Medicinrådet

Bilag til Medicinrådets vurdering af durvalumab i kombination med gemcitabin og cisplatin til behandling af resektabel muskelinvasiv blærekræft

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. durvalumab
2. Forhandlingsnotat fra Amgros vedr. durvalumab
3. Ansøgers endelige ansøgning vedr. durvalumab

Medicinrådet
Dampfærgevej 21-23, 3. sal
2100 København Ø

17.12.2025

Note regarding the draft assessment report on perioperative durvalumab treatment of muscle invasive bladder cancer (MIBC)

AstraZeneca would like to thank the DMC for assessing perioperative durvalumab with neoadjuvant gemcitabine/cisplatin in MIBC as investigated in NIAGARA and appreciates the opportunity to comment on the draft assessment report. Our consolidated comments follow below.

Study population and clinical relevance

The assessment report mentions that NIAGARA was conducted in a broader patient population than is traditionally offered neoadjuvant chemotherapy in Denmark, including older patients as well as those with N1 disease and reduced renal function. This ought to be considered as a strength, as the evidence thereby supports an option to improve the treatment of patients who are also seen in routine practice but who often currently have no access to neoadjuvant therapy. These patients may then potentially achieve a pathological complete response (pCR) and/or a reduction in circulating tumour DNA (ctDNA) before surgery.

The advantages of neoadjuvant immunotherapy are biologically well-grounded: it is delivered in an immunologically intact milieu with the tumour present, which promotes T-cell priming and clonal diversity. This is reflected in higher pCR rates and a greater proportion of ctDNA-negative patients at surgery (ctDNA data from NIAGARA were presented at ASCO 2025). The subsequent adjuvant durvalumab maintains the immune response and supports the observed, sustained effect.

It is correct that NIAGARA does not separate the effects of the neoadjuvant and adjuvant components. However, the focus should be on the overall treatment effect of the perioperative regimen, which is clinically meaningful and supported by the demonstrated survival benefit and the advantages of initiating immunotherapy pre-operatively.

Overall survival and choice of comparator

Overall survival (OS) is statistically significantly improved in NIAGARA (HR 0.75; 95% CI 0.59–0.93) with persistent separation of survival curves. Neoadjuvant gemcitabine/cisplatin alone without adjuvant therapy was selected as the comparator in the application, as this strategy represents the largest patient group in Danish practice. A minority of patients receive adjuvant nivolumab. It is methodologically not feasible to conduct a standard indirect, fully comparable analysis with adjuvant nivolumab as comparator because NIAGARA and CHECKMATE-274 differ fundamentally in design, randomisation timepoint and control arms.

Instead, a consolidated, survival-time-adjusted indirect analysis has been undertaken in case the DMC would have requested a comparison including nivolumab during the evaluation process. A hypothetical control arm was constructed by applying the effect of adjuvant nivolumab from CHECKMATE-274 to those patients in the NIAGARA control who would have been eligible for nivolumab (PD-L1 ≥1% and high risk after cystectomy), while other patients remain unchanged. The results show an advantage for the perioperative durvalumab strategy compared with neoadjuvant chemotherapy followed by adjuvant nivolumab in the relevant subpopulation. The method is a pragmatic supplement, but indirect

comparisons of two such different studies have large and inherent limitations; therefore, the analysis was not included as an element in the original application and is presented here should the Council wish the best possible methodological understanding of the relationship to neoadjuvant chemotherapy with and without adjuvant nivolumab.

Subsequent therapy and robustness of the OS effect

As noted, a lower proportion of patients in the durvalumab arm received subsequent immunotherapy than in the control arm, which is expected to reduce the measured OS gain with perioperative durvalumab. The documented improvement in OS can therefore be described as conservatively estimated and thus robust.

Even if subsequent immunotherapy is used more frequently in Denmark than in NIAGARA, this does not undermine the rationale for the perioperative NIAGARA strategy. Perioperative durvalumab delivers a proven, early OS benefit across the whole cisplatin-eligible population and ensures timely access to immunotherapy before postoperative eligibility constraints can arise. Consequently, the statistically significant overall survival benefit should be considered robust and clinically meaningful regardless of subsequent treatment patterns, as the NIAGARA regimen offers patients a potentially curative approach that may not be achievable in later lines of therapy.

Practical advantages of the perioperative strategy

The perioperative approach in NIAGARA offers important practical advantages: treatment access is independent of PD-L1, and pathological stage after cystectomy does not determine access to the planned adjuvant therapy. In this way, attrition among patients who cannot receive adjuvant immunotherapy due to postoperative conditions or biomarker requirements is avoided, and more patients have the opportunity for time-limited, curatively intended immunotherapy. Here it is worth noticing that the total duration of exposure to immunotherapy in the NIAGARA regimen (up to 12 weeks neoadjuvant + up to 32 weeks adjuvant) is shorter than a course based on one year of adjuvant nivolumab.

Proportional hazards and interpretation of OS

The proportional hazards assumption is considered fulfilled for OS. This strengthens the validity of the reported OS estimate (HR 0.75; 95% CI 0.59–0.93) and supports the clinical interpretation of a stable and sustained survival benefit with perioperative durvalumab. The consistent separation of survival curves confirm that the effect on OS is robust over time. Greater uncertainty for EFS does not alter this conclusion, as OS is the most clinically meaningful endpoint and here appears statistically sound and methodologically well-founded.

In summary, NIAGARA demonstrates a robust and clinically meaningful added value for patients with resectable, cisplatin-eligible MIBC, with a significant OS benefit, strong biological rationale for initiating immunotherapy neoadjuvantly, and a more inclusive access to immunotherapy than a selective adjuvant strategy. We therefore request that durvalumab in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by durvalumab as adjuvant monotherapy, will be recommended as a new standard of care in Denmark.

Kind regards,

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19.12.2025

LSC/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	AstraZeneca
Lægemiddel	Imfinzi (durvalumab)
Ansøgt indikation	Durvalumab (Imfinzi) i kombination med gemcitabin og cisplatin til behandling af voksne med resektabel muskelinvasiv blærekræft (MIBC) som neoadjuverende behandling, efterfulgt af adjuverende behandling med durvalumab som monoterapi efter radikal cystektomi.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (direkte indplacering)

Prisinformation

Amgros har følgende priser på Imfinzi (durvalumab):

Tabel 1: Udbudsresultat

Lægemiddel	Styrke (pakningsstørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Imfinzi	50 mg/ml (2,4 ml)	4.091,83	[redacted]	[redacted]
Imfinzi	50 mg/ml (10 ml)	16.943,88	[redacted]	[redacted]

Aftaleforhold

Imfinzi indgår i udbuddet på immunterapier.

[redacted]

[redacted] Der er mulighed for at aktivere en prisregulering i aftaleperioden.

Konkurrencesituationen

I Danmark tilbydes patienter med resektabel muskelinvasiv blærekræft (MIBC) neoadjuverende kemoterapi med gemcitabin og cisplatin før radikal cystektomi, og Imfinzi gives derfor som tillæg til nuværende standardbehandling i den neoadjuverende fase. Adjuverende behandling tilbydes på nuværende tidspunkt ikke som standard behandling, da kun en lille selekteret patientgruppe tilbydes adjuverende behandling.

Tabel 2 viser lægemiddeludgiften til Imfinzi for et behandlingsforløb, svarende til ca. 10 måneders behandling. Der er ikke medregnet lægemiddeludgifter til kemoterapi, da disse udgør en mindre del af den samlede lægemiddeludgift.

Tabel 2: Lægemiddeludgift pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandlingsforløb (SAIP, DKK)
Imfinzi	50 mg/ml (10 ml)	Neoadjuverende: 1.500 mg hver 3. uge i op til 4 serier, i.v. Adjuverende: 1.500 mg hver 4. uge i op til 8 serier, i.v.	[redacted]	[redacted]

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
England	Under vurdering	Link til status
Sverige	Under vurdering	Link til status

Opsummering

[redacted]

Application for the assessment of Imfinzi in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by Imfinzi as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]

Contact information

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Title	
Phone number	N/A
E-mail	

[If a company wishes to use external representation in relation to the application for evaluation of a new medicine / extension of indications, the following power of attorney must be completed and sent to ansogning@medicinraadet.dk.]

Table of contents

Tables and Figures

[redacted]

Abbreviations

Abbreviation	Explanation
BC	Bladder cancer
BTC	Biliary tract cancer
CEAC	Cost-effectiveness acceptability curves

CI	Confidence interval
DCO	Data cut-off
DFS	Disease-free survival
EFS	Event-free survival
EFS24	Event-free survival at 24 months
EMA	European Medicines Agency
FAS	Full analysis set
G+C	Gemcitabine and cisplatin
GFR	Glomerular filtration rate
GHS	Global health status
HCC	Hepatocellular carcinoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUVs	Health-state utility values
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
IV	Intravenous
JNHB	Joint Nordic HTA-Bodies
KM	Kaplan-Meier
MFS	Metastasis-free survival
MIBC	Muscle invasive bladder cancer
MMRM	Mixed models for repeated measures
NMIBC	Non-muscle invasive bladder carcinoma
NSCLC	Small cell lung cancer
OS	Overall survival
OS5	Overall survival at 5 years

PFS	Progression-free survival
QALYs	Incremental benefit
RC	Radical cystectomy
SCLC	Small cell lung cancer
SE	Standard error
SMD	Standardized mean difference
TMT	Trimodal therapy
UC	Urothelial carcinomas
pCR	Pathological complete response

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Imfinzi®
Generic name	Durvalumab
Therapeutic indication as defined by EMA	IMFINZI in combination with gemcitabine and cisplatin (G+C) as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).
Marketing authorization holder in Denmark	AstraZeneca
ATC code	L01FF03
Combination therapy and/or co-medication	Combination with G+C in the neoadjuvant phase
(Expected) Date of EC approval	2nd of July 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Non-Small Cell Lung Cancer (NSCLC): • Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, is indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements. • Durvalumab as monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. • Durvalumab in combination with tremelimumab and platinum-based chemotherapy is indicated for the first-line

Overview of the medicine	

	treatment of adults with metastatic NSCLC with no sensitising EGFR mutations or ALK positive mutations.
	
	Small Cell Lung Cancer (SCLC):
	• Durvalumab in combination with etoposide and either carboplatin or cisplatin is indicated for the first-line treatment of adults with extensive-stage small cell lung cancer (ES-SCLC).
	• Durvalumab as monotherapy is indicated for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.
	
	Biliary Tract Cancer (BTC):
	• Durvalumab in combination with gemcitabine and cisplatin is indicated for the first line treatment of adults with unresectable or metastatic BTC.
	
	Hepatocellular Carcinoma (HCC):
	• Durvalumab as monotherapy is indicated for the first line treatment of adults with advanced or unresectable HCC.
	• Durvalumab in combination with tremelimumab is indicated for the first line treatment of adults with advanced or unresectable HCC.
	
	Endometrial Cancer (EC):
	• Durvalumab in combination with carboplatin and paclitaxel is indicated for the first-line treatment of adults with primary advanced or recurrent endometrial cancer who are candidates for systemic therapy, followed by maintenance treatment with:
	  ○ Durvalumab as monotherapy in endometrial cancer that is mismatch repair deficient (dMMR)
	  ○ Durvalumab in combination with olaparib in endometrial cancer that is mismatch repair proficient (pMMR).

Other indications that have been evaluated by the DMC (yes/no)	Yes, the Danish Medicines Council (DMC) has previously evaluated durvalumab in the following indications: NSCLC: On May 30 2025, DMC recommended durvalumab for stage III NSCLC in adults with PD-L1 ≥ 1% whose disease has not progressed following platinum-based chemoradiation therapy. SCLC: On 25 September 2024, the DMC recommended durvalumab in combination with etoposide and either carboplatin or cisplatin for the first-line treatment of adults with ES-SCLC. BTC: On 04 March 2025, the DMC recommended durvalumab in combination with gemcitabine and cisplatin for the first-line treatment of adults with unresectable or metastatic BTC in performance status 0 or 1.

Overview of the medicine	
	HCC: On 05 December 2024, the DMC recommended durvalumab in combination with tremelimumab for the first-line treatment of adults with advanced or unresectable HCC. EC: On 02 May 2025, the DMC recommended durvalumab in combination with carboplatin and paclitaxel for the first-line treatment of adults with primary advanced or recurrent endometrial cancer. Currently ongoing assessment at DMC: NSCLC: Durvalumab in combination with platinum-based chemotherapy as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment, indicated for the treatment of adults with resectable NSCLC at high risk of recurrence and no EGFR mutations or ALK rearrangements. SCLC: Durvalumab as monotherapy is indicated for the treatment of adults with limited-stage small cell lung cancer (LS-SCLC) whose disease has not progressed following platinum-based chemoradiation therapy.
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? All countries recommend cisplatin-based neoadjuvant chemotherapy. Is the product suitable for a joint Nordic assessment? No If no, why not? No, as this assessment includes an indication extension for durvalumab and follows the DMC 14-week assessment process without a health economic assessment. Furthermore, Imfinzi is already recommended and funded in Norway, and in assessment in Sweden with a decision expected imminently.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	50 mg/ml, one vial of 10 ml concentrate for solution for infusion (500 mg) 50 mg/ml, one vial of 2.4 ml concentrate for solution for infusion (120 mg)

2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Indication relevant for the assessment	Imfinzi in combination with G+C as neoadjuvant treatment, followed by Imfinzi as monotherapy adjuvant treatment after

Summary	
	radical cystectomy, is indicated for the treatment of adults with resectable MIBC.
Dosage regiment and administration	Neoadjuvant treatment: Durvalumab 1,500 mg IV Q3W and gemcitabine + cisplatin (CrCl ≥60 mL/min: cisplatin 70 mg/m2 + gemcitabine 1,000 mg/m^2 Day 1, then gemcitabine 1,000 mg/m^2 Day 8, Q3W for 4 cycles CrCl ≥40–<60 mL/min: Split-dose cisplatin 35 mg/m^2 + gemcitabine 1000 mg/m2 Days 1 and 8, Q3W for 4 cycles) Adjuvant treatment: Durvalumab 1500 mg IV Q4W
Choice of comparator	Neoadjuvant G+C in the neoadjuvant phase, followed by radical cystectomy; no treatment in the adjuvant phase
Prognosis with current treatment (comparator)	Standard treatment for cisplatin-eligible patients with MIBC involves neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with pelvic-lymph-node dissection. Approximately 50% of patients with MIBC have recurrence within 3 years after cystectomy and are not cured with systemic therapies [1-3]. In Denmark, the three-year overall survival after diagnosis of MIBC is 56%, 95% CI (54%, 58%) and the five-year survival is 44% 95% CI (41%, 47%) [4]. The relative five-year survival in Denmark for MIBC (adjusting for background mortality) is 58% for men and 50% for women, indicating substantially higher mortality compared with the expected survival in the general population matched for age, sex, and calendar year[5]. Despite the current standard of therapy, a significant proportion of patients will still experience disease recurrence, underscoring a critical unmet need for more effective and durable treatment options in MIBC.
Type of evidence for the clinical evaluation	Head-to-head study
Most important efficacy endpoints (Difference/gain compared to comparator)	Pathological complete response (pCR): OR: 1.60; 95% CI: 1.227, 2.084; p-value: 0.0005 Event-free survival (EFS): HR: 0.68; 95% CI: 10.558, 0.817; p-value: < 0.0001 Overall survival (OS): HR: 0.75; 95% CI: 0.594, 0.934; p-value = 0.0106
Most important serious adverse events for the intervention and comparator	The most frequently reported SAEs for D +G+C vs G+C, safety analysis set, per period were similar: • Overall period: Urinary tract infection (11.1% vs 13.1%), and prostate cancer (6.6% vs 5.1%)

