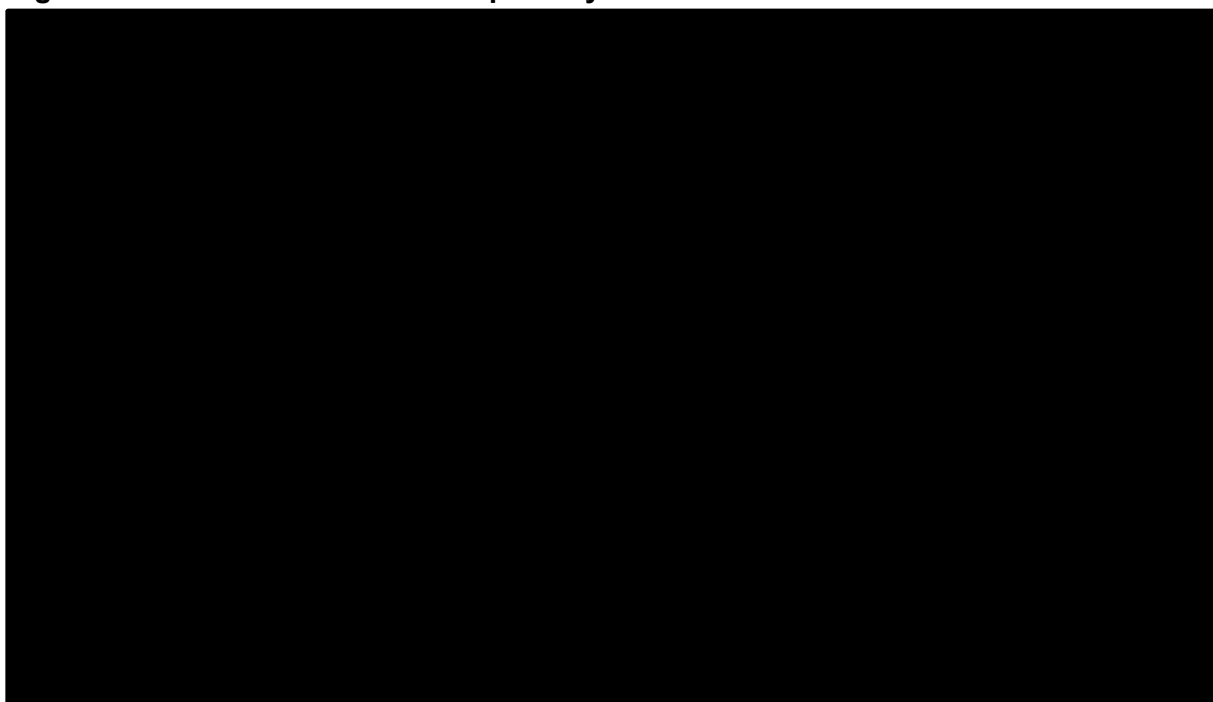
The cost effectiveness acceptability curve (Figure 35) for perioperative durvalumab versus SoC shows that the probability of perioperative durvalumab being cost effective at a WTP threshold of £20,000/QALY and £30,000/QALY is 96.4% and 100.0%, respectively.

Figure 34: Cost effectiveness plane (Incremental costs and QALYs perioperative durvalumab versus SoC) – base-case



Abbreviations: Cis: cisplatin; Durva: durvalumab; Gem: gemcitabine, QALY: quality-adjusted life years; SoC: standard of care.

Figure 35: Cost effectiveness acceptability curve – base-case



Abbreviations: Cis: cisplatin; Durva: durvalumab; Gem: gemcitabine.

All plausible ICERs are below NICE WTP threshold (110).

3.11.2 Deterministic sensitivity analysis

A deterministic one-way sensitivity analysis (OWSA) was conducted by varying key input parameters (e.g., management resource use and costs, utility inputs etc.) one at a time while the other parameters were kept at base case values. As the base case ICERs for perioperative durvalumab versus SoC were in the north-east quadrant (positive incremental costs and QALYs), ICER was considered to be an appropriate outcome measure to present OWSA results.

The top ten most influential parameters based on their impact on the ICER are presented below in tabulated format and tornado diagram for perioperative durvalumab versus SoC (Table 60, Figure 36).

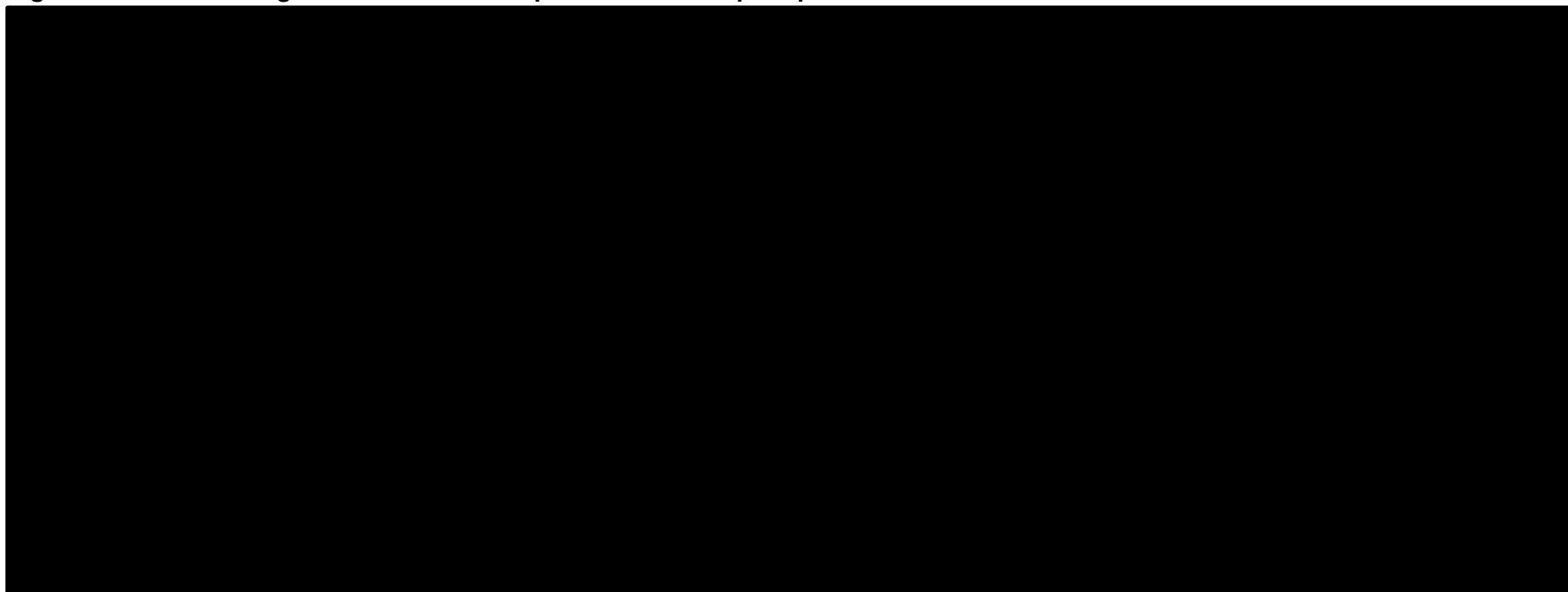
In the comparison between perioperative durvalumab versus SoC, results were most sensitive to the percentage of patients undergoing RC in the perioperative durvalumab arm, the percentage of patients undergoing RC in the control arm (SoC) and the discount rate used for QALYs.

Table 60: Top ten parameters based on the impact on ICER for perioperative durvalumab versus SoC

Parameter	Inputs			ICER (£ per QALY)		
	Base case value	Low	High	Low	High	Absolute difference
Percentage of patients undergoing RC in perioperative durvalumab arm (%)	████	████	████	11,840	15,166	3,326.78
Percentage of patients undergoing RC in control arm (SoC) (%)	████	████	████	15,992	12,768	3,224.60
Discount rate used for QALYs (%)	████	████	████	13,001	15,258	2,257.15
Proportion of patients receiving subsequent treatments in control arm (SoC) (%)	████	████	████	14,629	13,477	1,151.96
Percentage of PD patients receiving nivolumab in control arm (SoC) (%)	████	████	████	14,384	13,686	698.36
Duration of treatment with nivolumab (months)	████	████	████	14,329	13,768	560.92
Discount rate used for costs (%)	████	████	████	14,261	13,847	414.13
Proportion of patients receiving subsequent treatments in perioperative durvalumab arm (%)	████	████	████	13,875	14,224	348.84
EFS utility	████	████	████	14,227	13,879	348.69
Frequency of oncologist consultation per month for locoregional health state	████	████	████	14,209	13,888	320.30

Abbreviations: ICER: incremental cost effectiveness ratio; QALY: quality-adjusted life years; RC: radical cystectomy; PD: progressed disease; SoC: standard of care

Figure 36: Tornado diagram based on the impact on ICER for perioperative durvalumab vs. G+C



Abbreviations: D+G+C: durvalumab, gemcitabine, cisplatin; DR: Distant recurrence; EF: event free; G+C: gemcitabine, cisplatin; ICER: incremental cost effectiveness ratio; ICUR: incremental cost-utility ratio; LR: Locoregional recurrence; LY: life years; PD: Progressed disease; QALY: quality-adjusted life years; RC: radical cystectomy; RD: recurrent disease or failed/refused surgery.

3.11.3 Scenario analysis

Alternate scenarios were tested as part of the sensitivity analysis to test the uncertainty around certain key assumptions used in the base-case of the CEM that were expected to be influential on the modelled outcomes. Table 61 presents the scenario analyses conducted for the current appraisal.

Table 61: List of scenario analyses

#	Scenario	Base case input	Scenario analysis input	Rationale
1	EFS curve selection for perioperative durvalumab arm	Spline odds (1-knot)	Spline odds (2-knots)	Explore impact of using alternative extrapolations deemed to produce plausible long-term extrapolations by clinical experts.
2	EFS curve selection for control arm	Spline normal (2-knots)	Spline hazard (2-knots)	
3	MFS curve selection for perioperative durvalumab arm	Spline hazard (1-knot)	Spline normal (3-knots)	
4	MFS curve selection for control arm	Spline hazard (1-knot)	Spline normal (2-knots)	
5	OS curve selection for perioperative durvalumab arm	Gompertz	Log-normal	
6	OS curve selection for control arm	Log-logistic	Log-normal	
7	OS curve selection for control arm	Log-logistic	Gompertz	
8	Larger decrement for RC disutility	0.06	0.08	The disutility value for surgery (0.06) considered for the base-case resulted in a QALY loss of 0.03. This scenario explores impact of assuming a larger QALY loss for surgery
9	IO use in subsequent treatment in the perioperative and control arms not included*	Included	Excluded	Exploring the impact of excluding IO rechallenge

Note: *In this scenario, the percentage of patients receiving subsequent therapy was proportionally distributed to non-IO therapies.

Abbreviations: EF: Event-free; EFS: Event-free survival; ICER: incremental cost effectiveness ratio; IO: Immuno-oncology; MFS: metastasis-free survival; OS: overall survival; RC: Radical cystectomy; QALY: quality-adjusted life year.

Table 62 presents the results of the scenario analyses and show how the use of alternative model assumptions and input values impact model outcomes.

Table 62: Scenario analyses results

#	Scenario	Input	Incremental costs	Incremental QALYs	ICER Perioperative durvalumab versus control (£/QALY)	Change from base case ICER (%)
Base case (deterministic)			████████	████	£14,048.47	█
1	EFS curve selection for perioperative durvalumab arm	Spline odds (2-knots)	████████	████	£14,054.25	████
2	EFS curve selection for control arm	Spline hazard (2-knots)	████████	████	£13,510.07	████
3	MFS curve selection for perioperative durvalumab arm	Spline normal (3-knots)	████████	████	£14,050.46	████
4	MFS curve selection for control arm	Spline normal (2-knots)	████████	████	£14,063.99	████
5	OS curve selection for perioperative durvalumab arm	Log-normal	████████	████	£15,564.07	████
6	OS curve selection for control arm	Log-normal	████████	████	£14,648.51	████
7	OS curve selection for control arm	Gompertz	████████	████	£18,794.43	████
8	Larger decrement for RC disutility	Increased in disutility from 0.06 to 0.08	████████	████	£14,052.19	████
9	IO use in subsequent treatment in the perioperative and control arms not included*	Included	████████	████	£13,583.21	████

Note: *In this scenario, the percentage of patients receiving subsequent therapy was proportionally distributed to non-IO therapies.

Abbreviations: EF: Event-free; EFS: Event-free survival; ICER: incremental cost effectiveness ratio; IO: Immuno-oncology; MFS: metastasis-free survival; OS: overall survival; RC: Radical cystectomy; QALY: quality-adjusted life year.

The estimated pairwise ICERs for perioperative durvalumab versus SoC, ranged from £13,510 (when EFS curve selection was set to spline hazard (2-knots) for the control arm [SoC]) to £18,794 (when OS curve selection was set to Gompertz for the control arm). Overall, in all the explored scenario analyses, the ICER for perioperative durvalumab versus SoC remained cost effective at a WTP threshold below £20,000/QALY.

3.11.3.1 Additional scenario analysis

An additional scenario comparing perioperative durvalumab to NAC and RC followed by no treatment or adjuvant nivolumab in PD-L1 $\geq 1\%$ high-risk patients ('G+C+N'), was conducted in response to the final scope issued by NICE (13). The inputs for G+C+N used in the analysis are presented in detail in Appendix K. The deterministic results show that perioperative durvalumab is associated with higher LYs (■■■■ versus ■■■■) and QALYs (■■■■ versus ■■■■) as compared to G+C+N. This translated into an additional ■■■■ LYs and ■■■■ QALYs for perioperative durvalumab versus G+C+N. Total costs associated with perioperative durvalumab were higher than G+C+N (■■■■■ versus ■■■■■) with an incremental cost of ■■■■■ and an ICER of £13,723 (demonstrating to be cost-effective at a WTP of £20,000/QALY threshold (110).

The total and incremental cost effectiveness results of the pairwise comparison between perioperative durvalumab and G+C+N are presented in Table 63.

A visual representation of the cost effectiveness plane and cost effectiveness acceptability curve comparing perioperative durvalumab versus adjuvant nivolumab is provided in Figure 37 and Figure 38, respectively. Figure 37 shows that most points lie in the north-east quadrant, thereby confirming that perioperative durvalumab treatment results in higher QALYs than G+C+N at incremental cost. Figure 38 shows that the probability of perioperative durvalumab being cost effective versus G+C+N at a WTP threshold of £20,000/QALY and £30,000/QALY is 96.4% and 100.0% respectively.

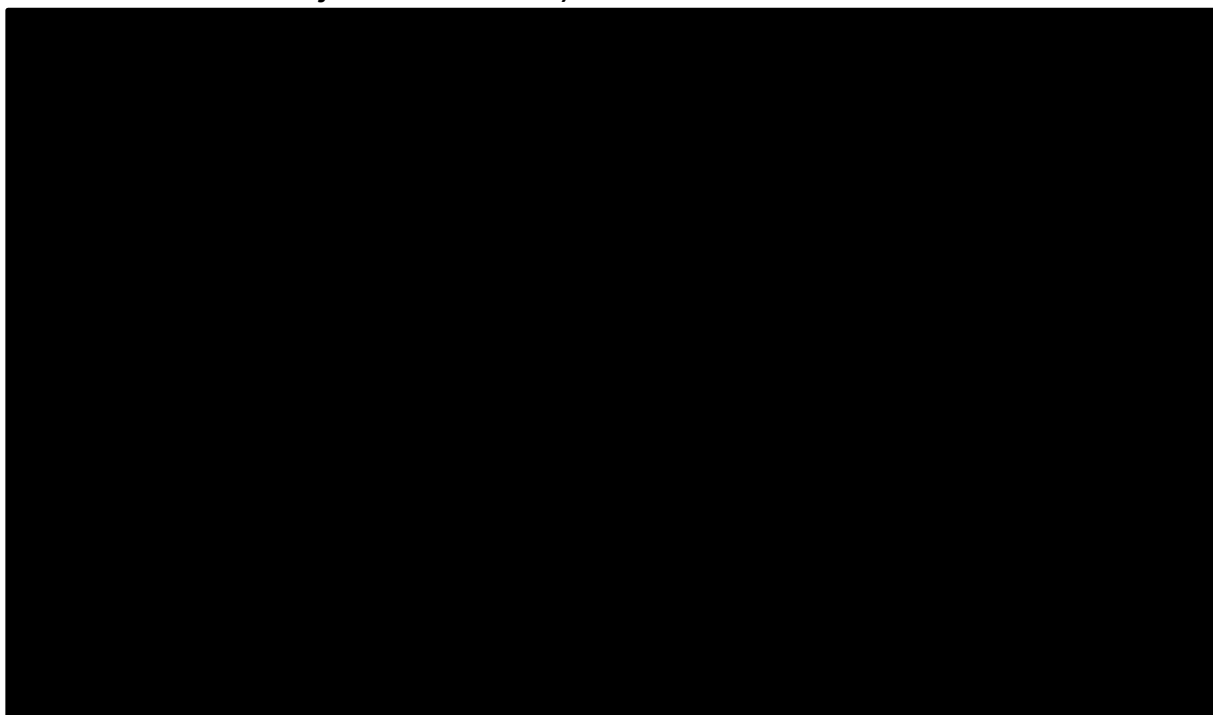
Table 63: Pairwise incremental cost effectiveness results – scenario analysis (deterministic)

	Perioperative durvalumab	G+C+N	Incremental
Total costs (£)	■■■■■	■■■■■	■■■■■
Total LYs	■■■■	■■■■	■■■■
Total QALYs	■■■■	■■■■	■■■■
ICER (£ per QALY)	-	-	13,723

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LY, life years; N: nivolumab; QALYs, quality-adjusted life years.

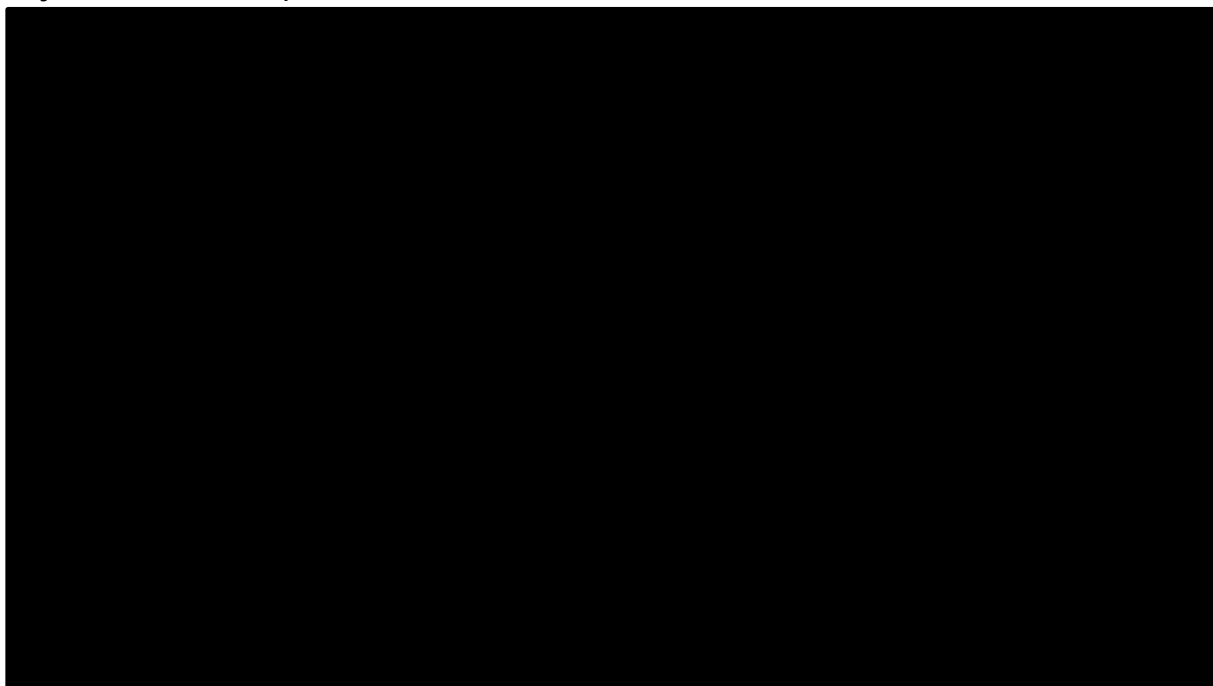
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Figure 37: Cost effectiveness plane (Incremental costs and QALYs perioperative durvalumab versus adjuvant nivolumab)



Abbreviations: Cis: cisplatin; Durva: durvalumab; Gem: gemcitabine; QALY: quality-adjusted life years; vs: versus; Inc: incremental

Figure 38: Cost effectiveness acceptability curve (perioperative durvalumab versus adjuvant nivolumab)



Abbreviations: Cis: cisplatin; Durva: durvalumab; Gem: gemcitabine.

3.12 Subgroup analysis

No further exploration of subgroups was considered other than the analysis presented in section 3.11.3.1.

3.13 Benefits not captured in the QALY calculation

Perioperative durvalumab is the first clinical practice-changing perioperative IO regimen to be approved in MIBC based on the substantial improvements in the clinical outcomes demonstrated in the NIAGARA trial (71).

Although economic model captures benefits related to the quality of life of patients over a lifetime, as well as increments in the survival years, patient-reported outcomes are often overlooked (145).

The company emphasises the importance of NICE considering benefits beyond those measured by the QALY calculation in the assessment of perioperative durvalumab. These additional benefits have a significant impact on both patients and their support networks. Taking them into account will provide a more comprehensive evaluation, supporting practitioners and commissioners in ensuring the best possible care for patients, while also capturing the patient perspective.

In the case of the perioperative durvalumab regimen in MIBC, such patient-centred benefits not captured by QALY calculations include:

- **Value of hope associated with new treatment achieving early and sustained survival benefit:** perioperative durvalumab offers patients a treatment option that reduces risk of recurrence, metastasis and, death due to bladder cancer, in a patient population who undergo highly impactful surgery and neoadjuvant chemotherapy treatment with uncertain outcomes regarding the likelihood of reducing the risk of recurrence. The certainty of the survival benefit elicited by perioperative durvalumab in what represents the last opportunity for cure in BC enhances patients' and their families' ability to cope with difficult circumstances, promoting an emotional state that indirectly contributes to positive emotional outcomes and should also be considered (71).

As detailed in Section 1, the currently available IO options in the treatment landscape for cis-eligible resectable MIBC cannot be used in the neoadjuvant setting, preventing patients from the benefits of priming anti-tumour immunity before radical cystectomy. Furthermore, the use of these therapies as adjuvant treatments is limited to patients at high-risk of recurrence after RC and with PD-L1 positive tumours, significantly limiting

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the number of patients who can benefit from the sustained immunosurveillance that eliminates micro-metastatic disease after surgery.

- **Option Value:** Patients also face uncertainty about when and how future advances in medicine will occur, making life extension a valuable outcome that allows patients to potentially benefit from these unpredictable future advancements. This concept of a “real option value” arises when a life-extending health technology creates opportunities for patients to reap benefits from future medical progress. (146). This benefit is especially significant in therapeutic areas such as bladder and advanced or metastatic urothelial cancer, where promising novel agents are in development, aiming to change the treatment paradigm in the coming years (146).
- **Early treatment planning:** Perioperative regimens are established right after diagnosis, allowing patients and caregivers the opportunity to plan in advance and make necessary adjustments to their daily lives (71). In addition to the clarity provided regarding upcoming steps, this approach reduces the emotional impact of undergoing additional tests and receiving pessimistic news of the need for adjuvant treatments post-surgery. This change in the patient journey will also be perceived as an improvement in the quality of care by healthcare professionals, as discussed below.
- **Informal care and impact on caregivers and family members:** It is estimated that approximately 18.64% of the total health cost of bladder cancer in the UK is due to informal care, the cost of unpaid care, i.e., the time (work and/or leisure) that caregivers forgo to care for relatives with cancer (147). Utilising innovative treatments that have proven to enhance the efficacy of the standard of care in MIBC, could alleviate some of this strain, enabling caregivers to resume their professional lives and societal contributions.
- **Society benefits:** health benefits for the patients may be translated to society benefits, if a patient’s health is improved enough for them to return to work or their daily life. Considering the median age at the diagnosis, most of MIBC patients are retirees, with daily activities that include volunteering, pursuing hobbies, continuing education, mentoring, and engaging in physical and creative activities. Measuring the impact of these activities often involves assessing personal satisfaction, social connections, and the development of new skills or knowledge, which has a broader benefit to society.
- **Personal Social Services (PSS) perspective:** a regimen like perioperative durvalumab, which has been shown to decrease the risk of recurrence and therefore avoid progressing to mBC, consequently improving the patient's quality of life and

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fostering autonomy, could result in reduced long-term care costs from a PSS perspective (71). By preserving higher levels of functionality and independence, effective treatments provide significant advantages for the overall well-being of the patients and economic burden on the payers.

- **Address inequalities:** As mentioned in Section 1.4 there are persistent outcome gaps among different populations with BC, especially women and people with a lower socioeconomic status: Equitable access to perioperative durvalumab is essential to improving outcomes and addressing these entrenched inequalities. Disparities are driven by systemic factors such as implicit bias, unequal access to specialised care, and socioeconomic barriers that increase risk factors and delay diagnosis and treatment. Beyond being a clinical imperative, it is a societal necessity to improve access to perioperative approaches, as it offers the chance to close gaps and deliver better outcomes for all populations affected by MIBC.

The above-mentioned benefits positively impact patients and caregivers and translate into improved quality of care from the perspective of the healthcare professional.

The reduction in relapse and progression, along with improved overall survival, may lead to cost savings by decreasing the need for advanced treatments, hospitalisations, and palliative care associated with mBC. Early treatment planning benefits both healthcare professionals and the system by enabling efficient scheduling, clearer communication, and reducing the need for repeated visits and tests related to adjuvant treatment decisions (e.g., PD-L1).

The most compelling added value of perioperative durvalumab—though not fully captured in QALY metrics—is its ability to address a critical unmet need in MIBC, offering what may be the last opportunity for cure before disease progression to metastatic BC.

3.14 Validation

3.14.1 Model technical quality control

The CEM was subject to extensive review and quality control prior to finalisation. This included the verification of calculations by a modeler from the HTA and Modelling Science team at AstraZeneca who was not involved in the original model development. The internal review identified minor issues that were addressed in the model, including cell errors, minor miscalculations, and incorrect referencing. Post the initial quality control, the CEM was also validated using the technical verification (TECH-VER) checklist (148).

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3.14.2 External validation of cost effectiveness analysis

The company conducted external validation interviews with a panel of clinical and economic experts to gather insights on post-progression management, survival extrapolation analyses, utility values, and healthcare resource use that inform the cost effectiveness model. The opinions of experts on survival extrapolation analyses, utility, healthcare resource use values and post-progression management are presented in the respective sections (section 3.3, 3.4 and 3.5, respectively). An additional topic of discussion and experts' insights not covered under sections presented above is detailed below.

Assumption of cure

Within NHS clinical practice, it is common for patients to be discharged from specialist follow-up after a period of five years, at which point they are often considered to be in remission or effectively cured. However, there is variation in clinical opinion and practice (118). Some clinical experts choose to extend follow-up to ten years, particularly in cases where the risk of late relapse is perceived to be higher (118). In instances where a patient experiences a relapse beyond ten years post-treatment, this is frequently managed as a new primary presentation rather than a continuation of the original disease episode (118). Therefore, the explicit assumption of cure was not applied in the current analysis to avoid introducing uncertainty, ensuring consistency with clinical practice and minimising speculative bias in long-term projections.

3.15 Interpretation and conclusions of economic evidence

Overview of the cost effectiveness analysis: A *de novo* economic model was developed to evaluate the cost effectiveness of perioperative durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment prior to RC, followed by durvalumab monotherapy as adjuvant treatment for adult patients with MIBC. The economic model comprehensively considered relevant costs, resources, and outcomes from a NHS and PSS perspective, in line with the NICE reference case (110). The design is straightforward, aligning with the NIAGARA trial, disease progression in clinical practice and leveraging model structure in terms of post-recurrence survival states and modelling approaches utilised in other neoadjuvant, adjuvant and perioperative oncology assessments reviewed by NICE (11, 71, 99, 100).

The deterministic base-case analysis showed that treatment with perioperative durvalumab results in increased LYs (■■■■) and QALYs (■■■■) as compared to the current SoC at an ICER of £14,048, demonstrating to be cost-effective at a WTP of £20,000/QALY threshold. The results of the deterministic sensitivity analyses demonstrate that the percentage of patients

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undergoing RC in the perioperative durvalumab arm is the most influential determinant of the ICER. Since this parameter is considered reflective of UK routine clinical practice, based on expert clinical opinion regarding the generalisability of data from the NIAGARA trial, the overall results from the analysis are also considered representative of the UK practice (14).

Overall, the results of sensitivity and scenario analyses support the cost effectiveness of perioperative durvalumab, in the indication under consideration, with all plausible ICERs substantially below the WTP of £20,000/QALY.

Strengths of the current analysis: Key strengths of the presented analysis include:

- The cost effectiveness analysis of perioperative durvalumab is presented against neoadjuvant cisplatin-based chemotherapy — the direct comparator in the NIAGARA trial — which reflects the current SoC treatment option recommended in clinical guidelines in this setting (4, 31), and has been validated by the UK-based clinical experts as representative of the UK clinical practice (14).
- The CEM uses standard and flexible parametric survival models to accurately predict the within-trial EFS, MFS and OS curves of the NIAGARA trial. The availability of at least five years of follow-up data in the NIAGARA trial for EFS and OS provided certainty with the extrapolations (71). Flexible parametric models (i.e., Royston-Parmar models) were used to capture the time-varying and non-monotonic hazard functions observed in the NIAGARA trial data (71). This modelling approach resulted in a hazard trajectory for disease recurrence that progressively diminished after year five and approached, but did not reach, zero over the longer term. These extrapolations aligned with clinical expert opinion that patients with MIBC who remain event- or disease-free for at least five years are typically considered functionally cured and are discharged from routine follow-up. Clinical experts acknowledged a small but non-zero risk of events beyond this point, which supports the continued use of a diminishing hazard rather than imposing a structural cure point (118).
- The four-state structure in the CEM overcomes a number of criticisms from past appraisals in terms of the limited modelling of post-recurrence survival and the lack of differentiation for LR and DM states (97, 98).
- The current analysis uses the most appropriate modelling approach (PSM) given the mature OS data available from the NIAGARA trial, in line with Teitsson *et al.* (10).
- The availability of at least five years of follow-up data in the NIAGARA trial for EFS and OS eliminated the need to apply a structural cure assumption (71). Instead, flexible parametric models (i.e., Royston-Parmar models) were used to capture the time-Company evidence submission for durvalumab as neoadjuvant (with gemcitabine and cisplatin) and adjuvant (as monotherapy) treatment for MIBC [ID6168]

varying and non-monotonic hazard functions observed in the NIAGARA trial data (71). This modelling approach resulted in a hazard trajectory for disease recurrence that progressively diminished after year five and approached, but did not reach, zero over the longer term. These extrapolations aligned with clinical expert opinion that patients with MIBC who remain event- or disease-free for at least five years are typically considered functionally cured and are discharged from routine follow-up. Clinical experts acknowledged a small but non-zero risk of events beyond this point, which supports the continued use of a diminishing hazard rather than imposing a structural cure point (118). The use of flexible models to account for cure without imposing a structural assumption was also viewed as a methodological strength by health economic experts in the advisory board, particularly when compared to previous adjuvant nivolumab appraisal, where a fixed 5-year cure point had to be imposed due to immature trial data — an approach the appraisal committee previously identified as a limitation (11).

- HSU were obtained from the NIAGARA trial and validated against external data from the CheckMate-274 trial and an unpublished analysis of the ProBCI registry (59, 130).
- For parameters not informed by the NIAGARA trial, data from prior NICE TAs were used (e.g., HCRU associated with disease management based on TA817) ensuring alignment with evidence previously accepted by NICE and an accurate representation of the UK treatment pathway (11).
- Rigorous testing of uncertainties was performed using sensitivity analyses and various scenarios to affirm conclusions about the cost effectiveness of perioperative durvalumab in MIBC.
- The model structure and approach were validated by clinical and economic experts.
- As adjuvant nivolumab and perioperative durvalumab occupy distinct points in the treatment pathway and target different populations, the relevance of nivolumab as a comparator for cost effectiveness decision-making in a perioperative setting is uncertain. However, in response to the final scope issued by NICE, an additional scenario comparing perioperative durvalumab to NAC and RC followed by no treatment or adjuvant nivolumab in PD-L1 $\geq 1\%$ high-risk patients was provided (13).

Limitations of the current analysis: Limitations of the analysis presented include:

- The NIAGARA trial was started before routine availability of adjuvant nivolumab. Standard ITC methods were deemed unsuitable, prompting the use of a survival time-

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adjusted ITC approach to address methodological challenges and better inform decision-making. While the ITC was performed using the best available evidence, the resulting comparison is subject to uncertainty due to the difference in the populations intended to receive both treatments.

- The frequency of HCRU during the neoadjuvant phase was assumed to be the same as that in the adjuvant phase, based on TA817, and was considered equal across all comparators due to lack of evidence (11). However, as neoadjuvant therapy costs are expected to be broadly similar between comparators and the duration of neoadjuvant treatment is relatively short, this limitation is unlikely to significantly affect modelled outcomes.
- Although validated by clinical experts, the HSUs for LR and DM in the NIAGARA trial were based on a relatively small number of observations collected after recurrence (118).

The observed clinically meaningful improvement in EFS and OS with the perioperative durvalumab regimen versus the current SoC translated into extended survival, increased opportunity for restrict disease recurrence/progression in patients at an early stage of the MIBC treatment pathway, addressing a significant unmet medical need (71). Consequently, perioperative durvalumab has been demonstrated to represent a highly cost-effective treatment option at the £20,000/QALY threshold across a range of scenarios and sensitivity analysis.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

**Durvalumab with gemcitabine and cisplatin
before surgery (neoadjuvant) then alone after
surgery (adjuvant) for treating muscle-invasive
bladder cancer [ID6168]**

Summary of Information for Patients (SIP)

June 2025

File name	Version	Contains confidential information	Date
ID6168_Durvalumab MIBC_SIP	1.0	No	25th June 2025

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the [Health Technology Assessment International – Patient & Citizens Involvement Group](#) (HTAi PCIG). Information about the development is available in an open-access [IJTAHC journal article](#).

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: Durvalumab (1).

Brand name: Imfinzi® (1).

1b) Population this treatment will be used by

Please outline the main patient population that is being appraised by NICE:

The appraisal focuses on durvalumab for adults which are cisplatin-eligible with muscle-invasive bladder cancer (MIBC) whose tumours can be surgically removed (hereafter referred to as resectable MIBC). Durvalumab is administered in combination with chemotherapy (gemcitabine and cisplatin) before surgery (radical cystectomy) and alone after surgery.

1c) Authorisation

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The Medicines and Healthcare Products Regulatory Agency (MHRA) and the European Medicines Agency (EMA) are government regulatory agencies responsible for approval of medicines in the United Kingdom (UK) and the European Union (EU) respectively. The marketing authorisation for durvalumab by MHRA is currently pending. An application for UK MHRA marketing authorisation for perioperative durvalumab in adults with cis-eligible resectable MIBC has been submitted and is expected to be approved before November 2025.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

1d) Disclosures

Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

The company declares no conflict of interest.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

What is resectable MIBC?

Bladder cancer (BC) is the most common cancer of the urinary system and starts from the cells lining the urinary tract (2). The most common type of bladder cancer is called urothelial carcinoma, which makes up over 90% of all cases (3, 4). Urothelial carcinoma can be divided into three types based on how deeply the cancer spreads into the muscle layers of bladder wall (5-7): Non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC) and metastatic disease

MIBC: Cancer spreads deep into the thick muscle layers of the bladder. MIBC tumours grow fast, and about half of the patients treated with the intent to cure eventually have cancer coming back and with cancer spreading to other parts of the body (5, 8).

MIBC cases have a higher likelihood of spreading to lymph nodes and other organs. MIBC represents the final stage at which curative treatment remains a viable option for patients, with the primary goal of preventing progression to advanced or mBC involving distant organs and tissues. (5, 6).

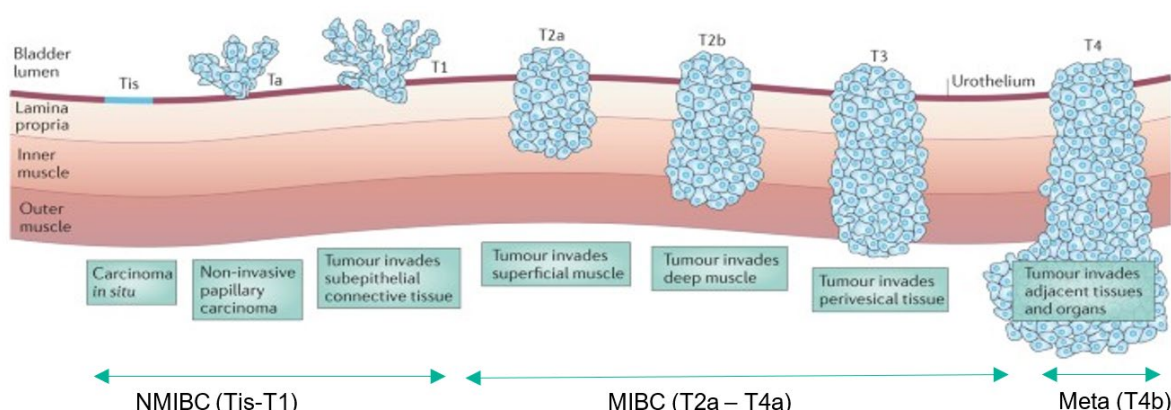
A key symptom of bladder cancer is blood in the urine, which can either be visible to the naked eye or only detected under a microscope (9, 10). Many patients with MIBC also experience urinary issues frequent urination, a sudden urge to urinate, or pain while urinating (9). Some people may not show any symptoms and might only find out they have bladder cancer through imaging tests, or a procedure called cystoscopy.

This is the focus of the submission.

The disease course of bladder cancer and the invasion of the muscle layers are presented in Figure 1.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Figure 1. Disease course of bladder cancer



Abbreviations: BC: bladder cancer; NMIBC: non-muscle-invasive bladder cancer; MIBC: muscle-invasive bladder cancer; Meta: Metastatic bladder cancer; Tis: Carcinoma in situ; Ta: Non-invasive papillary carcinoma; T1: Tumour invades subepithelial connective tissue; T2: Tumour invades muscle; T2a: Tumour invades superficial muscle; T2b: Tumour invades deep muscle; T3: Tumour invades perivesical tissue; T4: Tumour invades any of the following: [(T4a) prostate stroma, seminal vesicles, uterus, vagina] [(T4b) pelvic wall, abdominal wall].

Adapted from Knowles et al., 2015 (11)

How many people have MIBC?

Worldwide, BC ranks as the 9th most common cancer and the thirteenth leading cause of cancer-related deaths (2). In the UK, it is the eleventh most common cancer. In 2022, the proportion of individuals with bladder cancer within the last five years was 79,763 per 100,000 (12). In England, bladder cancer was the seventh most common cancer in 2021, with about 108 cases per 100,000 people over five years. BC accounts for about 75% of cases in men and was the seventh most common cancer in UK males in 2022 (13). In the UK, the annual incidence rate of BC is 0.04%, translating to approximately 17,872 new cases each year (14).

MIBC accounts for 25% of newly diagnosed BC cases (15).

Burden of the disease

A systematic literature review found that MIBC mortality rates in the UK range from 53.9% to 60.4%, with variations influenced by the timing of outcome measurements and the scheduling of the treatment in relation to surgical removal of the bladder (radical cystectomy), as delays or suboptimal timing may impact disease progression and long-term survival outcomes (16, 17). BC imposes a significant burden on patients and the National Health Service (NHS) due to high recurrence rate. MIBC is particularly aggressive, with nearly 50% of patients undergoing curative-intent treatment eventually relapsing and developing metastatic disease, most commonly within the first five years.

MIBC significantly impacts the quality of life for both patients and their families. The return of the disease (typically within two or three years post-surgery) and progression affects patients physically, causing symptoms like pain and fatigue, and mentally, leading to anxiety and depression (18). Caregivers also face significant challenges, including helping to adapt a new life post-surgery, managing symptoms and making end-of-life decisions (19).

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is resectable MIBC diagnosed?

The European Association of Urology (EAU) guidelines for MIBC recommend a comprehensive approach that includes clinical check-ups, imaging tests, and examining tissue samples. Imaging tests like computed tomography (CT) scans, magnetic resonance imaging (MRI), and ultrasound is crucial for spotting potential bladder tumours. If imaging clearly shows a tumour, patients can directly undergo a procedure called transurethral resection of the bladder tumour (TURBT) without needing a cystoscopy. Cystoscopy allows doctors to examine the lining of the bladder through a thin tube which is inserted through the urethra and into the bladder. Other techniques, like photodynamic diagnosis (PDD) for detecting certain types of BC and checking the prostate area in men, are recommended to improve accuracy and ensure a more precise diagnosis (20).

Imaging tests and clinical exams are used to classify the stage of bladder cancer, also known as clinical staging (21). However, accurate staging can be challenging, which can lead to inaccurate staging or 'mis-staging'. Studies show that many patients initially thought to have a less severe stage (T2N0) are found to have a more advanced stage (T3 or T4) after surgery (in cancer staging, "T" represents the size and extent of the tumour, while "N" indicates whether the cancer has spread to nearby lymph nodes). This can affect their access to treatment and overall health outcomes (22-25).

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider: if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
- are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What treatment guidelines are available for patients with MIBC in the UK?

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Guidelines for treating patients with MIBC are provided by the EAU and European Society for Medical Oncology (ESMO) (20, 26). UK clinicians follow EAU and ESMO guidelines (27).

What are the current treatment options?

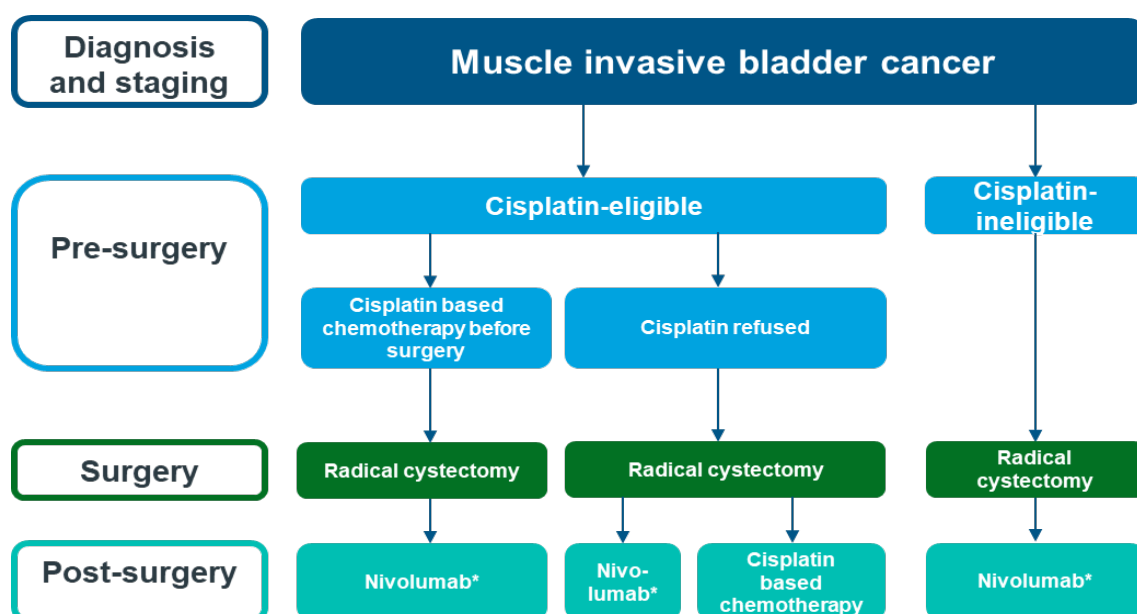
All the three European guidelines recommend surgical removal of the bladder (radical cystectomy) as the standard treatment for resectable MIBC. To improve survival outcomes, this surgery is often combined with cisplatin-based chemotherapy administered before the operation (20). About 50% to 70% of MIBC patients are suitable for this chemotherapy (28-30). Cisplatin-based chemotherapy has been the main treatment for those eligible for over 40 years, but new immunotherapy options are being explored. The standard of care chemotherapy in the UK is gemcitabine-cisplatin. Trials combining chemotherapy with immunotherapy have shown potential benefits for MIBC patients (20, 31-33). The EAU guidelines highlight the improved clinical outcomes in patients with resectable MIBC who take perioperative durvalumab (the immunotherapy medication object of this appraisal) combined with gemcitabine plus cisplatin (chemotherapy medications) before surgery and as monotherapy after surgery compared to those taking only gemcitabine plus cisplatin before surgery in the NIAGARA trial (20, 34), and consequently updated the recommendations and include perioperative durvalumab accordingly. This is the first and only immunotherapy trial to show improved survival rates as perioperative treatment (before and after surgery). Perioperative durvalumab regimen is currently unavailable in the UK and it is the focus of this appraisal.

In the current treatment landscape, patients that are identified as high-risk, with remaining MIBC after surgery, may be advised to get additional treatment post-surgery, known as adjuvant therapy. Adjuvant therapy options include chemotherapy for patients who have not received chemotherapy before surgery and the recently approved immunotherapy drug nivolumab for high-risk patients with a high expression of the PD-L1 protein (detailed in section 3a) (20, 35).

The ESMO recommendations are similar to EAU guidelines and are pending to be updated to incorporate the latest treatments approved. In the UK, treatment practices follow similar guidelines (36).

The current treatment pathway for MIBC is illustrated in Figure 2 below.

Figure 2. Current treatment pathway for patients with MIBC based European guidelines



*Nivolumab is only administered to high-risk patients with a high level of expression (PD-L1 $\geq$ 1%). In the UK, nivolumab is further restricted to patients who are ineligible to receive chemotherapy post-surgery.

What are the limitations of the current treatment options?

Despite standard treatments like surgery and neoadjuvant chemotherapy, less than 60% of patients survive five years after diagnosis (20). Some chemotherapy regimens (specifically gemcitabine plus cisplatin) can improve survival (only an 5% increase in five-year survival), but many eligible patients do not receive them due to factors such as advanced age, race, severity of their condition, marital status, and socioeconomic factors (20, 37).

After surgery, about 15% of patients may experience a return of their cancer in the pelvic area, while nearly 50% may have cancer spread to other parts of the body, often leading to poor survival rates (38, 39). Recurrence and progression significantly decline patients' overall wellbeing, necessitates greater healthcare resource use, including frequent hospitalisations, advanced imaging, and additional therapeutic interventions (18).

The limitations of the current treatments highlight an unmet need for an effective treatment option in both neoadjuvant and adjuvant settings.

- Neoadjuvant chemotherapy: offers limited survival benefits and is associated with high recurrence rates, necessitating the need for a more effective treatment.
- Adjuvant immunotherapy: adjuvant nivolumab is only given in the case of high-risk of recurrence after surgery, representing a reactive intervention (detailed in Section 3a) (20). This intervention is further limited to patients whose tumours express PD-L1 $\geq$ 1%, restricting the opportunity for early, proactive treatment planning and depriving

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

patients of the potential benefits of immune priming with neoadjuvant immunotherapy. A perioperative regimen, deploying the same IO therapy before and after surgery, has the potential to improve surgery outcomes by priming anti-tumour immunity before surgery (neoadjuvant setting) and sustaining immunosurveillance to eliminate micro-metastatic disease after surgery (adjuvant setting), thereby enhancing the likelihood of long-term disease control, both of which are associated with a high risk of recurrence (40).

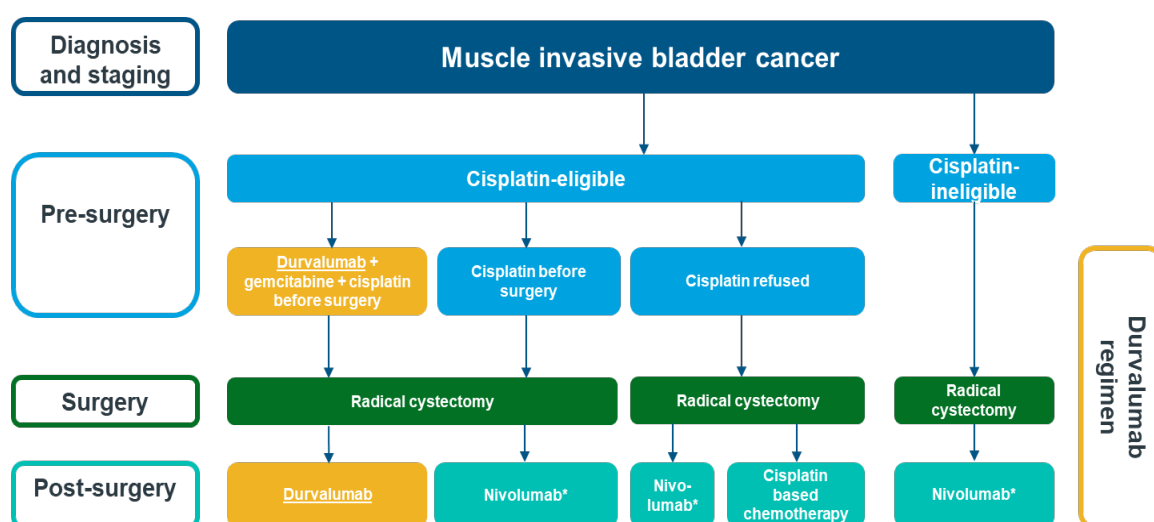
Adopting perioperative regimens that establish both pre- and post-surgical treatment decisions at a single, early point in the disease course provides greater certainty in treatment planning, enabling proactive management to reduce the risk of recurrence and facilitate timely interventions.

UK-based clinical experts emphasised the importance of effective treatments for resectable MIBC, highlighting the need to minimise the risk of relapse across a broader spectrum of patients (27).

What is the role of durvalumab in the treatment of resectable MIBC patients?

Durvalumab will be used in two phases: first, along with chemotherapy for three months before surgery, and then by itself for six months after surgery (Figure 3).

Figure 3. Current pathway of care, including proposed place of perioperative (before and after surgery) durvalumab in MIBC



*Nivolumab is only administered to high-risk patients with a high level of expression of PD-L1. In the UK, nivolumab is further restricted to patients who are ineligible to receive chemotherapy post-surgery.

Note: Durvalumab is administered in combination with gemcitabine and cisplatin every 3 weeks for 4 cycles before surgery, and as a standalone therapy, every 4 weeks for up to 8 cycles after surgery. Nivolumab can be administered every 2, 3 or 4 weeks until disease recurrence but with maximum duration of use of 12 months.

2d) Patient-based evidence (PBE) about living with the condition

Several aspects of PBE have been identified for perioperative durvalumab which positively impact patients' lives. Perioperative durvalumab provides substantial health-related

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

benefits, emphasising the importance of patient-reported outcomes, which include psychological advantages, reduced treatment burdens, and fewer hospital visits. For MIBC patients facing uncertain outcomes, durvalumab offers hope by reducing the risk of recurrence, helping patients and their families cope better emotionally. The potential to live longer and see future therapies gives patients hope and helps them manage the disease burden. Establishing perioperative durvalumab right after diagnosis allows patients and caregivers to plan their lives in advance, reducing emotional stress and improving the quality of care. Innovative treatments like perioperative durvalumab can alleviate the strain on caregivers, enabling them to resume their professional lives and societal contributions. By decreasing the risk of recurrence and improving patient autonomy, this regimen can reduce long-term care costs and enhance overall quality of care from the healthcare system's perspective.

When deciding on the type of treatment, patients with MIBC consider that survival is the most important factor, followed by the risk of chronic complications and changes to body image. Regarding trade-offs, patients are willing to accept a higher risk of long-term complications to improve life expectancy and body image (41-43).

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

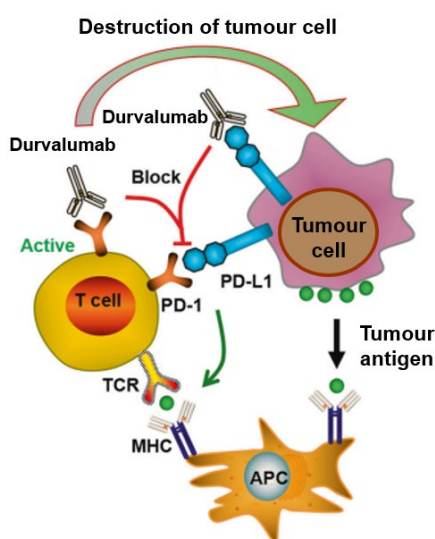
If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

PD-L1 (Programmed Death-Ligand 1) and PD-1 (Programmed Cell Death Protein 1) are immune proteins that regulate immune responses. PD-L1 is found on cancer cells, and PD-1 is found on T-cells, which are a type of immune cell. When PD-L1 on cancer cells connects with PD-1 on T-cells, it stops the T-cell from attacking the cancer cells. This mechanism allows the cancer cells to hide from the immune system and grow further. Another protein, CD80, also interacts with PD-1, adding more control to this process. In various cancers, cancer cells make more PD-L1, which helps them avoid being attacked by the immune system and allows the tumour to grow (44).

Durvalumab is a monoclonal antibody known as an 'immune checkpoint inhibitor'. Durvalumab blocks the interaction between PD-L1 and PD-1, as well as CD80 (checkpoint proteins). By inhibiting these interactions, durvalumab enhances T-cell activation and promotes attack on cancer cells, potentially leading to tumour elimination (34).

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Figure 4. Durvalumab mechanism of action



Abbreviations: APC: antigen-presenting cell; MHC: major histocompatibility complex; PD-1: programmed death protein 1; PD-L1: programmed death-ligand 1; TCR: T-cell receptor.

Source: Meng *et al* (45)

The MHRA summary of product characteristics (SmPC) and patient information leaflet (PIL) can be downloaded from the below links:

- Imfinzi 50 mg/mL concentrate for solution for infusion (SmPC): [link](#)
- Imfinzi 50 mg/mL concentrate for solution for infusion (PIL): [link](#)

This SmPC and PIL include general characteristics of the drug and use in other indications. The MIBC indication will be included after the expected approval in November 2025.

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- **Yes / No**

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Durvalumab is intended to be used in combination with two chemotherapy treatments, gemcitabine, and cisplatin, prior to surgery. After surgery, durvalumab is intended to be used as standalone therapy (1).

Gemcitabine and cisplatin are chemotherapy drugs. Gemcitabine stops cancer cells from making DNA, while cisplatin damages their DNA, causing them to die. Together, they work to reduce the tumour size and kill cancer cells. These chemotherapy drugs are widely

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

available and commonly used in cancer treatment. Main side effects are similar to those of perioperative durvalumab and include nausea, vomiting, fatigue, and risk of infections due to low white blood cell counts (34).

The synergistic effect of immuno-oncology and chemotherapy in the neoadjuvant setting has become an important area of research and clinical interest. Combining IO agents, such as immune checkpoint inhibitors, with chemotherapy aims to enhance anti-tumour responses before surgical intervention. Chemotherapy can induce immunogenic cell death, increasing antigen presentation and priming the immune system. This process may create a more favourable tumour microenvironment, allowing IO therapies to be more effective in activating T cells and driving a sustained immune response against cancer cells (46-50).

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Frequency:

Durvalumab is intended for administration:

- in combination with gemcitabine and cisplatin every 3 weeks for 4 cycles before surgery, and
- as a standalone therapy, every 4 weeks for up to 8 cycles after surgery (1).

Figure 5 presents the dosing and frequency of durvalumab in the NIAGARA trial.

Administration method:

- The regimen of durvalumab (both in combination before surgery and as a standalone treatment after surgery) is fixed and administered for a defined maximum duration (rather than until disease progression). Durvalumab is an intravenous drug. It must be administered as an intravenous infusion over 1 hour (1).

Dosage:

Durvalumab:

- 1500 mg in combination with chemotherapy every 3 weeks for 4 cycles before surgery, followed by 1500 mg every 4 weeks as monotherapy for up to 8 cycles after surgery (1).
- In case a patient's body weight is below 30 kg, they must receive weight-based dosing of durvalumab at 20 mg/kg - in combination with chemotherapy, durvalumab is dosed at 20 mg/kg every 3 weeks before surgery, followed by standalone therapy at 20 mg/kg every 4 weeks after surgery until weight increases to more than 30 kg.

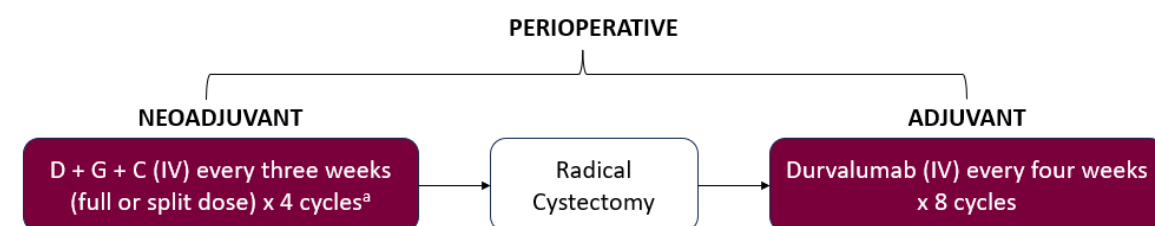
Gemcitabine and cisplatin:

- Gemcitabine is administered at a dose of 1000 mg per square meter of body-surface area on days 1 and 8 of each 3-week cycle.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

- Cisplatin is administered at a dose of 70 mg per square on day 1 of each 3-week cycle.

Figure 5. Dosing chart of durvalumab in NIAGARA trial



Abbreviations: C: Cisplatin; D: Durvalumab; G: Gemcitabine; IV: intravenous.

^a Patients with borderline renal function received split-dose G+C and were limited to up to 20% of the targeted global population.

Source: Powles et al. (2024) (34)

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Durvalumab is studied in one global phase III trial (which is referred to as NIAGARA trial) (34). This trial compares durvalumab plus gemcitabine and cisplatin before surgery followed by durvalumab alone after surgery with gemcitabine and cisplatin alone before surgery in eligible patients with resectable MIBC.

The trial included 1,063 participants over the age of 18, both male and female, with resectable MIBC and eligible for cisplatin-based chemotherapy. The NIAGARA trial recruited patient in 22 countries, including four sites in the UK. Patients were randomly assigned to receive either:

- durvalumab combined with gemcitabine and cisplatin, followed by surgery and standalone durvalumab,
- or
- gemcitabine and cisplatin followed by surgery only.

Baseline characteristics were generally balanced between the trial groups. The trial population was representative of the overall population of patients with MIBC in the UK according to the clinical validation interviews conducted by the company.

The NIAGARA trial recruitment was completed in August 2021. Results from interim analysis were presented in ESMO 2024, American Society of Clinical Oncology (ASCO) genitourinary (GU) 2025 and American Urological Association (AUA) 2025.

Durvalumab is currently being studied for its use in various settings of bladder cancer in combination with other treatments, including non-muscle invasive bladder cancer (NMIBC),

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

cisplatin-ineligible muscle-invasive bladder cancer (MIBC), and advanced or metastatic urothelial cancer.

Details about the NIAGARA trial is available at:

<https://clinicaltrials.gov/study/NCT03732677>

More information can be found in the following publication:

- Powles T, Catto JW, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. The New England journal of medicine. 2024:1-14.

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

The NIAGARA trial considered pathological complete response and event-free survival as co-primary endpoints and overall survival as the key secondary endpoint. Other secondary endpoints explored disease-specific survival and metastasis-free survival.

The results of the NIAGARA trial support the use of perioperative durvalumab (before and after surgery) across a broad set of cisplatin-eligible resectable MIBC patients (without any restrictions), addressing a key unmet need. This is the first and only trial of a perioperative IO regimen that has shown a clear improvement in overall survival for cisplatin-eligible resectable MIBC patients, reducing the risk of recurrence, metastasis and death caused by bladder cancer. Early findings indicate that this treatment approach lowers the chance of cancer returning or becoming worse by 32%, the risk of metastasis by 33%, the risk of death due to cancer by 31% and the overall risk of death by 25% compared to gemcitabine and cisplatin administered before surgery alone. The benefits across all survival endpoints were consistent across different patient subgroups.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs)**.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

EuroQol 5 Dimension 5 Level (EQ-5D) is the tool that is preferred by NICE to measure health-related quality of life (HRQoL) in adults (51). In the NIAGARA trial, both EQ-5D and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) were used to measure HRQoL.

Results from the NIAGARA trial showed that the EQ-5D questionnaire scores were similar between patients receiving durvalumab with gemcitabine and cisplatin and patients receiving gemcitabine and cisplatin alone at the start of the trial. Additionally, health scores decreased by slightly and similarly in both treatment groups throughout the study.

The EORTC QLQ-C30 questionnaire showed similar results between the two treatment groups in all areas (overall health, physical functioning, fatigue, and pain), except for less appetite loss in the durvalumab arm.

These results suggest that the addition of durvalumab to the standard chemotherapy treatment (gemcitabine and cisplatin) does not lead to a negative impact on patients' quality of life, despite increasing treatment burden.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety of durvalumab was in line with what is already known from other indications, with no new safety issues and no increase in patients stopping treatment due to side effects compared to gemcitabine and cisplatin alone (34).

Patients who received the combination treatment were able to complete four cycles of chemotherapy (52). Importantly, adding durvalumab did not lead to more surgery-related complications, delays or impede the surgery itself (radical cystectomy) (52).

Almost all patients experienced at least one side effect during the study in both treatment groups. In both treatment arms, the most common AEs of any cause were nausea, anaemia, and constipation. More patients in the durvalumab group experienced serious side effects and had to stop treatment compared to the chemotherapy-only group. Despite this, the rate of severe side effects was similar in both groups (52).

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

The key benefits of durvalumab for patients with resectable MIBC, their caregivers, and society include:

- Perioperative durvalumab reduced the risk of worsening or returning by 32% and the specific risk of metastasis by 33% compared to current standard of care.
- Perioperative durvalumab also reduced the risk of death from bladder cancer by 31% and the overall risk of death by 25% in comparison with standard of care.
- Perioperative durvalumab provided a similar quality of life to the standard of care in the phase III NIAGARA trial.
- Perioperative durvalumab is the only before and after surgery treatment that has shown a survival benefit in patients suffering from resectable MIBC, regardless PD-L1 expression.
- Perioperative durvalumab is administered via intravenous infusion with chemotherapy before surgery, hence no additional hospital visits are required compared to chemotherapy alone.
- The treatment decision point and fixed regimen of perioperative durvalumab (up to three months before surgery and six months after surgery) helps early planning, increased predictability for patients and healthcare professionals, and reduce treatment burden and potential long-term side effects for patients.

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Durvalumab in combination with chemotherapy has been shown to have a good safety and tolerability profile, similar to the current standard of care and in line with what is already known. Being an immunotherapy, durvalumab is contraindicated in certain patients with autoimmune conditions and requires specific follow-up for immune related side effects. This is a characteristic of all immunotherapies, including nivolumab. Moreover, after surgery (radical cystectomy), durvalumab requires additional hospital visits than chemotherapy alone, however, the total number of post-surgery hospital visits is lower compared to

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

adjuvant nivolumab. There are no specific disadvantages of durvalumab compared with the existing treatment options.

3j) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

To aid decision-making in the investment in new treatments, it is crucial to demonstrate value to healthcare systems from their limited budgets. This requires comparing the cost increase of incorporating the intervention with the additional benefit it provides. For this purpose, pharmaceutical companies, and health-technology-assessment (HTA) bodies use economic models (a theoretically constructed representation of a process in which the costs and benefits of a new treatment are compared with the existing treatments for that disease area). In this theoretical exercise, not only is the cost of the additional benefit evaluated, but also the degree of certainty that this model will be replicated in real life. Therefore, the predictability of both the expenditure and the benefit plays a key role.

NICE evaluation requires both, cost-effectiveness model and budget impact model, with cost-effectiveness analysis having a greater impact on decision making.

The model reflects the experience of patients living with MIBC

Based on a literature review of published cost-effectiveness models, clinical evidence from the NIAGARA trial and the most recent treatment guidelines for bladder cancer, a health economic model was created to evaluate the costs and benefits of adding durvalumab to the current care pathway (26, 53-58). This model accurately reflects the experience of patients with MIBC in England and Wales and uses evidence from the NIAGARA clinical trial.

The cost-effectiveness model compares the costs and benefits of using perioperative durvalumab, versus chemotherapy alone before surgery and no treatment after surgery. A separate analysis was also conducted to compare against chemotherapy alone before

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

surgery and nivolumab after surgery for patients at high risk of disease recurrence and a high PD-L1 protein expression. However, it is to be noted that both treatments are not interchangeable, due to differences in the patient populations that they are intended for, and no patient who has initiated durvalumab treatment will be eligible to receive adjuvant nivolumab. Nivolumab use is limited for patients who are at high risk of recurrence and are ineligible to receive cisplatin treatment.

A budget impact model was also prepared to assess the impact of introduction of durvalumab on the costs that payers incur. The budget impact analysis compares the budget impact on NHS England and Wales of two hypothetical scenarios of using durvalumab with chemotherapy before surgery, followed by durvalumab alone after surgery, versus chemotherapy alone before surgery and no treatment after surgery.

What do the results of the cost-effectiveness analysis tell us?

When evaluating health technologies, their clinical effectiveness and cost is considered. A dominant health technology provides better health outcomes at a lower cost while a dominated technology is not cost-effective. If a health technology is cost-effective, it achieves good health benefits without being overly expensive. Conversely, a cost-ineffective technology either fails to deliver desired health outcomes or delivers improved health outcomes at a high cost.

The costs associated with the addition of durvalumab to chemotherapy (gemcitabine and cisplatin) are partially offset by lower disease management costs associated with a delayed disease recurrence, and consequently less time spent in the recurred disease state.

The company base case is below that of the standard NICE thresholds. The findings from the model reiterate that introducing perioperative durvalumab to the pathway of care provides clinical benefits, such as improved survival. This is due to the lower chances of cancer worsening or returning post durvalumab treatment establishing it as a clinically effective treatment option.

What do the results of the budget impact analysis tell us?

Perioperative durvalumab, has a predictable budget impact. This is due to its targeting of a well-defined patient population and a maximum prespecified treatment duration of up to 1 year with the regimen. Though the results of the budget impact analysis show an increased budget, they should be interpreted with caution because the analysis only shows the increase in the treatment costs with the introduction of new therapy but does not take into account the reduced number of treatment cycles (of the standard therapy) and prevention of cost escalation by restricting the disease progression to metastatic stage.

Model uncertainties were explored

Additional analyses were conducted to investigate how sensitive the model results are to changes in certain parameters. Different scenarios using alternative data were also tested to see their impact on the results. This helps decision-makers understand how reliable the model results are and provides extra evidence to support their decision about using durvalumab in the NHS. The results from these analyses confirmed that durvalumab is a cost-effective option with robustly validated clinical benefits.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

3k) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

If durvalumab is approved, it would be the first and only clinical practice-changing perioperative immunotherapy for patients with resectable MIBC. The durvalumab regimen significantly reduced the risk of recurrence by 32% and the risk of death by 25% compared to neoadjuvant chemotherapy alone. The NIAGARA phase III trial demonstrated that more than 80% of patients treated with the durvalumab regimen were alive at two years, indicating a positive outlook on long-term survival. This is a substantial improvement over current treatments for MIBC, which is associated with high rates of disease recurrence and poor prognosis even after surgery. Durvalumab's innovative perioperative approach and demonstrated effectiveness marks a transformative step in the treatment of MIBC, offering a new hope to patients with the potential for rapid adoption into the standard of care (27, 59, 60).

3l) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

No inequality considerations are anticipated to arise with the introduction of this technology within clinical practice.

However, the bladder cancer burden is unequal, with persistent outcome gaps among different populations. Although men are more likely to develop BC, women often present with more advanced disease and have worse prognosis (61). The latter is explained by a longer diagnostic delay in women and not by treatment patterns (62, 63). Women showed lower survival rates only within the first two years after diagnosis, partly due to a higher T stage at initial diagnosis (64). People with a lower socioeconomic status are anticipated to be more impacted by BC. Factors such as lifestyle and occupation contribute to higher rates of BC, and these can often be attributed to lower-paid work and socioeconomic status. For example: Globally, 33.72 % of deaths caused by BC could be attributed to smoking and around 10 % of BC arise following occupational exposure to carcinogen in jobs such as steel, foundry, metal, engineering and transport industries (65, 66).

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.

- European Society for Medical Oncology guidelines (26):
<https://pubmed.ncbi.nlm.nih.gov/34861372/>
- National Comprehensive Cancer Network guidelines (67):
<https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1417>
- European Association of Urology guidelines (20):
<https://uroweb.org/eau-guidelines/citing-usage-republication>
- NICE guidelines (55):
<https://www.nice.org.uk/guidance/ng2?UID=5081173642025320104642>
- American Urological Association guidelines (56):
<https://pubmed.ncbi.nlm.nih.gov/28456635/>
- French Urology Association guidelines (57):
<https://pubmed.ncbi.nlm.nih.gov/36400480/>
- Canadian Urological Association guidelines (58):
<https://pubmed.ncbi.nlm.nih.gov/30763236/>
- NHS – bladder cancer (68):
<https://www.nhs.uk/conditions/bladder-cancer/>

Further information on NICE and the role of patients:

- Public Involvement at NICE:
[Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- NICE's guides and templates for patient involvement in HTAs:
[Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector \(VCS\) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE](#)
- EUPATI guidance on patient involvement in NICE:
<https://www.eupati.eu/guidance-patient-involvement/>
- EFPIA - Working together with patient groups:
<https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf>

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

- National Health Council Value Initiative:
<https://nationalhealthcouncil.org/issue/value/>
- INAHTA: <http://www.inahta.org/>
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:
http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

- **Budget impact model (BIM):** A tool used to estimate the financial impact of adopting a new health technology within a specific budget context. BIMs predict changes in healthcare expenditures and help decision-makers plan resource allocation and assess affordability.
- **Cost-effectiveness model (CEM):** A method used to assess the value of a health technology by comparing its costs and health outcomes. CEMs help determine whether a technology provides good value for money by analysing the costs and benefits associated with its use.
- **Computed tomography:** A medical test that uses X-rays to take detailed pictures of the body's internal structures. It is often used to diagnose and monitor various conditions, including tumours.
- **Cystoscopy:** A medical procedure that uses a thin tube with a camera (cystoscope) to examine the inside of the bladder and urethra, often used to diagnose bladder conditions.
- **Durvalumab:** An immune checkpoint inhibitor that targets the PD-L1 protein, used in cancer treatment to help the immune system recognize and attack cancer cells.
- **EORTC QLQ-C30:** A standardized measure of health-related quality of life specifically designed for cancer patients. It assesses health status across multiple dimensions, including physical, emotional, and social functioning. This questionnaire is considered a 'generic' tool within oncology because it is applicable to a wide range of cancer types and treatments.
- **EQ-5D:** A standardised measure of health-related quality of life that assesses health status in terms of five dimensions of health (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). It is considered a 'generic' questionnaire because these dimensions are not specific to any one patient group or health condition.
- **Gemcitabine and cisplatin:** A combination of two chemotherapy drugs commonly used to treat various types of cancer, including bladder cancer, by interfering with the cancer cells' ability to grow and divide. The combination is the only current standard of care for bladder cancer.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

- **Health Technology Assessment (HTA):** A systematic evaluation of a health technology to determine its value and impact on a health system. An HTA considers clinical effectiveness, safety, cost-effectiveness, and social and ethical implication.
- **Magnetic resonance imaging:** A medical test that uses strong magnets and radio waves to take detailed pictures of the body's internal structures.
- **Muscle-invasive bladder cancer:** A type of bladder cancer that has spread into the muscle layer of the bladder wall, indicating a more advanced stage that typically requires more aggressive treatment
- **NIAGARA:** A clinical trial evaluating durvalumab in combination with gemcitabine and cisplatin before surgery (radical cystectomy) and durvalumab as a standalone therapy after surgery as a treatment for MIBC.
- **Nivolumab:** A immune checkpoint inhibitor that blocks the PD-1 protein, used in cancer therapy to enhance the body's immune response against tumours.
- **PD-L1:** A protein expressed on some cancer cells that helps them evade the immune system; targeting PD-L1 with therapies like durvalumab can improve immune responses against tumours.
- **PD-1:** A protein on the surface of T-cells (a type of immune cell) that, when activated, can inhibit immune responses; blocking PD-1 with drugs like nivolumab helps reactivate T-cells to attack cancer.
- **Radical cystectomy:** A surgical procedure to remove part or all the bladder, typically performed to treat bladder cancer or other serious bladder conditions.
- **T-cell:** A type of white blood cell that is crucial for the immune response, particularly in recognising and destroying infected or cancerous cells.

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

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[perioperative-regimen-reduced-risk-recurrence-by-32-risk-death-by-25-vs-neoadjuvant-chemotherapy-alone-in-mibc-niagara-phase-iii-trial.html](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10000000/).

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

**Durvalumab with gemcitabine and cisplatin
before surgery (neoadjuvant) then alone after
surgery (adjuvant) for treating muscle-invasive
bladder cancer [ID6168]**

Clarification questions

July 2025

File name	Version	Contains confidential information	Date
ID6168 durvalumab clarification questions 14072025ZH [CON]	V2.0	Yes	14 July 2025

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

NIAGARA trial

Trial Design

A1. PRIORITY: Powles (2024)(1) acknowledge that the open-label design of the NIAGARA trial is a limitation, which was “somewhat mitigated” by measures including blinded independent central review of tumour assessment. Please discuss the potential impact of the open-label design on the conduct of the trial, including: neoadjuvant therapy uptake and compliance; proportion of participants undergoing radical cystectomy; adjuvant therapy uptake and compliance; co-interventions; and subsequent therapies.

Consistent with most ongoing clinical trials evaluating peri-operative treatments in bladder cancer, the NIAGARA study utilized an open-label design, whereby both patients and investigators were unblinded to treatment allocation (2-14). This approach allowed patients in the standard-of-care (SoC) arm (gemcitabine in combination with cisplatin [G+C] arm) to avoid unnecessary placebo infusions, a common practice for trials whereby the administration of the intervention and control arm differ.

To preserve the integrity of the data and prevent interpretational bias, a sponsor-blinded model was implemented. Specifically, while the study remained open label for investigators, patients, and regulatory authorities, the sponsor was kept blinded. Individual patient efficacy data were subject to cleaning using dummy identifiers, and medical review and data cleaning of patient safety data were restricted to selected personnel. No aggregated summaries of data by treatment arm were generated until unblinding occurred.

Regarding statistical endpoints, both the primary analyses of pathological complete response (pCR) and event-free survival (EFS) were conducted using blinded independent central review, thereby eliminating the potential for bias due to knowledge of treatment group.

To specifically address the potential impact of the open-label design, the available data show that, as reflected in CS Table 6, the proportion of patients who completed neoadjuvant therapy was similar between arms (417 [78.7%] in the perioperative durvalumab arm and 389 [74%] in the control arm), demonstrating that the open-label design had no impact on neoadjuvant uptake and compliance. For patients undergoing cystectomy, a slightly lower percentage did not undergo the planned surgery in the perioperative durvalumab arm compared to the control arm (63 [11.8%] vs. 84 [15.8%], respectively). Moreover, reasons potentially influenced by the open-label design, such as patient decision (6.0% in perioperative durvalumab arm vs 6.8% in control arm) or investigator decision not to perform surgery (0.9% in perioperative durvalumab arm vs 1.1% in control arm), were well balanced across arms, proving that the design did not influence the likelihood of undergoing surgery, nor did it affect surgical outcomes. Similarly, during the adjuvant phase, the main reasons for treatment discontinuation were adverse events (6.4%) and disease relapse (6.4%), while the only reason potentially influenced by the open-label design—patient decision—accounted for just 2.8% of cases.

In oncology studies, even in double-blind designs, it is standard practice for investigators to become unblinded after discontinuation of study treatment in order to appropriately assess and select subsequent disease-related anticancer therapies. This practice is broadly acknowledged in regulatory guidance, such as the FDA's guidelines on oncology drug approval and ICH Good Clinical Practice standards,

which note that subsequent therapy selection should be based on a clear understanding of prior treatment response (FDA, 2018; ICH E6[R2]). Such unblinding is particularly important in trials of immuno-oncology and targeted therapies, where post-progression treatment decisions are frequently influenced by response to previous treatment or duration of the response. Therefore, the choice of subsequent therapy is not directly influenced by the study design itself, but rather by the investigator's clinical assessment of the patient's response to previous treatment.

Population

A2. PRIORITY: Please describe the demographics of the population of patients with muscle-invasive bladder cancer (MIBC) eligible for radical cystectomy in the UK and compare this to the NIAGARA trial population. The EAGs clinical adviser pointed to SACT data and the BAUS MITRE audit (Aug 2022) (15); please consider these, as appropriate.

The representativeness and generalisability of the NIAGARA study population relative to UK patients with resectable, cisplatin-eligible MIBC was specifically discussed with UK-based clinicians during five clinical validation interviews conducted by the company (16). All clinicians unanimously confirmed that the NIAGARA trial population was reflective of the patient population they see in clinical practice, align with the scope of the appraisal. The BAUS MITRE audit captures a broad population of patients with MIBC in the UK, encompassing both those who receive active treatment and those who do not. Notably, 50.6% of patients included in the audit did not receive any active treatment, while only 20.9% underwent cystectomy. Of the patients who had surgery, just 38.7% received neoadjuvant chemotherapy. As such, although the BAUS MITRE audit provides important insight into the overall MIBC population in the UK, its overlap with the perioperative durvalumab-eligible population—specifically those who are fit for cisplatin-based neoadjuvant chemotherapy and subsequent radical cystectomy, as per the scope of this appraisal—is very limited. Only 8.08% of the overall audit population truly represent the population under consideration in the NIAGARA trial and for the current NICE appraisal.

Direct comparison between the demographics described in the BAUS MITRE audit and the NIAGARA trial population is therefore at high risk of bias due to intrinsic differences in patient selection and eligibility criteria. To enable a meaningful

comparison, it would be necessary to characterise the demographics of this specific subgroup—patients eligible for both neoadjuvant cisplatin-based chemotherapy and radical cystectomy—within the UK setting.

For this reason, differences between the two datasets—such as the median age (76 years [range 35–104] in the BAUS MITRE audit vs 65 years [32–84] in the NIAGARA trial)—should be interpreted with caution. This age disparity likely reflects the broader inclusion criteria in the audit, which incorporates a higher proportion of patients who are cisplatin-ineligible or unsuitable for radical cystectomy, criteria often closely linked to advancing age. Consequently, the BAUS MITRE audit median age cannot be directly compared with the more stringently defined, NIAGARA trial population.

Additionally, there are differences in the completeness and categorisation of smoking status between the datasets. In the BAUS MITRE audit, smoking status was unknown for 33.9% of patients, while only 2.2% of cases were unknown in the NIAGARA trial, complicating direct comparisons. Among patients with known status, 23.7% in the NIAGARA trial were current smokers compared to 16.5% in the audit; 49.3% and 25.5% were former smokers, respectively, while a similar proportion in each cohort were never smokers (24.8% in NIAGARA and 24.1% in the audit). This disparity further illustrates the limited overlap and comparability between the broader audit population and the more narrowly defined trial population.

Differences in nodal and metastatic status (N/M status) between the two datasets also reflect differences in the populations under consideration. In the BAUS MITRE audit, 73.5% of patients were N0M0 compared with 94.5% in the NIAGARA trial, while 7.7% were N1M0 in the audit versus 5.5% in NIAGARA. Notably, NIAGARA did not include patients with N2 or higher nodal status, nor those with metastatic disease (M1), whereas these groups were included in the audit (3.3% and 15.5% of the population, respectively), the reasons to exclude this patient population are explained in the response to Question A3. This further demonstrates the need for caution when attempting to compare or draw conclusions from these populations. Full demographic details from NIAGARA trial population can be found in the CS Table 7.

A3. PRIORITY: The EAGs clinical adviser indicated that they would expect durvalumab to be suitable for some patients with lymph node (N2-3) TCCD/UC. Please comment on this and explain the rationale for this patient group being excluded from the NIAGARA trial.

The NIAGARA study protocol was developed in line with AJCC 8th edition criteria and ESMO clinical guidelines, including only patients suitable for radical cystectomy and lymphadenectomy. The AJCC 8th edition reclassified node-positive disease into stage IIIa (cN1) and IIIb (N2/N3), now distinguishing between patients with more favourable (N1) and less favourable (N2/N3) prognosis. Reflecting this, the 2018 NCCN guidelines recommend neoadjuvant chemotherapy followed by radical cystectomy for stage IIIa patients, but not for those with N2 or N3 disease, who are not considered standard candidates for surgery (17). Based on these criteria, NIAGARA included patients with T2-4N1 disease but excluded those with N2 and N3 disease.

While durvalumab may be suitable for some patients with more advanced nodal disease, as noted by the EAG clinical adviser, NIAGARA was designed specifically to assess perioperative durvalumab in patients eligible for neoadjuvant chemotherapy followed by radical cystectomy. As such, N2/N3 patients were not included, and the efficacy of this regimen in that group cannot be determined from this trial. Clinical evaluation should focus on patients under the scope of the appraisal, covered by the current trial evidence.

Perioperative treatment sequence

A4. PRIORITY: Please clarify the following subgroups of patients in the NIAGARA trial.

- a. Explain why some patients discontinue neoadjuvant treatment (21.3% in durvalumab arm) but do undergo cystectomy (11.8% did not undergo cystectomy in durvalumab arm), as detailed in the company submission(18) (CS), Table 6, p. 38.**

According to the study protocol, delay or discontinuation of neoadjuvant therapy was permitted under certain circumstances. In cases where durvalumab was discontinued or delayed in accordance with toxicity management guidelines, G+C chemotherapy could continue as scheduled. If G+C chemotherapy was discontinued due to

treatment-related toxicity, patients were instructed to proceed to radical cystectomy when clinically feasible, with any remaining neoadjuvant doses of durvalumab skipped. Adjuvant therapy with durvalumab could resume following cystectomy. Additionally, if the Investigator felt that a patient might benefit from completing the remaining neoadjuvant durvalumab cycles without chemotherapy, AstraZeneca could be consulted to grant an exception.