Summary	
	• Neoadjuvant period: Urinary tract infection (1.3% vs 2.7%) and anemia (0.8% vs 2.9%) • Adjuvant period: Urinary tract infection (6.0% vs 7.0%), acute kidney injury (2.9% vs 2.1%), pyelonephritis (2.1% vs 2.1%), and hydronephrosis (2.1% vs 1.6%)
Impact on health-related quality of life	EORTC QLQ-C30: A trend towards deterioration from baseline was observed in the first 25 weeks for all scales in both arms, followed by a decrease in deterioration or a return to baseline levels thereafter. Prioritised EORTC QLQ-C30 scales in NIAGARA consisted of GHS/QoL, physical functioning, fatigue, and pain. There were no observable differences between treatment arms in the prioritised and non-prioritised scales (aside from appetite loss, which was greater in the G+C arm). The perioperative durvalumab regimen prolonged time to deterioration in comparison to G+C alone in most prioritised scales. Therefore, adding durvalumab to neoadjuvant G+C and receiving durvalumab monotherapy as adjuvant therapy did not have a detrimental effect on HRQoL, physical functioning, or patient-reported symptoms. Health economic model: N/A
Type of economic analysis that is submitted	N/A
Data sources used to model the clinical effects	N/A
Data sources used to model the health-related quality of life	N/A
Life years gained	N/A
QALYs gained	N/A
Incremental costs	N/A
ICER (DKK/QALY)	N/A
Uncertainty associated with the ICER estimate	N/A
Number of eligible patients in Denmark	Incidence: Ca 100 per year Prevalence: Since cystectomy is a one-time curative intervention, there is no ongoing prevalence of resectable cases
Budget impact (in year 5)	N/A

3. The patient population, intervention, choice of comparator(s) and relevant outcomes

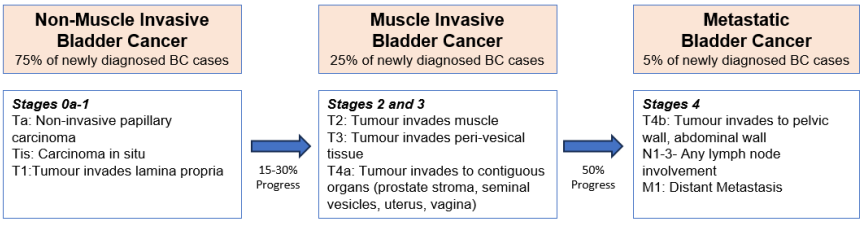
3.1 The medical condition

Bladder cancer (BC) is the most common malignancy of the urinary system and originates from bladder cells lining the interior of the urinary tract. It is the tenth most prevalent cancer in the world, with the highest incidence in developed regions like Europe and North America [6, 7]. The disease is more common in men than women and is the ninth leading cause of cancer death in men globally [6].

Urothelial carcinomas (UC), also known as transitional cell carcinoma, are a highly prevalent histologic subtype and constitute over 90% of BC cases [8, 9]. The other subtypes, such as squamous cell and adenocarcinoma of the bladder, are uncommon and account for <5% cases [10]. For clinical and treatment purposes, UC can be categorised into non-muscle-invasive bladder carcinoma (NMIBC), muscle-invasive bladder carcinoma (MIBC) and metastatic, which are differentiated based on the extent of tumour growth into the bladder wall [10-12].

MIBC, seen in approximately 25% of diagnosed BC, permeates the deeper (detrusor) muscle layers of the bladder [12], and the stage includes tumours of pathologic classification stage T2–T4a [13]. Bladder cancer that has spread outside the bladder into other areas is called metastatic BC, also known as stage 4 (T4b) BC [14] (Figure 1).

Figure 1 Grouping of bladder cancer based on the stage of invasion



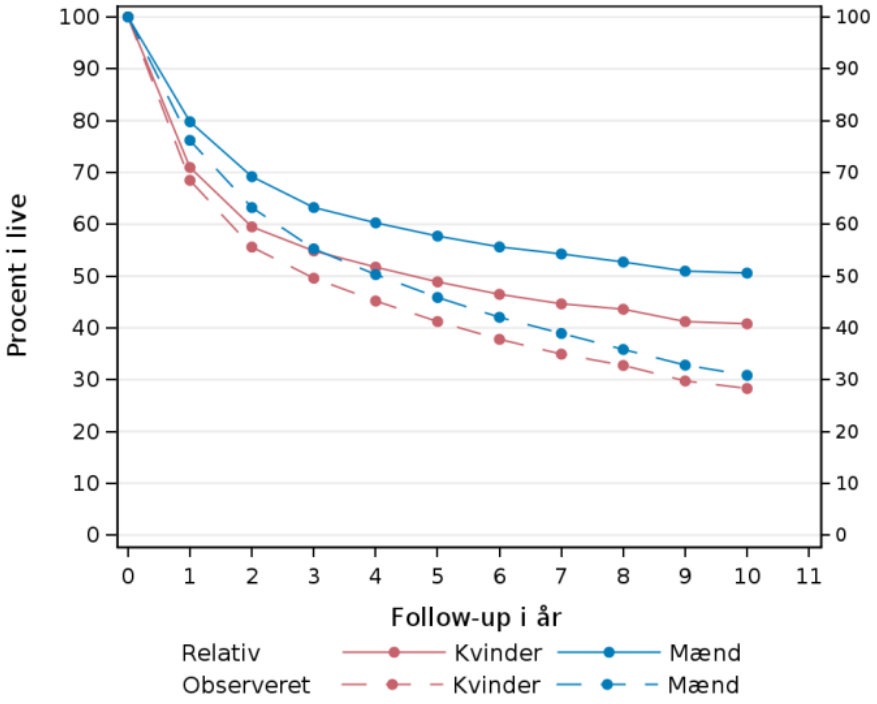
Source: Adapted from [11]

In Denmark, between 2020 and 2024, the yearly incidence (diagnosed) MIBC ranged from 917 to 941 individuals [5]. MIBC is associated with a high rate of recurrence after cystectomy and poor overall prognosis [11], most recurrences occur within the first two

to three years after cystectomy, and the majority of patients with recurrence after cystectomy are not cured with systemic therapies [1-3].

In the DaBlaCa yearly report 2024 [5], the three-year survival after diagnosis of MIBC was 56% and the five-year survival 44%. The relative survival for MIBC in Denmark is shown in Figure 2 indicating a fast decline during the first three years, and with lower survival for women than for men [5]. Using relative survival—which benchmarks patient outcomes against age, sex, and calendar-year matched life tables—patients with MIBC experience substantially higher mortality than expected for their advanced age.

Figure 2 Cumulative relative and observed survival of muscle invasive bladder cancer, by gender



Source: DaBlaCa yearly report 2024 [5]

3.2 Patient population

BC imposes a substantial burden on healthcare systems as it is the tenth most prevalent cancer and the thirteenth leading cause of cancer death worldwide [6].

In Denmark, a total of 917 new cases of MIBC were registered between September 2023 and August 2024, out of which 282 underwent cystectomy [5]. The median age at diagnosis was 75 years, but women were generally older than men at diagnosis [5]. A total of 73% of diagnosed patients were men, which, in addition to smoking, may be due to various occupational exposures and other, as yet unknown causes [5]. Approximately half of the patients were diagnosed with tumour stage T1 (T stage determined by transurethral resection of the bladder, TUR-B), and just over half of the patients had one or more serious comorbid conditions at the time of diagnosis [5]. The 3-year survival

after diagnosis of invasive BC was reported to be 56% (95% CI: 54%, 58%), which is a very slight improvement from 55% in 2018/2020 and 53% in 2016/18 [5].

The age-standardised incidence rate for MIBC has been decreasing from around 2017 onwards. Tobacco smoking is a significant risk factor, and the trend towards reduction in the incidence is probably due to a decrease in the number of smokers in Denmark. It is assumed that the age-standardised incidence will decrease further over the next few years, but that an older population composition will have an impact on the total number [5].

The number of patients with invasive bladder cancer who underwent cystectomy between 2020 and 2024 is presented in Table 1.

Table 1 Incidence and prevalence in the past 5 years: patients with MIBC who underwent cystectomy

Year	2019/20[1]	2020/21[2]	2021/22[3]	2022/23[4]	2023/24[5]
Incidence in Denmark	314	288	297	281	282
Prevalence in Denmark[6]	N/A	N/A	N/A	N/A	N/A
Global prevalence	N/A	N/A	N/A	N/A	N/A

Notes: reporting period: [1]September 2019-August 2020; [2]September 2020-August 2021; [3]September 2021-August 2022; [4]September 2022-August 2023; [2]September 2023-August 2024;[6]Since cystectomy is a one-time curative intervention, there is no ongoing prevalence of resectable cases

References: DaBlaCa yearly reports 2020-2024 [4, 5, 15-17]

The patient population relevant for this application are patients with MIBC who are eligible for the treatment with neoadjuvant cisplatin-based chemotherapy and subsequent cystectomy. In the latest 2023/2024 yearly report, the DaBlaCa database reports just over 100 patients in Denmark who were eligible for neoadjuvant chemotherapy [4] the target population for this application.

The estimated number of patients eligible for treatment are presented in Table 2.

Table 2 Estimated number of patients eligible for treatment

Year	2026	2027	2028	2029	2030
Number of patients in Denmark who are eligible for treatment in the coming years	100	100	100	100	100

3.3 Current treatment options

Patients with MIBC can be offered neoadjuvant chemotherapy with cisplatin-based regimens, either four cycles of G+C or six cycles of dose-dense methotrexate, vinblastine, adriamycin and cisplatin (ddMVAC) [18]. In Denmark, G+C is the preferred regimen and represents clinical practice, as there are concerns over the tolerability of ddMVAC.

Radical cystectomy is the first choice for curative treatment of patients with MIBC, for patients who can tolerate extensive surgery and who accept urinary diversion. In selected patients with a well-functioning bladder, trimodal therapy (TMT) is probably an equivalent treatment to radical cystectomy.

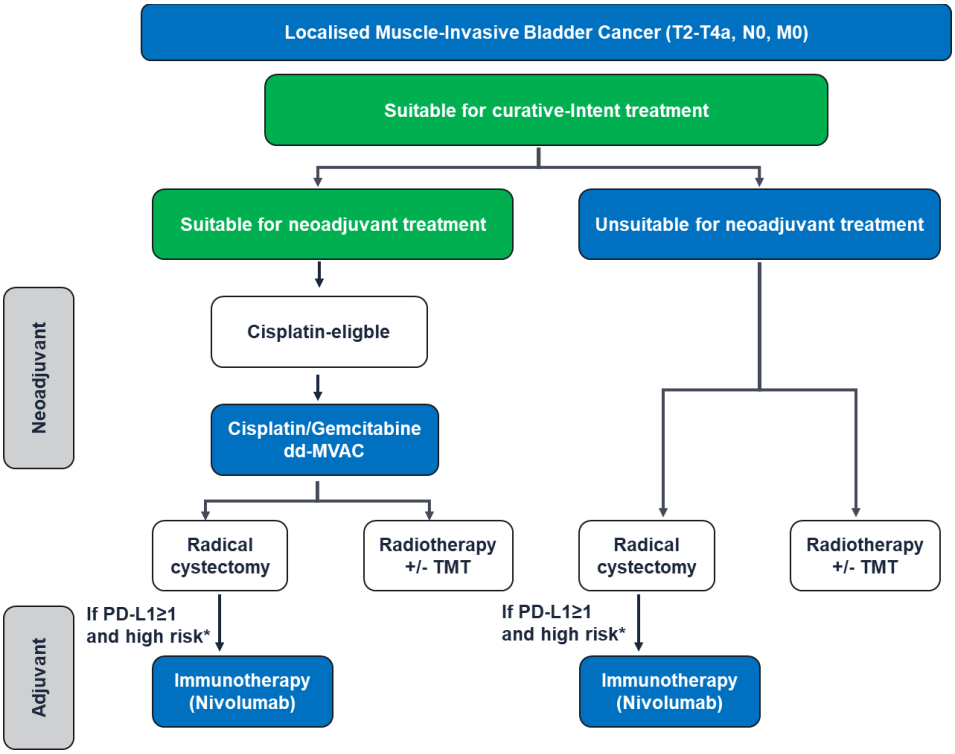
Cystectomy is performed 21-42 days after the start of the last cycle of chemotherapy. GFR is measured before the 3rd and after the 4th cycle. If GFR < 50 ml/min or toxicity grade IV, chemotherapy is discontinued and the patient is referred for surgery.

Denmark has a development goal that over 55% of newly diagnosed patients with MIBC should undergo an intended curative treatment (cystectomy or radiation therapy). This goal was not met in the last reported period of September 2020 and August 2023 [5].

The high risk of recurrence after curative surgical treatment of bladder cancer supports the use of perioperative systemic oncology treatment. The Danish bladder cancer guideline also reports that, based on clinical trial and meta-analysis data, neoadjuvant chemotherapy with a cisplatin-containing combination regimen before cystectomy or radiation can significantly prolong survival in patients with MIBC [18].

Routine adjuvant chemotherapy is not recommended [19]. Adjuvant immunotherapy with nivolumab is only available in a small subpopulation of patients with urothelial carcinoma, PD-L1 positive tumour and high risk of recurrence after radical cystectomy (see Figure 3) [18]. High risk is defined as either pT2-pT4a (pathological tumour stage 2-4a) and/or N+ (regional lymph node involvement) if neoadjuvant chemotherapy has been given; or > pT3-pT4a and/or N+ if neoadjuvant chemotherapy has not been given [18].

Figure 3 Treatment algorithm for oncology treatment of muscle-invasive bladder cancer [19]



*Nivolumab eligible patients are: PD-L1 positive, have a high risk of relapse after cystectomy, defined as > pT2 and/or N+ if neoadjuvant chemotherapy has been given or > pT3 and/or N+ if neoadjuvant chemotherapy has not been given).

Source: Adapted based on the Danish guidelines, Behandling og opfølgning af muskelinvasiv blærekræft [19].

3.4 The intervention

Durvalumab is an immune checkpoint inhibitor (ICI) that selectively blocks the interaction of PD-L1 with PD-1 and cluster of differentiation 80 (CD80). The blockade of PD-L1/PD-1 and PD-L1/CD80 communication prevents the inhibition of immune responses caused by overexpressed PD-L1, allowing the immune system to exert a cytotoxic T cell-driven response against PD-L1-expressing tumour cells [20].