As reported in the CS, 21.3% of patients in the perioperative durvalumab arm and 26% in the control arm discontinued neoadjuvant treatment, with the primary reason in both arms being adverse events (15.5% and 15.2% of cases, respectively). Importantly, the occurrence of adverse events—and thus neoadjuvant treatment discontinuation—does not necessarily preclude patients from proceeding to radical cystectomy, provided they remain clinically eligible for surgery. This explains why the proportion of patients who discontinued neoadjuvant treatment is higher than the proportion who did not undergo cystectomy. The decision to proceed or not with radical cystectomy is evaluated independently from discontinuation of neoadjuvant treatment. This pattern is consistent with how, according to the expected SmPC and clinical expert feedback, a perioperative regimen is anticipated to perform in real-world clinical practice and, therefore, supports an appropriate assessment of the evidence for its use within the NHS.

- b. The company submission (CS), Table 6, p. 38, shows that 19% of patients in NIAGARA who received treatment in the durvalumab arm had a cystectomy but did not start adjuvant treatment. Please state the reasons for not starting adjuvant treatment in these patients.**

According to the NIAGARA trial protocol, patients may discontinue study treatment at any stage, including after successfully undergoing radical cystectomy. The protocol outlines several possible reasons for not starting adjuvant treatment following cystectomy, such as withdrawal of consent to continue with the investigational product, occurrence of adverse events, documented recurrence (by RECIST 1.1-defined radiological progression or positive tumour biopsy post-cystectomy), pregnancy or intention to become pregnant, non-compliance with the study protocol, or initiation of alternative anticancer therapy. Importantly, discontinuation of study treatment did not preclude continued participation in study follow-up.

Of the 86 patients in the durvalumab (D)+G+C arm who underwent radical cystectomy but did not start adjuvant durvalumab, a targeted review of relevant electronic Case Report Form (eCRF) data identified potential reasons for 38 patients (19):

- 19 patients permanently discontinued durvalumab in the neoadjuvant period and did not restart after cystectomy
- 14 patients had an adverse event leading to death in the post-surgical period
- Nine patients experienced disease progression after surgery per investigator assessment.

These reasons were not mutually exclusive, and for the remaining 48 patients, no specific reason was captured in the available records.

The fact that not all patients receive adjuvant therapy after radical cystectomy is representative of actual clinical practice, should perioperative durvalumab be approved. In perioperative regimens, it is common to observe a reduction in the proportion of patients receiving adjuvant versus neoadjuvant therapy—particularly following radical procedures or in older patients who may require longer recovery periods. Thus, the pattern observed in NIAGARA aligns with known challenges in standard clinical care and the expected product label.

c. Did any participants in the durvalumab arm who did not receive radical cystectomy as planned receive adjuvant durvalumab? If so, please provide the proportion of patients.

Receiving adjuvant durvalumab without undergoing radical surgery was only possible for patients eligible to enter the non-cystectomy extension phase of the study. According to the protocol, this phase was available exclusively to patients who refused radical cystectomy at the specified time after achieving a complete clinical response, as locally determined by multimodal assessment and without additional interventions (e.g., TURBT). Entry into the non-cystectomy extension phase required consultation and agreement with AstraZeneca. In this setting, patients in the perioperative durvalumab arm could receive up to eight doses of durvalumab 1500 mg (as monotherapy), mirroring the adjuvant phase, while those randomized to the control arm did not receive further active treatment.

Only six patients (1.1%) in the perioperative durvalumab arm entered the non-cystectomy extension phase. There are currently no results available from this phase but given the very small proportion of the overall study population (six out of 1,063 patients), the impact on the overall study results is minimal. Furthermore, it is important to note that this practice falls outside the indication under evaluation.

A5. The CS, Table 31, pp.91-92, reports non-zero mean and median durations of exposure to durvalumab of 11.6 and 12.0 weeks respectively in the control arm. This is at odds with the study protocol, which did not permit participants in the control arm to cross-over to durvalumab. Please clarify.

This question appears to result from a misunderstanding. As detailed in the CS, Table 31, the mean duration of exposure was 33.5 weeks for the perioperative durvalumab arm and 11.6 weeks for the control arm, with median durations of 44.0 weeks and 12.0 weeks, respectively. These data accurately reflect the study protocol: participants in the control arm did not receive durvalumab, and there was no cross-over allowed. The reported durations refer to exposure to the assigned treatments per protocol for each arm. Please see the relevant data from The CS Table 31 below for clarification.

Table 1: Overview of duration of exposure, in the SAS (overall period, data cut-off [DCO] 29 April 2024)

	Perioperative durvalumab arm (D+G+C) (N=530)	Control arm (G+C) (N=526)
Duration of exposure (weeks)		
Mean (SD)	33.5 (16.33)	11.6 (3.12)
Median (min, max)	44.0 (1, 84)	12.0 (1, 27)

Abbreviations: C: cisplatin; D: durvalumab; DCO: data cut-off; G: gemcitabine; IA-2: second interim analysis; SAE: serious adverse event; SD: standard deviation; Min: minimum; Max: maximum.
Source: Powles *et al.* 2024 (1), AZ NIAGARA trial CSR (20)

Results

A6. PRIORITY: In the CS, Table 19, p. 58, lists rates of death in the absence of distant metastasis. Please provide a summary of cause for death in these patients, including proportions for each cause.

Among patients who died in the absence of recorded distant metastasis, deaths were attributed either to bladder cancer or other causes. causes were further classified into those due to bladder cancer and those due to other causes. In agreement with the definitions provided:

- *Death due to bladder cancer* refers to patients who died as a result of local progression, recurrence, or other clinical manifestations of bladder cancer without evidence of distant metastasis. These include any death where the primary or contributing cause was listed as “bladder cancer,” “urothelial carcinoma,” “tumour progression,” or equivalent terminology indicating death resulting from non-metastatic progression or local recurrence of the primary tumour.
- *Death not due to bladder cancer* includes deaths attributed to other specific causes. This category encompasses all other causes, such as: other primary malignancies (e.g., lung cancer, colorectal carcinoma), cardiovascular events (e.g., myocardial infarction, heart failure, stroke, cardiac arrest), infectious diseases (e.g., sepsis, pneumonia, COVID-19), other medical causes (e.g., renal failure, respiratory failure), accidents or trauma, unknown/unspecified causes (when the exact cause was not ascertained).

The specific cause of death within each category is available on an individual basis only for patients who experienced this event, and not for patients who had not experienced metastasis. This approach ensures each death is assigned according to the detailed underlying or immediate cause as specified in the clinical trial’s cause-of-death records. The distinction between deaths due to bladder cancer and those attributable to other causes (such as cardiovascular, infection, or other primary tumours) aligns with standard approaches for endpoint adjudication and provides greater clinical granularity.

Table 19 of the CS summarizes metastasis free survival (MFS) status for both treatment arms of the study. Specifically, for deaths occurring in the absence of distant metastasis, we provide below an updated version of the table with additional breakdown of these deaths according to their reported cause (Table 2).

Table 2. Analysis of MFS in the NIAGARA trial (full analysis set [FAS] intention to treat [ITT] population, DCO 29 April 2024)

MFS status	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)
Total MFS events, n (%)	152 (28.5)	201 (37.9)
Distant metastasis	54 (10.1)	77 (14.5)
Death in the absence of distant metastasis	98 (18.4)	124 (23.4)
Death due to bladder cancer	51 (52%)	76 (61.3%)
Death not due to bladder cancer	47 (48%)	48 (38.7%)
Hazard ratio ^{c,d}	0.67	
95% CI for hazard ratio	0.541, 0.826	
Two-sided p-value ^e	0.0002	

^c Based on stratified Cox PH model; the stratification factors are renal function (adequate versus borderline), tumour stage (T2N0 versus > T2N0), and PD-L1 status (high versus low/negative) per IVRS, with ties handled by the Efron approach.

^d A hazard ratio < 1 favours perioperative durvalumab to be associated with a longer MFS than control.

^e p-value is based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in c. p-value is nominal as MFS is not included in the MTP.

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; DCO: data cut-off; FAS: full analysis set; G: gemcitabine; IA-2: second interim analysis; IVRS: interactive voice response; ITT: Intention-To-Treat; MFS: metastases-free survival; MTP: multiple testing procedure; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Source: AZ NIAGARA trial CSR (20)

Subsequent treatments

A7. PRIORITY: Please discuss the potential confounding effect of subsequent therapies on overall survival (OS) estimates, using trial evidence as appropriate (e.g. progression-free survival 2 [PFS2]).

The potential confounding effect of subsequent therapies on OS estimates in the NIAGARA trial is limited. The observed OS benefit is consistent with improvements seen in EFS, disease-specific survival (DSS), MFS, and PFS-2. DSS is informative as it does not include death from other causes that can otherwise confound OS assessment. Similarly, MFS is highly relevant in the setting of this appraisal, which targets a pre-metastatic disease stage, providing further assurance that the benefit is related to disease control. This alignment across multiple clinical endpoints increases confidence that the survival benefit is attributable to perioperative durvalumab, rather than to confounding by post-progression therapies.

Regarding subsequent therapy, and as detailed in the response to Question A8, the overall proportion of patients receiving at least one subsequent anticancer therapy was relatively low (9.9% in the perioperative durvalumab arm versus 17.5% in the control arm). Importantly, the proportion of patients receiving novel therapies such as immunotherapy or targeted therapy was also lower in the perioperative durvalumab arm (immunotherapy: 3.4% vs 11.7%; targeted therapy: 0.6% vs 1.3% for perioperative durvalumab and control arms, respectively). Given the limited proportion of patients receiving novel therapies in the trial, and especially in the perioperative durvalumab arm, it can be concluded that their impact on OS is minimal.

PFS-2 results reinforce this conclusion. As described in CS Section 2.6.7, patients in the perioperative durvalumab arm experienced a clinically meaningful improvement in PFS-2 compared to those in the control arm, with a hazard ratio of 0.76 (95% CI: 0.605, 0.949; $p=0.0155$), equating to a 24% overall reduction in the risk of a PFS-2 event—most of which were deaths. The Kaplan–Meier (KM) curves for PFS-2 were similar for approximately the first six months, after which a clear and sustained separation emerged (see CS Figure 12), again underscoring the durable clinical benefit of perioperative durvalumab.

In conclusion, these findings show that the OS benefit observed in NIAGARA is unlikely to be confounded by subsequent therapies or other causes of death and is instead a robust effect attributable to perioperative durvalumab treatment.

A8. PRIORITY: Please clarify what treatments were provided after progression in NIAGARA and the proportion of patients who received each treatment by trial arm (separately for durvalumab and control arm).

Overall, at IA-2, the overall proportion of patients who had received at least one subsequent anticancer therapy across arms was 13.7%; however, a lower proportion of patients had received at least one anticancer therapy poststudy treatment discontinuation in the D+G+C arm (9.9%) as compared to the G+C arm (17.5%). The most common subsequent anticancer therapies administered were immunotherapy (3.4% vs 11.7% of patients in the D+G+C arm compared with the G+C arm), cytotoxic chemotherapy-based regimens (6.4% vs 8.3%), and radiotherapy (4.9% vs 5.8%) (Table 3).

Table 3: Post-discontinuation disease-related anticancer treatment

Anticancer Therapy ^a	Treatment	Number (%) of patients		
		Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1063)
Number of patients with post-discontinuation anticancer therapy		53 (9.9)	93 (17.5)	146 (13.7)
Radiotherapy		26 (4.9)	31 (5.8)	57 (5.4)
Immunotherapy		18 (3.4)	62 (11.7)	80 (7.5)
	ATEZOLIZUMAB	2 (0.4)	10 (1.9)	12 (1.1)
	AVELUMAB	3 (0.6)	9 (1.7)	12 (1.1)
	BINTRAFUSP ALFA	0	1 (0.1)	1 (0.1)
	BLINDED THERAPY	0	1 (0.1)	1 (0.1)
	CEMPIIMAB	0	1 (0.1)	1 (0.1)
	DOMVANALIMAB	0	1 (0.1)	1 (0.1)
	DURVALUMAB	0	1 (0.1)	1 (0.1)
	ENFORTUMAB VEDOTIN	1 (0.2)	0	1 (0.1)
	NIVOLUMAB	1 (0.2)	4 (0.8)	5 (0.5)
	PEMBROLIZUMAB	13 (2.4)	34 (6.4)	47 (4.4)
	SAR 439459	0	1 (0.1)	1 (0.1)
	ZIMBERELIMAB	0	1 (0.1)	1 (0.1)
Cytotoxic chemotherapy		34 (6.4)	44 (8.3)	78 (7.3)
	CABOZANTINIB	1 (0.2)	1 (0.2)	2 (0.2)
	CAPECITABINE	1 (0.2)	0	1 (0.1)
	CARBOPLATIN	11 (2.1)	15 (2.8)	26 (2.4)
	CISPLATIN	10 (1.9)	19 (3.6)	29 (2.7)
	CISPLATIN; GEMCITABINE HYDROCHLORIDE	0	1 (0.2)	1 (0.1)
	DOCETAXEL	5 (0.9)	3 (0.6)	8 (0.8)
	DOXORUBICIN	1 (0.2)	1 (0.2)	2 (0.2)
	ENFORTUMAB VEDOTIN	1 (0.2)	1 (0.2)	2 (0.2)
	FLUOROURACIL	1 (0.2)	1 (0.2)	2 (0.2)
	FLUOROURACIL; GLUCOSE	0	1 (0.2)	1 (0.1)
	GEMCITABINE	16 (3.0)	22 (4.2)	38 (3.6)
	GEMCITABINE HYDROCHLORIDE	2 (0.4)	7 (1.3)	9 (0.8)
	METHOTREXATE	0	1 (0.2)	1 (0.1)
	METHOTREXATE SODIUM	1 (0.2)	0	1 (0.1)
	MITOMYCIN	1 (0.2)	1 (0.2)	2 (0.2)
	NEDAPLATIN	0	1 (0.2)	1 (0.1)
	OXALIPLATIN	1 (0.2)	1 (0.2)	2 (0.2)
	PACLITAXEL	10 (1.9)	6 (1.1)	16 (1.5)
	PEMETREXED	1 (0.2)	1 (0.2)	2 (0.2)
	PIRARUBICIN	0	1 (0.2)	1 (0.1)
	TEGAFUR; URACIL	1 (0.2)	0	1 (0.1)
	VINBLASTINE	1 (0.2)	0	1 (0.1)

Anticancer Therapy ^a	Treatment	Number (%) of patients		
		Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1063)
	VINBLASTINE SULFATE	0	1 (0.2)	1 (0.1)
	VINFLUNINE	3 (0.6)	2 (0.4)	5 (0.5)
Targeted therapy		3 (0.6)	7 (1.3)	10 (0.9)
	ENFORTUMAB VEDOTIN	2 (0.4)	4 (0.8)	6 (0.6)
	ENFORTUMAB VEDOTIN EJFV	0	1 (0.2)	1 (0.1)
	NIRAPARIB	1 (0.2)	0	1 (0.1)
	SACITUZUMAB GOVITECAN	0	1 (0.2)	1 (0.1)
	TRASTUZUMAB DERUXTECAN	0	1 (0.2)	1 (0.1)
Radiopharmaceuticals		1 (0.2)	0	1 (0.1)
	YTTRIUM (90 Y) CHLORIDE	1 (0.2)	0	1 (0.1)
Other		8 (1.5)	6 (1.1)	14 (1.3)
	ENFORTUMAB VEDOTIN	3 (0.6)	2 (0.4)	5 (0.5)
	ENFORTUMAB VEDOTIN EJFV	3 (0.6)	4 (0.8)	7 (0.7)
	LETROZOLE	1 (0.2)	0	1 (0.1)
	SACITUZUMAB GOVITECAN	1 (0.2)	0	1 (0.1)

Abbreviations C: Cisplatin; D: Durvalumab; G: Gemcitabine.

^a Therapies recorded after the discontinuation of study treatment. Source: CSR DCO IA2 AstraZeneca

A9. PRIORITY: CS Section 3.5.6, p.138, states that “Whilst many of the subsequent treatments received” following treatment discontinuation in the NIAGARA trial “are commonly used in UK clinical practice, some of the proportions received are not reflective of the UK.”

- a. Please elaborate on this comment and clarify which therapies and proportion of patients who received them are and are not reflective of UK practice.**

The NIAGARA trial was a global, multicentre study, which means that post-progression clinical practice—including the use of subsequent therapies—varied between centres. This variation was influenced by the range of approved and reimbursed therapies available in each country, as well as the local availability of clinical trials or use of non-approved agents in compassionate use settings. Consequently, while many of the subsequent treatments received in the NIAGARA

trial align with standard UK clinical practice, some therapies and the proportions of patients receiving them are not fully representative of UK practice.

A key reason for this discordance relates to certain immunotherapy and targeted therapy options that were permitted within the context of the trial but are not routinely used in UK clinical practice. For example, some investigational agents, immunotherapies not yet approved or reimbursed in the UK, and targeted therapies available only in specific markets were accessed by patients in some countries participating in NIAGARA. Conversely, other treatments (e.g., erdafitib) are recommended by NICE but were not received in the trial. In addition, access to clinical trials or expanded access programs would have further shaped treatment choices in some regions.

Table 4 provides a summary of the subsequent anti-cancer treatments included in Table 3, with detailed annotations on which therapies are not relevant in the UK context and the proportion of patients in NIAGARA who received each treatment.

Table 4: Post-discontinuation disease-related anticancer treatment not representative of UK clinical practice

Treatment	Number (%) of patients			Reason to not consider the treatment as UK clinical practice
	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1063)	
ENFORTUMAB VEDOTIN / ENFORTUMAB EJFV	10 (2%)	12 (2%)	22 (2%)	NICE FDG expected publication date 21st August 2025 ID6332
SACITUZUMAB GOVITECAN	0	2 (0.4%)	2 (0.2%)	NICE appraisal discontinued 19 June 2025 ID6150
TRASTUZUMAB DERUXTECAN	0	2 (0.4%)	2 (0.2%)	NICE awaiting development for unresectable or advanced HER2-positive solid tumours
NIRAPARIB	1 (0.2%)	0	1 (0.1%)	Under investigation
YTTRIUM (90 Y) CHLORIDE	1(0.2%)	0	1 (0.1%)	Not approved, used or under investigation for bladder cancer
ZIMBERELIMAB	0	1(0.2%)	1 (0.1%)	Under investigation
CEMPLIMAB	0	1(0.2%)	1 (0.1%)	Under investigation
DOMVANALIMAB	0	1(0.2%)	1 (0.1%)	Under investigation
BINTRAFUSP ALFA	0	1(0.2%)	1 (0.1%)	Investigation ended
DURVALUMAB	0	1(0.2%)	1 (0.1%)	Under investigation

Treatment	Number (%) of patients			Reason to not consider the treatment as UK clinical practice
	Perioperative durvalumab arm (D+G+C) (N=533)	Control arm (G+C) (N=530)	Total (N=1063)	
PEMBROLIZUMAB	13 (2.4%)	34 (6.4%)	47 (4.4%)	Appraisal terminated 2021
SAR439459	0	1(0.2%)	1 (0.1%)	Under investigation

Abbreviations: C: cisplatin; D: durvalumab; FDG: final draft guidance; G: gemcitabine; HER2: human epidermal growth factor receptor 2; NICE: National Institute for Health and Care Excellence; UK: United Kingdom.

It is also important to note that, while post-discontinuation chemotherapy is established practice in the UK, the specific regimens and sequencing of therapy can vary internationally. Therefore, adapting the subsequent therapy data from NIAGARA to reflect UK clinical practice—through detailed consultation with UK-based clinical experts—has been an essential step in ensuring an accurate and meaningful cost-effectiveness evaluation of perioperative durvalumab for the UK NHS.

b. Please discuss the extent to which differences in subsequent therapies between the NIAGARA trial and NHS practice may affect the applicability of OS estimates from NIAGARA to NHS practice.

The proportion of patients receiving subsequent therapy in the NIAGARA trial was relatively low overall (13.7%). The use of immune-oncology (IO) agents as subsequent therapy following discontinuation in either treatment arm was 7.5% overall, with a higher use in the control arm (11.7%) compared to perioperative durvalumab arm (3.4%). This pattern supports that the observed statistically significant OS benefit can be primarily attributed to perioperative durvalumab itself rather than to differences in later lines of therapy. Given the low frequency of subsequent therapies, their potential influence on overall survival outcomes is inherently limited.

Furthermore, as detailed in CS Section 2.6.7 and previously mentioned in Question A7, PFS-2 outcomes show that even after progression and initiation of a subsequent anticancer therapy, patients in the perioperative durvalumab arm demonstrated superior outcomes compared to the control arm, with a 24% PFS-2 improvement observed. Since this benefit cannot be explained by a greater use of innovative therapies in the perioperative arm, this indicates that the sustained separation of the Kaplan–Meier curves beyond six months underscores the durable clinical benefit of perioperative durvalumab seen in NIAGARA.

The feedback from UK clinical experts suggested that there would be a higher proportion of patients receiving subsequent therapies in clinical practice, with experts agreeing that IO-based regimens are an important post-progression treatment option to be considered in the management of MIBC (see response to Question B12 and Company submission Section 3.5.6). It is challenging to quantify the potential impact on OS resulting from increased subsequent therapy use in both arms, but we contend that the relative treatment effect observed in the NIAGARA trial would likely be preserved, and that differences in the use of subsequent therapies between the NIAGARA trial and NHS practice are unlikely to meaningfully affect the applicability of the trial's OS estimates to NHS clinical practice.

Indirect treatment comparisons (ITC)

A10. Section 2.9.2 of the CS, when describing Step 1 of the ITC, please provide details of the software and packages used to:

a. Reconstruct the Kaplan-Meier (KM) data;

WebPlotDigitizer (v5) was used to recover data from published KM curves. Pseudo patient data were recovered from published KM plots using the Guyot et al. algorithm (21, 22).

b. Fit all accelerated failure time (AFT) models (including the flexible parametric models);

The analysis was performed in R version 4.3.2 using the flexsurv package.

c. Calculate the time-varying acceleration factor (AF) (the CS mentions the “flexure” package for estimating quantiles of the fitted survival models but does not specify the software used).

The analysis was performed in R version 4.3.2 using the flexsurv package. “flexure” was a typographical error.

A11. Section 2.9.2 of the CS, when describing Step 1 of the ITC, please clarify what quantiles were used in all analyses, and whether the AF estimates were sensitive to the choice of quantiles.

In a standard AFT model, the treatment effect (i.e., the AF) is modelled as a constant multiplicative shift in the outcome distribution across all survival quantiles. Standard models were used for EFS and OS base case. The time-varying AF allows the ratio of quantiles (and hence AFs) to vary over quantile (and hence time) (23). Time-varying analyses were only used in the sensitivity analysis for DFS as the standard AFT models yielded a sufficient fit to the trial data for OS, as described in the CS page 79-80.

Quantile survival times ranging from 0.01 to 0.99 for each arm were estimated using the best-fitting model and the predict function from the flexsurv package. Steps of 0.01 were considered sufficiently granular to capture time-varying changes in the AF. The range used (0.01-0.99) captures the full range of possible quantiles. The AF by quantile time for DFS was provided in Appendix B4 Figure 7. The time-varying AF (using the 3-knot spline model) followed an approximately bell-shaped curve with a single peak. These results suggest that the effect of nivolumab (compared to a null AF of 1.0) initially declines up to the 10th quantile, before increasing over time ('delayed effect'), peaking around the median (50th) quantile, before diminishing in the long term. Across all quantiles, the constant AF based on the log-logistic model was 4.13.

A12. PRIORITY: In the CS (paragraph before Table 28) it states that hazard ratios (HRs) for event-free survival (EFS) excluding re-censoring are shown in Appendix B.4. Similarly, in the paragraph before Table 29, it is stated that HRs for OS excluding re-censoring are shown in Appendix B.4. Please provide the table numbers in Appendix B.4 where these are available or reproduce the tables here if missing.

EFS HR excluding re-censoring for the base case analysis and OS HR excluding HR were mistakenly omitted from the Appendix, thank you for raising this.

Table 5 presents the hazard ratios for EFS with and without re-censoring. Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of NIAGARA, due to the effect of nivolumab in extending (by a factor of 4.13) survival

times in the G+C+ nivolumab (N) arm. The application of re-censoring leads to similar follow-up across arms. The impact of re-censoring on the HR is very minimal.

Table 5: Hazard ratios and 95% Confidence intervals for EFS comparing versus G+C and G+C+N (loglogistic)

	HR vs G+C ('Control arm')			HR vs G+C+N ('Counterfactual arm')		
	HR ¹	Lower 95% CI ¹	Upper 95% CI ¹	HR ¹	Lower 95% CI ¹	Upper 95% CI ¹
Without re-censoring						
G+C						
D+G+C						
G+C+N						
xxxx xx-xxxxxxxxxx						
G+C						
D+G+C						
G+C+N						

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; EFS: event-free survival; G: gemcitabine; HR: hazard ratio; N: nivolumab.

Table 6 presents the hazard ratios for OS with and without re-censoring. Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of NIAGARA, due to the effect of nivolumab in extending (by a factor of) survival times in the G+C+N arm. The application of re-censoring leads to similar follow-up across arms. The impact of re-censoring on the HR is very minimal.

Table 6: Hazard ratios and 95% Confidence intervals for OS comparing versus G+C and G+C+N

	HR vs G+C ('Control arm')			HR vs G+C+N ('Counterfactual arm')		
	HR ¹	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
Without re-censoring						
G+C						
D+G+C						
G+C+N						
With re-censoring						
G+C						
D+G+C						
G+C+N						

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; G: gemcitabine; HR: hazard ratio; OS: overall survival; N: nivolumab.

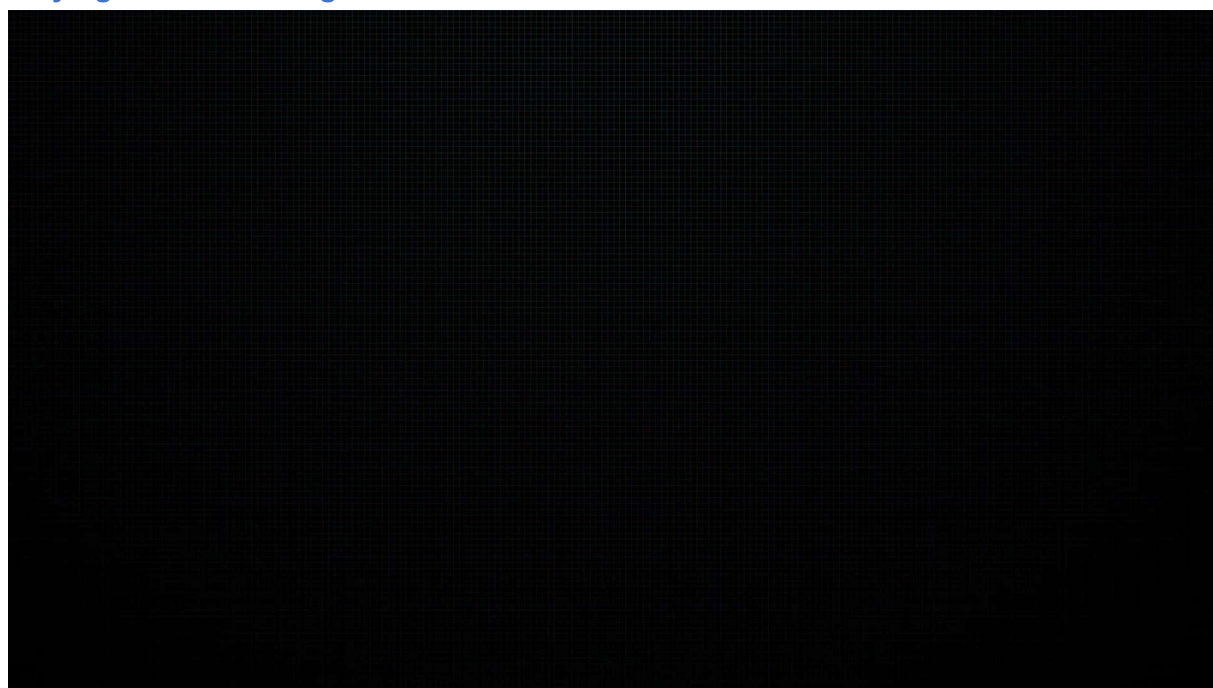
A13. To better understand the difference between results using the constant and time-varying AF for EFS (with re-censoring), please produce a KM plot for these two options, i.e. a plot that includes the data in Figure 19 of the Main submission

and in Figure 10 of Appendix B. The scale of the plot can be changed if that will help distinguish the curves.

Figure 1 provides a comparison of the Kaplan-Meier survival probabilities for EFS with re-censoring using the constant (red dotted line) and time-varying AFs (blue dotted line). The curves are presented alongside the Kaplan-Meier survival probabilities for the original G+C arm (green line). As suggested, the plot y-axis has been re-scaled to between 40 and 100% to help distinguish the curves.

The plot shows that any separation in the curves is observed during the initial period from approximately month 6 to month 30, with the time-varying AF analysis producing a lower (i.e. inferior) survival curve than the constant AF approach. Beyond month 30, there is little difference in survival across arms. This comparison confirms that the constant AF approach used in the base case provides the most conservative estimate of the effect of G+C+N, and that the choice of constant or time-varying AFs has a very limited impact on survival.

Figure 1: Kaplan-Meier plot showing the EFS with re-censoring for constant AF, time-varying-AF and the original G+C arm



Abbreviations: AF: acceleration factor; C: cisplatin; EFS: event-free survival; G: gemcitabine; N: nivolumab.

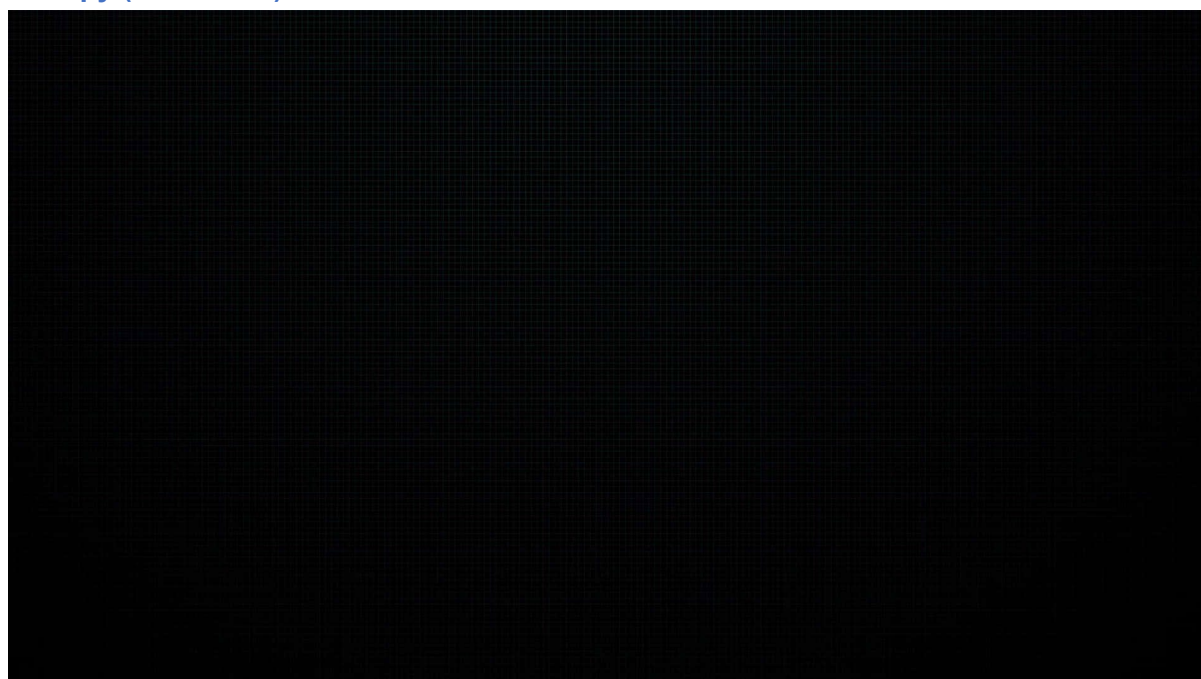
A14. Appendix B, paragraph below Figure 5, gives the “AF estimated for the MIBC subgroup (x.xx)”. Please provide a source for this value along with its 95% confidence interval.

The value “x.xx” was a typographical error.

A15. Appendix B, Figure 8: the colours on the pie chart do not match the colours in the legend. Please provide an update figure with correct labelling and with each percentage clearly displayed on the chart. Alternatively provide a table with the percentages clearly presented.

The colours in the Appendix B Figure 8 pie chart were formatted to emphasise the proportion with 'high risk, PD-L1 expression, with no residual disease after surgery'. An alternative revised pie chart (Figure 2) and table (Table 7) are provided below.

Figure 2: Chart showing the proportion of patients from the NIAGARA trial eligible for therapy (full colour)



Abbreviation: PD-L1: programmed death-ligand 1.

Table 7: Proportion of patients from the NIAGARA trial eligible for therapy (full colour)

Status	Eligible	n	Prevalence
Low risk with residual disease after surgery	N	■	■
High risk with residual disease after surgery	N	■	■
High risk, PD-L1 expression, with no residual disease after surgery	Y	■	■
High risk, non-PD-L1 expression, with no residual disease after surgery	N	■	■
No surgery	N	■	■
Low risk with no residual disease after surgery	N	■	■

Abbreviations: PD-L1: programmed death ligand 1;

A16. PRIORITY: Appendix B, Table 59 shows the HR for disease-free survival (DFS), for Nivolumab-eligible patients in NIAGARA (based on the counterfactual calculation) compared to no adjuvant Nivolumab after surgery.

a. Please confirm if these results are based on the data in the KM curves displayed in Figure 9 and that they are based on [REDACTED] and [REDACTED] patients, respectively.

In total, [REDACTED] patients [REDACTED] from the NIAGARA control arm (G+C) were considered eligible for adjuvant nivolumab, having fulfilled the following criteria:

- undone cystectomy;
- disease-free at the adjuvant baseline visit/no residual disease after surgery;
- tested positive for tumour PD-L1 expression >1%; and,
- considered at a high risk of recurrence.

The calculated AF for adjuvant nivolumab was applied to this control arm, forming the counterfactual arm. The HR reported in Table 59 of Appendix B was estimated from a Cox regression model fitted to a dataset containing the survival times and event flags of nivolumab-eligible patients in the control and counterfactual arms ([REDACTED] in both arms). The HR can be interpreted as the treatment effect of adjuvant nivolumab on DFS, estimated through the application of the CheckMate-274 AF. Therefore, there were also [REDACTED] in the counterfactual arm to calculate the HR in Table 59.

Table 58 in Appendix B provides a summary of eligibility for adjuvant nivolumab in the NIAGARA trial, including number of patients and prevalence. The [REDACTED] patients referenced are those in the control arm of NIAGARA who were low risk, or high-risk without PD-L1 who had undergone surgery and were disease-free at adjuvant visit ([REDACTED]). These were not used to calculate the HR in Table 59.

b. Please comment on how this HR should be interpreted, particularly compared to the HR for adjuvant Nivolumab compared to Placebo in CheckMate-274, noting the differences in populations and assumptions.

Appendix B Table 59 presents the Cox regression analysis comparing adjuvant nivolumab with no treatment in the PD-L1 positive ($\geq 1\%$) high-risk subgroup of the NIAGARA trial and which yielded a hazard ratio of 0.38 (95% CI 0.22-0.66), indicating that adjuvant nivolumab was associated with a 62% reduction in the risk of a DFS event compared to no adjuvant treatment. This is aligned with the DFS hazard ratio in CheckMate-274 (0.44, 95% CI 0.30 to 0.63) for MIBC patients with PD-L1 $\geq 1\%$ (7).

The subgroup data available from CheckMate-274 is shown in Table 8. CheckMate-274 includes patients with MIBC and muscle-invasive urothelial carcinoma (MIUC). For the comparison to NIAGARA, it is important to use the MIBC subgroup from CheckMate-274 in order to reflect the population of this appraisal. The EMA regulatory label and NICE recommendation is in patients who have PD-L1 $\geq 1\%$, therefore it is also important to consider the PD-L1 $\geq 1\%$ subgroup from CheckMate-274. CheckMate-274 reports efficacy data for the PD-L1 $\geq 1\%$ and MIBC subgroup but not baseline characteristics. The PD-L1 $\geq 1\%$ and MIBC subgroup from the CheckMate-274 trial was selected for the analysis as it corresponds closest with the population in the NICE recommendation for adjuvant nivolumab in this setting (24).

Table 8: Subgroup data available from CheckMate-274 trial

Patient subgroup from CheckMate-274	Baseline characteristics available?	Efficacy data available?
MIUC (ITT)	Yes	Yes
MIBC	Yes	Yes
PD-L1	Yes	Yes
<i>PD-L1 and MIBC*</i>	No	Yes
PD-L1 and prior NAC	No	Yes (HR only)
MIBC and prior NAC	No	Yes
PD-L1 and MIBC and prior NAC	No	No

Abbreviations: HR: hazard ratio; ITT: intention-to-treat; MIUC: muscle-invasive urothelial carcinoma; MIBC: muscle-invasive bladder cancer; NAC: neoadjuvant chemotherapy; PD-L1: programmed death-ligand 1.

* aligns with NICE recommendation for adjuvant nivolumab and NIAGARA trial

For the analysis to be possible, it was necessary to assume that the relative effects of nivolumab in the MIBC PD-L1 positive subgroup of CheckMate-274 are generalisable

to the corresponding NIAGARA population. The CheckMate-274 PD-L1 $\geq 1\%$ population has been compared to the NIAGARA population eligible for adjuvant nivolumab (high risk with PD-L1 $\geq 1\%$) in Table 9. Baseline characteristics for PD-L1 $\geq 1\%$ and MIBC could not be identified from CheckMate-274 (7, 25), and therefore the comparison is to the PD-L1 $\geq 1\%$ subgroup patient characteristics. After restricting the NIAGARA population to those that would be eligible for nivolumab, PD-L1 status, age and gender are similar between the populations. Due to differences in available data, a comparison of tumour stage between NIAGARA and CheckMate-274 is not possible. Both studies report tumour stage at study baseline, which is at different timepoints in the treatment pathway and so cannot be compared (i.e., at initiation of neoadjuvant treatment for NIAGARA and at resection for CheckMate-274).

Prior cisplatin use is notably different between the populations: whilst all participants in the NIAGARA trial received neoadjuvant gemcitabine plus cisplatin, 40.7% of CheckMate-274 participants randomised to nivolumab with PD-L1 $\geq 1\%$ received prior cisplatin (prior gemcitabine plus cisplatin use not reported). As listed in Table 8, prior and no prior cisplatin subgroup results (HR for DFS) have been published for the PD-L1 $\geq 1\%$ and MIBC populations, but not for the MIBC PD-L1 $\geq 1\%$ population. In the absence of these subgroup results, it is unclear whether prior receipt of cisplatin therapy would further modify the effect of nivolumab in the treatment of patients with PD-L1 MIBC. Furthermore, we do not know the proportion of MIBC PD-L1 $\geq 1\%$ patients who received prior neoadjuvant cisplatin.

The differential timing of treatment decisions in the studies and lack of reporting of patient characteristics for subgroups has precluded an extensive comparison of characteristics between trials. However, where characteristics are available in both trials, the studies can be considered similar, although a difference in the proportion that received prior neoadjuvant cisplatin remains between studies. Due to the reporting of the CheckMate-274 trial, it is not possible to adjust for prior neoadjuvant cisplatin in the analysis of the PD-L1 positive MIBC population; however, a scenario analysis has been provided in response to question A17 which considers this subgroup.

Table 9: Comparison of baseline characteristics between NIAGARA high risk PDL1 positive control and CheckMate-274 PDL1 positive nivolumab arm

Characteristic	NIAGARA high risk with PD-L1 $\geq$ 1%, gemcitabine plus cisplatin arm N = 73	CheckMate-274 PD-L1 $\geq$ 1%, nivolumab arm (25) N= 140
Prior neoadjuvant treatment		
Gemcitabine plus cisplatin	73 (100%)	57 (40.7%)*
Age	Median (IQR): 63 (58, 69)	Mean (range) 64.4 (34-92)
Sex		
Female	15 (21%)	39 (27.95%)
Male	58 (79%)	101 (72.1%)
1 n (%); Median (IQR) * number who received neoadjuvant cisplatin, data on combination with gemcitabine not available		

Abbreviations: IQR: interquartile range; PD-L1: programmed death-ligand 1.

A17. PRIORITY: Evidence for the relative efficacy of nivolumab vs. placebo is drawn from a subgroup from CheckMate-274 that includes participants with and without prior neoadjuvant chemotherapy, rather than only patients with prior neoadjuvant chemotherapy. This limits the comparability between the NIAGARA and CheckMate-274 populations included in the ITC. Please discuss whether, and to what extent, this mix introduces uncertainty in the ITC results and consider exploring results for alternative subgroups, where available.

The PD-L1 MIBC subgroup from CheckMate-274 was selected for the analysis as it aligns closest with the NICE recommendation for adjuvant nivolumab. Once the relevant subgroups from NIAGARA were selected to align with this population, available patient characteristics were considered similar (see response to Question A16b). There is no evidence of whether prior cisplatin use further modifies the effect of nivolumab in patients with PD-L1 MIBC, and we do not know the proportion of PD-L1 MIBC patients that received prior neoadjuvant cisplatin. The use of other published subgroups, such as MIBC with prior cisplatin (i.e., not restricting to PD-L1 patients) (7, 25), means using a population which is outside the label of adjuvant nivolumab in the UK and outside NICE recommendations (24, 26).

A18. The NIAGARA trial included [REDACTED] patients with high risk of recurrence and PD-L1 $\geq$ 1% patients, out of [REDACTED] who underwent surgery and were disease-free at adjuvant visit.

a. Please comment on whether this proportion is reflective of NHS practice (and provide sources where appropriate).

The observed proportion of 21.7% of patients with high risk of recurrence after surgery and PD-L1 $\geq$ 1% in the NIAGARA trial is considered appropriate and reflective of NHS practice. It is expected that the overlap between adjuvant nivolumab and perioperative durvalumab would be very limited. Nivolumab is positioned as a rescue or escalation therapy, given only to those who, following surgery, are found to have both high risk of recurrence and PD-L1 $>$ 1%. In contrast, perioperative durvalumab is anticipated to be used proactively in all cisplatin-eligible patients from the neoadjuvant setting, meaning the relevant populations for each intervention are fundamentally distinct. This distinction is further compounded by the different timing of eligibility assessment: while adjuvant nivolumab is only considered for patients assessed as high-risk after surgery, perioperative durvalumab eligibility is established before surgery. As a result, the extent of overlap between the populations cannot be prospectively quantified. In addition, adjuvant nivolumab is used in NHS clinical practice in both cisplatin-eligible and cisplatin-ineligible patients with high risk of recurrence. Therefore, figures for adjuvant nivolumab from sources such as the SACT dataset cannot be assumed to accurately reflect use within the narrower appraisal population.

To ensure that the two key elements for estimating the overlap—the positioning of adjuvant nivolumab in clinical practice and the patient population in the NIAGARA trial—accurately reflect NHS clinical practice, both factors were discussed with UK-based clinical experts as part of the company's clinical validation. These experts confirmed that both the approach and the expected proportion of patients with high-risk of recurrence and PD-L1 $\geq$ 1% are consistent with what is observed in UK clinical practice. Furthermore, the company's methodology for the ITC specifically captures this full positioning of nivolumab for the relevant appraisal population—namely, patients who have received neoadjuvant chemotherapy, are high risk at the adjuvant baseline, and have PD-L1 $>$ 1%. This is considered the best available approach given existing clinical data.

Finally, both the ITC methodology and its outcomes were validated with UK-based clinical and HTA experts to ensure alignment with NHS routine practice, as described in the company's submission. No additional factors beyond those encompassed by the positioning of adjuvant nivolumab according to the BlueTeq criteria for the population under scope, cisplatin eligibility, and radical cystectomy eligibility criteria influence the use of G+C+N in the NHS. All these factors are captured in the estimation performed.

In conclusion, based on the differentiated positioning of each therapy, the specific eligibility criteria at different treatment stages, the clinical expert validation processes, and methodological considerations, the [REDACTED] observed in NIAGARA provides an appropriate and representative estimate for NHS practice.

It is important to note that the ITC results and their integration into the cost effectiveness model (CEM) were included as a scenario to address specific questions from the NICE scope, despite having limited impact on decision making.

- b. The EAG considers that the ITC results presented in Tables 28 and 29 of the CS may be sensitive to assumptions about the prevalence of high-risk PD-L1 $\geq$ 1% patients. Please comment on the extent to which assumptions about the prevalence of high-risk PD-L1 $\geq$ 1% patients in the adjuvant setting may affect the ITC results, supported by sensitivity analyses as appropriate.**

As outlined in response to question A18 a, [REDACTED] of patients in the NIAGARA trial were identified as being at high risk of recurrence after surgery and PD-L1 $\geq$ 1%, which is considered representative of UK clinical practice. This proportion is fixed, as the ITC relies on the observed control arm data in the NIAGARA trial to inform the counterfactual (G+C+N) arm. Changing the proportion of nivolumab eligible patients in the control arm of NIAGARA is not possible as we have not observed the outcomes for a population with a different prevalence of high-risk PD-L1 $\geq$ 1% status that would be eligible for nivolumab.

A19. PRIORITY: Please supply the ITC analysis and results for distant metastasis-free survival (DMFS) as this outcome is used in the economic model and KM curves in the 3-year extended follow-up of the CheckMate-274 trial(27)

for the MIBC population with PD-L1 expression $\geq 1\%$ are available. Alternatively, please explain why DMFS was not considered in the ITC.

We have performed an ITC with the DMFS endpoint using the same approach as previously described for the EFS and OS ITCs. In short, the analysis involved estimating the acceleration factor (AF) for nivolumab versus placebo from pseudo-patient data recovered from the DMFS curve of the PD-L1 MIBC subgroup of CheckMate-274, reported in supplementary figure 4D of Galsky et al, and applying this AF to the 'adjuvant period' MFS survival times of the G+C arm of NIAGARA.

The aim of the analysis was to estimate the MFS for the control arm of NIAGARA that included the effect of adjuvant nivolumab (referred to as "counterfactual arm"). The ITC is then performed by comparing D+G+C with this counterfactual arm (representing G+C+N), and by comparing G+C+N with G+C.

The full methodology and results are presented in Appendix - CQs. A summary of the results is presented here.

Estimated AF

The AF for nivolumab versus placebo was estimated using parametric survival models fitted to a data set containing both arms of CheckMate-274 and including a treatment covariate. This covariate represents the effect of nivolumab in decelerating the time to an event compared to placebo. The best fitting model according to AIC and BIC was the generalised gamma. Based on visual fit, this model failed to adequately predict the trial data as it appeared to systematically underestimate survival in the nivolumab arm and overestimate survival in the placebo arm. Among the fitted models, the generalised gamma predicted the lowest AF for nivolumab versus placebo of [REDACTED].

With log-normal, log-logistic and Weibull, the AF's ranged from 2.89 to 3.37, with the log-logistic AFT yielding the most conservative (and largest) estimate of the effect of nivolumab. However, of these models, the Weibull demonstrated the poorest visual fit to the Kaplan-Meier data, with log-normal and log-logistic providing a similar level of fit to the DMFS curve. Due to time constraints, it was not possible to perform the ITC utilizing time-varying AFs for DMFS. Nevertheless, as observed in the ITCs for EFS,

implementing time-varying AFs had minimal impact on the outcomes and, when applied, generally resulted in a more conservative estimation of nivolumab's effect.

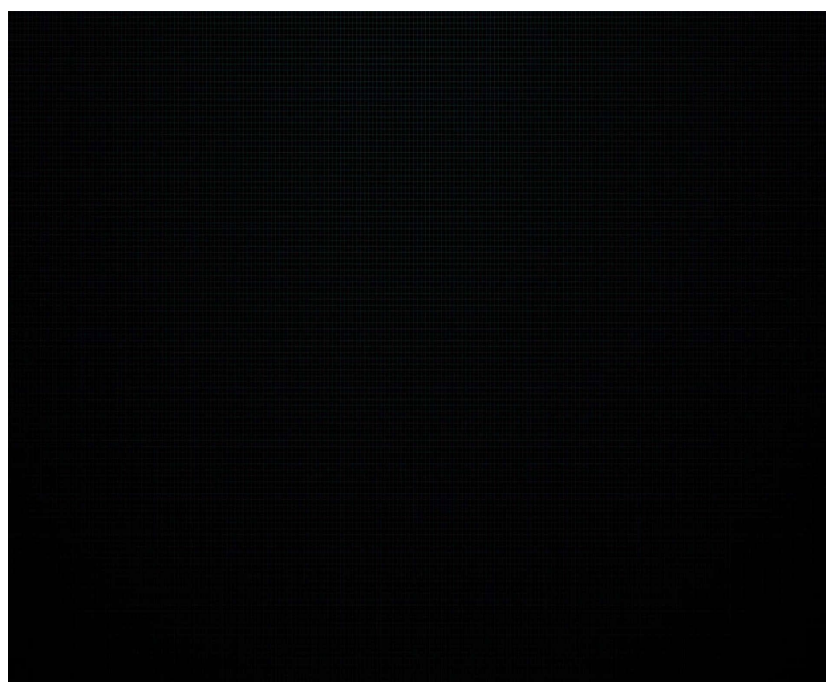
Of the standard AFT models, the log-logistic (AF= [REDACTED]) was considered most suitable for the ITC as it provided the most optimistic and conservative estimate of treatment effect for nivolumab.

Counterfactual Survival

The counterfactual arm was created using the control arm of NIAGARA and applying the AF of adjuvant nivolumab from CheckMate-274 to the 'adjuvant period' MFS survival times of patients eligible for treatment. As described previously in the Company Submission (Section 2.9.2), in total, [REDACTED] patients ([REDACTED]%) were considered eligible for adjuvant nivolumab having undergone cystectomy, were disease-free at the adjuvant baseline visit, tested positive for tumour PD-L1 expression >1% and considered at a high risk of recurrence.

Figure 3 presents the 'adjuvant period MFS' according to high with PD-L1 and other risk MIBC in the G+C arm of NIAGARA. As expected, patients with high-risk PD-L1 1% positive MIBC had inferior DFS when compared with patients with other risk MIBC.

Figure 3: Kaplan-Meier plot showing MFS according to high with PD-L1 and other risk status in the G+C arm of NIAGARA

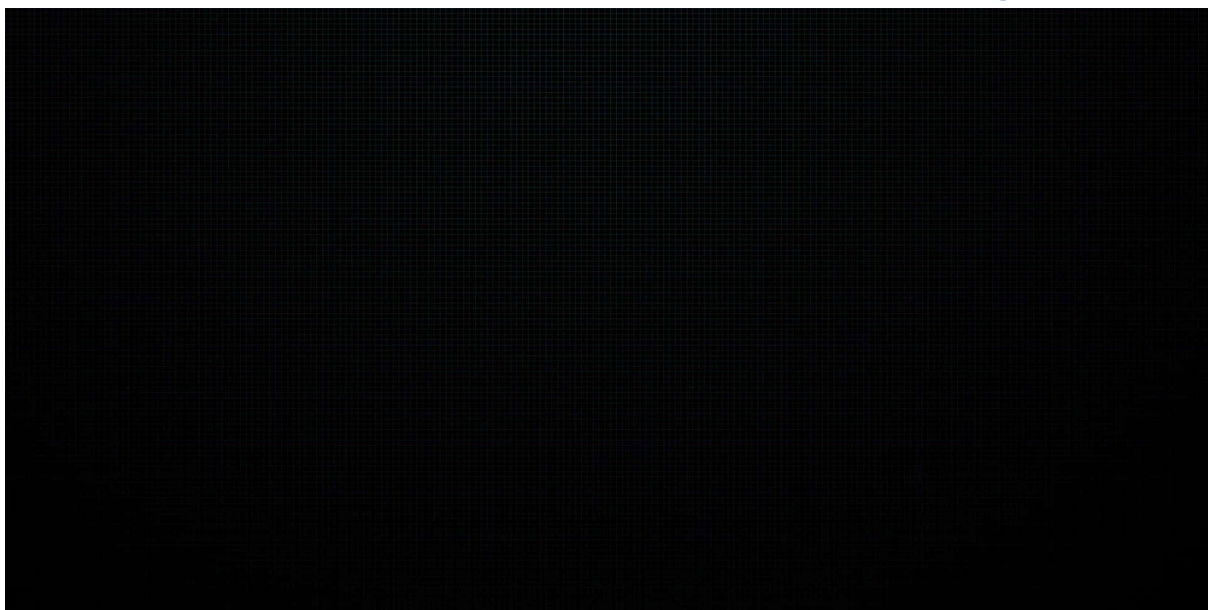


Abbreviations: C: cisplatin; G: gemcitabine; MFS: metastasis-free survival; PD-L1: programmed death-ligand 1.

Figure 4 presents the Kaplan-Meier curves for adjuvant-MFS for G+C and G+C+N in the high-risk PD-L1 and other groups using the constant AF from the log-logistic model.

As expected, the application of the AF for nivolumab to adjuvant-MFS in the eligible 'high-risk' PD-L1 cohort of NIAGARA led to improved outcomes, with adjuvant nivolumab increasing the time to distant metastatic disease (left panel). Patients with low risk or non-PD-L1 positive MIBC, and who are ineligible for adjuvant nivolumab, had the same outcomes across arms.

Figure 4: Kaplan-Meier plots for adjuvant-MFS in the high risk and non-high-risk groups in the control and counterfactual arm of NIAGARA (without re-censoring)



Abbreviations: C: cisplatin; G: gemcitabine; MFS: metastasis-free survival; N: nivolumab; PD-L1: programmed death-ligand 1.

The Cox regression analysis comparing adjuvant nivolumab with no treatment in the high-risk PD-L1 subgroup yielded a hazard ratio of [REDACTED], which is lower (and more favourable) than the corresponding DMFS hazard ratio in CheckMate-274 (0.52, 95% CI 0.35-0.78). This discrepancy may be due to several factors, including the use of a conservative estimate of the AF from the log-logistic model. The ITC may conservatively overestimate the effect of nivolumab.

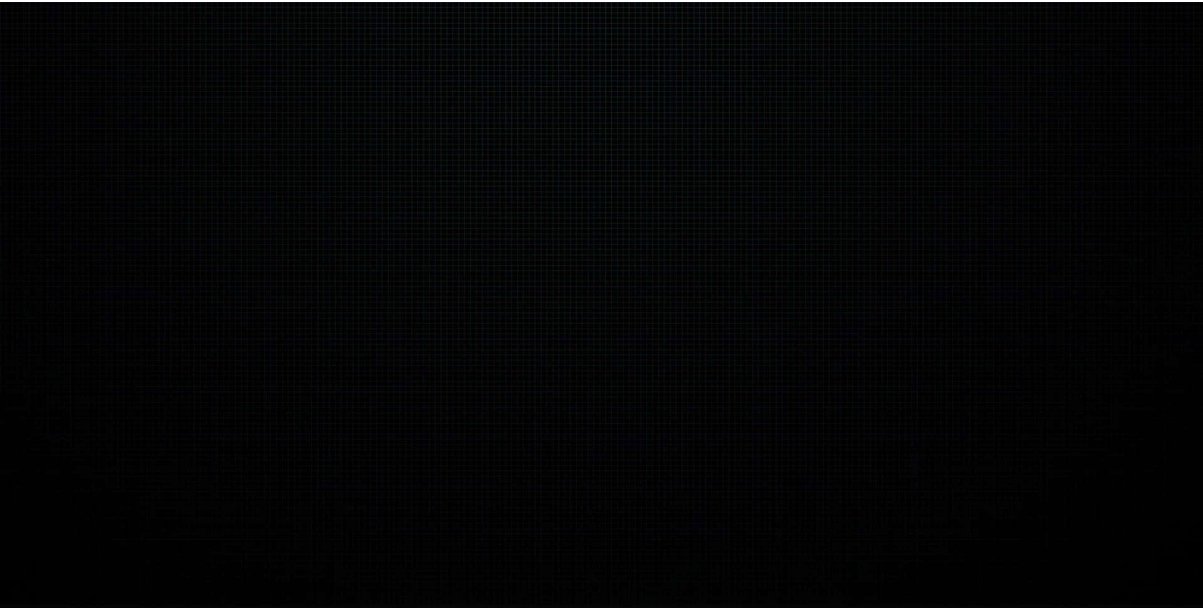
Indirect treatment comparison

Figure 5 presents the Kaplan-Meier plots of MFS for the D+G+C, G+C and G+C+N arms of NIAGARA, with and without the application of re-censoring.

Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of NIAGARA, due to the effect of nivolumab in extending (by a factor of ██████) adjuvant-MFS times in the counterfactual arm. The application of re-censoring leads to similar follow-up across arms.

In both analyses, perioperative durvalumab led to improved MFS versus both control and counterfactual arms, with the curves separating and favouring perioperative durvalumab after the first 6 months of study follow-up.

Figure 5: Kaplan-Meier plot of MFS comparing D+G+C with G+C and G+C+N, with and without re-censoring



Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; MFS: metastasis-free survival; N: nivolumab.

In both analyses, perioperative durvalumab led to improved MFS versus both control and counterfactual arms.

Table 10 presents the hazard ratios for MFS compared to the control and counterfactual arms.

Table 10: Hazard ratios and 95% Confidence intervals for MFS comparing versus G+C and G+C+N

	HR vs G+C ('Control arm')			HR vs G+C+N ('Counterfactual arm')		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
Without re-censoring						
G+C	██████████	██████████	██████████	██████████	██████████	██████████
D+G+C	██████████	██████████	██████████	██████████	██████████	██████████
G+C+N	██████████	██████████	██████████	██████████	██████████	██████████
With re-censoring						
G+C	██████████	██████████	██████████	██████████	██████████	██████████

	HR vs G+C ('Control arm')			HR vs G+C+N ('Counterfactual arm')		
	HR	Lower 95% CI	Upper 95% CI	HR	Lower 95% CI	Upper 95% CI
D+G+C	■	■	■	■	■	■
G+C+N	■	■	■	■	■	■
With re-censoring, piecewise (for use in economic models)						
G+C+N, 0-6 months	■	■	■	■	■	■
G+C+N, 6 months plus	■	■	■	■	■	■

Abbreviations: CI: confidence interval; C: chemotherapy; D: durvalumab; G: gemcitabine; HR: hazard ratio; MFS: metastasis-free survival; N: nivolumab.

The results show that perioperative durvalumab is associated with a significant (upper 95% confidence interval of less than one) improvement in MFS versus the control and counterfactual arms. The use of adjuvant nivolumab in the G+C+N arm led to a small numerical improvement in MFS versus G+C. The application of re-censoring had a minimal impact on the hazard ratio for MFS.

An assessment of the proportional hazards assumption has been provided in response to question A22.

When these HR are implemented in the model, there is a very minor change in total QALYs in the G+C+N arm, provided to three decimal places to distinguish between these options (Table 11). This translates into a minor increase in the ICER compared to the Company base case (£13,711 vs. £13,723, see Table 12), and demonstrates that D+G+C remains a highly cost-effective treatment option compared to G+C+N in this scenario. As outlined in the Company Submission, comparing adjuvant and perioperative settings presents challenges. Nevertheless, we have provided this analysis in response to the NICE final scope using a novel methodology. The relevance of nivolumab as a comparator in the perioperative setting remains uncertain, so these results should be considered as a scenario only.

Table 11: QALY breakdown in the G+C+N arm for EFS modelled with a HR vs. independently fit splines

QALY breakdown	Company submission using HR for EFS	CQ22a response using independent model for EFS
Progression free	■	■
Progressed disease	■	■
Loco-Regional recurrence	■	■
Distant recurrence	■	■

QALY breakdown	Company submission using HR for EFS	CQ22a response using independent model for EFS
Adverse events	████	████
Radical cystectomy	████	████
Total QALYs	████	████

Abbreviations: C: cisplatin; CQ: clarification question; EFS: event-free survival; G: gemcitabine; HR: hazard ratio; N: nivolumab; QALY: quality-adjusted life year.

Table 12: Incremental cost results for perioperative durvalumab versus G+C+N using DMFS

	Perioperative durvalumab	G+C+N	Incremental
Total costs (£)	████	████	<u>£20,416</u>
Total LYs	████	████	████
Total QALYs	████	████	████
ICER (£ per QALY)	-		<u>13,711</u>

Abbreviations: C: cisplatin; G: gemcitabine; ICER: incremental cost-effectiveness ratio; LY: life year; N: nivolumab; QALY: quality-adjusted life year.

A20. In the absence of an ITC for safety outcomes, please comment on the safety profile across the three interventions of interest: perioperative durvalumab (D+G+C), adjuvant nivolumab counterfactual (G+C+N) and the control arm (G+C).

The ITC focused on the key efficacy endpoints of EFS and OS. The ITC did not evaluate the safety and/or tolerability of D+G+C versus G+C+N. These endpoints are typically evaluated in terms of risk (ratios or differences) and/or odds (ratios) and are reported in terms of the number of patients with an event. Without Kaplan-Meier plots, it is not possible to utilize the survival-time adjusted method to predict safety outcomes with adjuvant nivolumab in NIAGARA. The comparison of safety outcomes across adjuvant phases is at the same risks of bias as the efficacy analysis, such as the impact of prior immunotherapy, prior chemotherapy and trial population.

To provide context to the EAG, some descriptive safety data from NIAGARA and CheckMate-274 are summarised below without any cross-trial comparison.

In the NIAGARA trial, the reported frequencies of grade 3 and 4 events were of similar magnitude in the D+G+C arm compared to the G+C arm, and these occurred predominantly during the neoadjuvant part of the study. This suggests that chemotherapy plays a contributory role in the most commonly reported grade 3 and 4

adverse events. When comparing the overall period of the NIAGARA study to the durvalumab pan-tumour pool, a higher incidence of grade 3 and 4 adverse events is observed in NIAGARA, which is to be expected given the platinum-based backbone of the regimen and its associated toxicity (28).

The risk of experiencing an immune-mediated adverse event (ImAE) during the overall period was 20.9% for patients receiving D+G+C, compared to 3% for those receiving G+C. For comparison, the risk of ImAEs in the Durvalumab Pan-tumour pool was 17.7%.

Based on the CheckMate-274 trial, treatment with adjuvant nivolumab was associated with an increased risk of any grade and grade 3 or above treatment-related adverse events when compared with placebo (Grade 3+: 17.3% vs. 5.8% in nivolumab and placebo arms, respectively, in the MIBC population). The proportion of immune-mediated adverse events observed was 34.5% in the nivolumab arm and 6.9% in the placebo arm. There is no safety data on G+C+N. The higher proportion of patients experiencing Grade 3+ treatment-related adverse events in the NIAGARA trial relative to the CheckMate-274 trial is consistent with the known safety profile of chemotherapy, which is already standard of care in UK clinical practice.

A21. Appendix B, paragraph below Figure 9 states that baseline characteristics of patients from NIAGARA eligible and non-eligible for Nivolumab are given in Table 58. However, this table just states the number of patients eligible or non-eligible for Nivolumab, along with reasons and does not include details of their characteristics, e.g. age, sex, staging, levels of PG-L1 expression, renal function etc. Please provide a table displaying the summary characteristics of the ■ patients in the NIAGARA control arm who were eligible for adjuvant nivolumab, after surgery and before adjuvant therapy. Please compare these patient characteristics with the MIBC/PD-L1 subgroup in the CheckMate-274 population, where available; or with the MIBC population of CheckMate-247 if patient characteristics for MIBC/PD-L1 subgroup are not available. (29) Please comment on any relevant differences, and provide AF estimates adjusted for those population differences with corresponding ITC results.

A comparison of the available patient characteristics in both trials has been included in response to question A16b.

Without access to the individual patient data for CheckMate-274, it is not possible to adjust the nivolumab acceleration factor for population differences between studies. The use of subgroup data from the MIBC and PD>L1≥1% or above subgroup of CheckMate-274 ensures that the ITC effect of adjuvant is in line with adjuvant nivolumab's NICE recommendation. Once the relevant subgroups from NIAGARA were selected to align with this population as closely as possible, available patient characteristics were considered balanced (see response to Question A16b).

A22. PRIORITY: Please provide a detailed assessment of the proportional hazards assumption (consistent with the methods used in Appendix L) across the three arms, after 6 months post-randomisation (piecewise approach used in the economic model), in the ITC i.e., the perioperative durvalumab (D+G+C, active), G+C (control) and G+C+N (counterfactual) arms of the NIAGARA trial, for both constant and time-varying acceleration factors.

A detailed assessment of the proportional hazards assumption in the NIAGARA trial for D+G+C vs. G+C was provided in the Company Submission Section 3.3.2. The proportional hazards assumption in the Company submission was assessed over the entire trial horizon, which is appropriate for modelling D+G+C. As outlined in Company evidence submission, there was uncertainty about whether the proportional hazards assumption was valid for EFS and OS for D+G+C vs. G+C and therefore the modelling was performed using independent parametric survival models fitted to patient-level data from each arm of NIAGARA study for both endpoints.

To support the application of a piecewise hazard ratio for G+C+N versus G+C in the economic model, the proportional hazards assumption in the post-6-month period has been evaluated using the Schoenfeld residual plot and the Grambsch-Therneau test statistic.

In the original submission, piecewise hazard ratios were provided for the base case analysis only (constant-AF with re-censoring), as the ITC results showed consistent outcomes across scenarios with and without re-censoring, and for the analysis involving time-varying Afs for EFS. The assessment of proportional hazards beyond month 6 for EFS and OS was therefore conducted for the base case only.

Figure 6 shows the Schoenfeld plot and test statistics for post-6-month EFS. The plot suggests some minor departure from the proportional hazards assumption after month

6 given a slight upward slope for the log-hazard ratio. Despite this, there was no significant trend to support departure from proportional hazards, $p>0.05$.

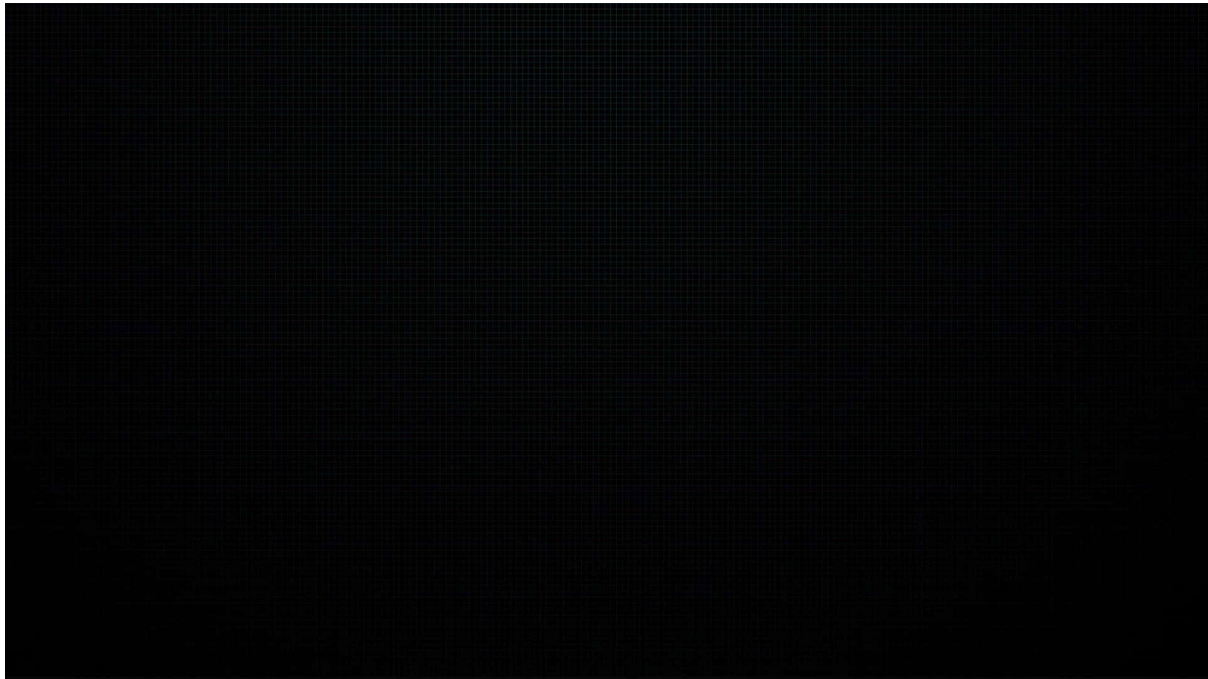
Figure 6: Schoenfeld residual plot for the hazard ratio of G+C+N vs G+C in the post-6-month period (EFS with censoring)



Abbreviations: C: cisplatin; EFS: event-free survival; G: gemcitabine.

The corresponding Schoenfeld plot and test statistics for post-6-month OS is shown in Figure 7. The plot suggests no major departure from the proportional hazards assumption given the absence of a clear slope in the log-hazard ratio over time and the test statistic of $p>0.05$.

Figure 7: Schoenfeld residual plot for the hazard ratio of G+C+N vs G+C in the post-6-month period (OS with censoring)

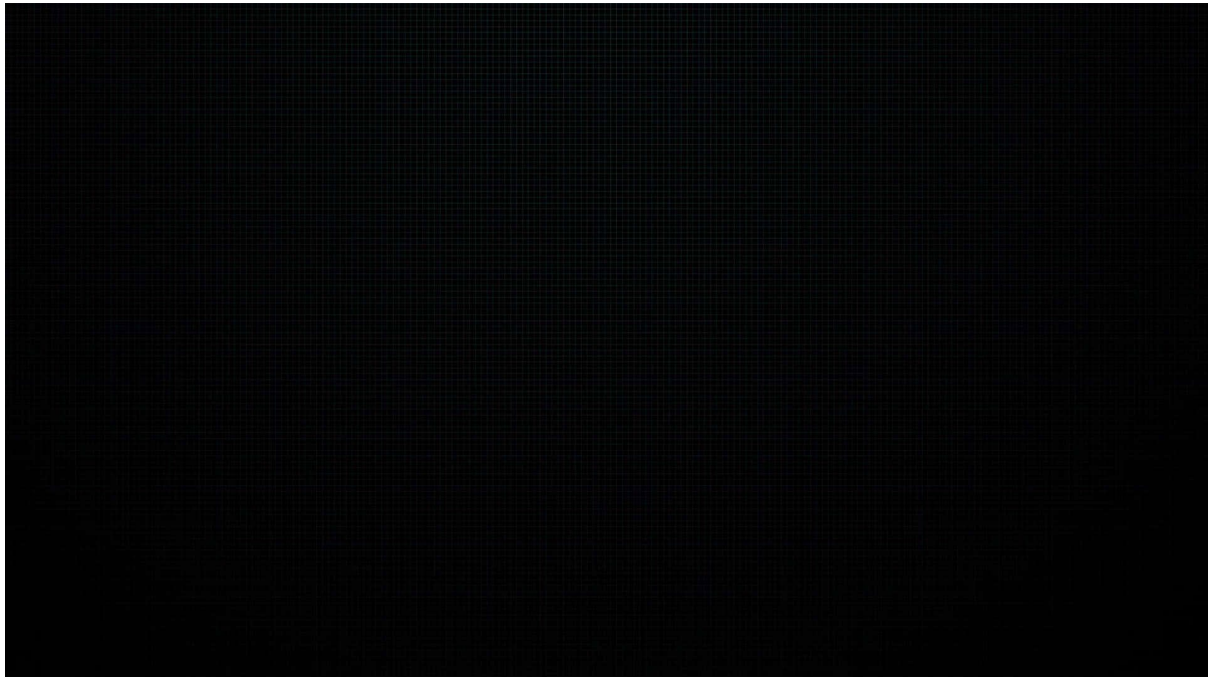


Abbreviations: C: cisplatin; G: gemcitabine; OS: overall survival.

For completeness, and to support the application of a piecewise hazard ratio for G+C+N versus G+C in the economic model, a test of the proportional hazards assumption in the post-6-month period of MFS was performed.

Figure 8 shows the Schoenfeld plot and test statistics. The plot supports the assumption of proportional hazards from month 6 onwards given the approximately straight line for the log-hazard ratio and the test statistic of $p > 0.05$.

Figure 8: Schoenfeld residual plot for the hazard ratio of G+C+N vs G+C in the post-6-month period (censored MFS)



Abbreviations: C: cisplatin; G: gemcitabine; MFS: metastasis-free survival.

- a. For outcomes in which the proportional hazards assumption is violated, please update the economic model to enable scenarios using independent parametric survival curves fitted to patient-level data of the perioperative durvalumab (D+G+C, active) and G+C+N (counterfactual) arms of the NIAGARA trial.**

Independent curves were used to model D+G+C for all endpoints, and this is justified in the Company submission.

For G+C+N, across the three endpoints of EFS, MFS and OS, there was no strong evidence of non-proportional hazards beyond 6-months, which would otherwise warrant the use of independent models in a base case analysis. However, as there were some minor departures for EFS, a series of independent survival models were fitted to the G+C+N arm and used to explore the impact of independent extrapolations instead of hazard ratios, on results.

Consistent with the base case selections for EFS for the D+G+C and G+C arms, the analysis was performed using flexible survival models (Royston-Parmar spline models) fitted to EFS for G+C+N. In total, 12 models were considered, including spline

models with hazard, odds and probit (normal') link functions and 1 to 4 knots. The models were fit to EFS (with re-censoring), as measured since randomization.

Table 13 provides a summary of the goodness of fit statistics (Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC]) for the 12 models, and Figure 9 and Figure 10 shows the accuracy of the models in predicting the Kaplan-Meier and hazard estimates.

According to AIC and BIC, the best fitting models were the 3-knot spline normal, odds and hazards models. Among these models, there was no clear difference in goodness of fit statistics. In terms of visual fit, all of the models produced a similarly accurate fit to the Kaplan-Meier and hazard function. Beyond follow-up, the curves yield a similar hazard pattern and long-term survival probabilities, indicating that the choice of model is unlikely to materially impact on model extrapolations.

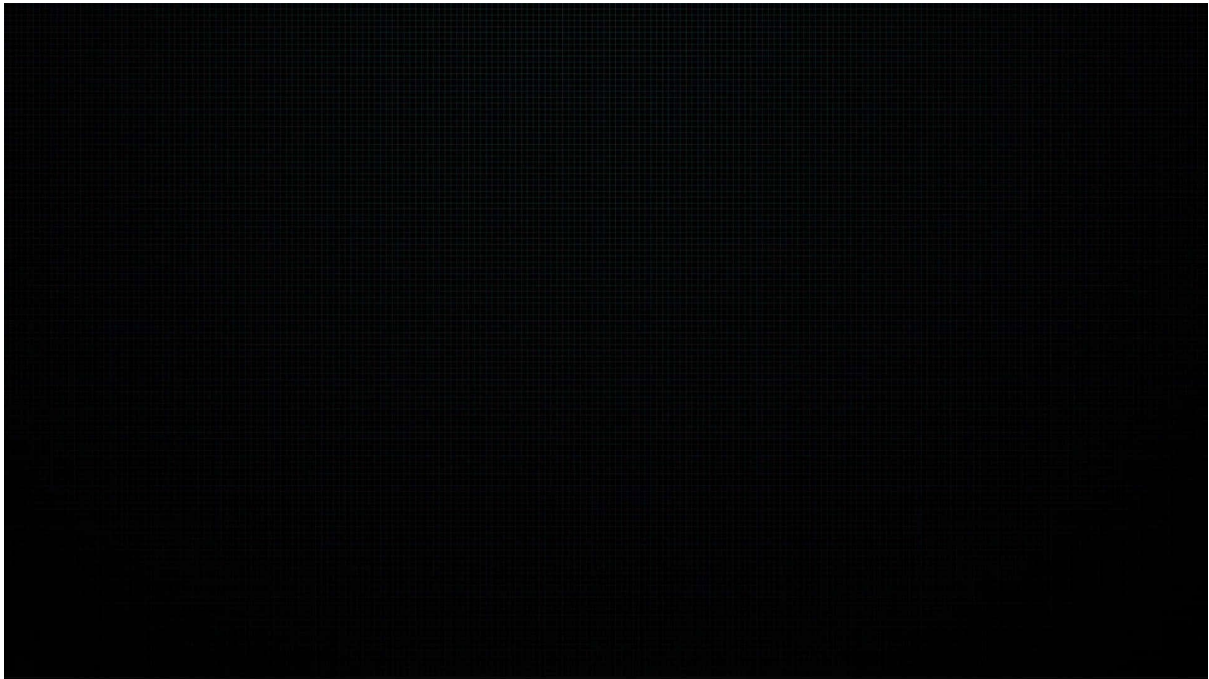
Given this, the best-fitting model (3-knot spline normal) has been implemented in the CEM as a deterministic scenario to the scenario which includes G+C+N as a comparator. Parameters of the other two best-fitting models are provided in Table 14 for information.

Table 13: Goodness of fit statistics for splines fitted to EFS (with re-censoring)

Link function	Number of knots	AIC	BIC	AIC rank	BIC rank
Normal	1	2296.6	2309.4	10	6
Normal	2	2287.6	2304.7	7	1
Normal	3	2284.0	2305.3	1	2
Normal	4	2287.1	2312.7	6	10
Odds	1	2305.0	2317.8	11	11
Odds	2	2291.3	2308.4	8	5
Odds	3	2284.1	2305.4	2	3
Odds	4	2286.5	2312.1	5	9
Hazard	1	2306.5	2319.3	12	12
Hazard	2	2292.9	2310.0	9	7
Hazard	3	2284.1	2305.5	3	4
Hazard	4	2286.2	2311.8	4	8

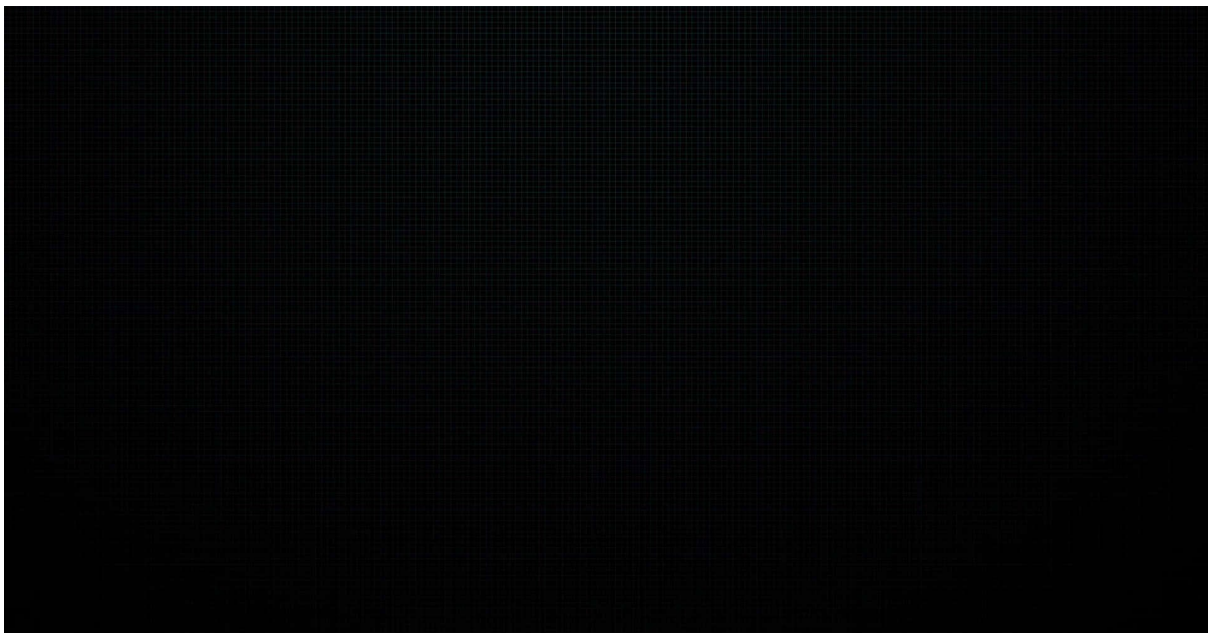
Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion; EFS: event-free survival.

Figure 9: Fit of spline models to EFS (with re-censoring) for G+C+N on the survival curve (Kaplan-Meier)



Abbreviations: C: cisplatin; EFS: event-free survival; G: gemcitabine; N: nivolumab.

Figure 10: Fit of spline models to EFS (with re-censoring) for G+C+N on the hazard scale



Abbreviations: C: cisplatin; EFS: event-free survival; G: gemcitabine; N: nivolumab.

Table 14: Spline model parameters and knot locations for EFS (since randomisation, with re-censoring) fitted to G+C+N

Name	Knot number	Knot location (log-time)	Parameter	Parameter	L95.	U95.
Spline normal 3- knot	x (xxxxxxxxx)	-x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x (xxxxxxxxx)	x.xxx	xxxxxxx	x.xxx	-x.xxx	x.xxx
Spline odds 3-knot	x (xxxxxxxxx)	-x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x (xxxxxxxxx)	x.xxx	xxxxxxx	x.xxx	-x.xxx	x.xxx
Spline hazard 3- knot	x (xxxxxxxxx)	-x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx
	x	x.xxx	xxxxxxx	-x.xxx	-x.xxx	-x.xxx
	x (xxxxxxxxx)	x.xxx	xxxxxxx	x.xxx	x.xxx	x.xxx

Abbreviations: C: cisplatin; EFS: event-free survival; G: gemcitabine; N: nivolumab.

When implemented in the model, there is a very minor change in total QALYs in the G+C+N arm, provided to three decimal places to distinguish between these options (Table 15). This translates into a minor decrease in the ICER compared to the Company base case (£13,307 vs. £13,723, see Table 16), and demonstrates that D+G+C remains a highly cost-effective treatment option compared to G+C+N in this scenario. As outlined in the Company Submission, comparing adjuvant and perioperative settings presents challenges. Nevertheless, we have provided this analysis in response to the NICE final scope using a novel methodology. The relevance of nivolumab as a comparator in the perioperative setting remains uncertain, so these results should be considered as a scenario only.

Table 15: QALY breakdown in the G+C+N arm for EFS modelled with a HR vs. independently fit splines

QALY breakdown	Company submission using HR for EFS	CQ22a response using independent model for EFS
Progression free	x.xx	x.xx
Progressed disease	x.xx	x.xx
Loco-Regional recurrence	x.xx	x.xx
Distant recurrence	x.xx	x.xx
Adverse events	-x.xxx	x.xx
Radical cystectomy	-x.xxxx	-x.xx
Total QALYs	x.xxx	x.xxx

Abbreviations: EFS: event-free survival; G: gemcitabine; HR: hazard ratio; N: nivolumab; QALY: quality-adjusted life year.