The combination of PDC and durvalumab is believed to enhance anti-tumour responses through immunogenic effects and upregulation of PD-L1 expression, which may increase tumour sensitivity to immune checkpoint blockade. Chemotherapy-induced tumour cell death can promote antigen presentation, while increased PD-L1 expression may improve the efficacy of anti-PD-(L)1 therapies in poorly immunogenic tumours [21, 22]. Combining immunotherapy with chemotherapy has shown superior anti-tumour activity and response rates and may also help reduce the risk of treatment resistance [23, 24]. At ESMO-MCBS scorecard durvalumab has been evaluated as A (curative), which in that ranking is the highest score [25].

The overview of the intervention is presented in Table 3.

Table 3 Overview of the intervention, durvalumab (Imfinzi®)

Overview of intervention	
Indication relevant for the assessment	IMFINZI in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by IMFINZI as monotherapy adjuvant treatment after radical cystectomy, is indicated for the treatment of adults with resectable muscle invasive bladder cancer (MIBC).
ATMP	N/A
Method of administration	Intravenous infusion
Dosing	1,500 mg* in combination with chemotherapy every 3 weeks for 4 cycles prior to surgery, followed by 1,500 mg* every 4 weeks as monotherapy for up to 8 cycles after surgery.
Dosing in the health economic model (including relative dose intensity)	N/A
Should the medicine be administered with other medicines?	Yes, with gemcitabine and cisplatin in the neoadjuvant phase
Treatment duration / criteria for end of treatment	Neoadjuvant phase: until disease progression that precludes definitive surgery or unacceptable toxicity, or a maximum of 4 cycles Adjuvant phase: until recurrence, unacceptable toxicity, or a maximum of 8 cycles after surgery.
Necessary monitoring, both during administration and during the treatment period	Patients are monitored during the administration of the drugs and during the course of the treatment period.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No N/A
Package size(s)	50 mg/ml, one vial of 10 ml concentrate for solution for infusion (500 mg) 50 mg/ml, one vial of 2.4 ml concentrate for solution for infusion (120 mg)

* Patients with a body weight of 30 kg or less must receive weight-based dosing of IMFINZI at 20 mg/kg.

3.4.1 Description of ATMP

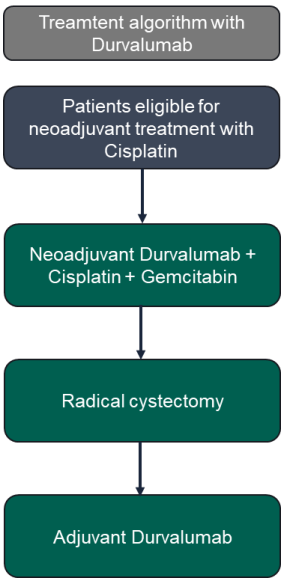
N/A

3.4.2 The intervention in relation to Danish clinical practice

Neoadjuvant G+C is the current SoC for MIBC patients before radical cystectomy. Adjuvant treatment with nivolumab may be considered for the small subgroup of patients with a high risk of recurrence after radical cystectomy, and with PD-L1 tumour cell expression exceeding 1%.

The expected place in therapy for durvalumab, is the perioperative setting, in which durvalumab is given in combination with G+C as neoadjuvant treatment, followed by durvalumab as monotherapy as adjuvant treatment after radical cystectomy for adults with resectable MIBC (Figure 4). This means that durvalumab will be an addition to the current SoC of neoadjuvant therapy alone.

Figure 4 Expected treatment algorithm with durvalumab



3.5 Choice of comparator(s)

For cisplatin-eligible MIBC, the Danish treatment guideline recommends cisplatin-based chemotherapy with G+C or ddMVAC in the neoadjuvant setting. In Danish clinical practice, G+C is used for the majority of patients, with G+C having a more favourable tolerability profile and suitability for a broader patient population [19].

Adjuvant nivolumab is recommended only for the small subgroup of BC patients, who have a high risk of relapse after cystectomy for urothelial carcinoma and have PD-L1-positive tumours (>1%) [18]. As the decision point to start a treatment is taken at a different time point, nivolumab is not considered to be a comparator for perioperative treatment, where neoadjuvant cisplatin-based chemotherapy followed by observation, is the current SoC for the targeted patient population.

Based on this, neoadjuvant G+C followed by observation was selected as the relevant comparator. This combination was administered together with the study drug durvalumab and alone in the comparator arm in the NIAGARA trial.

The comparator, which is two medicines used in combination, is presented in Table 4.

Table 4 Overview of comparator - neoadjuvant gemcitabine and cisplatin

Overview of comparator	Cisplatin	Gemcitabine
Generic name	Cisplatin	Gemcitabine
ATC code	L01XA01	L01BC05
Mechanism of action	Cisplatin binds directly to DNA, creating cross-links that block replication and transcription, leading to the death of cancer cells. [26]	Gemcitabine is a pyrimidine analogue that disrupts DNA synthesis by depleting deoxynucleotides and incorporating into DNA, ultimately blocking replication and inducing cell death. [27]
Method of administration	Intravenous infusion	Intravenous infusion
Dosing	70 mg/m², is given at day 1 of the 21-days treatment cycle for 4 cycles [28]	1000 mg/m², is given at day 1 and day 8 of the 21-days treatment cycle for 4 cycles [28]
Dosing in the health economic model (including relative dose intensity)	N/A	N/A
Should the medicine be administered with other medicines?	In combination with gemcitabine	In combination with cisplatin
Treatment duration/ criteria for end of treatment	4 cycles of neoadjuvant treatment	4 cycles of neoadjuvant treatment
Need for diagnostics or other tests (i.e. companion diagnostics)	No	No
Package size(s)	1 mg/ml in a vial of 50 ml	10 mg/ml in a vial of 220 ml

Source: [26-28]

3.6 Cost-effectiveness of the comparator(s)

Chemotherapy with G+C followed by observation is well established in Danish clinical practice for the neoadjuvant treatment of adults with resectable MIBC and is low in cost due to generic competition. Therefore, no additional analysis of the CE for the comparator is presented in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

The efficacy outcomes relevant for this application were sourced from the pivotal clinical trial NIAGARA [29] and are presented in Table 5.

Table 5 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Pathologic complete response rate (pCR) per central review NIAGARA	Time Frame: Up to 6 months	The proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via radical cystectomy following the neoadjuvant treatment.	Assessed per central pathology review. Measured on IA-2 for pCR on 29 April 2024
Event-free survival (EFS) per central review NIAGARA	Time Frame: Up to 48 months	Event Free Survival (EFS) is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who are medically precluded from a radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in patients with residual disease, or the time of death due to any cause, whichever occurs first.	Assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion Measured on IA-2 for EFS on 29 April 2024
Event-free survival (EFS) per local Investigator NIAGARA	Time Frame: Up to 48 months	Event Free Survival (EFS) is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time	Assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		of first documented progression in patients who are medically precluded from a radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in patients with residual disease, or the time of death due to any cause, whichever occurs first.	Measured on IA-2 for EFS on 29 April 2024
Overall survival (OS) NIAGARA	Time Frame: Up to 84 months	The time from the date of randomization until death due to any cause, regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy	Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. Measured on IA-2 for EFS on 29 April 2024

* Time point for data collection used in analysis (follow up time for time-to-event measures)

Abbreviations: IA-2: The interim analysis 2

Source: [29]

Validity of outcomes

According to European Medicines Agency (EMA) guidelines on the evaluation of anticancer medicinal products [30], EFS as a primary or co-primary endpoint is especially accepted in neoadjuvant and adjuvant settings or in treatments with potentially curative intent, and when there is a high likelihood of early events. The other co-primary endpoint pCR, is recognised by the EMA as being associated with long-term outcomes [31]. In the context of breast cancer, for example, pCR has been proposed as a surrogate endpoint to assess the efficacy of therapies targeting invasive breast cancer without distant metastasis. EMA may accept approval based on pCR when added to the standard (neo)adjuvant regimen for high-risk early-stage breast cancer, as long as the mechanism of action is well understood and the increase in pCR is substantial with minimal added toxicity.

EFS was preferred over PFS as PFS is often used as endpoint in clinical trials involving patients with advanced/metastatic disease, where an event is defined as disease progression or death. EFS is a broader endpoint more suitable for the perioperative curative-intent MIBC setting as it also captures other clinically relevant failures across the perioperative pathway (e.g. inability to proceed with planned surgery).

OS remains gold standard in anti-cancer trials where the aim is to prolong survival [30]. However, EFS can provide earlier indications of treatment efficacy, especially in settings where long-term survival data may take extended periods to mature [30]. Therefore, when appropriately defined and justified, EFS serves as a meaningful endpoint in the assessment of anticancer therapies.

4. Health economic analysis

This section is not applicable for this submission.

4.1 Model structure

N/A

4.2 Model features

N/A

Table 6 Features of the economic model N/A

Model features	Description	Justification
Patient population	N/A	N/A
Perspective	N/A	N/A
Time horizon	N/A	N/A
Cycle length	N/A	N/A
Half-cycle correction	N/A	N/A
Discount rate	N/A	N/A
Intervention	N/A	N/A
Comparator(s)	N/A	N/A
Outcomes	N/A	N/A

5. Overview of literature

5.1 Literature used for the clinical assessment

The main analysis of the application is based on a within-trial comparison; as such, no SLR was done.

The literature used is presented in Table 7.

Table 7 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Powles T, Catto JWF, Galsky MD, Al-Ahmadie H, et al; NIAGARA Investigators. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. N Engl J Med. 2024 Nov 14;391(19):1773-1786. doi: 10.1056/NEJMoa2408154. Epub 2024 Sep 15. PMID: 39282910. [32]	NIAGARA	NCT03732677	Start (actual): 16/11/2018 Completion (estimated): 30/06/2026 Data cut-off (DCO): 29/04/2024	Durvalumab plus chemotherapy (cisplatin, gemcitabine) vs. chemotherapy (cisplatin, gemcitabine), for patients with resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology
Clinical Study Report AstraZeneca Durvalumab-D933RC00001, Data on file, 2024 September 16 [29]	NIAGARA	NCT03732677	Start (actual): 16/11/2018 Completion (estimated): 30/06/2026 DCO: 29/04/2024	Durvalumab plus chemotherapy (cisplatin, gemcitabine) vs. chemotherapy (cisplatin, gemcitabine), for patients with resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology
James W. F. Catto, Hikmat Al-Ahmadie, Michiel S. van der Heijden, et al.; Surgical	NIAGARA	NCT03732677	Start (actual): 16/11/2018	Durvalumab plus chemotherapy (cisplatin, gemcitabine) vs.

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
outcomes and neoadjuvant safety with perioperative durvalumab for muscle-invasive bladder cancer (NIAGARA). 40th Annual EAU Congress abstract AM25-6261. [33]			Completion (estimated): 30/06/2026 DCO: 29/04/2024	chemotherapy (cisplatin, gemcitabine), for patients with resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology
Matthew D. Galsky, Michiel S. van der Heijden, James W. F. Catto et al; Additional efficacy and safety outcomes and an exploratory analysis of the impact of pCR on long-term outcomes from NIAGARA. ASCO, abstract #659, 2025. [34]	NIAGARA	NCT03732677	Start (actual): 16/11/2018 Completion (estimated): 30/06/2026 DCO: 29/04/2024	Durvalumab plus chemotherapy (cisplatin, gemcitabine) vs. chemotherapy (cisplatin, gemcitabine), for patients with resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

Health-related quality of life was measured in the NIAGARA trial, and this will be presented in this application. A separate search was not conducted for HRQoL data.

Table 8 Relevant literature included for (documentation of) health-related quality of life (See section 10) N/A

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
N/A	N/A	N/A

5.3 Literature used for inputs for the health economic model

No health economic analysis was performed for this submission.

Table 9 Relevant literature used for input to the health economic model N/A

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
N/A	N/A	N/A	N/A

6. Efficacy

6.1 Efficacy of neoadjuvant durvalumab+G+C and adjuvant durvalumab compared to neoadjuvant G+C for patients with muscle-invasive bladder cancer

6.1.1 Relevant studies

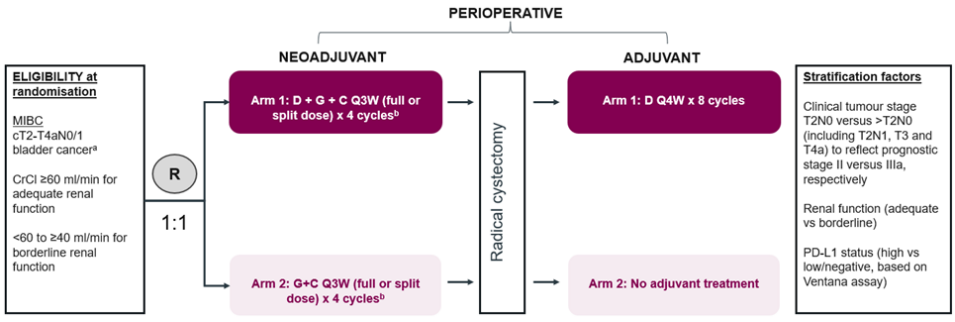
The NIAGARA clinical trial is a pivotal head-to-head Phase 3 study evaluating the efficacy and safety of neoadjuvant durvalumab+ gemcitabine+ cisplatin (D + G+C) combination therapy, followed by a radical cystectomy (RC) and adjuvant durvalumab (D) monotherapy, compared with neoadjuvant G+C alone (with no adjuvant therapy) in terms of pCR and EFS [29].

The target population includes patients with histologically or cytologically confirmed, resectable MIBC and transitional cell carcinoma of the urothelium. NIAGARA is an ongoing, randomised, open-label, multicentre international trial (Figure 5).

European Committee decision (approval) for the extension of indication variation was issued on 2nd July 2025 for the treatment combination of durvalumab G+C as neoadjuvant therapy, and durvalumab monotherapy as adjuvant treatment [35]. The approval was based on the latest DCO date of 29 April 2024, which is also used for all results presented in this application.

For this application, the ITT population is used. An overview of the NIAGARA trial is presented in Table 10 and described in detail in Appendix A.

Figure 5 NIAGARA study design



Abbreviations: C: cisplatin; CrCl: creatinine clearance; D: durvalumab; G: gemcitabine; MIBC: muscle invasive bladder cancer; N: node; PD-L1: programmed death-ligand 1; Q3W: every 3 weeks; Q4W: every 4 weeks; R: randomisation; T: tumour Notes: a Enrolment of patients with T2N0 disease was limited to approximately 40% of the targeted global population (for both treatment arms). b Patients with borderline renal function received split-dose G+C and were limited to up to 20% of the targeted global population.

Source: Adapted from AZ NIAGARA clinical study protocol [36].

Table 10 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
NIAGARA, NCT03732677 [32]	Randomised, open-label, ongoing, multicentre international Phase 3 trial.	Ongoing	Patients with histologically or cytologically documented, resectable MIBC and transitional cell carcinoma of the urothelium, as outlined in the inclusion/exclusion criteria (see Appendix A)	Four cycles of neoadjuvant durvalumab (1500 mg on day one) + gemcitabine (1,000mg/m^2 on day one and eight) + C (70 mg/m^2 on day one) IV Q3W followed by radical cystectomy then up to eight cycles of adjuvant durvalumab (1500 mg) IV Q4W.	Four cycles of gemcitabine (1000mg/m^2 on day one and eight) + C (70 mg/m^2 on day one) IV Q3W followed by radical cystectomy.	**Primary endpoints (Time frame: DCO 29 April 2024):** -pCR (using assessments per central pathology review) -EFS (using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion) **Secondary endpoints:** -pCR (using assessments per local pathology review), DCO 14 January 2022. -EFS (using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion), DCO 29 April 2024. - Event-free survival at 24 months (EFS24) - MFS and DSS, DCO 29 April 2024. - OS, DCO 29 April 2024. - OS at 5 years - DFS, DCO 29 April 2024. - PFS2, DCO 29 April 2024. **Other seconday endpoints:** -EORTC QLQ-C30 scale/item scores, DCO 29 April 2024.

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
						- Serum concentration of durvalumab and non-compartmental PK parameters. **Safety endponts (Time frame: DCO 29 April 2024):** - AEs, laboratory findings, vital signs, and ECGs. **Exploratory endpoints (Time frame: DCO of 29 April 2024):** - PRO-CTCAE - PGIC and PGIS - EQ-5D-5L health state utility index

6.1.2 Comparability of studies

As the efficacy and safety of D G+C as neoadjuvant and D monotherapy as adjuvant treatment for MIBC is based on the head-to-head study NIAGARA, the following section will not compare the NIAGARA with any other study. Baseline characteristics for the two arms in NIAGARA are provided below.

6.1.2.1 Comparability of patients across studies

The baseline demographics and disease characteristics were largely balanced between the intervention arm, D + G+C, and the comparator arm G+C (Table 11). The median age of participants was 65 years, and 81.8% were male. A substantial proportion were smokers (73%), with 23.7% being current smokers.

Tumour stage > T2N0 was observed in 59.7% of patients, and 84.5% had invasive urothelial carcinoma [29, 32].

Table 11 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

		NIAGARA		
		D + G+C (N = 533)	**G+C (N = 530)**	**Total (N = 1063)**
Age years	Median (range)	65 (34–84)	66 (32–83)	65.0 (32, 84)
	≥75	58 (10.9)	63 (11.9)	121 (11.4)
Sex, n (%)	Male	437 (82.0)	433 (81.7)	870 (81.8)
	Female	96 (18.0)	97 (18.3)	193 (18.2)
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)
Region, n (%)	Asia	151 (28.3)	143 (27.0)	294 (27.7)
	Europe	265 (49.7)	287 (54.2)	552 (51.9)

		NIAGARA		
		D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
	North America and Australia	66 (12.4)	62 (11.7)	128 (12.0)
	South America	51 (9.6)	38 (7.2)	89 (8.4)
ECOG performance-status score — no. (%)	0	418 (78.4)	415 (78.3)	833 (78.4)
	1	115 (21.6)	115 (21.7)	230 (21.6)
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)
Histologic type — no. (%)	Invasive urothelial carcinoma, not otherwise specified	457 (85.7)	441 (83.2)	898 (84.5)
	Urothelial carcinoma with squamous differentiation	38 (7.1)	49 (9.2)	87 (8.2)
	Urothelial carcinoma with glandular differentiation	10 (1.9)	15 (2.8)	25 (2.4)
	Urothelial carcinoma with other	28 (5.3)	25 (4.7)	53 (5.0)

		NIAGARA		
		D + G+C (N = 533)	G+C (N = 530)	Total (N = 1063)
	histologic subtype			
Tumor stage — no. (%)	T2N0	215 (40.3)	213 (40.2)	428 (40.3)
	> T2N0	318 (59.7)	317 (59.8)	635 (59.7)
Regional lymph-node stage — no. (%)	N0	505 (94.7)	500 (94.3)	1005 (94.5)
	N1	28 (5.3)	30 (5.7)	58 (5.5)
Creatinine clearance — no. (%)	≥60 ml/min/1.73 m2	431 (80.9)	431 (81.3)	862 (81.1)
	40 to <60 ml/min/1.73 m2	102 (19.1)	99 (18.7)	201 (18.9)
Tumour PD-L1 expression level — no. (%)	High	389 (73.0)	388 (73.2)	777 (73.1)
	Low/Negative	144 (27.0)	142 (26.8)	286 (26.9)

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

The trial population in NIAGARA is assumed to be representative of Danish patients receiving treatment for resectable MIBC (Table 12). In Denmark, the mean age of patients with MIBC is 75 years. The proportion of males is substantially higher than that of females, 73.4% versus 26.6% respectively. In contrast, the median age in the NIAGARA study was lower, at 65 years. However, the gender distribution was similar to that observed in the Danish population, with 81.8% male and 18.2% female.

Table 12 Characteristics in the relevant Danish population and the health economic model

	Value in Danish population [5]	Value used in health economic model (reference if relevant)
Age	75 years	N/A

Gender		
Male	73.4%	N/A
Female	26.6%	N/A

Source: DaBlaCa yearly report 2024 [5].

6.1.4 Efficacy – results per NIAGARA

At the latest DCO on April 29, 2024, 533 participants had been assessed in the durvalumab arm (D + G+C arm) and 530 participants in the comparator arm (G+C arm). At this point, the study had been ongoing for 5 years and 5.5 months. The results presented are based on this data cut and the ITT/full analysis set (FAS) population. This assessment includes the two primary endpoints, pCR rate and EFS, as well as the secondary endpoint OS, including OS at 5 years.

NIAGARA demonstrated statistically significant and clinically meaningful improvement in EFS (HR, 0.68; 95% CI, 0.56–0.82) and is the only RCT with statistically significant OS (HR, 0.75; 98.457% CI, 0.563–0.985; p = 0.0106), and with a 10% improvement in pCR rate [32]. Addition of durvalumab to neoadjuvant cisplatin based chemotherapy did not impact the rate or timing of RC and did not increase the rate of surgical complications [33].

6.1.4.1 Pathologic complete response rate

The pCR rate (per central review) was a significant improvement, with about a 10% increase in the D + G+C arm (37.3%) compared to the G+C arm (27.5%) [29, 32]. See Table 13 for further details.

Table 13 Analysis of dual primary endpoint: pCR rate, based on central pathology, in NIAGARA (ITT, final analysis)

pCR by central pathology	D + G+C (N = 533)	G+C (N = 530)
Patients with pCR, n (%)	199 (37.3)	146 (27.5)
95% CI (%)[a]	33.2, 41.6	23.8, 31.6
Odds ratio[b]	1.60	
95% CI for odds ratio[b]	1.227, 2.084	
Two-sided p-value[b,c]	0.0005	

Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; FAS: full analysis set; G: gemcitabine; pCR: pathologic complete response.

Notes: a 95% CIs are calculated using the Clopper Pearson method. b Odds ratio and the corresponding CI, and p-value are obtained using logistic regression adjusted for the stratification factors (renal function [adequate vs

borderline], tumour stage [T2N0 vs > T2N0] and PD-L1 status [high vs low/negative] per IVRS). c Threshold for significance, p = 0.001. An odds ratio > 1 favours D+G+C over G+C.

Source: Powles et al, 2024 [32], AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

6.1.4.2 Event-free survival

EFS was the other primary endpoint, with a median follow-up of 34.7 months for the D + G+C arm and 27.7 months for the G+C arm. EFS demonstrated a statistically significant and clinically meaningful improvement in the D + G+C arm compared with the G+C arm. The hazard ratio (HR) was 0.68 (95% CI: 0.558, 0.817; p<0.0001) indicating a 32% reduction in the risk of an EFS event for patients in the D + G+C arm compared with the G+C arm. The median EFS was not reached in the D + G+C arm, whereas it was 46.1 months in the G+C arm. The median duration of follow-up for EFS was comparable between treatment arms for all patients, including those who were censored. Most patients were censored ≤ 24 weeks prior to the DCO (see Table 14 and Figure 6) [29].

EFS was evaluated in both the pCR and non-pCR subgroups by comparing outcomes between the D + G+C arm and the G+C arm. In both subgroups, the probability of EFS was higher in the D + G+C arm, with [redacted] in the pCR group and [redacted] in the non-pCR group, compared to [redacted] and [redacted] respectively in the G+C arm. In the pCR subgroup, the median EFS was not reached in either arm (see Table 15 and [redacted]). In contrast, in the non-pCR subgroup, the median EFS was [redacted] months (95% CI: [redacted] in the D + G+C arm, compared to [redacted] months (95% CI: [redacted]) in the G+C arm. The HR favored the D + G+C arm in both subgroups, with an HR of [redacted] in the pCR subgroup and [redacted] in the non-pCR subgroup (see Table 15) (data on file [34]).

Table 14 Analysis of dual primary endpoint: EFS, per BICR or central pathology review, in NIAGARA (ITT, IA-2).

EFS status	D + G+C (N = 533)	G+C (N = 530)
Total EFS events, n (%)	187 (35.1)	246 (46.4)
Progression in patients precluding RC	9 (1.7)	9 (1.7)
Refused or failed to undergo RC in patients with residual disease	40 (7.5)	60 (11.3)
Recurrence of disease after RC	69 (12.9)	87 (16.4)
Death in the absence of other EFS events	67 (12.6)	85 (16.0)
Partial cystectomy medically not justified	1 (0.2)	5 (0.9)
Failure to undergo delayed cystectomy	1 (0.2)	0
Censored patients, n (%)	346 (64.9)	284 (53.6)
Event-free at time of analysis	337 (63.2)	265 (50.0)

No neo-adjuvant baseline data	3 (0.6)	3 (0.6)
Lost to follow-up	0	0
Withdrawal by patient	6 (1.1)	16 (3.0)
Other	0	0
Median EFS (months) [a]	NR	46.1
EFS rate at 6 months % [a] (95% CI)	87.7 (84.5, 90.2)	82.4 (78.8, 85.4)
EFS rate at 12 months % [a] (95% CI)	76.0 (72.0, 79.4)	69.9 (65.7, 73.7)
EFS rate at 24 months % [a] (95% CI)	67.8 (63.6, 71.7)	59.8 (55.4, 64.0)
EFS rate at 36 months % [a] (95% CI)	63.7 (59.3, 67.7)	53.6 (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	

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

Notes: a Calculated using the Kaplan-Meier technique. b Based on stratified Cox PH model; the stratification factors are tumour stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach. c A hazard ratio < 1 favours D+G+C to be associated with a longer EFS than G+C. 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.

Source: Powles et al, 2024 [32], AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

Radical cystectomy (RC in Table 14) was recommended within 56 days of last dose of neoadjuvant therapy. Adjuvant therapy was recommended to begin as soon as the patient recovered from radical cystectomy and within 120 days after, and no earlier than 42 days after radical cystectomy.

Patients who do not proceed to radical cystectomy are either classified as progressed or enter a non-cystectomy extension phase. Patients with suspected microscopic disease (confirmed by imaging) or documented macroscopic disease at completion of neoadjuvant therapy who refuse radical cystectomy are declared progressed, with an EFS event at the time of expected surgery. Patients with a complete clinical response who decline the initial cystectomy may enter a non-cystectomy extension phase. In this phase, EFS is time to first recurrence after any delayed cystectomy (if performed); if delayed cystectomy is refused or medically precluded, EFS is recorded at unequivocal progression, or death from any cause. In total, there were six (1.1%) patients in the

adjuvant phase that had not undergone a cystectomy and were part of the non-cystectomy extension phase (included in the ITT results).

Table 15 Median times to treatment

	D + G+C	G+C
Median time from randomisation to RC	[redacted]	
Median time from last dose of neoadjuvant therapy to radical cystectomy		
Proportion of patients with cystectomy within 56 days after last dose of neoadjuvant therapy		
Median time from radical cystectomy to start of adjuvant therapy		

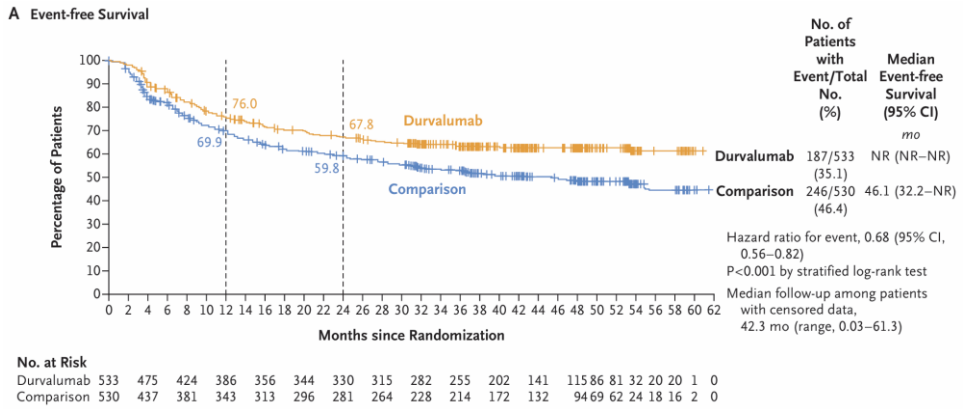
AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

Table 16 Analysis of dual primary endpoint: EFS for subgroups, pCR and non-pCR, in NIAGARA (ITT, IA-2).

EFS status	D + G+C (N = 533)	G+C (N = 530)
Probability of EFS		
pCR subgroup	[redacted]	
Non- pCR		
No.events, n (%)		
pCR subgroup		
Non- pCR		
Median EFS (95% CI) (months)		
pCR subgroup		
Non- pCR		
EFS HR (95% CI)		
pCR subgroup		
Non- pCR		

Source: Data on file [34].

Figure 6 Kaplan-Meier plot of EFS per BICR or by central pathology in NIAGARA (ITT, IA-2)



Abbreviations: BICR: Blinded Independent Central Review; C: cisplatin; CI: confidence interval; D: durvalumab; G: gemcitabine; FAS: full analysis set; EFS: event-free survival; HR: hazard ratio; IA-2: second interim analysis; IVRS: interactive voice response system; NR: not reached; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Notes: Median EFS calculated using the Kaplan-Meier 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 D + G+C to be associated with a longer EFS than G+C.

Source: Powles et al, 2024 [32].