Table 16: Incremental cost results for perioperative durvalumab versus G+C+N using parametric curves to model G+C+N

	Perioperative durvalumab	G+C+N	Incremental
Total costs (£)	xx,xxx	57,279	19,881
Total LYs	xx.xx	8.71	1.94
Total QALYs	x.xx	6.88	1.49
ICER (£ per QALY)	-		xx,xxx

Abbreviations: C: cisplatin; G: gemcitabine; ICER: incremental cost-effectiveness ratio; LY: life year; N: nivolumab; QALY: quality-adjusted life year.

- b. When using independent curves, please adjust the economic model to enable the results from different approaches for reconstructing the G+C+N (counterfactual) arm to be considered: time-varying versus constant acceleration factors, and with versus without re-censoring.**

As described in the Company Submission, there are challenges with conducting comparisons between the adjuvant and perioperative settings. However, the Company have provided this comparison in response to the NICE final scope using a novel methodology which is the most appropriate when comparing across treatment settings. The Company maintain that the relevance of nivolumab as a comparator for cost effectiveness decision-making in a perioperative setting is uncertain due to the limitations of this comparison and therefore, we provided the cost-effectiveness results of the comparison between D+G+C vs. G+C+N as a scenario in the NICE submission.

In response to question A22 a, the company have provided a further extension to this scenario by independently modelling EFS for G+C+N, given that there was some evidence of a minor departure in the proportional hazards assumption for EFS. No such concern was apparent for OS or MFS. This additional scenario was performed using the base case ITC results; that is, using a constant acceleration factor and including re-censoring. This has shown that the model results are not sensitive to the use of a HR for EFS compared to the statistically best-fitting independently fit model.

Guidelines for treatment switching analysis recommend consideration of the use of re-censoring when applying counterfactual survival time methods (30). This helps to guard against informative censoring bias in the counterfactual data set which may occur through the adjustment of survival times of eligible 'high-risk' patients but not for ineligible patients in the NIAGARA trial. These include patients who did not have surgery, those who had residual disease after surgery and those considered at a low risk of recurrence. Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of the NIAGARA trial, due to the effect of nivolumab in extending (by a factor of x.xx for EFS) survival times in the counterfactual arm. The application of re-censoring leads to similar follow-up across arms. The ITC results showed that there was very minimal impact between including compared to excluding re-censoring for EFS on the HR (see response to question A12).

Similarly, the submitted ITC results showed there was very minimal impact between the results using a constant AF vs. time-varying AF for EFS. The hazard ratio for EFS comparing D+G+C with G+C+N was 0.739 (95% CI: 0.595, 0.887) using the time-varying AF, which is close to the corresponding hazard ratio of 0.742 (95% CI: 0.610, 0.899) from the base case with constant AF.

In summary, the company consider that the Company have sufficiently addressed uncertainty around the appropriateness of applying HRs in the CEM through with the scenario extension provided in response to A22a. Given this, performing the analysis with and without re-censoring for constant and time-varying models will not significantly change the conclusion that the model results are not sensitive to the use of a HR for EFS compared to the statistically best-fitting independently fit model.

Section B: Clarification on cost-effectiveness data

Model structure

B1. PRIORITY: The company performed a systematic review to identify previous relevant economic evaluations. Although previous studies applied a state transition modelling, the company decided to apply partitioned survival modelling in their submission.

a. Please provide a more comprehensive justification for the chosen modelling approach and outline the potential limitations associated with using this approach. Please ensure your response covers the following aspects: 1) the maturity of the OS data in relation to the overall extrapolation period, 2) the maturity of post-EFS and post-MFS data, and 3) potential differences in the management of patients in the trial compared to usual practice in the NHS for patients in the post-EFS and post-DMFS states (or 'partitions') and the inability of the partitioned survival modelling approach to formally adjust for any differences.

A partitioned survival model (PSM) was selected because it allows direct incorporation of key trial endpoints (EFS, OS, and MFS) using the patient-level data from NIAGARA, which represents the most robust source of evidence available for the treatment efficacy of perioperative durvalumab in MIBC patients. By fitting parametric curves to

the Kaplan-Meier data from NIAGARA, the PSM enables transparent extrapolation of long-term outcomes. NIAGARA has comprehensive time-to-event data which has substantial follow-up (maximum follow-up extends beyond five years) and was considered sufficiently mature for a PSM to be appropriate (see Table 17).

It is common for CEMs, particularly those in early cancer settings, to require extrapolation beyond the follow-up period of the trial. This is a typically a requirement regardless of the modelling approach adopted. Alternative model structures, such as a semi-Markov model, were considered at the model conceptualisation stage. A semi-Markov model would still be informed by the NIAGARA trial as this would remain the best available source of evidence to inform transitions out of the LR and DM health states (i.e., no external literature was identified that would better reflect UK clinical practice, and this approach was validated in consultation with UK-based clinical experts). Given that such a model would also rely on the estimation of transition probabilities and may be less reflective of the observed survival dynamics, a PSM was ultimately preferred.

One NICE technology appraisal in urothelial cancer was identified in the SLR of cost-effectiveness studies (TA817), which evaluated adjuvant nivolumab. It is notable that this appraisal adopted a semi-Markov approach. This was necessary because analysis of OS and post-recurrence survival from the trial informing the model (CheckMate-274) were not carried out prior to the submission as insufficient OS events had occurred to trigger the analysis and the data was blinded to the Company. The Company modelled post-recurrence survival using a static transition probability sourced from the literature. Two sources were identified which reported the median post-recurrence survival, which the Company pooled and weighted assuming a 50:50 split. This is converted into a weekly transition probability of recurrence to death assuming an exponential distribution. This approach, whilst considered suitable by NICE for decision making, requires very strong assumptions which were necessary given that OS data was not available for CheckMate-274.

Clinicians interviewed confirmed that the NIAGARA trial is representative of UK clinical practice, and when discussing survival extrapolations, consideration was given to the distribution of subsequent treatments received in UK clinical practice.

Table 17. Data maturity by endpoint

	Perioperative durvalumab arm	Control arm
OS	25.5% maturity*	31.9% maturity*
EFS	35.1% maturity	46.4% maturity
MFS	28.5% maturity	37.9% maturity

Abbreviations: EFS: event-free survival; MFS: metastasis-free survival; OS: overall survival.

Note: median follow-up for OS in the perioperative durvalumab arm and control arm was 42.3 months and 39.6 months, respectively

b. The EAG notes that in the model, patients who are in the locoregional recurrence (LR) health state cannot move back to event-free health state. Please provide additional justification to support/validate this assumption.

Patients enter the model in the event free (EF) state and immediately start treatment with neoadjuvant chemotherapy, either with or without perioperative durvalumab, followed by radical cystectomy, if eligible. The EF health state in the PSM represents the period during which patients have not experienced local recurrence, distant metastasis, or death, aligning with the definition of event-free survival (EFS) in the NIAGARA trial. Once a patient experiences a local recurrence, they have, by definition, had an event and are no longer event-free within the context of the model. Transitions to the local recurrence (LR) health state are therefore captured by the difference between the MFS and EFS endpoints, consistent with how the NIAGARA trial defined these events.

The model structure reflects the typical clinical course of MIBC patients. Patients who progress to local recurrence face a different prognosis and treatment pathway. Additionally, this model structure of not allowing patients in LR health state to move back to EF health state is consistent with other technical appraisals in early-stage cancer, such as TA1030 and TA851 (31, 32).

Therefore, the chosen structure is appropriate and grounded in both trial design and MIBC patient pathway.

Study endpoints used in the model

B2. PRIORITY: The definition of EFS represents the pre-recurrence phase, including patients who progress before surgery or decline or are unfit for surgery. From Table 6 of the CS, the EAG notes that while 11.8% patients did

not undergo cystectomy as planned, only 1.7% did not undergo cystectomy due to the disease progression.

- a. **For the subgroup of patients who decline surgery, please clarify if they are treated as recurrence in the definition of EFS. That is, does the locoregional recurrence health state in the model include patients who had refused surgery? If yes, please provide additional justification to support/validate this assumption and explain the impact of this assumption on the model results.**

In the NIAGARA trial, the definition of EFS as a primary endpoint, developed in consultation with regulators (33), includes “the time of first documented progression in patients who were medically precluded from a radical cystectomy, or time of expected surgery in patients who refused to undergo a radical cystectomy or failure to undergo a radical cystectomy in participants with residual disease, or the time of death due to any cause, whichever occurred first”. Thus, failure or refusal to undergo surgery for any reason was captured as an EFS event in the primary analysis.

When modelling these outcomes, any patient who did not receive surgery and remained free of distant metastasis entered the locoregional recurrence health state. Patients—regardless of surgery status—who developed distant metastases were registered as an event in MFS in the NIAGARA trial and were assigned to the distant metastasis health state in the model.

Including all patients who did not undergo surgery as planned is appropriate, as this reflects the trial’s endpoint definition and avoids the arbitrariness of censoring such patients. To further validate this approach, a post-hoc analysis was conducted in which patients who refused or failed to undergo radical cystectomy were censored for EFS in both BICR and central pathology analyses, rather than counted as events. The resulting hazard ratio (HR 0.69 [95% CI: 0.556–0.858]) were consistent with the primary analysis (HR 0.68 [95% CI: 0.558–0.817]).

- b. **Please clarify if costs for the patients who did not undergo cystectomy as planned were included in the model.**

For patients who did not undergo cystectomy as planned, all neoadjuvant treatment exposure was captured in the time-on-treatment analysis. Drug costs and drug

administration costs for these patients were included in the model in the neoadjuvant phase.

The six patients who refused cystectomy but achieved a complete clinical response entered the non-cystectomy extension phase and received durvalumab for up to eight additional cycles, following their initial four cycles of neoadjuvant durvalumab plus chemotherapy. Cycles administered during the non-cystectomy extension phase were excluded from the treatment cost calculation as the licensed indication specifies perioperative durvalumab use before and after surgery. As these six patients, representing only 1.1% (6/530) of the perioperative durvalumab arm, were technically treated off-label, their exclusion has a negligible impact on overall model results.

Importantly, patients who did not undergo cystectomy were still included in the safety analysis, ensuring that costs for adverse event management were fully captured. As outlined in response B2.a, non-surgery patients were included in all health states within the model, meaning that resource use costs, end-of-life costs, and subsequent treatment costs were appropriately applied to these patients in respective health states. This ensures a comprehensive accounting of costs and outcomes across all relevant patient groups within the model.

B3. Based on Table 4, EFS definition is per investigator or local biopsy review and MFS definition is per investigator assessment or local biopsy review. However, EFS used in the model is per blinded independent central review and MFS is per investigator only according to Table 35.

a. Please clarify which definition for EFS and for MFS is used in the model and justify the choice.

As detailed in Table 4 in the CS, one of the two primary outcomes of NIAGARA is EFS, defined as the time from randomisation to the first recurrence of disease after radical cystectomy (RC), the time of first documented progression in patients who are medically precluded from a RC, or time of expected surgery in patients who refuse 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 occurs first as evaluated by BICR or by central pathology review. Secondary outcomes include EFS per investigator and MFS,

per investigator assessments (or local biopsy review if a biopsy was required for a suspected new lesion).

The model used the primary endpoint EFS per BICR and secondary endpoint MFS per Investigator assessments, both of which required a local biopsy review if a biopsy is required for a suspected new lesion. MFS assessed by BICR was not a predefined endpoint of the study and is therefore not available for use in the model.

EFS per BICR was selected to use in the model as it is a primary endpoint of the NIAGARA trial. BICR assessments minimise potential bias as they are conducted independently of the trial sites and are blinded to treatment assignments. For MFS, only investigator-assessed data were available from the trial, therefore it was used in the model.

b. Please explain the impact of using different definitions of EFS and MFS on the model results.

As detailed in CS Section 2.6.2, EFS results per investigator or local biopsy review and per BICR followed a similar trend. Both KM plots showed a separation of curves in favour of the perioperative durvalumab arm at approximately two months and the separation was clear and sustained thereafter (Figure 5 and Figure 8 in CS). The EFS hazard ratios using the two definitions are both 0.68, with minimal difference in the 95% confidence interval (EFS per BICR: 0.558, 0.817; EFS per investigator or local biopsy review: 0.562, 0.812) (FAS [ITT population], DCO 29 April 2024). EFS using the two definitions also showed the same overall 32% reduction in the risk of an EFS event compared to the control arm.

Both EFS per BICR and per investigator demonstrated a clinically meaningful improvement in EFS in patients treated with perioperative durvalumab, consistent across assessment methodologies. This consistency demonstrates the robustness of the positive treatment effect and suggests that there is minimal variation in the modelled effectiveness for EFS due to the assessment method. Therefore, the model results are unlikely to be affected by the choice of EFS definition.

For MFS, there is only a single definition available in the NIAGARA trial. Therefore, it is not possible to evaluate the impact of alternative assessment methods on model outcomes.

B4. PRIORITY: The NIAGARA trial included a PFS-2 outcome, which represents the time from randomisation to subsequent progression or recurrence post EFS event or progression-free survival after second-line therapy. The EAG considers this endpoint as important in the perioperative setting to reflect the durability of treatment benefit beyond the first treatment.

a. Please clarify why this endpoint has not been used in the model to provide more granularity in the modelling of events over time.

Although PFS2 demonstrated the durability of perioperative durvalumab treatment effect beyond the first event, the exclusion of PFS2 data from the cost-effectiveness model was an intentional structural decision, informed by both clinical and modelling considerations. The model is based around the primary EFS endpoint and the secondary endpoints used (OS and MFS) fully captured the clinical and economic outcomes in this setting. The MFS health state in particular is widely recognised as clinically meaningful and directly relevant for tracking both disease progression and its impact on costs and patient quality of life in this disease context. The 4-state model structure and the selected endpoints used to inform the model have been validated and supported by HTA experts in an advisory board conducted by AstraZeneca. Furthermore, the approach of utilising similar primary and secondary endpoints instead of PFS-2 even though it was collected in the clinical trial is aligned with previous NICE appraisals (such as TA871, TA683 and TA816) (34-36).

b. Please consider amending the existing model structure to also incorporate PFS-2 data. If this is not feasible within the proposed time frame of responses, please provide some qualitative commentary on the potential implications of excluding this data within the existing model structure.

Incorporating PFS2 alongside MFS would substantially complicate the model structure. To ensure health states remain mutually exclusive and exhaustive, it would be necessary to define health states in terms of both PFS2 and MFS, to capture those patients who enter MFS directly from EFS (and have no PFS2 event) and those who

first have a recurrence and then enter the distant metastases state (and have a PFS2 event). This would require additional, potentially non-standard state definitions and transition pathways, introducing extra complexity and uncertainty into the model for questionable analytic gain.

The current use of MFS already robustly captures the main clinical and economic consequences of progression in this setting. MFS is a composite endpoint and is well-validated as a predictor of both survival and quality-adjusted life expectancy. Not including PFS2 in the cost-effectiveness analysis is unlikely to bias the results, as the key clinical and resource use inflection points are all directly modelled. While PFS2 may provide additional granularity regarding the timing and sequence of subsequent events, its omission does not neglect any major clinical or economic milestone relevant for the model, as these are already reflected in the chosen states and transitions. Furthermore, the significant improvement in PFS2 observed in NIAGARA (outlined in response to question A7) strengthens confidence that the modelled benefits of perioperative durvalumab are not a consequence of post-progression therapies but are due to a direct and persistent treatment effect.

In summary, while it is theoretically possible to revise the model to include PFS2, doing so would reduce transparency and add complexity, without meaningfully improving decision-making accuracy in this context, and it has therefore not been provided.

Survival modelling

B5. PRIORITY: To inform the partition survival model, the company conducted survival modelling for EFS, MFS and OS, with each curve fitted independently. As a result, applying the following structural constraints was required: OS is constrained to $\leq$ general population survival, MFS is constrained to values $\leq$ OS and EFS is constrained to values $\leq$ MFS. The company followed the NICE Decision Support Unit Technical Support Document (TSD) 14 and TSD 21 when conducting the survival modelling, including an assessment of the proportional hazards and accelerated failure time, generation of statistical goodness of fit, visual inspection of model fit to the trial data and an assessment of the clinical

plausibility of extrapolation. However, the survival modelling and its assessment was performed for each curve in isolation.

a. For the combination of curves used in the company base-case, please evaluate whether there are any logically consistent functions that could be used across EFS, MFS and OS that would not require constraints to be imposed in the model. If applying the constraints is needed, please identify which constraints are used in the model and the time points at which these constraints need to be imposed.

For the combination of survival curves used in the company base-case, it was necessary to impose a constraint related to general population survival. This requirement arises due to the early-stage disease setting with a notable trend toward cure, and the lifetime horizon used in the model. The general population constraint ensures that projected survival in both arms of the model does not exceed what would be expected in the overall population, providing a logical and clinically meaningful upper limit for survival probabilities.

In the company base-case, without any adjustments, for the G+C+D arm EFS is always positioned below OS, with the exception of month 1, where a minor inconsistency appears. EFS remains below MFS up to month 89. When general population mortality is accounted for, the difference between EFS and MFS diminishes substantially, so that only a small corrective adjustment is needed to maintain logical consistency between the endpoints. For the G+C arm, EFS stays below OS up to month 228 (excluding month 1), and remains below MFS through to month 400. As with the D+G+C arm, introducing the general population constraint shrinks the requirement for the second adjustment to OS and MFS.

When assessing whether it is possible to identify alternative survival functions that logically align EFS, MFS, and OS without the need for such constraints, it is generally not feasible for the vast majority of parametric distributions. At minimum, the constraint to not exceed general population survival is virtually always necessary, although the specific time points at which it is applied differs between models. However, selecting a distribution solely based on this property could come at the expense of poor fit in earlier portions of the curve, which would negatively impact the overall validity of the model.

To ensure clinical relevance and consistency for decision making, all survival models validated with UK clinicians included the adjustment for general population survival.

b. The EAG notes a setting in the model that specifies the dominant curve for extrapolation (OS=EFS after crossing or EFS=OS after crossing). Please explain these assumptions and explain why OS=EFS after crossing is chosen as the base case.

By definition, EFS must always be equal or less than OS, since a patient cannot be event-free if they are not alive. If, due to extrapolation, the EFS curve is modelled to exceed OS at any time point, this creates a clinically implausible scenario. In such cases, the model applies an adjustment to OS to match EFS (OS=EFS), or EFS to match OS (EFS=OS), at the point of crossing. This correction maintains a logical relationship between endpoints.

The choice of the OS=EFS setting in the base case is based on the clinical expectation that patient achieving long-term remission in the EFS state are likely to be cured of disease and subsequently experience only background all-cause mortality. These patients remain in the EFS state until death from general population mortality. By maintaining OS = EFS in the long-term, the model ensures that patients in the EFS state face only background mortality risks over time. Conversely, if set to EFS=OS, the EFS curve could suddenly align with a lower OS curve at the point of crossing, potentially resulting in an abrupt and unrealistic decline in EFS. This would incorrectly imply a rapid increase in mortality among patients otherwise considered at minimal risk except for age- or sex-related background mortality.

However, with the current base case extrapolations for OS and EFS in both D+G+C and G+C arms, EFS already consistently remains below OS at all time points after the constraint of general population mortality has been applied. This demonstrates that the model already adheres to the expected clinical relationship of OS being greater than or equal to EFS. As a result, switching the model setting to EFS=OS at any crossing point had no impact on the results. Therefore, the choice regarding this setting does not affect the model outcomes or the conclusions of the economic evaluation.

B6. PRIORITY: The company fitted a number of standard parametric survival as well as flexible spline models for EFS and MFS and chose the flexible models due to the absence of clear evidence supporting either the proportional hazard (PH) or AFT assumption and poor visual fit of the KM curves to the standard models. For OS, the company did not consider flexible spline models because they assessed the hazard pattern to be relatively simple and the hazard profiles to be well-captured by standard parametric models. However, when comparing the raw and smoothed hazards of OS (Figure 19, Appendix L) and MFS (Figure 10, Appendix L), the EAG notes that the hazard patterns are relatively similar. Additionally, the company stated that clear evidence supporting either PH or AFT assumptions (shown in Appendix L) was lacking.

a. Please clarify and provide a comprehensive justification for why the company did not consider flexible models for OS, which is inconsistent with the approach for EFS and MFS.

The decision on whether to use flexible models was based on by the complexity of the hazard profiles for each endpoint and the observed fit of the simple parametric models to the trial data. For EFS and MFS, the underlying hazard functions exhibited complexities that warranted a more flexible approach. Specifically, the control arm MFS hazard profile demonstrated a distinct flattening from around 36 months onward, which could be bettered captured with a flexible model. This was supported by a visual inspection of the fit of the flexible and standard parametric models provided in the Company submission.

In contrast, the OS hazards were considered to be well characterised by standard parametric models. Visual inspection (see Figure 14 in Appendix L and Figure 31 in the CS) indicated that simple parametric models provided a sufficient fit to the observed data, with no clear evidence that a more flexible approach would be warranted.

Nevertheless, to further support the EAG's assessment, flexible models for OS were fitted to NIAGARA trial data, as detailed in the response to B6.b. Flexible models produced results consistent with simple parametric models, demonstrating that the conclusion that perioperative durvalumab represents a cost-effective treatment option demonstrated from the submitted Company model can be considered robust.

b. Please fit flexible models for OS and include them in the model as a potential survival modelling option.

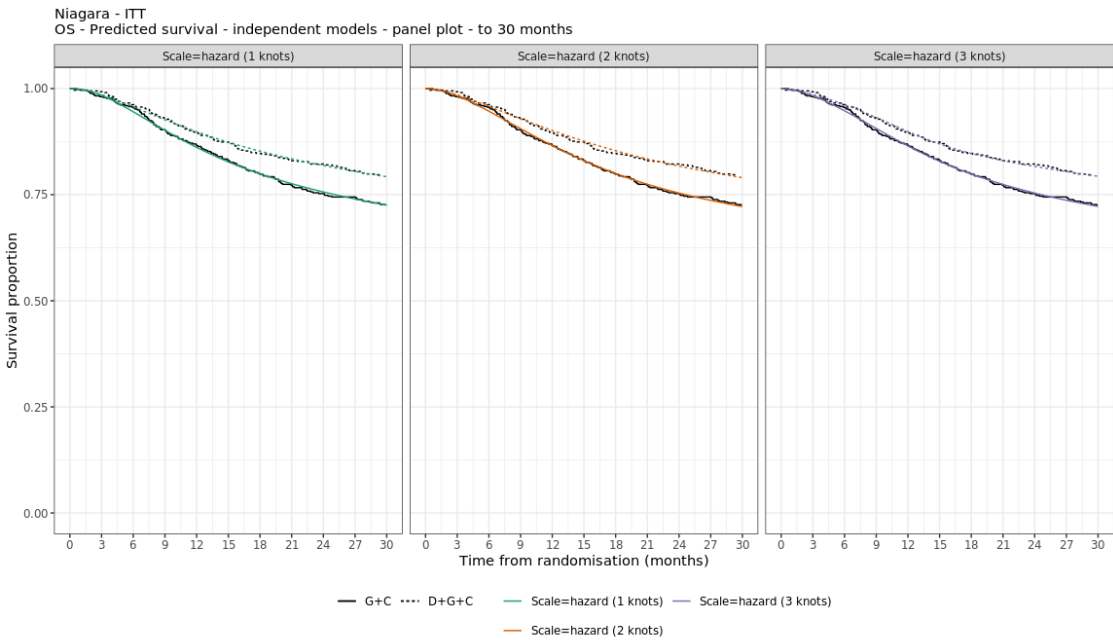
To assist the EAG’s assessment, flexible models for OS (DCO 29 April 2024) have been fit to both the D+G+C arm and G+C arm and implemented in the cost-effectiveness model. The nine flexible models fitted show very similar visual and statistical fit to the trial data, as demonstrated in Table 18, Figure 11, Figure 12 and Figure 13.

Table 18: Goodness of fit statistics for standard parametric models for OS

Model	Akaike Information Criterion		Bayesian Information Criterion	
	Control arm	Perioperative durvalumab arm	Control arm	Perioperative durvalumab arm
Scale=hazard (1-knot)	1900.7	1621.7	1913.5	1634.5
Scale=hazard (2-knots)	1902.0	1623.7	1919.1	1640.8
Scale=hazard (3-knots)	1904.0	1622.9	1925.3	1644.3
Scale=normal (1-knot)	1903.7	1625.8	1916.5	1638.7
Scale=normal (2-knots) ^a	1902.0	-	1919.1	-
Scale=normal (3-knots)	1903.7	1622.1	1925.1	1643.5
Scale=odds (1-knot)	1900.9	1621.7	1913.7	1634.5
Scale=odds (2-knots)	1902.0	1623.6	1919.1	1640.7
Scale=odds (3-knots)	1903.9	1622.6	1925.3	1644.0

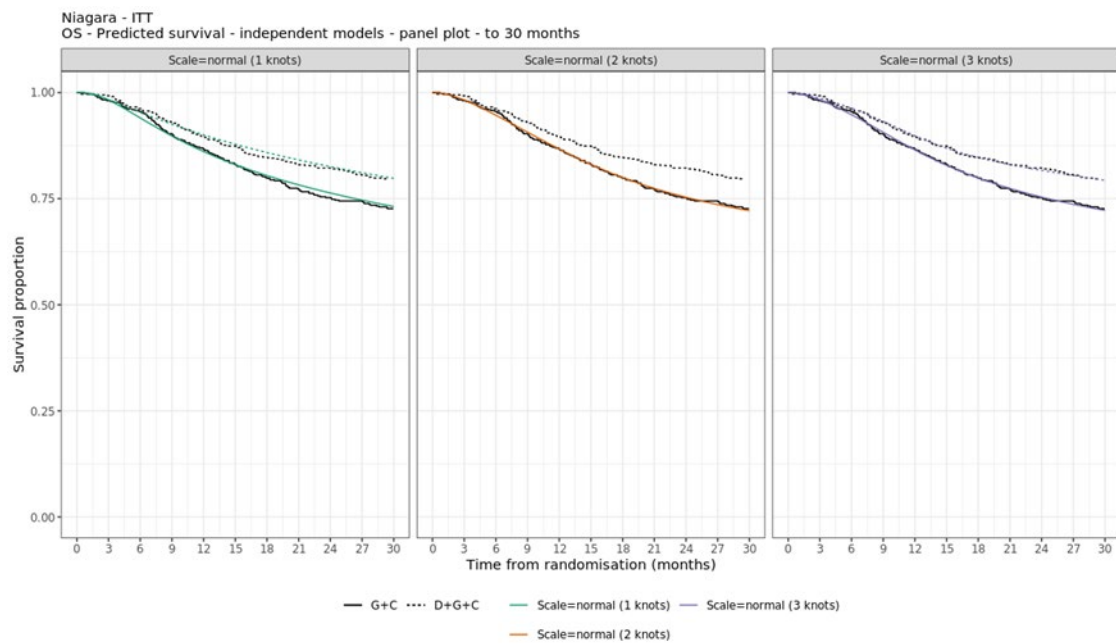
Abbreviations: OS: overall survival.
^a Perioperative durvalumab arm converges with the control arm using scale=normal (2-knots), therefore the statistical criteria for model fit cannot be produced.

Figure 11: Independent spline hazard curves for OS



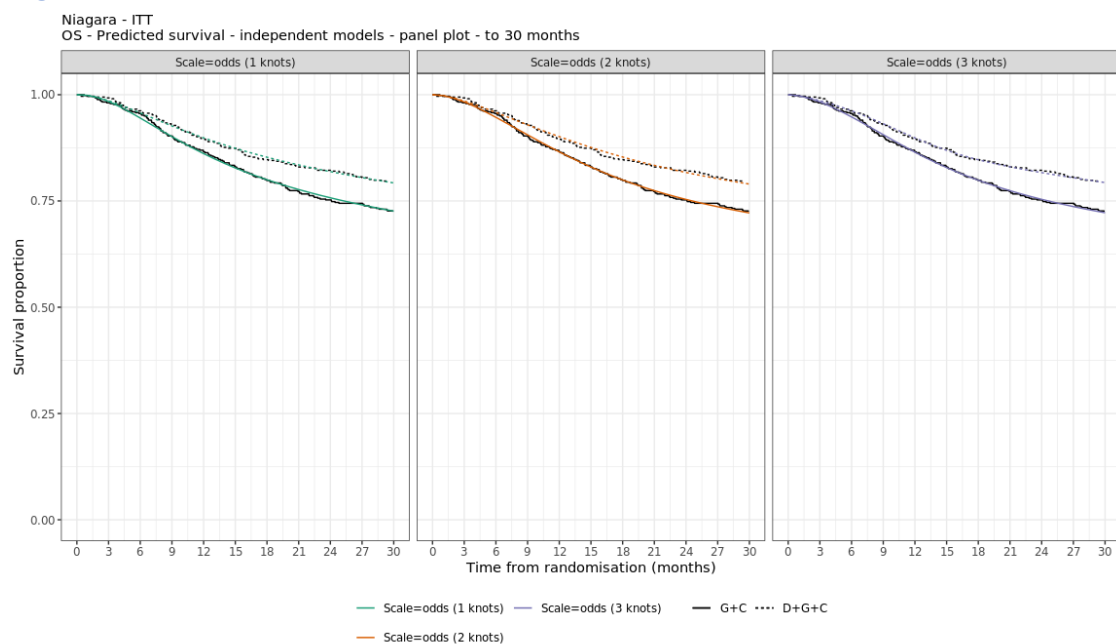
Abbreviations: C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat; OS: overall survival

Figure 12: Independent spline normal curves for OS



Abbreviations: C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat; OS: overall survival

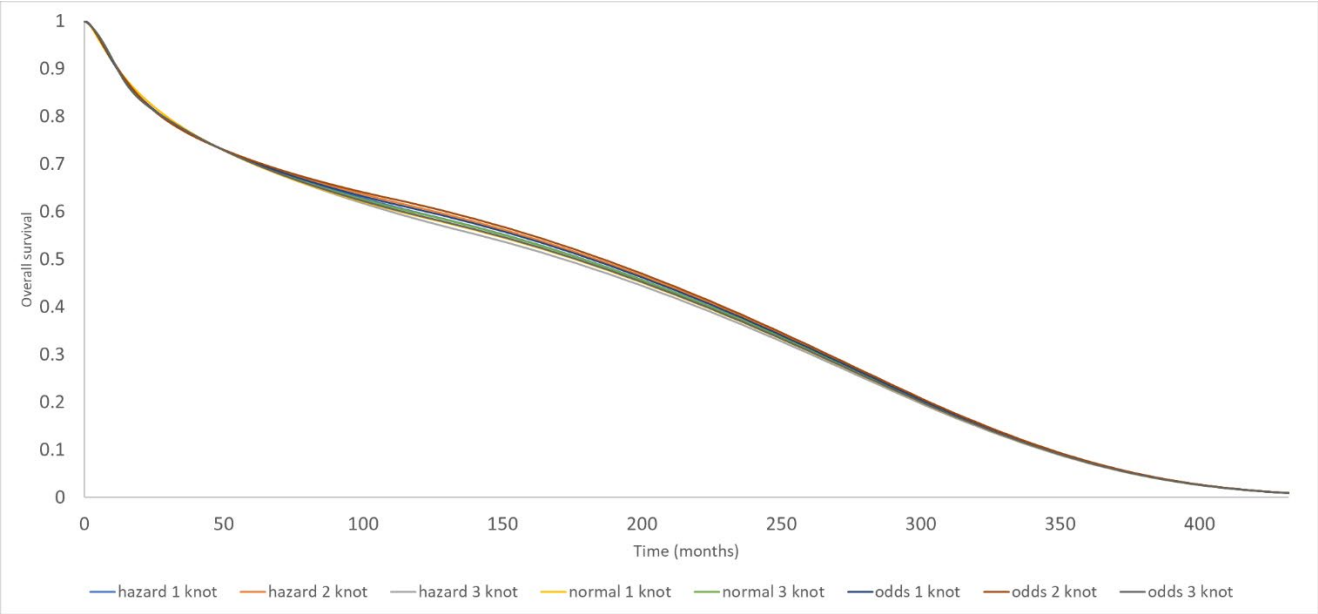
Figure 13: Independent spline odds curves for OS



Abbreviations: C: cisplatin; D: durvalumab; EFS: event-free survival; G: gemcitabine; ITT: intention-to-treat; OS: overall survival

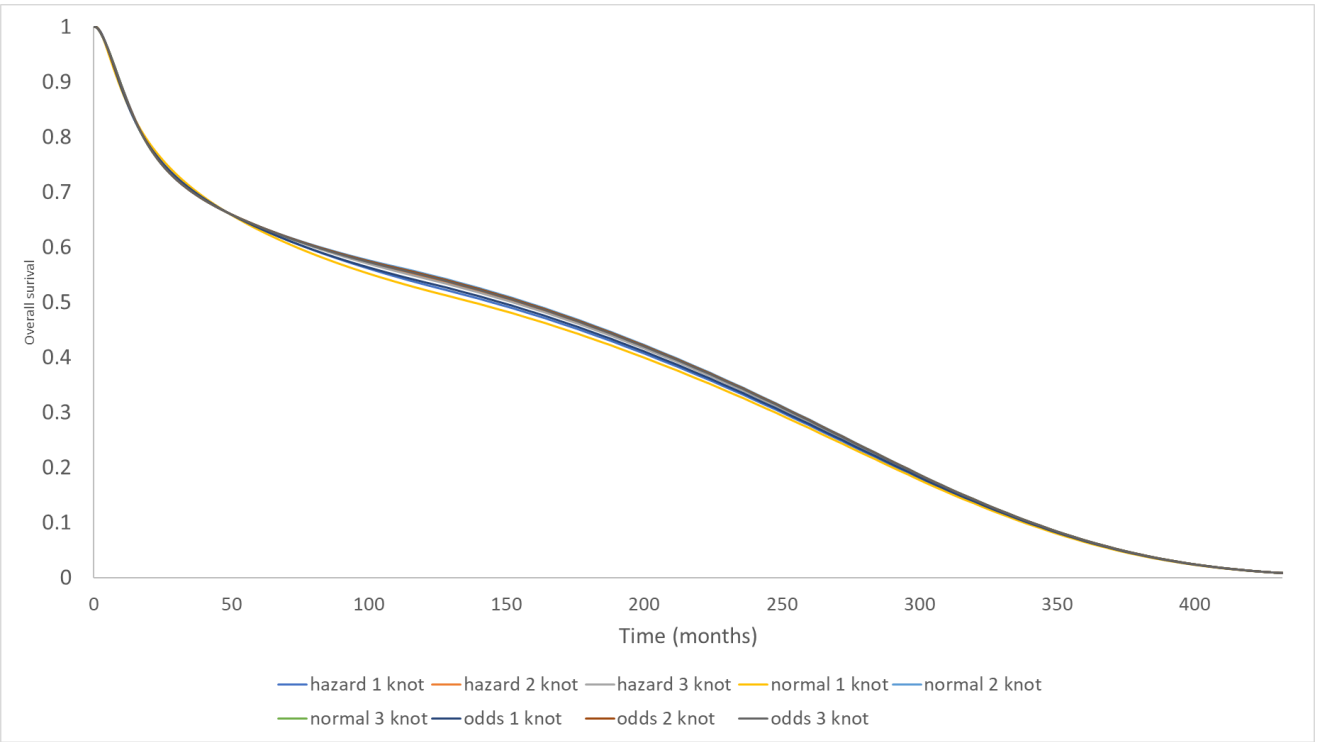
The extrapolations projected over the lifetime time horizon of the model including adjustment for general population mortality are presented in Figure 14 for D+G+C and Figure 15 for G+C. This shows consistency in the projected extrapolations of the spline-based models.

Figure 14: Spline-based models fit to D+G+C OS data, including general population constraint



Abbreviations: C: chemotherapy; D: durvalumab; G: gemcitabine; OS: overall survival.

Figure 15: Spline-based models fit to G+C OS data, including general population constraint



Abbreviations: C: chemotherapy; G: gemcitabine; OS: overall survival.

Given the consistency of these extrapolations, we have selected the statistically best-fitting splines to compare to the Company base case at selected landmarks (Table 19).

Table 19: Landmark OS including general population constraint

	Perioperative durvalumab arm		G+C arm	
Timepoint (months)	Company base case (Gompertz)	Best fitting spline: Odds 1 knot	Company base case (Loglogistic)	Best fitting spline: Hazard 1 knot
60	71%	71%	60%	63%
120	62%	60%	43%	53%
240	38%	37%	24%	32%
300	21%	20%	14%	18%
420	1%	1%	1%	1%

Abbreviations: C: cisplatin; D: durvalumab; G: gemcitabine; OS: overall survival.

There is a high degree of consistency between the company the selected base case distribution and the best fitting spline model for the perioperative durvalumab arm. For the G+C arm, the best-fitting spline model provides slightly higher short- and medium-term estimates of overall survival. The spline model OS prediction for the G+C arm is considered to be an overestimation of patient survival outcome based on external literature in MIBC patients (OS at 5 years: 49%-65%, OS at 10 years: 36%-43%), as detailed in Section 3.3.2 in the CS. Additionally, extrapolations with similar landmark OS as the spline model predictions were considered overly optimistic by the UK clinical experts interviewed. Therefore, the base case curve selection is still considered the most appropriate and clinically plausible OS model for the G+C arm.

In the Company submission, a more optimistic curve choice for OS for the G+C arm was selected in a scenario analysis (Gompertz) as it was favoured by one of the four experts interviewed. As shown in Table 62 in the CS, using this distribution resulted in an ICER of £18,794.43, consistently demonstrating perioperative durvalumab's cost-effectiveness at a willingness-to-pay threshold of £20,000.

The cost-effectiveness of using the best-fitting splines has been considered (Table 20). Consistent with the base case and the scenario analysis utilising Gompertz for

the G+C arm, model results using flexible OS models demonstrated cost-effectiveness of perioperative durvalumab at a willingness-to-pay threshold of £20,000 per QALY.

Table 20: Pairwise incremental cost effectiveness results using flexible models for OS

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
<i>Best statistical-fit flexible models used for OS (G+C: spline hazard 1 knot; D+G+C: spline odds 1 knot)</i>			
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)	-	-	£18,532

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care; OS: overall survival.

c. In Table 39, page 127 of the CS, Clinician 3 concluded that generalised gamma and Gompertz models are not plausible for the extrapolation of the OS curve of the control arm, and the preferred model was log-logistic. However, the EAG notes that generalised gamma and Gompertz models appear to reflect a similar pattern for the OS hazard trajectory (i.e. initially increasing then decreasing and later convergence - Figure 32, page 125 of the main submission) and the preferred log-logistic model does not seem like a better fit. Please provide further information on why Clinician 3 considered them implausible for the NIAGARA control arm.

Clinician 3 selected the log-logistic model based not only on the goodness of fit of trial data but also the long-term extrapolation. Clinician 3 considered log-logistic providing more accurate projection in patient outcomes compared to the other models. Clinician 3 commented generalised gamma and Gompertz “do not look like a good fit” after commenting on the log-logistic model. Since clinician 3 did not provide further detailed justification, it is assumed that they did not consider the long-term extrapolation of generalised gamma and Gompertz plausible.

It was acknowledged that one out of four clinicians selected the Gompertz model to be the preferred extrapolation for the control arm. In recognition of this, the Gompertz model was included as a scenario analysis in the CS. The ICER using the Gompertz extrapolation (£18,794.43) remained cost-effective at the £20,000 willingness-to-pay threshold, indicating that the results for perioperative durvalumab are robust to the choice of OS extrapolation for the control arm.

d. Based on Figure 32 in the CS, the EAG notes that generalised gamma and Gompertz models seem to best fit the hazard rates of both arms and best reflect the relation of hazard rates between the two arms, e.g., only in these two parametric models the hazard rates are converging, which correctly reflects the hazard rates observed in the NIAGARA trial. Please provide a comprehensive justification for why the chosen model for the control arm was log-logistic even though it was the fourth best-fitting model.

A systematic and comprehensive approach was used for the selection of extrapolations for all endpoints, including an assessment of the proportional hazards and accelerated failure time, statistical goodness of fit, visual inspection of model fit to the trial data and clinical plausibility of long-term extrapolation assessed by UK clinical experts and external literature where available. Curve selection was not based solely on statistical goodness-of-fit, but rather on a balanced assessment of both quantitative and qualitative factors.

The log-logistic model was selected as the base case for the control arm OS because among all curves nominated by clinicians (log-logistic, log-normal, and Gompertz), the log-logistic model demonstrated the closest alignment with long-term OS data for MIBC patients in the best external evidence identified, as detailed in Section 3.3.2 of the CS and summarised in Table 40, supporting its selection as the most appropriate base case model. Additionally, the log-logistic model was the most preferred model by clinicians consulted, with two out of four experts identifying it as the most clinically plausible when presented with long-term OS projections adjusted for general population mortality.

While generalised gamma provides the best statistical fits according to AIC and BIC, it was not selected as the primary model because none of the consulted clinicians considered it the most appropriate for long-term extrapolation. However, the log-normal model was preferred by one clinician and provides the second-best fit statistically, and the Gompertz model was also preferred by one clinician. The log-normal and Gompertz model were both included as scenario analyses. Importantly, these scenarios both produced ICERs that remained below the £20,000 per QALY threshold, supporting the conclusion that perioperative durvalumab is a cost-effective treatment option.

To further inform the EAG's decision making, a scenario analysis using generalised gamma, the best statistically fit model, for the control arm OS was also conducted. As shown in Table 21, the ICER of £16,995 demonstrates that perioperative durvalumab remains cost-effective at the £20,000 willingness-to-pay threshold.

Table 21: Pairwise incremental cost effectiveness results with generalised gamma extrapolation for OS in the control arm

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			£16,995

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care; OS: overall survival.

B7. PRIORITY: The EAG notes that the OS hazards of durvalumab and control arms converge towards the end of trial follow up, based on Figure 32 in the CS. This suggests that the OS hazards in both arms appear similar by 5 years.

a. Please justify why this result was not reflected when fitting and choosing survival models.

The convergence of the treatment arms towards the end of the follow-up may be unduly influenced by lower numbers at risk, and so this was not explicitly considered when selecting the extrapolations for each arm. The application of the general population constraint means that hazards do converge in the model, at around 177 months. When considering the selection of survival models, the general population constraint was taken into account, and so converging hazards were implicitly considered.

b. To reflect this convergence trend, the company could either apply flexible models with equal hazard rates after 5 years or use standard parametric models with a HR=1 after year 5. Please incorporate these two approaches in the model. That is, please fit flexible models that will reflect converging hazard rates after 5 years and adapt the economic model to allow for scenarios with parametric

models where the user can define hazard rates for the two arms to become similar after 5 years.

The functionality was implemented in the model to allow for scenarios with parametric models and flexible model where hazards were made equivalent between D+G+C and G+C arms after five years. When this option is selected, there is a visible kink in the D+G+C OS curve when applied to the Company base case.

The results for the standard models with the assumption of equal hazards from five years resulted in an ICER of £15,571, which is 10.8% higher than the company base case (see Table 22).

When flexible models were selected using the best-fitting models described in response to Question B6 b, the hazards do converge, with equal hazards being reached at around 89 months. Rather than apply an arbitrary point at which hazards become equal, we have provided the results for the flexible models without this rule.

In both scenarios, perioperative durvalumab is a cost-effective treatment option at a willingness-to-pay threshold of £20,000/QALY compared to G+C.

Table 22: Pairwise incremental cost effectiveness results with equal hazard rates after 5 years (standard models) and splines

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
<i>Scenario Analysis: Standard parametric models with equal hazards after year 5</i>			
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			£15,571
<i>Best statistical-fit flexible models used for OS (G+C: spline hazard 1 knot; D+G+C: spline odds 1 knot)</i>			
Total costs (£)	xx,xxx	xx,xxx	xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			18,532

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

B8. In Appendix K, page 6, the company states: “In the CEM, the effect of G+C+N was set equal to ■ in the first 6 months”. Please clarify how this was implemented in the model.

There was a minor typographical error in Table 2 in Appendix K. The following table should have been provided:

Table 23: Summary of the ITC results for the first and subsequent 6 months of follow-up

Endpoint	HR for G+C+N vs G+C (95% CrI)	
	0-6 months	6+ months
EFS	x.xxx (x.xxx- x.xxx)	x.xxx (x.xxx-x.xxx)
OS	x.xx (x.xxx-x.xxx)	x.xxx (x.xxx-x.xxx)

Abbreviations: CI: confidence interval; EFS: event-free survival; HR: hazard ratio; ITC: indirect treatment comparison; OS: overall survival; vs: versus

Note: * in the ITC, the hazard ratio was equal to 0.989, as a small number of patients had started adjuvant nivolumab before this time point)

Source: AstraZeneca – survival time-adjusted ITC (section 2.9 of the company evidence submission and Appendix B.4.2).

To clarify, the HR was calculated based on the ITC for both 0-6 months and 6+ months (provided in the Company submission Table 28 and Table 29). The 6 months time point aligns with the approximate time of surgery. For OS, the HR was calculated to be 1.00 (x.xx (x.xxx-x.xxx) in the first 6 months. The EFS hazard ratio in the first 6 months was x.xxx (x.xxx- x.xxx) in the ITC. This was driven by a small number of patients who initiated adjuvant nivolumab before month 6, causing a slight improvement in treatment effect compared with the G+C arm. To ensure accuracy, a hazard ratio of x.xxx for both EFS and MFS was used in the model for the first 6 months.

Cure

B9. PRIORITY: The EAG notes that the OS curve for the durvalumab arm converges with and subsequently falls below the age- and gender-adjusted general population mortality rate after x.xx years, at which point xx% of the patient cohort remains alive. This can be interpreted to imply that xx% of patients are considered cured of cancer after x.xx years, also based on the decreasing and plateauing hazard rates for EFS and MFS shown in Figures 1, 6, 7, 10, 15-18 in Appendix L. Please justify whether this model estimate is

clinically plausible and consistent with the current understanding of the long-term MIBC prognosis.

To address the plausibility of the model estimate regarding cure in the durvalumab arm, previous appraisals in the MIBC setting were reviewed to understand different approaches for estimating long-term outcomes in health technology assessments. In TA817 assessing adjuvant nivolumab in urothelial cancer, the Company incorporated a structural cure assumption in the CEM at five years— after five years in the initial DFS health state, patients were assumed to be cured (that is, the cancer can no longer recur) and all patients were moved to the LT DFS health state where the mortality risk was assumed to be the same as an age- and sex-matched general population mortality (24). While the appraisal committee acknowledged uncertainty regarding the most appropriate timepoint to assume cure (five or ten years), they accepted five years as appropriate for decision making. This assumption aligns with clinical practice in the NHS, where recurrence beyond five years is considered uncommon and therefore patients are typically discharged from routine follow-up, as described in the guidelines for the management of bladder cancer published by the West Midland Expert Advisory Group for Urology Cancer (37).

Implicitly modelling cure at x.xx years can therefore be considered a conservative and clinically plausible approach. To further inform the company's approach and in response to the concerns raised by the committee during TA817, feedback was sought from UK-based clinical experts through clinical validation interviews. Uniformly, clinical experts indicated a preference for using the term "risk of recurrence" rather than "cure assumption." There was no consensus among experts regarding whether a five- or ten-year timepoint would be preferable should a specific point of cure need to be defined. Given the lack of consensus over the timing of cure and the prevailing clinical preference to frame long-term outcomes as risk of recurrence, the company decided not to incorporate an explicit cure assumption in the CEM. This approach is further supported by the behaviour of the survival curves themselves, which indicate a de facto 'cure' through declining hazard rates for EFS, MFS, and OS, together with the application of background mortality adjustments.

Resource use and costs

B10. PRIORITY: Please clarify how the time on treatment was estimated. Does the time on treatment in the trial include people who did and did not receive cystectomy?

In the CEM, the time on treatment for the neoadjuvant and adjuvant components of the D+G+C and G+C arms is modelled using the observed proportions of patients who received each scheduled cycle in each arm of the NIAGARA trial.

Table 24 shows the number of cycles completed by number of patients. This shows that from the 530 patients that received study treatment in the D+G+C arm (see CONSORT diagram provided in Appendix B of the Company submission), 85.28% had four cycles of neoadjuvant durvalumab and 86.23% had four cycles of neoadjuvant G+C. From the 383 patients treated in the adjuvant phase, 74.67% completed the full eight cycles of adjuvant durvalumab. From the 526 patients that received study treatment in the G+C arm, 81.18% completed the four cycles in the neoadjuvant phase.

The model starts with 100% of patients receive treatment. The proportions in Table 24 are then subtracted from each cycle as patients discontinue. For example, for neoadjuvant durvalumab, 100% are on treatment in cycle 1, 96.79% of patients are on treatment in cycle 2 (100% - 3.21%), and 93.77% of patients are on treatment in cycle 3 (96.79% - 3.02%), etc,. The full table reporting the proportion on treatment in each cycle is provide in the Company Submission Section 3.5.2 Table 49.

As of the data cutoff date, no patient remained on neoadjuvant or adjuvant treatment in the NIAGARA trial. Therefore, the observed proportions of patients who received each neoadjuvant and adjuvant treatment cycle can be used directly, without the need for extrapolation.

Table 24: Number of cycles completed by number of patients

Setting	Treatment Cycle	Week	Number of cycles completed by number of patients		
			Durvalumab	G + C	G+C
			N= 530		N= 526

Setting	Treatment Cycle	Week	Number of cycles completed by number of patients		
Neoadjuvant	1	0	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)
	2	3	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)
	3	6	xx (x.xx%)	xx (x.xx%)	xx (x.xx%)
	4	9	xxx (xx.xx%)	xxx (xx.xx%)	xxx (xx.xx%)
Surgery					
			Durvalumab	G + C	G+C
			N= 383		
			-		
Adjuvant	1	24	xx (x.xx%)	-	-
	2	28	xx (x.x%)	-	-
	3	32	xx (x.xx%)	-	-
	4	36	x (x.xx%)	-	-
	5	40	xx (x.xx%)	-	-
	6	44	xx (x.xx%)	-	-
	7	48	xx (x.xx%)	-	-
	8	52	xxx (xx.xx%)	-	-

Abbreviations: D + G + C: durvalumab, gemcitabine, cisplatin; G + C: gemcitabine, cisplatin.

Source: NIAGARA

Radical cystectomy was to be performed as soon as possible after completion of, and recovery from, neoadjuvant therapy and was recommended to occur within two to eight weeks after the last dose of neoadjuvant therapy (20). The initiation of adjuvant durvalumab was recommended to occur between 42 and 120 days of cystectomy, after a period of adequate recovery from radical cystectomy.

In the model, the first dose of adjuvant durvalumab is applied at week 24 of the time horizon. This is aligned to the median times from randomization to cystectomy (16.3 weeks) and the time from cystectomy to adjuvant therapy (8.57 weeks) (20).

As detailed in response to Question A4.c and B2.b, for patients who did not undergo cystectomy as planned, all neoadjuvant treatment exposure was captured in the time-on-treatment analysis. Drug costs and drug administration costs for these patients were included in the model in the neoadjuvant phase. The six patients who refused cystectomy but achieved a complete clinical response entered the non-cystectomy extension phase and received durvalumab for up to eight additional cycles, following their initial four cycles of neoadjuvant durvalumab plus chemotherapy. Cycles

administered during the non-cystectomy extension phase were excluded from the treatment cost calculation as the licensed indication specifies perioperative durvalumab use before and after surgery. Given that this represents only 1.1% of patients, the exclusion of these additional doses is anticipated to have a negligible impact on the overall model outcome.

B11. Please clarify what is meant with ‘non-cystectomy extension phase’ (Table 6, page 38 of the CS). Who are these patients? How are these patients included in the analysis and what are the implications for EFS, health-related quality of life (HRQoL) and resource use and costs?

The definition of non-cystectomy extension phase according to the protocol of NIAGARA trial can be found in Question A4.c, this phase was available exclusively to patients who refused radical cystectomy at the specified time after achieving a complete clinical response, as locally determined by multimodal assessment and without additional interventions. Only six patients (1.1%) in the perioperative durvalumab arm entered the non-cystectomy extension phase. Non-cystectomy extension phase patients were administered durvalumab 1500 mg as monotherapy every 28 days for a maximum of eight doses (corresponding to a maximum exposure of 12 months).

The non-cystectomy extension phase patients were included as a part of the ITT population in the survival outcomes, HRQoL and safety analyses. Details regarding the inclusion of costs for these patients in the model are provided in the response to Question B2.b and B10. For these six patients, the model accounts for drug costs incurred during the neoadjuvant phase, resource use and subsequent treatment costs within the appropriate health states, as well as costs related to adverse event management. Drug costs related to the adjuvant phase are not included.

These patients represent a very small proportion of the overall study population, and the inclusion of these patients is anticipated to have minimal impact on the overall study results.

B12 PRIORITY: Subsequent treatments after progression used in the economic model were informed by clinical opinion (average estimate across 4 UK-based

clinical experts). However, the OS data used to inform the model reflect treatments received in the NIAGARA trial.

a. Please comment on how reflective of NHS practice these subsequent treatments provided are (see also question A8), and the impact of this assumption on the results.

A detailed list of post-discontinuation anticancer therapies administered in the NIAGARA trial can be found in the response to Question A8. As noted in Question A9.a, the NIAGARA trial was a large, global, multicentre study that included a range of post-progression treatment practices, determined by the approval and reimbursement status of therapies in each participating country, local access to clinical trials, and the availability of non-approved agents through compassionate use. Consequently, while many of the subsequent treatments provided during the NIAGARA trial align with NHS practice, both the range of therapies used and the proportion of patients receiving them do not perfectly reflect the UK setting.

To ensure the economic analysis reflects NHS clinical practice, four UK-based clinical experts were consulted on the use and distribution of subsequent therapies. The average of these expert insights was applied in the model so that the proportion and types of post-progression treatments mirror expectations for NHS patients, making this the most robust and UK-relevant evidence available. The feedback from UK clinical experts suggested that there would be a higher proportion of patients receiving subsequent therapies in clinical practice compared with the NIAGARA trial in both arms, with experts agreeing that IO-based regimens are an important post-progression treatment option to be considered in the management of MIBC (see response to Question B12 and Company submission Section 3.5.6).

It is important to note that the issue of additional subsequent therapies being available in NIAGARA affects both study arms. As noted in response to question A9b, it is challenging to quantify the potential impact on the results arising from increased subsequent therapy use in both arms, but we contend that the relative treatment effect observed in the NIAGARA trial would likely be preserved, and that differences in the use of subsequent therapies between the NIAGARA trial and NHS practice are unlikely to meaningfully affect the outcomes of the CEM.

In addition, the survival curves used in the economic model were validated by the same UK clinical experts to ensure that projected overall survival outcomes align with what would be expected for this patient population within NHS clinical practice. This expert validation provides further reassurance that the survival estimates in the model are appropriate and reflective of UK experience and the subsequent treatments receive, despite differences in the distribution of subsequent therapies between the trial and real-world NHS settings.

Attempting to further adjust survival outcomes in the model to account for these differences would be challenging and could introduce additional uncertainties or bias, without necessarily improving the reliability of the results.

b. The EAG notes that the assumption on the proportion of patients receiving subsequent treatments based on clinical opinion is substantially higher (xx.x% for the durvalumab arm and xx.x% for the control arm) than in the NIAGARA trial (xx.x%). Please clarify why the proportions assumed in the economic model are substantially higher than what was observed in the NIAGARA trial, and the impact of assuming a higher proportion of subsequent treatments on the model results.

As outlined in the response to Question B12.a, the NIAGARA trial was a global study that included a range of subsequent therapies approved and reimbursed in each participating country. These treatment patterns are not fully representative of UK clinical practice due to differences in approval and reimbursement. Therefore, the most reliable approach was to base subsequent treatment proportions on insights from UK clinical experts. The average proportions across the four interviewed UK experts were xx.x% for the perioperative durvalumab arm and xx.x% for the control arm. These estimates were applied in the model to all patients who experienced progression (i.e., upon leaving the EFS health state), reflecting UK real-world experience for recurred patients who may receive one or more lines of subsequent therapy in their lifetime.

To further support the EAG's assessment, proportions of subsequent treatments based on the NIAGARA trial (9.9% in the perioperative durvalumab arm and 17.5% in the G+C arm) were applied to the model as a scenario analysis. As shown in Table 25, applying these lower proportions resulted in an ICER of £15,339 per QALY, reaffirming that the model results are robust to different assumptions about

subsequent treatment use and consistently demonstrate the cost effectiveness of perioperative durvalumab for patients with MIBC.

Table 25: Pairwise incremental cost effectiveness results: overall subsequent treatment proportions based on NIAGARA trial

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			£15,339

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

B13 PRIORITY: Please clarify whether the subsequent treatments combine treatments for locoregional recurrence and metastatic recurrence. If this is the case, please explain whether locoregional recurrence and metastatic recurrence are treated with the same treatments in the UK clinical practice and the impact of the assumption to combine these treatments and apply to both LR and distant metastasis (DM) health states on the model results.

The model applies subsequent treatment costs as an aggregated one-off cost to all patients who experience any recurrence upon leaving the EFS state. In other words, subsequent treatment in the model represents a pooled combination of treatments for patients entering both the locoregional recurrence (LR) and distant metastasis (DM) health states. This approach captures the entire range of subsequent therapies a patient may receive over their lifetime, regardless of whether the recurrence is locoregional or metastatic. It is a commonly adopted assumption in cost-effectiveness modelling to apply a one-off cost upon disease progression, given the practical challenges and limited data available for modelling every possible treatment sequence following progression.

Under the aggregated subsequent treatment assumption, all treatments received post-recurrence are reflected in the distribution of subsequent therapies, meaning that all relevant costs and resource use are captured irrespective of the location of recurrence. As a result, whether LR and DM patients receive identical or different subsequent treatments should have minimal impact on the overall model results.

B14. In the scenario analysis that includes nivolumab as part of the clinical pathway, the subsequent treatments and proportions of patients receiving each treatment are assumed to be the same for nivolumab (Table 1 in Appendix K) as for the durvalumab arm (Table 54 in CS). Please provide justification for this assumption and explain whether it reflects clinical practice in the UK.

Nivolumab's subsequent treatments and the proportion of patients receiving it are based on four UK clinical experts' opinion. There was no published data identified on CheckMate-274 subsequent treatments, including subsequent treatments for patients who received neoadjuvant G+C in CheckMate-274. Therefore, UK-based expert's opinion was considered the most relevant source of information to reflect clinical practice in the UK.

The overlap between patients eligible for perioperative durvalumab and those eligible for adjuvant nivolumab among PD-L1 $\geq$ 1% resectable MIBC patients is minimal. Therefore, the analysis comparing perioperative durvalumab with G+C+N was included in the submission as a scenario analysis only.

B15. PRIORITY: Please clarify whether any discounting was applied to the cost of subsequent treatments after progression.

A discount rate of 3.5% as per NICE reference case is applied to all costs in the model (38). For the subsequent treatment costs this is applied in the "model" sheet cell BP6 for the G+C arm, and cell FH6 for the D+G+C arm. The discounting is applied to the weighted average of the subsequent therapies after progression, accounting for drug cost and the average duration of the therapy.

B16. PRIORITY: In the Excel model accompanying the CS, the cost of subsequent treatment is set to **xxxx** (column J13 worksheet Costs_SubTx). Please provide the source of this post-progression fixed treatment cost per month and explain how this cost was estimated and what it consists of.

Post progression fixed treatment cost per month of **£x,xxx** is not used in the cost-effectiveness analysis. This input was a placeholder and can be disregarded.

Health-related quality of life

B17. PRIORITY: The company used the HRQoL data from the NIAGARA trial to inform health state utility values in the economic model. EQ-5D-5L disposition and compliance by time and overall (Full analysis set) and EQ-5D-5L scores over time and change from baseline (Full analysis set) are provided in the CSR Addendum (Tables 14.2.9.12 and 14.2.9.13). However, this information is only provided by the treatment arm and not across both treatments (durvalumab and the control arm combined). Please provide details of the numbers of participants providing EQ-5D data at each time point across the treatment arms (durvalumab and control arm combined) and summary statistics of these data, which were used to inform utility values for each health state in the model, including the number of participants, number of missing values, mean, median, min, max.

As noted in the question, compliance, including the numbers of participants providing EQ-5D scores at each time point were provided in the CSR Addendum Tables 14.2.9.12. Values are provided for each arm separately and pooled across treatment arms.

Summary statistics of this data and the change from baseline for each arm was provided in Table 14.2.9.13, as noted in the question. These values are not available pooled in the same format.

B18. PRIORITY: Please clarify how missing data were dealt with when performing the mixed effects repeated measures (MMRM) analysis.

The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression (EFS or MFS, N= 321 observations). Due to censoring, the EQ-5D-5L observations obtained during this period have an unknown/missing health status and therefore, must be omitted from the analysis. Linear mixed effects models provide a valid approach where missing data may be considered missing at random (39). Further information on MMRM methodology is included in the next section (38, 40, 41).

B19. PRIORITY: Please provide comprehensive details on the methods used to estimate health state utility values, including all MMRM analyses performed, the obtained results, and model fit.

Section 3.4.2 of the Company Submission provides a detailed report of the methodology used to estimate health state utility values using the MMRM methodology. The MMRM methodology is routinely used to analyse repeated clinical outcome measures for regulatory and HTA submissions and is the preferred approach to analysing HRQoL data in clinical guidelines (42). The results of an MMRM analysis provides inferences that account for the within-subject correlations from longitudinal measures and is appropriate when handling data that are missing at random (43).

Key methodological considerations will be repeated and added to here, but most of the details on the methods, results and model fit were provided in Section 3.4.2 of the Company submission.

The MMRM analysis accounts for the following states;

1. Pre-progression (EFS investigator),
2. Post EFS (investigator) progression and pre-MFS (investigator) progression,
3. Distant metastatic state (Post MFS progression),
4. Recurrent with unknown metastatic status.

The recurrent with unknown metastatic status is defined as scenarios where, i) MFS is censored prior to EFS event, so we are uncertain if the patient is non-metastatic or distant metastatic at EFS event time, ii) MFS is censored after EFS event.

Where EFS (investigator) times are recorded after MFS (investigator) times, we define rules for assigning utilities as follows:

- EFS (investigator) censoring after MFS (investigator) event All EQ-5D measures up to MFS event, set to “event-free state”; Any EQ-5D collected after MFS, set to “distant met state”.
- EFS (investigator) event after MFS (investigator) censoring - All EQ-5D measures up to EFS (investigator) event, set to “event-free state”.

- EFS (investigator) event after MFS (investigator) event - All EQ-5D measures up to MFS (investigator) event, set to “event-free state”; Any EQ-5D collected after MFS(investigator), set to “distant met”.
- Additionally, observations that occur after EFS event and MFS censoring in subjects where this MFS censoring was after the EFS event date are treated as recurrent with unknown metastatic status.

The MMRM analysis was performed on a dataset excluding any observations recorded after the time of censoring for progression (see response to Question B18).

The statistical relationship between EQ-5D-5L health state utility and treatment, and health status was assessed using regression analysis. Analysis was performed in R 4.3.1 using the mrmr package 0.3.14 for model fitting. The MMRM analysis was performed using the restricted maximum likelihood method (REML) with the following covariates included as fixed effects:

- (Randomised) Treatment
- Progression status (pre-progression, post-progression)
- Treatment + Progression status
- Treatment + Progression status + Treatment * Progression status (Both terms and their interaction included).

The correlation of repeated utility measurements within subjects over time was captured via the specification of covariance structures for the MMRM. The results from the models using the first covariance structure in the sequence that successfully converged for all models are presented here (i.e., for each of the four covariate options). If for a particular set of covariates none of the models converged, then no results are presented for that model, and the remaining model results are based on the most flexible covariance structure for which the models converged.

The hierarchy of covariance structures tested, in order of most to least flexible, is shown below:

1. Unstructured – each visit is allowed to have a different variance, and each combination of visits is allowed to have a different covariance.

2. Toeplitz with heterogeneity – each visit is allowed to have a different variance, covariances between measurements depend on how many visits apart they are.
3. Autoregressive, order 1 (AR(1)) with heterogeneity – each visit is allowed to have a different variance, and covariances decrease based on how many visits apart they are. Covariances decrease towards zero as the number of visits between observations increases.
4. Toeplitz – as above for number 2, but each visit shares the same variance.
5. Autoregression, order 1 (AR(1)) – as above for number 3, but each visit shares the same variance.

For each model, parameter estimates, and marginal ('least square') means are provided below including 95% confidence intervals. The marginal ('least square') mean provides a model-based estimate of the mean utility score by status (treatment and/or Progression status) that is averaged over observations and with adjustment for repeated measures.

In total, 12,880 EQ-5D-5L observations were available from 986 patients. Of these, 12,130 observations were recorded in the event-free state, 150 observations were recorded in the post-EFS-pre-metastatic state, 128 observations were recorded in the distant metastatic state, 151 observations were recorded recurrent with unknown metastatic status, and 321 were recorded after censoring for MFS.

Baseline HSU were similar across arms, with mean values of **x.xx** (standard deviation=**x.xx**) and **x.xx** (standard deviation=**x.xx**) for G+C and G+C+D, respectively. The MMRM analyses were therefore performed without adjustment for baseline HSU.

The correlation of repeated utility measurements within subjects over time was captured via Autoregressive - order 1 with Heterogeneity as this successfully converged for all models. Table 26 shows the best fitting model in terms of AIC was the model including a term for progression status.

Table 26 Goodness of fit statistics

Description	Converges	AIC	BIC
Treatment	TRUE	-14562.5	-14327.8
Progression status	TRUE	-14597.6	-14362.9
Treatment + Progression status	TRUE	-14593.4	-14358.7
Treatment * Progression status	TRUE	-14584.2	-14349.5

Abbreviations: AIC: Akaike information criterion; BIC: Bayesian information criterion.

Table 27 presents the parameter estimates for each model and Table 28 presents the marginal means. Across all applicable models, there was no significant ($p>0.05$) or meaningful difference in HSU across arms. In contrast, there was a consistent, meaningful and significant effect of disease state on HSU across all models. As expected, the mean decrease in HSU associated with DM versus EF was larger than the decrement associated with LR. In the best fitting MMRM, the effect of DM versus EF was -0.106 and the effect of LR versus EF was -0.069. In summary, these results indicate that HSU is more closely related to disease state than treatment arm.

Table 27. Summary of point estimates

Parameter		Randomised group only	Disease state	Randomised group + disease state	
				Without interaction	With interaction
Intercept		x.xxx [xx = x.xxx]	x.xxx [xx = x.xxx]	x.xxx [xx = x.xxx]	x.xxx [xx = x.xxx]
Randomised group	D+G+C versus G+C	x.xxx [xx = x.xxx] (x = x.xxx)		x.xxx [xx = x.xxx] (x = x.xxx)	x.xxx [xx = x.xxx] (x = x.xxx)
Disease state	LR versus EF state		-x.xxx [xx = x.xxx] (x = x.xxx)	-x.xxx [xx = x.xxx] (x = x.xxx)	-x.xxx [xx = x.xxx] (x = x.xxx)
	DM versus EF state		-x.xxx [xx = x.xxx] (x = <x.xxx)	-x.xxx [xx = x.xxx] (x = <x.xxx)	-x.xxx [xx = x.xxx] (x = <x.xxx)
	Recurrent with unknown metastatic status versus EF state		-x.xxx [xx = x.xxx] (x = x.xxx)	-x.xxx [xx = x.xxx] (x = x.xxx)	-x.xxx [xx = x.xxx] (x = x.xxx)
Interaction between	D+G+C: LR (interaction)				x.xxx [xx = x.xxx] (x = x.xxx)

Parameter		Randomised group only	Disease state	Randomised group + disease state	
				Without interaction	With interaction
randomised group and disease state	D+G+C: DM state (interaction)				x.xxx [xx = x.xxx] (x = x.xxx)
	D+G+C: Recurrent with unknown metastatic status (interaction)				x.xxx [xx = x.xxx] (x = x.xxx)

Abbreviations: AIC: Akaike information criterion; C: cisplatin; D: durvalumab; DM: distant metastases; EF: event-free; G: gemcitabine; HSU: health state utility; LR: loco-regional recurrence; MMRM: mixed model for repeated measures; SE: standard error.

Note: The correlation of repeated measurements of HSU within subjects was captured via the specification of a covariance structure. A series of covariance structures were considered in order of most to least flexible. The most flexible covariance structure that achieved convergence for all models was selected for the base case. The final covariance structure was autoregressive order 1 with heterogeneity. Prior to this, the unstructured and Toeplitz with heterogeneity structures failed to converge.

Source: Data on file

Table 28. Summary of marginal means

Parameter	Treatment	Progression status	Treatment + Progression status	Treatment * Progression status
G+C	x.xxx (x.xxx, x.xxx)			
D+G+C	x.xxx (x.xxx, x.xxx)			
Event-free state		x.xxx (x.xxx, x.xxx)		
Post-EFS-pre-metastatic		x.xxx (x.xxx, x.xxx)		
Distant met state		x.xxx (x.xxx, x.xxx)		
Recurrent with unknown metastatic status		x.xxx (x.xxx, x.xxx)		
G+C:Event-free state			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
D+G+C:Event-free state			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
G+C:Post-EFS-pre-metastatic			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
D+G+C:Post-EFS-pre-metastatic			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
G+C:Distant met state			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
D+G+C:Distant met state			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
G+C:Recurrent with unknown metastatic status			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)
D+G+C:Recurrent with unknown metastatic status			x.xxx (x.xxx, x.xxx)	x.xxx (x.xxx, x.xxx)

Abbreviations: C: cisplatin; D: durvalumab; DM: distant metastases; EF: event-free; G: gemcitabine; LR: loco-regional recurrence; OS: overall survival.

B20. PRIORITY: The EAG notes that the utility values used for the event-free health state, derived from the NIAGARA trial, appear to be relatively high and

are close to those typically observed in the general population. Clinical experts have advised that patients with MIBC continue to experience a substantial impact on quality of life even while in the event-free state, often due to ongoing painful symptoms and treatment-related effects. Please:

a. Present a comparison of these NIAGARA trial utility values with other published utility values for patients with MIBC in the event-free state.

As detailed in Section 3.4 in the CS and Appendix E, a systematic literature review (SLR) was conducted and identified 24 studies reporting HRQoL data in patients with MIBC. Only one publication evaluating the cost-effectiveness of adjuvant nivolumab by Brodtkorb et al provided relevant health state utility data, although this value is for the disease-free state rather than event-free, given the design of the CheckMate-274 trial (44). The mean disease-free health state utility applied was 0.863. This is consistent with the HSU value used for the EF health state in the NIAGARA model (0.847). It should be noted that the Brodtkorb et al utility was derived using a United States based dataset. In the NICE appraisal of adjuvant nivolumab (TA817), the Company explained that the HRQoL within disease-free (DF) from the trial exceeded age-dependent general population values, and so to address this, all patients in the DF state in the model had age-matched population values. Although the trial values were redacted and not publicly available, this indicates that trial values were used in the CheckMate-274 trial.

Whilst an unpublished source, the Prospective Bladder Cancer Infrastructure (ProBCI) registry provides valuable insight into the HRQoL data from MIBC patients. We provided some detail of this registry in the Company submission, and feel it may be valuable to provide more context here.

This registry collects prospective clinical and HRQoL data from patients with MIBC, non-muscle invasive and metastatic bladder cancer, recruited from 25 hospitals in the Netherlands. AstraZeneca is a partner organization to ProBCI, providing financial support for its research initiatives. As a partner, AstraZeneca can submit analysis requests to the ProBCI. To support reimbursement submissions for perioperative durvalumab, AstraZeneca requested an analysis to explore the impact of recurrence on HSU and HRQoL. This analysis was performed on a subpopulation of ProBCI that best matched the key inclusion criteria of the NIAGARA trial:

- A first recurrence of MIBC with stage cT2-4a, N0/1, M0, and
- Purely urothelial cell carcinoma or with a urothelial cell carcinoma component, and
- Primary treatment for MIBC was radical cystectomy with or without neoadjuvant chemotherapy or radiotherapy
- No prior systemic chemotherapy or immunotherapy for MIBC.

A recurrence event included local or distant recurrence of disease or progressive disease. The association between recurrence and HSU was estimated using a MMRM analysis with covariates for recurrence and the calendar date of HSU collection, measured in terms of the quarter of each year (e.g., quarter 1, 2024). The data set used in the analysis contained 257 EQ-5D-5L observations from 166 subjects.

At the time of writing, HSU were available for the 5L UK value set by Devlin et al, as well as the Dutch, French and Canadian 5L value sets. The following results are based on the UK HSUs by Devlin et al (40).

Table 29 details the MMRM results for the UK 5L HSU in ProBCI. This analysis reveals a significant and meaningful effect of recurrence on the HSU of patients with MIBC. The difference in HSU between pre- and post-recurrence states was -0.126 (95% CI of -0.223 to -0.028). There was no significant or meaningful effect of time/calendar date on HSU. The mean HSU for patients in the pre-event state was 0.852.

Table 29. Results of MMRM analysis for UK 5L HSU (Devlin et al) in ProBCI

Parameter	Estimate	Standard error	Lower 95%	Upper 95%
Intercept	0.852	0.018	-	-
Time (calendar date)	0.001	0.003	-0.003	0.007
Post-recurrence versus pre-recurrence	-0.126	0.049	-0.223	-0.028

Abbreviations: HSU: health state utility; MMRM: mixed model for repeated measures; ProBCI: Prospective Bladder Cancer Infrastructure; UK 5L: United EuroQol 5-Dimension 5-Level.

The results of the ProBCI analysis support the findings of the NIAGARA analysis, in demonstrating a significant and meaningful effect of recurrence on HSU. The change in HSU comparing pre- versus post-recurrence in ProBCI (-0.126) is consistent with the NIAGARA trial results for DM MIBC (-0.106), while the mean HSU for a pre-event

state is similar to the means HSU for EF in NIAGARA (0.852 ProBCI versus 0.847 for NIAGARA).

As the 5L Devlin et al value set is no longer recommended by NICE in the UK, and because the ProBCI analysis does not differentiate results based on LR or DM, the results of ProBCI is only used to validate the findings of the NIAGARA trial analysis. The results of the ProBCI analysis support the findings of the NIAGARA analysis, with the mean HSU for a pre-event state being similar to the mean HSU for EF in NIAGARA study (0.852 ProBCI versus 0.847 for NIAGARA study).

b. Comment on the appropriateness of using these relatively high utility values in the model, given the clinical context, and outline the potential impact of this assumption on the model results.

The health state utility values were based on the EQ-5D-5L data collected in the NIAGARA trial and further validated in interviews conducted with UK clinical experts. As discussed in response to Question B20 a, the value used in the EF state is appropriate and aligned with external sources of evidence in this setting. We therefore maintain that the values used in the Company submission base case are appropriate and aligned with the NICE reference case (38).

To test the sensitivity of the model results to lower utility values, we have conducted a scenario applying an arbitrary decrement to the EF utility. In TA817, the EAG had previously suggested a 0.02 utility decrement to address concerns that the disease-free survival health state utility, using the age- and sex-matched general population utility value, was too high. This was applied up until the timepoint in the model where patients were considered 'cured', as a structural cure was assumed. Here we present the same 0.02 decrement applied to the EF utility in a scenario analysis. This is considered conservative given that it is applied for the duration of the time spent in the EF state and despite the fact that TA817 used higher utility values to begin with (matching general population values). As shown in Table 30, the adjustment made negligible impact on the ICER compared to the base case, demonstrating that the model results are robust to reductions in the EF health state utility.

It is important to highlight that in TA817, clinical and patient experts agreed that, after a period of adjustment, people with resected urothelial cancer often adapt very well to

post-surgical changes and often achieve a good quality of life with a fully functional lifestyle. Furthermore, the appraisal committee acknowledged the application of a utility decrement as arbitrary, since there is insufficient evidence to precisely quantify the appropriate value.

Overall, these findings confirm that the model's conclusions regarding the cost-effectiveness of perioperative durvalumab remain stable, even when applying a lower utility for the event-free health state.

Table 30: Pairwise incremental cost effectiveness results: 0.02 decrement applied to EF utility

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			£14,406

Abbreviations: C: cisplatin; EF: event-free; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

B21. PRIORITY: Clinical experts have advised EAG that locoregional recurrence in MIBC has a substantial negative impact on patients' quality of life, often resulting in symptoms that are more painful and debilitating than those experienced with distant metastases. However, this clinical perspective does not appear to be reflected in the utility values derived from the NIAGARA trial. Please:

a. Provide a comparison of the NIAGARA trial utility values for locoregional recurrence with values reported in the published literature for comparable patient populations.

As detailed in Section 3.4 in the CS and Appendix E, a systematic literature review (SLR) was conducted and identified 24 studies reporting HRQoL data in patients with MIBC. As mentioned in the response to question B20.a, the only relevant publication is by Brodtkorb et al., reporting mean HSU of 0.793 for the LR health state. This is consistent with the LR HSU used in the model **x.xxx**.

b. Describe the potential impact of using these relatively high utility values for locoregional recurrence on model results

Similar to the response provided to Question B20.b, the health state utility values were based on the EQ-5D-5L data collected in the NIAGARA trial and further validated in interviews conducted with UK clinical experts. As discussed in response to Question B21 a, the value used in the LR state is appropriate and aligned with external sources of evidence in this setting. We therefore maintain that the values used in the Company submission base case are appropriate and aligned with the NICE reference case (38).

To address the EAG's concerns and assess the impact of varying the utility assigned to the LR health state, a scenario was conducted applying an arbitrary decrement to the LR utility. We have copied the approach outlined in response to Question B20b, applying an arbitrary 0.02 decrement to the LR health state. As shown in Table 31, the adjustment made negligible impact on the ICER with a 0.49% decrease compared to the base case, demonstrating that the model results are robust to reductions in the LR health state utility.

Overall, these findings confirm that the model's conclusions regarding the cost-effectiveness of perioperative durvalumab remain stable, even when applying a lower utility for the locoregional recurrence health state.

Table 31: Pairwise incremental cost effectiveness results: 0.02 decrement applied to LR utility

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)			£13,980

Abbreviations: C: cisplatin; G: gemcitabine; ICER: incremental cost-effectiveness ratio; LR: loco-regional recurrence; LY: life year; N: nivolumab; QALY: quality-adjusted life year; SoC: standard of care.

B22. PRIORITY: The company applied a utility decrement for patients who underwent surgery to reflect the negative impact of cystectomy on HRQoL. This decrement was applied for 6 months after the surgery. The EAG consulted with UK clinical experts who noted that the acute impact of the surgery is expected to last over 1 year. Furthermore, in the previous TA817,(45) for nivolumab the

duration of the negative acute impact of the surgery was assumed to be 1-2 years.

a. Please justify the choice of the duration of the acute negative impact in the analysis.

As detailed in Section 3.4.5 in the CS, the impact of radical cystectomy on HRQoL was modelled using HSUs from the UK Life After Bladder Cancer (LABC) study (41). The LABC study collected EQ-5D-5L questionnaires at baseline, and at 6, 9 and 12 months after diagnosis. HSUs were estimated using the Van Hout et al 5L to 3L crosswalk algorithm for the UK value set (46) and mapped to 'baseline' (prior to surgery), 'post-treatment' (first survey after surgery) and 'recovery' (at least 6 months since surgery) phases. Compared to the NIAGARA cohort, the cohort in LABC was older on average (39% aged >75 years old versus 11% in NIAGARA) but had a similar sex distribution (79% Male in LABC versus 82% in NIAGARA).

In patients who received radical radiotherapy or cystectomy, there was a decline in mean EQ-5D-5L HSU of approximately $-x.xx$ from baseline to the post-treatment phase (46). At the recovery phase (6-12 months after surgery), there was no difference in general HRQoL when compared to baseline (46). These findings indicate that cystectomy may lead to an initial QALY loss of approximately $x.xx-x.xx$ per surgery patient, calculated as the utility loss of $x.xx$ multiplied by the $x.x-xx-x.x$ -year recovery period. In the NIAGARA cost-effectiveness base case, the recovery period after surgery was set to 6 months. In the next question (B22.b) the negative impact is expanded to 12-month as a sensitivity analysis. The results shows that there is a minimal impact on the conclusion that perioperative durvalumab represents a cost-effective treatment option in this setting at the £20,000 WTP threshold.

b. Please include a scenario analysis with the duration of this decrement set to 1 year.

A scenario analysis was performed as requested with the duration of utility decrement of surgery set to 1 year. As shown in Table 32, the variation caused a negligible impact in the cost-effectiveness results, indicating the robustness of the model outcome regardless of the duration of utility decrement.

Table 32: Pairwise incremental cost effectiveness results – Scenario analysis of 12-month duration of disutility (deterministic)

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)	-	-	£14,060

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

B23. PRIORITY: Clinical advice to the EAG was that cystectomy is expected to have a life-long impact on HRQoL due to the need of a urostomy bag for the rest of patients' life. This impact is in addition to the acute negative impact associated with the surgery.

a. Please explain why the life-long impact of using urostomy bag was not included in the analysis

The company acknowledges the rationale behind this question. During the submission process, careful consideration was given to whether to include a life-long utility decrement associated with the use of a urostomy bag. Ultimately, this was excluded, consistent with feedback received during the technical engagement for TA817.

During this engagement, both clinical experts and patient advocacy groups (NCRI-ACP-RCP-RCR, Action Bladder Cancer, and Fight Bladder Cancer) concluded that, while many individuals experience negative impacts from permanent changes in urinary and sexual function, these impacts are generally short-lived as patients adapt over time. Importantly, the loss of function or presence of a disability does not necessarily equate to a sustained loss in quality of life, and it is entirely possible for individuals with such disabilities to experience a high quality of life. It was also noted that the quality of life for individuals with resected high-risk urothelial cancer is similar to those who are disease-free.

Furthermore, none of the previous eight urothelial carcinoma medicines assessed by NICE included an additional disutility for the life-long impact of using a urostomy bag. This is aligned with the view that inclusion of a long-term decrement is not warranted in this context.

Given this evidence and considering that any long-term disutility associated with a urostomy bag would apply equally to both treatment arms involving cystectomy (G+C and D+G+C), thus effectively cancelling itself out in terms of incremental analysis, it was determined that including such a decrement in the cost-effectiveness model would not be informative for decision making. For these reasons, a lifelong HRQoL decrement due to urostomy was not included in the analysis.

b. In the economic model, please incorporate a scenario analysis that applies a life-long health utility decrement for patients who underwent cystectomy.

A scenario analysis was performed as requested with the duration of utility decrement of surgery set for a lifetime horizon of 432 months (36 years). As shown in Table 33, the variation caused a negligible impact in the cost-effectiveness results, indicating the robustness of the model outcome regardless of the duration of utility decrement.

Table 33: Pairwise incremental cost effectiveness results: 432-month duration of cystectomy disutility

	Perioperative durvalumab	Control (G+C) – the current SoC	Incremental
Total costs (£)	£xx,xxx	£xx,xxx	£xx,xxx
Total LYs	xx.xx	x.xx	x.xx
Total QALYs	x.xx	x.xx	x.xx
ICER (£ per QALY)	-	-	£14,889

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LYs: life years; QALYs, quality-adjusted life years; SoC: standard of care.