6.1.4.3 Overall survival

Median follow-up of OS was 42.3 months in the D + G+C arm and 39.6 months in the G+C arm. The median follow-up duration for OS was slightly lower in all patients compared with those who were censored in both treatment arms [29, 32]. The NIAGARA trial is the

only RCT in MIBC to demonstrate statistically significant and clinically meaningful improvement in OS with D + G+C compared with G+C, HR 0.75 (98.457% CI: 0.563, 0.985; p = 0.0106, crossing the boundary of 0.01543), corresponding to a 25% overall reduction in the risk of death. Median OS had not been reached for either treatment arm. Although the OS rate at five years (OS5) will be formally tested at the final analysis per the multiple testing procedure, a descriptive analysis at the 29 April 2024 DCO showed a higher survival in the D +G+C arm (71.1% [95% CI: 66.3, 75.3]) than in the G+C arm (63.9% [95% CI: 58.9, 68.5]) with an HR of [redacted] (95.1% CI: [redacted]) [29].

The results of the OS analysis are detailed in Table 17 and the KM curve is illustrated in Figure 8.

Table 17 Analysis of overall survival in NIAGARA (ITT, IA-2)

OS status	D + G+C (N = 533)	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
Median OS (months)[d]	NR	NR
Hazard ratio (D +G+C vs G+C)[e,f]	0.75	
98.457% CI	0.563 – 0.985	
95% CI	0.594, 0.934	
Two-sided p-value [g]	0.0106	
Survival rate at 6 months % [d] (95% CI)	96.2 (94.2, 97.5)	95.6 (93.4, 97.0)
Survival rate at 12 months % [d] (95% CI)	89.5 (86.6, 91.9)	86.5 (83.3, 89.2)
Survival rate at 24 months % [d] (95% CI)	82.2 (78.7, 85.2)	75.2 (71.3, 78.8)
Survival rate at 36 months % [d] (95% CI)	76.6 (72.7, 80.0)	69.8 (65.5, 73.6)
Survival rate at 60 months % [d] (95% CI)	71.1 (66.3, 75.3)	63.9 (58.9, 68.5)
[redacted]		

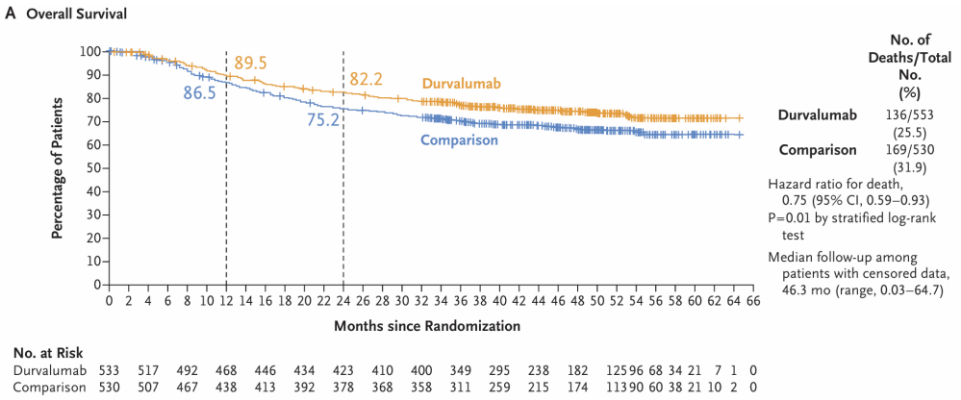
[redacted]

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

Notes: 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 Kaplan-Meier technique. e Based on stratified Cox PH model; the stratification factors were renal function (adequate vs borderline), tumour stage (T2N0 vs > T2N0), and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach. f A hazard ratio < 1 favours D + G+C to be associated with a longer OS than G+C. g Based on a stratified log-rank test, and the stratification factors are the same as the ones indicated in e. h 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 0.01543 for a 4.9% overall alpha. i HR and CI were obtained using Kaplan-Meier estimator of OS5 using Klein approach (Klein et al 2007). A hazard ratio < 1 favours D +G+C to be associated with a longer overall survival than G+C. j p-value is based on a chi-squared test with one degree of freedom.

Source: Powles et al, 2024 [32], AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

Figure 8 Kaplan-Meier plot of overall survival in NIAGARA (FAS, IA-2)



Abbreviations: C: cisplatin; CI: confidence interval; D: durvalumab; G: gemcitabine; FAS: full analysis set; IA-2: second interim analysis; IVRS: interactive voice response system; NR: not reached; OS: overall survival; PD-L1: programmed death-ligand 1; PH: proportional hazards.

Notes: Overall survival is defined as the time from the date of randomization until death due to any cause regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy (i.e., date of death or censoring – date of randomization + 1). Median OS calculated using the Kaplan-Meier technique. HR based on stratified Cox PH model; the stratification factors were tumour stage (T2N0 vs > T2N0), renal function (adequate vs borderline) and PD-L1 status (high vs low/negative) per IVRS, with ties handled by the Efron approach. A hazard ratio < 1 favours D + G+C to be associated with a longer OS than G+C.

Source: Powles et al, 2024 [32].

6.1.4.4 Subsequent anticancer treatment

The proportion of patients who had received a subsequent anticancer therapy was [redacted] The most common subsequent anticancer therapies administered are presented in Table 18 below. A more detailed table can be found in Appendix B.

Table 18 Proportion of patients that recieved subsequent treatment after discontinuation of study treatment

Anticancer therapy*	Number (%) of patients		
	D + G+C (N = 533)	G+C (N = 530)	Total (N=1063)
Radiotherapy	[redacted]		
Immunotherapy			
Cytotoxic chemo			
Targeted therapy			
Radiopharmaceuticals			
Other			

*therapies recorded after discontinuation of study treatment

Source: Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

6.1.5 Efficacy – results per [study name 2]

N/A

7. Comparative analyses of efficacy

Since the clinical evidence is derived from a head-to-head trial, the subsequent section on comparative analysis is not applicable. The key results from the NIAGARA trial, comparing D + G+C with G+C in patients with muscle-invasive bladder cancer, are presented in Table 19. This table has been completed in accordance with the DMC template guidelines using data from the NIAGARA trial.

7.1.1 Differences in definitions of outcomes between studies

N/A

7.1.2 Method of synthesis

N/A

7.1.3 Results from the comparative analysis

The key results from the NIAGARA trial comparing D + G+C and G+C for patients with muscle-invasive bladder cancer are presented below (see Table 19).

For other outcomes see Appendix B.

Table 19 Results from the comparative analysis of neoadjuvant D + G+C and adjuvant durvalumab vs. neoadjuvant G+C for patients with muscle-invasive bladder cancer

Outcome measure	D + G+C (N = 533)	G+C (N = 530)	Result
mEFS, median follow-up 34.7 months (D + G+C) and 27.7 months (G+C)	NR (95% CI: NR-NR)	46.1 (95% CI: 32.2-NR)	NA HR: 0.68 (95% CI: 0.558, 0.817)
mOS, median follow-up 42.3 months (D + G+C) and 39.6 months (G+C)	NR (NR-NR)	NR (NR-NR)	NA HR: 0.75 (95% CI: 0.594, 0.934)

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29].

7.1.4 Efficacy – results per [outcome measure]

[Complete a section for each outcome measure.]

8. Modelling of efficacy in the health economic analysis

N/A

8.1 Presentation of efficacy data from the clinical documentation used in the model

N/A

8.1.1 Extrapolation of efficacy data

N/A

8.1.1.1 Extrapolation of [effect measure 1]

N/A

Table 20 Summary of assumptions associated with extrapolation of [effect measure] N/A

Method/approach	Description/assumption
Data input	N/A
Model	N/A
Assumption of proportional hazards between intervention and comparator	N/A
Function with best AIC fit	N/A
Function with best BIC fit	N/A
Function with best visual fit	N/A
Function with best fit according to evaluation of smoothed hazard assumptions	N/A
Validation of selected extrapolated curves (external evidence)	N/A
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	N/A
Adjustment of background mortality with data from Statistics Denmark	N/A
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	N/A

8.1.1.2 Extrapolation of [effect measure 2]

N/A

8.1.2 Calculation of transition probabilities

N/A

Table 21 Transitions in the health economic model N/A

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	N/A	N/A	N/A
	N/A	N/A	N/A
Recurrence	N/A	N/A	N/A
Health state/Transition	N/A	N/A	N/A

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

N/A

Table 22 Estimates in the model N/A

	Modelled average [effect measure] (reference in Excel)	Modelled median [effect measure] (reference in Excel)	Observed median from relevant study
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A

Table 23 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model) N/A

Treatment	Treatment length [months]	Health state 1 [months]	Health state 2 [months]
N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A

9. Safety

9.1 Safety data from the clinical documentation

Safety events reported in the NIAGARA trial are presented in Table 24 based on the data cut from 29 April 2024 [29]. The analysis is based on the safety analysis set and covers the overall trial period, including neoadjuvant, post-surgical and adjuvant therapy periods. The safety analysis set includes 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.

The overall period was defined as date of first dose of study treatment until the earliest of:

- D + G+C arm: 90 days after the last dose of study treatment, or date of surgery (whichever occurs later), date of first dose of subsequent anticancer therapy, or date of DCO.
- G+C arm: 90 days after the last neoadjuvant treatment, date of surgery, or adjuvant study visit (whichever occurs later), date of first dose of subsequent anticancer therapy, or date of DCO.

Considering the overall treatment period, the median duration of exposure in the safety analysis set was as follows:

- Durvalumab: 44 weeks (min 1 max 84) corresponding to 12 cycles (min 1 max 12)
- G + C exposure on the durvalumab combination arm: 12.2 weeks (1 to 23) corresponding to 4 cycles (1 to 4)
  Comparator arm G + C exposure: 12 weeks (1 to 27) corresponding to a median of 4 cycles (1 to 4) [29].

The majority of patients experienced at least 1 AE in the overall period (99.4% in the D + G+C arm vs 99.8% in the G+C arm) and the proportions of patients experiencing AEs of CTCAE Grade 3 or 4 were similar in the D + G+C arm and G+C arm (69.4% and 67.5%). At the DCO, serious adverse events (SAEs) were reported in a slightly higher proportion of patients in the D + G+C arm (61.5%) than the G+C arm (54.6%).

The most frequently reported SAEs in the overall period (reported in ≥ 5% of patients in both the D + G+C and G+C arms) were urinary tract infection (11.1% and 13.1% of patients), and prostate cancer (6.6% and 5.1% of patients). In the neoadjuvant period the most frequently reported SAEs (reported in ≥ 2% of patients in either arm) were urinary tract infection (1.3% vs 2.7%) and anemia (0.8% vs 2.9%), in the adjuvant period (reported in ≥ 2% of patients in either arm) were urinary tract infection (6.0% vs 7.0%), acute kidney injury (2.9% vs 2.1%), pyelonephritis (2.1% vs 2.1%), and hydronephrosis (2.1% vs 1.6%).

Table 24 Overview of safety events in the safety analysis set, overall period (cutoff: 29 April 2024)

	D + G+C (N=530)	G+C (N=526)	Difference, % (95 % CI)
Number of adverse events, n	NA	NA	
Number and proportion of patients with ≥1 adverse events, n (%)	527 (99.4)	525 (99.8)	[redacted]
Number of serious adverse events*, n	NA	NA	
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	326 (61.5)	287 (54.6)	
Number of CTCAE grade ≥ 3 events, n	NA	NA	
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%) **Grade 3-4**	368 (69.4)	355 (67.5)	
Number and proportion of patients with any AE with outcome of death, n (%)	27 (5.1)	29 (5.5)	
Number of adverse reactions, n	NA	NA	
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	502 (94.7)	487 (92.6)	
Number and proportion of patients who had a dose reduction or dose interruption, n (%)	305 (57.5)	247 (47.0)	

	D + G+C (N=530)	G+C (N=526)	Difference, % (95 % CI)
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NA	NA	
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	112 (21.1)	80 (15.2)	[redacted]

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

§ CTCAE v. 5.0 must be used if available.

NA: Not available

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

Table 25 Serious adverse events with frequency of ≥ 5% recorded on either treatment arm in the study, safety analysis set, overall period

Adverse events	D + G+C (N=530)		G+C (N=526)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Urinary tract infection	59 (11.1)	NA	69 (13.1)	NA
Prostate cancer	35 (6.6)	NA	27 (5.1)	NA

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

As no health economic analysis was conducted, Table 26 is not applicable.

Table 26 Adverse events used in the health economic model N/A

Adverse events	Intervention	Comparator		
	Frequency used in economic	Frequency used in economic	Source	Justification

Adverse events	Intervention	Comparator
	model for intervention	model for comparator
Adverse event, n (%)	Not applicable	

9.2 Safety data from external literature applied in the health economic model N/A

No health economic model was developed for this submission; thus, this section is not applicable.

Table 27 Adverse events that appear in more than X % of patients N/A

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

10. Documentation of health-related quality of life (HRQoL)

Exploratory endpoints in the NIAGARA study consisted of patient-reported outcomes examining the impact of neoadjuvant and adjuvant therapy on disease-related symptoms, physical function, and patients' health-related quality of life (HRQoL).

Table 28 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC QLQ-C30	NIAGARA, Data on file	To evaluate disease-related symptoms, physical function, and other HRQoL

The NIAGARA trial recorded other HRQoL measures as exploratory endpoints, which are not presented in this assessment. These were EQ-5D-5L, Patient's global impression of change (PGIC), Patient's global impression of severity (PGIS), and PRO-CTCAE (Patient-reported outcome common toxicity criteria for adverse events).

10.1 Presentation of the health-related quality of life EORTC QLQ-C30

10.1.1 Study design and measuring instrument

European Organisation for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30) was a secondary endpoint in the NIAGARA trial. It was selected as secondary endpoint, because the QoL measure covers both general cancer-related symptoms and functional impact domains[36].

The QLQ-C30 incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), a global health status (GHS) / QoL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease [37]. Prioritized scales in the NIAGARA trial were GHS/QoL, physical functioning, fatigue, and pain [36].

The EORTC QLQ-C30 questionnaires were filled out by the patients on a handheld electronic patient outcome (ePRO) device at study sites or at home. Patients were instructed to fill this questionnaire first. They were completed on the days specified by the schedule of assessment for screening and neoadjuvant treatment [36].

Missing data was handled based on the EORTC QLQ-C30 scoring manual [36].

10.1.2 Data collection

Patients were followed up for the HRQoL on day 1 of treatment and every 4 weeks thereafter.

While the neo-adjuvant treatment lasted for 11 weeks, additional time after the last dose was needed for the radical cystectomy (which occurred >14-56 days [>2-8 weeks] after the last neo-adjuvant dose) and a pre-surgery scan. The pre-surgery scan was completed as part of the pre-surgery work up. There was also an adjuvant scan completed 42 days (6 weeks+/- 2 weeks) after the radical cystectomy to assess eligibility for adjuvant treatment. This totals to 25 weeks.

Patients in the adjuvant phase were assessed every 4 weeks during treatment. Because a 4-week interval after the assessment at week 29 would fall in week 33—beyond the treatment period that ends at week 32—the final assessment was scheduled at week 29, while patients were still on treatment. Patients that had progressed or discontinued treatment in the adjuvant phase were followed every 8 weeks. Patients could have progressed after completing treatment.

Table [redacted] Pattern of missing data and completion in EORTC QLQ-C30, NIAGARA, both treatment arms

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
	Durvalumab + G+C				G+C			
Baseline	533	[redacted]	533	[redacted]	530	[redacted]	530	[redacted]
Week 5	533		[redacted]		530		[redacted]	
Week 9	533				530			
Week 13	533				530			
Week 17	533				530			
Week 21	533				530			
Week 25	533				530			
Adjuvant week 1	533				530			

Adjuvant week 5	533	[redacted]	530	[redacted]
Adjuvant week 9	533		530	
Adjuvant week 13	533		530	
Adjuvant week 17	533		530	
Adjuvant week 21	533		530	
Adjuvant week 25	533		530	
Adjuvant week 29	533		530	
Follow-up 1	533		530	
Follow-up 2	533		530	
Follow-up 3	533		530	
Follow-up 4	533		530	
Follow-up 5	533		530	
Follow-up 6	533		530	
Follow-up 7	533		530	
Follow-up 8	533		530	
Follow-up 9	533		530	

Follow-up 10	533	[redacted]	530	[redacted]
Follow-up 11	533		530	
Follow-up 12	533		530	
Follow-up 13	533		530	
Follow-up 14	533		530	
Follow-up 15	533		530	
Follow-up 16	533		530	
Follow-up 17	533		530	
Follow-up 18	533		530	
Follow-up 19	533		530	
Follow-up 20	533		530	
Follow-up 21	533		530	
Follow-up 22	533		530	
Follow-up 23	533		530	
Follow-up 24	533		530	
Follow-up 26	533		530	

Follow-up 26	533	[redacted]	530	[redacted]
Follow-up 27	533		530	
Follow-up 28	533		530	
Follow-up 29	533		530	
Follow-up 30	533		530	
Follow-up 31	533		530	
Follow-up 32	533		530	
Follow-up 33	533		530	

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

10.1.3 HRQoL results

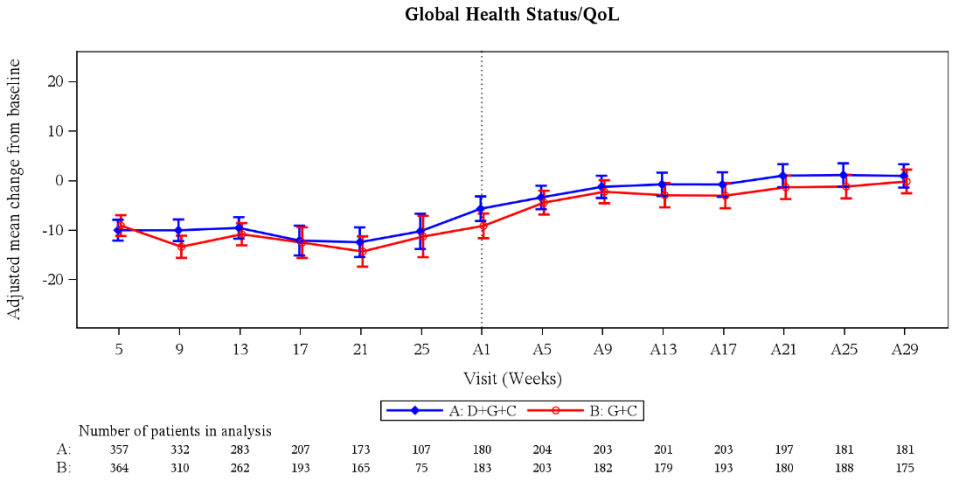
Higher scores on the global health status and function scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

Adjusted mean change from baseline is plotted in the tables showing the summary statistics for all priority domains presented. Change from baseline was analysed using a mixed-model for repeated-measures (MMRM) model, based on restricted likelihood methods, with treatment, visit, treatment by visit interaction as explanatory variables and baseline score as a covariate. Only patients with an evaluable baseline score and at least one evaluable post-baseline score were included in the analysis model. Results were analysed together, but separate analyses were also conducted for each subscale. An MMRM analysis of all the post-baseline scores for each visit was used to determine the adjusted mean change from baseline in the main assessment of each subscale. The model included treatment, visit, treatment by visit interaction, and stratification variables as explanatory variables, and the baseline score as a covariate. Some domains were treated as priorities in the assessment, which will be presented in detail.

A trend towards deterioration from baseline was observed in the first 25 weeks for all scales in both arms, followed by a decrease in the deterioration or a return to baseline levels thereafter. There were no observable differences between treatment arms in the prioritised and non-prioritised scales (aside from appetite loss, which was greater in the G+C arm), suggesting that adding durvalumab to neoadjuvant G+C, and receiving durvalumab monotherapy as adjuvant therapy, was not detrimental to HRQoL, physical functioning or patient-reported symptoms.

10.1.3.1 Global Health Status/Quality of Life

Figure 9 Change from baseline in EORTC QLQ-C30 by MMRM analysis, line graph (Full analysis set)



EORTC = European Organization for Research and Treatment of Cancer, QLQ-C30 = 30 item core quality of life questionnaire, QoL = quality of life, C = Cisplatin, D = Durvalumab, G = Gemcitabine

A1 is first analysis week for the adjuvant phase.

Table [redacted] Global Health Status/Quality of Life summary statistics Change from baseline in EORTC QLQ-C30 by MMRM analysis (Full analysis set)

	Intervention D + G+C		Comparator G+C		Intervention vs. comparator
	N=533	Mean* (SE)	N=530	Mean* (SE)	Difference (95% CI) p-value**
Baseline	439	[redacted]	450	[redacted]	
Week 5	357		364		
Week 9	332		310		
Week 13	283		262		
Week 17	207		193		
Week 21	173		165		
Week 25	107		75		
Adjuvant week 1	180		183		
Adjuvant week 5	204		203		
Adjuvant week 9	203		182		
Adjuvant week 13	201		179		
Adjuvant week 17	203		193		
Adjuvant week 21	197		180		
Adjuvant week 25	181		188		
Adjuvant week 29	181		175		
Over all visits	[redacted]				1.6 (-0.44, 3.69) [redacted]

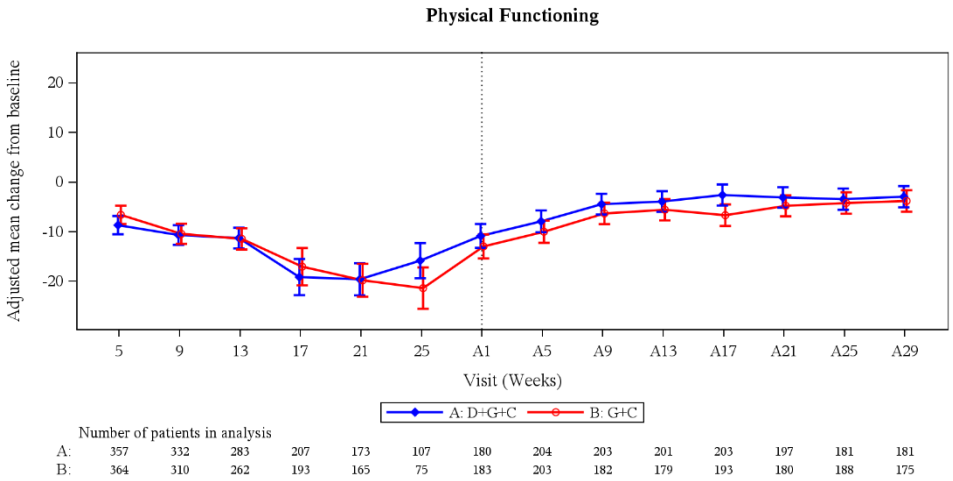
* Adjusted mean represents the change from baseline. Change from baseline is analyzed using a MMRM model, based on restricted likelihood methods, with treatment, visit, treatment by visit interaction, and stratification variables as explanatory variables and baseline score as a covariate. Only patients with an evaluable baseline score and at least one evaluable post-baseline score are included in the analysis model. The stratification factors are renal function [adequate versus borderline], tumor stage [T2N0 versus >T2N0] and PD-L1 status [high versus low/negative] per IVRS.

** The difference between the D+G+C and G+C with respect to the change from baseline. A positive difference favours the D+G+C on the global health status and function scales but favours the G+C on symptom scales

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

10.1.3.2 Physical functioning

Figure 10 Change from baseline in EORTC QLQ-C30 by MMRM analysis, line graph (Full analysis set)



EORTC = European Organization for Research and Treatment of Cancer, QLQ-C30 = 30 item core quality of life questionnaire, QoL = quality of life, C = Cisplatin, D = Durvalumab, G = Gemcitabine, CI = Confidence interval, MMRM = Mixed Model Repeated Measures. A1 is first analysis week for the adjuvant phase.

Table [redacted] Physical functioning summary statistics Change from baseline in EORTC QLQ-C30 by MMRM analysis (Full analysis set)

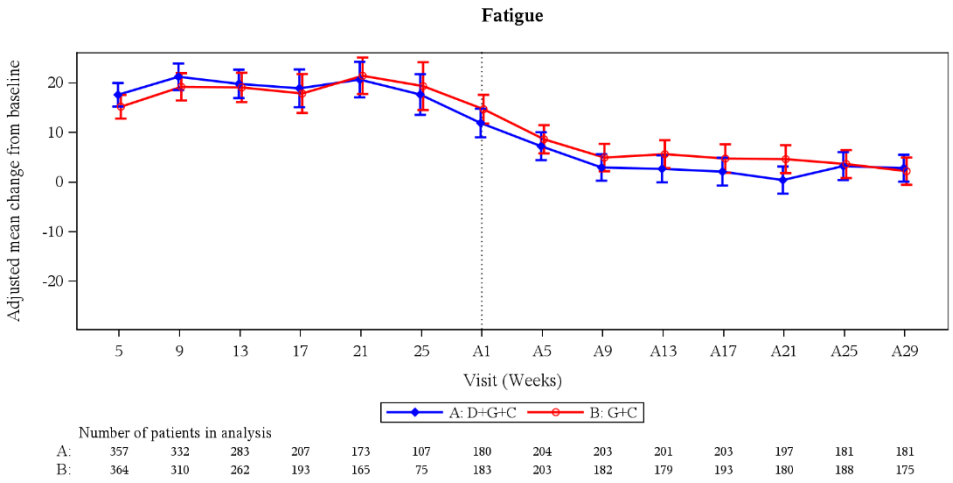
	Intervention D + G+C		Comparator G+C		Intervention vs. comparator
	N=533	Mean (SE)	N=530	Mean (SE)	Difference (95% CI) p-value
Baseline	439	[redacted]	450	[redacted]	
Week 5	357		364		
Week 9	332		310		

	Intervention D + G+C	Comparator G+C	Intervention vs. comparator
Week 13	283	262	[redacted]
Week 17	207	193	
Week 21	173	165	
Week 25	107	75	
Adjuvant week 1	180	183	
Adjuvant week 5	204	203	
Adjuvant week 9	203	182	
Adjuvant week 13	201	179	
Adjuvant week 17	203	193	
Adjuvant week 21	197	180	
Adjuvant week 25	181	188	
Adjuvant week 29	181	175	
Over all visits	[redacted]		1.2 (-0.80, 3.17) [redacted]

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

10.1.3.3 Fatigue

Figure 11 Change from baseline in EORTC QLQ-C30 by MMRM analysis, line graph (Full analysis set)



EORTC = European Organization for Research and Treatment of Cancer, QLQ-C30 = 30 item core quality of life questionnaire, QoL = quality of life, C = Cisplatin, D = Durvalumab, G = Gemcitabine

A1 is first analysis week for the adjuvant phase.

Table [redacted] Fatigue summary statistics Change from baseline in EORTC QLQ-C30 by MMRM analysis (Full analysis set)

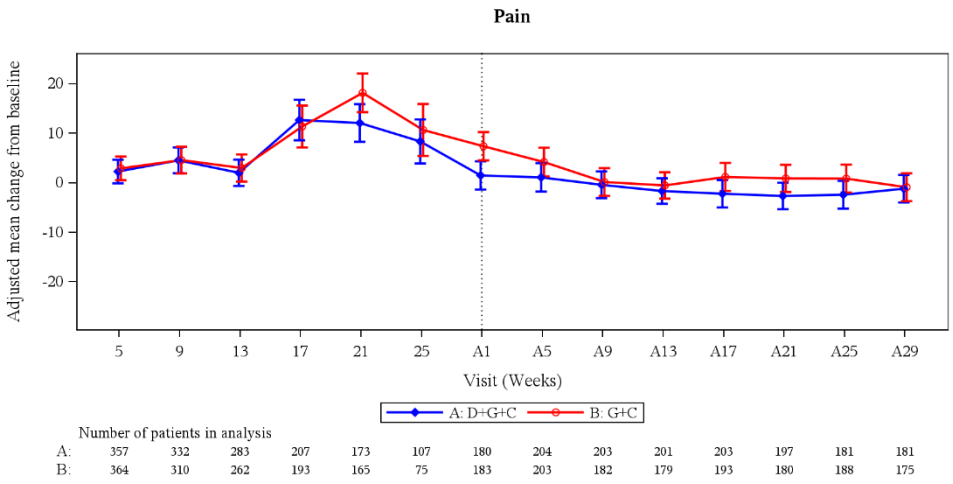
	Intervention		Comparator		Intervention vs. comparator
	N=533	Mean (SE)	N=530	Mean (SE)	Difference (95% CI) p-value
Baseline	439	[redacted]	450	[redacted]	
Week 5	357		364		
Week 9	332		310		
Week 13	283		262		
Week 17	207		193		
Week 21	173		165		
Week 25	107		75		
Adjuvant week 1	180		183		

	Intervention	Comparator	Intervention vs. comparator
Adjuvant week 5	204	203	
Adjuvant week 9	203	182	
Adjuvant week 13	201	179	
Adjuvant week 17	203	139	
Adjuvant week 21	197	180	
Adjuvant week 25	181	188	
Adjuvant week 29	181	175	
Over all visits			-0.9 (-3.25, 1.52)

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

10.1.3.4 Pain

Figure 12 Change from baseline in EORTC QLQ-C30 by MMRM analysis, line graph (Full analysis set)



Abbreviations: EORTC = European Organization for Research and Treatment of Cancer, QLQ-C30 = 30 item core quality of life questionnaire, QoL = quality of life; C = Cisplatin, D = Durvalumab, G = Gemcitabine, CI = Confidence interval, MMRM = Mixed Model Repeated Measures. A1 is first analysis week for the adjuvant phase.

Table [redacted] Pain summary statistics Change from baseline in EORTC QLQ-C30 by MMRM analysis (Full analysis set)

	Intervention		Comparator		Intervention vs. comparator
	N=533	Mean (SE)	N=530	Mean (SE)	Difference (95% CI) p-value
Baseline	439	[redacted]	450	[redacted]	
Week 5	357		364		
Week 9	332		310		
Week 13	283		262		
Week 17	207		193		
Week 21	173		165		
Week 25	107		75		
Adjuvant week 1	180		183		
Adjuvant week 5	204		203		
Adjuvant week 9	203		182		
Adjuvant week 13	201		179		
Adjuvant week 17	203		193		
Adjuvant week 21	197		180		
Adjuvant week 25	181		188		
Adjuvant week 29	181		175		
Over all visits	[redacted]				-2.1 (-4.44, 0.16) [redacted]

Source: AZ NIAGARA Clinical Study Report 29 April 2024 DCO [29]

10.2 Health state utility values (HSUVs) used in the health economic model

This section is not applicable for this application.