Section C: Textual clarification and additional points

Search strategies

C1. For the clinical searches in Appendix B, the PRISMA diagram for the original searches on page 41 does not add up correctly for the databases. There are 3,065 records in total for the databases with 676 records removed in total, which comes to 2,380 rather than 2,406. Please can the company correct this error?

The company has reviewed the PRISMA diagram and cannot find the number 3,065.

Based on the PRISMA diagram for the search conducted in July 2024, the total number of records identified from electronic database searches was 3,082 instead of 3,065 (Medline®: 791; Embase®: 1,538; CENTRAL®: 736 and CSRD®: 17).

After removing 676 duplicate records, 2,406 records indeed remained for screening, therefore the calculation appears correct.

C2. For the clinical searches in Appendix B, the PICO structure does not appear to be appropriate for this systematic review. According to the eligibility criteria (Table 1, page 7), any treatment or placebo is the comparator. Therefore, why have any interventions been searched for at all? Or does this mean any studies where the comparator is directly compared against an intervention of interest? Please clarify if any relevant evidence was missed as a result.

The company confirms that the latter interpretation is correct: studies were eligible only if an intervention of interest (i.e., an intervention listed in the PICO table, in the column “Inclusion criteria” and in the row “Interventions”) was directly compared against any other treatment, including placebo. No relevant evidence was missed as a result of the PICO structure.

C3. For the clinical searches in Appendix B, removing ineligible study types (e.g. systematic reviews) in the search strategy is questionable. For sensitivity, it is better to limit to only the study types of interest rather than removing those not of interest. Just because this is in the exclusion criteria doesn't mean it should be applied in the searches. Please can the company clarify if any relevant evidence was missed as a result.

The company understands the question refers to the exclusion of pre-clinical/non-human/animal model studies, cross-sectional and systematic review studies, such as in rows 60-72 in Table 2 of Appendix B (Page 13) (“Embase search strategy for clinical SLR: Embase 1974 to July 22, 2024; searched on 22 July 2024”). These terms are part of the validated filter for randomised controlled trials (RCTs) developed by Cochrane (2023 update for EMBASE via Ovid, taken from the IISG filters resource) (47).

In addition, the company undertook extensive searches beyond the electronic databases. Trial registries and the reference lists of recent published systematic reviews were searched, to ensure all relevant evidence was captured (48, 49).

Based on the validated nature of the Cochrane filter, and the extensive hand-searches, the company does not expect that any evidence has been missed as a result.

C4. For the various searches in Appendix E (for cost-effectiveness, health-related quality of life, and cost and healthcare resource identification, measurement, and valuation studies), the Embase search strategy employed a line to remove certain records on non-muscle invasive bladder cancer (line 107). This could have risked removing relevant records; just because a record refers to non-muscle in the title does not necessarily mean that the record does not also include any information of relevance. Please clarify if any relevant evidence was missed as a result.

The exclusion of records with the term 'non-muscle' in the title was not used in isolation. Instead, the company only excluded records where 'non-muscle' was present in the title, while the indexing term for 'muscle-invasive bladder cancer' was absent from the record, thus indicating the record did not focus on the indication of interest. No relevant evidence was missed as a result.

C5. For both the clinical searches in Appendix B and the various searches in Appendix E (for cost-effectiveness, health-related quality of life, and cost and healthcare resource identification, measurement, and valuation studies) the search terms for the condition could have been more sensitive. For instance, including some of the following examples (which are not exhaustive): Urinary Bladder Neoplasms/ as a subject heading on MEDLINE, CDSR and CENTRAL. Moreover, the free-text terms could have included: tumor, tumour, myoinvasive, locally advanced bladder cancer, metastatic or advanced bladder cancer, and truncated invasive at invas* to retrieve terms like invade, invasion etc. Please clarify if any relevant evidence was missed as a result.

The search terms used in the search strategies were developed after examining the search strategies used in two relevant published SLRs (48, 49) and discussion with AstraZeneca medical expert. The two published SLRs used broad terms for BC instead of terms specific to MIBC. The present SLR used terms specific to MIBC to maintain balance between sensitivity and specificity of the searches. To examine the impact of using MIBC terms instead of BC terms, the recall performance of the search was assessed using a test-set of four studies for the clinical SLR and four studies for the economic SLR (50-57). All studies were successfully retrieved by the search. This decision was validated by AstraZeneca medical review. To ensure all relevant evidence was captured, we conducted complementary searches in reference lists of

recent published systematic reviews (identified through the database searches), and trial registries, to identify any additional RCTs relevant to the research objective. Details regarding the grey literature searches are available in the Appendix section B.1.5.2, Table 10.

Finally, among the treatments examined in the SLR, the only relevant comparators for the assessment were cisplatin-based chemotherapy and nivolumab. For cisplatin-based chemotherapy, the comparison is informed by the NIAGARA trial, an RCT (the gold standard evidence) which presents the direct comparison against the current standard of care in the UK. The key study informing evidence for nivolumab, CheckMate-274, is included in the SLR.

In conclusion, the company confirms no relevant evidence was missed as a result of the population terms used in the search strategy.

C6. For the clinical searches in Appendix B, the search terms for the interventions were limited. The free-text terms could have been much more sensitive in various respects, such as (but not limited to): searching for a wider range of synonyms (e.g. radical cystectomy is bladder removal but this term isn't searched for); searching for acronyms (e.g. MTX for methotrexate); searching a wider range of brand names for drugs (e.g. for the intervention cisplatin: cis-platinum, dichlorodiammineplatinum, biocisplatinum, platidium, or platino); and searching for drugs in additional field codes relating to drugs on both MEDLINE and Embase. Moreover, some of the intervention terms were searched for in combination with other subject headings or terms rather than separately. Although this may reflect the specific combinations of drugs listed in the inclusion criteria, it is more sensitive to search for drug terms separately as so many different names and terms can be used for each drug. Please clarify if any relevant evidence was missed because of these limitations to the intervention terms.

Please refer to the answer to question C5, which outlines the rationale behind the search strategy design, as it also applies to the terms used for searching the interventions. The intervention search terms were selected to reflect the pharmacological treatments relevant to the SLR and were refined through consultation with AstraZeneca medical expert. The strategy was tested using a predefined set of

key studies, all of which were successfully retrieved. This validation confirmed that the search was sufficiently sensitive to identify the relevant evidence and that no relevant studies were missed due to the intervention terms used.

C7. Is the EAG correct in assuming the indirect treatment comparison searches referred to on page 71 of the CS, the search strategies are the same as those presented in Appendix B to find clinical evidence? If not, please provide the search strategies.

Yes, the searches for indirect treatment comparison referred to on page 71 of the CS are the same as the search strategies presented in Appendix B for clinical evidence.

Indirect treatment comparisons

C8. Section 2.9.2 of the company submission, point 1 gives reference 15 for the estimation of the acceleration factor for the PD-L1 subgroup in CheckMate-274. However, this reference does not report on the CheckMate-274 trial. Please confirm the correct reference.

Thank you for checking. The company notes this reference did not get updated in EndNote® library refresh. The correct reference is as follow:

Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med. 2021;384(22):2102-14.

C9. Appendix B, please clarify the meaning of “residual disease-free” in the 4th row of Table 58.

The phrase “residual disease-free” in the 4th row of Table 58 is a typographical error. It should read “patients who underwent surgery and had residual disease at adjuvant visit,” not “residual disease-free.”

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

**Durvalumab with gemcitabine and cisplatin
before surgery (neoadjuvant) then alone after
surgery (adjuvant) for treating muscle-invasive
bladder cancer [ID6168]**

Clarification questions

**Indirect treatment comparison for distant metastasis-free
survival**

August 2025

File name	Version	Contains confidential information	Date
ID6168_Durvalumab MIBC_Appendix	1.0	Yes	1st August 2025

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Introduction

The distant metastasis-free survival (DMFS) indirect treatment comparison (ITC) was performed using the same approach as described in the Company Submission for the event free survival (EFS) and overall survival (OS) ITCs. The analysis involved estimating the acceleration factor (AF) for nivolumab versus placebo from pseudo-patient data recovered from the DMFS curve of the PD-L1 $\geq$ 1% muscle-invasive bladder cancer (MIBC) subgroup of CHECKMATE-274, reported in supplementary figure 4D of Galsky et al [1]. This AF was then applied to the 'adjuvant period' MFS survival times of the gemcitabine in combination with cisplatin (G+C) arm of NIAGARA.

The aim of the analysis was to estimate the MFS for the control arm of NIAGARA that included the effect of adjuvant nivolumab (referred to as "counterfactual arm", or G+C+N). The ITC is then performed by comparing durvalumab plus gemcitabine in combination with cisplatin (D+G+C, or perioperative durvalumab) with this counterfactual arm (representing G+C+N), and by comparing G+C+N with G+C.

Estimating the AF for nivolumab

Pseudo patient data for DMFS in the PD-L1 >1% MIBC subgroup of CHECKMATE-274 were generated by digitising the Kaplan-Meier curve from Galsky et al and applying the Guyot algorithm. Figure 1 displays the Kaplan-Meier curve derived from these pseudo patient data, while Table 1 outlines the corresponding landmark probabilities, median survival times, and the hazard ratio for nivolumab versus placebo.

The pseudo patient data produced survival estimates that were consistent with the original results reported by Galskey et al. The treatment effect estimate derived from these data closely matches the results presented in CHECKMATE-274 (HR = 0.52, 95% CI 0.35-0.78). Additionally, the recovered data closely predicts the landmark and median survival estimates from the study publication (48.4% and 42.7% for placebo at months 24 and 36, and 68.8% and 64.3% for nivolumab at months 24 and 36, respectively. Median survival was not reached for nivolumab and was reported as 17.9 months for placebo).

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Figure 1: Kaplan-Meier plot of Distant Metastases-Free survival (DMFS) using the recovered patient data from the MIBC with prior neoadjuvant chemotherapy subgroup of CHECKMATE-274

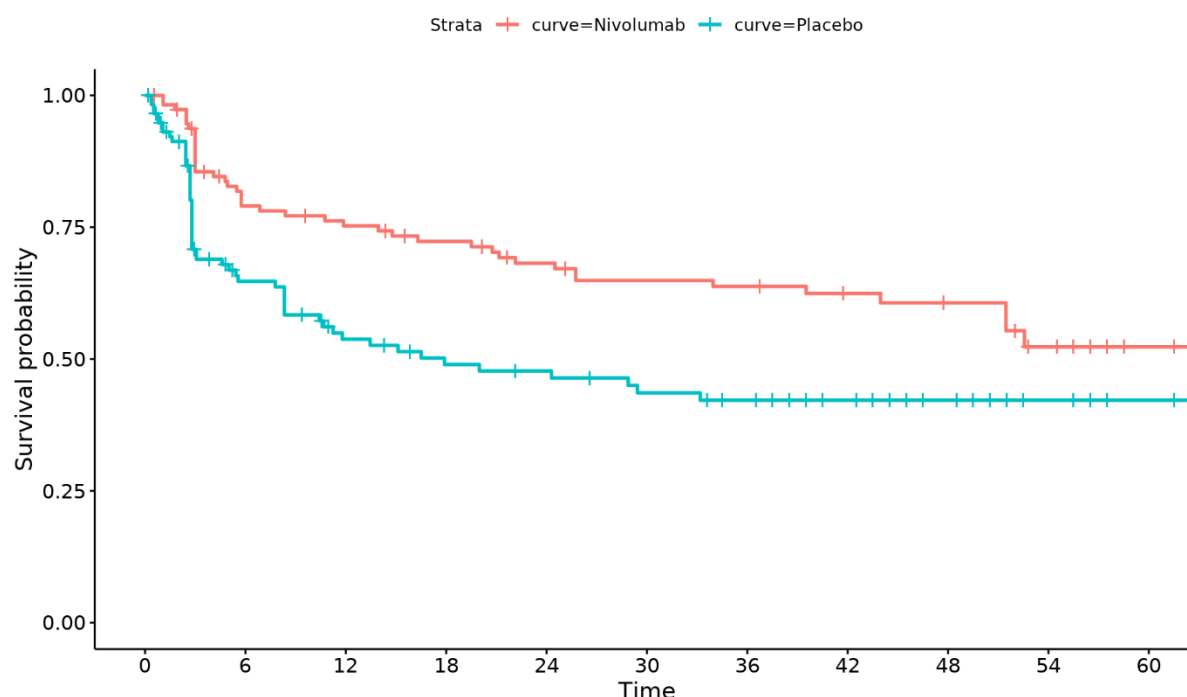


Table 1: Summary of survival probabilities at 24 and 36 months, median survival and hazard ratio for the MIBC with prior neoadjuvant chemotherapy subgroup of CHECKMATE-274

Characteristic	Landmark		Median survival	Treatment effect	
	24 Months	36 Months	Months	HR ¹	95% CI ¹
Arm					
Placebo	48% (39%, 59%)	42% (33%, 54%)	18 (8.3, —)	—	—
Nivolumab	68% (60%, 78%)	64% (55%, 74%)	— (51, —)	0.53	0.36, 0.80
¹ HR = Hazard Ratio, CI = Confidence Interval					

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The AF for nivolumab versus placebo was estimated using parametric survival models (Weibull, log-logistic, lognormal and generalised gamma) fitted to a data set containing both arms of CHECKMATE-274 and including a treatment covariate. This covariate represents the effect of nivolumab in decelerating the time to an event compared to placebo.

Table 2 presents the estimated AF for nivolumab, and Figure 2 illustrates the fit of the AFT models to the Kaplan-Meier curves. An AF value of greater than one indicates that treatment would increase or improve the time to recurrence. An AF value of less than one indicates that treatment would decrease or worsen the time to recurrence.

Table 2: Summary of goodness of fit statistics and AF parameter estimates for models fitted to the PD-L1 >1% MIBC subgroup of CHECKMATE-274

Model	GOF AIC ¹	GOF BIC ¹	Estimate	Standard error	Lower 95 CI ²	Upper 95 CI ²
Generalised gamma	908.1328	921.8851				
Lognormal	927.2861	937.6003				
Log-logistic	936.5162	946.8305				
Weibull	948.1181	958.4324				
¹ GOF = goodness of fit; AIC = Akaike Information Criteria; BIC = Bayesian Information Criteria						
² CI = Confidence Interval						

The best fitting model according to AIC and BIC was the generalised gamma. Based on visual fit, this model failed to adequately predict the trial data as it appeared to systematically underestimate survival in the nivolumab arm and overestimate survival in the placebo arm. Among the fitted models, the generalised gamma predicted the lowest AF for nivolumab versus placebo of 2.61 [95% CI 1.60 – 4.26].

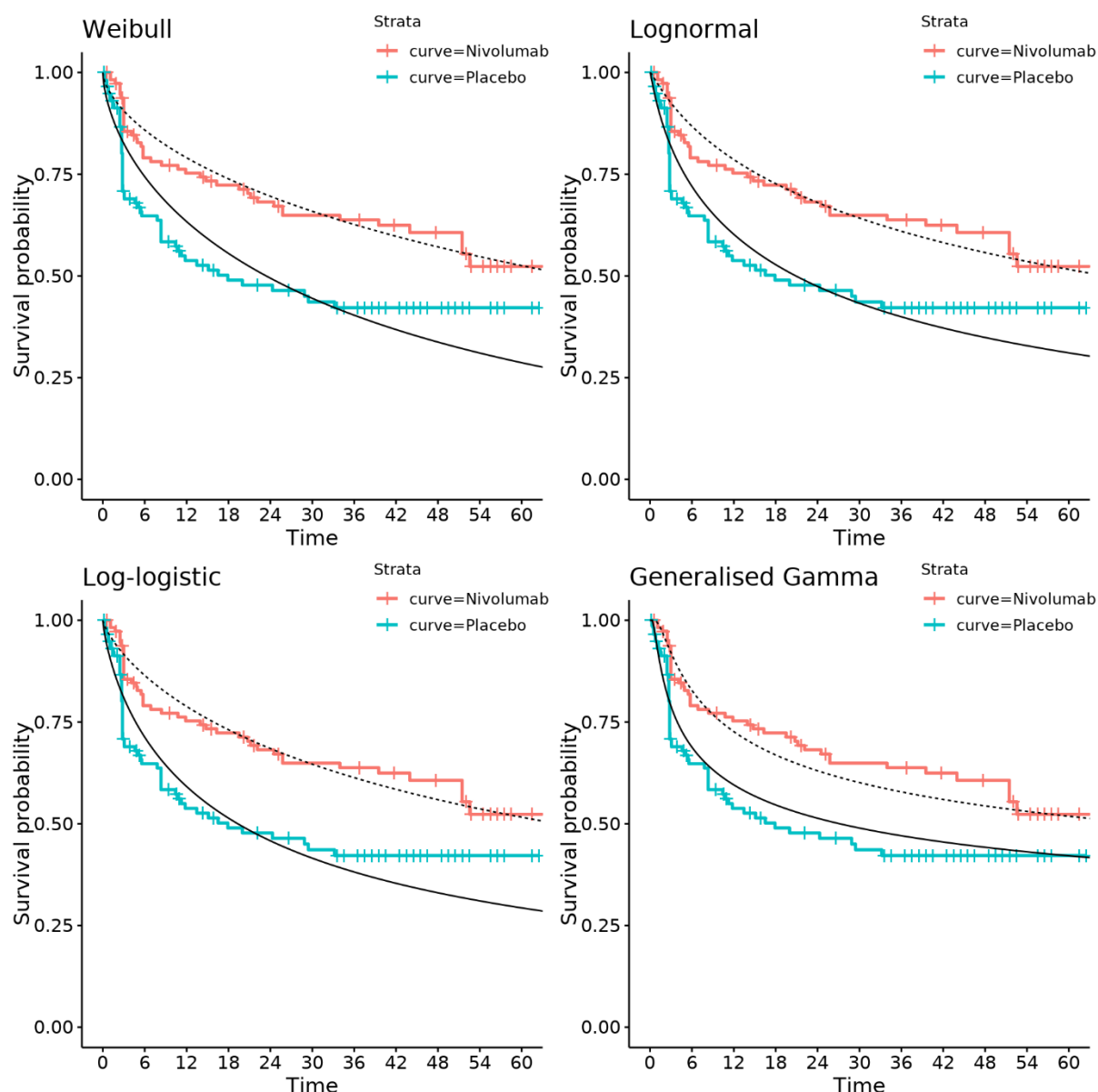
Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

With log-normal, log-logistic and Weibull, the AF's ranged from [REDACTED], with the log-logistic AFT yielding the most conservative (and largest) estimate of the effect of nivolumab (AF=[REDACTED]). Of these models, the Weibull demonstrated the poorest visual fit to the Kaplan-Meier data, with log-normal and log-logistic providing a similar level of fit to the DMFS curve. During the earlier phases of follow-up, both the lognormal and log-logistic models tended to overestimate the survival of both arms. At later time points, the opposite trend was observed where the models tended to underestimate survival for both arms. Overall, these models displayed a similar pattern of overestimation and underestimation of survival in both arms, suggesting that their estimates of treatment effect (i.e., relative difference between arms) are unlikely to be systematically biased in favor of either arm.

Due to time constraints, it was not possible to perform the ITC utilizing time-varying AFs for DMFS. Nevertheless, as observed in the ITCs for EFS and OS, implementing time-varying AFs had minimal impact on the outcomes and, when applied, generally resulted in a more conservative estimation of nivolumab's effect.

Of the standard AFT models, the log-logistic was considered most suitable for the ITC as it provided the most optimistic and conservative estimate of treatment effect for nivolumab.

Figure 2: Fit of AFT models to the Kaplan-Meier curves for DMFS in the PD-L1 >1% MIBC subgroup of CHECKMATE-274



Counterfactual survival

The counterfactual arm was created using the control arm of NIAGARA and applying the AF of adjuvant nivolumab from CHECKMATE-274 to the 'adjuvant period' MFS survival times of patients eligible for treatment.

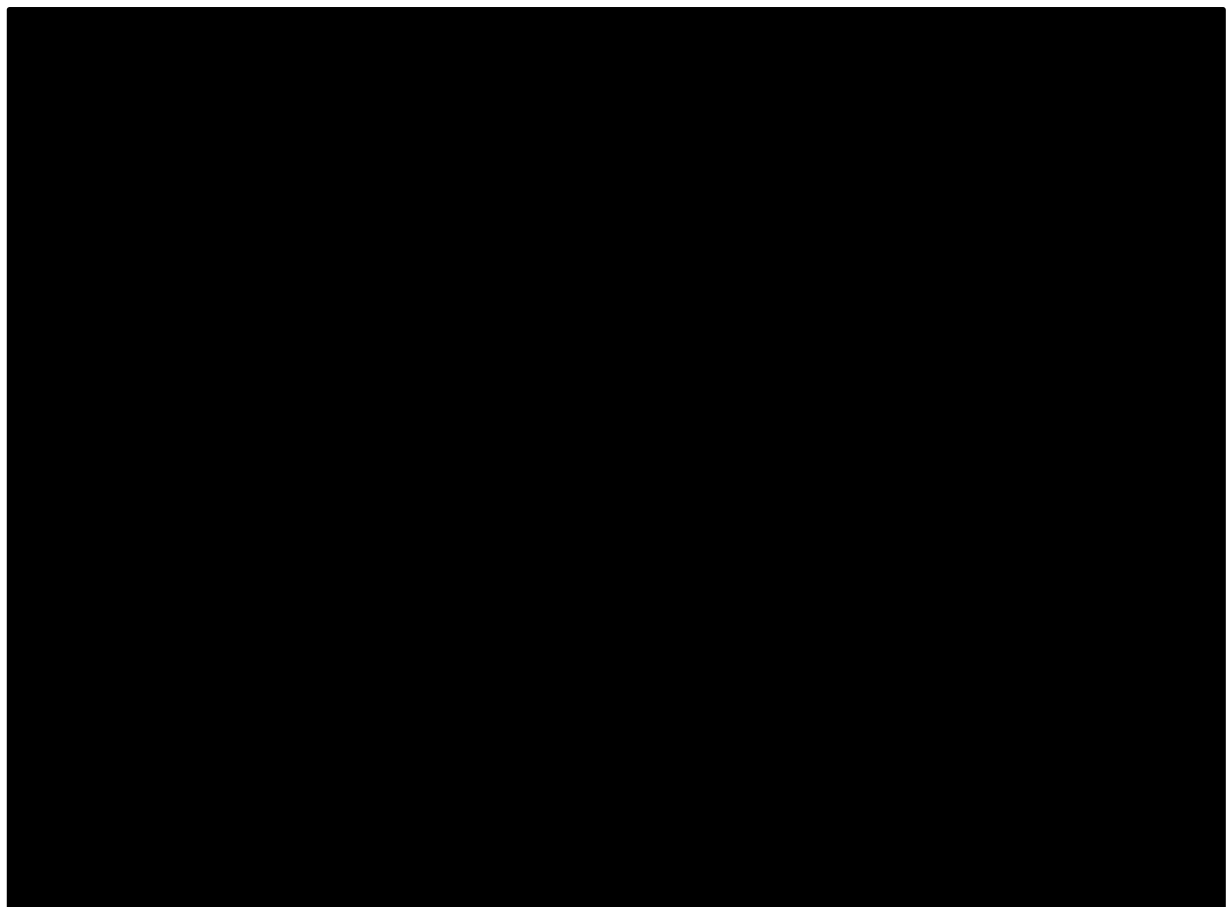
- Eligibility for adjuvant nivolumab includes:

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- underwent cystectomy and was disease-free (eligible for DFS in NIAGARA and CHECKMATE-274)
- high risk MIBC based on staging criteria in CHECKMATE-274
- PD-L1 tumour expression of at least 1%

Figure 3 illustrates the proportion of patients eligible for treatment. In total, 73 patients (13.8%) were considered eligible for adjuvant nivolumab having undergone cystectomy, were disease-free at the adjuvant baseline visit, tested positive for tumour PD-L1 expression >1% and considered at a high risk of recurrence. Patients' ineligible for adjuvant nivolumab include those who failed to undergo cystectomy, high risk patients with residual disease or with PD-L1 <1%, and patients with non-high risk MIBC (Table 3).

Figure 3: Summary of number of patients who are eligible for adjuvant nivolumab in control arm of NIAGARA



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Table 3: Summary of number of patient who were eligible for adjuvant nivolumab in the control arm of NIAGARA

Status	Eligible for nivolumab	n	Proportion
Total cohort		██████	██████
No surgery	No	██████	██████
Patients who underwent surgery and had residual disease-free at adjuvant visit		██████	██████
+Low risk of recurrence	No	██████	██████
+High risk of recurrence	No	██████	██████
Patients who underwent surgery and were disease-free at adjuvant visit		██████	██████
+High risk of recurrence and PD-L1 1% positive	Yes	██████	██████
+ High risk of recurrence and PD-L1 1% negative	No	██████	██████
+Low risk of recurrence	No	██████	██████

Figure 4 presents the ‘adjuvant period MFS’ according to high with PD-L1 and other risk MIBC in the G+C arm of NIAGARA. As expected, patients with high-risk PD-L1 1% positive MIBC had inferior DFS when compared with patients with other risk MIBC.

Figure 4: Kaplan-Meier plot showing MFS according to high with PD-L1 and other risk status in the G+C arm of NIAGARA

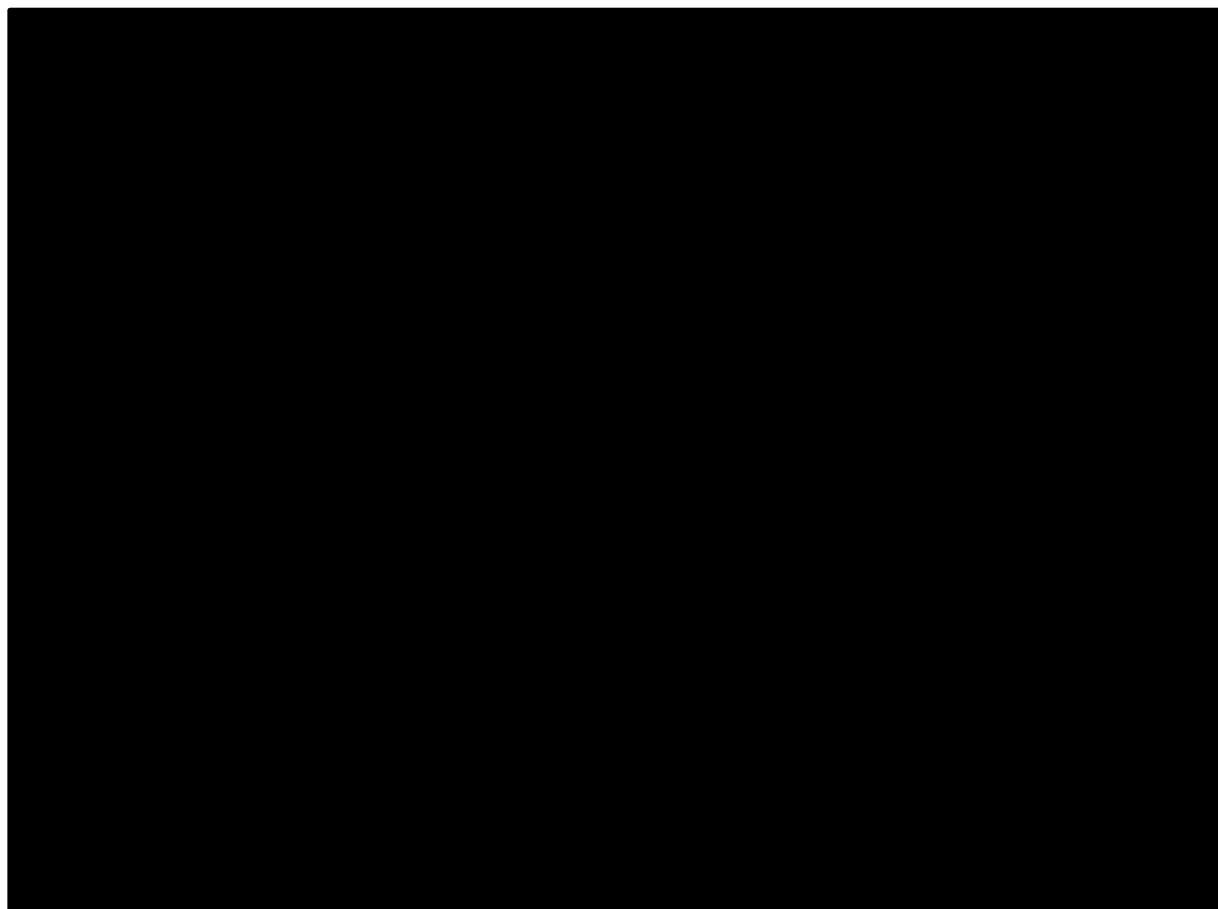
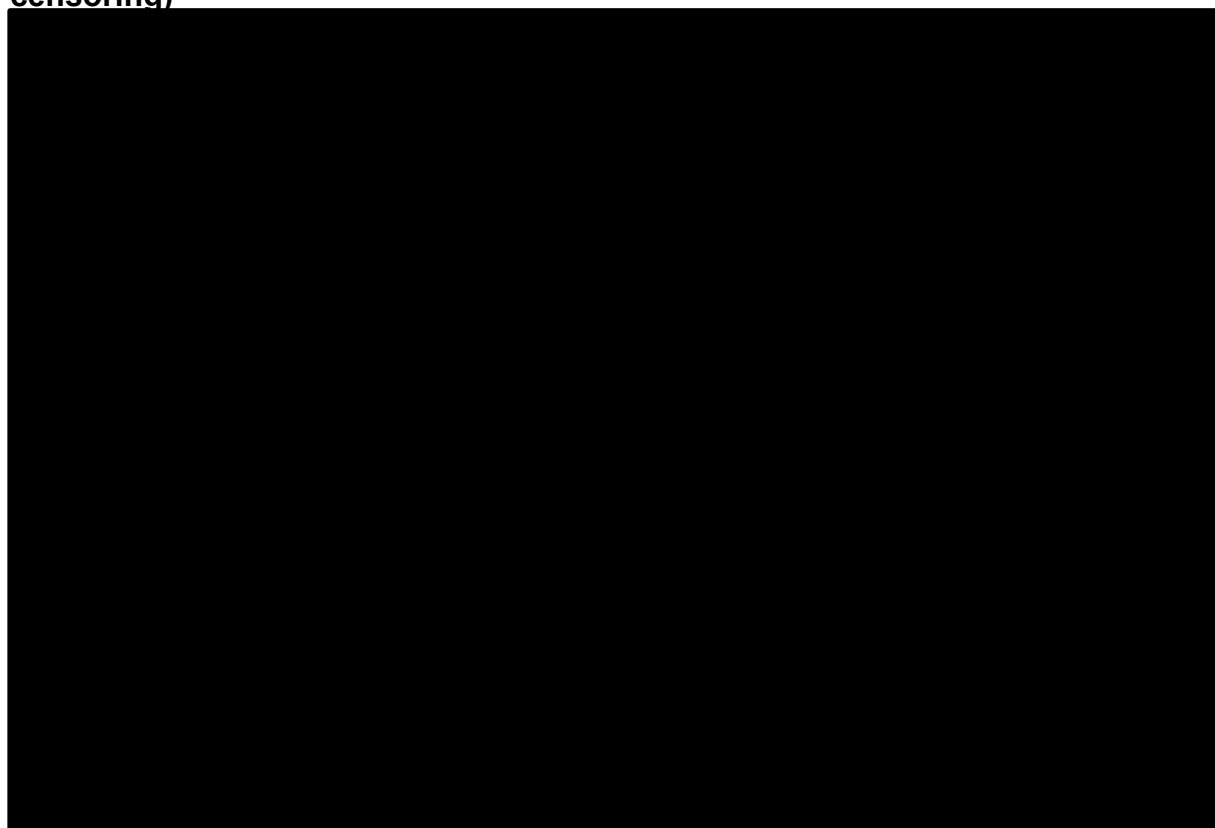


Figure 5 presents the Kaplan-Meier curves for adjuvant-MFS for G+C and G+C+N in the high-risk PD-L1 and other groups using the constant AF from the log-logistic model.

As expected, the application of the AF for nivolumab to adjuvant-MFS in the eligible 'high-risk' PD-L1 cohort of NIAGARA led to improved outcomes, with adjuvant nivolumab increasing the time to distant metastatic disease (left panel). Patients with low risk or non-PD-L1 positive MIBC, and who are ineligible for adjuvant nivolumab, had the same outcomes across arms.

Figure 5: Kaplan-Meier plots for adjuvant-MFS in the high risk and non-high-risk groups in the control and counterfactual arm of NIAGARA (without re-censoring)



The Cox regression analysis comparing adjuvant nivolumab with no treatment in the high-risk PD-L1 subgroup yielded a hazard ratio of 0.40 (95% CI: 0.29 – 0.99), which is lower (and more favourable) than the corresponding DMFS hazard ratio in CHECKMATE-274 (0.52, 95% CI 0.35-0.78). This discrepancy may be due to several factors, including the use of a conservative estimate of the AF from the log-logistic model. The ITC may conservatively overestimate the effect of nivolumab.

Indirect treatment comparison

Figure 6 presents the Kaplan-Meier plots of MFS for the D+G+C, G+C and G+C+N arms of NIAGARA, with and without the application of re-censoring.

Without re-censoring, the survival times of the counterfactual arm extends beyond the follow-up of NIAGARA, due to the effect of nivolumab in extending (by a factor of 3.37) adjuvant-MFS times in the counterfactual arm. The application of re-censoring leads to similar follow-up across arms.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

In both analyses, perioperative durvalumab led to improved MFS versus both control and counterfactual arms, with the curves separating and favoring perioperative durvalumab after the first 6 months of study follow-up.

Figure 6: Kaplan-Meier plot of MFS comparing D+G+C with G+C and G+C+N, with and without re-censoring

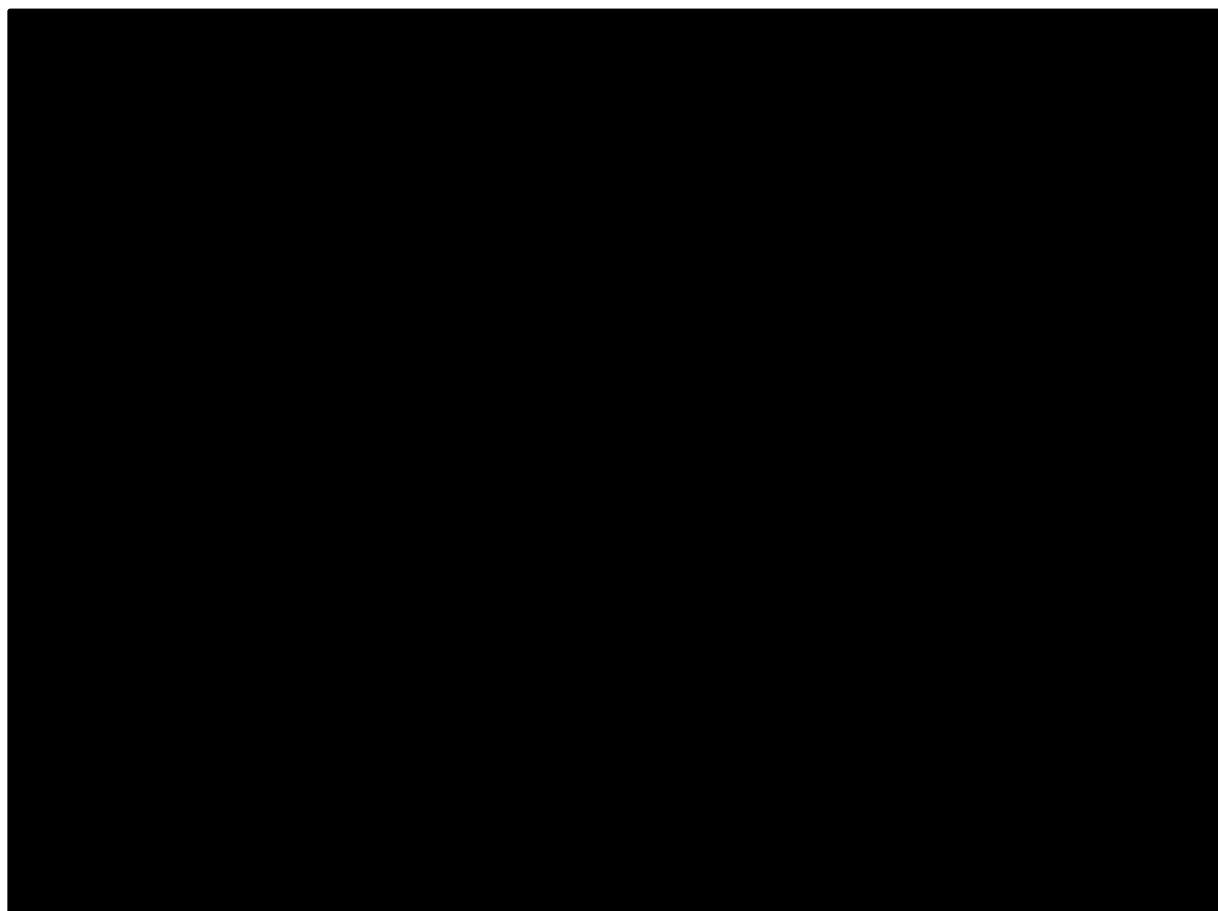


Table 4 presents the hazard ratios for MFS compared to the control and counterfactual arms.

Table 4: Hazard ratios and 95% Confidence intervals for MFS comparing versus G+C and G+C+N

	HR vs G+C ('Control arm')			HR vs G+C+N ('Counterfactual arm')		
	HR ¹	Lower 95% CI ¹	Upper 95% CI ¹	HR ¹	Lower 95% CI ¹	Upper 95% CI ¹
Without re-censoring						
G+C	0.78	0.68	0.89	0.85	0.75	0.96
D+G+C	0.82	0.72	0.93	0.85	0.75	0.96
G+C+N	0.85	0.75	0.96	0.85	0.75	0.96
With re-censoring						
G+C	0.78	0.68	0.89	0.85	0.75	0.96
D+G+C	0.82	0.72	0.93	0.85	0.75	0.96
G+C+N	0.85	0.75	0.96	0.85	0.75	0.96
With re-censoring, piecewise (for use in economic models)						
G+C+N, 0-6 months	0.85	0.75	0.96	0.85	0.75	0.96
G+C+N, 6 months plus	0.85	0.75	0.96	0.85	0.75	0.96
¹ HR = Hazard Ratio, CI = Confidence Interval estimated by bootstrapping						

The results show that perioperative durvalumab is associated with a significant (upper 95% confidence interval of less than one) improvement in MFS versus the control and counterfactual arms. The use of adjuvant nivolumab in the G+C+N arm led to a small numerical improvement in MFS versus G+C. The application of re-censoring had a minimal impact on the hazard ratio for MFS.

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

1. Galsky, M.D., et al., *Adjuvant Nivolumab in High-Risk Muscle-Invasive Urothelial Carcinoma: Expanded Efficacy From CheckMate 274*. J Clin Oncol, 2025. 43(1): p. 15-21.

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	ACTION BLADDER CANCER UK
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Bladder Cancer UK is a national registered charity dedicated to providing information and support to those with bladder cancer and their families and carers; raising awareness; improving outcomes; providing health professional learning and funding research. ABC UK is governed by a trustee board (10 members) and has a full time Chief Executive and paid core staff team, specialist and project staff and many patient volunteers, and a network of patient support groups. ABC UK is funded by public donations, legacies, grants and fundraising, together with a smaller amount of corporate arms length grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	No funding received from this company in the past 12 months.

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE
5. How did you gather information about the experiences of patients and carers to include in your submission?	A core remit of ABC UK is to provide support and information for those with bladder cancer and their carers. We work closely with many patients (or family members) every year by providing direct support by phone helpline and email – many of these contacts with patients will concern treatment choices (or lack of), the effects of treatment and the impact of bladder cancer on daily life and coping with this disease along what can be a long, and sometimes complicated, treatment pathway. We set up and sustain patient support groups across the UK. We run a programme of patient support events. We also collect information about patient experience through our extensive education programme for specialist urology/cancer nurses. We conduct patient surveys to gather information on the direct impact of bladder cancer, impacts of treatments and on-going surveillance and monitoring and potential recurrence of bladder cancer. We provide patient views and input to many clinical trials and research projects. We also encourage many research projects to include PROMS aspect to their research, sometimes funding this work or providing patient participants for this research. As part of our core Governance, patients make up 50% of our Trustee board (together with clinicians forming the other 50%). We have many patient volunteers who help us to deliver our work and programmes, including a regular patient focus group who provide direct input and act as a forum for discussion. We work closely with patients on the production, and regular updating, of all of our ABC UK information materials and web content. Patients also input into all submissions to both NICE and SMC regarding use of medicines for the treatment of bladder cancer, and have reviewed and inputted into this submission.

Living with the condition 6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	MIBC is a disease with few treatment options and potentially poor patient outcomes. Even with the treatments currently available (including radical cystectomy) the risk of recurrence can be as high as c50% of patients. A common psychological impact is patients struggling to come to terms with the very poor outcomes presented on their diagnosis. It is also very distressing to realise that treatment options are extremely scarce. Many of the calls we get from these patients (or a family member) ask whether there are any other treatment options available for them. In addition to coming to terms with the very poor outlook they must also endure the adverse side effects of currently available treatments, leaving patients both emotionally and physically exhausted. This can have a toll on more general health, including mental health. The current treatment pathway can often involve delays – chemotherapy can sometimes result in delays to planned major surgery (cystectomy), due to adverse response to the treatment. Delays in surgery can have an impact on outcomes. Any post surgery treatment is often reactive – waiting to see the response to surgery. This can be debilitating for the patient, causing a general deterioration in health, and a source of great stress for carers. Current treatment options do not allow a planned treatment pathway for the patient from the outset at diagnosis – causing uncertainty, stress and a ‘stop-start’ approach to treatment which exacerbates the negative impact of the diagnosis on both the patient and families and undermines mental well-being. Patient and family members often contact ABC UK support services at this point, to seek support in understanding the delays, to talk about their anxiety at these delays, and to raise the question of what other options there might be. Family members and carers struggle between providing optimistic support and hoping that the ordeal they are forced to witness gets no worse, or lasts too long, giving rise in many cases to feelings of guilt at their own mixed emotions. They can also feel anger or helpless at the lack of availability of alternative treatments and the poor quality of life the patient is having to endure.

	There can be a considerable carer burden due to quality of life for the patient together with common negative side effects from existing treatments, frequency of hospital visits arising from this, resulting delays in planned surgery or uncertainty of any future treatment options and anxieties about recurrence. Our patient groups, our patient survey responses and patient support helpline enquiries all reflect these views and similar experiences for patients with this condition. ABC UK are often asked by these patients (or a carer/family member) what else can be done – if there are other treatment options, or treatments which may have less adverse treatment effects than already undergone. Of significant concern to these patients is the lack of any progress in new treatment options for MIBC over very many years, especially compared with most other forms of cancer. 69yr old male MIBC patient, now with advanced bladder cancer: <i>'I had some chemotherapy, then there was a wait and some tests. The urologist had talked at the beginning about taking my bladder away, so then they eventually did that. But then they found that it has spread further and is in my lymph system and I've got to have checks on liver and other things now before they decide what to do. I suppose it's not looking good, we don't know how long.'</i>

Current treatment of the condition in the NHS 7. What do patients or carers think of current treatments and care available on the NHS?	Standard treatment for cisplatin eligible patients with muscle-invasive bladder cancer involves neoadjuvant cisplatin based chemotherapy followed by radical cystectomy with pelvic-lymph-node dissection. Neoadjuvant chemotherapy with bladder removal has been the main treatment for patients with muscle-invasive bladder cancer for some decades. Cisplatin-based neoadjuvant chemotherapy has demonstrated some benefit in overall survival. However, many patients are not eligible for this treatment approach. Neoadjuvant chemotherapy is not always offered – studies indicate that only c40% of patients did receive neoadjuvant chemotherapy either before surgery or radiotherapy. An additional point to note (particularly in the context of an appraisal for a potential new treatment for this patient group and any review of comparative treatments) is that a significant number of patients with MIBC will not receive definitive treatment. Studies show that c48% of MIBC patients will go untreated. This may be due to tolerability of existing treatments, suitability for current treatments due to age, overall health and comorbidities etc. Therefore, treatment options for these patients are, in real terms, very limited. The risk of disease recurrence for patients with MIBC is still high. Half of patients will still experience a disease recurrence. With regard to the existing treatment pathway, even those patients who do undergo radical cystectomy and cisplatin-based chemotherapy remain at high risk of recurrence and progression to advanced disease. Approximately 50% of patients will face recurrence within 2 years. Variation in treatment: approach can vary in treatment for those MIBC patients who do receive any treatment. Some may undergo a cystectomy (bladder removal), while others receive radiotherapy or chemotherapy plus radiotherapy. There is also considerable variation in treatment practices across UK regions. Planning a treatment pathway: It is currently hard for clinicians to plan a longer-term treatment pathway for MIBC patients from the point of diagnosis. Side effects of chemotherapy can often mean that proposed surgery (Cystectomy) is delayed, this delay can mean a decline in the general health of the patient which can then have a further delaying effect on planned

surgery. Any treatment post surgery may be reactive – that is, waiting to see effects of chemotherapy and then surgery – rather than planned. This can mean a patient pathway which can seem disjointed to the patient, with delays at various points, and repeated hospital visits for further testing – leading not only to great concern and anxiety for patients and families, but a negative impact on potential recurrence and outcomes.

Disease progression means a deterioration in patient quality of life and an increasing impact on carers. These patients will also need to access health services at an increasing rate.

Male MIBC patient, 70yr old, now with advanced disease following recurrence: *There were a lot of delays, lots of waiting to hear. I was told I needed a bladder removal and would have chemotherapy first, they gave me a date for the operation. So my wife and myself thought we had an idea of what was coming. I had a bit of trouble with the chemotherapy. Then my surgery date was changed, that was because I wasn't well. That worried us, we thought it was meant to happen soon. After the surgery we had to wait until I'd recovered from the operation, and then had to have more check ups before they decided what to do next.'*

Daughter speaking of 63yr old father with MIBC who has since died: *'My father had muscle invasive bladder cancer. He had some chemotherapy first, but they stopped it because it made him pretty ill, he was sick or felt sick. Then they started it again, they gave him something else for the sickness, so that was a bit better. Then he had to stop that because he had an infection, a couple of infections I think, and they had to check his kidneys. They had talked about an operation to remove his bladder, but this had to be put on hold because of the effects he'd had from the chemo and infections, and he was weaker by then. They gave him some radiotherapy later. This all took a while. He said he felt worse after the treatment than he had done before. He kept saying I don't know what they're going to do next.'*

8. Is there an unmet need for patients with this condition?	There is significant, and urgent, unmet need for new treatments for those patients with MIBC. Treatment options for muscle invasive bladder cancer are limited and patient outcomes are poor. Bladder cancer patients with MIBC will have high-grade tumours, these are difficult to treat and more likely to spread through the bladder wall and outside the bladder. Immediate treatment is required, with as little delay as possible, and should be aggressive. 50% of MIBC patients will progress to develop advanced disease. Cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy is the current standard of care for MIBC, however, less than half of patients are candidates for this treatment. Existing treatments can show high levels of lack of tolerability and adversely affect quality of life. Patients often experience recurrence or spread of the disease. There's an urgent unmet need for treatments that demonstrate effectiveness in reducing recurrence and the current poor survival rate. An effective treatment for MIBC, and a treatment which reduces the current high risk of recurrence, is vital as it represents the last chance for curing the patient before the disease progresses to advanced, metastatic bladder cancer. A point to note (particularly in the context of an appraisal for a potential new treatment for this patient group and any review of comparative treatments) is that a significant number of patients with MIBC will not receive definitive treatment. Studies show that c50% of these patients will go untreated. This may be due to tolerability of existing treatments, suitability for current treatments due to age, overall health and comorbidities etc. Planning treatment – the patient benefit In the current treatment pathway for MIBC patients, there is limited scope to draw up a longer-term treatment plan to be at the point of diagnosis, which will encompass treatment before surgery, necessary major surgery, and treatment post surgery. Treatment at the post surgery stage can be reactive. Therefore, an improvement in the management of MIBC is needed to improve outcomes and reduce recurrence in these patients. There is an urgent need for alternative, effective, treatments for these patients.

Advantages of the technology. What do patients or carers think are the advantages of the technology?	Patients with MIBC desperately need treatment options and the hope of better outcomes. Durvalumab with chemotherapy before surgery and as a monotherapy after surgery significantly reduced the chance of recurrence and extended survival. The evidence from the clinical trial suggest a long term survival benefit for eligible MIBC patients compared to standard treatment, together with an improvement in recurrence levels. This is an important step forward in treating these patients. Durvalumab is felt to be a significant advance in the treatment of MIBC, and has the potential to help to transform the standard of care for these patients. Neoadjuvant chemotherapy followed by radical cystectomy is the current standard treatment for cisplatin-eligible patients with MIBC. Recent clinical and preclinical research in metastatic urothelial carcinoma supports the benefit of combining cisplatin-based chemo therapy with immune-checkpoint inhibitors. Trial evidence has shown that adding perioperative immunotherapy to the treatment pathway for MIBC patients can improve outcomes. The trial evidence also demonstrates a substantial reduction in recurrence levels – MIBC currently has a very high level of recurrence, a significant factor in the risk of developing advanced disease and in the burden for both patients and families. Trial evidence shows compelling improvements in both event-free survival and overall survival compared to neoadjuvant chemotherapy with radical cystectomy alone. Over 80% of the patients treated with Durvalumab regimen were alive after two years. This is an exciting development in significantly extending overall survival in muscle-invasive bladder cancer. It also enables treatment plans for these patients to be developed at the earliest stage possible to maximise benefit and outcomes for patients. Trial results for Durvalumab demonstrate improved survival, and progression free survival and significantly reduced the risk of recurrence: • The estimated event-free survival at 24 months was 67.8% in the durvalumab group and 59.8% in the comparison group. • The estimated overall survival at 24 months was 82.2% in the durvalumab group and 75.2% in the comparison group.

- Showed a 32% reduction in recurrence.
- The event-free survival benefit was broadly consistent across subgroups.

Benefits of this treatment

Durvalumab may be used both before and after surgery to remove the bladder - neoadjuvantly with gemcitabine and cisplatin, and then as an adjuvant monotherapy.

Benefits of earlier treatment decision:

The treatment decision for Durvalumab can be made upon diagnosis, pre-surgery. It is a major advantage for a patient, and improves the current uncertainty, to have a treatment plan made at an earlier stage, and before any major treatment or surgery starts. Patients can better understand their treatment journey, and they (and their family) have an opportunity to plan their daily lives. Currently, the patient has to endure waiting and assessing before a decision as to whether another treatment option is used or even possible. This compares with the decision for Nivolumab treatment, which would usually be made post surgery.

The ability to take a treatment decision to use Durvalumab at an earlier stage, has another major benefit in terms of not delaying other treatment. If given neoadjuvant chemotherapy, the patient may suffer adverse side effects from the chemotherapy which may result in the surgery being delayed. This consequent delay in surgery can then adversely affect the patient's overall health, and influence any subsequent decision regarding treatment options post surgery. Delayed surgery may result in poorer outcomes.

There is an acute need for effective new treatments for MIBC. The unmet need for this patient group, lack of treatments, the high percentage of patients who do not received definitive treatment, high level of recurrence and poor outcomes, and the high cost of current unsuccessful treatment are all key factors in the consideration of Durvalumab in the treatment pathway for MIBC. The evidence for the use of Durvalumab in improving levels of recurrence and patient outcomes is compelling.

Need for a new, effective, MIBC treatment

It is of note that in recent years a number of new drugs have been evaluated for advanced/metastatic bladder cancer. ABC UK and bladder cancer patients now welcome this Appraisal for a treatment for Muscle Invasive

	Bladder Cancer – which is an earlier stage disease, however one with a high rate of recurrence – the last possible stage for treatment to prevent progression to more advanced disease. ABC UK, patients and carers welcome this potential new treatment option for the use of durvalumab for eligible patients with muscle-invasive bladder cancer.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Disadvantage will arise if Durvalumab is not equally available for all eligible patients, or not made accessible within the NHS for all eligible MIBC patients, without any restrictions to access.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	All sub groups of eligible patients may benefit.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of access – eg those in remote rural communities may have to travel for treatment. However, some of these inequalities may be alleviated by the fact the a treatment plan may be drawn up at an early stage with Durvalumab, enabling patients and their families to plan their lives in advance and prepare for planned phases of treatment. Gender equality: women are often diagnosed at a later stage than men, with poorer outcomes.

Other issues 13. Are there any other issues that you would like the committee to consider?	Lack of effective existing treatments for bladder cancer, and supporting progress There is lack of new treatments available in the UK for bladder cancer – a common cancer with poor outcomes and high recurrence rates. It is important that Durvalumab is viewed in that context. There is concern amongst patients, patient groups and clinicians about the slow pace for new therapies to become widely available for use in treating bladder cancer in the UK, particularly in the context of the lack of effective treatment options available. The UK is now out of step with other countries, such as those within the EU, and has fallen behind in terms of effective treatments being made available for those with bladder cancer. The term the ‘gold standard’ of treatment, which is sometimes used within these appraisals as a comparative terms, may no longer be an applicable term when applied to the treatment options for bladder cancer which are currently available for wide clinical use in the UK. Bladder cancer has been badly neglected in terms of research spend and in the development of much-needed new treatments, which is reflected in late diagnosis, high levels of recurrence, and poor outcomes – and has remained one of the most expensive cancers to treat. Now that demonstrably effective new treatments are available for a disease with distressingly poor outcomes, it is of the utmost importance to patients that this welcome progress is not delayed, and that patients (and their clinicians) have access to these treatments to improve their outcomes. Progress is long overdue. Quality of Life and health related benefits It is of great importance to acknowledge, and for the committee to consider in depth, the direct impact on patients and patient well-being within this appraisal’s quality of life assessments. The effect on patients of access to new, innovative and effective treatments would be profound – with significant emotional and psychological benefits as well as the direct clinical benefit of improved survival and level of possible recurrence. This is particularly important for MIBC patients who undergo highly impactful surgery and neoadjuvant chemotherapy treatment with uncertain outcomes regarding the likelihood of achieving a cure or reducing the risk of recurrence.

	Access to such an effective, new treatment would bring hope to a group of patients where treatment options are very limited - bringing hope to patients and families, in very difficult circumstances, of a last opportunity for curative treatment, and also bringing the knowledge that a Durvalumab regimen has shown a reduction in recurrence risk. Improvement in the burden of treatment A new, effective treatment could have a significant impact in reducing the burden of disease for the patient and families: • Improving outcomes and levels of recurrence could result in a reduction in the number of hospital visits, and the negative impact on overall health and well-being due to adverse treatment side effects. • Having access to a new, effective, treatment will help patients and families to deal with the emotional burden of serious disease, maintaining hope, and providing a more positive emotional and mental state that could indirectly support a more positive outcome. • The possibility of disease progression that prevents surgery, and also of disease recurrence after surgery, are significant concerns for patients, which have a serious negative impact on subsequent prognosis and health-related quality of life. • Provides patients and families with the prospect of living longer, in a better state of health, perhaps to see other developments to provide additional treatment options if required. Early treatment planning • As Durvalumab supplies a perioperative treatment option currently not available, which would be considered after diagnosis, a longer term treatment plan is then able to be drawn up. This would give patients and their families the opportunity to plan in advance, and plan their daily lives. • Having such a treatment plan, would alleviate some serious anxieties and uncertainties – patients and families could understand what is coming next (many patients contact ABC UK at this point as the uncertainty is the cause of much distress).

- Currently, the delays which may occur in a treatment pathway – delays due to tolerability issues with cisplatin chemotherapy; delays in surgery due to chemotherapy side effects or related weakening of general health; any decision regarding treatment post surgery being reactive etc.
- This treatment planning at an earlier stage not only gives more clarity and information to the patient about future steps in their treatment, this approach reduces the negative emotional impact of delays and additional tests, and also receiving bad news after cystectomy surgery, which can often happen in the current treatment pathway. Providing the potential for a direct improvement in the quality of care for those patients with MIBC.

Economic Impact of current poor outcomes and recurrence levels

The availability of effective treatment options for this patient group facing poor outcomes is of pressing need, and has an urgency for the NHS. Due to the high recurrence rate, and likelihood of progression, together with continuing monitoring, the lifetime treatment costs per patient of bladder cancer is very high compared to other cancers. Bladder cancer is one of the most expensive cancers to treat. Within the economic analysis section of this appraisal, it is imperative that due consideration and weight is given not just to the cost of this new treatment, but to the high on-going cost of continued and unsuccessful treatment for those with MIBC, and the high potential for progression to advanced disease.

There is also a need for rapid action to consider and assimilate new advances in treatment of bladder cancer into the health system.

Future potential: A point of wider interest which this appraisal should note is that, whilst the Durvalumab trial evidence being considered was concerned with those patients who had a cystectomy, c 50% of UK patients will currently have bladder preserving treatment, usually radiotherapy. Trial results from the RAD-IO trial, show that Durvalumab can also be used in combination with radiotherapy with efficacy. Therefore, there is considerable potential for wider effective use of Durvalumab with those patients who will not receive cystectomy.

Guideline NG2: Note should be taken that Bladder cancer: diagnosis and management (2015) NICE guideline NG2 – is now over 10 years since publication in February 2015 (and reviewed evidence available to 2014). The Guideline does not adequately cover the introduction, evidence of efficacy and availability of new treatments for bladder cancer.

14. Under current clinical practice do people have neo-adjuvant treatment, followed by surgery and then adjuvant treatment? If so, what treatments are used as neo-adjuvant and adjuvant therapies?	The standard surgical treatment for patients with urothelial MIBC and MIBC with subtypes is radical cystectomy. However, cystectomy only provides five-year survival in c50% of patients. To improve survival in patients with cN0M0 disease, cisplatin-based neo-adjuvant chemotherapy has been used since the 1980s. Just over half of MIBC patients receive curative-intent treatment. Of them, only 43% receive neo-adjuvant chemotherapy. Some patients may be offered chemotherapy after surgery, particularly if not used before surgery, or the cancer is found to be more advanced during surgery than was originally thought.
15. If the answer to Q14 is no, what do most people currently have as treatments around (before and/or after) their surgery for muscle-invasive bladder cancer?	Some patients may receive radiotherapy if they are not suitable for surgery, or choose not to have surgery. This is usually combined with chemotherapy.

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• MIBC is a disease with few treatment options and very poor patient outcomes. • There is a significant unmet need for new, effective treatments for MIBC. Progress is urgently needed to provide hope for these patients. • Even with the treatments currently available (including radical cystectomy) the risk of recurrence and progression to advanced disease can be as high as c50% of patients. • Trial results for Durvalumab demonstrate improved survival, and progression free survival and significantly reduces the risk of recurrence. • Durvalumab provides the opportunity to plan a patient treatment pathway for those with MIBC from the point of diagnosis.

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Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

1. Your name	
2. Name of organisation	Fight Bladder Cancer
3. Job title or position	
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a registered Charitable Incorporated Organisation in Scotland (SC051881), England and Wales (1198773), and was initially established as an unincorporated charity in England and Wales (1157763). It also operates in Northern Ireland Fight Bladder Cancer is a patient advocacy group and charity dedicated to supporting people affected by bladder cancer, raising awareness of the disease, and advocating for improved research and treatment options. The charity provides information, support, and resources for patients, carers, and healthcare professionals. It runs a 24/7 private online support forum with approx. 7,000 users, as well as a helpline and online and in-person support groups Fight Bladder Cancer is funded by individual donations, fundraising events, and grants from trusts and Industry. The organisation has a community of thousands, including patients, carers, healthcare professionals, and supporters
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in	Company: Astra Zeneca £5.384 – Improving bladder cancer detection and awareness among GP's and minority communities

Patient organisation submission

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer
[ID6168]

the appraisal stakeholder list.] If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We reached out to the members of our private online forum of many patients and carers to ask their opinions on their diagnosis and treatments before and after a radical cystectomy, as well as by personal conversations and emails. We also spoke to medical oncologists and nurses in order to better understand the experience of patients and carers

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Muscle-invasive bladder cancer is an aggressive disease. Patients can have gone through painful and worrying symptoms before a diagnosis, and then must make difficult treatment decisions on radical treatments Most people will undergo a cystectomy and must then live with a stoma bag or a neobladder (reconstructed bladder) This causes many daily challenges for example with managing incontinence, stoma care, pain. Many people are elderly and go through things on their own which is very difficult to do, particularly the day-to-day things at home. The deep psychological impact of anxiety and fear of a recurrence in other areas of the body with this systemic disease can follow for many years. Some people do well once they are more used to things, but for others stoma issues can cause a lot of stress and discomfort, with urinary leakage, stoma and bag problems, sexual function, body image, and the stigma associated with bladder cancer and a stoma bag. Carers are also heavily affected, they often have to juggle the constant medical appointments with work, family, the ability to have time on their own. Not only is there the constant worry of their loved one getting a recurrence with a disease like bladder cancer, but many neglect their own well-being. After the radical surgery looking after someone can be like a full-time job, particularly when changing a stoma or a neobladder is a new, there are a lot of learning curves and it can put a huge strain on a relationship.

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	They are mostly shocked that to remove the bladder cancer their whole bladder and usually reproductive organs for women and the prostate for men, are also removed. Large amounts of them aren't given any option on their urinary diversions, offered a neobladder, and it is far less likely that they will be offered radiotherapy which can be very upsetting to hear that bladder sparing surgery may have been an option. Chemotherapy before such a big operation can leave them very tired and unwell, and the road to recovery after surgery is long. The treatment burdens are significant They are concerned about the lack of specialist staff, we have been told that this has had a major impact on the quality of their lives, sexual wellbeing and overall outcomes. They also worry about being abandoned post-surgery, with insufficient knowledge about their stoma. Carers report that they are scared about not knowing what to do when their loved one gets home, as often they haven't been designated a stoma nurse for contact "I had my bladder removed, it was the only way to save my life. Do I worry about it coming back? No, well yes, sometimes. It's hard not to, but you've got to get on with things. I know of course that there are never any certainties" "My diagnosis was a shock, I definitely could have done with some sort of mental health support. I had an RC and some chemo. I don't worry about things so much these days, well except for when the CT scan is due!"
8. Is there an unmet need for patients with this condition?	There is a clear unmet need for treatments and support that improve outcomes and quality of life. After a bladder removal patients can experience recurrence or progression. Many can't tolerate chemo, particularly as they may have kidney issues or be elderly. They also lack psychosocial care to help with their rehabilitation and sexual and mental health, they would like advances that would meaningfully reduce the risk of recurrence and make life easier, a holistic approach

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	They are encouraged to think that there is something which could improve both survival and reduce recurrence. They feel that the addition of durvalumab to give the hope of a better outcome would give them hope and relieve some of the anxiety. "It would allow us to grab some of our life back, think ahead for a change". Many are encouraged to hear that durvalumab doesn't dramatically increase harsh side-effects. "Despite my husband's post-op challenges, having immunotherapy post-surgery is something he would have considered. He would have wanted clear and concise information about it before making a decision, but if he felt the benefits outweighed the decision he would have said yes. I would have supported him in whatever decision he made."

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Their main concerns are on the burden of extra treatments, particularly the extra hospital visits before and particularly after surgery. Some were concerned about the distance they had to travel, and wondering if they would feel like it after surgery. "I've had so many procedures already, I will then have my "bag for life" and I'm feeling "hospitalled out" already!" Side effects and the unknown were a worry for some, they felt that less was known about what might happen, and others didn't know if the benefits would be worth it when balanced with any "risk of side-effects on top of everything else". "Had chemo then RC last year, still cancer free. I was offered immunotherapy after but opted for close observation. Since I was cancer free after the operation and it never made it to my lymph nodes, I felt it wasn't worth risking in case of side-effects. If there would be a recurrence I would, of course, take or remove whatever is necessary to get rid of it again."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	This technology would benefit patients with muscle-invasive bladder cancer who are fit enough for cisplatin-based chemotherapy, with people of different ages and sex having a similar benefit. “After chemo I had an RC. My scan at one year showed cancer had metastasised to my lungs. I never imagined this could happen in a year. I have heard of others who have been offered a course of immunotherapy after their RC as a preventative measure, but this was never offered to me” Those who are very elderly, or frail, or have bad kidney function may not be suitable for cisplatin, and therefore wouldn't be suitable for this, and would receive surgery without adjuvant treatments or radiotherapy as an alternative

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Bladder cancer predominantly affects older people, potentially with comorbidities that mean cisplatin based chemotherapy would not be suitable and so they would be excluded Women with bladder cancer often have worse outcomes than men, are diagnosed later, and experience differences in post-treatment issues. Both sexes have issues with sexual dysfunction, but on top of the stigma related to bladder cancer, men are even less likely to discuss their needs and symptoms. There are socio-economic and geographical issues, people in deprived, or rural areas should be able to get the treatment. These are the people who are more likely to be diagnosed later and have less options on their procedures

Other issues

13. Are there any other issues that you would like the committee to consider?	With the hope of new treatments improving survival rates, it is important that other supportive services are improved. Currently patients report lack of help after their surgery, they need more help with their rehabilitation, stoma care and continence issues. Few have counselling of any kind and most have no sexual counselling before or after surgery. It is important to also consider the carers, as any treatment decision will of course affect them too. Understanding the treatment plan reduces anxiety, and educational resources with clear information about durvalumab's benefits and risks should be provided in patient-friendly language at the beginning of discussions with patients and carers on this potential regimen Patients should be told if they are also suitable for bladder sparing treatments
14. Under current clinical practice do people have neo-adjuvant treatment, followed by surgery and then adjuvant treatment? If so, what treatments are used as neo-adjuvant and adjuvant therapies?	Around half of the patients have neo-adjuvant chemotherapy currently. Only those with high risk features such as T3 or T4, or with a N1 after cystectomy would get adjuvant chemotherapy. If they are PD-L1-positive they could have adjuvant immunotherapy. Patients who are not suitable for cisplatin would go directly to a radical cystectomy or radiotherapy might be considered
15. If the answer to Q14 is no, what do most people currently have as treatments around (before and/or after) their surgery for muscle-invasive bladder cancer?	

Key messages

16. In up to 5 bullet points, please summarise the key messages of your submission.	• MIBC has high relapse rates, the addition of durvalumab to chemo could mean a real improvement in survival and cure rates. and a relief from constant worry of a recurrence after surgery which may or may not be treatable • With no significant increase in severe toxicity compared to chemo alone, patients hope that this could lengthen their survival without imposing extra harsh side-effects • Patients feel that there is insufficient attention to quality of life after a radical cystectomy, and with advances in treatments and the potential for a longer life, issues like mental and sexual health are often neglected • Patients and carers would like to know of their options, to understand the choices and have chance to discuss bladder sparing treatments if they are suitable • All eligible patients, regardless of their location, should have access to the drug and the necessary supportive care

Thank you for your time.

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Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you

1. Your name	
2. Name of organisation	British Uro-Oncology Group
3. Job title or position	
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	British Uro-Oncology Group is the main professional organisation for oncologist treating urological (including bladder cancer). Its focus is supporting and providing education/professional development of its members. It aims to support best practice for urological cancer patients. Its is funded by membership subscriptions and via sponsorship by commercial sponsors to its annual meeting and other activities
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	British Uro-Oncology group have received meeting sponsorship from the following organisations 2025: Accord-UK, MSD UK, Johnson & Johnson, Aspire, Eisai, Ipsen, Astellas, Novartis. Bayer Plc, Merck, Astra Zeneca, Pfizer Ltd 2024: AstraZeneca, Merck, Novartis, Accord-UK, Astellas, Bayer Plc, Eisai, Genesis Care, Ipsen, Johnson & Johnson, MSD UK, Pfizer Ltd Sponsorship is provided for annual general meeting and other activities and ranged from £5000-£25000 depending on level of sponsorship

**5c. Do you have any
direct or indirect links
with, or funding from,
the tobacco industry?**

NO

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To reduce and prevent recurrence, and improve overall survival
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A significant in overall survival of >5% at 5 years and reduction of recurrence/improvement of disease free survival by 15-25%
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes Despite the use of neoadjuvant chemotherapy 5 year survival of patients with muscle invasive bladder cancer remains on average at 50-60%. This has not changed substantially for over 20 years and there is need for better treatments to reduce post radical therapy relapse and improve survival. Reducing relapse would be expected to improve patient experience and HRQOI and reduce psychological stress. Improving responses also holds hope to change local treatment paradigms and reduce reliance on radical surgery (cystectomy) and promote bladder preserving approaches.

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	Patients fit enough and with good renal function receive cisplatin and gemcitabine chemotherapy x 3-4 cycles followed by radical cystectomy and chemo-radiotherapy. Patients unable to receive initial cisplatin/gemcitabine receive local radical treatment and then considered for adjuvant chemotherapy or nivolumab. Patients with poor clinical response to neoadjuvant therapy who are PDL1 positive may receive adjuvant nivolumab
9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	NG2 NICE guideline (2015) NICE Single technology assessment of adjuvant nivolumab. ESMO and EAU guidelines are also influential.
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is widely recommended and accepted but there is wide variation in the use of neoadjuvant and adjuvant therapies with a few sites using little neoadjuvant therapy with wider use of adjuvant therapies. The use of neoadjuvant therapy may vary according to patient fitness and renal function that may affect usage.
9c. What impact would the technology have on the current pathway of care?	The technology would replace neoadjuvant cisplatin/gemcitabine plus selective adjuvant nivolumab. It would mean that most fit patients would receive immunotherapy for up to 1 year.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes with addition of weekly Durvalumab
10a. How does healthcare resource use differ	After cystectomy/local treatment patients will receive 4 weekly Durvalumab so will require additional IV slots. This is the same as if receiving adjuvant nivolumab which may have been used for a proportion of patients.

Professional organisation submission

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[ID6168]

between the technology and current care?	Addition screening tests for immunological toxicity will need performing as per local practice eg Thyroid function tests, possibly nt-BNP, Amylase. Potential increase use of supportive services to manage immunological toxicity eg dermatology, endocrinology, gastroenterology but as many patients would receive PD1/PDL1 treatment in other contexts this may be limited increase
10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary/Tertiary care
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Adequate resources for outpatient patient assessment, iv delivery and toxicity management
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes Niagara trial showed >30% reduction in recurrence and 10% increase in pathological CR rate
11a. Do you expect the technology to increase length of life more than current care?	Niagara trial a 25% reduction in risk of death at 2 years with 7% absolute gain in survival.
11b. Do you expect the technology to increase health-related quality of life more than current care?	Yes but this isn't yet reported. Fewer recurrences and improved survival should lead to better HRQoL but is balanced against increased immunological toxicity – though toxicity rates are reported to be overall similar to control group.

12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	The technology would be limited to those suitable for cisplatin chemotherapy only. It may be contra-indicated in those with autoimmune disease. It is noteworthy that benefit was seen independent to PDL1 status unlike in the adjuvant setting with Nivolumab making benefit available to broader population

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Clinicians who would use the technology are familiar with both the baseline chemotherapy and the use of PDL1 inhibitors. They are not used together in other situations so may be some learning about combining the two treatments but in my experience to date this has been straightforward so would expect this not to be a significant issue. Tests for patient assessment are used in other settings Patients would need to accept longer treatment period (up to 1 year) which may be an issue for people who need to travel for treatment.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I assume that people who progress on treatment would stop therapy but this would be assessed by routine follow up imaging/assessments. Patients may stop Durvalumab for toxicity reasons as per recognised PDL1 guidelines/SoC

15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	It is questionable whether the benefits of avoiding relapse/improved would be fully captured in the HRQoL study as data on relapsed patients may not be fully captured with patients censored at relapse. Depends if modelling adequately collects the impact of relapse in QALY model
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	YES It will provide potential benefit of immunotherapy to patients in more certain way and at earlier stage of disease process. Many high risk patients don't receive adjuvant immunotherapy due to absence of PDL:1 or negative assessment. There are also a significant proportion of patients that don't receive adjuvant immunotherapy because they develop early relapse or suffer prolonged side effects of cystectomy so are too unwell or refuse treatment. Patients electing chemo-radiotherapy are ineligible for adjuvant immunotherapy at present.
16a. Is the technology a 'step-change' in the management of the condition?	YES to some extent.

	I have add to 'some extent' as Immunotherapy has been shown beneficial in a number of settings in bladder cancer previously <u>but</u> this is first demonstrating clear survival benefit in the Neo-adjuvant setting and in combination with chemotherapy
16b. Does the use of the technology address any particular unmet need of the patient population?	Yes – improved outcomes in patients with poor outcomes
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There are immunological toxicities that can affect patients but most are time limited and resolve fully with treatment. Though a proportion of patients may have persistent toxicities predominatly endocrine effects most commonly thyroid dysfunction. These are usually straight-forwardly managed by simple treatments.

Sources of evidence

18. Do the clinical trials on the technology reflect current UK clinical practice?	In the main but a significant number of patients are managed using bladder preserving strategies in the UK -mainly chemo-radiotherapy. These patients were excluded from the Niagara trial.
18a. If not, how could the results be extrapolated to the UK setting?	A UK trial -RaDio has investigated this technology in this population and shown that can be administered with radiotherapy. https://ascopubs.org/doi/10.1200/JCO.2025.43.5_suppl.778

	A European (Greek) trial has shown similar if not greater benefit using similar technology in patients receiving chemo RT. Summarised at https://www.urotoday.com/conference-highlights/esmo-2024/esmo-2024-bladder-cancer/154932-esmo-2024-nivolumab-plus-chemoradiotherapy-in-patients-with-non-metastatic-muscle-invasive-bladder-cancer-nmmibc-not-undergoing-cystectomy-a-phase-ii-randomized-study-by-the-hellenic-gu-cancer-group.html So believe should be allowable in all patients who eligible for neoadjuvant therapy even if they subsequently elect not to have cystectomy but decide for chemo radiotherapy as per NG2 guidance.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Event free and overall survival Measured though overall survival was secondary end point
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	n/a path CR was a primary endpoint that can reflect other survival endpoints but may not be adequate surrogate
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No – though people have questioned if adjuvant phase is required in those with path CR. Unknown from trial data.

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	The data on chemoradiotherapy listed above. Other trials in this area are ongoing with trials of EV/Pembro of interest
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA817?	No
21. How do data on real-world experience compare with the trial data?	Likely similar though tendency for trial patients to be fitter, higher socioeconomic class than some 'real world patients'. Real world patients may be more likely to stop treatment in face of toxicity issues.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I am aware of.
22b. Consider whether these issues are different from issues with current care and why.	n/a

Topic-specific questions

23. Further to question 9, under current clinical practice do people have neo-adjuvant treatment, followed by surgery and then adjuvant treatment? If so, what treatments are used as neo-adjuvant and adjuvant therapies?	As commented SoC in most UK centres is Neoadjuvant treatment followed by surgery or chemoradiotherapy. If patients are unable to have neoadjuvant therapy eg due to severe symptoms, renal impairment or physician or patient choice then many people would offer adjuvant therapy; Either Nivolumab if fit criteria of TA817 (pT3 or worse, PDL 1 positive) or adjuvant chemotherapy if PDL1 negative, selected pT2 patients or by choice If patients have had neoadjuvant chemotherapy and have residual muscle invasive (pT2+) and are PDL1 positive are offered adjuvant nivolumab
24. How would having an immunotherapy as part of neo-adjuvant and/or adjuvant treatment affect the treatment options should the cancer progress to advanced or metastatic disease?	If immunotherapy is used neoadjuvantly/adjuvantly then this would not be available as second line option if they relapse under current guidance/approvals. (I would suggest NICE consider review the current guidelines for 2nd line atezolizumab to see if could be used if relapse does occur some time after neo/adjuvant treatment).

Key messages

25. In up to 5 bullet points, please summarise the key messages of your submission.	• Patients with locally muscle invasive bladder cancer continue to have poor (50-60%) long term survival with little change over recent decades. • Neoadjuvant and adjuvant Durvalumab in combination with cisplatin and gemcitabine improves overall survival in people with Muscle invasive bladder cancer. • Using neoadjuvant durvalumab improves access for people with MIBC and will allow more secure and equitable access to immunotherapy which will allow a broader range of people to benefit from this technology. • The treatment is reported to be well tolerated by people with limited increase in toxicity. • Oncologists are familiar with technology and can be applied with limited training.

Thank you for your time.

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Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Clinical expert statement

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

1 of

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Clinical expert statement

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2 of

Part 1: Treating muscle-invasive bladder cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Syed A Hussain
2. Name of organisation	University of Sheffield (Nominated by Astra Zeneca)
3. Job title or position	Professor of Medical Oncology and Honorary consultant
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with muscle-invasive bladder cancer ? ☒ A specialist in the clinical evidence base for muscle-invasive bladder cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

3 of

8. What is the main aim of treatment for muscle-invasive bladder cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	Treatment for organ-confined muscle-invasive bladder cancer (MIBC) consists of cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy or, in selected cases, organ-preserving approaches. However, patients who undergo cystectomy and are found to have residual muscle-invasive disease remain at high risk of early relapse, disease progression, and cancer-related mortality. At this stage, the primary objective is to achieve better disease control and increase the proportion of patients who are cured, thereby improving overall survival. Perioperative chemotherapy plays a pivotal role in eradicating micrometastatic disease, contributing to improved disease-free and overall survival. Enhancing the efficacy of neoadjuvant chemotherapy regimens offers the greatest opportunity to increase durable disease control and cure rates in patients with organ-confined disease.
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	Improvement in pathological complete responses is linked to better outcomes and survival. Improvement in disease control by 6 months or more is likely to significantly improve patient outcome in this setting of high-risk muscle invasive bladder cancer. Risk of disease relapse is highest in the first 24 months. Improvement of this magnitude is likely to impact on survival.
10. In your view, is there an unmet need for patients and healthcare professionals in muscle-invasive bladder cancer ?	NICE has worked closely with genitourinary (GU) oncology to enable access to several transformative treatments for advanced and metastatic urothelial cancer — including atezolizumab (second-line), avelumab first line (maintenance), erdafitinib (biomarker-selected second-line metastatic disease), and more recently, enfortumab vedotin plus pembrolizumab in the first-line metastatic setting. Approval for adjuvant nivolumab in PD-L1–positive patients was also secured in 2022. We are already seeing tangible benefits from these decisions:

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

4 of

	patients are living longer, and a growing proportion are achieving durable remissions and potential cure. Despite this progress, an unmet clinical need remains. Outcomes for patients who relapse or progress after initial therapy are still limited, with median survival currently ranging from 18 to 24 months — though this has steadily improved, largely due to successive positive NICE technology appraisals. To further enhance long-term outcomes, improving disease-free survival through effective neoadjuvant strategies offers the most promising avenue. By increasing cure rates in the curative-intent setting, we can, not only, improve patient survival but also reduce future reliance on systemic therapies in the palliative phase.
11. How is muscle-invasive bladder cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	• NICE guidelines are routinely followed for the management of patients with muscle-invasive bladder cancer (MIBC). • In the UK, the majority of eligible patients receive cisplatin-based neoadjuvant chemotherapy. Patients with high-risk disease following cystectomy are offered adjuvant nivolumab if PD-L1 positive, in line with NICE recommendations. • The treatment pathway is well established and consistently implemented across centres. • The introduction of durvalumab in combination with standard-of-care chemotherapy in the neoadjuvant setting, and as adjuvant therapy following neoadjuvant chemotherapy, represents a significant advancement. This approach

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

5 of

	is expected to enhance disease control and substantially delay disease progression. • Results from the NIAGARA trial demonstrate the transformative benefit of durvalumab in the perioperative setting, with statistically and clinically significant improvements in event-free survival, pathological complete response, metastasis-free survival, and overall survival. These findings establish durvalumab as an important addition to the standard treatment paradigm for MIBC.
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	The proposed technology introduces the immune checkpoint inhibitor durvalumab earlier in the treatment pathway by integrating its use into the Neo-adjuvant setting. This treatment should be delivered within secondary care in specialist hospital centres with established oncology services. As immune checkpoint inhibitors are already in routine clinical use for advanced urothelial cancer and in the adjuvant setting for PD-L1–positive patients—as well as for several other tumour types—no additional infrastructure, investment, or major service adaptation is required to implement this technology
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	• Results from the phase 3 NIAGARA trial show that the addition of perioperative durvalumab to neoadjuvant chemotherapy significantly improves outcomes for patients with muscle-invasive bladder cancer (MIBC). • The NIAGARA trial demonstrated a significantly improved event-free survival (EFS) and overall survival (OS) with the addition of perioperative durvalumab to neoadjuvant gemcitabine and cisplatin.

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

- Pathological complete responses (pCRs) were more likely among patients who received durvalumab (37.3% compared with 27.5%), but benefit with durvalumab was seen both in patients who did and did not achieve a pCR.
- The addition of perioperative durvalumab to neoadjuvant chemotherapy significantly improves outcomes including event-free, metastasis-free, and overall survival (OS) in patients with MIBC. (Powles, Catto, Galsky et al NEJM, 2024)

In summary, The **NIAGARA trial** represents a pivotal advance in the management of muscle-invasive bladder cancer (MIBC), establishing the role of perioperative immunotherapy in improving long-term outcomes. In this large, international phase III study, the addition of **durvalumab** to standard cisplatin-based neoadjuvant chemotherapy followed by adjuvant durvalumab led to **transformative clinical benefits**. The trial demonstrated a **significant improvement in event-free survival** (HR 0.68), along with marked increased **overall survival** (HR 0.75). End -points of **pathological complete response rates, metastasis-free survival significantly improved as well favouring the experimental arm**.

These results provide compelling evidence that early integration of immune checkpoint inhibition into the curative treatment pathway enhances both systemic disease control and local tumour eradication. The NIAGARA data redefine the standard of care for organ-confined MIBC, offering the potential to **increase cure rates, delay or prevent relapse, and extend overall survival** for a broader population of patients. The findings are both **clinically and statistically significant**, underscoring the value of durvalumab as a key component of perioperative therapy in this disease.