10.2.1 HSUV calculation

N/A

10.2.1.1 Mapping

N/A

10.2.2 Disutility calculation

N/A

10.2.3 HSUV results

N/A

Table 34 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not applicable				

10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

Not applicable.

10.3.1 Study design

N/A

10.3.2 Data collection

N/A

10.3.3 HRQoL Results

N/A

10.3.4 HSUV and disutility results

N/A

Table 35 Overview of health state utility values [and disutilities] N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not appliacable				

Table 36 Overview of literature-based health state utility values N/A

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Not aplicable				

11. Resource use and associated costs

Not applicable.

11.1 Medicines - intervention and comparator

N/A

Table 37 Medicines used in the model N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
[Name of the intervention]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]
[Name of the comparator]	[E.g. 5 mg]	[E.g. 97 %]	[E.g. every second week]	[Yes/no]

11.2 Medicines– co-administration

N/A

11.3 Administration costs

N/A

Table 38 Administration costs used in the model N/A

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
N/A				

11.4 Disease management costs

N/A

Table 39 Disease management costs used in the model N/A

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
[Activity]	[E.g. every 3rd week]			DRG 202[X]

11.5 Costs associated with management of adverse events

N/A

Table 40 Cost associated with management of adverse events N/A

	DRG code	Unit cost/DRG tariff
N/A		

11.6 Subsequent treatment costs

N/A

Table 41 Medicines of subsequent treatments N/A

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
N/A				

11.7 Patient costs

N/A

Table 42 Patient costs used in the model N/A

Activity	Time spent [minutes, hours, days]
N/A	

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

N/A

12. Results

N/A

12.1 Base case overview

N/A

Table 43 Base case overview N/A

Feature	Description
Comparator	N/A
Type of model	N/A
Time horizon	N/A
Treatment line	N/A
Measurement and valuation of health effects	N/A

Feature	Description
Costs included	N/A
Dosage of medicine	N/A
Average time on treatment	N/A
Parametric function for PFS	N/A
Parametric function for OS	N/A
Inclusion of waste	N/A
Average time in model health state	N/A
Health state 1	
Health state 2	
Health state 3	
Death	

12.1.1 Base case results

N/A

Table 44 Base case results, discounted estimates N/A

	[Intervention]	[Comparator]	Difference
Medicine costs	N/A		
Medicine costs – co-administration			
Administration			
Disease management costs			
Costs associated with management of adverse events			
Subsequent treatment costs			
Patient costs			
Palliative care costs			

	[Intervention]	[Comparator]	Difference
Total costs			
Life years gained (health state A)			
Life years gained (health state B)			
Total life years			
QALYs (state A)			
QALYs (state B)			
QALYs (adverse reactions)			
Total QALYs			
Incremental costs per life year gained		**N/A**	
Incremental cost per QALY gained (ICER)		**N/A**	

12.2 Sensitivity analyses

N/A

12.2.1 Deterministic sensitivity analyses

N/A

Table 45 One-way sensitivity analyses results N/A

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	N/A				

12.2.2 Probabilistic sensitivity analyses

N/A

13. Budget impact analysis

N/A

Number of patients (including assumptions of market share)

N/A

Table 46 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share) N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
[Name of intervention]	N/A				
[Name of comparator]					
			Non-recommendation		
[Name of intervention]					
[Name of comparator]					

Budget impact

N/A

Table 47 Expected budget impact of recommending the medicine for the indication N/A

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended					
The medicine under consideration is NOT recommended					
Budget impact of the recommendation					

14. List of experts

N/A

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Appendix A. Main characteristics of studies included

Table 48 Main characteristics of studies included

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	**NCT number: NCT03732677**
Objective	A global study to determine the efficacy and safety of durvalumab (D) in combination with gemcitabine + cisplatin (G+C) for neoadjuvant treatment followed by durvalumab alone for adjuvant treatment in patients with muscle-invasive bladder cancer
Publications – title, author, journal, year	Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. Thomas Powles, M.D., James W.F. Catto, Ph.D., F.R.C.S.(Urol.), Matthew D. Galsky, M.D., Hikmat Al-Ahmadie, M.D., Joshua J. Meeks, M.D., Ph.D., Hiroyuki Nishiyama, M.D., Ph.D., Toan Quang Vu, M.D., the NIAGARA Investigators*, New England Journal of Medicine, Volume 391 • Number 19 • November 14, 2024, Pages: 1773-1786
Study type and design	Phase 3, global, open-label, randomized trial, used an interactive voice-response system to assign patients in a 1:1 ratio, to the durvalumab or comparison group. Randomization was stratified on the basis of clinical tumor stage (T2N0 or higher than T2N0), renal function (creatinine clearance of 40 to <60 ml per minute per 1.73 m2 or ≥60 ml per minute per 1.73 m2), and tumor PD-L1 expression level (high expression or low or no expression). No crossover was allowed.
Sample size (n)	*A total of 1530 patient had been enrolled, 1063 randomised.* *Durvalumab group N = 533* *Comparison N = 530*
Main inclusion criteria	• Patient resectable muscle-invasive bladder cancer with clinical stage T2-T4aN0/1M0 with transitional and mixed transitional cell histology • Patients must be planning to undergo a radical cystectomy • Patients who have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC • ECOG performance status of 0 or 1 • Must have a life expectancy of at least 12 weeks at randomization • All sexes, aged above 18 years
Main exclusion criteria	• Evidence of lymph node (N2-N3) or metastatic (M1) disease at time of screening.

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	NCT number: NCT03732677

	• Prior pelvic radiotherapy treatment within 2 years of randomization to study • Prior exposure to immune-mediated therapy (with exclusion of Bacillus-Calmette Guerin [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 investigational product (IP). The following are exceptions to this criterion: Intranasal, inhaled, topical steroids, or local steroid injections (eg, 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 (eg, CT scan premedication) • Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. • Uncontrolled intercurrent illness • Active infection including Tuberculosis, Hepatitis B, Hepatitis C, and Human Immunodeficiency
Intervention	Treatments and dosing regimens for neoadjuvant therapy: • Patients with adequate renal function (creatinine clearance [CrCl] ≥ 60 mL/min): D + G+C: Day 1: durvalumab 1500 mg intravenously (IV), cisplatin 70 mg/m2, gemcitabine 1000 mg/m2; Day 8: gemcitabine 1000 mg/m2; every 21 days for 4 cycles. • Patients with borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min): D + G+C: Day 1: durvalumab 1500 mg IV, cisplatin 35 mg/m2, gemcitabine 1000 mg/m2; Day 8: gemcitabine 1000 mg/m2, cisplatin 35 mg/m2; every 21 days for 4 cycles. Treatments and dosing regimens for adjuvant therapy (regardless of renal status): • D + G+C: Day 1: durvalumab 1500 mg IV; every 28 days for 8 cycles. Patients in either treatment arm who refused to undergo cystectomy and had a complete clinical response could enter a non-cystectomy extension phase instead of the follow-up phase. Patients enrolled into the D + G+C arm who entered the non-cystectomy extension phase could be administered durvalumab 1500 mg as monotherapy every 28 days for a maximum of 8 doses (corresponding to a maximum exposure of 12 months). Patients were to receive 4 cycles of study treatment in the neoadjuvant setting prior to radical cystectomy. After radical cystectomy and adequate recovery, unless specific study discontinuation criteria were

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	NCT number: NCT03732677
	met, patients in the D + G+C arm received adjuvant treatment for up to a maximum of 8 cycles of durvalumab monotherapy, and those in the G+C arm received no adjuvant treatment. • Randomised: 533 • Received treatment: 530 • Completed neoadjuvant treatment: 417 • Underwent cystectomy: 470 • Entered non-cystectomy phase: 6 • Started adjuvant treatment: 383 (completed 8 cycles: 287) At interim analysis 2 (IA-2 DCO) 379 patients were ongoing on this arm in the survival follow-up.
Comparator(s)	Treatments and dosing regimens for neoadjuvant therapy: • Patients with adequate renal function (creatinine clearance [CrCl] ≥ 60 mL/min): G+C: Day 1: cisplatin 70 mg/m2, gemcitabine 1000 mg/m2; Day 8: gemcitabine 1000 mg/m2; every 21 days for 4 cycles. • Patients with borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min): G+C: Day 1: cisplatin 35 mg/m2, gemcitabine 1000 mg/m2; Day 8: gemcitabine 1000 mg/m2, cisplatin 35 mg/m2; every 21 days for 4 cycles. No adjuvant treatment on this arm. • Randomised: 530 • Received treatment: 526 • Completed neoadjuvant treatment: 389 • Underwent cystectomy: 445 • Entered non-cystectomy phase: 0 • Completed adjuvant treatment: Not applicable • Ongoing in the survival follow-up phase: 333
Follow-up time	Median follow-up 42.3 mo (range, 0.03–61.3)
Is the study used in the health economic model?	N/A
Primary, secondary and exploratory endpoints	**Primary**: Pathologic complete response (pCR) rates at time of cystectomy [Time Frame: Up to 6 months], per central pathology review

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	NCT number: NCT03732677

Event-free survival (EFS) per BICR or by central pathology review if a biopsy is required for a suspected new lesion, defined as time from randomization to event [Time Frame: Up to 48 months]

Secondary:

Proportion of patients who achieve <P2 at time of cystectomy [Time Frame: Up to 6 months] per local pathology review

EFS using assessment per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion

EFS at 24 months (EFS24) defined as time from randomization to event [Time Frame: Up to 24 months] per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion

Overall Survival [Time Frame: Up to 84 months]

Overall survival rate at 5 years [Time Frame: Up to 60 months]

PFS2 defined as time from randomization to event following subsequent therapy [Time Frame: Up to 84 months] defined by local standard clinical practice

Safety and Tolerability as evaluated by adverse events occurring throughout the study [Time Frame: Up to 84 months]

Immunogenicity of durvalumab when used in combination with gemcitabine/cisplatin as measured by presence of antidrug antibodies (ADA) [Time Frame: Up to 12 months]

Metastasis-free survival (MFS) per investigator assessment or local biopsy review. [Time Frame: Up to 48 months]

Disease-specific survival per investigator assessment or local biopsy review. [Time Frame: up to 48 months]

Proportion of patients who undergo radical cystectomy

Disease-free survival (DFS) [Time Frame: Up to 48 months] in patients who undergo radical cystectomy

HRQoL measured through EORTC QLQ-C30 PRO

Safety endpoints:

Adverse events, laboratory findings, vital signs, ECGs

Exploratory endpoints:

PRO-CTCAE (items preselected based on systemic treatment arms) – descriptive summary of responses

PGIC and PGIS – descriptive summary of responses

The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	NCT number: NCT03732677
	Association of tumor-based assessments with efficacy and clinical parameters Association of circulating tumor DNA, whole blood gene expression, and urine biomarkers with efficacy and clinical parameters. **Endpoints included in this application:** pCR and EFS were primary endpoints according to central pathology review. From secondary endpoints OS, adverse events and HRQoL was reported. **Other endpoints:** N/A
Method of analysis	The analysis of data using the FAS follows the principles of intention to treat, all analysis was conducted on this set. All categorical response endpoints (pCR and the patients who achieved < P2) were analyzed by logistic regression adjusted for the stratification factors, odds ratio, and corresponding confidence intervals. Event-time outcomes fell into four analysis groups: • EFS was tested by a stratified log-rank test for the P-value and quantified via a stratified Cox proportional-hazards model (HR + 95% CI). • OS used a stratified log-rank test, while the 5-year OS rate (OS5) was estimated by Kaplan–Meier at 5 years. • EFS24 employed Kaplan–Meier to estimate the 24-month EFS rate by treatment arm. • MFS, DSS, DFS, and PFS2 were all compared between arms using a stratified log-rank test. The simple proportion of patients who underwent radical cystectomy was summarized as a point estimate with its 95% confidence interval.
Subgroup analyses	Age at randomization (65 or under, over 65), sex (male, female), histology (transitional cell carcinoma, transitional cell carcinoma – other), prior bacillus Calmette-Guerin therapy (Yes/no), lymph node positive (N0, N1), Tumour stage at baseline per IVRS (T2N0, >T2N0), Renal function per IVRS (adequate, borderline), PD-L1 status per IVRS (high, low/negative), TC1 (>=1%, <1%), TC25 (>=25%, <25%), race (white, non-white), region (Asia, Europe, North America and Australia, South America), All visible tumour removed during TURBT procedure prior to study entry (Yes/No)

Trial name: Durvalumab+ Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (NIAGARA)	NCT number: NCT03732677
	The subgroup analysis was performed using an unstratified Cox PH model, with treatment as only covariate and ties handled by Efron approach. The analysis was pre-specified.
Other relevant information	N/A

Appendix B. Efficacy results per study

Results per study

Table 49 Results per study

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
pCR rate	D+G+C	533	199 (37.3%) (33.2, 41.6)	9.8	4.19-15.39	0.0006	Odds ratio: 1.60	1.227, 2.084	0.0005	Logistic regression adjusted for the stratification factors, odds ratio and the corresponding CI. The 95% CIs are calculated using the Clopper Pearson method. Threshold for significance, p = 0.001.	[32] [29]
	G+C	530	146 (27.5%) (23.8, 31.6)								[32] [29]
EFS											
Total EFS events, n (%)	D+G+C	533	187 (35.1%) (95% CI: N/A)	-11.3	-17.17, -5.43	0.00016	NA	NA	NA	Stratified log-rank test to obtain the p-value, stratified Cox PH model to obtain the HR and the corresponding CI	[32] [29]
	G+C	530	246 (46.4%) (95% CI: N/A)								[32] [29]

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
EFS, Hazard ratio	D+G+C	533	NA	NA	NA	NA	0.68	0.558, 0.817	p<0.0001	HR was estimated using a stratified Cox proportional hazard model, where TC25 was included as a categorical covariate. The model was stratified by two factors: tumour stage [T2N0 versus >T2N0] and renal function [adequate versus borderline]. Efron's method was used to handle ties.	[32] [29]
	G+C	530	NA								[32] [29]
EFS, median	D+G+C	533	NR (NR-NR)	NA	NA	NA	NA	NA	NA	Median EFS calculated using the Kaplan-Meier technique.	[32] [29]
	G+C	530	46.1 (32.2-NR)								[32] [29]
EFS rate at 6 months %	D+G+C	533	87.7 (84.5, 90.2)	5.3	[redacted]		NA	NA	NA	See above EFS	[32] [29]
	G+C	530	82.4 (78.8, 85.4)								[32] [29]