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Benefit was seen across the various subgroups. The immunotherapy agent improves outcomes both in patients who do and do not achieve a pCR.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	Immune check point inhibitors are used routinely in NHS. Management of toxicities with this class of drugs has improved nationally with better education of clinicians and patients. There are no practical implications or requirements of additional tests for its use.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The study showed no new safety signals. Quality of life in the experimental arm was well maintained.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial	Yes; Moving Immune check point inhibitor from advanced metastatic setting and adjuvant setting into earlier setting as neo-adjuvant treatment, where Improvement in event free survival is translating into improvement in OS and

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

8 of

impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	higher percentage of patients achieving cure is likely to be a "step change 'in the management of urothelial cancer. The clinical gains are likely to impact positively with further improvement in QOL of our patients.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	There were no new safety signals.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes, the data from the clinical trials reflects UK clinical practice. UK contributed significantly to this trial.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance TA817?	No

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

23. How do data on real-world experience compare with the trial data?	In real world, we do not use Neo-adjuvant immune check point inhibitors. In high risk MIBC post cystectomy adjuvant Nivolumab is used for pdl-1 positive patients.
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why.	Nothing to add here

Clinical expert statement

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[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

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Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Bringing immune check point inhibitor durvalumab in earlier disease setting as neo-adjuvant treatment in combination with chemotherapy improves event free survival, pathological complete response, metastases free survival and over-all survival compared to chemotherapy alone.

These gains are transformative and by improving cure rate will reduce the burden of palliative systemic treatments.

Addition of durvalumab to chemotherapy was well tolerated

Benefit was seen across the various subgroups. The immunotherapy agent improves outcomes both in patients who do and do not achieve a pCR.

Quality of life is well maintained with the addition of durvalumab as perioperative treatment.

Thank you for your time.

Professor Syed A Hussain, MBBS, MSc, MD, FRCP, Professor of Medical Oncology, University of Sheffield, & Sheffield Teaching Hospitals, Sheffield, South Yorkshire, United Kingdom.

Past Member: NCRI Bladder and renal group

Past Chair: NCRI Advanced Bladder cancer sub-group

Conflicts of interest:

Grants: CR UK, MRC/NIHR, Boehringer Ingelheim, Roche, Janssen.

Consulting fee/Advisory board: Pierre Fabre, Bayer, Janssen, Roche, Merck, Bristol-Myers Squibb, AstraZeneca, Pfizer, MSD, Astellas, Gilead, GSK, Boehringer Ingelheim.

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Support for attending meetings and/or travel: Janssen- Cilag, Bayer, Boehringer Ingelheim, Pierre Fabre, Pfizer, Roche, Bristol-Myers Squibb, AstraZeneca and MSD Oncology.

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Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please also send a second version of your comments with that information redacted. See [Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals](#) (section 3.2) for more information.

The deadline for your response is **5pm** on **<insert deadline>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

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Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 1: Treating muscle-invasive bladder cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Professor Robert Huddart
2. Name of organisation	Institute of Cancer Research and Royal Marsden Hospital, London, UK and representative of British Uro-Oncology Group
3. Job title or position	Professor of Urological Cancer, Honorary Consultant Clinical Oncologist, Education Secretary and Trustee British Uro-oncology group
4. Are you (please tick all that apply)	☒ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with muscle-invasive bladder cancer ? ☒ A specialist in the clinical evidence base for muscle-invasive bladder cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☒ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

8. What is the main aim of treatment for muscle-invasive bladder cancer ? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	
10. In your view, is there an unmet need for patients and healthcare professionals in muscle-invasive bladder cancer ?	
11. How is muscle-invasive bladder cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic)	

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? - Do you expect the technology to increase length of life more than current care? - Do you expect the technology to increase health-related quality of life more than current care?	
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	
17. Do you consider that the use of the technology will result in any substantial health-related benefits that	

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

are unlikely to be included in the quality-adjusted life year (QALY) calculation? Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? - Is the technology a 'step-change' in the management of the condition? - Does the use of the technology address any particular unmet need of the patient population?	
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	
20. Do the clinical trials on the technology reflect current UK clinical practice? - If not, how could the results be extrapolated to the UK setting? - What, in your view, are the most important outcomes, and were they measured in the trials? - If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? - Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	
22. Are you aware of any new evidence for the comparator treatment since the publication of NICE technology appraisal guidance TA817?	
23. How do data on real-world experience compare with the trial data?	
24. NICE considers whether there are any equality issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population	

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

- lead to recommendations that have an adverse impact on disabled people.

Please consider whether these issues are different from issues with current care and why.

More information on how NICE deals with equalities issues can be found in the [NICE equality scheme](#).

[Find more general information about the Equality Act and equalities issues here.](#)

Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Click or tap here to enter text.

Thank you for your time.

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Clinical expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

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Information on completing this form

In [part 1](#) we are asking you about living with muscle-invasive bladder cancer or caring for a patient with muscle-invasive bladder cancer. The text boxes will expand as you type.

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Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

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Your response should not be longer than 15 pages.

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Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 1: Living with this condition or caring for a patient with muscle-invasive bladder cancer

Table 1 About you, muscle-invasive bladder cancer, current treatments and equality

1. Your name	Melanie Costin
2. Are you (please tick all that apply)	☐ A patient with muscle-invasive bladder cancer ? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with muscle-invasive bladder cancer ? ☒ A patient organisation employee or volunteer? ☒ Other (please specify): NMIBC Patient
3. Name of your nominating organisation	Fight Bladder Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☒ I agree with it and do not wish to complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☐ I agree with it and will be completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

	☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with muscle-invasive bladder cancer ? If you are a carer (for someone with muscle-invasive bladder cancer) please share your experience of caring for them	
7a. What do you think of the current treatments and care available for muscle-invasive bladder cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	
8. If there are disadvantages for patients of current NHS treatments for muscle-invasive bladder cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? 9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?	

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

9c. Does this treatment help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these. For example, are there any risks with this treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering muscle-invasive bladder cancer and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics	

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

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13. Are there any other issues that you would like the committee to consider?	

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

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- Click or tap here to enter text.
- Click or tap here to enter text.
- Click or tap here to enter text.
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Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 1: Living with this condition or caring for a patient with muscle-invasive bladder cancer

Table 1 About you, muscle-invasive bladder cancer, current treatments and equality

1. Your name	Anne Wass
2. Are you (please tick all that apply)	☒ A patient with muscle-invasive bladder cancer ? ☒ A patient with experience of the treatment being evaluated? (Gemcitabine and Cisplatin) ☐ A carer of a patient with muscle-invasive bladder cancer ? ☒ A patient organisation employee or volunteer? (volunteer) ☐ Other (please specify):
3. Name of your nominating organisation	Fight Bladder Cancer
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☒ Yes, my nominating organisation has provided a submission ☐ I agree with it and do not wish to complete a patient expert statement ☐ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and do not wish to complete this statement ☒ I agree with it and will be completing

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

5. How did you gather the information included in your statement? (please tick all that apply)	☒ I am drawing from personal experience ☐ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience: ☐ I have completed part 2 of the statement after attending the expert engagement teleconference ☐ I have completed part 2 of the statement but was not able to attend the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with muscle-invasive bladder cancer ? If you are a carer (for someone with muscle-invasive bladder cancer) please share your experience of caring for them	I was diagnosed with high grade Muscle Invasive Bladder Cancer G3pT2 TCC in May 2020 during the pandemic. I had one TURBT followed by three cycles of Gemcitabine and Cisplatin chemotherapy prior to my robotically assisted Radical Cystectomy (bladder removal). At the same time of my bladder removal, I also had a full hysterectomy, partial vaginal removal and 41 lymph nodes removed. The surgery took 6 hours. I now live with a stoma and Urostomy bag. I have had regular check ups (blood tests and CT scans) as one of my lymph nodes had cancer present. My diagnosis had a huge impact on my well-being. As well as the shock of receiving a Cancer diagnosis I also had to cope with the knowledge I was not able to be accompanied by my husband at any of my hospital appointments, scans and surgery due to Covid restrictions. I felt completely isolated and extremely low during the 9 days I was in hospital post my Radical Cystectomy trying to recover and adapt to a new way of life. I have worked hard to overcome any mental health issues I had but this is still difficult to control as the date of results of checks and scans approach. Living with and adapting to having a stoma was daunting in the beginning. Over time I have adapted and manage my daily life well, but it has taken a long time to get where I am today.

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

	I try not to think or dwell about a recurrence but the worry never truly goes away and is always heightened before appointments. I have chosen not to look too closely at survival statistics as I find this overwhelming. Instead, I focus on living day to day and enjoying life.
7a. What do you think of the current treatments and care available for muscle-invasive bladder cancer on the NHS? 7b. How do your views on these current treatments compare to those of other people that you may be aware of?	Making the decision to have chemotherapy prior to my Radical Cystectomy was a tough, but necessary choice. I was prepared to undergo this treatment to give myself the best possible outcome. Radical Cystectomy surgery and the recovery afterwards is a very long road.
8. If there are disadvantages for patients of current NHS treatments for muscle-invasive bladder cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	Side effects of chemotherapy were harsh at times. Swollen red face, fatigue, stomach cramps, nausea. I have been left with Neuropathy in my left foot despite my last cycle of chemotherapy being 5 years ago. Sometimes the tingling is minimal and other times it feels like I am being stabbed in the foot with hot needles. It has never stopped. I have learned to live with it and the benefits of having the chemotherapy treatment outweighs what I now live with. I was not able to work during the cycles of chemotherapy and I was very aware that I was at risk of catching Covid due to my immune system being suppressed. My treatment took place before the vaccine was available. The knowledge I underwent chemotherapy to give myself a better outcome helps with my anxiety and emotional well being about a recurrence happening.
9a. If there are advantages of this treatment over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others?	The benefits of receiving the new treatment could have a big impact for patients. To have a good quality of life with a potentially longer life expectancy cannot be underestimated. Having an additional treatment after surgery may help reduce the risk of recurrence, which is one of my greatest fears. Having the new treatment could provide reassurance and peace of mind that something more is being done.

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why? 9c. Does this treatment help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these	If effective, it could help extend a patient's life whilst improving quality of life by reducing any anxiety surrounding the cancer returning. The new treatment is more tolerable to have with less side effects. It may reduce hospital visits and will reduce anxiety and fear of recurrence. Had the new treatment been available to me at the time, I would have welcomed the chance to have it. The knowledge of the positive outcomes regarding life expectancy and quality of life by having this treatment would have eased my fear and anxiety of recurrence.
10. If there are disadvantages of this treatment over current treatments on the NHS please describe these. For example, are there any risks with this treatment? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from this treatment or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	Patients who are not able to tolerate the side effects of chemotherapy would benefit from having this new treatment post surgery. Recovery from major surgery (bladder removal) is long and tough and having a less invasive more tolerable treatment post surgery would reduce anxiety and provide hope. The new treatment would also reduce fear of recurrence.
12. Are there any potential equality issues that should be taken into account when considering muscle-invasive bladder cancer and this treatment? Please	Treatment options are not always available at your local hospital. My nearest hospital (3 miles away) could not provide the neo-adjuvant chemotherapy being offered to me and I had to travel to another hospital 20 miles away, a journey that took 40-45 minutes. I was fortunate to have someone who could drive me to my chemotherapy appointments but this may not be the case for others who may live

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	alone, who are elderly or have a disability. I could not have got there easily by public transport and in fact would not have been well enough to travel by myself during treatment. The treatment needs to be offered and available to everyone at their local hospital.
13. Are there any other issues that you would like the committee to consider?	I am grateful for the opportunity to share my experience. For patients like me, a treatment that can lower the chance of recurrence and provide hope after major surgery is very important. Thank you for taking the time to read this document.

Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Peace of mind that something else is being done to move forwards in the treatment of Muscle Invasive Bladder Cancer
- Reduced anxiety of a recurrence with better outcomes
- Enhanced quantity of life alongside a good quality of life
- More tolerable side effects, therefore treatment easier to cope with post major surgery
- Had this treatment been available to me post surgery, I would have welcomed the chance to secure myself a better outcome

Thank you for your time.

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Patient expert statement

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

EXTERNAL ASSESSMENT GROUP REPORT

Durvalumab with gemcitabine and
cisplatin before surgery
(neoadjuvant) then alone after
surgery (adjuvant) for treating
muscle-invasive bladder cancer
[ID6168]

Produced by

York Technology Assessment Group, University of York, Heslington, York, YO10 5DD

Authors

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Dias S²

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Declared competing interests of the authors

None.

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Rider on responsibility for report

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Phung TH, Uphoff E, Gc V, Llewellyn A, Chen J, Fulbright H, Kunst N, Rothery C, Dias S. Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer: A Single Technology Appraisal. York Technology Assessment Group, 2025.

Contributions of authors

THP performed the critical review of the economic analyses, validated the economic model, conducted the EAG additional analyses and contributed to the writing of sections 4 and 5 of the report. EU wrote sections 2, 3.3, and part of 3.4, and contributed to the writing of other clinical sections of the report. VG performed the critical review of the economic analyses, reviewed and validated the economic model, and contributed to writing section 4 of the report. AL wrote parts of section 1, parts of section 3.4 and 3.5, and contributed to the writing of other clinical sections of the report. JC wrote sections 3.1, 3.2, and part of section 3.3. HF critically appraised the search strategies for the literature reviews and provided information support. NK performed the critical review of the economic analyses and contributed to the writing of section 4 of the report. CR led the critical review of the economic analyses, contributed to the writing of sections 1, 4 and 5 of the report, reviewed and commented on the whole report, and takes joint responsibility for the report. SD provided advice, critiqued the indirect comparisons, reviewed and commented on the whole report, and takes joint responsibility for the report.

Note on the text

All commercial-in-confidence (CON) data have been highlighted in blue and underlined.

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Table of Contents

Table of Contents	4
List of Tables	7
List of Figures	8
List of abbreviations	9
Glossary	11
1 Executive summary	12
1.1 Overview of the EAG's key issues	12
1.2 Overview of key model outcomes	13
1.3 EAG's key issues	13
1.4 Secondary issues identified by the EAG	17
1.5 Company's modelling errors identified by the EAG	18
1.6 Summary of EAG's preferred assumptions and resulting ICER	18
1.7 Outline of confidential comparator or subsequent treatment prices	19
2 Background	20
2.1 Critique of the company's description of underlying health problem	20
2.1.1 Muscle-invasive bladder cancer (MIBC)	20
2.1.1.1 Survival rates of patients with MIBC	22
2.2 Critique of the company's overview of current service provision	24
2.2.1 Current neoadjuvant treatment	24
2.2.2 Current adjuvant treatment	25
2.3 Critique of company's definition of decision problem	25
3 Clinical Effectiveness	30
3.1 Critique of the methods of review	30
3.1.1 Inclusion criteria	30
3.1.2 Critique of study selection and data extraction	30
3.1.3 Quality assessment	31
3.1.4 Evidence synthesis	31
3.2 Critique of the methods of the trials of the technology of interest	31
3.2.1 Study design	31
3.2.2 Critical appraisal	35
3.2.3 Baseline characteristics of NIAGARA participants	36
3.2.4 Applicability of the NIAGARA results to the NHS setting	37
3.2.5 Patient disposition	38
3.3 Critique of the results of the trials of the technology of interest	39
3.3.1 Efficacy	39
3.3.1.1 Overview of NIAGARA efficacy endpoints	39

3.3.1.2	Results for outcomes informing the economic model	39
3.3.1.3	Results for additional outcomes	43
3.3.1.4	Subgroup analyses	43
3.3.2	Safety	44
3.3.2.1	Summary of adverse events	45
3.3.2.2	Discontinuation due to adverse events	45
3.3.2.3	Immune-mediated adverse events (imAEs)	45
3.3.2.4	Serious adverse events (SAEs) and deaths	45
3.4	Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison	46
3.4.1	Trial design and participants	47
3.4.1.1	Study population	47
3.4.1.2	Study endpoints and analyses	48
3.4.2	Critical appraisal	49
3.5	Critique of the indirect comparison or multiple treatment comparison	49
3.5.1	Methods	50
3.5.1.1	Sources of CheckMate-274 results data	52
3.5.2	Results	53
3.5.3	EAG comments	55
3.6	Additional work on clinical effectiveness done by the EAG	57
3.7	Conclusions of the clinical-effectiveness section	57
4	Cost-effectiveness	58
4.1	Critique of the review of cost-effectiveness evidence	58
4.1.1	Summary of company's submission	58
4.1.2	Points for critique	58
4.2	Critique of the submitted economic evaluation	60
4.2.1	NICE reference case checklist	61
4.2.2	Model structure	62
4.2.2.1	Summary of company's submission	62
4.2.2.2	Points for critique	62
4.2.3	Population	65
4.2.3.1	Summary of company's submission	65
4.2.3.2	Points for critique	65
4.2.4	Interventions and comparators	66
4.2.4.1	Summary of company's submission	66
4.2.4.2	Points for critique	67
4.2.5	Treatment effectiveness and extrapolation	68
4.2.5.1	Summary of company's submission	68

4.2.5.2	Points for critique	71
4.2.6	Health related quality of life	82
4.2.6.1	Summary of company's submission	82
4.2.6.2	Health state utilities	83
4.2.6.3	Disutility associated with AEs and cystectomy	84
4.2.7	Resources and costs	85
4.2.7.1	Summary of company's submission	85
4.2.7.2	Points for critique	89
4.2.7.3	Summary of the costs included in the company's scenario with nivolumab	91
4.2.7.4	Points for critique	91
5	Cost-effectiveness results	92
5.1	Company's cost effectiveness results	92
5.1.1	Company's base case	92
5.1.2	Company's sensitivity and scenario analyses	93
5.2	EAG's additional analyses	94
5.2.1	Model validation and face validity check	94
5.2.2	EAG's exploratory analyses using company's base case	95
5.2.3	EAG's preferred assumptions	98
5.2.4	Scenario analyses using EAG's preferred assumptions	100
5.3	Decision modifiers	101
5.3.1	QALY weighting for severity	101
5.3.2	Uncaptured benefits	101
5.3.3	Health inequalities	102
5.4	Confidential comparator and subsequent treatment prices	102
5.5	Conclusions of the cost-effectiveness section	102
6	References	104
	Appendices	109
	Appendix 1. Clinical evidence searches	109
	Appendix 2. Cost-effectiveness, Health-related quality of life, cost and healthcare resource identification, measurement, and valuation searches	111
	Summary	111
	Search strategy	111
	Appendix 3. TECH-VER Checklist	113

List of Tables

Table 1 Summary of key issues	12
Table 2 Summary of EAG's preferred assumptions and ICER – EAG base case 1	18
Table 3 Summary of EAG's preferred assumptions and ICER – EAG base case 2	19
Table 4 Tumour-Node-Metastasis (TNM) classification ⁵	20
Table 5. Demographics and 5-year survival for patients with MIBC in clinical practice.....	22
Table 6 Summary of decision problem.....	27
Table 7 Overview of NIAGARA outcomes for which results are reported in the CS.....	32
Table 8 Clinical effectiveness studies of technology of interest.....	33
Table 9 EAG's quality assessment results for NIAGARA trial.....	36
Table 10 Summary of key efficacy results from NIAGARA (DCO 29 April 2024).....	40
Table 11 EFS events NIAGARA (full analysis set), based on CSR Table 23.....	41
Table 12 CheckMate-274 Kaplan-Meier data informing ITC for DFS and MFS, and alternative sources for OS	51
Table 13 HRs (95% CI) comparing adjuvant nivolumab to no adjuvant treatment in high-risk PD-L1 patients in the NIAGARA trial (using counterfactual survival times) compared to the relevant CheckMate-274 subgroup.....	54
Table 14 NICE reference case checklist	61
Table 15: Health state utility values used in the model (reproduced from Table 44, CS)	83
Table 16: Disutilities associated with AEs (reproduced from Table 45, CS)	85
Table 17: Summary of costs used in the company's base case analysis	87
Table 18 Company's deterministic base-case cost-effectiveness results (disease severity modifier of 1.0).....	92
Table 19 Company's probabilistic base-case cost-effectiveness results (disease severity modifier of 1.0).....	93
Table 20 Cost-effectiveness results for scenario 9 reported in the CS and EAG validation.....	93
Table 21 Company's scenario results with adjuvant nivolumab (disease severity modifier of 1.0).....	93
Table 22 Results of EAG's corrected company base case	94
Table 23 Results of EAG's corrected company scenario with adjuvant nivolumab.....	95
Table 24 Summary of EAG's exploratory analyses using company's base case.....	95
Table 25 Results of EAG's exploratory analyses using company's [corrected] base case (deterministic analysis).....	97
Table 26 Results of EAG's exploratory analyses using company's [corrected] scenario with nivolumab (deterministic analysis).....	97
Table 27 Deterministic results using EAG's preferred model assumptions [EAG's base case 1].....	99
Table 28 Deterministic results using EAG's preferred model assumptions [EAG's base case 2].....	99
Table 29 Probabilistic results for EAG base case 1 and 2	100
Table 30 Summary of EAG's scenario analyses using EAG's preferred assumptions.....	101
Table 31 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions	101

Table 32 EAG appraisal of evidence identification	109
Table 33 EAG appraisal of evidence identification	111
Table 34 EAG appraisal of the model using TECH-VER Checklist	113

List of Figures

Figure 1 One-year survival of MIBC in UK NHS patients.....	24
Figure 2 Survival curves used in the company's base case analysis for the perioperative durvalumab and control arms (with constraints implemented for curve crossing and all-cause general population risk of death).....	70
Figure 3 Survival curves used in the company's base case analysis (without adjuvant nivolumab) and the company's scenario with adjuvant nivolumab for the control arm.....	71
Figure 4 Independent hazard rate plots for EFS, MFS and OS compared to general population mortality hazards by treatment arm	73
Figure 5 Extrapolated OS using the four best-fitting standard parametric models	74
Figure 6 Comparison of OS extrapolations using standard parametric and best fitting flexible models in the perioperative durvalumab and control arms	76
Figure 7 Hazard rates of OS in the company's base case analysis for the perioperative durvalumab and control arms	77
Figure 8 Hazard rates of OS using the Gompertz and generalised gamma models for the perioperative durvalumab and control arms	78
Figure 9 Hazard rates of OS using the best-fitting flexible models for the perioperative durvalumab and control arms	78
Figure 10 OS extrapolations in the perioperative durvalumab and control arms by starting age used in the model	81

List of abbreviations

Abbreviation	Definition
1L	First-line
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike Information Criteria
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
BAUS	British Association of Urological Surgeons
BCG	Bacillus Calmette–Guérin
BIC	Bayesian Information Criteria
BICR	Blinded independent central review
BNF	British National Formulary
BSC	Best supportive care
C	Cisplatin
CDA-AMC	Canadian Drug Agency – Advisory Management Committee
CI	Confidence interval
CrCl	Creatinine Clearance
CS	Company submission
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
D	Durvalumab
D+G+C	Durvalumab + gemcitabine + cisplatin
DCO	Data cut-off
DFS	Disease-free survival
DM	Distant Metastasis
DMFS	Distant metastasis-free survival
DSS	Disease-specific survival
EAG	Evidence Assessment Group
EAU	European Association of Urology
ECOG PS	Eastern Cooperative Oncology Group performance status
EF	Event-Free
EFS	Event-Free Survival
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D-5L	EuroQol 5-Dimensions 5-Levels
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
G+C	Gemcitabine plus cisplatin
G+C+D	Gemcitabine plus cisplatin plus durvalumab
G+C+N	Gemcitabine plus cisplatin plus nivolumab
HCRU	Healthcare Resource Use
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HSU	Health State Utility

Abbreviation	Definition
HTA	Health Technology Assessment
ICER	Incremental cost effectiveness ratio
imAE	immune-mediated adverse event
IP	Investigational product
IPD	Individual patient data
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive Voice/Web Response System
KM	Kaplan–Meier
LABC	Life After Bladder Cancer
LR	Locoregional recurrence
M0	no distant metastasis
MFS	Metastasis-free survival
MHRA	Medicine and Healthcare products regulatory agency
MI	Myocardial Infarction
MIBC	Muscle-Invasive Bladder Cancer
MITRE	Muscle Invasive Bladder Cancer at Transurethral Resection of Bladder (audit)
MIUC	Muscle-invasive urothelial cancer
MMRM	Mixed Effects Repeated Measures model
NAC	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCRAS	National Cancer Registration and Analyses Service
NCT	National Clinical Trial
NDRS	National Disease Registration Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NL	Netherlands
NMA	Network meta-analysis
NR	Not reported
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OS	Overall Survival
PAS	Patient Access Scheme
PBAC	Pharmaceutical Benefits Advisory Committee (Australia)
pCR	Pathologic Complete Response
PD-L1	Programmed Cell Death Ligand 1
PFC	Points of clarifications
PFS	Progression Free Survival
PICOS	Population, Intervention, Comparator, Outcomes, Study design
ProBCI	Prospective Bladder Cancer Infrastructure registry
PSM	Partitioned survival model
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year

Abbreviation	Definition
QoL	Quality of Life
RC	Radical Cystectomy
RCT	Randomised controlled trial
SACT	Systemic Anti-Cancer Therapy
SAE	Serious adverse event
SAS	Safety analysis set
SC	subcutaneous
SD	Standard deviation
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
STM	State transition model
TCC	Transitional Cell Carcinoma
TNBC	Triple-negative breast cancer
TNM	Tumour-Node-Metastasis
TSD	Technical Support Document
UC	Urothelial Carcinoma

Glossary

Term	Definition in the context of this appraisal
Neoadjuvant	Treatment given prior to the main treatment, usually surgery, to reduce the tumour.
Adjuvant	Treatment given after the main treatment, usually surgery, to reduce the risk of cancer recurrence.
Perioperative	The same treatment is given before and after surgery.

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the external assessment group (EAG) as being potentially important for decision making. It also includes the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Section 1.3 explains the key issues in more detail. Secondary issues and modelling errors identified by the EAG are explored in sections 1.4 and 1.5. Background information on the condition, technology and evidence, and non-key issues are presented in later sections of the EAG report.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1 Summary of key issues

ID6168	Summary of issue	Impact on results	Report sections
1	Uncertainty in the relative effectiveness of perioperative durvalumab when the comparator includes adjuvant nivolumab	Unknown	3.4, 3.5
2	Extrapolation of immature data	Low for EFS and MFS. High for OS.	3.2, 4.2.5.2
3	Model selection for the extrapolation of OS	High	4.2.5.2
4	Starting age of modelled cohort	High	3.2.4, 4.2.5.2
5	Increased risk of non-cancer-related death	High	4.2.5.2

The key differences between the company's preferred assumptions and the EAG's preferred assumptions are:

- The EAG considers the relevant comparator to be neoadjuvant chemotherapy and radical cystectomy (RC), followed by no treatment or adjuvant nivolumab in eligible patients.
- The OS extrapolations are informed by the best fitting flexible spline models for each arm: for perioperative durvalumab this is the 1-knot spline odds and for the control arm this is the 1-knot spline hazard. This contrasts with the company's standard parametric models, with the Gompertz distribution selected for the perioperative durvalumab arm and the log-logistic distribution for the control arm.
- Subsequent treatments post-recurrence excludes nivolumab (nivolumab is not licensed as a treatment for recurrent/metastatic MIBC), which is included in the company's base case.

- The EAG includes the cost of PD-L1 testing when the comparator arm includes adjuvant nivolumab.

The EAG identified other uncertainties, which the EAG is unable to resolve based on the data currently available. These are described further in the sections below.

1.2 Overview of key model outcomes

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Increasing the proportion of patients who are alive (improvement in OS), event-free and metastasis-free (which is associated with improved health-related quality of life) over time relative to neoadjuvant cisplatin-based chemotherapy alone.

Overall, the technology is modelled to affect costs by:

- Additional drug acquisition and administration costs associated with durvalumab compared to neoadjuvant cisplatin-based chemotherapy alone
- Lower costs associated with reduced disease progression and subsequent therapy and terminal care costs from improved event-free and metastasis-free survival for durvalumab.

The modelling assumptions that have the greatest effect on the ICER are:

- Model selection for the extrapolation of OS in the comparator arm
- The starting age of the modelled cohort
- Increased risk of non-cancer-related death.

1.3 EAG's key issues

Issue 1 Uncertainty in the relative effectiveness of perioperative durvalumab when the comparator includes adjuvant nivolumab

Report section	3.4, 3.5
Description of issue and why the EAG has identified it as important	TA817 recommends nivolumab as an option for the adjuvant treatment of muscle-invasive urothelial cancer (MIUC) that is at high risk of recurrence after radical resection in adults whose tumours express PD-L1 at a level of 1% or more. Adjuvant nivolumab is therefore a relevant comparator for a subset of the population within the scope of this appraisal. There is no head-to-head trial evidence comparing perioperative durvalumab with neoadjuvant chemotherapy followed by adjuvant nivolumab in eligible patients.

	The company presented an alternative ‘survival-time adjusted indirect treatment comparison (ITC)’ approach, which simulated a scenario where eligible high-risk PD-L1 $\geq 1\%$ patients in the control arm of the NIAGARA trial, received adjuvant nivolumab instead of no treatment after neoadjuvant chemotherapy followed by radical cystectomy. The CheckMate-274 RCT which compared adjuvant nivolumab with placebo in MIUC patients with prior radical surgery who were at high risk of recurrence, was used to inform the ITC. However, the results of the ITC are highly uncertain because: - It is unclear whether the effect of adjuvant nivolumab observed in CheckMate-274 is exchangeable with the NIAGARA trial, i.e. whether the effect of nivolumab compared to placebo observed in CheckMate-274 also applies to patients in the adjuvant phase of NIAGARA. - The subgroup data from CheckMate-274 used to inform the ITC does not fully match the target population of high-risk PD-L1 positive, MIBC patients who received NAC (only a minority of patients in CheckMate-274 received NAC), and baseline characteristics for the CheckMate-274 subgroup data are not available.
What alternative approach has the EAG suggested?	Adjuvant nivolumab therapy was not included in the company’s base-case, although the ITC results informed a scenario analysis. The EAG considers adjuvant nivolumab to be part of the treatment pathway in the NHS therefore this is included in one of the alternative EAG base-cases.
What is the expected effect on the cost-effectiveness estimates?	Evidence presented by the company suggests that the ITC analyses are conservative and may overestimate the effectiveness of adjuvant nivolumab. This in turn affects the survival estimates for the comparator arm when nivolumab is included. However, the effectiveness results from the ITC are uncertain and the expected effect on the cost-effectiveness estimates is unknown.
Could any additional evidence or analyses be provided to resolve this key issue?	Further evidence on the efficacy of nivolumab for the subset of patients with prior neoadjuvant platinum-based chemotherapy followed by radical cystectomy and high-risk PD-L1 $\geq 1\%$ would be helpful to assess the applicability of CheckMate-274 data informing the ITC.

Issue 2 Extrapolation of immature data

Report section	3.2, 4.2.5.2
Description of issue and why the EAG has identified it as important	The company’s analysis uses immature data from the April 2024 interim analysis of the NIAGARA trial, where median EFS was reached only in the control arm, and median MFS and OS were not reached in either arm. Extrapolating this immature data beyond the trial's follow-up introduces uncertainty in the long-term effectiveness of perioperative durvalumab relative to the control arm. This uncertainty also affects the model's implicit "cure" assumption, where a large portion of patients are considered cured when their risk of a cancer-related event becomes equal to the general population's all-cause mortality risk. In the company's base case analysis, this occurs after [REDACTED] years for the perioperative durvalumab arm and [REDACTED] years for the control arm, where [REDACTED]% of patients in the perioperative durvalumab arm and [REDACTED]% in the control arm are considered to have no risk of progression/recurrence or cancer-related death.
What alternative approach has the EAG suggested?	The impact of alternative parametric models for the extrapolation of the interim data are explored in Section 5.2.2.

What is the expected effect on the cost-effectiveness estimates?	The EAG analyses suggest that the cost-effectiveness estimates are not highly sensitive to different long-term extrapolations for EFS and MFS, but they are significantly influenced by the long-term extrapolations for OS, particularly in the control arm – See Issue 3.
Could any additional evidence or analyses be provided to resolve this key issue?	The final EFS analysis and second interim OS analysis are planned for when approximately 451 EFS events in the FAS (ITT population) have occurred across the two arms (43% maturity, 451/1,050). The final OS analysis is expected to be approximately 60 months after the last patient is randomised. The plan for the final MFS analysis is not stated in the CS. While the exact timing of these analyses is unclear, the more mature data will reduce the existing uncertainty regarding the long-term effectiveness of perioperative durvalumab compared to the control arm.

Issue 3 Model selection for the extrapolation of OS

Report section	4.2.5.2
Description of issue and why the EAG has identified it as important	The trend in OS hazard rates between the perioperative durvalumab and control arms in the company's base case analysis is inconsistent with the observed hazard rates over time from NIAGARA. The OS hazard rates for both arms reach a peak at around 10 months post-randomisation. After this point the observed differences between arms start to converge, moving towards near-zero rates by the end of the follow-up period. However, the company's base case model selection for OS extrapolation results in diverging hazards, implying that the hazard ratio is increasing with time before eventually converging due to the general population mortality constraint. The EAG considers that there is no empirical evidence to suggest that the hazard is increasing over time.
What alternative approach has the EAG suggested?	The model selection for the extrapolation of OS should reflect the convergence in the observed hazards between arms in NIAGARA. The EAG considers that flexible parametric models, specifically a 1-knot odds model for the perioperative durvalumab arm and a 1-knot hazard model for the control arm, capture the OS hazard profiles effectively and provide a good visual fit to the OS data.
What is the expected effect on the cost-effectiveness estimates?	The company's (corrected) base case ICER increases from £14,280 to £19,016 when the best fitting flexible models (1-knot odds for durvalumab, 1-knot hazard for control) are used for OS extrapolation.
Could any additional evidence or analyses be provided to resolve this key issue?	More mature OS data is required.

Issue 4 Starting age of modelled cohort

Report section	3.2.4, 4.2.5.2

Description of issue and why the EAG has identified it as important	The starting age of the modelled cohort has a large impact on the extrapolated OS probabilities. This is because the hazard rate of OS is constrained to be at or above the age- and gender-matched all-cause general population risk of death. Therefore, the time point at which the risk of death approaches that of the general population depends on the starting age used in the model. Clinical experts advised that NHS patients are generally older than those in the NIAGARA trial, where the mean age was 64.4 years. Data provided by NHS England for the North East suggests a mean age of 66 years for patients with resectable MIBC receiving neoadjuvant cisplatin-based chemotherapy, but it is unclear if this is representative of all patients across England and Wales.
What alternative approach has the EAG suggested?	The impact of a modelled starting age of 70 years is explored in Section 5.2.2.
What is the expected effect on the cost-effectiveness estimates?	The life years gained for perioperative durvalumab vs. control in the company's base case analysis reduce from ■■■ years (modelled starting age of 64.4 years) to ■■■ years with a starting age of 70 years old. The company's (corrected) base case ICER increases from £14,280 to £19,000.
Could any additional evidence or analyses be provided to resolve this key issue?	Further nationwide information on the age and sex distribution of patients who receive NAC followed by RC would help resolve this issue.

Issue 5 Increased risk of non-cancer-related death

Report section	4.2.5.2
Description of issue and why the EAG has identified it as important	People with MIBC in the NIAGARA trial are likely to have a higher risk of non-cancer-related death compared with the general population. This is because participants have mortality risk factors including smoking (23.7% current smokers and 49.3% ex-smokers) and other comorbidities. This means that even after removing the risk of cancer-related death, the overall risk of death for this population is likely to be higher than the general population mortality risk. An excess risk has not been considered in the company's base case analysis.
What alternative approach has the EAG suggested?	Inclusion of an excess risk of non-cancer-related deaths in the target population compared to the general population risk. An increased death risk can be calculated using the probability of cancer non-related deaths in NIAGARA and the corresponding mortality rate in age- and gender- matched general population.
What is the expected effect on the cost-effectiveness estimates?	With an increased non-cancer-related death risk (hazard ratio of 1.42) in the target population compared to the general population risk, the company's (corrected) base case ICER increases from £14,280 to £16,322.
Could any additional evidence or analyses be provided to resolve this key issue?	Information on the increased death risk due to comorbidities in patients with MIBC in the NHS.

1.4 Secondary issues identified by the EAG

Issue 6 Subsequent treatments post-recurrence

Report section	4.2.7.2
Description of issue and why the EAG has identified it as important	The subsequent treatments post-recurrence were based on the opinion of four UK clinical experts, not the treatments used in the NIAGARA trial. While the EAG's clinical advisors considered the company's estimates for post-recurrence treatments reasonable, they noted the actual proportion of patients receiving such treatments in the NHS is uncertain. They also pointed out that nivolumab is not licensed for recurrent/metastatic MIBC and that both nivolumab and atezolizumab are available in subcutaneous form (the company's analysis assumed only intravenous administration).
What alternative approach has the EAG suggested?	The EAG excludes nivolumab from the subsequent treatments post-recurrence. The EAG considers a scenario that assumes 25% of patients receive atezolizumab and nivolumab subcutaneously in NHS practice (i.e., 25% SC use and 75% IV use)
What is the expected effect on the cost-effectiveness estimates?	With the exclusion of nivolumab from the subsequent treatments post-recurrence, the company's (corrected) base case ICER increases from £14,280 to £14,348. With the administration of atezolizumab and nivolumab set at 75% IV and 25% SC, the company's (corrected) base case ICER increases from £14,280 to £14,286, while the company's (corrected) scenario with nivolumab ICER increases from £14,004 to £14,152.
Could any additional evidence or analyses be provided to resolve this key issue?	Accurate figures for the proportion of patients receiving different subsequent treatments in the NHS and the proportion of SC vs. IV use of therapies.

Issue 7 PD-L1 testing for adjuvant nivolumab

Report section	4.2.7.4
Description of issue and why the EAG has identified it as important	In the scenario with adjuvant nivolumab, the company did not account for the cost of testing patients for the presence of PD-L1 expression $\geq 1\%$. In the perioperative durvalumab arm, all patients receive adjuvant durvalumab regardless of their PD-L1 expression level but in the control arm, patients eligible to receive adjuvant nivolumab need to be at high risk of recurrence after radical resection and tumours must express PD-L1 at a level of 1% or more. Therefore, testing for PD-L1 expression is required for patients at high-risk of recurrence in the control arm when adjuvant nivolumab is considered.
What alternative approach has the EAG suggested?	Include the costs for PD-L1 test (£121.08) in the control arm with adjuvant nivolumab.
What is the expected effect on the cost-effectiveness estimates?	With costs of PD-L1 testing, the company's (corrected) scenario with nivolumab ICER decreases from £14,004 to £13,982.

Could any additional evidence or analyses be provided to resolve this key issue?	None required.

1.5 Company's modelling errors identified by the EAG

The EAG reviewed the company's model in detail and applied the TECHNical VERification (TECH-VER) checklist (see Appendix 3)¹. The EAG corrected the following modelling errors:

1. The extrapolated MFS curve picked up the extrapolated EFS curve at the point of crossing, while the CS states that '*EFS is constrained to values that are less than or equal to MFS*'. The EAG corrected this error such that the EFS curve picked up the MFS curve at the point of crossing.
2. Calculation formulae in the model workbook, with details provided in Section 5.2.1.

1.6 Summary of EAG's preferred assumptions and resulting ICER

As discussed in key issue 1, the EAG considers the relevant comparator to be neoadjuvant chemotherapy and RC, followed by no treatment or adjuvant nivolumab in eligible patients. The comparator with adjuvant nivolumab was excluded from the company's base case but included as a separate scenario. Therefore, the EAG presents two base cases:

- (i) EAG base case 1 with the same comparator as the company's base case (i.e., without adjuvant nivolumab); and
- (ii) EAG base case 2 with comparator consisting of neoadjuvant chemotherapy and RC, followed by no treatment or adjuvant nivolumab in eligible patients.

Table 2 summarises the EAG's preferred assumptions and resulting ICER for EAG base case 1, while Table 3 presents the results for EAG base case 2.

Table 2 Summary of EAG's preferred assumptions and ICER – EAG base case 1

Scenario	Incremental cost	Incremental QALYs	ICER (change from company's base case)
Company's base case [deterministic, post-clarification]	██████	██	£14,048
EAG's corrected company base case	██████	██	£14,280 (+1.65%)

Scenario	Incremental cost	Incremental QALYs	ICER (change from company's base case)
Key issue 3: OS extrapolations: spline 1-knot odds for durvalumab, spline 1-knot hazard for control	██████	████	£19,016 (+35.36%)
Additional EAG preferred assumptions (secondary issue 6): exclude nivolumab as a subsequent treatment	██████	████	£14,348 (+2.14%)
EAG's preferred base-case 1 deterministic [combining all above]	██████	████	£19,150 (+36.32%)
EAG's preferred base-case 1 probabilistic [combining all above]	██████	████	£21,905 (+55.93%)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years

Table 3 Summary of EAG's preferred assumptions and ICER – EAG base case 2

Scenario	Incremental cost	Incremental QALYs	ICER (change from company's base case)
Company's scenario with nivolumab [deterministic, post-clarification]	██████	████	£13,723
EAG's corrected company scenario with nivolumab	██████	████	£14,004 (+2.05%)
Key issue 3: OS extrapolations: spline 1-knot odds for durvalumab, spline 1-knot hazard for control	██████	████	£20,404 (+48.68%)
Additional EAG preferred assumptions (secondary issue 6): exclude nivolumab as a subsequent treatment	██████	████	£13,934 (+1.54%)
Additional EAG preferred assumptions (secondary issue 7): include cost for PD-L1 test (£121.08) for ██████ patients in the NIAGARA control arm	██████	████	£13,982 (+1.89%)
EAG's preferred base-case 2 deterministic [combining all above]	██████	████	£20,186 (+47.10%)
EAG's preferred base-case 2 probabilistic [combining all above]	██████	████	£23,242 (+69.37%)

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality-adjusted life years

1.7 Outline of confidential comparator or subsequent treatment prices

The confidential appendix to this report includes analyses using confidential prices for atezolizumab, avelumab, nivolumab, and erdafitinib. The confidential appendix presents the results of the company base-case analysis, sensitivity and scenario analyses and the results of EAG base cases and exploratory analyses reflecting the application of confidential discounts.

2 BACKGROUND

This report critiques the company submission for durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after radical cystectomy (adjuvant) for treating patients with resectable muscle-invasive bladder cancer (MIBC). This regimen is also referred to as ‘perioperative durvalumab’.

The company received marketing authorisation for perioperative durvalumab for this indication from the Medicines and Healthcare products Regulatory Agency (UK MHRA) in August 2025 after approval by the European Medicines Agency (EMA) in February 2025 and the US Food & Drug Administration (FDA) in March 2025.^{2,3}

2.1 Critique of the company’s description of underlying health problem

The company provides a clear description of bladder cancer, including the clinical presentation and the diagnosis and staging of MIBC. The company submission Document B (CS) briefly describes the epidemiology and burden of disease, mostly relating to bladder cancer generally. It highlights the burden of disease for patients, which is marked by pain, psychological distress, and limitations on daily life and routines. One of the EAG’s clinical advisers similarly stressed that MIBC is a type of cancer which presents with symptoms which significantly affect quality of life before, during, and after treatments.

2.1.1 Muscle-invasive bladder cancer (MIBC)

The company estimate that MIBC, which are primarily urothelial carcinomas, account for approximately 25% of bladder cancer cases. The most recent NHS data freely available online, recorded between 2013 and 2019, showed 20.4% of bladder cancer patients to have MIBC.⁴

Clinical staging of MIBC is based on the Tumour-Node-Metastasis (TNM) classification, which is summarised in Table 4 (based on CS pp. 19-20). Stages relevant to this appraisal are T2-T4a in combination with N0 (no lymph node involvement) or N1 (metastasis in one lymph node) and M0 (no distant metastasis).⁵

Table 4 Tumour-Node-Metastasis (TNM) classification⁵

Stage	Explanation	Categories
T (tumour)	Depth of invasion of the primary tumour	1 invasion of subepithelial connective tissue 2 muscle invasion 3 invasion of perivesical tissue 4 invasion of adjacent tissues

Stage	Explanation	Categories
N (node)	Number and location of infected lymph nodes	0 no lymph node involvement 1 metastasis in one lymph node 2 metastases in multiple regional lymph nodes 3 metastases in iliac lymph node(s)
M (metastasis)	Presence of distant metastasis	0 no distant metastasis 1 distant metastasis

In a clarification question to the company (A2), the EAG asked for further information on the demography of patients with MIBC eligible for radical cystectomy (RC) in the UK. The company provided some additional comments on the data collected in the 2022 British Association of Urological Surgeons (BAUS) audit of Muscle Invasive Bladder Cancer at Transurethral Resection of Bladder (MITRE),⁶ but no further data on the characteristics of patients with MIBC eligible for RC in the UK.

Data from the 2022 BAUS MITRE audit⁶ includes a total of 641 complete data records across 98 UK hospitals submitted in the first quarter of 2019. Most of the population (81.2%) had no distant metastasis and no or limited nodal involvement (stage N0/M0 or N1/M0). The mean age of patients with MIBC was 76 (range 35-104). The company commented in the response to clarification question A2 that the MITRE data set concerns a broader population than the population in scope for this appraisal, and that the broader population of patients with MIBC is generally older and less fit than those eligible for neoadjuvant chemotherapy. Only 46 out of 641 patients (7.2%) in the MITRE dataset received neoadjuvant chemotherapy prior to cystectomy.⁶

A study by John et al. (2021) reported on NHS data from 2016 on non-metastatic MIBC.⁷ Of all patients with stage T2-4 non-metastatic MIBC, 8.7% received neoadjuvant chemotherapy and cystectomy. The median age of patients was 76, but this varied by type of treatment. Patients who received neoadjuvant chemotherapy and RC had a median age of 67 (9% of patients), compared to a median age of 80 for patients who had radiotherapy without neoadjuvant treatment (15%). However, no age data were available specifically for the population in the NICE scope (resectable MIBC, cisplatin eligible).

The EAG requested information from NHS England on the characteristics of UK patients with resectable MIBC who receive neoadjuvant cisplatin-based chemotherapy, as these patients would be eligible for perioperative durvalumab. NHS England shared that, in the Northeast of England, patients are on average 66 years old. The period of data collection is unknown, and it is not certain that the mean age of patients in the Northeast is representative of the national population.

In conclusion, the group of patients with MIBC in scope for this appraisal have resectable MIBC and are eligible to receive gemcitabine and cisplatin (T2N0/1M0 to T4aN0/1M0) (Section 2.3). This is a subset of all MIBC patients, and this subset is younger and fitter than the broader population of patients with MIBC. There is a lack of published evidence on the characteristics of the population in the scope, and it is therefore difficult to provide an accurate and detailed overview of the demographics of this population in the NHS.

2.1.1.1 *Survival rates of patients with MIBC*

Survival rates of patients with MIBC are not explicitly discussed in the background section of the CS, but an overview of evidence from various trials and other sources is provided by the company in Table 40, p. 128. These data are difficult to interpret, given the range of data sources, countries and period of data collection. The oldest included trials with data collection completed before the year 2000, predating the introduction of neoadjuvant chemotherapy for MIBC.⁸ The EAG has supplemented these data with additional sources of information, prioritising more recent and UK/European real-world evidence identified through a pragmatic search of the literature (Table 5).

One of the EAG's clinical advisers indicated that survival rates observed in clinical practice are significantly lower than in clinical trials, regardless of the type of treatment. Using NHS data, Catto et al (2023) estimated a five-year survival rate of 24.1% for patients with urothelial MIBC between the years of 2013 and 2019, although they did not provide estimates for the population in the NICE scope (resectable MIBC, cisplatin eligible).⁴

The National Disease Registration Service (NDRS) dataset from 2013 recorded an overall 5-year survival rate of 34.3%, based on 3290 patients with local (T2, N0, M0) or locally advanced (T3/T4a or N1-N3) urothelial MIBC (Table 5).⁹ There were marked differences in 5-year survival between men (48.0%) and women (36.9%).

Table 5. Demographics and 5-year survival for patients with MIBC in clinical practice.

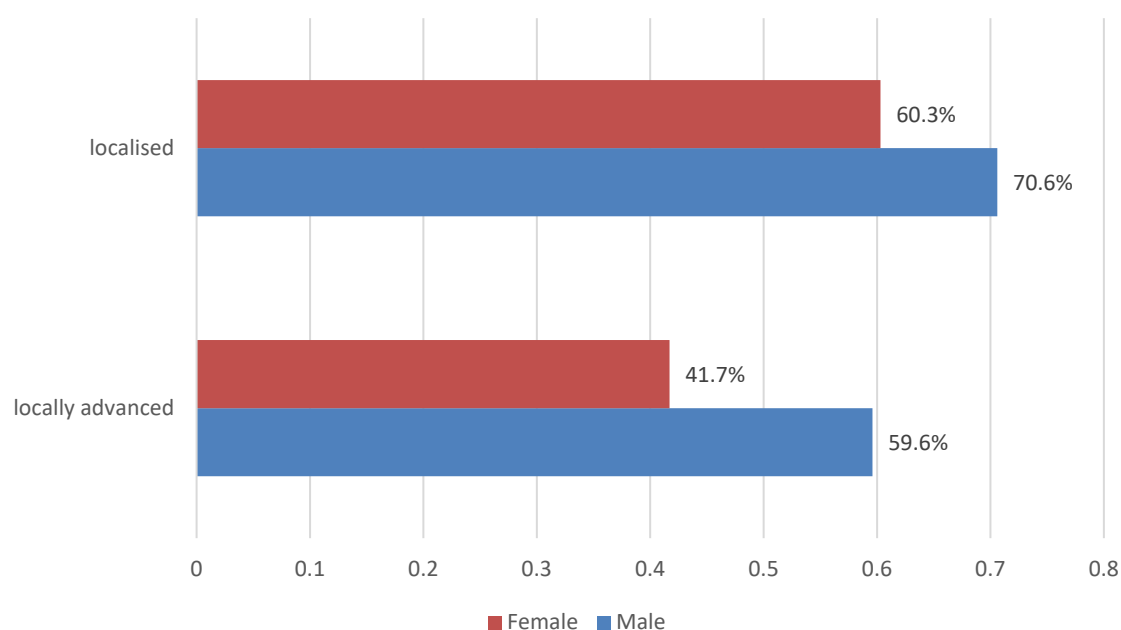
Reference	Data source	Country	Population	Demographics	5- and 10-year survival
<i>Data based on NHS patient records</i>					
Catto 2023 ⁴	Medical records 2013-2019	England	Bladder cancer; subgroup of 2944 pts with urothelial MIBC	NR (bladder cancer generally 57% aged > 75, 75% male).	5-year survival: 24.1% (21.4; 27.0)
John 2021 ⁷	Medical records (NCRAS), 2016.	England	2519 pts with MIBC (cT2-4N0/M0).	median age 76 (69 for RC pts), 71% male.	NR

Reference	Data source	Country	Population	Demographics	5- and 10-year survival
NDRS 2013 ⁹	Medical register, 2013 data.	England	3290 pts with urothelial, localised or locally advanced MIBC.	73% male	5-year survival: 48.0% men, 36.9% women.
<i>Other countries</i>					
Nikulainen 2025 ¹⁰	National cancer registry, 2005-2017	Finland	338 MIBC patients with NAC and RC	median age 65, 82% male.	5-year survival: 89% (T0/N2), 82% (T2/N0)
Brück 2024 ¹¹	National cancer registry, 2017-2019	NL	1432 pts with urothelial MIBC, cT2-4aN0/M0.	median age 71, 74% male.	NR
Mahoney 2025 (abstract) ¹² (CS Table 40)	Medical records, 2 institutions 2008-2017	Canada	57 MIBC patients with NAC (cisplatin) then radiotherapy	Median age 72, 11% regional nodal metastasis	5-year survival: 65% (50.7; 75.5)
Faraj 2021 ¹³ (CS Table 40)	Medical records 1 institution 2008-2017.	US	Urothelial MIBC adults who had cystectomy.	Median age 69 NAC, 74 no NAC. 81% male.	5-year survival: 53.2% 10-year survival: 42.7%
Vlaming 2020 ¹⁴ (CS Table 40)	Medical records 1 institution 1998-2016.	NL	313 pts with de novo urothelial MIBC who had a radical cystectomy	Mean age 65, 72% male	5-year: survival 49% 10-year: survival 39%
Mak 2014 ⁸ (CS Table 40)	Pooled analysis of MIBC radiotherapy trials, recruitment 1988-2007.	various	468 pts with MIBC; 61% T2.	Median age 66, 83% male.	5-year survival: 45% in those having cystectomy; 62% for those with T2 stage cancer. 10-year survival: 18% in those having cystectomy; 41% for those with T2 stage cancer.

Abbreviations: CS; company submission, MIBC; muscle-invasive bladder cancer, NAC; neoadjuvant chemotherapy, NCRAS; National Cancer Registration and Analyses Service; NL; Netherlands, NR; not reported, RC; radical cystectomy, US; United States.

For more recent NDRS data from 2020, survival outcomes up to one year are available. Average one-year survival is 67.8 months for localised cancer (N=2282) and 53.8 months for locally advanced cancer (N=443), with variation by gender (Figure 1) and age category.⁹

Figure 1 One-year survival of MIBC in UK NHS patients



Source: National Disease Registration Service (NDRS) 2020.⁹ Figure created by the EAG, using data that has been provided by patients and collected by the NHS as part of their care and support. Data are collated, maintained and quality assured by the National Disease Registration Service, which is part of NHS England.

2.2 Critique of the company's overview of current service provision

The CS shows the current clinical pathway for resectable MIBC in the UK in Figure 1 (p. 24).

Clinical advice to the EAG confirmed that the diagram is an accurate illustration of NHS practice and is aligned with the European Society for Medical Oncology (ESMO) Clinical Practice Guideline for diagnosis, treatment, and follow-up, and European Association of Urology (EAU) Guidelines on Muscle-Invasive and Metastatic Bladder Cancer. The pathway illustrated in the diagram (CS Figure 1, p. 24) is split between the neoadjuvant treatment phase, prior to RC, and the adjuvant phase after RC. The current standard of care for patients eligible to receive neoadjuvant chemotherapy is gemcitabine plus cisplatin. Clinical advice to the EAG was that radiotherapy is also a treatment option for this patient population, which is omitted from the company's representation of the treatment pathway. Radiotherapy can be offered to patients for whom treatment with neoadjuvant chemotherapy (NAC) is unsuitable, or as an alternative to RC for patients for whom NAC is suitable. It is therefore not a comparator for perioperative durvalumab, and not relevant to the decision problem for this appraisal.

2.2.1 Current neoadjuvant treatment

As shown in Figure 1 (CS p. 24), patients who are fit enough will be offered neoadjuvant gemcitabine plus cisplatin, which is referred to as NAC in this report. Clinical advice to the EAG is that, after

assessment of fitness, comorbidities, performance status, and renal function, around 70% of patients will be eligible to receive NAC. Most patients will then undergo a RC; a surgical procedure in which the bladder and any surrounding tissue affected by the tumour are removed. A small proportion of patients may not initially be eligible to proceed to RC but may become eligible after receiving cisplatin-based therapy.

The BAUS MITRE audit found that cystectomy was performed in 20.9% of patients with MIBC, and 38.7% of this group received NAC. Catto et al. reported treatment choices for 23,373 patients with urothelial MIBC from 2013 to 2019 and found that 23.7% of patients received RC.⁴

2.2.2 Current adjuvant treatment

The current clinical pathway (CS Figure 1, p. 24) has multiple options for adjuvant treatment, depending on whether patients are at high or low risk of recurrence, and whether they are suitable to receive adjuvant chemotherapy if at high risk of recurrence.

Post-surgery, MIBC is considered at high risk of recurrence if classed as pathological stage T3 (invasion into perivesical tissues), T4a (invasion into adjacent structures), or N+ (lymph node involvement) (see also Section 2.1.1).¹⁵ Patients considered at low risk of recurrence after RC will receive ‘best supportive care’ (BSC) (CS Figure 1, p. 24). Clinical advisers to the EAG clarified that BSC after a RC includes stoma care follow-up, clinical review and testing of renal function, and scans at 6, 12, and 24 months as a minimum, and annually thereafter for five years.

Patients considered at high risk of recurrence may receive BSC, or adjuvant chemotherapy (gemcitabine plus cisplatin) if they did not receive NAC. In addition, nivolumab was recommended by NICE in 2022¹⁵ for adjuvant treatment of muscle-invasive urothelial cancer in adults if

- Programmed Cell Death Ligand 1 (PD-L1) is expressed at a level of 1% or above, also described as ‘PD-L1 positive’, and
- Adjuvant treatment with platinum-based chemotherapy is unsuitable, and
- The cancer is at high risk of recurrence.

If patients considered high risk in a post-surgery assessment, PD-L1 testing is undertaken to determine suitability for adjuvant nivolumab.

2.3 Critique of company’s definition of decision problem

The company’s decision problem is largely in line with the NICE scope. Deviations from the NICE scope are justified and considered acceptable by the EAG, see Table 6 for details.

The submission by the British Uro-Oncology Group mentioned the possible use of durvalumab after chemo-radiotherapy for patients who do not have a RC. The EAG's clinical advisers agreed this would be desirable, but this is not in scope for this appraisal.

Table 6 Summary of decision problem

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope (summary)	EAG comment
Population	Adults with resectable MIBC who are eligible to receive gemcitabine and cisplatin.	Adults with resectable MIBC who are eligible to receive gemcitabine and cisplatin.	Aligns with scope.	Aligns with scope.
Intervention	Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant).	Durvalumab (IMFINZI®) in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after RC	Aligns with scope.	Aligns with scope.
Comparator(s)	Established clinical management without durvalumab, including but not limited to: • As neoadjuvant (before surgery) treatment: - o cisplatin-based chemotherapy • As adjuvant (after surgery) treatment: - o nivolumab (for people whose tumours express PD-L1 at a level of 1% or more) - o best supportive care	Established clinical management without durvalumab: • Cisplatin-based chemotherapy (gemcitabine + cisplatin) followed by RC and: - o No treatment - or - o Nivolumab (for patients whose tumours express PD-L1 $\geq 1\%$ and present high-risk of recurrence (ypT2 to ypT4a or ypN+) after surgery)	The comparators considered in the current appraisal are aligned with current practice as validated through interviews with UK-based MIBC clinical experts.	The EAG agrees the company's comparators align with clinical practice. Clinical advice to the EAG explained that 'best supportive care' consists of stoma care, check-ups, and follow-up scans, which will form part of routine care for all patients after RC. The company's base case uses cisplatin-based chemotherapy, followed by RC and no adjuvant treatment as a comparator. Adjuvant nivolumab for the subset of patients whose tumours express PD-L1 $\geq 1\%$ and are at high-risk of recurrence is considered by the company as a comparator in a scenario analysis.
Outcomes	The outcome measures to be considered include: • OS • EFS	The outcome measures to be considered include: • OS • EFS	PFS was not an endpoint in the NIAGARA trial due to limited utility of PFS for decision-making in perioperative	The EAG agrees that the additional outcomes are informative for this appraisal.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope (summary)	EAG comment
	• PFS • DFS • RR • AE • HRQoL	• pCR • MFS • DSS • DFS • PFS-2 • AE • HRQoL	regimens in comparison to OS and EFS. Additional outcomes have been included in line with the NIAGARA trial outcomes where relevant to perioperative treatment of MIBC.	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability and cost of biosimilar and generic products should be taken into account.	Cost effectiveness evidence has been provided for the full licensed patient population for NIAGARA trial - durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as monotherapy adjuvant treatment after RC, for the treatment of patients with resectable MIBC. The cost effectiveness analysis conducted is aligned with the specifications requested in the final scope.		Aligns with scope.
Subgroups	If the evidence allows subgroups will be considered based on: • PD-L1 status	Subgroup analyses from the NIAGARA trial have been presented in Section 2.7 to demonstrate the efficacy of		No concerns.

-	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope (summary)	EAG comment
		perioperative durvalumab across prespecified subgroups, among other patient characteristics. Stratification factors included clinical tumour stage, renal function, and tumour PD-L1 expression level.		
Special considerations including issues related to equity or equality	N/A	AstraZeneca do not anticipate any equality issues to arise with the introduction of perioperative durvalumab in the UK clinical practice. However, evidence suggests that men are more likely to develop BC, while women often present with more advanced and high-grade disease and have a worse prognosis due to longer diagnostic delays rather than differences in treatment patterns (19-21).		The EAG acknowledges the evidence of poorer prognosis and lower survival for women compared to men in UK clinical practice. As this appears to be a problem related to diagnosis rather than treatment, treatment with durvalumab is unlikely to impact on inequalities.

3 CLINICAL EFFECTIVENESS

This section presents a summary and critique of the clinical-effectiveness evidence included in the company's submission. Section 3.1 focuses on the company's review of clinical and safety evidence. Sections 3.2 to 3.3 provide a critique of the included studies and clinical-effectiveness analyses. Sections 3.4 to 3.5 critique any indirect comparisons presented by the company.

3.1 Critique of the methods of review

The company conducted a systematic literature review (SLR) to identify clinical evidence on treating MIBC in adults. Overall, an adequate range of relevant databases were searched alongside a good range of conference proceedings, grey literature sources and trials registries. The reporting of the searches was mainly clear and the structure of the search, its limits and filters were appropriate. The search terms could have been more comprehensive. The EAG is not aware that relevant evidence was missed, although it is unable to verify this systematically due to time constraints.

The original company submission included searches to identify clinical evidence for treating MIBC in adults. A description of the searches and the search strategies were included in Appendix B (pp. 1-41). In response to the EAG's clarification questions C1-C7, the company provided additional information.

The EAG's appraisal of evidence identification can be found in Table 32, Appendix 1.

3.1.1 Inclusion criteria

The eligibility criteria for identifying relevant clinical evidence in the SLR were presented in CS Appendix B Table 1. These criteria were broadly appropriate to address the decision problem. Adults with untreated (first-line, 1L) muscle-invasive urothelial cancer (MIUC) or MIBC ($\geq 75\%$ bladder cancer), including those receiving adjuvant therapy after prior neoadjuvant therapy, were eligible for inclusion. A wide range of intervention treatments were considered eligible as monotherapy or in combination, including various chemotherapy regimens, immune checkpoint inhibitors, and combination therapies, administered in either the neoadjuvant or adjuvant setting. There was no requirement to limit treatments to a specific perioperative phase, and receipt of RC was also not required for study inclusion. Comparators included any treatment or placebo and only Phase II–IV RCTs published in English were included.

3.1.2 Critique of study selection and data extraction

Study selection was performed independently by two reviewers against pre-specified eligibility criteria at both the title/abstract and full-text stages. Disagreements were resolved through discussion or by a third reviewer. Data extraction was done by one reviewer and checked by another.

The EAG believes that the study selection process was methodologically sound and well-documented. The exclusions were appropriate based on study design, intervention, population, and relevance of outcomes to the PICOS (Population, Intervention, Comparator, Outcomes, Study design) criteria.

3.1.3 Quality assessment

RCTs included for data extraction were assessed using the RoB 2 tool.¹⁶ One reviewer used the checklist to independently assess the quality of the included studies, and a second reviewer checked their assessment. Disagreements were resolved through discussion or by involving a third reviewer. Risk of bias was assessed by outcome as per Cochrane guidance, mainly for overall survival (OS), event-free survival (EFS), and pathological complete response (pCR). In a few cases, risk of bias varied across different outcomes within the same study. The EAG's assessment of the NIAGARA trial is reported in Section 3.2.2.

3.1.4 Evidence synthesis

Because only one relevant trial (NIAGARA) evaluating perioperative durvalumab for the treatment of patients with resectable MIBC was identified, a meta-analysis of effectiveness outcomes was not conducted. Instead, a narrative synthesis of effectiveness and safety outcomes was provided (CS Appendix B, Section B.1.8.3) for 58 studies, including two perioperative studies, 27 neoadjuvant studies, 14 adjuvant studies, and 15 studies that evaluated other treatment settings.

A standard indirect comparison of perioperative durvalumab with adjuvant nivolumab was not feasible due to differences in the control arms, timing of randomisation, and the inclusion criteria. Therefore, an alternative 'survival time-adjusted ITC' was conducted, which is discussed in sections 3.4 and 3.5.

3.2 Critique of the methods of the trials of the technology of interest

3.2.1 Study design

The NIAGARA trial (NCT03732677) is an ongoing phase 3, randomised, open label, multicentre study to examine the efficacy and safety of perioperative durvalumab in patients with MIBC. The trial evaluated neoadjuvant durvalumab in combination with gemcitabine and cisplatin, followed by adjuvant durvalumab monotherapy (intervention arm), compared neoadjuvant gemcitabine and cisplatin with no adjuvant therapy (control arm). A total of 1,063 patients were randomised in a 1:1 ratio and included in the intention-to-treat (ITT) analysis. The dual primary endpoints of the trial were EFS and pCR, both assessed by blinded independent central review (BICR). Table 7 shows the outcomes relevant to this appraisal and their descriptions as presented in the CS, supplemented with

descriptions from the clinical study report (CSR). Additional and exploratory outcomes relating to safety and pharmacokinetics are not included here.

Table 7 Overview of NIAGARA outcomes for which results are reported in the CS.

Abbreviation	Outcome	Definition	Endpoint included in economic model?
Primary			
EFS	Event-free survival per blinded independent central review (BICR) or central pathology review	Time from randomisation to the first recurrence of disease after RC, the time of first documented progression in patients who are medically precluded from RC, or time of expected surgery in patients who refuse to undergo RC or failure to undergo RC in patients with residual disease, or the time of death due to any cause, whichever occurs first (CS p. 49).	yes
pCR	Pathologic complete response per central pathology review	Proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via RC following the neoadjuvant treatment (NIAGARA CSR Table 6, p. 54).	no
Secondary			
OS	Overall survival	Time from randomisation to death due to any cause (NIAGARA CSR Table 6, p. 54).	yes
EFS	Event-free survival per investigator or local biopsy review	Time from randomisation to the first recurrence of disease after (RC), the time of first documented progression in patients who are medically precluded from RC, or time of expected surgery in patients who refuse to undergo RC or failure to undergo RC in patients with residual disease, or the time of death due to any cause, whichever occurs first (CS p. 49).	no
MFS	Metastasis-free survival per investigator assessment or biopsy review	Time from date of randomisation until the first recognition of distant metastases or death, whichever occurs first (CS p. 57).	yes
DSS	Disease-specific survival	Time from randomisation to death specifically due to bladder cancer (CS p. 59).	no
DFS	Disease-free survival	Time from the date of RC to the first recurrence of disease post RC, or death due to any cause, whichever occurs first (CS p. 61).	no
PFS-2	Time from randomisation to subsequent progression or recurrence post-EFS event.	The time from the date of randomization to the earliest date of progression which occurred on subsequent therapy following an EFS event or death (NIAGARA CSR Table 6, p. 55).	no
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30.	Adjusted mean change from baseline and time to definitive clinically meaningful deterioration (TDD) on the quality of life (QOL), physical functioning, fatigue, and pain subscales of the EORTC QLQ-C30 (NIAGARA CSR Table 5, p. 52).	no
-	Proportion of patients who undergo RC	The proportion of patients who underwent RC after the neoadjuvant treatment (NIAGARA CSR Table 6, p. 55).	yes
Exploratory			

Abbreviation	Outcome	Definition	Endpoint included in economic model?
EQ-5D-5L	EuroQoL 5- Dimension 5-Level Questionnaire.	Mean index score and visual analogue scale (VAS) score of the EQ-5D-5L.	yes

Abbreviations: RC: radical cystectomy

The trial design and eligibility criteria are summarised in Table 8. One of the EAG’s clinical advisers noted that the inclusion of patients with N1 disease, variant histology, and reduced renal function is consistent with routine care. Another clinical adviser noted that some patients with N2–N3 disease may respond to neoadjuvant chemotherapy and undergo cystectomy and could potentially benefit from durvalumab. However, the company explain in response to a clarification question A3 that patients with N2-N3 disease are not currently standard candidates for surgery as per National Comprehensive Cancer Network (NCCN) recommendations.¹⁷ Consequently, the trial included patients with T2–4N1 disease but excluded those with N2/N3 disease. The EAG’s clinical advisers noted that standard practice for preoperative N2/N3 M0 disease is neoadjuvant chemotherapy followed by chemoradiotherapy, with cystectomy reserved for only a very small proportion of patients with an exceptional response, and this is not standard practice. The EAG considers this exclusion appropriate.

By comparing different treatment sequences, the NIAGARA design precludes the possibility of isolating the neoadjuvant from the adjuvant effect on efficacy and safety outcomes. However, discontinuation due to adverse events were reported for the neoadjuvant and adjuvant phases separately.

Table 8 Clinical effectiveness studies of technology of interest

-	NIAGARA trial (NCT03732677)
Role in this evaluation	- Evidence on primary endpoints EFS and pCR, and secondary endpoints including OS, directly comparing perioperative durvalumab in combination with neoadjuvant cisplatin-based therapy, and neoadjuvant cisplatin-based therapy. - Survival-time adjusted ITC comparing EFS, MFS and, OS for perioperative durvalumab in combination with neoadjuvant cisplatin-based therapy, and neoadjuvant cisplatin-based therapy with adjuvant nivolumab. - In the economic model, NIAGARA provides trial-based estimates of EFS, MFS, and OS, which are used as inputs in a partitioned survival model and extrapolated to estimate long-term outcomes - EQ-5D data from NIAGARA is used to inform health state utility values in the model.
Study type	Ongoing, Phase III, randomised, open label, multicentre, international study

-	NIAGARA trial (NCT03732677)
Patient group	• Age ≥ 18 years • Histologically or cytologically documented muscle-invasive TCC/UC of the bladder ◦ Transitional cell and mixed transitional/non-transitional cell/variant transitional histologies ◦ Clinical tumour stage T2N0/1M0-T4aN0/1M0 ◦ Medically fit for treatment with neoadjuvant therapy prior to RC. ◦ Medically fit to undergo a RC. ◦ No prior systemic chemotherapy or immunotherapy for MIBC • ECOG PS of 0 or 1 at enrolment • Known tumour PD-L1 status prior to randomisation. • Adequate organ and marrow function as defined by: ◦ Haemoglobin ≥ 9.0 g/dL ◦ Absolute neutrophil count $\geq 1.5 \times 10^9/L$ ◦ Platelet count $\geq 100 \times 10^9/L$ ◦ Serum bilirubin $\leq 1.5 \times ULN^a$ ◦ ALT and AST $\leq 2.5 \times ULN$ ◦ CrCl calculated by Cockcroft-Gault equation or measured by 24-hour urine collection for determination. CrCl for Borderline Renal Function arm: ≥ 40 mL/min to <60 mL/min. CrCl for Adequate Renal Function arm: ≥ 60 mL/min
Subgroups	• Age at randomisation (<65 years versus ≥ 65 years) • Sex (male versus female) • Race (white versus non-white) • Geographic region (Asia, Europe, North America and Australia, South America) • Histologic type at baseline (Urothelial carcinoma versus Urothelial carcinoma with divergent differentiation or histologic subtypes) • Prior BCG therapy (Yes versus No) • Regional lymph node stage at baseline (N0 versus N1) • Tumour stage (T2N0 versus $>T2N0$) at baseline per IVRS • Creatinine clearance at baseline (≥ 60 ml/min/1.73 m² versus <60 ml/min/1.73m²) • PD-L1 expression level at baseline (high, low/negative) per IVRS
Exclusion criteria	Specific medical conditions including, but not limited to: • Evidence of lymph node (N2-3) or metastatic TCC/UC (M1), extravesical TCC/UC • Inoperable tumour(s) with fixation to the pelvic wall on clinical exam • Certain comorbidities (e.g. autoimmune/inflammatory disorders) • History of a MI six months prior to randomisation • NYHA Class III or IV heart failure • Contraindication to platinum (cisplatin)-based doublet chemotherapy Specific prior/concomitant therapy including but not limited to: • Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment • Prior exposure to immune-mediated therapy, live vaccine, major surgery, radiotherapy or immunosuppressants Prior/concurrent clinical study experience
Intervention	Perioperative durvalumab arm Durvalumab 1500 mg IV Q3W with gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and adjuvant Durvalumab 1500 mg IV Q4W for up to eight 28-day cycles (32 weeks, eight months).

-	NIAGARA trial (NCT03732677)
Comparator	Control arm Neoadjuvant gemcitabine and cisplatin for four 21-day cycles (12 weeks, three months), followed by RC and no adjuvant treatment. Gemcitabine and cisplatin was dosed at 1000 mg/m ² IV on Days 1 and 8 Q3W (gemcitabine) and 70 mg/m ² IV on Day 1 Q3W (cisplatin) for patients with adequate renal function (CrCl $\geq$ 60 mL/min) and at 1000 mg/m ² IV on Days 1 and 8 Q3W (gemcitabine) and 35 mg/m ² IV on Days 1 and 8 Q3W (cisplatin) for patients with borderline renal function (CrCl $\geq$ 40 mL/min to < 60 mL/min) for both arms.
Duration	Patients were to receive 4 cycles (every 3 weeks) of study treatment in the neoadjuvant setting prior to RC. After RC and adequate recovery, unless specific study discontinuation criteria were met, patients in the D + G+C arm received adjuvant treatment for up to a maximum of 8 cycles (every 4 weeks) of durvalumab monotherapy, and those in the G+C arm received no adjuvant treatment.
Location	168 sites in 22 countries across Europe, Asia-Pacific, North America, and South America. The trial included four sites based in the UK: London, Sheffield, Wirral and Edinburgh.

Sources: CS Table 4, 5

Abbreviations: ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BCG: Bacillus Calmette–Guérin; CrCl: Creatinine clearance; D: Durvalumab; EFS: Event-free survival; ECOG PS: Eastern Cooperative Oncology Group performance status; EQ-5D-5L: EuroQol 5-Dimensions 5-Levels; G+C: Gemcitabine plus cisplatin; HRQoL: Health-related quality of life; IP: Investigational product; ITC: Indirect treatment comparison; IV: Intravenous; IVRS: Interactive voice/web response system; MFS: Metastasis-free survival; MIBC: Muscle-invasive bladder cancer; MI: Myocardial infarction; N0: No regional lymph node metastasis; N1: Single regional lymph node metastasis; N2: Multiple regional lymph node metastases; N3: Metastasis in common iliac lymph nodes; NYHA: New York Heart Association; OS: Overall survival; pCR: Pathologic complete response; PD-L1: Programmed death-ligand 1; PFS-2: Progression-free survival 2; RC: Radical cystectomy; SoC: Standard of care; TCC: Transitional cell carcinoma; UC: Urothelial carcinoma; ULN: Upper limit of normal.

3.2.2 Critical appraisal

The company presented two quality assessments of the NIAGARA trial. One assessment focused on NIAGARA alone using a tool adapted from CRD's guidance, presented in section 2.5 of the CS. The second was conducted using the RoB 2 tool and included NIAGARA alongside the other 57 studies identified from the SLR in CS Appendix B. The company concluded that NIAGARA was at low risk of bias.

The EAG performed its own assessment of NIAGARA based on CRD guidance as shown in Table 9. The EAG agrees that the methodology of NIAGARA appears generally robust and to have minimised the risk of most biases. However, NIAGARA is an open-label study, which may introduce bias, particularly through patient expectations or differential drop-out. Clinical advisers acknowledged that patients are likely to prefer durvalumab plus NAC over NAC alone. However, they consider it unlikely this will bias results. In response to clarification question A1, the company stated that potential bias was mitigated through BICR of primary endpoints (pCR, EFS) and a sponsor-blinded data management process. Completion of neoadjuvant therapy was similar between arms (78.7% for the durvalumab arm vs 74.0% for the control arm), as were rates of proceeding to cystectomy and discontinuation for patient decision, suggesting the open-label design did not materially affect treatment uptake, surgical intervention, or retention. Overall, the EAG agrees that the risk that the risk

of bias from the open-label design of NIAGARA is low. However, the lack of participant blinding means that HRQoL, which relies on self-reported information, is at high risk of bias.

Table 9 EAG's quality assessment results for NIAGARA trial

Question	Company response	EAG response
Was randomisation carried out appropriately?	Yes	Yes. Randomisation was implemented centrally using an interactive web response system (IWRS)
Was the concealment of treatment allocation adequate?	Yes	Yes. Allocation concealment was through central randomisation
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes. Baseline characteristics were balanced between the two treatment arms
Were the care providers, patients and outcome assessors blind to treatment allocation?	Yes	No for patients and care providers (open-label). Yes for key outcome assessors. Key outcomes (EFS and pCR) were assessed by BICR, OS was based on survival status and is not subject to assessor bias.
Were there any unexpected imbalances in drop-outs between groups?	No	No. There were no imbalances or unexpected drop-outs.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No. All outcomes were reported for data which were available.
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes. The primary analysis population was the ITT population.

Abbreviations: IWRS: Interactive web response system; EFS: Event-free survival; pCR: Pathological complete response; OS: Overall survival; BICR: Blinded independent central review; ITT: Intention-to-treat.

3.2.3 Baseline characteristics of NIAGARA participants

Baseline characteristics of participants included in NIAGARA are presented in CS Table 7 (pp. 40-41). Characteristics were broadly comparable between the perioperative durvalumab (durvalumab + gemcitabine + cisplatin, D+G+C) and control (G+C) arms. The median age was 65 years, 82% were male, 67% were White, and 73% had high PD-L1 expression. Most patients had ECOG PS 0 (78%), adequate renal function (81%), and tumour stage > T2N0 (60%). The trial population had numerically higher proportion of smokers in the control arm, but clinical advisers did not consider this to affect prognosis or treatment efficacy.

In CS appendix B, Table 58 and Figure 8 present the distribution of patients by post-surgical risk category, PD-L1 status, and residual disease. In total, [REDACTED] of trial participants were classified as high risk with PD-L1 $\geq 1\%$ expression and no residual disease after surgery, meeting the NHS criteria for adjuvant nivolumab; however, this subgroup was not treated with nivolumab in the NIAGARA control arm. Other categories included high risk with residual disease ([REDACTED]), high risk non-PD-L1

with no residual disease (■■■■), low risk with residual disease (■■■■), low risk with no residual disease (■■■■), and no surgery (■■■■).

Medical history data reported in the CSR (Section 10.4.3) show that common comorbidities among NIAGARA participants included [REDACTED]

3.2.4 Applicability of the NIAGARA results to the NHS setting

The NIAGARA trial included four UK centres out of 168 global sites. The countries with the most sites were Japan (20), America (14), Brazil (12), Germany (12) and Poland (10).

A limitation to the applicability of the NIAGARA trial results to the NHS setting is the control arm, which does not capture the potential use of adjuvant nivolumab after NAC and RC in PD-L1 positive patients at high-risk of recurrence after RC. In addition, there is uncertainty about the applicability of the demographics of the NIAGARA trial participants to the NHS population eligible for treatment with perioperative durvalumab.

Firstly, in NHS practice, a subset of patients who undergo RC and are at high risk of recurrence with PD-L1 positive tumours are offered adjuvant nivolumab, in line with current NICE guidance. This option was not available in the NIAGARA control arm, where patients received no adjuvant therapy. Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence and PD-L1 positive was recommended by NICE in August 2022, and recruitment for NIAGARA finished in July 2021.¹⁸ In response to a clarification request from the EAG (question A8), the company reported that just [REDACTED] patients in the control arm received nivolumab as subsequent therapy following trial therapy discontinuation. Consequently, the control arm of the NIAGARA trial does not reflect current NHS practice, in which a proportion of patients at high risk of recurrence are eligible for nivolumab after RC. However, in response to an EAG request, communication from NHS England indicated that only 5-10% of post-RC patients in the NHS would be eligible for adjuvant nivolumab with only 7-8 patients per month starting this regimen in England.

Secondly, as discussed in Section 2.1.1, there is a lack of published evidence on the characteristics of patients with MIBC who are eligible for NAC and RC. The average age of participants in the NIAGARA trial was 64.4 years (SD 8.94), and 81.8% were male (18.2% female), which was comparable across arms. One clinical adviser to the EAG noted that although the trial population was considered broadly representative of patients undergoing RC, patients treated in UK clinical practice tend to be slightly older. One of the company's clinical advisers similarly stated that the median baseline age in the trial was younger than the typical UK patient, estimated to be 70 years old.¹⁹

Based on information from the Systemic Anti-Cancer Therapy (SACT) data set and BAUS MITRE audit⁶ one of the EAG's clinical advisers suggested a median age closer to 70–76 years for MIBC patients. The EAG agrees with the company that the BAUS MITRE audit reports on a broader MIBC population than the population in scope, and that this general population can be expected to be older and less fit than patients eligible for NAC and RC (see clarification response A2).

The EAG notes that the target population of patients eligible for perioperative durvalumab represents a very small proportion of the overall UK MIBC population. In response to an EAG request, communication from NHS England indicated that, patients with resectable MIBC receiving neoadjuvant cisplatin-based chemotherapy have a mean age of 66 years with 75% being male. These figures are broadly consistent with the NIAGARA trial population (mean age 64.4 years; 81.8% male). However, the NHS England estimates were from data in the Northeast of England only, with the reporting period and patient numbers not specified, which raises uncertainty about applicability to the wider NHS setting.

The extent to which the NIAGARA trial population reflects the NHS population is therefore uncertain. This uncertainty is also relevant to the company's economic model (Section 4.2.5.2), because the modelled baseline age has an impact on the cost-effectiveness results. Given the potential implications for cost-effectiveness estimates, the EAG considers this a key issue.

3.2.5 Patient disposition

Patient disposition in the NIAGARA trial is summarised in Table 6 and Figure 3 in CS appendix B. A total of 1,063 patients were randomised in the NIAGARA trial between 16 November 2018 and 23 August 2021, with 533 assigned to the perioperative durvalumab arm and 530 to the control arm. Nearly all patients (99%) received the allocated study treatment. Of these, 78.7% in the durvalumab arm and 74.0% in the control arm completed neoadjuvant treatment.

Neoadjuvant treatment was discontinued for 21.3% of patients in the durvalumab arm and 26% in the control arm. The most common reason in both arms was adverse events (15.5% in the durvalumab arm and 15.2% in the control arm). In response to clarification question A4a, the company stated discontinuation of neoadjuvant therapy did not necessarily preclude patients from undergoing RC. In the durvalumab arm, 88% underwent RC compared with 83.2% in the control arm.

Of those in the durvalumab arm who had surgery, 72.3% initiated adjuvant durvalumab with 53.8% completing all eight cycles. Nineteen percent of patients who had surgery did not start adjuvant treatment. The company identified reasons in a subset of these patients: permanent discontinuation of durvalumab during the neoadjuvant phase without reinitiation (n=19), post-surgical death due to

adverse events (n=14), or post-surgical disease progression (n=9). No specific reason was recorded for the remainder.

A small number of participants in the durvalumab arm (n=6; 1.1%) entered a non-cystectomy extension phase during which they received durvalumab 1500 mg as monotherapy every 28 days for a maximum of eight doses. Participants could enter the non-cystectomy extension phase if they refused RC at the specified time after achieving a complete clinical response and without additional interventions. Participants in this group were included in the ITT population for survival outcomes, HRQoL, and safety analyses.

Clinical advisers to the EAG considered the rates of treatment completion, discontinuation, and surgical uptake to be consistent with clinical expectations in the NHS. They noted that three to four cycles of NAC are standard in practice, with early discontinuation in patients experiencing renal decline, neuropathy, or bladder-related complications. Clinical advisers also noted that such patients often remain operable and may still be eligible for adjuvant immunotherapy such as nivolumab. Overall, patient flow and retention were broadly comparable between arms, with no major imbalances that would limit the interpretation of trial results.

3.3 Critique of the results of the trials of the technology of interest

3.3.1 Efficacy

3.3.1.1 Overview of NIAGARA efficacy endpoints

The company report results for the ITT population for the primary outcomes EFS evaluated by blinded independent central review (BICR) and pCR evaluated by blinded central pathology review (BCPR), and a range of secondary and exploratory outcomes (Table 7).

The latest data cut-off (DCO) was 29th of April 2024. At this time, 433 EFS events and 305 OS events had been recorded. Data on pCR from the first DCO (14 January 2022) was re-analysed following the discovery of a mistake in the earlier calculations. Post-hoc analyses were conducted for EORTC QLQ-C30 and EQ-5D-5L to correct for a programming error leading to missing data.

Further analyses are planned when the EFS data have reached 451 events (43% maturity), and when the OS data have reached 428 events (41% maturity) across arms (CS Table 11, pp. 44-45).

3.3.1.2 Results for outcomes informing the economic model

The economic model is informed by data on EFS, MFS, and OS from NIAGARA for the perioperative durvalumab and control arms (Section 4.2). The outcome data from NIAGARA used in the indirect comparison between perioperative durvalumab (and NAC) with NAC followed by nivolumab in PD-L1 positive patients at high risk of recurrence include EFS, MFS and OS (see

Section 3.5 for details) and is used in the company's scenario analysis. The outcome called MFS in the NIAGARA trial is called distant metastasis free survival (DMFS) in the CheckMate-274 trial of nivolumab used in the indirect comparison. We will use MFS throughout this report as outcomes were comparable (see Section 3.4.1.2 for further details).

The percentage of participants in NIAGARA undergoing RC is used to apply a one-off cost and quality-adjusted life year (QALY) decrement associated with RC in the model.

Results are reported in the company submission in Table 6 (pp. 38-39) and CSR Table 29 (p. 123) for proportion of patients undergoing RC, Section 2.6.1.1 for EFS (pp. 50-52), Section 2.6.2.1 for OS (pp. 53-57) and Section 2.6.2.4 for MFS (pp. 57-59). A summary is provided in Table 10.

Table 10 Summary of key efficacy results from NIAGARA (DCO 29 April 2024)

Outcome	Perioperative durvalumab arm (N=533)	Control arm (N=530)
Proportion of patients undergoing RC		
RC, n (%)	469 (88.0)	441 (83.2)
Odds Ratio, 95% CI		
EFS		
Total EFS events	187 (35.1)	246 (46.4)
Median EFS (months), 95% CI	NR	46.1
EFS rate at 12 months, 95% CI	76.0 (72.0; 79.4)	69.9 (65.7; 73.7)
EFS rate at 24 months, 95% CI	67.8 (63.6; 71.7)	59.8 (55.4; 64.0)
Hazard ratio, 95% CI	0.68 (0.59; 0.82)	
OS		
Deaths, n (%)	136 (25.5)	169 (31.9)
Median OS (months)	NR	NR
Survival rate at 12 months, 95% CI	89.5 (86.6; 91.9)	86.5 (83.3; 89.2)
Survival rate at 24 months, 95% CI	82.2 (78.7; 85.2)	75.2 (71.3; 78.8)
Hazard ratio, 95% CI	0.75 (0.59; 0.93)	
Survival rate at 60 months, 95% CI (OS at 5 years)		
Hazard ratio, 95% CI		
MFS		
Distant metastasis, n (%)	54 (10.1)	77 (14.5)
Death in the absence of distant metastasis, n (%)	98 (18.4)	124 (23.4)
Median MFS survival (months)	NR	NR
MFS rate at 12 months (%)	84.5 (80.9; 87.4)	80.1 (76.1; 83.4)
MFS rate at 24 months (5)	75.1 (71.0; 78.8)	65.1 (60.6; 69.3)

Outcome	Perioperative durvalumab arm (N=533)	Control arm (N=530)
Hazard ratio, 95% CI	0.67 (0.54; 0.83)	

Abbreviations: CI: Confidence interval; DCO: Data cut-off; EFS: Event-free survival; MFS: Metastasis-free survival; NR: Not reached; OS: Overall survival; RC: Radical cystectomy.

Proportion of patients undergoing RC

A numerically greater proportion of patients in the durvalumab arm underwent RC (Table 10), although the difference was not statistically significant. The EAG's clinical advisers judged the proportion of patients not receiving RC (12% in durvalumab arm, 16.8% in the control arm) to be representative of clinical practice. See Section 3.2.5 for details on the trial participant flowchart.

EFS

EFS is longer for participants in the durvalumab arm compared to participants in the control arm (Table 10), with median EFS reached in the control arm but not in the durvalumab arm.

Kaplan Meier (KM) curves for the two trial arms separate prior to the RC, from two months after randomisation in the neoadjuvant treatment phase (CS Figure 5, p. 51). The company argue this implies a noticeable benefit of durvalumab in the neoadjuvant period (CS p. 50). However, as shown in Table 7, EFS events include time to recurrence, progression or death, and time to expected surgery for patients who do not proceed to RC. Information provided in the CSR and shown in Table 11 shows ████████ in progression prior to RC, but a ████████ of patients with residual disease not proceeding to RC in the control arm (CSR Table 23, p. 106). Reasons for not proceeding with surgery include patient decision, unfit for surgery, death, and study discontinuation (CS Table 6, p. 38). It is not clear that the difference in refusal or failure to undergo RC in patients with residual disease can be explained by differential efficacy of the study treatments.

Table 11 EFS events NIAGARA (full analysis set), based on CSR Table 23.

EFS events	Durvalumab arm (D+G+C) N=533	Control arm (G+C) N=530
Total EFS events, n (%)	200 (37.5)	261 (49.2)
Progression in patients precluding RC	██████	██████
Refused or failure to undergo RC in patients with residual disease	██████	██████
Recurrence of disease after RC	██████	██████
Death in the absence of other EFS events	██████	██████
Partial cystectomy medically not justified	██████	██████

EFS events	Durvalumab arm (D+G+C) N=533	Control arm (G+C) N=530
Failure to undergo delayed cystectomy		

Abbreviations: D+G+C: Durvalumab with gemcitabine and cisplatin; G+C: Gemcitabine and cisplatin; EFS: Event-free survival; RC: Radical cystectomy.

MFS

Median MFS was also not reached at the April 2024 DCO. The hazard ratio showed a benefit of durvalumab compared to neoadjuvant gemcitabine plus cisplatin (Table 10). The KM plot shows a sustained difference in the probability of MFS from around 6 months onwards (CS Figure 9, p. 59). High rates of censoring from approximately 30-32 weeks makes interpretation of results beyond this follow-up duration difficult.

In the response to clarification question A6, the company provided further information regarding the ‘deaths in the absence of distant metastasis’, which encompasses death due to bladder cancer and death not due to bladder cancer. Compared to the control arm, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED].

OS

Median OS was not reached for either trial arm, with 71.1% of participants in the durvalumab arm and 62.8% of patients in the control arm still alive and in follow-up at the time of the April 2024 DCO (Table 10). KM curves diverge from approximately 6 months after randomisation (CS Figure 7, p. 55), showing a greater survival rate for durvalumab compared to the control arm. Five-year OS was a prespecified endpoint and is reported separately in the CS (p.55). However, the immaturity of the OS data, and high rates of censoring from approximately 32 weeks follow-up and limited numbers of patients at risk mean that these results are relatively uninformative.

The EAG requested that the company provide information on the potential confounding effect of subsequent therapies following discontinuation on OS estimates, using trial evidence as appropriate. The information provided showed that very few patients received nivolumab in the comparator arm and that several subsequent therapies received in NIAGARA are not commonly used in the NHS (response to clarification question A8, Table 3).

An analysis of data on PFS-2 (progression or recurrence after the first EFS event) (NIAGARA CSR Section 11.1.3.7) added limited additional information. Because most PFS-2 events were deaths

(durvalumab arm [REDACTED], control arm [REDACTED] of PFS-2 events) (CSR Table 32, p. 126) and rates of censoring were high, the results largely align with the OS results.

The impact of subsequent treatments on OS therefore remains uncertain. Further follow-up data would help to explore the extent to which subsequent therapies may impact on longer-term OS.

3.3.1.3 Results for additional outcomes

Other efficacy outcomes reported include a higher pCR rate for durvalumab versus the control group upon re-analysis of the data at DCO April 2024 (CS section 2.6.1.2, pp. 52-53), improved DSS (CS section 2.6.2.5, pp. 59-60), longer DFS (CS Section 2.6.2.6, pp. 61-62), and greater PFS-2 (CS Section 2.6.2.7, pp. 62-63).

Quality of life

Quality of life was measured using the EORTC QLQ-C30 and EQ-5D-5L questionnaires. A substantial proportion of the data was missing at baseline and later timepoints (compliance 73.1% and 71.7% in the durvalumab and control arms, respectively, for the EORTC QLQ-C30, and 78.2% and 81.1%, respectively, for the EQ-5D-5L) (CS pp.64-65). It is unclear whether data were missing at random, which affects the certainty of the results.

Using the prioritised EORTC QLQ-C30 subscales (Table 7), the company found that mean scores measured at week 25 and week 29 were similar between the study groups, and concluded that perioperative durvalumab does not negatively affect quality of life compared to the control arm. The EQ-5D-5L results similarly showed little difference in mean scores between the study arms at the different follow-up times over the duration of the study.

3.3.1.4 Subgroup analyses

Prespecified subgroup analyses are presented in the CS section 2.7, pp.67-69, including Figure 13 for EFS (p. 68) and Figure 14 for OS (p. 69). Although these analyses are generally underpowered, with low numbers of patients in some subgroups, the EAG is satisfied that the analyses do not show a difference in the efficacy of perioperative durvalumab with neoadjuvant cisplatin-based therapy compared to neoadjuvant cisplatin-based therapy for any of the subgroups.

The NICE scope included PD-L1 status as a possible subgroup analysis (CS Table 1, p. 14), because nivolumab is recommended in the UK for the subgroup of patients with high risk of post-surgery recurrence and PD-L1 $\geq 1\%$. In subgroup analyses, hazard ratios for EFS (CS Figure 13, p. 68) and OS (CS Figure 14, p. 69) were similar for high versus low or no PD-L1 expression at baseline. The company advised caution regarding the emphasis on PD-L1 expression when considering evidence of durvalumab efficacy, arguing that it is not considered relevant in clinical decision-making as the value

of PD-L1 expression as a prognostic marker is unclear and evaluation of PD-L1 status is not required for perioperative durvalumab or NAC. The EAG's clinical advisers agreed.

3.3.2 Safety

The company provide summary of adverse events (AE) in CS Section 2.10 (pp. 91-94), with further detail in CS appendix D. The safety analysis set (SAS) in NIAGARA was defined as all patients who received at least one dose of study treatment. Median duration of durvalumab treatment was 44.0 weeks (range 1-84), with median exposure during the neoadjuvant and adjuvant periods of 12.1 and 32.0 weeks respectively.

Table 10 Overview of duration of exposure, AEs and treatment discontinuation in the safety analysis set.

	Durvalumab arm (D+G+C) N=533	Control arm (G+C) N=530
Duration of exposure to durvalumab (weeks)		
Mean (SD)	33.5 (16.33)	11.6 (3.12)
Median (min, max)	44.0 (1, 84)	12.0 (1, 27)
AEs of any cause		
Event of any grade, n (%)	527 (99.4)	525 (99.8)
Event of grade 3 or 4 ^b , n (%)	368 (69.4)	355 (67.5)
SAE, n (%)	326 (61.5)	287 (54.6)
Event leading to death (%)	27 (5.1)	29 (5.5)
Event leading to discontinuation of trial treatment ^c , n (%)	112 (21.1)	80 (15.2)
Event leading to discontinuation of durvalumab, n (%)	86 (16.2)	-
Event leading to discontinuation of chemotherapy, n (%)	72 (13.6)	80 (15.2)
Event leading to cancellation of surgery ^d , n (%)	6 (1.1)	7 (1.3)
Event leading to a delay in surgery ^d , n (%)	9 (1.7)	6 (1.1)
Treatment-related adverse events		
Event of any grade, n (%)	502 (94.7)	487 (92.6)
Event of grade 3 or 4 ^{b,c} , n (%)	215 (40.6)	215 (40.9)
SAE, n (%)	86 (16.2)	63 (12.0)
Event leading to death ^f , n (%)	3 (0.6)	3 (0.6)
Durvalumab-related event leading to discontinuation, n (%)	42 (7.9)	-

	Durvalumab arm (D+G+C) N=533	Control arm (G+C) N=530
Chemotherapy-related event leading to discontinuation, n (%)	55 (10.4)	64 (12.2)

Abbreviations: AE: adverse event; C: cisplatin; D: durvalumab; DCO: data cut-off; G: gemcitabine; IA-2: second interim analysis; SAE: serious adverse event; SAS: safety analysis set SD: standard deviation; Min: minimum; Max: maximum.

3.3.2.1 Summary of adverse events

AEs were common in both treatment arms, with nearly all patients experiencing at least one AE of any grade (99.4% in the perioperative durvalumab arm vs 99.8% in the control arm). The most frequently reported AEs ($\geq 15\%$ of patients in either arm) included nausea, anaemia, constipation, fatigue, and urinary tract infection. Grade 3 or 4 AEs occurred in a similar proportion of patients across arms (69.4% in the durvalumab arm vs 67.5% in the control arm). The pattern and severity of these events were broadly consistent with the known toxicity profiles of the individual agents.

3.3.2.2 Discontinuation due to adverse events

More patients in the perioperative durvalumab arm experienced AEs leading to permanent discontinuation of any study treatment than in the control arm (21.1% vs 15.2%). Notably, 16.2% discontinued durvalumab, with 7.9% of patients discontinuing due to AEs considered possibly related to durvalumab. In the neoadjuvant period, ■■■ of patients in the durvalumab arm discontinued any study treatment due to AEs, whereas ■■■ discontinued durvalumab during the adjuvant period. This may be clinically relevant given the intention for prolonged adjuvant use. AE-related dose interruptions or reductions were also more common with perioperative durvalumab (57.5% vs 47.0%). These findings suggest a higher overall treatment burden in the durvalumab group.

3.3.2.3 Immune-mediated adverse events (imAEs)

Immune-related toxicities were more frequent in the perioperative durvalumab arm (20.9%) compared to control (3.0%). Most events were low grade, but some, including pneumonitis, hepatitis, renal events, and hypothyroidism, required systemic corticosteroids or led to discontinuation. Hypothyroidism affected over 10% of patients in the durvalumab arm, with most cases unresolved by DCO. The need for endocrine therapy was also considerably higher (12.3% in the durvalumab arm vs 1.7% in the control arm).

3.3.2.4 Serious adverse events (SAEs) and deaths

SAEs were reported in 61.5% of patients in the durvalumab arm and 54.6% in the control arm. The most common SAEs were infections, urinary tract disorders, and incidental prostate cancer detected post-surgery. The proportion of deaths attributed to AEs was similar across groups (5.1% in the

durvalumab arm vs 5.5% in the control arm), with only one AE-related death considered possibly related to durvalumab (cardiorespiratory arrest).

3.4 Critique of studies identified and included in the indirect treatment comparison or multiple treatment comparison

The final scope issued by NICE included NAC followed by RC and adjuvant nivolumab as a comparator. However, the NIAGARA trial did not allow adjuvant nivolumab to be given in the G+C arm (control arm), for patients that would be eligible for adjuvant nivolumab in NHS practice (PD-L1 positive tumours at high risk of recurrence, see Table 6). Therefore, a direct comparison of perioperative durvalumab with NAC (D+G+C) to NAC followed by no additional adjuvant treatment or adjuvant nivolumab for eligible patients (G+C+N) is not available.

The comparison between perioperative durvalumab (D+G+C) and adjuvant nivolumab (G+C+N) is complicated by, among other factors, the difference in the decision point for treatment in NHS clinical practice, and consequent differences in the populations. In NHS clinical practice, eligibility for adjuvant nivolumab is decided only after RC, based on PD-L1 status and risk of recurrence. Thus, patients are only eligible for nivolumab if they have successfully undergone NAC, RC and have PD-L1 positive tumours at high risk of recurrence. Eligibility for perioperative durvalumab is decided prior to RC, based on eligibility for NAC, thus some patients eligible for perioperative durvalumab will end up not completing the course of neoadjuvant treatment, or not having surgery. In addition, PD-L1 status will not necessarily be known at the point of eligibility for perioperative durvalumab, nor will it be known if the cancer will be at high risk of recurrence post-surgery (since eligibility for perioperative durvalumab is determined pre-surgery).

Whilst the company acknowledged that adjuvant nivolumab is a relevant treatment option in NHS clinical practice, due to the differences in decision time points the company claimed that the overlap between patients eligible for perioperative durvalumab and adjuvant nivolumab is minimal. Therefore, a comparison of perioperative durvalumab with the use of adjuvant nivolumab in high-risk PD-L1 positive patients following NAC and RC was only considered as a scenario in the company's cost-effectiveness analysis and not included in the company's base case (Section 4.2.4.2).

As no direct evidence for the comparison between perioperative durvalumab and NAC followed by no treatment or adjuvant nivolumab was identified, the company conducted an indirect treatment comparison (ITC) (CS Section 2.9). The systematic literature review (Section 3.1) identified the CheckMate-274 RCT as the only trial aligned with the NICE final scope of this appraisal and relevant to the UK clinical setting that considered adjuvant nivolumab after NAC.²⁰

3.4.1 Trial design and participants

CheckMate-274 was a phase III, parallel double-blind RCT. A total of 709 patients with muscle-invasive urothelial carcinoma were randomised to adjuvant nivolumab or placebo after RC.²⁰

Patients with urothelial carcinoma were eligible to enrol in CheckMate-274 if they had received prior radical surgery within 120 days from randomisation, with or without neoadjuvant cisplatin-based chemotherapy, and were at high risk of recurrence (pathological stage of pT3, pT4a, or pN+ and not eligible for or declined adjuvant cisplatin-based combination chemotherapy for patients who had not received neoadjuvant cisplatin-based chemotherapy and pathological stage of ypT2 to ypT4a or ypN+ for patients who received neoadjuvant cisplatin). See Section 2.1.1 for an explanation of disease stages.

Participants received adjuvant nivolumab (240 mg intravenously) or placebo every two weeks for up to a year after surgery. In the ITT population, 43% of participants had received neoadjuvant cisplatin (308 out of 709).²¹

In order to match nivolumab patients to the TA817¹⁵ indication, which focused on a narrower population of high-risk patients with PD-L1 $\geq 1\%$, only subgroup data from CheckMate-274 were included in the indirect treatment comparison. However, data for the subgroup matching the decision problem were not available. This is further discussed in Section 3.5.1.

3.4.1.1 Study population

The NIAGARA and CheckMate-274 participants start the trial at different points in their treatment pathway. NIAGARA participants were randomised to receive neoadjuvant durvalumab plus chemotherapy (gemcitabine and cisplatin) or chemotherapy alone (gemcitabine and cisplatin), prior to RC, followed by adjuvant durvalumab or no treatment regardless of the success of RC, whereas CheckMate-274 participants were only randomised to receive nivolumab after RC if they were deemed at high-risk of recurrence (post-RC). Thus, all participants in CheckMate-274 had surgery and were considered to be at high-risk of recurrence, whilst NIAGARA participants were allocated to trial therapies prior to RC. A proportion of patients in NIAGARA did not receive RC (ITT population: 11.8% durvalumab arm and 15.8% control arm) including some who did not receive RC due to progression or death (ITT population: 2.6% durvalumab arm, 3.2% control arm – see Section 3.2.5).

During TA817, the EAG commented that CheckMate-274 participants were young compared to the patient population expected to be treated in the NHS.¹⁵ Compared to NIAGARA, CheckMate-274 participants were of a similar age, but more likely to be female. In terms of disease characteristics, CheckMate-274 participants were worse affected in their daily activity (NIAGARA 78.4% ECOG 0,

CheckMate-274 60.2% ECOG 0) and their disease had progressed further (NIAGARA 94.5% N0, CheckMate-274 45.9% N0).

No baseline characteristics were available for the subset of patients from CheckMate-274 with MIBC, prior NAC, PD-L1 $\geq 1\%$ and high risk of recurrence. Therefore, the applicability of CheckMate-274 to the NHS, and the comparability of the CheckMate-274 and NIAGARA relevant subpopulations are uncertain. This is further discussed in Section 3.5.1.1.

3.4.1.2 *Study endpoints and analyses*

A summary of differences in endpoints and analyses between the NIAGARA (EFS, OS) and CheckMate-274 results (DFS, OS) is presented in CS Table 24. In response to a clarification request from the EAG (question A19), the company provided results for DMFS, which, like DFS, were informed by an extended three-year follow-up analysis from CheckMate-274.²¹ There was uncertainty regarding the source of OS results, which is discussed in Section 3.5.1.1.

In NIAGARA, EFS included events in both the neoadjuvant and adjuvant phases (see Table 7). In CheckMate-274 DFS was defined as the time between randomisation (start of adjuvant phase) and first recurrence (local or distant) or death. The EAG agrees with the company that EFS as defined in NIAGARA covers different phases of treatment compared to DFS, so EFS and DFS cannot be directly compared across studies. However, in the context of the ITC, the EAG considers that the company's pragmatic decision to use DFS from CheckMate-274 to inform EFS in the adjuvant phase of the control arm with adjuvant nivolumab is acceptable.

DFS endpoints in the adjuvant phase are broadly equivalent between the two trials, as they were both measured at a similar timepoint, although the EAG agrees with the company that differences in inclusion criteria between NIAGARA and CheckMate-274 limit direct comparability between the trials for this outcome.

DMFS was defined in CheckMate-274 as the time between randomisation and any non-local recurrence (i.e. outside the urothelial tract, pelvic soft tissue or pelvic nodes below the aortic bifurcation) or death, whichever occurred first. For subjects who remained alive and distant recurrence-free, DMFS was censored on the date of last disease assessment. The definition of DMFS in CheckMate-274 and MFS in NIAGARA both include distant metastases and exclude local metastases (see Table 7). However, the time from randomisation between the two trials differs, as CheckMate-274 only included participants in the adjuvant phase following RC. For the sake of simplicity, DMFS will be referred to as MFS throughout.

OS in NIAGARA captures death in the neoadjuvant and adjuvant phases and for patients who did not undergo RC, whereas CheckMate-274 only measured death after surgery. The EAG agrees with the company that direct comparisons of OS between the trials are of limited relevance.

3.4.2 Critical appraisal

The company reported a critical appraisal of CheckMate-274 as part of the literature review (CS, Appendix B). The Risk of Bias 2 tool was used, and overall ratings per domain are reported.¹⁶ Each domain was found to be at low risk of bias. The EAG broadly agrees with this assessment. Although results for outcome-specific domains (missing outcome data, outcome measurement, reporting) were not reported by outcome, the EAG agrees these domains are at low risk of bias for EFS, MFS, and OS.

As part of the nivolumab appraisal (TA817), the EAG noted that discontinuation due to drug toxicity was substantially higher in the nivolumab arm (14%) than the placebo arm (2.3%).¹⁵ Pneumonitis, rash, colitis, and increased alanine aminotransferase level were among the reasons for discontinuation relating to treatment with nivolumab.²⁰ Clinical advice to the EAG suggests that side effects of nivolumab are normally infrequent, and well-tolerated.

3.5 Critique of the indirect comparison or multiple treatment comparison

The EAG agrees with the company that due to differences in trial design and patient populations at randomisation between NIAGARA and CheckMate-274, standard ITC methods are not suitable for a comparison between perioperative durvalumab with NAC, versus NAC followed by no treatment or adjuvant nivolumab in high-risk PD-L1 positive patients. The EAG agrees with the company that an unadjusted comparison of only the adjuvant phases of both trials would be at high risk of bias.

The company proposed an ITC using a survival time-adjusted approach where survival times for the control arm of the NIAGARA trial are adjusted to simulate a scenario where eligible (high-risk PD-L1 positive) patients received nivolumab instead of no treatment after NAC and RC. The analysis is presented for EFS and OS in the CS (CS, Table 24), and for MFS in response to EAG clarification question A19. An adjusted comparison of safety or tolerability outcomes was not conducted.

The company's survival time-adjusted analysis is based on existing recommendations to adjust for treatment switching²² (where in this case eligible patients who did not have adjuvant treatment are "adjusted" to have nivolumab), which appear to have been appropriately applied and well described in the CS and accompanying appendices, supplemented by additional information provided in response to the clarification questions. However, as far as the EAG is aware, this methodology has not previously been used in the context of the adjustments required in this appraisal and therefore its

performance in this context has not been externally validated. We provide an overview and critique of the proposed method below.

3.5.1 Methods

To simulate the scenario where eligible patients in the control arm of NIAGARA receive adjuvant nivolumab, the company used counterfactual survival time methods where the estimated counterfactual survival time represents the survival time that would have been observed for an individual under a different treatment than the one experienced. A counterfactual control arm was estimated to represent the outcomes of NAC followed by no treatment or adjuvant nivolumab in high-risk, PD-L1 positive patients (G+C+N), for the outcomes of EFS, MFS and OS, which are then used to compare perioperative durvalumab with NAC (D+G+C), to NAC followed by no treatment (G+C). The simulated counterfactual arm G+C+N aligns with the current treatment pathway in the NHS.

The full ITT population of the NIAGARA trial and subgroup data from CheckMate-274 were used for the ITC. Pseudo-IPD were reconstructed from published KM curves from CheckMate-274 post-hoc subgroups and used to conduct the analysis (for further details see Section 3.5.1.1).

For each outcome, the analysis consisted of 3 steps: 1) estimate an acceleration factor (AF) expressing the survival increase associated with adjuvant nivolumab; 2) create the counterfactual survival estimates for survival outcomes; and 3) conduct the ITC to provide relative estimates of EFS, MFS and OS. Following guidance, analyses were conducted with and without re-censoring.^{22, 23} Re-censoring was used to reduce the risk of informative censoring bias (i.e. censoring that is related to prognostic characteristics) in the counterfactual data set which may occur through the adjustment of survival times of eligible 'high-risk' patients but not of ineligible patients in the NIAGARA trial. The methods are briefly described below, with further details provided in CS Section 2.9.2.

First, an AF for the effect of nivolumab compared to placebo was estimated by fitting different acceleration failure time (AFT) models to the pseudo-IPD from both arms of CheckMate-274 subgroup data (Table 12), with a covariate representing treatment. Where standard AFT models were considered to not fit well, models with time-varying effects were also considered for EFS and OS. In response to EAG clarification question A19, the company provided analyses for MFS, although time-varying effects were not considered due to time limitations. The calculation and application of time-varying AFs for EFS and OS is detailed in Section 2.9.2 of the CS with further details provided in response to clarification question A11.

Table 12 CheckMate-274 Kaplan-Meier data informing ITC for DFS and MFS, and alternative sources for OS

Survival outcomes	Population and potential applicability limitations	Median follow-up	HR (95% CI) nivolumab vs. placebo (adjuvant setting)
EFS	Not applicable	Not applicable	Not reported
DFS	MIBC subgroup with PD-L1 $\geq$ 1%	36.7 months	0.44 (0.30 to 0.63)
MFS	Includes mix of patients with and without prior cisplatin neoadjuvant therapy (% unknown)		0.52 (0.35 to 0.78)
OS: Galsky 2024 ^{21, a}	MIUC with PD-L1 $\geq$ 1% Includes 79% MIBC and mix of patients with and without prior cisplatin neoadjuvant therapy (% unknown)	23.4 months	0.56 (0.36 to 0.86) ^a
OS: Milowsky 2025 ^{24, b}	MIBC subgroup with PD-L1 $\geq$ 1%	NR (36.1 months for overall ITT population)	0.48 (0.29 to 0.77) ^b

Sources: Galsky (2024)²¹, Milowsky (2025)²⁴

Note: HR below 1 favours nivolumab

^aclosely matches both the recovered OS K–M curve and the reported survival probabilities at 24 and 36 months (see Figure 11 and Table 61, Appendix B of the CS); ^bmatches CS 2.9.2 and Appendix B, Section B4.2.1.2. No K–M available.

Abbreviations: DFS: Disease-free survival; MFS: Metastasis-free survival; EFS: Event-free survival; OS: overall survival; MIBC: muscle-invasive bladder cancer; MIUC: muscle-invasive urothelial carcinoma; HR: hazard ratio; ITT: intention-to-treat; NR: not reached.

In step 2, the counterfactual survival times were created by applying the AFs for EFS, MFS and OS to patients eligible for adjuvant nivolumab in the ‘adjuvant phase’ (i.e. post-RC) of the control arm of the NIAGARA trial. The AF was applied as a multiplicative factor by which an individual’s survival time is expected to increase when using nivolumab instead of placebo. Survival times up to the adjuvant phase and for patients not eligible for adjuvant nivolumab were unchanged from those observed in the NIAGARA trial.

Step 2 requires the patients in the control arm of the NIAGARA trial who would have been eligible for adjuvant nivolumab to be identified, so that their counterfactual survival times can be calculated. The company identified █ patients from the NIAGARA control arm that fulfilled the criteria for adjuvant nivolumab (see Table 7 in the company’s response to clarification question A15). This is only █% of all patients randomised to the control arm of NIAGARA (n=530), but █% out of the █ patients who underwent surgery and were disease-free at adjuvant visit in the control arm of NIAGARA. Only these █ patients have their survival times “adjusted” for having adjuvant nivolumab instead of no adjuvant treatment. Therefore, the assumption that the proportion of nivolumab eligible patients in the NIAGARA trial (█% of all randomised patients or █% of patients who underwent surgery) is reflective of NHS practice is crucial for the validity of the

adjusted survival curves. In response to an EAG request, communication from NHS England indicated that 5-10% of post-RC patients in the NHS are eligible for adjuvant nivolumab with 7-8 patients per month starting this regimen in England.

Cox regression was used to compare the counterfactual survival times in the adjuvant nivolumab arm to the no adjuvant treatment arm in PD-L1 positive high-risk NIAGARA patients for each outcome. Resulting HRs were compared to those obtained in CheckMate-274 to check face validity.

The final step of the ITC compared the survival times of the perioperative durvalumab arm to the counterfactual control arm in the NIAGARA trial where the ■ eligible patients are assumed to have had NAC followed by adjuvant nivolumab, and the remaining patients had NAC followed by no treatment. This was done by analysing the perioperative durvalumab arm (with NAC, D+G+C), the NAC followed by no treatment or adjuvant nivolumab (G+C+N), and the NAC followed by no treatment arms (G+C), as if a 3-arm trial had been conducted. Because all patients were included in the NIAGARA trial, the company was able to use a stratified Cox-regression analysis as all baseline participant characteristics are known (see CS Section 2.9.2, Step 3, for details). Confidence intervals were obtained by bootstrapping to capture uncertainty in the estimated HRs.

Additional piecewise analyses were conducted to obtain HRs comparing the NAC followed by adjuvant nivolumab arm (G+C+N) with the NAC-only arm (G+C) over the first 6 months and post-6-months to use in the company's scenario that presents cost-effectiveness results with adjuvant nivolumab.

3.5.1.1 Sources of CheckMate-274 results data

In the absence of access to IPD, no efficacy data was available from CheckMate-274 specifically for the subgroup of patients with MIBC with prior NAC, PD-L1 $\geq 1\%$ and at high risk of recurrence. The ITC required KM data from CheckMate-274 to be available to generate pseudo-IPD. Whilst KM curves were available to inform the MIBC with PD-L1 $\geq 1\%$ subgroup from CheckMate-274 for DFS and DMFS (Galsky et al. 2024²¹), and a separate conference presentation reported an HR for the MIBC with PD-L1 $\geq 1\%$ subgroup analysis of OS,²⁴ the EAG could not identify a corresponding OS KM curve for this subgroup from the references provided by the company. Table 12 presents a summary of the evidence used to recover pseudo-IPD for EFS and MFS, and two possible OS data sources.^{21, 24} The exact source of subgroup data from CheckMate-274 used by the company to inform the ITC for OS is unclear.

In response to a request for clarification, the company provided a summary of the availability of baseline characteristics and efficacy data from CheckMate-274 subgroups (see response to clarification question A16b). The company argued that, given the available data, subgroup analyses

for MIBC patients with PD-L1 $\geq 1\%$ are most appropriate to inform the ITC. The company stated that the MIBC PD-L1 $\geq 1\%$ subgroup from CheckMate-274 was preferred as it most closely aligns with the NICE recommendation for adjuvant nivolumab. Although this subgroup includes patients both with and without prior NAC, the company noted the lack of evidence of whether prior cisplatin use is an effect modifier for nivolumab in patients with PD-L1 $\geq 1\%$ MIBC, and that using alternative data from a subgroup with MIBC with prior cisplatin regardless of PD-L1 expression would not be in line with the UK label and NICE recommendations for adjuvant nivolumab.

The EAG agrees that, given the limited evidence, the company's preferred choice of subgroup from CheckMate-274 to inform the ITC is justified. However, baseline characteristics for the PD-L1 $\geq 1\%$ and MIBC subgroup were not available, making the comparability of the CheckMate-274 and NIAGARA relevant subpopulations uncertain. The comparison of baseline characteristics between subgroups from NIAGARA (n=■) and CheckMate-274 (n=140) provided in response to an EAG clarification request (question A16, Table 9) is of limited relevance; although all CheckMate-274 participants have PD-L1 $\geq 1\%$, they include a broader MIUC population, a mix of patients with and without prior neoadjuvant cisplatin, and no data on tumour stage. It is also unclear to the EAG whether the CheckMate-274 subgroup characteristics in this table are those of the subgroup whose survival curves informed the ITC.

3.5.2 Results

Flexible parametric survival models were fitted to the EFS (DFS in CheckMate-274), MFS and OS KM curves generated from reconstructed IPD from CheckMate-274. For EFS, although the generalised gamma curve provided the best fit it appeared to underestimate survival for the nivolumab arm, so the log-logistic AFT was selected as the most conservative (it provided more optimistic results for nivolumab) and used in the base case ITC. Spline models with time-varying effects were also fitted and the 3-knot spline was used to estimate the AF in a sensitivity analysis (results are presented in Appendix B of the CS, which are similar to those obtained using the log-logistic – see also response to clarification question A13). For MFS all parametric models displayed poor fit to the data (see Figure 2 in the Appendix to the company's response to clarifications). Although the generalised gamma had the best fit, it again appeared to underestimate survival on nivolumab, predicting the lowest AFT for nivolumab compared to placebo so the log-logistic was chosen as the most conservative (spline models were not considered due to limited time). For OS all standard parametric models fitted well and yielded similar AFs so time-varying models were not considered. The log-normal was selected as the best fitting model. The AFs used for EFS and OS are given in Table 27 of the CS, and the AF for MFS is given in page 5 of the Appendix to the company's response to clarification questions. The AF is largest for EFS, slightly reduced for MFS and lowest for OS although all indicate improved outcomes on adjuvant nivolumab compared to placebo.

Consequently, applying the estimated AFs for nivolumab eligible patients in the NIAGARA control arm, improved all survival outcomes for these patients as expected (see Figures 17 and 18 in the CS and Figure 5 in the Appendix to the company’s response to clarifications).

Cox regression after applying the AFs for EFS, MFS and OS to the post-RC KM data of the ■■■ eligible patients in the NIAGARA control arm was used to estimate the HRs for adjuvant nivolumab compared to no adjuvant treatment in these patients. These are presented in Table 13 along with the corresponding HRs estimated in CheckMate-274. Although HRs for EFS and OS estimated in NIAGARA (using counterfactual survival times) are fairly similar to those in CheckMate-274, the MFS HR estimated for the NIAGARA patient population is more favourable for nivolumab than the one observed in CheckMate-274. All HRs estimated for NIAGARA are more uncertain than in CheckMate-274 and all suggest a greater benefit of adjuvant nivolumab compared to no treatment.

Table 13 HRs (95% CI) comparing adjuvant nivolumab to no adjuvant treatment in high-risk PD-L1 patients in the NIAGARA trial (using counterfactual survival times) compared to the relevant CheckMate-274 subgroup

Survival outcomes	NIAGARA (counterfactual)	CheckMate-274 (subgroup)
EFS	■■■■■	0.44 (0.30 to 0.63) ^a
MFS	0.40 (0.29 to 0.99)	0.52 (0.35 to 0.78)
OS	■■■■■	0.48 (0.29 to 0.77) ^b

Note: HR below 1 favours nivolumab.

Abbreviations: MFS: Metastasis-free survival; EFS: Event-free survival; OS: overall survival; HR: hazard ratio.

^a DFS results; ^b Milowksy (2025)²⁴, MIBC subgroup with PD-L1

The ITC was carried out using the adjusted survival times for EFS, MFS and OS with and without the application of re-censoring. Because the effect of nivolumab is to extend survival times, without re-censoring survival times for the G+C+N arm extend far beyond the observed period. Application of re-censoring leads to similar follow-up times across all arms and is the company’s preferred analysis. The EAG agrees that results using re-censoring are preferred. The KM curves and HRs for EFS, MFS and OS for perioperative durvalumab (D+G+C) compared to the counterfactual control arm which includes nivolumab for eligible patients (G+C+N) and the no adjuvant treatment control arm (G+C) are presented in Figure 19 and Table 28 of the CS, Figure 6 and Table 4 of the Appendix to the company’s response to clarifications, and Figure 20 and Table 29 of the CS, respectively.

The use of the “adjusted” survival times for the nivolumab eligible patients in NIAGARA led to a separation in the EFS, MFS and OS curves favouring G+C+N versus G+C. Because this separation only applied to the adjuvant period (all patients receive the same treatment up to RC) there is a delay in the separation of survival curves, thus the treatment effect for G+C+N versus the G+C varies over

time. To account for this in the cost-effectiveness model, the company estimated the survival-time adjusted hazard ratios for G+C+N versus G+C for 0 up to 6 months and beyond 6 months, in a piecewise Cox regression analysis. The 6-month cut point was selected to coincide with the start of adjuvant treatment in the economic model, and it also matches the time point at which the G+C and G+C+N curves start to separate and the expected timing of adjuvant therapy in practice. In response to clarification question A22, the company provided Schoenfeld residual plots for G+C+N versus G+C for EFS, MFS and OS after 6 months which support the assumption of an approximately constant and proportional effect in the post-6 months period. Whilst it is generally good practice to explore the impact of alternative cut-points in piecewise models, the EAG considers the 6-month cut-point to be clinically appropriate, reflecting the expected timeframe for starting adjuvant therapy. The EAG also considers that small variations around the 6-month cut-point would have minimal impact on cost-effectiveness results. In response to EAG clarification question A22b, the company provided an updated model enabling independent extrapolation for EFS using a spline-based model with a 3-knot hazard. However, as the proportional hazards assumption does not appear to be violated for any survival outcome, the company's piecewise approach is appropriate for use in the economic model.

As explained by the company in the response to clarification question A20, the ITC focused on efficacy rather than safety outcomes. The company therefore described the safety profile of CheckMate-274 without a formal comparison with NIAGARA. Patients in the adjuvant nivolumab arm were more likely to experience any grade or grade 3 or above treatment-related adverse events compared to placebo. Immuno-mediated adverse events were observed in 34.5% of the nivolumab arm and 6.9% of the placebo arm. The company state that the higher rates of adverse events and grade 3+ adverse events in the NIAGARA trial are explained by the side effects of chemotherapy, which is not given in the adjuvant phase.

3.5.3 EAG comments

The lack of a randomised comparison between perioperative durvalumab and current NHS practice (that is, NAC followed by RC and no adjuvant treatment or adjuvant nivolumab for high-risk PD-L1 positive patients) is a significant limitation of existing evidence. The CheckMate-274 RCT compared adjuvant nivolumab in the high-risk PD-L1 positive population but the limited comparability in designs and populations between NIAGARA and CheckMate-27 precludes standard comparisons. An ITC was conducted using an adjusted survival time approach based on post-hoc subgroup data from CheckMate-274 that included patients with and without prior NAC. The ITC relies on AFs calculated from CheckMate-274 which requires the assumption that the effect of adjuvant nivolumab is exchangeable across the CheckMate-274 and NIAGARA trials, i.e. that the effect of nivolumab compared to placebo observed in CheckMate-274 also applies to the patients in the adjuvant phase of

NIAGARA. However, the subgroup data available from CheckMate-274 does not fully match the population of high-risk PD-L1 positive, MIBC patients who received NAC (only a minority of patients in CheckMate-274 received NAC). It is unclear whether previous NAC is a treatment effect modifier for adjuvant nivolumab but if it is, the estimated AFs may not be transferrable to the NIAGARA population, leading to possible bias in the adjusted survival times.

The ITC also relies on adjusting survival times in the adjuvant phase for NIAGARA patients who would have been eligible for adjuvant nivolumab in NHS practice (■■■% of all randomised patients or ■■■% of patients who underwent surgery). The proportion of patients assumed to have received nivolumab in the ITC is therefore higher than NHS England's estimate of 5-10% of patients who had NAC followed by RC eligible for adjuvant nivolumab. However, the ITC method can only be used to create counterfactual survival times for patients in NIAGARA who fulfilled criteria for adjuvant nivolumab. If a lower proportion of patients are eligible for adjuvant nivolumab in clinical practice, the adjustment may overestimate the additional benefit of nivolumab in the NHS population.

The company compared the HRs of adjuvant nivolumab compared to no adjuvant treatment obtained from the adjusted analysis in eligible NIAGARA patients to the original HRs in CheckMate-274 (Table 13). All HRs from the adjusted analyses were more favourable to nivolumab than the HRs estimated in CheckMate-274, suggesting that the company's analyses may be conservative, i.e. they may overestimate the benefit of adjuvant nivolumab. This may somewhat mitigate the concerns regarding comparability of the populations in NIAGARA and CheckMate-274.

Due to the separation of the adjusted survival curves in the adjuvant period, the company carried out additional piecewise ITC over the first 6 month and post-6 months. The EAG believes it is inconsistent to present results for the whole period as the main results from the ITC, but then use the piecewise results in the economic model. However, the EAG agrees that the piecewise results better reflect the effect of adjuvant nivolumab as the proportional hazards assumption appears to hold beyond 6 months for all survival outcomes and the cut-off point at 6 months is justified. Therefore, the EAG agrees that the HRs from the piecewise analyses should be used in the economic model.

Overall, the EAG believes that the methods used by the company to adjust the survival times are appropriate. The lack of consideration of spline models for the ITC of MFS despite the poor fit of parametric models is a limitation, although it is unclear whether this would have meaningfully impacted the results. The ITC results are also associated with uncertainty due to the non-randomised nature of the comparison and required assumptions.

The lack of an ITC for safety outcomes was justified by the company and a narrative summary provided in response to a clarification request, although this is still a limitation. The relative safety of perioperative durvalumab compared to adjuvant nivolumab in eligible patients is uncertain.

3.6 Additional work on clinical effectiveness done by the EAG

None.

3.7 Conclusions of the clinical-effectiveness section

The clinical evidence submitted by the company was generally clearly presented. The evidence on the efficacy and safety of perioperative durvalumab in combination with neoadjuvant cisplatin-based therapy for MIBC comes from NIAGARA, an ongoing multicentre, open-label RCT. There is some uncertainty about the comparability of the trial participants to the NHS population. The EAG found NIAGARA to be at low risk of bias for EFS, MFS and OS; however, participants and care providers were not blinded for treatment allocation, which means that HRQoL results are at high risk of bias. At the 29 April 2024 data cut-off, median OS and MFS were not reached in either trial arm, and median EFS was only reached in the control arm. The NIAGARA trial provided statistically significant evidence that perioperative durvalumab improved EFS, MFS and OS compared to the control arm. Quality of life was similar between the two study arms. Participants in the durvalumab arm were more likely to experience immune-related adverse events and SAEs, which the EAG's clinical advisers judged to be consistent with the known safety profile of the treatments.

No direct evidence was available for the comparison between perioperative durvalumab and adjuvant nivolumab. It was not possible to indirectly compare evidence from NIAGARA and the CheckMate-274 trial of nivolumab using conventional methods, due to the differences in trial populations and designs so the company adapted methods commonly used to adjust for treatment-switching to perform the analyses. The EAG considers the company's approach for the ITC justified. Overall, this showed an improvement in outcomes in the control arm of NIAGARA where eligible patients were given adjuvant nivolumab (counterfactual control arm) but HRs for perioperative durvalumab compared to NAC alone or with adjuvant nivolumab for eligible patients suggested greater benefit for perioperative durvalumab for EFS, MFS and OS. However, the results of the ITCs are uncertain as they rely on the assumption that the effect of adjuvant nivolumab is exchangeable between CheckMate-274 and NIAGARA trials, although there is insufficient evidence to support this. In addition, the applicability of CheckMate-274 participants and results (EFS, MFS, OS) to the NHS population is uncertain. Finally, the relative safety of perioperative durvalumab versus NAC alone or followed by adjuvant nivolumab for eligible patients is uncertain as safety outcomes were not included in the ITC.

4 COST-EFFECTIVENESS

This section presents a summary and critique of the cost-effectiveness evidence included in the company's submission. Section 4.1 focuses on the company's review of the cost-effectiveness evidence from previous studies and section 4.2 covers the company's economic evaluation.

4.1 *Critique of the review of cost-effectiveness evidence*

4.1.1 Summary of company's submission

The company's systematic literature review did not identify any economic evaluations of durvalumab for the treatment of adults with MIBC (see Appendix E of the CS for a detailed description of the searches and results of the review). Three UK-based studies were identified that evaluated adjuvant nivolumab in MIBC, including NICE Technology Appraisal 817 (TA817) of nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence, published in 2022.^{15, 25, 26} In all three studies identified, the models reported were structurally identical and based on the same underlying evidence.

In addition, the company undertook a targeted search of previous appraisals published by NICE, the Australian Pharmaceutical Benefits Advisory Committee (PBAC) and Canada's Drug Agency (CDA-AMC) to compare modelling approaches in cost effectiveness analyses conducted for therapies in MIBC and oncology therapies in the perioperative setting outside of MIBC. From the targeted search for therapies in MIBC, two further appraisals for adjuvant nivolumab by PBAC and CDA-AMC (PC0272-000) were identified,^{27, 28} while in the perioperative setting outside MIBC, two appraisals were considered – pembrolizumab for triple-negative breast cancer (TA851)²⁹ and durvalumab for non-small cell lung cancer (TA1030).³⁰ The company provides a description of the studies identified in Section 3.1.2 of CS.

4.1.2 Points for critique

The literature searching for the company's review of cost-effectiveness evidence appears to have been conducted to a high standard and is well reported – See Appendix 2 for details. The EAG considers that all relevant publications are likely to have been identified.

The company's review of identified studies, reported in Section 3.1.2 of the CS, indicates that all previous studies used semi-Markov or Markov models to assess the cost effectiveness of the intervention under consideration, which differs from the company's *de-novo* approach using partitioned survival modelling (see Section 4.2.2 below). The company states that the use of semi-Markov state transition modelling in previous appraisals was motivated by the lack of OS data available at the time of the submissions for nivolumab (TA817) and pembrolizumab (TA851), while

OS data are available from the NIAGARA trial to allow a partitioned survival modelling approach (PSM) for durvalumab. However, the EAG notes that the use of semi-Markov state transition modelling versus PSM did not form part of the committee discussions in TA817 and TA851 and, therefore, the appropriateness of PSM for modelling therapies in MIBC has not been considered to date. Instead, previous committee discussions have centred on the assumptions used for the modelled health states and treatment lines, and the assumptions required to translate improvements in disease-free survival to OS when modelling long-term effects of treatment.

The company highlights that in the PBAC and CDA assessments of nivolumab, concerns were expressed about the use of a single health state for disease recurrence. Therefore, for durvalumab, the company splits disease recurrence into locoregional and distant metastasis health states to better reflect differences in outcomes post-recurrence in these health states. The EAG also notes that in TA817 for adjuvant nivolumab, the committee expressed concern that post-recurrence outcomes were not robustly modelled because the model did not allow for the consideration of survival outcomes from further treatment lines. The use of a standard PSM (progression-free and first occurrence of progressed disease) for durvalumab means that the model cannot explicitly consider the impact of subsequent treatments on survival outcomes, which the EAG considers to be a limitation from previous studies that the company's *de-novo* model for durvalumab has not addressed (see Section 4.2.2.2).

Previous studies for nivolumab have assumed a cure point at 5 years, with no disease recurrence after 5 years in the DFS state, which was supported by evidence from the CheckMate-274 trial (adjuvant nivolumab compared to placebo) in MIBC, showing that the risk of death approaches that of the general population at 5 years. However, the committee for TA817 also considered external evidence demonstrating an increased mortality risk for people with resected urothelial cancer compared with the general population, even after 5 years in a disease-free state. The committee concluded that there is evidence that disease recurrence may take place after 5 years and mortality risks remain elevated; therefore, it remains uncertain at what time point it is reasonable to assume that people are cured from cancer.¹⁵ In the company's *de-novo* model for durvalumab, the model does not include an explicit cure assumption, but it implicitly captures 'cure' through the selection of extrapolation curves to survival outcomes that imply decreasing hazards of events as observed in the follow-up period of the NIAGARA trial (see Section 4.2.5).

The review of previous appraisals also highlights the need to carefully consider the current standard of care as a relevant comparator in the economic analysis, even if the trials only include a placebo comparator arm. In TA817, the committee considered that adjuvant platinum-based chemotherapy was likely to be a suitable treatment option for people with urothelial carcinomas of the upper urinary tract and concluded that, when suitable, it is a relevant comparator. However, because the committee

had not been presented with any cost-effectiveness results comparing nivolumab with platinum-based chemotherapy, and the indirect comparison results showed no statistically significant difference in treatment effect between nivolumab and platinum-based chemotherapy, the NICE recommendation for adjuvant nivolumab was restricted to when adjuvant platinum-based chemotherapy is unsuitable. The population eligible for adjuvant nivolumab is also restricted to those at high risk of recurrence after radical resection in adults whose tumours express PD-L1 at a level of 1% or more, in line with its marketing authorisation in MIBC. The EAG considers that while adjuvant nivolumab and perioperative durvalumab occupy distinct points in the treatment pathway for MIBC and target different populations, the relevance of including adjuvant nivolumab for patients at high risk of recurrence and PD-L1 $\geq 1\%$ (when adjuvant cisplatin-based chemotherapy is unsuitable) as part of the treatment pathway for the neoadjuvant comparator to durvalumab (i.e., neoadjuvant cisplatin-based chemotherapy) needs to be carefully considered in the assessment of the cost-effectiveness of durvalumab in a perioperative setting (see Sections 2.2.2, 3.2.4).

4.2 Critique of the submitted economic evaluation

The company submitted a *de-novo* model to assess the cost-effectiveness of durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment in adults with resectable MIBC, followed by durvalumab as monotherapy adjuvant treatment after RC (referred to as perioperative durvalumab), compared with neoadjuvant gemcitabine and cisplatin (also termed NAC) followed by RC and either (i) no treatment (company's base case analysis) or (ii) adjuvant nivolumab for patients whose tumours express PD-L1 $\geq 1\%$ and present high-risk of recurrence (company's scenario analysis).

A PSM is used to estimate the long-term health outcomes and costs associated with progression and the clinical care pathway of resectable MIBC in the UK for patients eligible for neoadjuvant cisplatin-based chemotherapy prior to RC. In the PSM, the time-dependent risk of disease progression and death is modelled by extrapolating clinical trial endpoints from the NIAGARA trial to directly determine the proportion of patients alive, event-free (defined as no recurrence after RC, no documented progression or residual disease in patients precluded from RC, or death) and metastasis-free (i.e., free of distant metastases) over a lifetime horizon for both perioperative durvalumab and neoadjuvant cisplatin-based chemotherapy. The effects of subsequent anticancer therapies for disease recurrence on post-progression survival are implicitly accounted for in the extrapolated OS curve.

Perioperative durvalumab is modelled to affect QALYs by increasing the proportion of patients who are alive (improvement in OS) and event-free and metastasis-free (associated with improved health-related quality of life) over time relative to neoadjuvant cisplatin-based chemotherapy alone.

Perioperative durvalumab is modelled to affect costs primarily due to the additional drug acquisition and administration costs of durvalumab compared to neoadjuvant cisplatin-based chemotherapy alone. However, this cost is partially offset by lower costs associated with reduced disease progression and subsequent therapy and terminal care costs from improved event-free and metastasis-free survival for durvalumab.

4.2.1 NICE reference case checklist

The model submitted by the company is assessed in relation to the NICE reference case in Table 14.

Table 14 NICE reference case checklist

Element of health technology assessment	Reference case	EAG comment on company's submission
Perspective on outcomes	All health effects, whether for patients or, when relevant, carers	The CS is appropriate.
Perspective on costs	NHS and Personal Social Services	The CS is appropriate.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	The CS is appropriate.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The CS is appropriate. The time horizon is lifetime.
Synthesis of evidence on health effects	Based on systematic review	The CS is appropriate.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The CS is appropriate.
Source of data for measurement of health-related quality of life	Reported directly by patients, carers or both	The CS is appropriate.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The CS is appropriate.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the people having the health benefit, except in specific circumstances	The CS is appropriate.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	The CS is appropriate.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	The CS is appropriate.

CS: company submission; PSS: personal social services; QALYs: quality-adjusted life years; HRQoL, health-related quality of life; EQ-5D: standardised instrument for use as a measure of health outcome.

4.2.2 Model structure

4.2.2.1 Summary of company's submission

The model structure is a four-state PSM comprising health states for event-free (EF), locoregional recurrence (LR), distant metastatic disease (DM) and death (see Figure 21 of CS). The cohort enters the model in the EF health state to begin NAC, with or without perioperative durvalumab, followed by RC, if suitable. The EF state represents the pre-recurrence phase and includes patients who progress before surgery, decline surgery, or are deemed unfit for surgery. From the EF state, patients may transition to LR, DM or death states. LR includes recurrence in MIBC patients who are free of distant metastases, including those who did not undergo surgery, while DM includes patients with distant metastases. The recurrence phase is split into LR and DM to reflect the different prognosis of each state, where DM is associated with poorer survival and lower HRQoL compared to LR. The death state captures all-cause mortality.

The transitions from the EF state to LR, DM or death states are defined by the time-dependent EFS, MFS and OS curves from the NIAGARA trial and extrapolated beyond the available data using parametric models over a lifetime horizon (Section 4.2.5). The proportion of patients alive over time is estimated directly from the OS curve, with the hazard of death constrained to be at or above the corresponding age- and gender-matched all-cause general population risk of death by age. OS is partitioned into the proportion of patients who are alive with DM (OS minus MFS) and the proportion of patients who are alive without DM (MFS). The EFS curve partitions MFS into the proportion of patients who are EF, based on the cumulative survival probabilities of EFS, and those with a non-metastatic recurrence who occupy the LR state (MFS minus EFS). The EFS curve is constrained to values less than or equal to MFS, while the MFS curve is constrained to values less than or equal to OS. The hazard of EFS and MFS is also constrained to be at or above the age- and gender-adjusted all-cause general population risk of death by age. Figure 22 of the CS illustrates the PSM simulation for the four health states in the model.

4.2.2.2 Points for critique

The EAG considers the company's PSM structure to be broadly appropriate because it allows direct modelling of the key NIAGARA trial outcomes of EFS, MFS, and OS. PSM is widely accepted as an appropriate approach for economic evaluations in oncology and has been employed in 73% of NICE oncology submissions reviewed between May 2013-February 2016 in NICE Technical Support Document (TSD) 19.³¹ However, it is important to consider the suitability of PSM in the context of the decision problem and compared to the common alternative of state transition modelling (STM) because PSM and STM can produce substantively different survival extrapolations.³² Previous studies of adjuvant nivolumab for MIBC, along with the two NICE appraisals in the perioperative setting outside MIBC (identified in Section 4.1.1), used STM rather than PSM. The company justified its

approach by citing the availability of mature OS data from NIAGARA, which contrasted with previous NICE appraisals where limited OS data restricted the use of PSM.

The EAG considers the appropriateness of the company's PSM to be largely dependent on the maturity of the observed data informing survival outcomes, particularly OS. The extrapolation of outcomes over a lifetime horizon (see Section 4.2.5) is critical as uncertainty in long-term OS directly leads to uncertainty in the cost-effectiveness estimates. Despite the company's statement of mature OS data from NIAGARA, with a median follow-up of 42.3 months in the perioperative durvalumab arm and 39.6 months in the control arm, the EAG notes that only 305 death events had occurred corresponding to 28.7% maturity for OS overall (Table 17 of CS, OS IA-1 data-cut), and median OS has not yet been reached. Therefore, although the OS data from NIAGARA is relatively mature compared to data available in previous appraisals, it is still not fully mature with fewer than 50% of trial participants experiencing a death event.

One of the main limitations of PSM is that OS is determined independently of other clinical outcomes, including EFS and MFS, i.e., the survival curves that inform the estimates of health state membership are modelled completely independently. Therefore, when the OS data in the company's model is extrapolated over the long-term it is done completely independent of the other endpoints. This structural independence within a PSM makes it very difficult to judge the clinical and biological plausibility of the extrapolations of each endpoint in relation to one another, which is a fundamental difference from STMs where clinical events underlying the extrapolations can be structurally and explicitly related. Although the OS extrapolations in the company's model were validated against external data and expert clinical opinion (Section 4.2.5), the company did not present separate survival curves for pre-progression and post-progression deaths to allow exploration of the treatment effect pre- and post-progression (recurrence) on OS. Furthermore, due to the modelled independence between trial outcomes (lack of structural relationship between endpoints), the extrapolated intermediate outcomes of EFS and MFS may lie above the OS curve (e.g., a higher proportion of patients predicted to be in the EF, LR and DM health states than alive), or the extrapolated EFS curve may be greater than the extrapolated MFS curve. To avoid these logical inconsistencies in the model, the company imposed ad-hoc restrictions to the extrapolated survival outcomes. Specifically, the EFS curve is constrained to values less than or equal to MFS, and the MFS curve is constrained to values less than or equal to OS. While this approach overcomes the limitations of the PSM and is not, in principle, unreasonable, the restrictions do not reflect empirical data or inherent structural links between endpoints. Therefore, it is important to assess the appropriateness of the extrapolated survival curve fits (EFS, MFS and OS) relative to one another to ensure logical consistency across outcomes (Section 4.2.5).

Importantly, the company's model does not account for survival outcomes related to separate clinical events within the post-progression health state, beyond the distinction between LR and DM. This includes outcomes for patients in the post-recurrence period (e.g., post-recurrence events and deaths), which are likely to be affected by subsequent therapy use after recurrence. This means that the extrapolated survival outcomes only reflect subsequent anticancer therapies used in NIAGARA, and the PSM does not allow adjustment to the survival outcomes for the use of different types of post-progression therapies, such as those used in the NHS. Furthermore, the use of external data from metastatic trials cannot be incorporated into the PSM to more accurately reflect outcomes in the DM state. While the separation of the LR and DM states is important in MIBC, the modelled costs of subsequent therapies are expressed as a proportion of all progressed patients (Section 4.2.7). This means that any differences in costs (or benefits) of subsequent therapies cannot be attributed to the individual LR and DM health states, although the EAG's clinical advisor indicated that subsequent therapy costs are expected to be similar between these states.

Additionally, the PSM approach is only valid if patients move progressively through health states to a worse health state. This is a potential limitation if post-recurrence therapies can return a proportion of patients to an event-free state where their health-related quality of life and risk of future events is similar to patients in the pre-recurrence EF health state.

The EAG notes that the NIAGARA trial included a PFS-2 outcome, defined as the time from randomisation to subsequent progression or recurrence post-EFS event, or progression-free survival after second-line therapy. The EAG considers this endpoint important in the perioperative setting because it reflects the durability of treatment benefit beyond the first treatment and could offer greater granularity in modelling of events over time. At the clarification stage, the EAG requested that the company consider amending the existing model structure to incorporate PFS-2 data and, if this was not feasible, to provide qualitative commentary on the potential implications of excluding these data from the existing model structure (EAG clarifications, question B4). In their response, the company states that the exclusion of PFS-2 data from the model was an intentional structural decision, informed by both clinical and modelling considerations, for the following reasons: (i) the model based on the primary EFS and secondary OS and MFS endpoints fully capture the clinical and economic outcomes in the MIBC setting; (ii) the approach is aligned with previous NICE appraisals (TA871,¹⁵ TA683³³ and TA816³⁴) that utilised similar primary and secondary endpoints; (iii) the model structure and selected endpoints have been validated and supported by HTA experts in an advisory board meeting; and (iv) the model structure would require potentially non-standard health state definitions and transition pathways, introducing extra complexity and uncertainty into the model for questionable analytic gain. Whilst the EAG acknowledges these points, the EAG believes that PFS-2 data could provide additional granularity in the area between the EFS and MFS curves by providing information

on the timing and sequence of subsequent events, as well as the impact of subsequent treatments on long-term survival outcomes. This may be particularly important in the perioperative setting, where multiple phases of treatment are considered and long-term outcomes are influenced by both initial and subsequent therapies. PFS-2 data is also gaining increasing interest because it often correlates more strongly with OS than PFS alone,³⁵ especially when subsequent lines of therapy can confound OS. Nonetheless, the EAG notes that [REDACTED] in the NIAGARA trial (Figure 12 and Section 2.6.2.7 of the CS), indicating [REDACTED]. Therefore, it is reasonable to conclude that additional modelling of PFS-2 data from NIAGARA would offer limited further insight.

In summary, while the EAG considers the company's model structure to be appropriate, the EAG considers it important to acknowledge the limitations of the PSM compared to alternative STMs.

4.2.3 Population

4.2.3.1 Summary of company's submission

The target population consists of adults with resectable MIBC who are eligible to receive gemcitabine and cisplatin, in line with the anticipated marketing authorisation for perioperative durvalumab and the population included in the NIAGARA trial. The trial included adults with histologically or cytologically documented resectable MIBC (T2N0/1M0-T4aN0/1M0) who were cisplatin-eligible, candidates for RC, and had not received prior systemic chemotherapy or immunotherapy for MIBC.

The modelled population is based on the baseline characteristics of participants in the ITT population of the NIAGARA trial, with a mean age of 64.4 years, proportion of males 81.8%, and a mean weight of 77.1 kg (see Table 7 of CS).

No subgroups are considered in the model.

4.2.3.2 Points for critique

The EAG is satisfied that the modelled population aligns with the final scope issued by NICE and the anticipated marketing authorisation for perioperative durvalumab. However, as discussed in Section 3.2.1, the EAG has some concerns about the generalisability of the NIAGARA trial population to NHS patients. Specifically, the trial excluded patients with advanced lymph node N2 and N3 disease, and the EAG's clinical advisor considered the NIAGARA population may be younger than patients with MIBC who are eligible for RC in UK clinical practice. Although data provided by NHS England for the North East suggests that patients with resectable MIBC who receive neoadjuvant cisplatin-based chemotherapy have a mean age of 66 years and 75% male, which is not dissimilar to the

average age and percentage of males used in the model. However, it remains uncertain whether this regional data is representative of the whole of England and Wales.

In response to EAG clarifications (questions A2 and A3), the company states that the generalisability of the NIAGARA trial population was discussed with UK-based clinicians who unanimously confirmed that it was reflective of NHS patients eligible for cisplatin-based neoadjuvant chemotherapy. The company was unable to provide a comparison to SACT data and indicated that the BAUS MITRE audit only includes a small subset of patients (8.08% of the overall audit) representative of the target population.

The EAG specifically notes age as important because the cost-effectiveness of perioperative durvalumab is sensitive to the baseline starting age used in the model, where the modelled long-term extrapolation survival curves are adjusted for the corresponding age- and gender-matched general population hazard rates of all-cause mortality (Section 4.2.5).

The EAG considers it reasonable to not consider subgroups in the economic analysis because subgroup analyses from the NIAGARA trial (reported in Section 2.7 of CS) showed consistency in efficacy between the ITT population and the prespecified subgroups, including stratification by tumour PD-L1 expression level, clinical tumour stage, and renal function.

4.2.4 Interventions and comparators

4.2.4.1 Summary of company's submission

The intervention is neoadjuvant durvalumab (1500 mg IV) in combination with gemcitabine (Day 1 and Day 8 at dose 1000 mg/m²) and cisplatin (Day 1 at dose 70 mg/m²) for four cycles every three weeks prior to RC, followed by durvalumab as monotherapy adjuvant treatment after RC for up to eight cycles every four weeks post-surgery. Perioperative durvalumab represents a fixed-duration regimen. In the model, time on treatment for the neoadjuvant and adjuvant phases is based on the observed proportions of participants who received each scheduled cycle in each arm of the NIAGARA trial (Section 4.2.7).

The comparator in the company's base case analysis aligns with the single treatment decision point for perioperative durvalumab, which is made before surgery and determines both pre- and post-RC treatment. For the neoadjuvant period, the comparator treatment is gemcitabine (Day 1 and Day 8 at dose 1000 mg/m²) and cisplatin (Day 1 at dose 70 mg/m²) for four cycles every three weeks prior to RC, i.e., the same as the intervention arm but without durvalumab. For the adjuvant period following NAC and RC, the comparator includes no treatment, which aligns with the control arm of NIAGARA.

The company acknowledges that adjuvant treatment with nivolumab for people at high risk of recurrence after surgery and whose tumours express PD-L1 at a level of 1% or more was included in the NICE scope for this appraisal. In line with NICE TA817, nivolumab is recommended as an option for the adjuvant treatment of muscle-invasive urothelial cancer that is at high risk of recurrence after radical resection in adults whose tumours express PD-L1 $\geq 1\%$, only when adjuvant cisplatin-based chemotherapy is unsuitable. Accordingly, for cisplatin-eligible patients, adjuvant nivolumab is appropriate if the patient has already received NAC.

The company included adjuvant nivolumab (for the subset of patients meeting the treatment criteria) as part of the comparator arm in a scenario analysis only. The company's justification for excluding adjuvant nivolumab from its base case analysis follows:

- Adjuvant nivolumab and perioperative durvalumab occupy distinct points in the treatment pathway, where the decision on nivolumab treatment is only made after surgery: adjuvant nivolumab represents a reactive intervention based on post-surgical assessment and PD-L1 expression status, whereas the perioperative approach is a proactive strategy made pre-RC for all eligible patients.
- The introduction of perioperative durvalumab is expected to displace the use of NAC alone, which in turn will reduce the use of subsequent treatments such as adjuvant nivolumab.
- The control arm of NIAGARA did not include adjuvant nivolumab and the company acknowledges the challenges with conducting comparisons between adjuvant and perioperative settings.

In response to the NICE scope that included adjuvant nivolumab in the comparator, the company conducted a scenario analysis where eligible high-risk PD-L1 $\geq 1\%$ patients received adjuvant nivolumab instead of no treatment after neoadjuvant chemotherapy and RC. For this scenario, counterfactual survival times were estimated for the control arm of NIAGARA using a novel survival time-adjusted ITC approach (Section 3.5).

4.2.4.2 Points for critique

The primary issue with the comparator in the model is whether to include or exclude adjuvant nivolumab for the subset of patients eligible for this treatment. Adjuvant nivolumab is part of the current treatment pathway in the NHS for NAC patients at high-risk of recurrence post-surgery and with PD-L1 $\geq 1\%$. Thus, the appropriate comparator in the model to reflect established standard of care in the NHS should include a proportion of the population who meet the eligibility criteria receiving adjuvant nivolumab.

The NIAGARA trial was not designed to include adjuvant nivolumab in the control arm for the high-risk, PD-L1 $\geq 1\%$ population. Consequently, the control arm does not fully reflect the established standard of care in the NHS. To address this, the company conducted a scenario analysis that includes a proportion of the population receiving adjuvant nivolumab, based on NICE recommendations in TA817. This approach, however, required the company to estimate counterfactual survival times for the control arm of NIAGARA for the proportion of patients eligible for adjuvant nivolumab. As discussed in Section 3.5.3, the EAG acknowledges the limitations of the proposed survival time-adjusted ITC approach but, overall, considers the methods and approach used to include adjuvant nivolumab to be reasonable. Therefore, the EAG considers that the comparator arm should include a proportion of the population receiving adjuvant nivolumab to reflect the current treatment pathway in the NHS.

4.2.5 Treatment effectiveness and extrapolation

4.2.5.1 Summary of company's submission

The model includes three elements relating to the treatment effectiveness and extrapolation of effects from the NIAGARA trial over a patient's lifetime, separated by treatment arm:

- (i) EFS, i.e., the time from initiation of intervention until the first occurrence of one of the following events: recurrence of disease after RC, disease progression in patients precluded from RC, residual disease in patients who refuse or fail to undergo RC, or death due to any cause.
- (ii) MFS, i.e., the time from initiation of intervention until the first recognition of distant metastases or death due to any cause, whichever occurs first.
- (iii) OS, i.e., the time from initiation of intervention until death due to any cause.

The Kaplan-Meier (KM) time-to-event data from the NIAGARA trial (29 April 2024 data cut-off) for EFS, MFS, and OS is extrapolated over the long-term. This extrapolation uses parametric fitting to independent curves for each separate arm to determine health state membership (EF, LR, DM, or death) over time. Table 35 of the CS and section 3.2.1 (Table 5) summarises the endpoints included in the model.

The survival modelling for EFS, MFS and OS included an assessment of the proportional hazards and accelerated failure time assumption, statistical goodness-of-fit measures (Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC]), visual inspection of model fit to KM data, and an assessment of the clinical plausibility of the extrapolations. Standard parametric models (exponential, Gompertz, Weibull, log-normal, log-logistic, generalised gamma, and gamma) and flexible spline models (Royston-Parmar spline models with 1–3 knots, link functions including hazard, normal, or

odds) were considered. The company examined the hazard trend over time of the survival data to determine the candidate parametric or flexible models for each outcome independently.

For EFS, the hazard profiles for each arm of NIAGARA exhibits a different non-monotonic hazard pattern; therefore, the company considered flexible models to be well suited for this outcome. From the spline-based models, all models showed a good visual fit to the data and the company's clinical experts agreed that all curves presented could be plausible. The company selected the best-fitting spline model for each arm: for perioperative durvalumab this was 1-knot spline odds and for the control arm this was 2-knot spline normal. Figure 26 of CS shows the base case curve selection and fit to KM data for EFS.

For MFS, the hazard profiles were broadly similar across arms with rates initially increasing to a peak before declining towards zero over the remaining follow-up. Standard parametric curves were excluded from consideration due to poor visual fit to the KM data. From the spline-based models, all models showed a good visual fit to the data and the company's clinical experts agreed that all curves presented could be plausible. The company selected the best-fitting spline model for each arm: for both arms this was the 1-knot spline hazard. Figure 30 of CS shows the base case curve selection and fit to KM data for MFS.

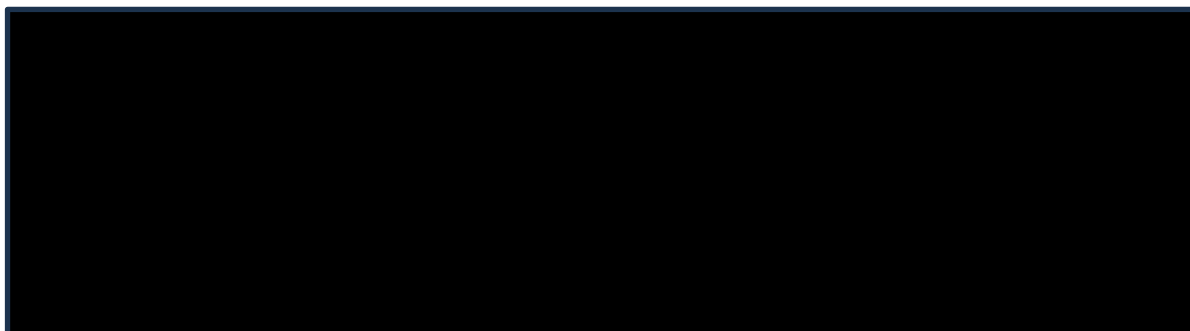
For OS, the company considered the hazard profiles to be well-captured by standard parametric models and therefore flexible models were not considered. In response to EAG clarifications question B6, the company provided spline-based models for OS; however, the company holds the view that standard parametric models are sufficient for OS extrapolation. For the perioperative durvalumab arm, the company selected the Gompertz distribution because it was preferred by two out of four clinical experts, even though it was not the best-fitting model according to goodness-of-fit statistics. For the control arm, the company excluded the best-fitting generalised gamma model from consideration because one clinical expert did not consider it plausible; although the reasons for this clinical opinion were not provided and no data presented to support it. In addition to assessing visual fit and clinical expert validation, the company compared the next three best-fitting distributions for the control arm (log-normal, Gompertz and log-logistic) with external literature for 5- and 10-year OS estimates (Table 40 of CS). The company selected the log-logistic distribution for the control arm because two out of the four clinical experts considered its long-term extrapolation more plausible and the 10-year estimate aligns more closely with external literature, even though it was the fourth best-fitting distribution and provided the lowest estimates of long-term OS. Figure 33 of CS shows the base case curve selection and fit to KM data for OS.

Tables 41 and 42 of CS summarise the model selection for EFS, MFS and OS by treatment arm in the base case and scenario analyses where these curves are varied, respectively.

The model uses UK life table data from the Office for National Statistics to constrain age- and gender-adjusted mortality.³⁶ This ensures that the risk of death remains at or above background levels by age, i.e., the model is prevented from predicting that a patient's risk of death is lower than the general population's risk by age. The hazards of EFS and MFS are also constrained to be at or above the age- and gender-adjusted all-cause general population risk of death by age. In addition, the EFS curve is constrained to values less than or equal to MFS, while the MFS curve is constrained to values less than or equal to OS.

Figure 2 shows the survival curves used in the company's base case analysis for the perioperative durvalumab and control arms. The time points indicated on the figure represent the points at which the curves pick up the all-cause general population risk of death. For perioperative durvalumab, the EFS picks this up at ■ years, the MFS curve at ■ years, and the OS curve at ■ years. For the control arm, the EFS curve picks up the all-cause general population risk at ■ years, the MFS curve at ■ years, and the OS curve at ■ years.

Figure 2 Survival curves used in the company's base case analysis for the perioperative durvalumab and control arms (with constraints implemented for curve crossing and all-cause general population risk of death)

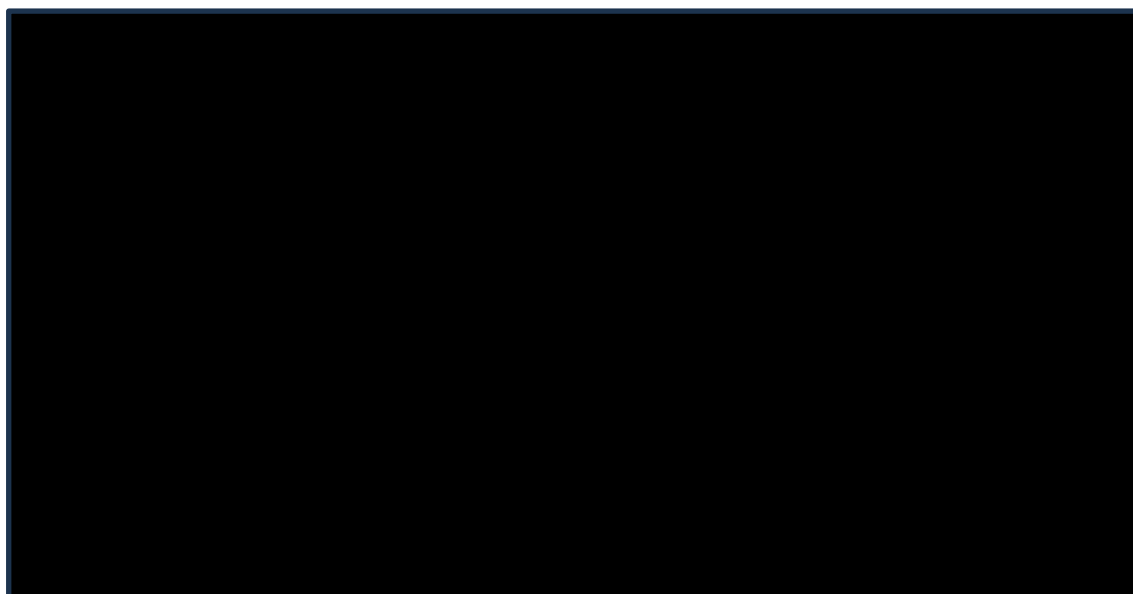


Company's scenario with adjuvant nivolumab

The effectiveness of the comparator in the company's scenario with adjuvant nivolumab (i.e., neoadjuvant chemotherapy and radical cystectomy followed by no treatment or adjuvant nivolumab in PD-L1 $\geq 1\%$ high-risk patients as a comparator) is based on the counterfactual survival estimates for EFS, MFS and OS for the control arm of NIAGARA (see Section 3.5 for a detailed discussion of the methods and results).

Figure 3 shows a comparison of the survival curves for EFS, MFS and OS in the company's base case analysis (without adjuvant nivolumab) and the company's scenario with adjuvant nivolumab for the control arm.

Figure 3 Survival curves used in the company's base case analysis (without adjuvant nivolumab) and the company's scenario with adjuvant nivolumab for the control arm



4.2.5.2 Points for critique

The EAG has three primary concerns relating to the treatment effectiveness evidence and assumptions used in the model:

- Immaturity of the OS data;
- Model selection for the extrapolation of OS; and
- Impact of starting age on survival outcomes.

Before discussing these concerns in detail, the EAG critiques the company's approach to modelling survival outcomes using independent curve fits and the implementation of model constraints. This is necessary to evaluate the survival extrapolations, including the implicit cure assumption in the long-term projections. The EAG also considers the risk of non-cancer-related death from comorbidities in the target population.

Model selection based on independent curve fit

When modelling the survival outcomes of EFS, MFS, and OS, the curves fitted to the KM data to allow for long-term extrapolations are selected independently for each outcome, i.e., for each separate outcome, the most appropriate model (standard parametric or flexible spline) is fitted to the trial data. The approach used by the company for model selection appropriately follows guidance in NICE Decision Support Unit Technical Support Document (TSD) 14³⁷ and TSD 21³⁸, which involves selecting a model with good statistical fit and clinical plausibility for each endpoint and with the extrapolated survival probabilities validated against clinical expert opinion and external literature.

However, when the endpoints are considered independently, the extrapolated outcomes may create clinically implausible scenarios, e.g., the intermediate outcomes of EFS and MFS may predict better survival than OS, or the extrapolated EFS curve may cross the MFS curve. To address these inconsistencies, the company added ad-hoc restrictions to the extrapolated survival outcomes in the model. While the EAG considers the added restrictions to be a reasonable approach, the EAG believes it is important to assess the appropriateness of the extrapolated survival curve fits (EFS, MFS and OS) relative to one another rather than examine the best fitting distribution to each outcome independently. This can be done by identifying a consistent set of extrapolation functions across all three outcomes that satisfy the requirement for $EFS \leq MFS \leq OS \leq$ general population mortality, thereby removing the need for ad-hoc constraints within the model.

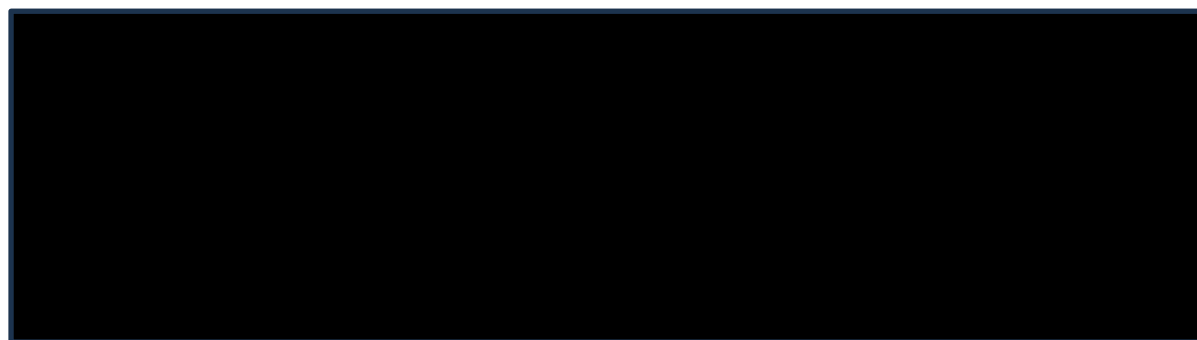
In response to EAG clarifications (question B5a), the company states that for most parametric distributions, it is not feasible to identify alternative survival functions that logically align EFS, MFS and OS without the need for such constraints. Within the company's model, the EAG explored different combinations of alternative survival functions in an attempt to logically align the three outcomes; however, the EAG noted that a trade-off is required between the model's fit to the trial data and logical consistency across the outcomes, i.e., the set of extrapolation curves that logically align are not among the best-fitting models to the KM data, either statistically or visually. The EAG also notes that models with excellent fit to the observed data may perform poorly in extrapolation.³⁹ Therefore, the EAG accepts that the company's approach is reasonable, but consideration must be given to the time points at which the logical constraints are imposed in order to assess the robustness of the extrapolations.

Implementation of constraints within the model

To overcome the logical inconsistencies in the model between the extrapolated curves for EFS, MFS, OS and background all-cause general population risk of death, constraints are implemented in the model using a two-step approach. In step 1, the hazard rates for EFS, MFS, and OS are constrained to be at or above the corresponding age- and gender-matched all-cause risk of death for the general population. For each treatment arm, Figure 4 shows the time points at which the hazard rate for each survival endpoint matches this background mortality rate, at which point the background hazard rate is applied. The hazard rate for OS in the perioperative durvalumab arm matches the background mortality hazard at ■■■ years, while in the control arm, this happens much later at ■■■ years. In the perioperative durvalumab arm, the hazard rates for EFS and MFS match the background mortality hazard at ■■■ and ■■■ years, respectively, while in the control arm the corresponding time points are ■■■ for EFS and ■■■ years for MFS.

These time points, at which the risk of an event approaches the background mortality of the general population, are important for interpreting the implied ‘cure’ from cancer arising from the model selection, and the impact of starting age in the model, both of which are discussed further below.

Figure 4 Independent hazard rate plots for EFS, MFS and OS compared to general population mortality hazards by treatment arm



In step 2, the survival probabilities for OS are constrained to be the maximum of EFS and MFS, while the EFS curve is constrained to values less than or equal to MFS. The EAG noted that the latter constraint was implemented within the electronic version of the model such that the MFS curve picked up the values of the EFS curve at the point of crossing rather than an adjustment to the EFS curve to match MFS (i.e., $EFS = MFS$ at the point of crossing) as implied in the CS by the statement that “*EFS is constrained to values that are less than or equal to MFS*”. The EAG updated the company’s electronic model to reflect this logical constraint on EFS (see Section 5).

The adjustment to OS was implemented in the model by specifying a dominant curve for extrapolation, with two options available in the electronic version of the model: (i) OS set equal to EFS at the point of crossing; or (ii) EFS set equal to OS at the point of crossing. In the base case analysis, the company chose option (i). When the EAG requested justification for this (clarifications question B5b), the company explained that patients who achieve long-term remission in the EFS state are likely to be cured of their disease and would only experience background all-cause mortality. The company argued against the alternative of setting EFS equal to OS at the crossing point because it could potentially lead to an abrupt decline in EFS, implying a rapid increase in mortality from the crossing point forward. However, the EAG notes that if the EFS curve is constrained to values less than or equal to MFS, and the MFS curve is constrained to values less than or equal to OS, then the EFS curve would never dominate the OS curve. Thus, the adjustment to OS is not required in the model when the adjustment to the EFS curve is made such that EFS is less than or equal to MFS.

Immaturity of the OS data used in the extrapolations

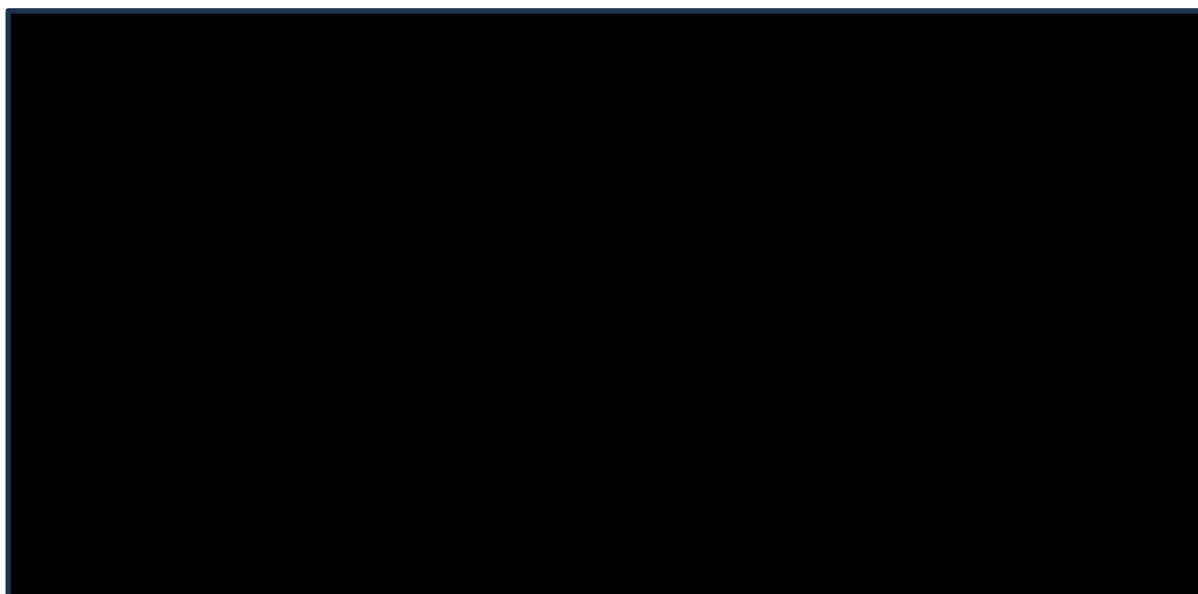
The OS data used in the company’s base case analysis from NIAGARA, as of the 29 April 2024 data cut-off, is immature (28.7% maturity overall with 305 death events). Median OS has not yet been

reached. The median duration of follow-up for OS was 42.3 months in the perioperative durvalumab arm and 39.6 months in the control arm. The date at which the final data cut for OS (IA-2) will become available is not indicated in the CS.

Different parametric extrapolations of the immature OS data lead to different projections of long-term survival. Figure 5 shows the extrapolated OS curves based on the four best-fitting parametric models (ranked by AIC/BIC, Table 38 of the CS), with constraints implemented. The 10-year survival probabilities for the perioperative durvalumab arm range from [REDACTED] using the log-logistic model (least optimistic parametric model for both arms) to [REDACTED] using the Gompertz model (most optimistic parametric model for both arms), while the corresponding probabilities for the control arm range from [REDACTED] to [REDACTED] for the log-logistic and Gompertz models, respectively. The implications of the different parametric OS extrapolations on the company's cost-effectiveness results are explored in Section 5.2.2, where the EAG explores the impact of selecting the most optimistic OS in both arms (Gompertz model) and the least optimistic OS in both arms (log-logistic model).

Importantly, the EAG notes that uncertainty in the OS projections not only impacts the survival benefit for perioperative durvalumab relative to the control arm, but it also has implications for the implied time point of 'cure' from cancer, where the risk of death becomes equal to that of the general population. Consequently, the starting age in the model is a key input as it directly determines the all-cause mortality risk in the general population.

Figure 5 Extrapolated OS using the four best-fitting standard parametric models



Model selection for extrapolation of survival outcomes

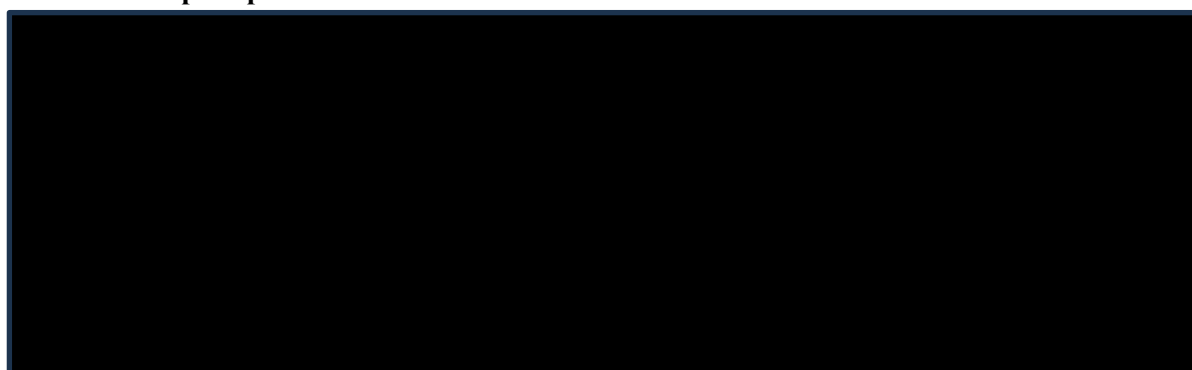
The EAG has no major concerns regarding model selection for the extrapolation of KM data for EFS and MFS. The approach used by the company aligns with guidance from the NICE DSU TSD 14 and TSD 21, and the EAG agrees with the company that the hazard profiles for both outcomes suggest flexible models may be more appropriate than standard parametric models. However, the EAG is unclear why the generalised gamma model was not considered suitable by the company for the extrapolation of EFS in the control arm. This model was ranked first by statistical AIC and BIC criterion across both the parametric and flexible models (Table 36 of the CS) and shows a good visual fit to the KM data. Whilst the company states that this model offers poor fit to the observed hazards, the EAG considers the fit comparable to that of the spline-based models (Figure 9 for generalised gamma model compared to Figures 6, 7 and 8 for spline-based models in Appendix L of the CS). In Section 5.2.2, the EAG explores the impact on the cost-effectiveness results of selecting the generalised gamma model for EFS in the control arm.

In contrast, the EAG has two major concerns regarding model selection for the extrapolation of OS. Firstly, the EAG considers the justification for selecting standard parametric models over flexible models for OS extrapolation to be inconsistent with the approach taken for MFS. The hazard profile for OS is not dissimilar to that for MFS; for both outcomes, the hazard rates initially increase to a peak before declining towards zero over the remaining follow-up - although the control arm MFS hazard appears to flatten slightly from 36 months onwards (see Figures 10 and 19 in Appendix L of the CS for MFS and OS, respectively). However, flexible models were not considered for the extrapolation of OS. Moreover, the presence of two turning points in the OS hazard plot for the control arm suggests that a flexible model may be appropriate. In response to EAG clarification question B6b, the company supplied an updated electronic version of the model that allows for flexible models (Royston-Parmar spline models with 1–3 knots, link functions including hazard, normal, or odds) to be implemented for OS extrapolation.

The EAG considers that the flexible models provide sufficient statistical and visual fit to OS for both arms of NIAGARA. The flexible models have lower AIC and BIC values than standard parametric models, suggesting better statistical fit (Table 18 of the company's response to EAG clarifications for flexible model and Table 38 of the CS for standard parametric models). The EAG also considers the visual fit of the alternative flexible models to be sufficient (Figures 11-13 of the company's response to EAG clarifications). The impact of using flexible models on the long-term OS projections when compared with the company's base case parametric model selections (Gompertz for the perioperative durvalumab arm and log-logistic for the control arm) differs by treatment arm. For the perioperative durvalumab arm, the company's base case selection closely aligns with the best-fitting flexible model of 1-knot odds (see Figure 6). In contrast, for the control arm, there is a substantial difference in the

OS projections between the best-fitting flexible model of 1-knot hazard and the company's base case selection of log-logistic (see Figure 6). Figure 6 also shows that the generalised gamma and Gompertz models are the standard parametric models that most closely align with the projections from the best fitting flexible model. Therefore, the EAG is satisfied that the model selection for OS in the perioperative durvalumab arm in the company's base case is reasonable, but the selection of the log-logistic model for the control arm may not be reasonable as it produces the least favourable OS compared to alternative better fitting models.

Figure 6 Comparison of OS extrapolations using standard parametric and best fitting flexible models in the perioperative durvalumab and control arms

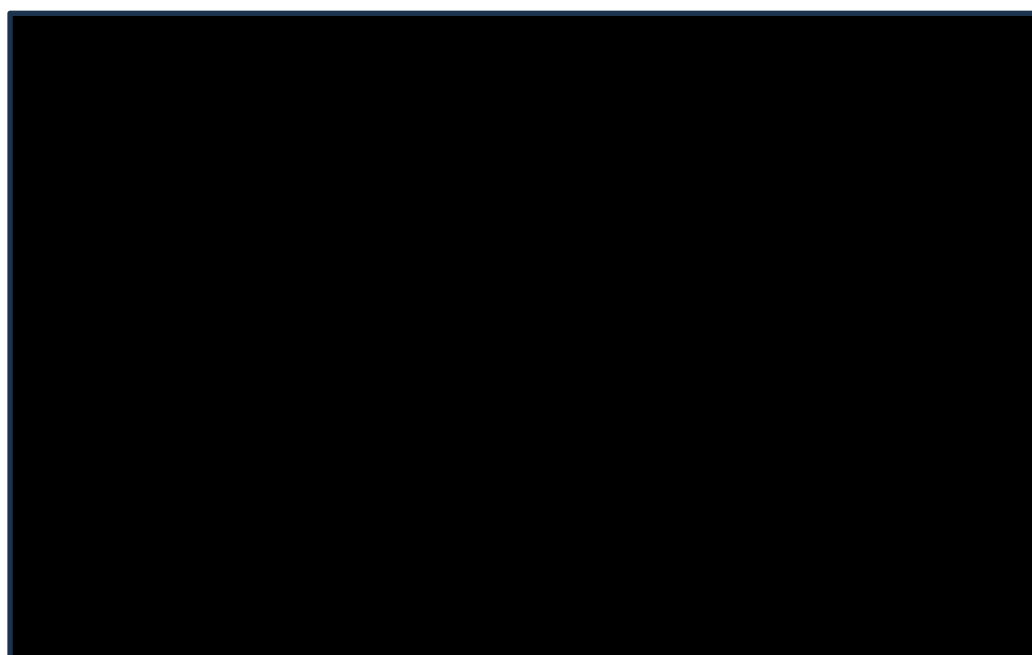


Secondly, the EAG is concerned that the trend in OS hazard rates between the perioperative durvalumab and control arms in the company's base case analysis is inconsistent with the observed hazard rates over time from NIAGARA. Figure 32 of the CS shows that the OS hazard rates in both the perioperative durvalumab and control arms reach a peak at around 10 months post-randomisation. After this point, the observed differences between arms start to converge, moving towards near-zero rates by the end of the follow-up period. The EAG believes the model selection for the extrapolation of OS should reflect this convergence between arms of the trial (i.e., the hazard ratio for the difference between arms should approach the value of one beyond the trial follow-up period to reflect the convergence in the observed hazards in NIAGARA). Therefore, the EAG considers the company's base case model selection for OS extrapolation in the control arm to be overestimating mortality in this arm, because the difference between the treatment arms over the long-term is implying that the hazard ratio is increasing over a longer period, but there is no empirical evidence to suggest that the hazard is increasing over time.

In response to EAG clarifications (question B7), the company argues that the observed convergence in the OS hazard rates between arms (Figure 32 of the CS) may be unduly influenced by a low number of participants at risk at the end of the trial follow-up period. Thus, the company did not explicitly consider this convergence when selecting the independent OS extrapolations for each arm. In addition, the company states that the application of the general population mortality constraint means

that hazards between arms eventually converge in the model. Whilst the EAG acknowledges this eventual convergence, the EAG considers that the convergence trend starts much earlier in the observed hazards for OS (i.e., not just in the tails of the KM data), where a reasonable number of participants are still at risk. The hazards for both arms eventually converge due to the general population mortality constraint, but this only occurs at the time point of ■■■ years, when the OS hazard rate in the control arm matches the general population mortality hazard rate. Therefore, the EAG considers the company's base case model selection for OS (Gompertz, which is the most optimistic model selection for the perioperative durvalumab arm, and log-logistic, which is the most pessimistic model selection for the control arm) to be inconsistent with the observed hazards from NIAGARA. Figure 7 shows that the hazard rates for OS in the perioperative durvalumab and control arms of the company's base case analysis increases over time until the general population mortality constraint is applied at ■■■ years.

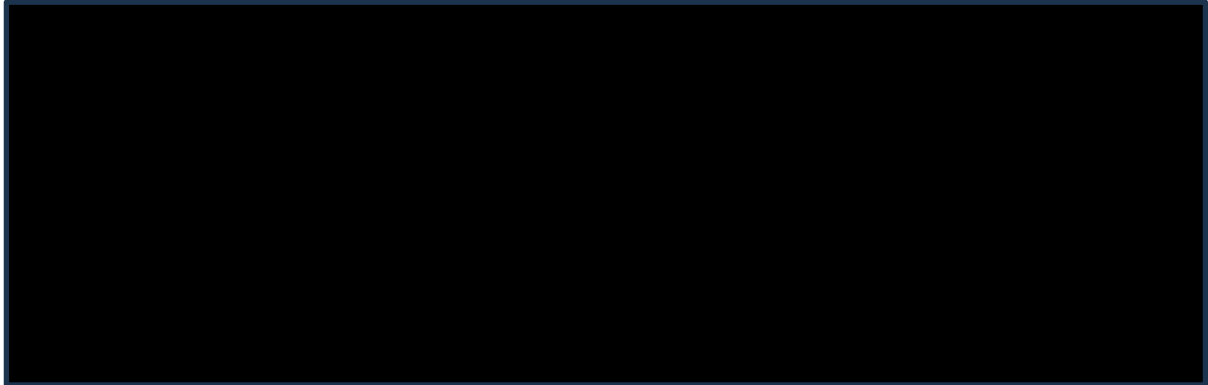
Figure 7 Hazard rates of OS in the company's base case analysis for the perioperative durvalumab and control arms



The EAG acknowledges that the near-zero hazard rates in the tail of the KM data for OS are subject to low numbers of participants at risk. However, the model selection should reflect the trend in convergence of hazard rates observed in NIAGARA over time between treatment arms. Among the standard parametric models, the EAG considers the Gompertz or generalised gamma models as potential candidates for both arms. Both models offer a sufficient visual fit to the KM data (see Figure 31 of the CS). For statistical fit, the Gompertz model ranks third amongst the standard parametric models, while the generalised gamma model ranks first for the control arm and second for the perioperative durvalumab arm (see Table 38 of the CS). In Figure 8, the EAG illustrates the hazard

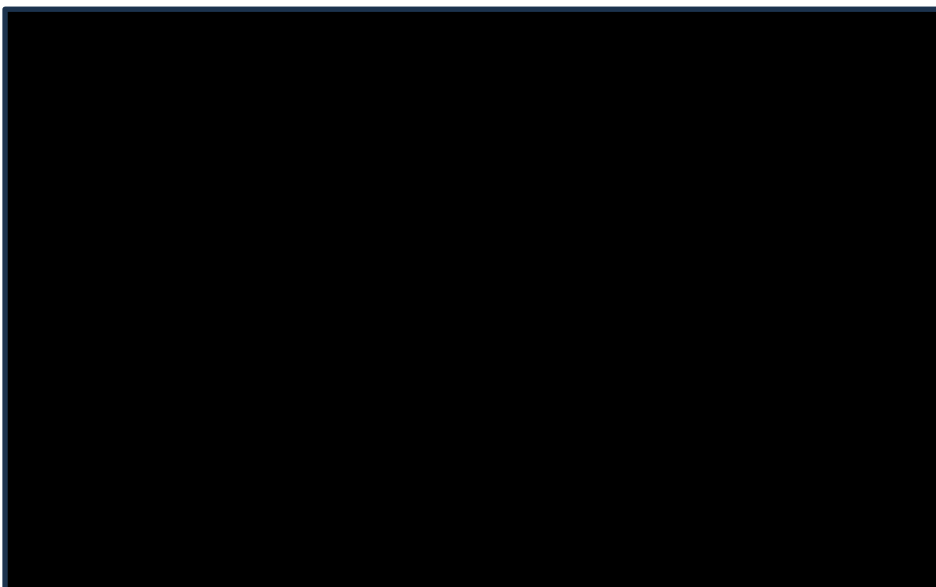
rates over time for the perioperative durvalumab and control arms using the Gompertz and generalised gamma models, after adjusting for the general population mortality constraint. Both models offer hazard rates that follow the profile of convergence in the KM data, with the timing of convergence closely aligned (■ years with the generalised gamma model and ■ years with the Gompertz model).

Figure 8 Hazard rates of OS using the Gompertz and generalised gamma models for the perioperative durvalumab and control arms



After the company submitted an updated electronic model in response to EAG clarifications that allows for flexible models to be selected for OS extrapolation, the EAG considers that the best-fitting flexible models also reflect the convergence of hazards. The best fitting flexible models are the 1-knot odds model for the perioperative durvalumab arm and the 1-knot hazard model for the control arm (see Figure 9).

Figure 9 Hazard rates of OS using the best-fitting flexible models for the perioperative durvalumab and control arms



In the company's base case, the log-logistic model was selected for OS in the control arm because it provided 10-year projections that closely align with external registry data and because two out of the four clinical experts consulted by the company considered it the most plausible long-term extrapolation (Tables 39 and 40 of the CS). Whilst the EAG agrees that long-term OS estimates should be externally validated, the relative effect between treatment arms must also be appropriately assessed. The company's approach of independently fitting models separately to each arm means that the relative effectiveness between arms has not been sufficiently validated. The EAG also notes that the population in the NIAGARA control arm and the external registry studies considered by the company for validation differ (see Table 5). In particular, none of the registry studies are UK-based; the median ages reported in Mahoney 2025 (72 years) and Faraj 2021 (69 years) are higher than in NIAGARA (64.4 years), Mak 2014 includes data collected between 1988 and 2007 and Vlamming 2020 is a single-institution study conducted in the Netherlands, with data collection from 1998 to 2016.

In summary, the EAG considers the best fitting flexible models (1-knot odds model for the perioperative durvalumab arm and the 1-knot hazard model for the control arm) to be the most appropriate model selection for OS extrapolation because they best reflect the observed hazard profile of OS in the NIAGARA trial. These models inform the EAG's preferred base case assumptions (Section 5.2.3)

Implicit cure assumption

In NICE technology appraisal (TA817) for adjuvant nivolumab, a cure assumption was explicitly modelled. This was based on evidence from CheckMate-274 which showed that the risk of death approaches that of the general population at 5 years. In TA817, the company's base case assumed a cure point of 5 years, while the EAG's exploratory analysis considered a 10-year cure point. However, the committee concluded that it remains uncertain at which time point it is reasonable to assume that people are cured of cancer. The committee noted that there is evidence that disease recurrence may take place after 5 years and mortality risks remain elevated.¹⁵

For perioperative durvalumab, the company's model does not include an explicit cure assumption. Instead, a time point for cure from cancer is implicitly modelled via the decreasing hazards of survival over time, particularly for the perioperative durvalumab EFS curve, where a large proportion of patients are implicitly treated as 'cured'. For a patient to be considered 'cured' of MIBC, two conditions must be met: (i) the risk of events (recurrence or progression) defined by the EFS curve must not be greater than the risk of all-cause death, and (ii) there must be no risk of cancer-related deaths. In the company's base case analysis, these conditions are met after [REDACTED] years in the perioperative durvalumab arm and after [REDACTED] years in the control arm (see Figure 2). At these time points, [REDACTED] of patients in the perioperative durvalumab arm and [REDACTED] of patients in the control arm

remain in the EF health state. These patients have no risk of recurrence, progression or cancer-related death, and their only risk is all-cause mortality. Therefore, a large proportion of patients are considered 'cured' in the company's base case analysis after ■■■ years in the perioperative durvalumab arm and ■■■ years in the control arm.

The clinical advisor to the EAG suggested that it is clinically plausible that a proportion of patients with MIBC can be considered cured if they have no disease recurrence after a significant period. However, this proportion is uncertain. The EAG notes that a comparison with TA817 cannot be made because the population (high-risk of recurrence) and timepoint of treatment (adjuvant following RC) is different from the perioperative setting. The EAG considers the proportion of patients implicitly assumed to be cured to be an uncertainty in the company's cost-effectiveness results. The time point of cure implied by the long-term projections of survival should be assessed in relation to the plausibility of the company's survival extrapolations, which are also impacted by the starting age of the modelled cohort.

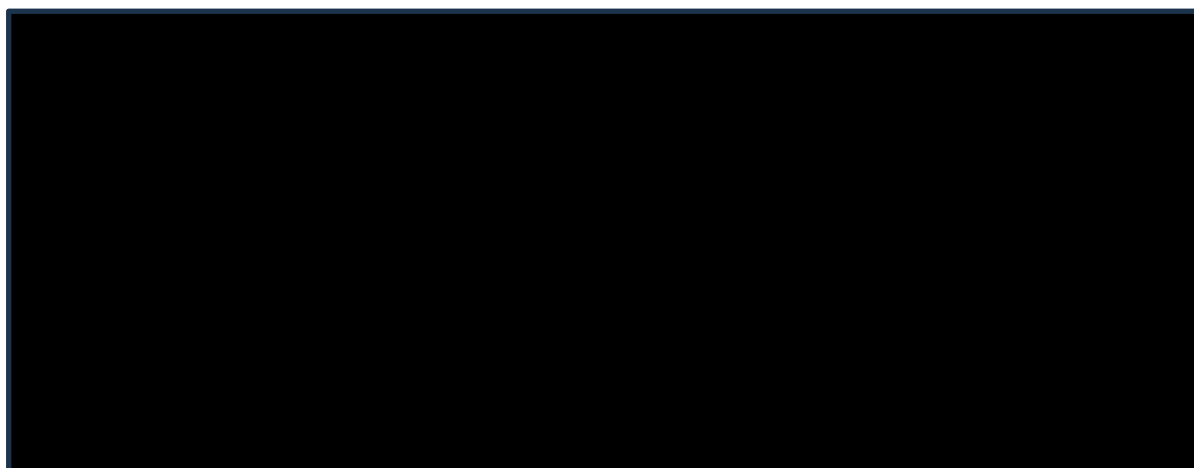
Impact of baseline age on modelled survival outcomes

The starting age of the modelled cohort has a large impact on the extrapolated OS probabilities (see Figure 10). This is because the hazard rate of OS is constrained to be at or above the age- and gender-matched all-cause general population risk of death. Therefore, the time point at which the risk of death approaches that of the general population depends on the starting age used in the model. The impact of age is more pronounced in the perioperative durvalumab arm than in the control arm for two main reasons: (i) the OS hazard rates in the perioperative durvalumab arm approach the general population mortality earlier than in the control arm (■■■ years vs ■■■ years, respectively); and (ii) a greater proportion of patients are still alive in the perioperative durvalumab arm compared to the control arm when the OS hazard rate is equal to the general population hazard of death (■■■ vs ■■■ respectively). Consequently, when the modelled cohort starts perioperative treatment at an older age (e.g., age 70 years in Figure 10 compared to the base case starting age of 64.4 years), where general population mortality rates are higher, the difference in survival between the two arms diminishes more rapidly after the point at which the hazards meet. This reduces the estimated life year gains for the perioperative durvalumab arm compared to the control arm from ■■■ years in the company's base case analysis to ■■■ years with a starting age of 70 years. The opposite is true for a younger starting age (e.g., age 60 years in Figure 10), where general population mortality rates are lower, the relative difference in survival between treatment arms is permitted to last longer, resulting in an increase in life year gains to ■■■ years.

One of the EAG's clinical advisors suggested that patients eligible for neoadjuvant chemotherapy for MIBC in the NHS are typically older than those in the NIAGARA trial, with many patients between 70 and 79 years of age. However, data provided by NHS England to the EAG suggests that NHS

patients in the North East with resectable MIBC who receive neoadjuvant cisplatin-based chemotherapy have a mean age of 66 years and 75% are male, which is not dissimilar to the company's base case starting age and gender distribution, but it is uncertain whether this data is representative of the whole of England and Wales. In Section 5.2.2, the EAG explores the impact on the cost-effectiveness results of using a starting age of 70 years in the model.

Figure 10 OS extrapolations in the perioperative durvalumab and control arms by starting age used in the model



Increased risk of non-cancer-related death due to comorbidities in population with MIBC

The EAG is concerned that people with MIBC in the NIAGARA trial are likely to have a higher risk of non-cancer-related death compared with the general population. This is because participants have mortality risk factors including smoking (23.7% current smokers and 49.3% ex-smokers; see Table 7 of the CS) and other comorbidities (section 3.2.3). The EAG clinical advisors confirmed that an increased mortality risk (cancer non-related) for this population is clinically plausible. This means that even after removing the risk of cancer-related death, the overall risk of death for this population is likely to be higher than the general population mortality risk.

An excess risk has not been considered in the company's base case analysis. The EAG notes that data from NIAGARA can provide some information about the increased risk due to comorbidities in the target population. In NIAGARA, there were 305 deaths in total across the two arms (see Table 17 of the CS); of these deaths, 199 were attributed to bladder cancer (see Table 20 of the CS). This indicates that at least 106 deaths were due to non-cancer-related causes over a 5-year follow-up period (longest follow up = 64.7 months) (it is "at least" because some deaths among withdrawals [n=53 across two arms – see Table 6 of the CS] may not have been recorded). The 5-year probability of non-cancer-related death in NIAGARA is therefore estimated to be 9.97%. The corresponding 5-year age- and gender-adjusted mortality probability for the general population is 7.11%.³⁶ Assuming an exponential model for simplicity, the hazard ratio (increased death risk) would be 1.42 for people in NIAGARA

versus the general population (details on how this risk is calculated are provided in the electronic version of the model). The EAG considers that this increased risk may provide a plausible scenario to reflect the mortality risk attributed to non-cancer causes in the target population. In Section 5.2.2, the EAG explores the impact on the cost-effectiveness results of using an increased death risk (hazard ratio of 1.42) in the target population compared to the general population risk.

4.2.6 Health related quality of life

4.2.6.1 Summary of company's submission

The company conducted a systematic literature review to identify studies reporting HRQoL data in patient with MIBC (see Appendix F of CS). Of the 24 studies identified, only one study⁴⁰ reported EQ-5D-5L UK data but did not provide utility values mapped to the EQ-5D-5L UK value set. Furthermore, another study⁴¹ provided relevant EQ-5D-3L utilities for the health states (as described in Section 4.2.2) used in the cost-effectiveness model. However, the utility values were based on the United States based value set. The company identified NICE appraisal TA817¹⁵ that used utility values relevant to the UK setting but the actual scores used in TA817 were redacted in the final reports. Therefore, the company considered the health state utilities identified in the SLR unsuitable for use in the cost-effectiveness analysis.

The NIAGARA trial collected individual patient-level HRQoL data using the EQ-5D-5L questionnaire. The health state utilities used in the cost-effectiveness analysis were derived from the analysis of the NIAGARA trial EQ-5D-5L data using Hernandez-Alava et al.'s 5L to 3L mapping algorithm⁴² and using a mixed effects repeated measures (MMRM) model. The utilities were modelled as treatment-independent estimates, assuming that a patient's HRQoL in a given health state is the same regardless of whether they receive perioperative durvalumab or the control arm.

The company used the prospective bladder cancer infrastructure (ProBCI) registry⁴³ to validate the utilities derived from the analysis of the NIAGARA trial. Health state utilities were capped by age- and sex-matched UK general population utility. The age-adjustment was modelled using the health state utilities by age equations from Ara and Brazier (2010)⁴⁴ and applied to each cycle for the duration of the time horizon.

HRQoL decrements (disutilities) are applied to the proportion of patients who underwent cystectomy and to patients experiencing AEs while on treatment. The one-off QALY adjustment was accrued at the start of the time horizon in the model as the model assumes that both cystectomy and treatment-related AEs are expected to have a temporary impact on HRQoL.

4.2.6.2 Health state utilities

To derive the health state utilities, the company performed four MMRM analyses with covariates for ‘randomised group only’, ‘disease state only’, and two models combining disease state and randomisation group, with and without interaction terms. The relative performance of each model was assessed using statistical goodness-of-fit based on AIC (see Table 43 of CS). The best-fitting model was the MMRM with covariates for ‘disease state only’. The analysis estimated utilities using the event times for EFS and MFS from the NIAGARA study.

The company used ProBCI registry,⁴³ which collects clinical and HRQoL (including EQ-5D-5L) data from patients with MIBC, non-muscle invasive and metastatic bladder cancer in the Netherlands, to validate the findings of the NIAGARA study. The changes in the health state utilities comparing pre- versus post-recurrence in ProBCI (■■■■) was considered consistent by the company with the NIAGARA results for DM MIBC (■■■■), while mean utilities for the pre-event state (■■■■) in ProBCI were also considered similar to the mean utility for EF in NIAGARA (0.847). The company notes that the analysis of ProBCI registry data does not yield different results based on LR or DM, and hence it is only used to validate the NIAGARA findings. The CS did not provide details about the patient characteristics from the ProBCI sample. However, in response to EAG clarifications (question B20) the company indicated that the difference in health state utilities between pre- and post-recurrence states was for a subpopulation of ProBCI that best matched the key inclusion criteria of the NIAGARA trial and valued using the UK 5L value set⁴⁵ (Table 29 of company’s response to EAG clarifications).

Table 15 summarises the health state utility values used in the company’s base case analysis.

Table 15: Health state utility values used in the model (reproduced from Table 44, CS)

Health state	Mean utilities (95% CI)
EF	0.847 (0.837, 0.857)
LR	■■■■
DM	■■■■

Abbreviations: CI: confidence interval; EF: event-free health state; LR: local recurrence health state; DM: distant metastases health state.

Points for critique

The EAG considers the company’s approach for estimating health state utilities to be appropriate. The approach used is consistent with that used in NICE TA817 for adjuvant nivolumab, and the justification for selecting the best-fitted model is appropriate. However, the EAG notes that the utility values derived from the NIAGARA study are ■■■■. In fact, the utility value for the EF health state is higher than the corresponding age- and gender-matched general population utility value of 0.816 based on Ara and Brazier (2010). This suggests that HRQoL for patients with MIBC in an EF

state in the NIAGARA study is greater than HRQoL of the UK general population without cancer, which may suggest that the population of the NIAGARA trial had better quality of life than patients who receive NAC in the NHS

The difference between the mean health state utilities for LR and DM is relatively small (■■■■). Clinical advice to the EAG stated that MIBC has a substantial impact on patients' HRQoL, with LR potentially having worse HRQoL than metastasis due to pain. The company states that the small difference in utility values between DM and EF from the NIAGARA study (■■■■) represents a conservative estimate for cost-effectiveness. This is because the perioperative durvalumab arm has a greater proportion of the cohort in the EF health state than in the DM state, relative to the control arm. The EAG agrees that the small difference for DM is potentially conservative as a larger decrement in HRQoL would be expected for DM, given its poorer prognosis and survival.

4.2.6.3 Disutility associated with AEs and cystectomy

The company's model considers HRQoL loss associated with treatment-related AEs and cystectomy. At the start of the model's time horizon, a one-off QALY decrement is applied to the proportion of patients who underwent cystectomy and to the proportion of patients who experienced treatment-related AEs. The utility decrements for these events were primarily sourced from published literature, mainly previous NICE TAs (see Table 45 of CS). The EAG notes that the company did not justify whether it was possible to derive utility decrements for these events from the analysis of EQ-5D-5L data collected in the NIAGARA study.

Cystectomy

The utility decrement for cystectomy was sourced from the Life After Bladder Cancer (LABC) study,⁴⁶ a prospective UK study in patients with a new bladder cancer diagnosis. The EAG's clinical advisor indicated that undergoing RC has a drastic impact on patient's HRQoL; while some patients adapt successfully to live well without their bladder, others experience severe leakage issues causing profound distress, embarrassment and diminished HRQoL. Many patients in this demographic have multiple age-related health complications, further complicating recovery.

The model applies a temporary impact on HRQoL in the early phases of treatment, with a disutility (-0.06) during the first 6 months after surgery. Advice from the EAG's clinical experts and published evidence⁴⁷ indicates that patients with a history of cystectomy have a detrimental effect on HRQoL compared with an average person of the same age and sex without MIBC.

Adverse events

Utility decrements associated with AEs (Table 16) were not treatment-specific and sourced from published literature. The included AEs are Common Terminology Criteria for Adverse Events (CTCAE) of grade 3 or 4 with an incidence of $\geq 5\%$ in either treatment arm of NIAGARA. The

impact of AEs was calculated as the sum of the product of disutility, frequency, and duration of the AE.

A similar assumption was applied in the company's scenario with adjuvant nivolumab to estimate the QALY loss associated with AEs. In this scenario, AEs of CTCAE grade 3 or higher was sourced from the CheckMate-274 trial.²⁰

Table 16: Disutilities associated with AEs (reproduced from Table 45, CS)

Adverse event	Disutility	Duration (days)	Freq of AE (perioperative Durvalumab)	Freq of AE (control)	Source
Anaemia	-0.119	16.07	13.8%	15.0%	NICE TA306 ⁴⁸
Lipase level increase	-0.050	28.00	0.0%	0.0%	Assumption
Neutropenia	-0.007	15.09	14.3%	0.2%	NICE TA306 ⁴⁸
Neutrophil count decrease	-0.007	15.09	7.0%	16.9%	Assumed the same as neutropenia
Thrombocytopenia	-0.108	7.00	14.2%	6.7%	NICE TA1036 ⁴⁹
Urinary tract infection	-0.005	28.00	0.0%	13.3%	Sullivan <i>et al.</i> (2011) ⁵⁰ , NICE TA599 ⁵¹

Points for critique

For the utility decrement for cystectomy, the EAG's clinical advisors considered a timeframe of 6 months for the impact on patients' HRQoL to be short. In response to EAG clarifications (question B22), the company performed two scenario analyses with the duration of the utility decrement set to (i) one year and (ii) life-long. The utility decrement duration had minimal impact on the cost-effectiveness results (see Tables 32 and 33 of company's response to EAG clarifications).

The selection of AEs for the perioperative durvalumab and control arms are described clearly in the CS. The EAG notes that the duration of AEs in the model is shorter than the model cycle length and the frequency of AEs is less than 20%. Therefore, AEs have minimal impact on the cost-effectiveness estimates.

4.2.7 Resources and costs

4.2.7.1 Summary of company's submission

The company conducted a systematic literature review to identify relevant cost and healthcare resource use (HCRU) data in patients with MIBC (see Appendix G of CS for details). Of the studies identified, only two studies provided resource use and cost data for a UK setting;^{52, 53} however, these studies did not provide sufficient detail and were not considered relevant for the model by the company.

The CS includes costs related to: (i) drug acquisition and administration; (ii) cystectomy; (iii) health state resource use; (iv) AE management; (v) subsequent treatments post-recurrence; and (vi) end of life care. Unit costs were informed by national published sources, including the National schedule of NHS costs, BNF, PSSRU costs and eMIT, inflated to 2023/24 prices where appropriate and discounted at an annual rate of 3.5%. The dosing regimen for each drug was based on their respective SmPCs. Table 17 summarises the costs included in the company's base case analysis.

The time on treatment for neoadjuvant and adjuvant components of both the perioperative durvalumab and control arms was modelled using the observed proportions of patients who received each scheduled cycle in each arm of the NIAGARA trial (see Table 24 of company's response to EAG clarifications). The proportions of patients receiving treatments from the NIAGARA study could be used directly in the model, without the need for extrapolation beyond the observed trial period, because no patients remained on neoadjuvant or adjuvant treatment at the data cut-off.

The administration form for all drugs considered was intravenous (IV), except for the subsequent treatment of erdafitinib, which takes oral form. The same administration costs (£394.17) were applied for all IV therapies in the model. If several drugs were given together, it was assumed they incurred a single administration cost.

The costs associated with cystectomy were based on the proportion of patients undergoing cystectomy in the NIAGARA trial. The company considered only patients who underwent RC (88% in the perioperative durvalumab arm and 83.2% in the control arm). The unit cost of RC was sourced from NHS reference costs 2023-24⁵⁴ and calculated as a weighted average of service codes associated with cystectomy, urinary diversion and reconstruction using NHS activity as weights (Table 52 of CS). The six patients in the NIAGARA trial (1.1% of participants included in the study) who refused cystectomy but achieved a complete clinical response and entered the non-cystectomy extension phase received durvalumab for up to eight additional cycles, following their initial four cycles of neoadjuvant durvalumab plus chemotherapy. The cost of cycles administered during the non-cystectomy extension phase were excluded from the treatment cost calculations used in the model.

HCRU associated with disease management was incorporated to capture costs of medical resource use by patients in each health state. The same disease management costs were applied to both treatment arms (Table 50 of CS).

The company included costs associated with AEs by estimating the sum product of the unit cost, duration and frequency, and applying it as a one-off cost at the start of the model time horizon. Unit costs for AE management were sourced from NHS reference costs 2023-24.⁵⁴ The company did not

include any AE costs for subsequent therapies post-recurrence because the company expected it to have minimal influence on incremental cost-effectiveness results.

The company included subsequent treatments post-recurrence by assuming that a different proportion of patients received subsequent cancer treatment in the perioperative durvalumab and the control arms. In the NIAGARA trial, the proportion of patients who received a subsequent anticancer therapy was [REDACTED]; however, a lower proportion of patients received at least one anticancer therapy post-study treatment discontinuation in the perioperative arm ([REDACTED]) as compared to the control arm ([REDACTED]). The company states that some of the treatments received in the NIAGARA trial are not reflective of UK clinical practice. Therefore, in order to align with UK clinical practice, the subsequent treatments used in the model are based on UK clinical expert opinion (see Table 17). The subsequent treatment use by treatment arm was derived as an average across the four clinical experts interviewed by the company, which was [REDACTED] for the perioperative durvalumab arm and [REDACTED] for the control arm. These estimates were applied in the model to all patients who experienced progression (i.e., upon leaving the EF health state). In response to EAG clarifications (question B12b), the company provided an additional scenario analysis using the proportions of subsequent treatments based on the NIAGARA trial (see Table 25 of company response to EAG clarifications).

The cost of end of life or terminal care was applied as a one-off cost upon entering the death state (Table 55 of CS).

Table 17: Summary of costs used in the company's base case analysis

Item	Model input (Unit cost)	Description
Drug acquisition costs		
Durvalumab	[REDACTED] per unit size of 500mg (acquisition cost per treatment cycle of [REDACTED])	Per cycle cost calculated based on the dosing of durvalumab in MIBC: 1500 mg dose per admin, with the admin frequency per cycle of 1 and unit size of 500 mg. Includes confidential PAS discount ([REDACTED] discount off the list price) for durvalumab.
Gemcitabine	£16.40 per unit size of 1000mg (acquisition cost per treatment cycle of £65.59)	Per cycle cost calculated based on the dosing of gemcitabine of 1000mg/m ² admin, with unit size of 1000mg and 2 admin per cycle.
Cisplatin	£3.67 per unit size of 10mg (acquisition cost per treatment cycle of £51.40)	Per cycle cost calculated based on the dosing of cisplatin of 70mg/m ² admin, with unit size 10mg and 1 admin per cycle.
Drug administration cost (per admin)		
Durvalumab	£394.17	Assuming treatment cycle length of 21 days and 1 admin per cycle in the neoadjuvant setting and 28 days and 1 admin per cycle in the adjuvant setting.

Item	Model input (Unit cost)	Description
Gemcitabine	£788.33	Assuming treatment cycle length of 21 days and 2 admin per cycle
Cisplatin	£394.17	Assuming treatment cycle length of 21 days and 1 admin per cycle
Diease monitoring (health state) costs		
EF health state	£136.53	Calculated as a sum product of unit cost of resouce items and proportionof patients receiving care in particular health state. Resource use was defined by the NIAGARA trial schedule of assessments, the NICE TA817, and EAU and ESMO guidelines. ^{15, 55-57} Unit costs were sourced from NHS reference costs 2023 24 and PSSRU 2022-23 service costs. ^{54, 58} See Table 50 of CS.
LR health state	£549.24	
DM health state	£548.91	
Cystectomy costs	£17,921.35	The cystectomy cost was estimated based on the unit cost of cystectomy with urinary diversion and reconstruction (LB39C and LB39D). Cost was applied based on the assumed frequency of radical cystectomy, which was 88.00% in perioperative durvalumab and 83.20% in control arm (see Table 51 of CS)
AE management costs		
Anaemia	£1,533.30	AE-associated cost was calculated as the sum product of the unit cost, duration, and frequency, and was applied as a one-off event at the start of the time horizon. Unit costs for AE management were sourced from the NHS reference costs 2023-24 ⁵⁴ (see Table 53 of CS).
Lipase level increase	£1,819.86	
Neutropenia	£1,533.30	
Neutrophil count decrease	£1,533.30	
Thrombocytopenia	£2,440.46	
Urinary tract infection	£2,472.27	
Subsequent treatment use post-recurrence, cost per administration		
Atezolizumab:	£3,807.69	The cost of subsequent treatments was estimated based on opinion from UK clinical experts on the drugs provided to MIBC patients who progressed and their frequencies. See Table 54 of CS.
Avelumab:	£3,072.00	
Nivolumab:	£2,633.00	
Carboplatin:	£17.16	
Cisplatin:	£48.19	
Gemcitabine:	£16.40	
Paclitaxel:	£34.88	
Erdafitinib:	£910.71	

Item	Model input (Unit cost)	Description
End of life (EOL) costs	Hospital care: £7,211.55 Social care: £543.62 Nurse community support: £719.93 GP: £446.90	Modelled as one-off cost applied to patients that enter the death state. The cost of EOL care was calculated from a study by Georghiou and Bardsley, ⁵⁹ and inflated to a 2023 using PSS pay and price index ⁵⁸ (See Table 55 of CS)

4.2.7.2 Points for critique

In general, the EAG considers the approach used by the company to derive resource use and costs to be appropriate. The drug acquisition and administration costs were informed with appropriate sources. The approach to estimate time on treatment based on the observed proportion of patients who received each scheduled treatment cycle in each arm of NIAGARA is appropriate as there is no reason to expect it to differ if administered in the NHS and no patient remained on neoadjuvant or adjuvant treatment in NIAGARA at the data cut-off. One limitation is that the costs of treatment cycles administered during the non-cystectomy extension phase were excluded from the treatment cost calculations. However, given that these patients represented only 1.1% of the trial population, this limitation is expected to have minimal impact on the results. In addition, these patients are expected to fall outside the licensed indication.

For the costs of cystectomy, the EAG notes that the company assumed different proportions of patients in each arm undergoing surgery based on the NIAGARA trial. The EAG assesses the assumption that durvalumab leads to a lower proportion of patients undergoing cystectomy as uncertain in NHS practice. However, the EAG's clinical advisor considered it a reasonable assumption in the absence of an alternative source.

The EAG notes that the company included costs associated with AEs for the intervention and comparator but did not include costs associated with AEs for subsequent treatments post-recurrence because any AE costs for subsequent therapies are expected to impact both arms of the model. However, the EAG notes that the company assumed different proportions of patients receiving subsequent treatments post-recurrence for the perioperative durvalumab and control arms; therefore, total costs associated with AEs would be expected to differ between the two arms. Nonetheless, the EAG notes that the company's assumption is potentially conservative given that the proportion of patients who received subsequent cancer treatment was higher in the control arm than the perioperative durvalumab arm. Therefore, the EAG does not expect the exclusion of AE costs associated with subsequent therapies to have a material impact on the cost-effectiveness results.

The EAG has some concerns about the assumptions used for subsequent treatments in the model. The EAG notes that the subsequent treatment use was based on the opinion of four UK clinicians rather than the subsequent treatments used in the NIAGARA trial. The company justifies this approach because the NIAGARA trial was a global, multinational study where post-progression clinical practice varied between centres and different treatments may be available in each country. In principle, the EAG agrees with the company's approach because the treatments used post-recurrence should reflect those available and most frequently used in NHS practice for MIBC. However, the extrapolated survival outcomes used in the model only reflect subsequent anticancer therapies used in NIAGARA. The model does not allow for adjustment to these survival outcomes to account for the different types of post-progression therapies, such as those used in the NHS. The EAG's clinical advisors reviewed the treatments included in the company's base case analysis and determined that most of them reflect UK clinical practice. However, they noted that nivolumab is not licensed as a treatment for recurrent/metastatic MIBC, i.e., not included as part of the subsequent treatments post-recurrence. Nivolumab is recommended as an adjuvant treatment for invasive urothelial cancer at high risk of recurrence. For this reason, in the EAG's base case, the EAG has excluded nivolumab from the subsequent treatments post-recurrence (Section 5.2.3). Adjuvant nivolumab is considered as part of the treatment pathway for the comparator arm for patients eligible to receive it.

The EAG's clinical advisor was uncertain about the proportion of patients receiving subsequent post-recurrence treatments in the NHS but agreed that the estimates in Table 54 of the CS are reasonable. The average cost of subsequent therapies was applied as a one-off cost to the proportion of all progressed patients, independent of the LR and DM health states. This means that any differences in costs of subsequent therapies cannot be attributed to the individual LR and DM health states. The EAG's clinical advisor considered this to be a reasonable assumption because treatment regimens are similar across local and distant recurrences for MIBC. The EAG does not expect differences in subsequent treatments for LR and DM to have a material impact on cost-effectiveness results.

The company has assumed that nivolumab and atezolizumab are used in IV form only. However, the EAG notes that both these drugs are also available in subcutaneous (SC) form. The EAG's clinical advisors were unable to provide an estimate of the proportion of SC use versus IV use in NHS practice but noted that the availability of subcutaneous administration was a factor when choosing a treatment because it has time and resource savings compared with intravenous administration. In the absence of an estimate of the proportion of SC use, the EAG has considered a scenario in Section 5.2.2 that assumes that 25% of patients receive these treatments subcutaneously in NHS practice (i.e., 25% SC use and 75% IV use) based on recommendations in NICE Technology Appraisal ID6346⁶⁰ for SC use. In this scenario, the cost of SC administration is based on NHS reference cost code N10AF (£110.64 from NHS national tariff 2022/23 for SC⁶⁰).

4.2.7.3 *Summary of the costs included in the company's scenario with nivolumab*

In Appendix K of the CS, the company provides information on HCRU and costs for the scenario that includes adjuvant nivolumab for PD-L1 expression $\geq 1\%$ and high-risk MIBC patients. The drug acquisition cost for nivolumab was sourced from the BNF (2025) and its dosing regimen was derived from the SmPC for nivolumab and the CheckMate-274 trial (Table 5 of Appendix K to CS). Drug acquisition costs for the other treatments that form part of the control arm remain unchanged from the company's base case.

Time on treatment data was not available from the CheckMate-274 trial; therefore, time on treatment for adjuvant nivolumab was estimated using the adjusted EFS curve from the ITC to determine the proportion of patients receiving treatment in each model cycle. It was assumed that 15% of patients would discontinue adjuvant nivolumab after a single dose due to adverse events, based on CheckMate-274 data, while the remaining 85% would continue treatment until recurrence (according to the survival-time-adjusted EFS data from the ITC) or until completion of 12 months of therapy. The proportion of patients receiving each cycle of treatment is provided in Table 7, Appendix K, of the CS.

The model used cost and healthcare resource use data for the health states from NICE TA817, which did not differ by treatment arm. The cost of cystectomy and AE management costs were based on assumptions made in the base-case analysis and assumed equal across arms (see AE frequencies provided in Table 3, Appendix K of CS). Subsequent treatment profiles for nivolumab were assumed to be the same as in the base-case analysis without nivolumab, but excluding the use of nivolumab as a subsequent treatment post-recurrence (see Table 8, Appendix K of CS). End-of-life costs were the same as the company's base-case analysis.

4.2.7.4 *Points for critique*

For the resource use and costs assumed in the scenario that includes nivolumab, the EAG considers the assumptions associated with drug acquisition and administration costs to be reasonable, except that SC nivolumab may be used for a proportion of patients in NHS practice.

The EAG notes that the company did not account for the cost of testing patients for the presence of PD-L1 expression $\geq 1\%$. In the perioperative durvalumab arm, all patients receive adjuvant durvalumab regardless of their PD-L1 expression level but, in the control arm, for patients to be eligible to receive adjuvant nivolumab they need to be at high risk of recurrence after radical resection and have tumours expressing PD-L1 at a level of 1% or more. Therefore, testing for PD-L1 expression is required for patients at high-risk of recurrence in the control arm. Consequently, the EAG has included the costs for PD-L1 testing in the scenario with nivolumab (Section 5.2.3). The unit cost for a PD-L1 test (£121.08) is based on NICE TA639.⁶¹ This cost is applied as a one-off cost to

the proportion of patients in the G+C+N arm (██████) the same as the proportion of patients who were at high risk of recurrence without residual disease after surgery in the NIAGARA control arm - see Table 7 of the company's response to EAG clarifications).

The company assumed the same subsequent treatments post-recurrence for the scenario with nivolumab as the base-case analysis, except with the exclusion of nivolumab as a post-recurrence treatment. The EAG notes that the use of adjuvant nivolumab could impact on the choice of subsequent therapies post-recurrence and, therefore, some differences may be expected in subsequent treatment use, with and without adjuvant nivolumab. Nonetheless, the EAG expects the impact of any differences on the cost-effectiveness results to be minor.

5 COST-EFFECTIVENESS RESULTS

Section 5.1 summarises the company's cost-effectiveness results, section 5.2 presents the EAG's additional work and preferred assumptions, and section 5.3 explores decision modifiers, if applicable.

5.1 Company's cost effectiveness results

5.1.1 Company's base case

The cost-effectiveness results presented in the CS are based on a confidential PAS discount (██████) off the list price of durvalumab, and the list price for comparator treatments. Table 18 and Table 19 present the company's deterministic and probabilistic base case results, respectively. The company states that "*it is not anticipated that perioperative durvalumab would qualify for a severity modifier in this indication*"; therefore, the company does not present results for alternative severity modifiers. The EAG checked eligibility for a severity modifier using the QALYs estimated from the control arm of the company's base case (total QALYs of 6.56) and the additional scenario with adjuvant nivolumab (total QALYs of 6.88). In both cases, the QALY estimates do not meet the thresholds for a QALY weight of 1.2 or 1.7 under absolute or proportional QALY shortfall calculations.

Table 18 Company's deterministic base-case cost-effectiveness results (disease severity modifier of 1.0)

-	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.0 weighting)	ICER (£/QALY) (x1.0 weighting)
Control (G+C)	51,704	6.56	-	-	-
Perioperative durvalumab	██████	██████	██████	██████	£14,048

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

Table 19 Company's probabilistic base-case cost-effectiveness results (disease severity modifier of 1.0)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.0 weighting)	ICER (£/QALY) (x1.0 weighting)
-					
Control (G+C)	50,909	6.57	-	-	-
Perioperative durvalumab	████	████	████	████	£14,081

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

5.1.2 Company's sensitivity and scenario analyses

The company presents results of the deterministic sensitivity analysis in section 3.11.2 of the CS. The EAG was able to replicate these analyses.

The company presents the list of scenario analyses and results in section 3.11.3 of the CS. The EAG was able to replicate these analyses, except scenario 9 "IO use in subsequent treatment in the perioperative and control arms not included". In this scenario, the percentage of patients receiving subsequent therapy was proportionally distributed to non-IO therapies. The company's results and EAG's validation results for scenario 9 are shown in Table 20.

Table 20 Cost-effectiveness results for scenario 9 reported in the CS and EAG validation

	Incremental costs (£)	Incremental QALYs	ICER Perioperative durvalumab versus control (£/QALY)	Change from base case ICER (%)
Company's results	████	████	£13,583.21	-3.31%
EAG's validation results	████	████	£15,812.94	+12.56%

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

The company conducted an additional scenario with adjuvant nivolumab included as part of the control arm for those eligible to receive nivolumab. The cost-effectiveness results for this scenario are presented in Table 21. The EAG was able to replicate these results.

Table 21 Company's scenario results with adjuvant nivolumab (disease severity modifier of 1.0)

	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs (x1.0 weighting)	ICER (£/QALY) (x1.0 weighting)
Control with nivolumab (N+G+C)	£56,744	6.88			
Perioperative durvalumab	████	████	████	████	£13,723

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

5.2 EAG's additional analyses

5.2.1 Model validation and face validity check

The EAG reviewed the company's model in detail and applied the TECHNical VERification (TECH-VER) checklist (see Appendix 3).¹ The EAG identified several errors in the electronic version of the model, which were corrected by the EAG:

1. The extrapolated MFS curve picked up the extrapolated EFS curve at the point of crossing, while the CS states that '*EFS is constrained to values that are less than or equal to MFS*'. The EAG corrected this error such that the EFS curve picked up the MFS curve at the point of crossing, in line with the statements in the CS. This correction also meant that an adjustment to the OS curve was not required in the model when the extrapolated EFS curve crossed the OS curve because when the EFS curve is constrained to values less than or equal to MFS, and the MFS curve is constrained to values less than or equal to OS, then the EFS curve would never implausibly dominate the OS curve.
2. The calculation formulae in worksheet 'Model', columns ER and HQ, rows 376-461 was not consistent with previous cells. For example, for cell ER376 the formulae =IF(Settings!\$G\$13="OS",MAX(EK376,EL376),EL376) was corrected to =MAX(EQ376,EL376).
3. The calculation formulae relating to the hazards for the company's scenario in response to EAG clarifications that sets the HR=1 after 5 years. However, this scenario does not form part of the company's base case or EAG analyses; therefore, the error has no impact on the cost-effectiveness results.
4. In the probabilistic setting for the Cholesky decomposition for OS (calculation errors when selecting flexible models for OS extrapolation). This error involved corrections to multiple cells in the 'parameters' worksheet.

Table 22 presents the results of the EAG corrected company base case, while Table 23 presents the results of the EAG corrected company scenario with adjuvant nivolumab.

Table 22 Results of EAG's corrected company base case

–	Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company's base case [Table 59 of the CS]	Control	£51,704	6.56			
	Durvalumab	■	■	■	■	£14,048
EAG's corrected company base case	Control	£51,704	6.56			
	Durvalumab	■	■	■	■	£14,280

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

Table 23 Results of EAG's corrected company scenario with adjuvant nivolumab

	Treatment	Total costs	Total QALYs	Incremental costs (£)	Incremental QALYs	Cumulative ICER £/QALY
Company's scenario with nivolumab [Table 63 of the CS]	Control	£56,744	6.88			
	Durvalumab					£13,723
EAG's corrected company scenario with nivolumab	Control	£56,743	6.88			
	Durvalumab					£14,004

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

5.2.2 EAG's exploratory analyses using company's base case

Table 24 provides a summary of the EAG's exploratory analyses using the company's corrected base case, while Table 25 and Table 26 present the results of the EAG's exploratory analyses for the company's base case and scenario with adjuvant nivolumab, respectively. A disease severity modifier of 1.0 applies to all EAG analyses. Deterministic results are presented due to the substantial time required to run all analyses probabilistically.

Table 24 Summary of EAG's exploratory analyses using company's base case

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
1	EFS extrapolation: 2-knot spline normal for control	EFS extrapolation: generalised gamma for control	To show sensitivity of results to parametric model selection using the best fitting generalised gamma model for the control arm	Section 4.2.5.2 Subheading: Model selection for extrapolation of survival outcomes
2	OS extrapolation: Gompertz for durvalumab, log-logistic for control	OS extrapolation: Gompertz for durvalumab, Gompertz for control	To show sensitivity of results to parametric model selection using the most optimistic OS in both arms (Gompertz model)	Section 4.2.5.2 Subheading: Immaturity of the OS data used in the extrapolations

Exploratory analysis number	Company's base-case assumption	EAG scenario	Justification for EAG assumption	Section in EAG report
3	OS extrapolation: Gompertz for durvalumab, log-logistic for control	OS extrapolation: log-logistic for durvalumab, log-logistic for control	To show sensitivity of results to parametric model selection using the least optimistic OS in both arms (log-logistic model)	Section 4.2.5.2 Subheading: Immaturity of the OS data used in the extrapolations
4	OS extrapolation: Gompertz for durvalumab, log-logistic for control	OS extrapolation: 1-knot spline odds for durvalumab, 1-knot spline hazard for control	Best fitting models for OS extrapolation that reflect the observed hazard profile of OS from NIAGARA	Section 4.2.5.2 Subheading: Model selection for extrapolation of survival outcomes
5	Model starting age: 64.4 years	Model starting age: 70 years	To show sensitivity of results to starting age used in the model	Section 4.2.5.2 Subheading: Impact of baseline age on modelled survival outcomes
6	Increased death risk due to comorbidities: none	Increased death risk due to comorbidities: hazard ratio of 1.42	To show sensitivity of results to an increased non-cancer-related death risk due to comorbidities in the target population compared to the general population risk.	Section 4.2.5.2 Subheading: Increased risk of non-cancer-related death due to comorbidities in population with MIBC
7	Subsequent treatments: include nivolumab	Subsequent treatments: exclude nivolumab	Nivolumab is not licensed as a treatment for recurrent/metastatic MIBC	Section 4.2.7.2
8	Administration of atezolizumab and nivolumab: 100% IV	Administration of atezolizumab and nivolumab: 75% IV and 25% SC	Atezolizumab and nivolumab are also available in SC form	Section 4.2.7.2
9 [for scenario with adjuvant nivolumab in the control]	Exclude cost for PD-L1 test in the scenario analysis with nivolumab	Include cost for PD-L1 test (£121.08) in the scenario analysis with nivolumab	Testing for PD-L1 expression is required for patients at high-risk of recurrence in the control arm to determine eligibility for adjuvant nivolumab	Section 4.2.7.2

Abbreviations: EFS, event-free survival; IV, intravenous; OS, overall survival; SC, subcutaneous

Table 25 Results of EAG's exploratory analyses using company's [corrected] base case (deterministic analysis)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's base case [corrected]	-	████	████	£14,280
1	EFS extrapolation: generalised gamma for control	████	████	£15,284
2	OS extrapolation: Gompertz for durvalumab, Gompertz for control	████	████	£19,289
3	OS extrapolation: log-logistic for durvalumab, log-logistic for control	████	████	£18,733
4	OS extrapolation: 1-knot spline odds for durvalumab, 1-knot spline hazard for control	████	████	£19,016
5	Model starting age: 70 years	████	████	£19,000
6	Increased death risk due to comorbidities: 1.42	████	████	£16,322
7	Subsequent treatment: exclude nivolumab	████	████	£14,348
8	Administration of atezolizumab and nivolumab: 75% IV and 25% SC	████	████	£14,286

Abbreviations: EFS, event-free survival; IV, intravenous; OS, overall survival; SC, subcutaneous

The EAG considers a disease severity modifier of 1.0 is appropriate.

Table 26 Results of EAG's exploratory analyses using company's [corrected] scenario with nivolumab (deterministic analysis)

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
Company's scenario with nivolumab [corrected]	-	████	████	£14,004
1	EFS extrapolation: generalised gamma for control	████	████	£15,083
2	OS extrapolation: Gompertz for durvalumab, Gompertz for control	████	████	£20,180
3	OS extrapolation: log-logistic for durvalumab, log-logistic for control	████	████	£20,066
4	OS extrapolation: 1-knot spline odds for durvalumab, 1-knot spline hazard for control	████	████	£20,404
5	Model starting age: 70 years	████	████	£19,043
6	Increased death risk due to comorbidities: 1.42	████	████	£16,133
7	Subsequent treatment: exclude nivolumab	████	████	£13,934
8	Administration of atezolizumab and nivolumab: 75% IV and 25% SC	████	████	£14,152

Exploratory analysis number	Scenario applied to company's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
9	Include cost for PD-L1 test (£121.08) in the scenario analysis with nivolumab			£13,982

Abbreviations: EFS, event-free survival; IV, intravenous; OS, overall survival; SC, subcutaneous

5.2.3 EAG's preferred assumptions

The EAG's preferred assumptions include the following changes to the company's base case:

- The EAG considers the relevant comparator to be neoadjuvant chemotherapy and radical cystectomy (RC), followed by no treatment or adjuvant nivolumab in eligible patients.
- The OS extrapolations are informed by the best fitting flexible spline models for each arm: for perioperative durvalumab this is the 1-knot spline odds and for the control arm this is the 1-knot spline hazard. This contrasts with the company's standard parametric models, with the Gompertz distribution selected for the perioperative durvalumab arm and the log-logistic distribution for the control arm.
- Subsequent treatments post-recurrence excludes nivolumab (nivolumab is not licensed as a treatment for recurrent/metastatic MIBC), which is included in the company's base case.
- The EAG includes the cost of PD-L1 testing for the comparator with adjuvant nivolumab.

The comparator with adjuvant nivolumab was excluded from the company's base case but included as a separate scenario by the company. Therefore, the EAG presents two base cases:

- (i) EAG base case 1 with the same comparator as the company's base case (i.e., without adjuvant nivolumab); and
- (ii) EAG base case 2 with comparator consisting of neoadjuvant chemotherapy and RC, followed by no treatment or adjuvant nivolumab in eligible patients.

Table 27 shows the cumulative impact of the EAG's preferred assumptions on the company's base case ICER – EAG base case 1, while Table 28 shows the cumulative impact of the EAG's preferred assumptions on the company's scenario with adjuvant nivolumab – EAG base case 2.

Table 29 shows the corresponding probabilistic results for EAG base case 1 and EAG base case 2. The EAG notes that the probabilistic ICERs are sensitive to greater uncertainty in the flexible spline models for OS.

Table 27 Deterministic results using EAG's preferred model assumptions [EAG's base case 1]

Preferred assumption	Exploratory analysis number	Treatment	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	Cumulative ICER £/QALY
Company's base case	NA	Control	£51,704	6.56			
		Durvalumab	████	████	████	████	£14,048
EAG's corrected company base case	NA	Control	£51,704	6.56			
		Durvalumab	████	████	████	████	£14,280
OS extrapolations: 1-knot spline odds for durvalumab, 1-knot spline hazard for control	4	Control	£58,834	7.32			
		Durvalumab	████	████	████	████	£19,016
Subsequent treatment: exclude nivolumab	4 + 7	Control	£58,606	7.32			
		Durvalumab	████	████	████	████	£19,150
EAG's base case 1: control arm without adjuvant nivolumab	4 + 7	Control	£58,606	7.32			
		Durvalumab	████	████	████	████	£19,150

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; QALYs, quality-adjusted life years

Table 28 Deterministic results using EAG's preferred model assumptions [EAG's base case 2]

Preferred assumption	Exploratory analysis number	Treatment	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Cumulative ICER £/QALY
Company's scenario with nivolumab	NA	Control	£56,744	6.88			
		Durvalumab	████	████	████	████	£13,723
EAG's corrected company scenario with nivolumab	NA	Control	£56,743	6.88			
		Durvalumab	████	████	████	████	£14,004
OS extrapolations: 1-knot spline odds for durvalumab, 1-knot spline hazard for control	4	Control	£63,557	7.62			
		Durvalumab	████	████	████	████	£20,404
Subsequent treatment: exclude nivolumab	4 + 7	Control	£63,557	7.62			
		Durvalumab	████	████	████	████	£20,239
	4 + 7 + 9	Control	£63,590	7.62			

Preferred assumption	Exploratory analysis number	Treatment	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Cumulative ICER £/QALY
Include cost for PD-L1 test (£121.08)		Durvalumab					£20,186
EAG's base case 1: control arm with adjuvant nivolumab	4 + 7 + 9	Control	£63,590	7.62			
		Durvalumab					£20,186

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; QALYs, quality-adjusted life years

Table 29 Probabilistic results for EAG base case 1 and 2

Preferred assumption	Exploratory analysis number	Treatment	Total costs	Total QALYs	Inc. costs (£)	Inc. QALYs	Cumulative ICER £/QALY
EAG's base case 1: control arm without adjuvant nivolumab	4 + 7	Control	£57,988	7.31			
		Durvalumab					£21,905
EAG's base case 2: control arm with adjuvant nivolumab	4 + 7 + 9	Control	£63,325	7.58			
		Durvalumab					£23,242

Abbreviations: ICER, incremental cost-effectiveness ratio; NA, not applicable; OS, overall survival; QALYs, quality-adjusted life years

5.2.4 Scenario analyses using EAG's preferred assumptions

Two important uncertainties remain that have a substantial impact on the cost-effectiveness results:

- The starting age used in the model.
- The increased death risk due to comorbidities.

The company's base case and scenario analyses are based on a starting age of 64.4 years from the NIAGARA trial. The starting age of the modelled cohort has a large impact on the extrapolated OS probabilities because the hazard rate of OS is constrained to be at or above the age- and gender-matched all-cause general population risk of death. The time point at which the risk of death approaches that of the general population depends on the starting age used in the model. Similarly, an increased death risk (1.42) relative to the general population risk due to comorbidities in the target population has a large effect on the extrapolated OS in the model due to mortality risk constraints.

Table 30 summarises the EAG's scenario analyses that use a starting age of 70 years and an increased death risk of 1.42 in the model to illustrate the impact on the cost-effectiveness results.

Table 31 shows the corresponding results for EAG base case 1 and EAG base case 2 with a starting age of 70 years rather than 64.4 years, and with an increased death risk of 1.42 rather than none.

Table 30 Summary of EAG's scenario analyses using EAG's preferred assumptions

-	EAG's base-case assumption	EAG's scenario
1	EAG's base case 1: Model starting age of 64.4 years	EAG's base case 1 + Model starting age of 70 years
2	EAG's base case 2: Model starting age of 64.4 years	EAG's base case 2 + Model starting age of 70 years
3	EAG's base case 1: no increased death risk due to comorbidities	EAG's base case 1 + increased death risk of 1.42
4	EAG's base case 2: no increased death risk due to comorbidities	EAG's base case 2 + increased death risk of 1.42

Table 31 Deterministic results of EAG's scenario analyses using EAG's preferred assumptions

Scenario analysis number	Scenario applied to EAG's base case	Incremental costs (£)	Incremental QALYs	ICER £/QALY
1	EAG's base case 1 + Model starting age of 70 years	████	████	£25,587
2	EAG's base case 2 + Model starting age of 70 years	████	████	£27,359
3	EAG's base case 1 + increased death risk of 1.42	████	████	£22,120
4	EAG's base case 2 + increased death risk of 1.42	████	████	£23,527

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

5.3 Decision modifiers

5.3.1 QALY weighting for severity

The company has not presented a case for a QALY weighting for severity. After checking eligibility for a severity modifier using QALYs estimated from the control arm of the company's and EAG's base case and the additional scenario with adjuvant nivolumab, the EAG agrees with the company that the intervention does not meet the thresholds for a QALY weight of 1.2 or 1.7 under absolute or proportional QALY shortfall calculations.

5.3.2 Uncaptured benefits

In section 3.13 of the CS, the company highlights several benefits not captured in the QALY calculations: the value of hope associated with a new treatment, option value, early treatment planning, costs of informal care and impact on caregivers and family members, society benefits, long-term care costs from a Personal Social Services perspective, addressing inequalities, and addressing an unmet need in MIBC.

The EAG considers the value of hope and option value to be subjective and difficult to quantify, whilst outside the NICE reference case. The benefits of early treatment planning are also outside the NICE reference case. The costs of informal care and impact on caregivers and family members could be a significant benefit that is not captured in the QALY calculations; however, the company have not presented any quantitative evidence to show that MIBC is associated with a substantial effect on carer's health-related quality of life and how the availability of perioperative durvalumab benefits carers. Similarly, the company have not provided comprehensive information on the costs of long-term care that are expected to be significantly different between perioperative durvalumab and the comparator. The EAG considers the extent of unmet need is reflected within the severity definition, but a disease severity modifier does not apply in this appraisal.

The EAG has identified a potential uncaptured benefit in the company's model, which is the impact of post-recurrence therapies. The model's long-term survival projections are based only on the subsequent cancer treatments used in the NIAGARA trial. However, a limitation is that some post-recurrence therapies might be so effective that they return a proportion of patients to a state of event-free survival. In this scenario, their quality of life and risk of future events may be similar to those of patients who never had a recurrence. If this is the case, the model may not be fully capturing the true, long-term benefits of these later-line treatments, which remains an uncertainty.

5.3.3 Health inequalities

The company has not presented any quantitative evidence to show that perioperative durvalumab substantially affects health inequalities, but the company states that the intervention addresses inequalities, especially for women and people with a lower socioeconomic status (Section 3.13 of CS).

5.4 Confidential comparator and subsequent treatment prices

The confidential appendix to this EAR includes analyses using confidential prices for atezolizumab, avelumab, nivolumab, and erdafitinib. The confidential appendix presents the results of the company base-case analysis, sensitivity and scenario analyses and the results of exploratory analyses conducted by the EAG, with results reflecting the application of confidential discounts.

5.5 Conclusions of the cost-effectiveness section

The company submitted a partitioned survival model to estimate the cost-effectiveness of perioperative durvalumab compared with neoadjuvant chemotherapy followed by RC and either (i) no treatment (company's base case analysis) or (ii) adjuvant nivolumab for patients whose tumours express PD-L1 $\geq 1\%$ and present high-risk of recurrence (company's scenario analysis). The EAG considers the relevant comparator to be neoadjuvant chemotherapy and RC, followed by no treatment

or adjuvant nivolumab in eligible patients (i.e., the company's scenario analysis) because this reflects established standard of care in the NHS. However, the NIAGARA trial was not designed to include adjuvant nivolumab in the control arm for the high-risk, PD-L1 $\geq 1\%$ population. Consequently, counterfactual survival times for the control arm of NIAGARA for the proportion of patients eligible for adjuvant nivolumab had to be estimated (Section 3.5). The EAG considers the approach used may overestimate the effectiveness of nivolumab; however, a control without adjuvant nivolumab as used in the company's base case analysis is likely to underestimate the effectiveness of the comparator. Consequently, the EAG presents two base case analyses, with and without adjuvant nivolumab.

The EAG considers the company's partitioned survival model to be appropriate, but its validity largely depends on the maturity of the survival data, particularly OS. Because the model projects survival outcomes over a patient's lifetime, any uncertainty in the long-term OS projections directly impacts the cost-effectiveness of perioperative durvalumab relative to the comparator. The EAG also notes that uncertainty in the OS projections not only impacts the survival benefit, but it also has implications for the implied time point of 'cure' from cancer, where the risk of death becomes equal to that of the general population. Consequently, the starting age in the model is a key input as it directly determines the all-cause mortality risk in the general population.

The EAG has a number of concerns in relation to the treatment effectiveness evidence and assumptions used in the model. The first concern is the extrapolation of immature data. The company's analysis relies on the NIAGARA interim results (April 2024 cut off), in which median EFS was reached only in the control arm, while median MFS and OS were not reached in either arm. Extrapolating the immature data beyond the trial follow-up introduces uncertainty in the long-term projections. The second concern is model selection for OS extrapolation. In the NIAGARA trial, OS hazard rates in both arms peak at around 10 months post-randomisation and then converge, approaching near-zero by the end of follow-up. In contrast, the company's base-case OS extrapolation produces diverging hazards, with the hazard ratio increasing over time before eventually converging due to the constraint of general population mortality. The EAG considers that there is no empirical evidence to support an increasing hazard ratio over time. The third concern is the effect of model starting age. The starting age of the modelled cohort strongly influences extrapolated OS probabilities because the hazard rate is constrained to be at or above the age- and sex-matched general population risk of death. Consequently, the time at which the predicted mortality approaches the general population depends on the cohort's starting age.

Another key concern for the EAG is that people with MIBC in the NIAGARA trial are likely to have a higher risk of cancer-non-related mortality than the general population. Many NIAGARA participants had risk factors such as smoking (23.7% current smokers and 49.3% ex-smokers) and

other comorbidities. As a result, even if cancer-related deaths are removed, the overall mortality risk in this population is likely to exceed that of the general population.

The EAG also has three minor concerns: (i) the inclusion of nivolumab in the basket of subsequent treatments post-recurrence, despite it not being licensed for recurrent or metastatic MIBC; (ii) the assumption that nivolumab and atezolizumab are administered intravenously, whereas subcutaneous formulations are recently available for both treatments; and (iii) the omission of costs for PD-L1 testing in the adjuvant nivolumab scenario.

The model assumptions with the greatest influence on the ICER are:

- The choice of extrapolation model for OS in the comparator arm
- The starting age of the modelled cohort
- Increased risk of non-cancer-related death.

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61. National Institute for Health and Care Excellence. *Atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer [TA639].* NICE; 2020. Available from: <https://www.nice.org.uk/guidance/ta639> [accessed 28 August 2025]

APPENDICES

APPENDIX 1. CLINICAL EVIDENCE SEARCHES

Table 32 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	PARTLY	In the original company submission: The strategy for the database INAHTA was separated from the other databases and this source is referred to as a 'website' which is incorrect. The database CDSR was accidentally referred to as CSRD in Table 5 and Table 9, which is incorrect. The date of the original searches is listed as 22nd July 2024 on page 38 but CDSR and CENTRAL were listed as being searched a day earlier. The company refer to removing duplicates on the databases (e.g., on page 41 in the PRISMA) but do not show this in the search strategy.
Were appropriate sources searched?	YES	An adequate range of relevant databases were searched. A good range of conference proceedings, grey literature sources and trials registries were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The PICO structure was for the condition and intervention and study types.
Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the condition could have been more sensitive such as including some of the following examples, (which are not exhaustive): Urinary Bladder Neoplasms as a subject heading on Medline, CDSR and CENTRAL. Moreover, the free-text terms could have included: tumor, tumour, myoinvasive, locally advanced bladder cancer, metastatic or advanced bladder cancer, and truncated invasive at invas* to retrieve terms like invade, invasion etc. This was raised as a point for clarification. In response, the company confirmed that no relevant evidence was missed. The search terms for the interventions were very limited. The free-text terms could have been more sensitive in various respects, such as (but not limited to) searching for a wider range of synonyms (e.g. radical cystectomy is bladder removal but this term isn't searched for); searching for acronyms (e.g. MTX for methotrexate); searching a wider range of brand names for drugs (e.g. (cis-platinum, dichlorodiammineplatinum, biocisplatinum, platidiam, or platino for the intervention cisplatin); searching drugs in additional field codes relating to drugs (which can be done on both Medline and Embase). Moreover, some of the intervention terms are searched for in combination with other subject headings rather than separately, which is not ideal – although the searcher is trying to reflect the combinations of drugs listed in the inclusion criteria, it is more sensitive to search for the drug terms separately as so many different terms, brand names etc can be used for each drug. This was raised as a point for clarification. In response, the company confirmed that no relevant evidence was missed.
Were any search restrictions applied appropriate?	YES	Irrelevant paper and publication types were removed in some of the search strategies as part of a validated RCT filter.

TOPIC	EAG RESPONSE	NOTE
Were any search filters used, validated and referenced?	PARTLY	Search filters were used but not referenced. However, a validated RCT filter has been used.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 2. COST-EFFECTIVENESS, HEALTH-RELATED QUALITY OF LIFE, COST AND HEALTHCARE RESOURCE IDENTIFICATION, MEASUREMENT, AND VALUATION SEARCHES

Summary

Overall, an appropriate adequate range of relevant databases were searched alongside conference proceedings and health technology assessment agency websites. The reporting of the searches was mainly clear, and the structure of the search and the limits applied were appropriate. The search terms could have been more comprehensive, but the company confirmed that no relevant evidence was missed.

Search strategy

The original company submission included searches to identify cost-effectiveness studies for muscle-invasive bladder cancer in adults. A description of the searches and the search strategies were included in Appendix E (pp. 1-36). The health-related quality of life searches referred to in Appendix F and the cost and healthcare resource identification, measurement, and valuation searches referred to in Appendix G were also described and documented in Appendix E (pp. 1-36). In response to the EAG's points for clarification, the company provided additional information and corrections to errors.

Table 33 EAG appraisal of evidence identification

TOPIC	EAG RESPONSE	NOTE
Is the report of the search clear and comprehensive?	YES	In the original company submission: The PRISMA in Figure 1 (page 35) would have been clearer if the records identified from databases showed the hits per each source.
Were appropriate sources searched?	YES	A range of relevant databases, conference proceedings, and health technology assessment agency websites were searched.
Was the timespan of the searches appropriate?	YES	The time span of the searches was appropriate.
Were appropriate parts of the PICOS included in the search strategies?	YES	The searches combined the condition and the study type.

TOPIC	EAG RESPONSE	NOTE
Were appropriate search terms used?	PARTLY	In the original company submission, the search terms for the condition could have been more sensitive such as including some of the following examples, (which are not exhaustive): Urinary Bladder Neoplasms as a subject heading on Medline, CDSR and CENTRAL. Moreover, the free-text terms could have included: tumor, tumour, myoinvasive, locally advanced bladder cancer, metastatic or advanced bladder cancer, and truncated invasive at invas* to retrieve terms like invade, invasion etc. This was raised as a point for clarification. In response, the company confirmed that no relevant evidence was missed. The Embase search strategy employed a line to remove certain records on non-muscle invasive bladder cancer (line 107). This could have risked removing relevant records. This was raised as a point for clarification. In response, the company confirmed that no relevant evidence was missed.
Were any search restrictions applied appropriate?	YES	There are language restrictions in the original searches.
Were any search filters used, validated and referenced?	PARTLY	Search filters were used but not referenced, therefore we cannot tell if they were validated.

EAG response = YES/NO/PARTLY/UNCLEAR/NOT APPLICABLE

APPENDIX 3. TECH-VER CHECKLIST

Table 34 EAG appraisal of the model using TECH-VER Checklist

Topic	EAG Response
<i>Pre-analysis calculations (Model input)</i>	
Does the technology (drug/device, etc.) acquisition cost increase with higher prices?	Yes, the drug acquisition cost increase with higher price.
Does the drug acquisition cost increase for higher weight or body surface area?	Yes
Does the probability of an event, derived from an OR/RR/HR and baseline probability, increase with higher OR/RR/HR?	Yes
In a partitioned survival model, does the progression-free survival curve or the time on treatment curve cross the overall survival curve?	No
If survival parametric distributions are used in the extrapolations or time-to-event calculations, can the formulae used for the Weibull (generalized gamma) distribution generate the values obtained from the exponential (Weibull or Gamma) distribution(s) after replacing/transforming some of the parameters?	Yes
Is the HR calculated from Cox proportional hazards model applied on top of the parametric distribution extrapolation found from the survival regression?	No
For the treatment effect inputs, if the model uses outputs from WINBUGS, are the OR, HR, and RR values all within plausible ranges? (Should all be non-negative and the average of these WINBUGS outputs should give the mean treatment effect)	Not applicable
<i>Event-state calculations</i>	
Calculate the sum of the number of patients at each health state	The sum adds up to the cohort size
Check if all probabilities and number of patients in a state are greater than or equal to 0	Yes, probabilities and number of patients in a given health state are greater than or equal to 0
Check if all probabilities are smaller than or equal to 1	Yes
Compare the number of dead (or any absorbing state) patients in a period with the number of dead (or any absorbing state) patients in the previous periods?	The number of dead is larger compared to the number of dead in previous periods
In case of lifetime horizon, check if all patients are dead at the end of the time horizon	Yes
Discrete event simulation specific: Sample one of the 'time to event' types used in the simulation from the specified distribution. Plot the samples and compare the mean and the variance from the sample	Not applicable (partition survival model)
Set all utilities to 1	QALYs and LYs are same
Set all utilities to 0	No utilities accumulated
Decrease all state utilities simultaneously (but keep event-based utility decrements constant)	Lower utility accumulated each time
Set all costs to 0	No costs accumulated in the model at any time
Put mortality rates to 0	Not possible to set mortality rates to 0 without editing the model trace
Put mortality rate at extremely high	Not possible to set a higher mortality rate without editing the model trace

Topic	EAG Response
Set the effectiveness-, utility-, and safety-related model inputs for all treatment options equal	Not possible to set the same effectiveness inputs without editing the model trace
In addition to the inputs above, set cost-related model inputs for all treatment options equal	Not possible to set the same effectiveness inputs without editing the model trace
Change around the effectiveness-, utility- and safety-related model inputs between two treatment options	Not possible to set the same effectiveness inputs without editing the model trace
Check if the number of alive patients estimated at any cycle is in line with general population life-table statistics	The proportion alive is lower or equal to the general population estimate
Check if the QALY estimate at any cycle is in line with general population utility estimates	Utility assigned is lower or equal to the general population utility
Set the inflation rate for the previous year higher	End of life costs are higher
Calculate the sum of all ingoing and outgoing transition probabilities of a state in a given cycle	Difference between ingoing and outgoing probabilities at a cycle in a given health state yield the change in number of patients at that state in that cycle
Calculate the number of patients entering and leaving a tunnel state throughout the time horizon	Not applicable
Check if the time conversions for probabilities were conducted correctly.	Yes
Decision tree specific: Calculate the sum of the expected probabilities of the terminal nodes	Not applicable
Patient-level model specific: Check if common random numbers are maintained for sampling for the treatment arms	Not applicable
Patient-level model specific: Check if correlation in patient characteristics is taken into account when determining starting population	Not applicable
Increase the treatment acquisition cost	Cost accumulates during the treatment period.
Population model specific: Set the mortality and incidence rates to 0	Not possible to implement without editing model trace
Result calculations	
Check the incremental life-years and QALYs gained results. Are they in line with the comparative clinical effectiveness evidence of the treatments involved?	Yes
Check the incremental cost results. Are they in line with the treatment costs?	Yes, more costly and effective
Total life years greater than the total QALYs	Yes
Undiscounted results greater than the discounted results	Yes
Divide undiscounted total QALYs by undiscounted life years	Yes, within the ranges of all utility value inputs
Subgroup analysis results: How do the outcomes change if the characteristics of the baseline change?	Subgroup analysis not performed (only scenario analysis performed)
Could you generate all the results in the report from the model (including the uncertainty analysis results)?	Yes, all base case results
Do the total life-years, QALYs, and costs decrease if a shorter time horizon is selected?	Yes
Is the reporting and contextualization of the incremental results correct?	Yes
Are the reported ICERs in the fully incremental analysis nondecreasing?	Yes

Topic	EAG Response
If disentangled results are presented, do they sum up to the total results (e.g. different cost types sum up to the total costs estimate)?	Yes
Check if half-cycle correction is implemented correctly (total life years with half-cycle correction should be lower than without)	Yes
Check the discounted value of costs/QALYs after 2 years	Yes
Set discount rates to 0	Discounted and undiscounted results are the same
Set mortality rate to 0	Not possible to implement without editing model trace
Put the consequence of adverse event/discontinuation to 0 (0 costs and 0 mortality/utility decrements)	Results are similar (£10 diff in ICER)
Divide total undiscounted treatment acquisition costs by the average duration on treatment	The quotient is similar to the unit cost of treatment acquisition
Set discount rates to a higher value	Discounted results decrease
Set discount rates of costs/effects to an extremely high value	Total discounted results were similar to the discounted results in the first cycles
Put adverse event/discontinuation rates to 0 and then to an extremely high level	Less cost and same QALYs when AEs=0; when AEs were set to extremely high, high cost but same QALYs/LYs
Double the difference in efficacy and safety between the new intervention and comparator, and report the incremental results	Not possible to check as this requires making changes in the model trace
Do the same for a scenario in which the difference in efficacy and safety is halved	Not possible to check as this requires making changes in the model trace
<i>Uncertainty analysis calculations</i>	
Are all necessary parameters subject to uncertainty included in the OWSA?	Yes
Check if the OWSA includes any parameters associated with joint uncertainty (e.g. parts of a utility regression equation, survival curves with multiple parameters)	No
Are the upper and lower bounds used in the one-way sensitivity analysis using confidence intervals based on the statistical distribution assumed for that parameter?	Yes
Are the resulting ICER, incremental costs/QALYs with upper and lower bound of a parameter plausible and in line with a priori expectations?	Yes
Check that all parameters used in the sensitivity analysis have appropriate associated distributions – upper and lower bounds should surround the deterministic value (i.e. upper bound ? mean ? Lower bound)	Yes
Standard error and not standard deviation used in sampling	Yes
Lognormal/gamma distribution for HRs and costs/resource use	Yes
Beta for utilities and proportions/probabilities	Yes
Dirichlet for multinomial	Not applicable
Multivariate normal for correlated inputs (e.g. survival curve or regression parameters)	Not applicable
Normal for other variables as long as samples do not violate the requirement to remain positive when appropriate	Yes
Check PSA output mean costs, QALYs, and ICER compared with the deterministic results. Is there a large discrepancy?	No

Topic	EAG Response
If you take new PSA runs from the Microsoft Excel model do you get similar results?	Yes
Is(are) the CEAC line(s) in line with the CE scatter plots and the efficient frontier?	Yes
Does the PSA cloud demonstrate an unexpected behavior or have an unusual shape?	No
Is the sum of all CEAC lines equal to 1 for all WTP values?	Yes
Do the explored scenario analyses provide a balanced view on the structural uncertainty (i.e. not always looking at more optimistic scenarios)?	Yes
Are the scenario analysis results plausible and in line with a priori expectations?	Yes
Check the correlation between two PSA results (i.e. costs/QALYs under the SoC and costs/QALYs under the comparator)	Low correlation
If a certain seed is used for random number generation (or previously generated random numbers are used), check if they are scattered evenly between 0 and 1 when they are plotted	Not applicable
Compare the mean of the parameter samples generated by the model against the point estimate for that parameter; use graphical methods to examine distributions, functions	Not applicable
Check if sensitivity analyses include any parameters associated with methodological/structural uncertainty (e.g. annual discount rates, time horizon)	Yes
Value of information analysis if applicable: Was this implemented correctly?	Not applicable, VOI analysis not performed
Which types of analysis? Were aggregated parameters used? Which parameters are grouped together? Does it match the write-up's suggestions?	Not applicable
Is EVPI larger than all individual EVPPIs?	Not applicable
Is EVPPI for a (group of) parameters larger than the EVSI of that (group) of parameter(s)?	Not applicable
Are the results from EVPPI in line with OWSA or other parameter importance analysis (e.g. ANCOVA)?	Not applicable
Did the electronic model pass the black-box tests of the previous verification stages in all PSA iterations and in all scenario analysis settings? (Additional macro can be embedded to the PSA code, which stops the PSA when an error such as negative transition probability is detected)	Yes
Check if all sampled input parameters in the PSA are correctly linked to the corresponding event/state calculations	Input parameters in the PSA for parametric survival model generated using cholesky decomposition were not linked correctly

Single Technology Appraisal

Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer [ID6168]

EAG report – factual accuracy check and confidential information check

“Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release.” (Section 5.4.9, [NICE health technology evaluations: the manual](#)).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 9 September 2025** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [REDACTED] should be highlighted in turquoise and all information submitted as '[REDACTED]' in pink.

Issue 1 Regulatory status

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2 Page 20 states: The company is awaiting marketing authorisation for perioperative durvalumab for this indication from the Medicines and Healthcare products Regulatory Agency (UK MHRA) after approval by the European Medicines Agency (EMA) in February 2025 and the US Food & Drug Administration (FDA) in March 2025	The company received marketing authorisation for perioperative durvalumab for this indication from the Medicines and Healthcare products Regulatory Agency (UK MHRA) in August 2025 after approval by the European Medicines Agency (EMA) in February 2025 and the US Food & Drug Administration (FDA) in March 2025	Regulatory status update after submission	Updated.

Issue 2 Patient demographics: Additional references use to describe demographics for patients with MIBC

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 2.1.1 Page 22 includes 4 new references describing MIBC patient's demographics, 3 of them include median age data that is not aligned with the patient population within the scope of this appraisal.	Provide comprehensive details of the mentioned demographics to ensure clarity and transparency for the reader or remove. Catto 2023 – No reported age or survival for patients under scope (resectable MIBC, cisplatin eligible) John 2021 – Only 8.9% (224) were resectable MIBC, cisplatin eligible patients – no median age reported for patients under scope Brück 2024 – Only 29.3% were resectable MIBC, cisplatin eligible patients – no median age or survival reported for patients under scope. Brück 2024 as reference from other another country should be substituted for Nikulainen, I et al The Finnish National Cystectomy Database Research Group. (2025). Neoadjuvant Chemotherapy in Muscle-Invasive Bladder Cancer: A Nationwide Analysis of Eligibility, Utilization, and Outcomes. <i>Cancers</i>, 17(3), 505. – This reference is specific for MIBC patients undergoing RC and the median age of patients receiving NAC + RC was 65 years, and 82% were men. The median age for	The references cited—Catto 2023, John 2021, and Brück 2024—each feature a heterogeneous mix of patients including those with MIBC and, in some cases, bladder cancer in general. Importantly, these cohorts include individuals eligible for RC, ineligible for NAC, and ineligible for treatment with curative intent. Presenting these aggregate data without clearly distinguishing them from the relevant context of this appraisal—resectable MIBC patients who are cisplatin-eligible—is inappropriate. Such an undifferentiated approach risks misleading the reader regarding the clinical and demographic characteristics of the population under consideration and does not support robust decision-making. This point is discussed	Not a factual inaccuracy. The fact that these references include a broader population is acknowledged and characteristics of the included populations are summarised in the text. For further clarity we have made additions to pp.21-23: “However, no age data were available specifically for the population in the NICE scope (resectable MIBC, cisplatin eligible).” added to pg 21 and “...although they did not provide estimates for the population in the NICE scope (resectable MIBC,

	patients receiving RC only was 72 years, and 80% were men.	in greater detail under Issues 3-5.	cisplatin eligible).” added to pg 23 Table 5, pg 23 includes Nikulainen et al. (2025)

Issue 3 Patient demographics: applicability to the NHS population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4 Page 37 states In addition, there is uncertainty about the applicability of the demographics of the NIAGARA trial participants to the NHS population eligible for treatment with perioperative durvalumab. Section 3.2.4 Page 38 states The extent to which the NIAGARA trial population reflects the NHS population is therefore uncertain.	Section 3.2.4 Page 37 Although there is some uncertainty regarding the exact correlation of demographic characteristics between UK patients and those included in the NIAGARA trial, and in the absence of robust UK evidence for patients eligible for treatment with perioperative durvalumab, none of the potential anecdotal differences are anticipated to affect the applicability of NIAGARA's results to the UK population, as clinical experts consulted by the company unanimously confirmed. Therefore, the NIAGARA population is considered	The company considers the assertion that there is uncertainty regarding the applicability of the NIAGARA trial demographics to the NHS population eligible for perioperative durvalumab is factually incorrect. The applicability of participant characteristics was systematically tested with five UK-based clinical experts, all of whom confirmed unanimously that the NIAGARA population accurately reflects their real-world clinical practice. The EAG consulted a smaller number of experts, and nowhere in their report is there any stated disagreement with the baseline demographics of NIAGARA. Furthermore, the UK was included among the trial countries including 4	Not a factual inaccuracy. Views on uncertainty regarding the applicability of the trial population are a matter of interpretation. We reflected the views of our clinical advisers. We also note that one of the company clinical advisers noted that the median age (65) in NIAGARA “is slightly younger than typical UK patients (70)” (AZ_Clinical validation).

	representative of UK real-world practice and relevant for decision-making. Section 3.2.4 Page 38 Five UK-based clinical experts consulted by the company validated that the NIAGARA trial population reflects their clinical practice.	sites, ensuring additional relevance. None of the registry data cited as evidence by the EAG correspond directly to the appraisal scope, nor do they provide extractable conclusions supporting a lack of representativeness. Therefore, the most robust piece of evidence remains the clinical validation provided by the company, which demonstrates consensus among experts on the relevance of NIAGARA's results for the UK population's demographic characteristics. Any specific concerns raised by the EAG regarding other demographic variables, such as age, are addressed under Issues 2, 4 and 5.	

Issue 4 Patient demographics: age of the population

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4 Page 37, states Clinical advisers noted that although the trial population	Clinical advisers noted that although the trial population was considered broadly representative of patients undergoing RC, patients treated in UK clinical practice tend to be slightly older than the ones included	The way this statement is currently phrased may inadvertently mislead the reader. It is important to differentiate between the	Not a factual inaccuracy. This reflects the EAG's clinical adviser's view. We have clarified this by adding "One clinical

was considered broadly representative of patients undergoing RC, patients treated in UK clinical practice tend to be slightly older.	in the trial. Although, MIBC patients undergoing RC and receiving cisplatin-based neoadjuvant chemotherapy are usually younger than MIBC patients undergoing RC in general.	broader group of MIBC patients undergoing RC and the more specific subgroup of MIBC patients undergoing RC and receiving NAC, in order to accurately reflect the population in scope for this appraisal. The latter population is typically younger because of the cisplatin eligibility criteria—including factors such as renal function, hearing capacity, and ECOG performance—which are directly influenced by age. This distinction has been acknowledged by the EAG throughout the report. Further evidence of this can be found in the patient characteristics of UK participants within the NIAGARA trial, which clearly demonstrate a younger cohort: among 19 patients recruited at four centres across the UK, the mean age was [REDACTED], median age [REDACTED], with a range from [REDACTED] years. Aligning the statement as is done elsewhere in the EAG report will help ensure clarity for	adviser to the EAG noted that...”

		decision-makers and a more accurate reflection of the population under evaluation.	

Issue 5 Patient demographics: Starting age of modelled cohort

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Sections 3.2.4, 4.2.5.2 Pages 37, 38, 80, 81. EAG critique of the applicability of NIAGARA results to England population due to potential differences in age and a scenario with starting age 70 years in the model	Remove the scenario	A starting age of 70 years old is not aligned with the expected starting age of patients in UK clinical practice. The EAG acknowledges in its report that the population within scope (patients with resectable MIBC who are eligible for gemcitabine and cisplatin (NAC and RC) is distinct, described as “younger and fitter than the broader population of patients with MIBC” (page 21), and further agrees that “the BAUS MITRE audit reports on a broader MIBC population than the population in scope, and that this general population can be expected to be older and less fit than patients eligible for NAC and RC” (page 38). Despite this, the EAG continues to cite age references—including those in Table 5 (see Issue 2—which are not specific to the relevant patient population. Robust, external evidence consistently demonstrates that cisplatin-eligible MIBC patients are substantially younger than the general MIBC population. For example, in the Finnish nationwide cohort registry, patients receiving NAC+RC had a mean age of 65 at treatment	Not a factual inaccuracy. The EAG has not removed the scenario for a model starting age of 70 years. This EAG scenario is presented to show the sensitivity of the cost-effectiveness results to the starting age used in the model, as explained in Table 24 of the EAR. In Section 4.2.5.2, p80-81, the EAG explains why the starting age of the modelled cohort has a large impact on the results and this is

		initiation, compared to 72 among cisplatin-ineligible patients (Nikulainen I et al., Cancers 2025, 17(3), 505)—with disease staging closely matching the NIAGARA trial population. Similarly, epidemiological data from the SAVANNAH study, a large real-world U.S. dataset (Optum Market Clarity), shows that cisplatin-eligible MIBC patients receiving NAC had a mean age of [REDACTED], while MIBC patients in general had a mean age exceeding 70. The 5.9-year age difference ([REDACTED] vs. [REDACTED] years, p value [REDACTED]) between cisplatin-eligible and the broader MIBC is clinically and statistically significant. The difference between MIBC cisplatin eligible and MIBC ineligible was even higher. Please see SAVANNAH study details in the table below. <table><tr><th>Age</th><th>Total (N=2,210)</th><th>Eligible Cisplatin (N=222)</th><th>Ineligible Cisplatin (N=1,003)</th><th>p-value</th></tr><tr><td>Mean</td><td>[REDACTED]</td><td>[REDACTED]</td><td>[REDACTED]</td><td>[REDACTED]</td></tr><tr><td>Median</td><td>[REDACTED]</td><td>[REDACTED]</td><td>[REDACTED]</td><td></td></tr></table> As explained in Issue 4, the UK cohort of the NIAGARA study show similar age patterns, with a mean age of 64.3 years and a median age of 64.0 years, as describe in detail in the following table.	Age	Total (N=2,210)	Eligible Cisplatin (N=222)	Ineligible Cisplatin (N=1,003)	p-value	Mean	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	Median	[REDACTED]	[REDACTED]	[REDACTED]		demonstrated in Figure 10 of the EAR. The starting age used in the EAG’s base case 1 and 2 is the same as that used in the company’s base case, i.e., a starting age of 64.4 years corresponding to the mean age of participants in the NIAGARA trial. The starting age of 70 years in the scenario analysis is to show the substantial impact that starting age has on the cost-effectiveness results. We make this clear throughout Section 4.2.5.2 and Sections 5.2.2 and 5.2.4 and at no point suggest that 70 years is the relevant starting age to be used in the model. The EAG considers it important that the committee is aware that the cost-effectiveness results are highly sensitive to the starting age used in
Age	Total (N=2,210)	Eligible Cisplatin (N=222)	Ineligible Cisplatin (N=1,003)	p-value														
Mean	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]														
Median	[REDACTED]	[REDACTED]	[REDACTED]															

		Age (years)	D+G+C N=533	G+C N=530	Total N=1063	the model, which is why the EAG has presented this scenario.
		N	7	12	19	
		Mean	████	████	████	
		SD	████	████	████	
		Median	████	████	████	
		Min	█	█	█	
		Max	█	█	█	
		Range	████	████	████	
		Notably, these findings are directly in line with the only NHS data for MIBC patients receiving NAC and RC, which come from North East England and report a mean age of 66 years for this specific population. The fact that a baseline age of 70 was adopted in other appraisals, such as TA817, does not justify its use in this context. TA817 included both cisplatin-eligible and cisplatin-ineligible patients, resulting in an older cohort overall, as demonstrated by the evidence presented. Adopting a baseline age of 70 in the economic model is inappropriate and inconsistent with the baseline age in the NIAGARA study (64.4 years				

		old), the primary evidence base for this appraisal. Baseline characteristics used in the economic model must ensure consistency with the most relevant source of evidence, i.e., the NIAGARA trial, on which other key parameters are based (e.g., efficacy data, treatment duration and utilities) and adopting external sources will lead to internal inconsistency in the economic analysis and bias interpretation of the outcomes. In conclusion, the scenario adopting a starting age of 70 years for patients in the economic model should be removed. It is not supported by clinical trial data, national and international registry evidence, or expert consensus. The population under appraisal—resectable MIBC patients eligible for cisplatin-based neoadjuvant chemotherapy—is consistently shown to be substantially younger than the broader MIBC population, with robust data demonstrating a mean age closer to 64 years. Including a scenario based on a starting age of 70 is methodologically unjustified, internally inconsistent with key efficacy and utility parameters, and risks distorting the appraisal's results and conclusions. For decision-making to be rigorous and clinically relevant, the age assumptions must accurately reflect the population in scope; therefore, the 70-year starting age scenario should not be considered.	

Issue 6 Contribution of phases clarification

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.1 Page 33 states By comparing different treatment sequences, the NIAGARA design precludes the possibility of isolating the neoadjuvant from the adjuvant effect on efficacy and safety outcomes	NIAGARA design precludes the possibility of isolating the neoadjuvant from the adjuvant effect on efficacy and safety outcomes. However, discontinuation due to adverse events were reported for neoadjuvant and adjuvant phases separately.	While the effect of previous neoadjuvant phase cannot be isolated from the contribution to adjuvant phase, it is important to clarify for readers how safety reporting was handled, as patient performance and fitness can differ before and after surgery. For appraisal purposes, the perioperative regimen must be assessed as a single, integrated treatment. Clinicians make prescribing decisions based on the overall benefit-risk of the complete regimen, which is supported by evidence for the full treatment course. It is neither appropriate nor clinically justified to separate the phases for evaluation; only the combined perioperative strategy provides a valid basis for decision-making.	Not a factual inaccuracy. For clarification, we have added: "However, discontinuation due to adverse events were reported for the neoadjuvant and adjuvant phases separately."

Issue 7 Open label design and HRQoL risk of bias

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.2 Page 34 states However, the lack of participant blinding means that HRQoL, which relies on self-reported information, is at high risk of bias.	However, the lack of participant blinding means that HRQoL, which relies on self-reported information, the extent and direction of bias is unknown.	While it is recognised that open-label trials may introduce some risk of bias in patient-reported outcomes such as HRQoL, the company notes that the direction and magnitude of this bias are not straightforward to determine. For example, patients receiving durvalumab could potentially report better QoL due to positive expectations about their treatment, yet they may also face additional challenges such as immune-related adverse events and the burden of more frequent hospital visits, which could negatively impact reported HRQoL. Given these counterbalancing factors, it is not possible to infer a definitive, high risk of bias, in either direction, solely based on the absence of blinding as there are conflicting factors that could both increase and decrease the likelihood of self-reported detriments in QoL. In this context, it is most appropriate to simply acknowledge the potential for bias and underlying uncertainty, rather than	Not a factual inaccuracy. This statement is not about direction, magnitude nor evidence of bias, but about risk of bias. The lack of blinding of participants and the subjective nature of the outcome are legitimate causes for concern. The EAG's risk of bias judgment for the HRQOL outcome followed the Cochrane ROB 2 tool (Domain 4), which is informed by meta-epidemiological evidence.

		categorically assigning a high risk without further supporting evidence.	

Issue 8 NIAGARA trial limitations: control arm

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.2.4 Page 37 states A key limitation to the applicability of the NIAGARA trial results to the NHS setting is the control arm, which is not representative of the current standard of care for all MIBC patients who are eligible for RC.	A key limitation to the applicability of the NIAGARA trial results to the NHS setting is the control arm, does not capture the potential use of adjuvant nivolumab after NAC and RC in high-risk of recurrence after RC, PD-L1 positive patients, which represent a 5-10% of the post-cystectomy patients according to NHSE England. This limitation was addressed by the company by providing a Survival Time Adjusted ITC including and including the use of adjuvant nivolumab as a scenario in the economic model.	The Company considers that stating that the control arm of the NIAGARA trial is not representative of the current standard of care for all MIBC patients eligible for RC in the NHS is inaccurate. It is essential to underline that the population under scope is patients eligible for RC and eligible for cisplatin-based therapy. For this specific group, NAC is universally recognized as the standard of care by ESMO and EAU guidelines. The generalizability and relevance of the NIAGARA control arm was validated by UK-based clinical experts, who unanimously agreed NAC is considered the SoC in the UK. Moreover, even if the EAG suggests that adjuvant nivolumab after NAC and RC for eligible high-risk PD-L1 patients should be considered as a comparator (as included in the ITC Section of the CS), its use is restricted to a	Not a factual inaccuracy. However, the statement was amended to provide further clarity: “A limitation to the applicability of the NIAGARA trial results to the NHS setting is the control arm, which does not capture the potential use of adjuvant nivolumab after NAC and RC in PD-L1 positive patients at high-risk of recurrence after RC.”

		subpopulation and cannot be considered an appropriate universal comparator for all patients within the scope of the NIAGARA appraisal. Moreover, in response to an EAG request, NHS England indicated that only 5–10% of post-cystectomy patients in the NHS are eligible for adjuvant nivolumab in England (page 37). This evidences the highly restricted use of adjuvant nivolumab within real-world practice. Therefore, gemcitabine plus cisplatin (G+C) neoadjuvant chemotherapy remains the standard of care and the only relevant universal comparator for this population. The statement about NIAGARA's control arm lacking representativeness does not reflect current expert consensus, established guideline recommendations, or the reality of clinical practice for the population under scope.	

Issue 9 NIAGARA trial limitations: Overall Survival

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.3.1 Page 42, states However, high rates of censoring from approximately 32 weeks follow-up and limited numbers of patients at risk mean that these results are relatively immature. The impact of subsequent treatments on OS therefore remains uncertain. Further follow-up data would help to explore the extent to which subsequent therapies may impact on longer-term OS	While censoring rates increase from around 32 weeks of follow-up, the number of patients at risk in both study arms remains substantial—exceeding 100 in each arm until week 54 and only declining below 50 at week 58. A clear plateau in the Kaplan-Meier curves forms before patient numbers fall significantly, indicating that additional censoring in later follow-up does not meaningfully affect the interpretation of long-term outcomes. Whilst the impact of subsequent treatments on OS cannot be entirely excluded; however, current evidence does not suggest significant confounding within the observed time horizon. The OS results are both clinically and statistically significant and are further reinforced by consistent benefit demonstrated across additional endpoints, including disease-specific survival (DSS), metastasis-free survival (MFS), and progression-free survival post subsequent treatment (PFS-2). The present findings already provide a	While censoring rates become higher from approximately 32 weeks of follow-up, it is important to note that the number of patients at risk in each arm remains substantial—exceeding 100 until at least week 54, and only dropping below 50 at week 58. This sample size supports the reliability of survival estimates in clinically relevant timeframes. Furthermore, an evident plateau in the Kaplan-Meier curves is established well before the patient numbers fall significantly, indicating that additional censoring in later follow-up does not meaningfully affect the interpretation of long-term outcomes. With regard to OS, the results are both clinically and statistically significant. This benefit is further reinforced by the multidimensional assessment, which consistently	Not a factual inaccuracy. CS Figure 7 clearly shows high rates of censoring from 32 weeks onwards. Median OS was not reached in either arm in the interim analyses presented in the CS. PFS-2 data provided in response to the EAG's clarification request added limited information with regards to the potential impact of subsequent therapies on OS. The sentence was amended slightly for further clarity: “However, the immaturity of the OS data, and high rates of censoring from approximately 32 weeks follow-up and limited numbers of patients at risk

	robust basis for assessing longer-term survival and clinical benefit.	demonstrates durable effect across other key endpoints: disease-specific survival (DSS), metastasis-free survival (MFS), and progression-free survival following subsequent treatment (PFS-2). The alignment of these endpoints offers a comprehensive and robust picture of efficacy. Achieving statistically significant OS results in a curative-intent, early-stage population is particularly noteworthy, as such outcomes often exceed what is typically observed or expected in similar malignancies. Taken together, the consistent and sustained efficacy across multiple endpoints should substantially reduce concerns regarding any residual uncertainty and provide strong reassurance of the overall long-term clinical benefit. Therefore, the EAG's statement suggesting the results are immature due to censoring and limited numbers at risk does not fairly represent the maturity and robustness of the data. This	mean that these results are relatively uninformative."

		statement should be removed or, at a minimum, modified to reflect the substantive evidence of data maturity and clinical relevance.	

Issue 10 OS and MFS hazard profiles

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5 Page 74 states The hazard profile for OS is not dissimilar to that for MFS; for both outcomes, the hazard rates initially increase to a peak before declining towards zero over the remaining follow-up (see Figures 10 and 19 in Appendix L of the CS for MFS and OS, respectively).	The OS and MFS hazard profiles demonstrate differences from around 36 months onward.	As stated in the response to Clarification Question B6.a, the difference in extrapolation approach between OS and MFS was warranted by the difference in complexity in hazard profiles. The control arm MFS hazard profile demonstrated a distinct flattening from around 36 months onward, which the company believes benefitted from a flexible model. In contrast, the OS hazard curve demonstrated a steady decline after the second peak, which was considered well captured by standard parametric models.	The EAG has edited the text to: “The hazard profile for OS is not dissimilar to that for MFS; for both outcomes, the hazard rates initially increase to a peak before declining towards zero over the remaining follow-up - although the control arm MFS hazard appears to flatten slightly from 36 months onwards (see Figures 10 and 19 in Appendix L of the CS for

			MFS and OS, respectively)." No other changes required.

Issue 11 Proportion of post-RC patients initiating nivolumab

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 3.5.1 Page 51 states An EAG clinical adviser commented that the proportion of post-RC patients who initiated nivolumab was approximately 25% out of the total number of cystectomies for MIBC.	Suggest to remove.	It is not clear if this refers to the nivolumab population that aligns with the population under appraisal, this data might include cis-eligible and cis-ineligible patients taking into consideration the difference between EAG clinical adviser and it is not aligned with the NHSE data reflecting 5-10% of use of adjuvant nivolumab in the post-cystectomy context. To ensure transparency for the reader, it is important that any statements regarding population eligibility and treatment utilisation clearly specify whether they refer to the	Not a factual inaccuracy, although we acknowledge that this figure includes cis-ineligible patients so is of limited relevance. This sentence has therefore been removed.

		relevant subgroup under appraisal.	

Issue 12 Subsequent treatments post-recurrence (Issue 6)

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section: Secondary issues identified by the EAG. Issue 6 – page 17 states. “The EAG considers a scenario that assumes 25% of patients receive atezolizumab and nivolumab subcutaneously in NHS practice (i.e., 25% SC use and 75% IV use).” Section: 4.2.7.2 – Points for critique – page 90 states. “The EAG has considered a scenario in Section 5.2.2 that assumes that 25% of patients receive these treatments subcutaneously in NHS practice (i.e., 25% SC use and 75% IV use) based on recommendations in NICE	SC nivolumab recently received an MHRA approval (30th of April 2025) with a current use estimated at ■ according to the company’s business intelligence. Based on the above, the 25% SC and 75% IV splits would overestimate the current SC use. Suggest to include “The proportion of SC nivolumab use is potentially overestimated and the current analysis is conservative.”	The EAG treatment split between IV and SC is based on an assessment in a different disease area (untreated extensive-stage small-cell lung cancer), for a medicine that is not relevant as a comparator (Serplulimab). The IV vs SC split considered during that assessment was introduced as an assumption in a scenario analysis, and not based on atezolizumab’s (SC vs IV) use data. Nivolumab as potential therapy displaced has been provided as a scenario analysis, therefore the most relevant source of information when assessing the IV vs SC split.	Not a factual inaccuracy. No data on SC use of nivolumab were available at the time of writing of the EAR and no information was provided in the company submission. The EAG scenario with administration of atezolizumab and nivolumab: 75% IV and 25% SC is used to show the sensitivity of the cost-effectiveness results to SC use (rather than 100% IV use). This scenario does

Technology Appraisal ID634659 for SC use.”			not form part of the EAG’s base case. The EAG places it as a secondary issue because the scenario demonstrates that SC use (25%) of atezolizumab and nivolumab has minimal impact on the cost-effectiveness results. No change is required.

Issue 13 OS curve selection

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.2 Page 79 states The EAG also notes that the population in the NIAGARA control arm and the external registry studies considered by the company for validation (non-UK and data collection range from the year 1988 to 2017) are likely to differ,	Suggest to remove the sentence “The EAG also notes that the population in the NIAGARA control arm and the external registry studies considered by the company for validation (non-UK and data collection range from the year 1988 to 2017) are likely to differ, including variations in treatment intent and clinical practice between studies. “	The company finds the EAG’s statement that external registry studies are “likely to differ” from the NIAGARA data to be vague and lacking substantive justification for excluding these studies from consideration. Furthermore, the EAG’s approach to curve selection for	Not a factual inaccuracy. The EAG has justified its approach to OS curve selection in Section 4.2.5.2. However, for clarity, the EAG edited the text in Section 4.2.5.2 Page 79 to:

including variations in treatment intent and clinical practice between studies. It also states In summary, the EAG considers the best fitting flexible models (1-knot odds model for the perioperative durvalumab arm and the 1-knot hazard model for the control arm) to be the most appropriate model selection for OS extrapolation because they best reflect the observed hazard profile of OS in the NIAGARA trial. These models inform the EAG's preferred base case assumptions (Section 5.2.3)	Suggest to add the sentence "Clinician opinions and external evidence should also be considered when selecting the most appropriate model for OS extrapolation."	NIAGARA control arm overall survival appeared to focus on hazard profile assessment, without incorporating comparisons to external registry data or clinical expert opinion. The company recommends that curve selection should be informed by a comprehensive assessment that includes external evidence and clinical perspectives to ensure the robustness and validity of the modeling. Therefore, adding the proposed comment ensures readers' understanding of the context of the suggested curve selection.	"The EAG also notes that the population in the NIAGARA control arm and the external registry studies considered by the company for validation differ (see Table 5). In particular, none of the registry studies are UK-based; the median ages reported in Mahoney 2025 (72 years) and Faraj 2021 (69 years) are higher than in NIAGARA (64.4 years), Mak 2014 includes data collected between 1988 and 2007 and Vlaming 2020 is a single-institution study conducted in the Netherlands, with data collection from 1998 to 2016".

Issue 1 Application of increased mortality risks

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.5.2 Page 81 states The 5-year probability of non-cancer-related death in NIAGARA is therefore estimated to be 9.97%. The corresponding 5-year age- and gender-adjusted mortality probability for the general population is 7.11%. Assuming an exponential model for simplicity, the hazard ratio (increased death risk) would be 1.42 for people in NIAGARA versus the general population (details on how this risk is calculated are provided in the electronic version of the model).	Suggest to add “This proposed application of a hazard ratio of 1.42 in the current appraisal should be viewed as highly conservative, and reflects a higher risk of death over the entire model time horizon compared to previous appraisals, notably TA817, where a standardised mortality rate (SMR) of 1.1 was applied to patients in the disease-free survival (DFS) health state only beyond 5 years, and was removed after 10 years of residing in the DFS state.” Further consideration of the strong assumption made by assuming the 1.42 HR is applied over the model time horizon would also be welcomed.	The company suggests that more context, including drawing on precedent set in previous appraisals, is required. Notably, in TA817, an SMR of 1.1 was applied to patients in the DFS health state beyond 5 years. After 10 years of residing in the DFS state, it was assumed that patients were fully cured and the hazard of death reverted to that of an age- and sex- matched population. Whilst the company recognise that a SMR and HR may differ in definition, both have a similar intent; that is, to increase the risk of death for patients in the model compared to the general population. The magnitude of increased risk in TA817 is modest, whilst the application of a constant HR of 1.42 represents a substantially higher relative risk of death compared to the general population.	Not a factual inaccuracy. The increased mortality risk is used in an EAG scenario to show the sensitivity of the cost-effectiveness results to an increased non-cancer-related death risk in the target population compared to the general population risk, as explained in Table 24 of the EAR. This increased risk is not included in the EAG’s base case but the EAG considers it important that the committee is aware that an increased non-cancer-related death risk could have a substantial impact on the cost-effectiveness results, which is demonstrated through the

		Furthermore, TA817 applies the increased risk for a discrete period, whereas the increased risk in the current appraisal is applied across the entire model time horizon. The company therefore considers the application of a HR by the EAG to be a pessimistic and inconsistent estimate of the impact of excess mortality in this indication. In addition, the company have some comments on how the HR was applied: The increased rate of death of 1.42 was estimated by assuming a constant hazard ratio over 5 years in the NIAGARA trial and was applied to the model time horizon. This approach will overestimate the excess risk of death in the long-term, as the first few years after cancer treatment are when the non-cancer risk of death is the highest due to post-treatment complications or comorbidities triggered by cancer therapy. After living cancer-free for several years, this effect	scenario with a HR of 1.42 (Section 5.2.4 of the EAR). In the absence of reporting of an increased risk in the company submission, the EAG estimated a value based on the 5-year probability of non-cancer-related deaths in NIAGARA and used some simplifying assumptions to derive the HR of 1.42. The EAG highlights under Issue 5 of the EAR that additional information on the increased death risk due to comorbidities in patients with MIBC in the NHS is required. The EAG notes that the increased death risk used in the EAR differs from the SMR used in TA817 (reflecting the assumption that cure could not occur before 10 years of residing in the DFS state), therefore the two risk adjustments

		diminishes and surviving patients' mortality rates become closer to general population the longer they live. Therefore, a consistent rate of 1.42 derived from 5-year NIAGARA data applied over the model lifetime is too punitive. In summary, the company requests clarification from the EAG on the rationale for using a much higher risk of death across an extended period and why this approach differs from the precedent in TA817, given the similarities in indication.	cannot be compared. This also explains why the EAG applies the increased risk to the entire time horizon whilst TA817 applied it only for a discrete period. No change is applied.

Issue 2 PD-L1 testing costs

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Section 4.2.7.3 Page 91 states Consequently, the EAG has included the costs for PD-L1 testing in the scenario with nivolumab (Section 5.2.3). The unit cost for a PD-L1 test (£121.08) is based on NICE TA639.60 This cost is applied	The CEM should be amended to reflect the texts included in the EAG report- i.e., that the "cost is applied as a one-off cost to the proportion of patients in the NIAGARA control arm who were at high risk of recurrence without residual disease after surgery".	The EAG stated that the PD-L1 testing cost was applied to the proportion of patients in the NIAGARA control arm who were at high risk of recurrence without residual disease after surgery. However, in the EAG cost-effectiveness model, the	Not a factual inaccuracy. The control arm in the scenario with nivolumab implies the G+C+N arm. However, for clarity, the

as a one-off cost to the proportion of patients in the NIAGARA control arm who were at high risk of recurrence without residual disease after surgery (27.6% - see Table 7 of the company's response to EAG clarifications).		testing costs were only assigned to 27.6% patients in the G+C+N arm instead of the control arm. The company considers it more appropriate to apply the PD-L1 testing cost to all high-risk patients without residual disease in both the G+C+N arm and the control arm of the trial. This reflects clinical reality, as all such patients would be eligible for PD-L1 testing post-surgery. Those who test negative for PD-L1 would receive neoadjuvant G+C, surgery, and no adjuvant treatment and fall under the control arm in the company base case, yet they still incur the testing cost. Therefore, testing costs should be consistently applied to eligible patients across both NIAGARA control arm and G+C+N arm of the model.	EAG has edited the text in Section 4.2.7.3 Page 91 to: “This cost is applied as a one-off cost to a proportion of patients in the G+C+N arm (■%), the same as the proportion of patients who were at high risk of recurrence without residual disease after surgery in the NIAGARA control arm - see Table 7 of the company's response to EAG clarifications).”

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Table 7 Section 3.2.1 page 32	pCR, OS, PFS-2 and EORTC QLQ-C30 definitions are marked as confidential	Unmarked definitions for all the outcomes included in Table 7	Unmarked as requested.

ID6168: Durvalumab with gemcitabine and cisplatin before surgery (neoadjuvant) then alone after surgery (adjuvant) for treating muscle-invasive bladder cancer (MIBC)

Summary

AstraZeneca appreciates the opportunity to comment and provide additional evidence regarding the preferred assumptions selected by the Committee as part of the streamlined decision process for appraisal ID6168. We are disappointed that the Committee was unable to issue a positive recommendation and remain concerned that the Committee's preferred assumptions, including an increased risk of non-cancer-related death (hereafter referred to as the standardised mortality ratio (SMR) for consistency with previous appraisals), age, and overall survival extrapolations, are overly pessimistic and lack validity. Moreover, the preferred assumptions adopted in ID6168 are inconsistent with previous appraisals, the available evidence base, and the outcome of clinical validation exercises.

MIBC poses a significant clinical challenge as it is associated with rapid progression, aggressive tumours, high recurrence rates, and limited effective therapeutic options. Despite standard treatments such as neoadjuvant chemotherapy and radical cystectomy, patients face high recurrence and progression rates, with less than 60% five-year overall survival (OS) and a substantial quality of life (QoL) impact.

The NIAGARA clinical trial is the first immuno-oncology trial to demonstrate superiority over standard of care in resectable, cis-eligible MIBC, with statistically significant improvements in event free survival (EFS) and OS. Perioperative durvalumab demonstrated a 32% reduction in the risk of recurrence or death (HR 0.68; 95% CI 0.59, 0.82) and a 25% reduction in the risk of death (HR: 0.75; 95% CI 0.59, 0.93) versus neoadjuvant gemcitabine and cisplatin (G+C), and is considered by clinical experts to be the next standard of care in this disease setting.

Given the unmet need and the recognition as the future standard of care, it is critical that the Committee can reach timely, pragmatic guidance for perioperative durvalumab. To address Committee's feedback and facilitate a streamlined decision for patient access, we have provided additional evidence on the following key areas:

- **Application of age in the model:** the Committee's preferred age assumption is not generalisable to the whole of England and Wales. Furthermore, deviating from the mean age in the NIAGARA trial, introduces internal inconsistency and bias in the economic analysis (Section A).
- **Application of SMR in the model:** applying a 42% uplift in mortality across the full-time horizon of the model imposes a disproportionate and unvalidated penalty, neither justified by the available evidence or clinical expert opinion, and is inconsistent with all precedents established in prior relevant NICE appraisals (Section B).
- **Overall Survival extrapolations:** because perioperative durvalumab achieves earlier EFS stabilization than G+C (as accepted by EAG and NICE), an earlier decline in excess mortality should be expected. Enforcing the cure times (as described by the

EAG) to align between arms through the selection of a 1-knot spline for the control arm inflates post-progression survival for control arms without clinical justification, disconnects OS from EFS/MFS, and undermines clinical plausibility. (Section C).

The following sections present further scenario analyses to explore the impact of starting age and SMR on the incremental cost-effectiveness ratio (ICER), and present further supportive evidence, including alternative approaches to address Committee's feedback and facilitate a streamlined decision. The scenario results confirm that, when correctly applied, these parameters do not materially influence decision-making, with perioperative durvalumab remaining cost-effective with ICERs ranging from £13,983 to £14,316 per QALY gained depending on the scenario.

Additionally, reflecting the Committee's preference for earlier convergence of OS hazards than in the Company's base case, we present an alternative OS scenario retaining the Committee's preferred 1-knot spline odds distribution for perioperative durvalumab arm and applying a log-normal curve to the control arm.

Furthermore, we tested the alternative SMR scenarios (Scenarios 1–2 in combination with the log-normal curve for OS for the control arm) and found perioperative durvalumab remains cost-effective across all scenarios with ICERs ranging from £14,759 to £16,821 per QALY gained.

Section A: Application of age in the model

AstraZeneca considers that the Committee should retain the mean age of 64.4 years from the NIAGARA clinical trial as the model starting age instead of the North-East data provided by NHSE during the development of the EAG report.

The North-East dataset has an unknown period of data collection and, as noted by the EAG, it is uncertain whether the mean age observed in that region is representative of the whole of England and Wales. Population statistics from the Office for National Statistics confirm that North-East England population is older than the national average (median age 41.7 years versus 40.2 years for England, mid-2020 estimates). A higher mean age in North-East data therefore likely reflects regional population ageing rather than characteristics of patients eligible for perioperative durvalumab. Without transparent metadata for the North-East dataset (period of collection, sample size, inclusion criteria) and evidence of national representativeness, it should not supersede the trial as the basis for a preferred assumption.

Furthermore, UK clinical experts indicated that NIAGARA trial baseline characteristics are broadly representative of clinical practice. Within NIAGARA trial, 19 patients were enrolled across four UK sites (Weston Park Hospital, Barts Health NHS Trust, Clatterbridge Cancer Centre NHS Foundation Trust, and Edinburgh Cancer Centre). The UK subset's mean age was 64.3 years, with a median of 64 years and a range of 51 to 77 years, which aligns closely with the overall trial mean of 64.4 years and supports transferability to the national setting.

Baseline characteristics used in the economic model should remain aligned with the trial to preserve internal consistency across key parameters such as efficacy (EFS, MFS and OS), treatment duration, and utilities. Substituting the starting age in the model with a regional

demographic while leaving the NIAGARA data inputs anchored to the trial cohort introduces internal inconsistency, particularly in a model where OS is constrained to be at or above age- and sex-matched general population mortality. Increasing the starting age mechanically brings forward the point at which modelled mortality approaches the general population rate, and thereby artificially reduces extrapolated survival for both arms in a way not driven by the NIAGARA trial data. Changing only the model starting age therefore risks biasing cost-effectiveness results and decision-making.

Section B: Application of SMR in the model

AstraZeneca maintains that adopting the Company's assumption would be more appropriate, given substantive methodological limitations implemented by the EAG, absence of clinical expert validation and the exploratory nature of the EAG scenario. The EAG's rationale to explore this issue relied on the hypothesis that the target population has an increased risk of non-cancer mortality due to comorbidities including smoking, hypertension, diabetes, and renal or urinary disorders. While clinical advisors discussed the plausibility of these comorbidities impacting survival, the technical approach is flawed and the hazard ratio used to quantify excess non-cancer mortality was not validated with clinical experts by the EAG. In contrast, the Company validated the plausibility of the OS curves, which incorporated non-cancer mortality, with clinical experts.

Given the lack of clinical plausibility in the Committee preferred assumptions on the SMR, relevant precedent in the same disease setting should not be dismissed. For example, in TA817, a time-limited excess mortality of 10% (i.e., HR of 1.1) was applied in the DFS health state beyond five years and removed after ten years, with patients thereafter reverting to age- and sex-matched general population mortality, acknowledging that excess non-cancer risk is modest and diminishes over time. In contrast to the current appraisal, TA817 comprised both cisplatin eligible and cisplatin ineligible patients. Because cisplatin ineligible patients have a greater comorbidity burden (e.g, renal impairment), they consequently exhibit higher baseline non-cancer mortality than cisplatin eligible populations alone. Accordingly, applying TA817 precedent would still overestimate risk and represent a conservative scenario for perioperative durvalumab in MIBC.

The Company also performed a targeted review of appraisals in other disease settings that applied an excess risk of death above the general population (see Appendix A Table 5). More broadly, other appraisals commonly adopt modest SMRs in the approximate range of 1.09 to 1.2, often beyond a cure point and sometimes time bounded. Large, permanent uplifts similar to 1.42 have only been applied in disease settings with markedly greater comorbidity burdens or persistent treatment-related risks than perioperative MIBC. This is explained in detail in Appendix A.

In the current appraisal, the EAG estimated an excess risk of death above the general population by comparing the probability of non-cancer-related deaths across the NIAGARA trial follow-up period (~ 5 years, 64.7 months) with the corresponding 5-year age- and sex-adjusted mortality probability for the general population using the Company base case age (64.4 years). Assuming an exponential model, the EAG translated this into a constant hazard ratio of 1.42 and applied it across the full-time horizon in the model. As previously mentioned, this contrasts with relevant precedent, where excess non-cancer risk is assumed to diminish over time.

A lifetime application of a constant excess non-cancer mortality (HR 1.42) is clinically implausible and overly simplistic. Excess non-cancer risk is typically concentrated in the early post-treatment period, reflecting complications and therapy-related comorbidities, and diminishes as survivors remain disease free, with mortality risk converging towards age and sex matched population levels over time. The EAG also acknowledged that further evidence is required before applying an SMR and did not include this in their preferred assumptions; different starting age and increased mortality risk were exploratory analysis, with no scenario implementing both concurrently.

Furthermore, the Committee's preference for a higher starting age and excess mortality risk of 1.42 is inconsistent. The excess risk calculated by the EAG was based on a model starting age of 64.4. If model starting age were to increase, background mortality would also increase. As demonstrated in Table 1, the ~5-year mortality probability for the general population is 7.11% when starting at age 64.4 vs. 8.16% when starting at age 66. When the excess mortality risk is recalculated, this drops to 1.23 with the higher starting age. We recognise that the excess mortality risk in NIAGARA trial may also change with age, but the general population is expected to increase more rapidly as age becomes the primary driver of mortality for both populations. Our example has illustrated that increasing the starting age of the model is highly likely to reduce the estimated excess risk. Moreover, applying a fixed excess-mortality rate across the lifetime horizon implies an effectively increasing risk of mortality over time. This is inconsistent with the accepted view that excess risk declines over time.

Table 1. Variations in SMR according to increased starting age.

Starting age	NIAGARA follow-up	Mortality probability at NIAGARA Follow-up		1 month mortality hazard		SMR
		NIAGARA population	General population	NIAGARA population	General population	
NIAGARA 64.4 years	64.7 months	9.97%	7.11%	0.001623601	0.001139962	1.42
North-East England 66 years			8.16%	0.001623601	0.001315324	1.23

Alternative SMR and age scenarios

Following the methodological and clinical basis outlined above, it can be concluded that the EAG's exploratory assumptions are inappropriate and should not be adopted by the Committee as part of the base case for decision making. To address the interest expressed by the Committee in exploring an increased mortality risk, even where this is not aligned with feedback from consulted clinicians, we present two scenarios that build on the above rationale and more closely reflect the available evidence, relevant precedent, and clinical plausibility. Both scenarios are conservative: 1) age aligned with NIAGARA trial and SMR of 1.1 applied for entire modelled time horizon and 2) age aligned with NIAGARA trial and using the EAG's calculated SMR 1.42 for the first five years, followed by a downward trend towards 1, front-loaded to reflect the post-treatment complications or therapy-related comorbidities.

Table 2: Alternative SMR and age scenarios

Scenario	Rationale	ICER ¹
Scenario 1 - Age 64.4 - SMR 1.1	- Age: Appropriately reflects clinical population, aligned with NIAGARA; avoids inconsistency - SMR: HR consistent with comparable appraisals (1.09–1.20), still overestimating risk according to clinical feedback and precedent population	£14,316
Scenario 2 - Age 64.4 - SMR 1.42, trending towards 1	- Age: Appropriately reflects clinical population, aligned with NIAGARA; avoids inconsistency - EAG findings on excess risk in first 5-years, then reflects clinical expectation	£13,983
¹ EAG base case 2 with company preferred OS curves: Company preferred OS curve extrapolations (log-logistics for control arm, Gompertz for durvalumab arm), PD-L1 testing included, nivolumab excluded as subsequent treatment		

The scenario results are provided to confirm that these parameters do not materially influence decision-making, as perioperative durvalumab remaining cost-effective in both cases. Nonetheless, consistent with clinical input, precedent, and model coherence, the base case should use an SMR of 1, with these higher-SMR scenarios serving only as sensitivity checks.

Section C: Overall survival extrapolation

OS curve selection

The NIAGARA trial provides the longest follow-up in this disease setting extending beyond five years (64.7 months). However, median OS was not reached, and 71.1% of participants in the durvalumab arm and 62.8% of patients in the control arm were still alive and in follow-up at the time of the April 2024 DCO, indicating high rates of right-censored observations.

Based on this, the company disagrees with the overly pessimistic OS curve selection in the EAG base case, as part of the Committee preferred assumptions. The EAG considered the 1-knot spline odds model for the perioperative durvalumab arm and a 1-knot spline hazard model for the control arm to be the best-fitting models for the extrapolation of OS. This judgement was made on the goodness-of-fit compared to the observed trial data, primarily on patterns observed in the hazard profiles, without integrating external registry evidence or clinical expert opinion. Prioritising best visual fit to the observed early data, and not considering the clinical validity of extrapolations, risks over-fitting to the immature tails, forcing premature convergence of arm hazards, and generating long-term survival patterns (e.g., in post-progression survival) that are inconsistent with external evidence, expert expectations, and the observed separation in EFS and MFS Kaplan Meier curves.

Extrapolation should place greater weight on external evidence on long-term survival, clinical expert expectations, and internal consistency across EFS, MFS, DSS, and OS endpoints. The Company selected the extrapolation for the control arm based on clinical plausibility and concordance with external long-term evidence. The OS log-logistic model was chosen as the base-case for the control arm because it aligned with external literature for long-term OS in MIBC (see CS document section 3.3.2, Table 40), and it was the clinician-preferred option, with two of four experts judging it most plausible.

Cure assumption

The EAG notes that the Company's model does not include an explicit cure assumption, and instead, the EAG considers the timepoints from which implicit cure is achieved. According to the EAG report, for a patient to be considered 'cured' of MIBC, two conditions must be met: (i) the risk of events (recurrence or progression) defined by the EFS curve must not be greater than the risk of all-cause death, and (ii) there must be no risk of cancer-related deaths. In the Company's base case analysis, these conditions are met after [REDACTED] years in the perioperative durvalumab arm and after [REDACTED] years in the control arm. Whilst it is important to consider the timepoints from which patients are 'cured', if perioperative durvalumab achieves earlier EFS stabilisation compared to G+C (e.g., the risk of recurrence or progression defined by the EFS curve is equal to the risk of all-cause death), which has been accepted by the EAG and the NICE committee, excess disease-related mortality should plausibly decline earlier in the perioperative durvalumab arm, and thus a difference in cure timepoint (as defined by the EAG) should be expected. A recent systematic review by Sternberg et al. (2025) found evidence of a strong association between EFS and OS treatment effects in neoadjuvant/perioperative MIBC trials, supporting the idea that earlier EFS stabilisation should translate into earlier cure, according to the definition by the EAG. In the NICE preferred based case analysis, the two conditions for patients to be cured are met after [REDACTED] years in the perioperative durvalumab arm and [REDACTED] years in the control arm, meaning that the early modelling of converging hazards resulting in closely matched cure times across arms has overlooked an expected EFS-driven difference.

The alignment of the cure timepoint (as defined by EAG) between arms through the selection of the 1-knot spline hazard model for G+C arm implicitly lengthens post-progression survival for G+C and G+C+N relative to perioperative durvalumab, and produces a disproportionately longer post progression survival for G+C and G+C+N versus perioperative durvalumab, that is not supported by clinical evidence (see Table 3). Mechanistically, longer post-progression survival could be justified if there were durable effects after treatment cessation typical of immunotherapy, or if patients in the G+C arm systematically accessed effective therapies at recurrence. However, neither of these explanations holds here. In the perioperative durvalumab versus G+C+N comparison, both regimens are immunotherapy-containing, and any immunologic persistence should be comparable. The model also assumes the same distribution of subsequent therapies across these arms, removing differential post-progression efficacy driven by treatments as an explanation. In the perioperative durvalumab versus G+C comparison, there is likewise no clinical basis for control patients to experience substantially longer survival after progression than those initially receiving an IO-based perioperative regimen, especially given the consistent improvements in EFS, MFS, DSS and PFS-2 with durvalumab. In contrast, the company base case using loglogistic for G+C provides a comparable distribution of pre- and post-progression LYs across arms, with the distribution of life-years remaining primarily in the event-free state and a smaller share accruing in post-progression, consistent with the observed EFS/MFS separation and the modelled similarity (G+C) or equivalence (G+C+N) in subsequent-therapy use.

Table 3: Total Life Years Gained

Treatment	OS curve selection	Progression free		Progressed disease		Total LYG
		Time spent in HS	Time % accumulated in HS	Time spent in HS	Time % accumulated in HS	
D+G+C	Gompertz	■	■	■	■	■
	Spline odds (1-knot)	■	■	■	■	■
G+C	Log-logistic	6.89	83%	1.42	17%	8.32
	Log-normal	6.89	80%	1.73	20%	8.62
	Spline hazard (1-knot)	6.89	73%	2.56	27%	9.45
G+C+N	Log-logistic	7.46	86%	1.25	14%	8.71
	Log-normal	7.46	83%	1.54	17%	9.00
	Spline hazard (1-knot)	7.46	83%	2.33	17%	9.80
Abbreviations: HS: Health state; LYG: Life years gained.						

Alternative curve selection

It is acknowledged that the Committee may prefer a scenario in which OS hazards converge earlier than in the company's base case, and the difference in time points between arms where 'cure' conditions are met is less. This could be represented by the log-normal curve for the control arm, which was considered a plausible alternative by clinicians in the interviews conducted by the Company. In this scenario, the committee's preference for the 1-knot spline odds distribution for durvalumab's arm has been retained. As with the Gompertz model, the 1-knot spline odds model yields comparable distributions of pre and post-progression life-years across arms with most life-years in the event-free state and fewer post-progression consistent with the observed EFS/MFS separation and the modelled similarity (G+C) or equivalence (G+C+N) in subsequent therapy use (see Table 3). The EAG's conditions for implicit 'cure' are met after ■ and ■ years for the control and perioperative durvalumab arms, respectively, converging earlier than company base case, yet preserving the EFS-driven difference.

Table 4: Pairwise incremental cost effectiveness results – scenario analysis (deterministic)

	Perioperative durvalumab	G+C+N	Incremental
Total costs (£)	■	£58,625	■
Total LYs	■	9.00	■
Total QALYs	■	7.08	■
ICER (£ per QALY)	■	-	£14,671

Abbreviations: C: cisplatin; G: gemcitabine; ICER, incremental cost effectiveness ratio; LY, life years; N: nivolumab; QALYs, quality-adjusted life years.

Note: EAG base case 2 with company alternative control arm OS curves: OS curve extrapolations (log-normal for control arm, 1 knot spline odds for durvalumab arm), PD-L1 testing included, nivolumab excluded as subsequent treatment

Replicating the alternative scenarios for age and SMR from Table 2, perioperative durvalumab still cost-effective across all scenarios, with ICERs of £15,138 for Scenario 1 (Age: 64.4; SMR: 1.10), and £14,759 for Scenario 2 (Age: 64.4; SMR: 1.42, trending toward 1).

Conclusion

The company maintains the preference for the OS curves as per the base case in the submission, as it is plausible, internally consistent, and grounded in external evidence and clinical validation. By anchoring OS extrapolation to standard parametric models (loglogistic/lognormal) that reflect a transparent, monotone decline in hazards consistent with perioperative bladder cancer data, the base case preserves coherence across EFS, MFS, DSS, and OS and avoids over-fitting immature NIAGARA tails with splines. This yields a credible “implicit cure” dynamic aligned with earlier EFS stabilization on perioperative durvalumab and produces balanced pre- and post-progression life-year distributions consistent with observed clinical trial data and subsequent therapy use.

If residual concerns remain that OS hazards should converge earlier than in the Company’s base case, the only clinically plausible and evidence-based option for the control arm is the log-normal curve, paired with the Committee preferred 1-knot spline odds for durvalumab. This alternative maintains methodological rigor (hazard-profile assessment and clinical validation), preserves internal consistency across endpoints, and continues to demonstrate perioperative durvalumab as cost-effective across tested age and SMR scenarios.

Appendix A. Targeted Review of relevant NICE appraisals applying SMR

In Table 5, a comprehensive summary is provided of appraisals that applied an SMR greater than 1, detailing the value applied, the justification, and the supporting evidence, to facilitate the committee's informed decision making considering relevant NICE precedents.

Some of the examples that illustrate the over conservative nature of the committee preferred assumptions are:

Appraisals including a SMR ~ 1.4

- TA649 in relapsed or refractory DLBCL anchored elevated non-cancer mortality to published evidence on infections and hematologic complications.
- TA1037 in resected NSCLC considered an SMR of 1.453 due to smoking-related comorbidities and post-surgical lung damage, with literature substantiation. In TA1037, the committee noted the SMR should be viewed as an upper estimate and cautioned against potential double counting with late recurrences.
- These high SMRs pertain to settings with markedly greater comorbidity burdens or persistent treatment-related risks than perioperative MIBC.

Appraisals of aggressive malignancies where treatment entails profound increase in comorbidities including a SMR < 1.1

Even in TA895 and TA894 concerning axicabtagene ciloleucel (CAR T cell therapy) for aggressive relapsed or refractory hematologic malignancies, where treatment entails profound lymphodepletion, sustained immunosuppression, and toxicity profiles approaching those seen with hematopoietic transplantation, the SMR applied was 1.09. In contrast, for MIBC following definitive surgery and immunotherapy, excess non-cancer mortality is expected to be lower and diminish over time.

Table 5: SMR precedence in previous NICE appraisals

TA	Product	Indication	SMR	SMR justification	SMR source
TA677	Brexucabtagene autoleucel	R/R MCL	1.09	Consistent with previous CAR-T TAs.	Maurer MJ et al. Event-free survival at 24 months as a robust endpoint in DLBCL treated with immunochemotherapy. J Clin Oncol. 2014;32(10):1066-1073.
TA894	Axicabtagene ciloleucel	R/R FL	1.09	In line with the prior NICE appraisal in DLBCL, in the absence of FL-specific data identified in the literature, an SMR of 1.09 was adopted.	Maurer MJ et al. Event-free survival at 24 months as a robust endpoint in DLBCL treated with immunochemotherapy. J Clin Oncol. 2014;32(10):1066-1073.
TA895	Axicabtagene ciloleucel	R/R DLBCL	1.09	In line with previous appraisals of CAR T-cell therapies, including the 3L DLBCL appraisals.	Maurer MJ et al. Event-free survival at 24 months as a robust endpoint in DLBCL treated with immunochemotherapy. J

					Clin Oncol. 2014;32(10):1066-1073.
TA1049	Blinatumomab with chemotherapy	Consolidation treatment of Philadelphia-chromosome-negative CD19-positive minimal residual disease-negative B-cell precursor ALL.	1.09	To account for any residual complications from ALL or after having a stem cell transplant. Scenarios tested include SMRs of 2.0 and 3.0. EAG's clinical advisors commented that it is appropriate to use a lower SMR in this population because few MRD-negative patients will receive alloSCT.	Maurer MJ et al. Event-free survival at 24 months as a robust endpoint in DLBCL treated with immunochemotherapy. J Clin Oncol. 2014;32(10):1066-1073..
TA817	Nivolumab	Adjuvant treatment of invasive UC at high risk of recurrence.	1.1	To explore the impact of using a SMR for patients with resected UC increasing their risk of death compared to an age- and sex-matched population.	Value suggested by the ERG.
TA765	Venetoclax with azacitidine	Untreated AML when intensive chemotherapy is unsuitable	1.2	Applied as a scenario analysis after technical assessment.	The company applied an SMR of 1.2. ERG also assessed a scenario with an SMR=2, based on precedence TA642.
TA979	Ivosidenib with azacitidine	Untreated AML with an IDH1 R132 mutation.	1.2	Aligns with previous NICE TA, such as the appraisal of venetoclax with azacitidine for untreated AML.	Reference to TA765.
TA649	Polatuzumab vedotin with rituximab and bendamustine	R/R DLBCL	1.41	The ERG found a US study of 18,047 DLBCL patients that reported an excess risk of mortality in DLBCL patients up to five years. This excess mortality was not only due to the chance of late relapse, but DLBCL patients were also found to be at a higher risk of death due to non-cancer causes such as gastrointestinal and blood diseases and infections (SMR=1.41; 95% CI (1.35, 1.48)).	Howlader N et al. Cancer-specific mortality, cure fraction, and noncancer causes of death in DLBCL in the immunochemotherapy era. Cancer. 2017;123(17):3326-3334.

TA1037	Pembrolizumab	Adjuvant treatment of resected NSCLC.	1.453	Common comorbidities in people with NSCLC who are likely to smoke or have smoked, or lasting damage to the lungs from cancer surgery.	Janssen-Heijnen ML et al. Long-term excess mortality for survivors of non-small cell lung cancer in the Netherlands. J Thorac Oncol. 2012;7(3):496-502. The company note that using the value from this paper double counts mortality from late-stage recurrences which are already accounted for in the model. The EAG agreed, the reference states that this excess mortality is, in part, driven by late recurrences. It also lists second tumours, late side effects, or a higher comorbidity mortality rate associated with cancer-related risk factors as potential explanations for the higher mortality.

EAG ADDENDUM

Review of the company's addendum:
Durvalumab with gemcitabine and
cisplatin before surgery (neoadjuvant)
then alone after surgery (adjuvant) for
treating muscle-invasive bladder cancer
[ID6168]

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Table of Contents

Table of Contents	3
List of Tables	3
List of Figures	3
1 Overview of the Company's response to the committee's preferred assumptions	4
2 Critique of the company's additional evidence	4
2.1 Starting age used in the model	4
2.2 Application of a standardised mortality ratio (SMR) in the model	5
2.3 Overall survival (OS) extrapolation	7
3 Critique of the company's additional Cost-Effectiveness analyses	11
3.1 Company's preferred assumptions and scenario analyses	11
4 References	12

List of Tables

Table 1 Summary of the ICER results for company's scenario analyses	11

List of Figures

Figure 1 Overall survival curves under the company's (blue lines) and committee's (orange lines) preferred extrapolations for both perioperative durvalumab (solid line) and control arms (dashed line)	11

1 OVERVIEW OF THE COMPANY'S RESPONSE TO THE COMMITTEE'S PREFERRED ASSUMPTIONS

The company provides additional evidence regarding the preferred assumptions the committee selected as part of the streamlined decision process for this appraisal. This additional evidence relates to the following key areas:

- Starting age used in the model
- Application of a standardised mortality ratio (SMR) in the model
- Overall Survival (OS) extrapolations.

Within the short timelines available to the EAG, the EAG provides a critical evaluation of the company's additional evidence. The EAG critique should be read in conjunction with the company's addendum with the additional evidence, and the Evidence Assessment Report (EAR).

2 CRITIQUE OF THE COMPANY'S ADDITIONAL EVIDENCE

2.1 Starting age used in the model

Background

In the EAR, the EAG noted that the starting age of the modelled cohort significantly impacts the extrapolated OS curves used in the model. This is because the hazard rate of OS, from extrapolating the NIAGARA OS data, is constrained to be at or above the age- and gender-matched all-cause general population risk of death, and the time point at which the hazard approaches that of the general population depends on the starting age.

The mean age of the NIAGARA trial population was 64.4 years. Data provided by NHS England for the North East suggests a slightly older mean age of 66 years for patients with resectable Muscle-Invasive Bladder Cancer (MIBC) receiving neoadjuvant cisplatin-based chemotherapy. The EAG stated that it is unclear whether the North East is representative of all patients across England and Wales, and that further nationwide information on the age and sex distribution of patients who receive neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) is required to resolve this issue.

The committee's preferred age assumption is 66 years, in line with the North East England dataset. The company rejects the use of the North East England data for modelling starting age because of: (i) the uncertainty of how representative it is of the whole of England and Wales; (ii) the dataset has an unknown period of data collection; and (iii) population statistics from the Office for National Statistics shows that the North East population is older than the national average (median age 41.7

years versus 40.2 years for England, mid-2020 estimates), which suggests that the higher mean age in the regional population is likely to reflect local population ageing, not the characteristics of the eligible patient group. The company argues that the baseline characteristics used in the model, including starting age, should remain aligned with the NIAGARA trial to preserve internal consistency across the key parameters of efficacy (EFS, MFS and OS), treatment duration, and utilities. Therefore, the company retains the view that a mean starting age of 64.4 years from NIAGARA should be used in the model.

EAG comments

In the absence of further nationwide information on the age and sex distribution of patients who receive NAC followed by RC, the EAG agrees with the company that the mean modelled age of 64.4 years from NIAGARA is preferred to retain internal consistency with the other modelled parameters, particularly survival outcomes, as per the EAG base case. However, the company has not provided any additional evidence to resolve the uncertainty regarding age distribution. EAG scenarios have shown that the starting age has a significant impact on the ICER results.

2.2 Application of a standardised mortality ratio (SMR) in the model

Background

In the EAR, the EAG noted that people with MIBC from the NIAGARA trial are likely to have a higher risk of non-cancer-related death compared with the general population. This is because participants have significant mortality risk factors, including high rates of smoking (23.7% current smokers and 49.3% ex-smokers) and other comorbidities. Consequently, the overall risk of death for this population, even when excluding cancer-related mortality, is likely to exceed the general population mortality risk. An excess mortality risk was not considered in the company's original base case.

In Section 4.2.5.2 of the EAR, the EAG explored the impact of including an excess mortality risk of non-cancer-related deaths in the target population compared to the general population risk. As the company provided no data to quantify this excess risk, the EAG conducted an exploratory scenario based on available data from NIAGARA. Over the five-year follow-up period, there were 305 deaths in total across the two arms. Of these, 199 deaths were attributed to bladder cancer, which indicates that at least 106 deaths were due to non-cancer-related causes. This results in an estimated 5-year probability of non-cancer-related deaths of 9.97%. The corresponding 5-year age- and gender-adjusted mortality probability for the general population is 7.11%. In the absence of data on the hazards of death by time, the EAG applied an exponential model to estimate a constant excess hazard ratio (HR) of 1.42 for NIAGARA trial participants versus the general population. The EAG considered that this increased risk may provide a plausible scenario to reflect the mortality risk

attributed to non-cancer causes in the target population, which the committee accepted as their preferred assumption.

The company argues against the use of the EAG's exploratory scenario of applying a constant non-cancer excess mortality HR of 1.42 because: (i) this HR was not validated with clinical experts; (ii) applying a constant HR over a lifetime horizon is clinically implausible; (iii) a large uplift of 1.42 contrasts with relevant precedents in other appraisals, where modest SMRs in the range of 1.09 to 1.2 have been adopted (except in disease settings with markedly greater comorbidity burdens or persistent treatment-related risks than perioperative MIBC), often with a time-bound duration e.g., in TA817, a time-limited excess mortality of 10% (i.e., HR of 1.1) was applied in the DFS health state beyond five years and removed after ten years, with patients thereafter reverting to age- and sex-matched general population mortality; and (iv) the committee preference of applying both a HR of 1.42 and an older starting age of 66 years is inconsistent since the EAG calculation of the HR is based on the NIAGARA trial with a mean age of 64.4 years; the company shows that the HR drops to 1.23 for a starting age of 66 years, due to the higher general population mortality risk with older age.

The company provides two alternative scenarios to address the interest expressed by the committee in exploring an increased mortality risk:

- Scenario 1 with a constant, modest risk over the entire modelled time horizon: NIAGARA trial starting age of 64.4 years combined with a modest SMR of 1.1 applied for the entire modelled time horizon.
- Scenario 2 with a time-bound, front-loaded risk: NIAGARA trial starting age of 64.4 years combined with a SMR of 1.42 only for the first five years, followed by a downward trend toward 1.0 to reflect the diminishing risk of post-treatment complications or therapy-related comorbidities over time.

However, the company retains the view that an SMR of 1.0 should be used in the model.

EAG comments

The EAG is aligned with the company's comments in relation to an excess mortality risk of non-cancer-related deaths in the target population compared to the general population risk. The EAG agrees with the company that it is inconsistent to apply both an excess HR of 1.42 and an older starting age of 66 years in the model since this HR was not based on the older age. If the committee retains their preferred assumption of a starting age of 66 years, then the HR of 1.23 should be applied.

The EAG noted the limitations of the HR estimate, most notably that it implied a constant risk over time, but concluded that it provided a plausible scenario in the absence of data on the time-dependent hazards of death. The EAG's clinical advisors confirmed the view that an increased mortality risk

(cancer non-related) for the target population is clinically plausible. In the EAR, the EAG acknowledged that additional evidence is required on the excess mortality risk and did not include the HR of 1.42 in its base case (nor did it apply a scenario with both different starting age and increased mortality risk concurrently).

The EAG does not consider the precedent SMR range from other appraisals to be relevant to this appraisal. This is primarily because the target populations and indications differ (see Table 5 of company's appendix) and the associated comorbidities that cause an excess mortality risk do not necessarily correspond to those in the NIAGARA population. Therefore, the EAG retains the view that for internal consistency with the survival outcomes from NIAGARA, the data from this trial should be used to provide any estimate of an excess mortality risk in the absence of specific target population data from the NHS.

The EAG accepts the company's comments that the excess mortality risk may diminish over time. Therefore, applying a time-bound, front-loaded risk may represent a more plausible scenario to reflect the diminishing excess risk as the population ages. For this reason, the EAG considers the company's scenario 2 as the most relevant scenario for modelling an excess mortality risk. This scenario, with a five-year time-bound, is internally consistent with the five-year follow-up period of NIAGARA, upon which the HR of 1.42 is estimated, and aligns with the duration used in TA817 for adjuvant nivolumab treatment of invasive urothelial cancer at high risk of recurrence.

2.3 Overall survival (OS) extrapolation

Background

The company disagrees with the OS curve selection in the EAG base case, which forms part of the committee's preferred assumptions, stating that it is overly pessimistic. The EAG chose flexible parametric models (a 1-knot spline odds model for the perioperative durvalumab arm and a 1-knot spline hazard model for the control arm) based primarily on the best visual fit and patterns in the hazard profiles of the observed NIAGARA trial data. The company argues that prioritising best visual fit to early, immature OS data risks over-fitting and forcing an unrealistically premature convergence of arm hazards. Consequently, this generates long-term survival patterns, which the company argues is inconsistent with external evidence, expert opinion, and the observed separation in the Event-Free Survival (EFS) and Metastasis-Free Survival (MFS) curves, which the company states should be given greater weight than best visual fit and hazard profile patterns of immature data. The company selected the log-logistic model as the base case for the control arm because it aligned with external literature on long-term OS for MIBC and was the clinician-preferred option for two of four experts judging it most plausible.

Furthermore, the company highlights that the EAG defines a patient as ‘cured’ of MIBC when two conditions are met: (i) the risk of progression/recurrence (EFS curve) is not greater than the risk of all-cause death, and (ii) there is no residual risk of cancer-related death. The company states that their base case estimates meet this cure criteria earlier for the perioperative durvalumab arm (■■■■ years) than for the control arm (■■■■ years), which they state is expected and clinically plausible. This is because the perioperative durvalumab arm achieved earlier stabilisation of EFS compared to the control arm and therefore the excess disease-related mortality is expected to decline earlier, leading to an earlier cure timepoint compared to control arm. The company argues that the NICE committee’s preferred base case results in closely matched cure timepoints across both arms (■■■■ years for perioperative durvalumab and ■■■■ years for control), which overlooks the expected EFS-driven difference. In addition, the company argues that the selection of the 1-knot spline hazard model for the control arm implicitly lengthens post-progression survival for the control relative to perioperative durvalumab, which the company argues is not supported by clinical evidence.

The company acknowledges that the committee may prefer a scenario in which OS hazards converge earlier than in the company’s base case. The company proposes the following scenario:

- Scenario 3 with log-normal curve for the control arm (considered a plausible alternative to the log-logistic by one of the four clinicians interviewed by the company) and committee’s preference of the 1 knot spline odds distribution for the perioperative durvalumab arm.

EAG comments

As noted in the EAR (Section 4.2.5.2), different parametric extrapolations of the immature OS data from the NIAGARA trial lead to different projections of long-term survival. In the context of the evidence presented in the company’s submission, the EAG disagrees that, when selecting the most appropriate curve fit, external evidence, expert opinion, and the separation between EFS and MFS should be weighted more heavily than best visual fit and hazard profile patterns of the NIAGARA data. Firstly, the EAG disagrees because the company have only validated OS in the control arm with external evidence, which has been fitted independently from the perioperative durvalumab arm. The company’s approach of independently fitting models separately to each arm means that the relative effectiveness between arms has not been sufficiently validated, and it is the relative effectiveness of the curves that matter for assessing the cost-effectiveness of perioperative durvalumab vs. the control. The EAG also noted in Section 4.2.5.2 of the EAR that the population in the NIAGARA control arm and the external registry studies considered by the company for validation differ. In particular, none of the registry studies are UK-based; the median ages reported in Mahoney 2025 (72 years) and Faraj 2021 (69 years) are higher than in NIAGARA (64.4 years), Mak 2014 includes data collected between 1988 and 2007 and Vlaming 2020 is a single-institution study conducted in the Netherlands, with data

collection from 1998 to 2016. Therefore, the EAG is not convinced that the external evidence presented by the company is sufficient to validate extrapolated OS in the control arm of NIAGARA.

Secondly, the company consulted four clinical experts by asking them to select a preferred curve from the four best-fitting standard parametric distributions for each arm (log-normal, generalised gamma, Gompertz and log-logistic) but not from the flexible spline-based models, which have been shown to provide sufficient statistical and visual fit to OS for both arms of NIAGARA. The approach used by the company for OS extrapolation is inconsistent with the approach used for the extrapolation of EFS and MFS. For EFS and MFS, the company selected the best-fitting spline models for each arm. In contrast, flexible spline-based models for OS were excluded from the company submission (only provided in response to EAG clarifications) and the company excluded the best-fitting standard parametric model (generalised gamma) based solely on the opinion of one clinical expert (whose reasons for this judgement were not provided in the company submission and no data were presented to support it). This is despite the fact that the hazard profile for OS is not dissimilar to that for MFS (i.e., for both outcomes, the hazard rates initially increase to a peak before declining towards zero over the remaining follow-up). Moreover, the presence of two turning points in the OS hazard plot for the control arm suggests that a flexible model is appropriate. Overall, the EAG notes that the flexible models demonstrate a better statistical fit than the standard parametric models, evidenced by their lower AIC and BIC values, and their visual fit is also sufficient. For the perioperative durvalumab arm, the company's base case selection (Gompertz) closely aligns with the best-fitting flexible model (1-knot spline odds). However, for the control arm, there is a substantial difference in the OS projections between the best-fitting flexible model of 1-knot hazard (committee's preferred assumption based on the EAG base case) and the company's base case selection of log-logistic, or the company's additional scenario 3 of log-normal (similar to the log-logistic).

Importantly, the EAG is primarily concerned that the trend in OS hazard rates between the perioperative durvalumab and control arms in the company's base case is inconsistent with the observed hazard rates over time from NIAGARA. As explained in Section 4.2.5.2 of the EAR, Figure 32 of the company submission shows that the OS hazard rates in both the perioperative durvalumab and control arms reach a peak at around 10 months post-randomisation, after which the observed differences between arms start to converge (i.e. not just in the tails of the data), moving towards near-zero rates by the end of the follow-up period. The EAG retains the view that the model selection for the extrapolation of OS should reflect the convergence between arms observed in the trial. Thus, the EAG considers the company's base case model selection for OS extrapolation in the control arm to be overestimating mortality in this arm, because the difference between the treatment arms over the long-term is implying that the hazard ratio is increasing over a longer period (only eventually

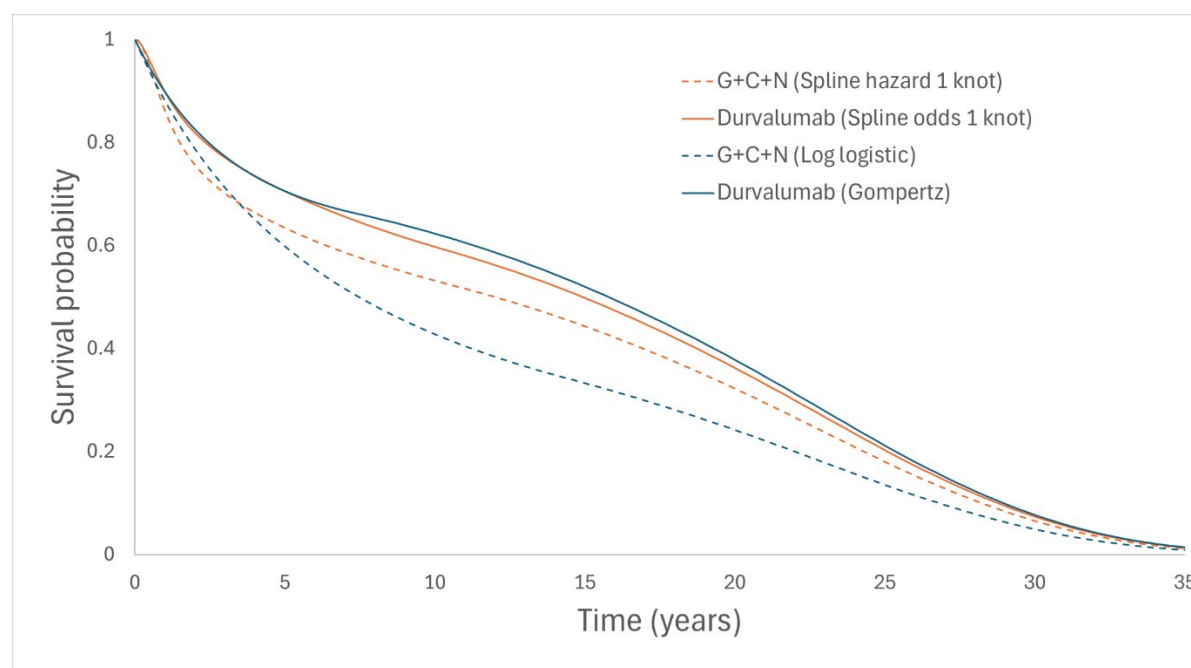
converging due to the general population mortality constraint), but there is no empirical evidence to suggest that the hazard is increasing over time.

Notwithstanding the above, the EAG does consider the company's arguments in relation to a strong association between EFS and OS treatment effects may hold, although such an association has not yet been demonstrated in the NIAGARA trial data. The recently published systematic review and meta-analysis by Sternberg et al. (2025) (published since the company submission) found evidence of a strong association between EFS and OS treatment effects for MIBC following neoadjuvant treatment. More specifically, significant survival outcome associations were observed between 3-year EFS and 5-year OS ($R^2 = 0.80$ [95% CI: 0.28–0.93]) and between median EFS time and median OS time ($R^2 = 0.97$ [95% CI: 0.45–1.00]). This suggests that the treatments effects on EFS may translate into corresponding treatment effects on OS, reinforcing the company's position that the modelling should preserve an EFS-driven difference in long-term survival outcomes.

Under the company's preferred assumptions for OS extrapolation (log-logistic for the control arm and Gompert for perioperative durvalumab), an implicit cure assumption is applied after [REDACTED] years in the perioperative durvalumab arm and after [REDACTED] years in the control arm (with adjuvant nivolumab in eligible patients). At these time points, [REDACTED] of patients in the perioperative durvalumab arm and [REDACTED] of patients in the control arm remain in the event-free health state, incurring no further risk of recurrence, progression or cancer-related death. In contrast, for the committee's preferred OS assumptions (with starting age of 64.4 years and no excess mortality risk, in line with the company's base case), the implicit cure assumption is applied at around [REDACTED] years in both arms, when [REDACTED] of patients in the perioperative durvalumab arm and [REDACTED] of patients in the control arm (with adjuvant nivolumab in eligible patients) are effectively cured and only face general population mortality risk. Figure 1 shows the differences between the OS curves under the company's and committee's preferred extrapolations for both perioperative durvalumab and control arms. The committee's preferred approach ensures that the EFS difference is applied long-term, but the mortality benefit of perioperative durvalumab converges with control over time, which aligns with the available empirical data from NIAGARA.

In conclusion, the EAG accepts that the company may have a valid point in relation to a strong association between EFS and OS treatment effects, which is not implied by the committee's preferred assumptions for OS. However, the trend in OS hazard rates between the perioperative durvalumab and control arms in the company's base case is not consistent with the observed hazard rates from the NIAGARA trial. There is no empirical evidence to suggest an increased hazard ratio between arms (before converging to the general population mortality risk). Therefore, the EAG concludes that this is an uncertainty that cannot be resolved until more mature OS data becomes available.

Figure 1 Overall survival curves under the company's (blue lines) and committee's (orange lines) preferred extrapolations for both perioperative durvalumab (solid line) and control arms (dashed line)



3 CRITIQUE OF THE COMPANY'S ADDITIONAL COST-EFFECTIVENESS ANALYSES

3.1 Company's preferred assumptions and scenario analyses

The company's base-case assumptions in relation to the three issues raised in their response to the committee's preferred assumptions remain the same, i.e., starting age of 64.4 years, no excess mortality risk (SMR = 1), and company preferred OS curves (log-logistic for control arm and Gompert for perioperative durvalumab). However, the company have provided the results of three scenario analyses (Scenario 1, 2, and 3 above) based on alternative assumptions for these three key issues. The results of the scenario analyses have been validated by the EAG and summarised in Table 1.

Table 1 Summary of the ICER results for company's scenario analyses

Scenario	ICER (£/QALY)
EAG base case 2 (committee preferred assumptions for OS, with control arm including adjuvant nivolumab in eligible patients, PD-L1 testing, and subsequent treatment without nivolumab)	£20,186
Company's preferred OS curves, with all other assumptions the same as EAG base case 2	£13,911
Scenario 1: SMR = 1.1, with company's preferred OS curves and all other assumptions the same as EAG base case 2	£14,316

Scenario	ICER (£/QALY)
Scenario 2: SMR = 1.42 for 5 years, with company's preferred OS curves and all other assumptions the same as EAG base case 2	£13,983
Scenario 3: Log-normal curve for control arm, with all other assumptions the same as EAG base case 2	£15,209*

Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival.

* The ICER reported in Table 4 of the company's response document is for a Gompertz curve for the perioperative durvalumab arm.

The EAG's preferred base case 2 and scenarios remain unchanged by the company's response, and none of the three areas of uncertainty have been resolved.

4 REFERENCES

Sternberg CN, Squires P, Song Y, Wu A, Gao Y, Kataria RS, Li H. Evaluation of Event-Free Survival as a Surrogate Endpoint for Overall Survival in Muscle-Invasive Bladder Cancer Following Neoadjuvant Treatment: A Systematic Review and Meta-Analysis. *Oncol Ther*. 2025 Dec;13(4):1225-1241.