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
EFS rate at 12 months %	D+G+C	533	76.0 (72.0, 79.4)	6.10	[redacted]		NA	NA	NA	See above EFS	[32] [29]
	G+C	530	69.9 (65.7, 73.7)								[32] [29]
EFS rate at 24 months %	D+G+C	533	67.8 (63.6, 71.7)	8.00			NA	NA	NA	See above EFS	[32] [29]
	G+C	530	59.8 (55.4, 64.0)								[32] [29]
EFS rate at 36 months %	D+G+C	533	63.7 (59.3, 67.7)	10.10			NA	NA	NA	See above EFS	[32] [29]
	G+C	530	53.6 (49.0, 57.9)								[32] [29]
Probability of EFS											
	D+G+C	533	92.1%	6.30		0.001	NA	NA	NA		[34]

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
pCR subgroup	G+C	530	85.8%		2.55, 10.05					EFS was evaluated for the pCR and non-pCR subgroups.	[34]
Non-pCR	D+G+C	533	53.3%	3.80	-2.20, 9.80	0.215	NA	NA	NA		[34]
	G+C	530	49.5%								[34]
No.events, n (%)											
pCR subgroup	D+G+C	533	23 (12%)	-8.00	-12.38, -3.62	0.00032	NA	NA	NA	See comment above for subgroups.	[34]
	G+C	530	29 (20%)								[34]
Non-pCR	D+G+C	533	164 (49%)	-8.00	-13.98, -2.02	0.0088	NA	NA	NA		[34]
	G+C	530	217 (57%)								[34]
Median EFS (months)											

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
pCR subgroup	D+G+C	533	NR (NR-NR)	NA	NA	NA	NA	NA	NA	See comment above for subgroups.	[34]
	G+C	530	NR (NR-NR)								[34]
Non-pCR	D+G+C	533	34.7 (20.5–NR)	11.90	6.51, 17.29		NA	NA	NA		[34]
	G+C	530	22.8 (15.5–30.6)								[34]
EFS HR											
pCR subgroup	D+G+C	533	NA	NA	NA	NA	0.58	0.332–0.999	0.052	See comment above for subgroups.	[34]
	G+C	530	NA								[34]
Non-pCR	D+G+C	533	NA	NA	NA	NA	0.77	0.631–0.948	0.012		[34]
	G+C	530	NA								[34]
OS											
	D+G+C	533	NR (NR-NR)	N/A	NA	NA	NA	NA	NA	Stratified log-rank	[32] [29]

Results of NIAGARA (NCT03732677)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median OS (months)	G+C	530	NR (NR-NR)							test for OS. Calculated using the Kaplan-Meier technique.	[32] [29]
Survival rate at 6 months %	D+G+C	533	96.2 (94.2, 97.5)	0.60	[redacted]		NA	NA	NA	See above OS	[32] [29]
	G+C	530	95.6 (93.4, 97.0)								[32] [29]
Survival rate at 12 months %	D+G+C	533	89.5 (86.6, 91.9)	3.00			NA	NA	NA	See above OS	[32] [29]
	G+C	530	86.5 (83.3, 89.2)								[32] [29]
Survival rate at 24 months %	D+G+C	533	82.2 (78.7, 85.2)	7.00			NA	NA	NA	See above OS	[32] [29]
	G+C	530	75.2 (71.3, 78.8)								[32] [29]

Results of NIAGARA (NCT03732677)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Survival rate at 36 months %	D+G+C	533	76.6 (72.7, 80.0)	6.80	[redacted]		NA	NA	NA	See above OS	[32] [29]
	G+C	530	69.8 (65.5, 73.6)								[32] [29]
Survival rate at 60 months %	D+G+C	533	71.1 (66.3, 75.3)	7.20			NA	NA	NA	See above OS	[32] [29]
	G+C	530	63.9 (58.9, 68.5)								[32] [29]
OS, Hazard ratio	D+G+C	533	NA	NA	NA	NA	0.75	0.594, 0.934	0.0106	The threshold for statistical significance was p = 0.0154.	[32] [29]
	G+C	530	NA								[32] [29]

Table 50 Post-discontinuation disease-related anticancer treatment (Full analysis set)

Anticancer therapy*	Treatment	Number (%) of patients		
		D+G+C (N=533)	G+C (N=530)	Total (N=1063)
Total	[redacted]			
Radiotherapy				
Immunotherapy				

Anticancer therapy*	Treatment	Number (%) of patients		
		D+G+C (N=533)	G+C (N=530)	Total (N=1063)
Cytotoxic chemotherapy	[redacted]			

Anticancer therapy*	Treatment	Number (%) of patients		
		D+G+C (N=533)	G+C (N=530)	Total (N=1063)
	[redacted]			
Targeted therapy				

Anticancer therapy*	Treatment	Number (%) of patients		
		D+G+C (N=533)	G+C (N=530)	Total (N=1063)
	[redacted]			
Radiopharmaceuticals				
Other				

*Therapies recorded after the discontinuation of study treatment

Appendix C. Comparative analysis of efficacy

N/A

Table 51 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication] N/A

Outcome		Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value		
N/A									

Appendix D. Extrapolation

N/A

D.1 Extrapolation of [effect measure 1]

D.1.1 Data input

N/A

D.1.2 Model

N/A

[redacted]

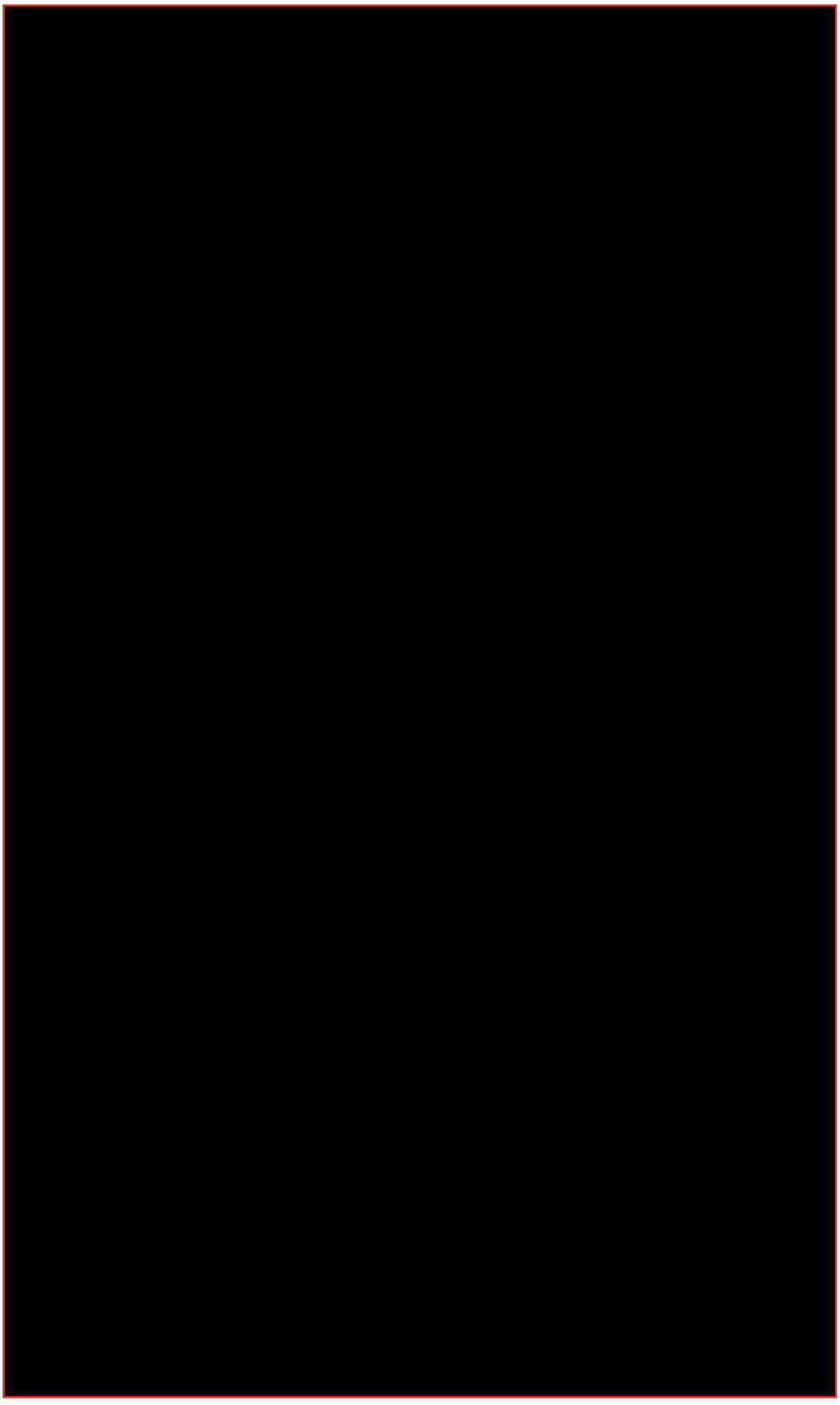
The Schoenfeld plot (Figure 13) displays a [redacted] The test statistic for proportional hazards was [redacted]

[redacted]

The EFS log-cumulative hazard and QQ plots (Figure 14 and Figure 15) provide [redacted]

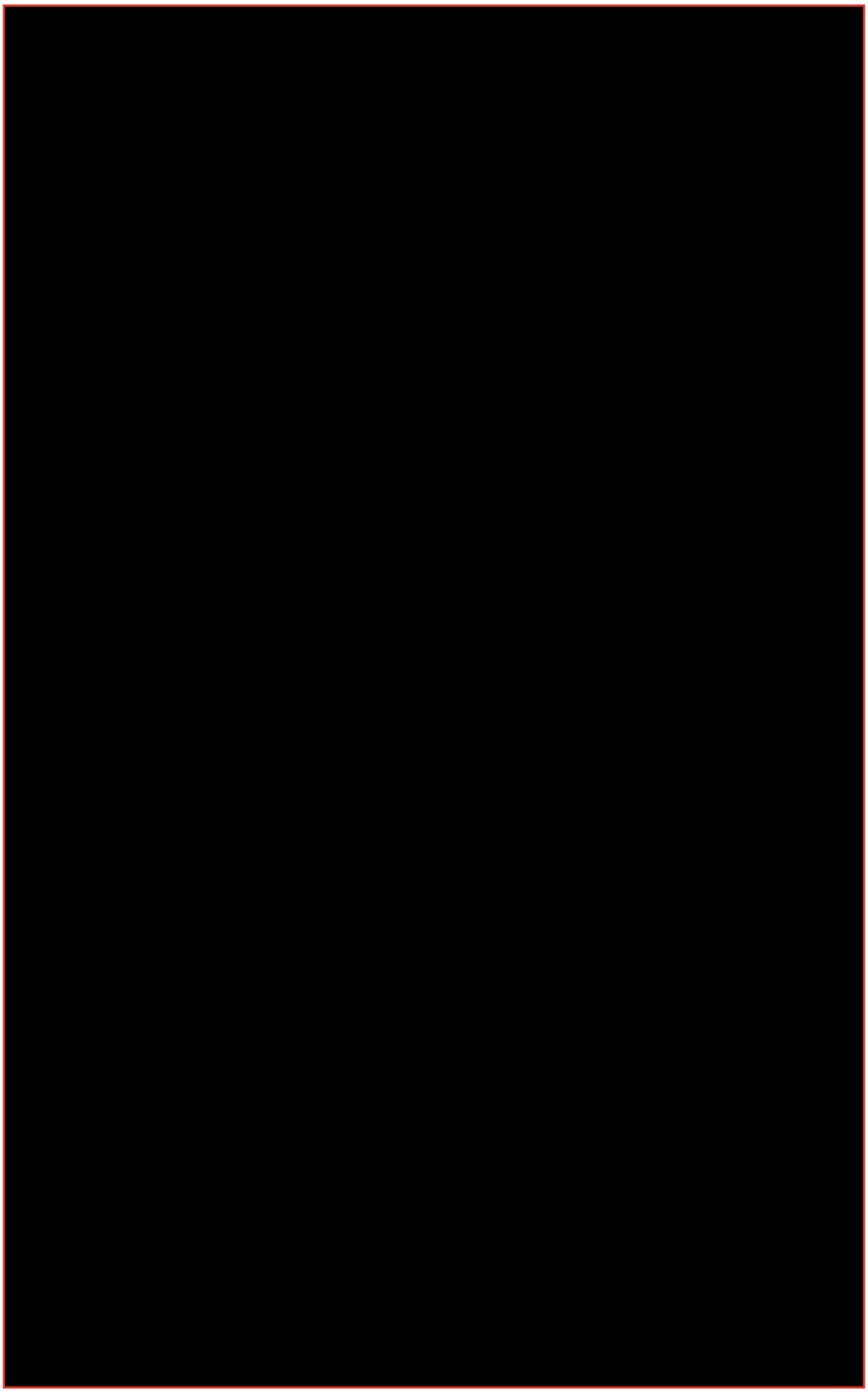
[redacted] Due to this, AstraZeneca produced a piecewise analysis, we provide here the time-varying hazard ratios (95% CI)

[redacted]



Key secondary enpoint: OS

The Schoenfeld plot (Figure 16) shows a [redacted] The test statistic for proportional hazards was [redacted] suggesting that there is [redacted] The log-cumulative hazard and QQ plots (Figure 17 and Figure 18) provide [redacted]



D.1.4 Evaluation of statistical fit (AIC and BIC)

N/A

D.1.5 Evaluation of visual fit

N/A

D.1.6 Evaluation of hazard functions

N/A

D.1.7 Validation and discussion of extrapolated curves

N/A

D.1.8 Adjustment of background mortality

N/A

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

N/A

D.2 Extrapolation of [effect measure 2]

N/A

Appendix E. Serious adverse events

Serious adverse events by system organ class and preferred term (Safety analysis set, overall period) from the NIAGARA trial are presented below based on the data cut of 29 April 2024 [29]. Only the number of patients with the adverse event is available, the number of events was not reported in the study CSR.

Table 52 List of serious adverse events in NIAGARA

System organ class / MedDRA Preferred term	D + G+C (N=530)	G+C (N=526)
Patients with any SAE	326 (61.5)	287 (54.6)
INFECTIONS AND INFESTATIONS	**153 (28.9)**	**136 (25.9)**
Abdominal abscess	[redacted]	
Abdominal infection		
Abscess		
Arthritis bacterial		
Bacteraemia		
Bacterial abdominal infection		
Bacterial pyelonephritis		
Bacterial sepsis		
Bacteroides bacteraemia		
Bronchitis		
COVID-19		
COVID-19 pneumonia		
Candida infection		
Catheter site infection		
Cellulitis		
Clostridium difficile colitis		
Clostridium difficile infection		

Cystitis	[redacted]
Dengue fever	
Device related infection	
Diarrhoea infectious	
Diverticulitis	
Endocarditis	
Erysipelas	
Escherichia infection	
Escherichia sepsis	
Fungaemia	
Fungal endocarditis	
Fungal peritonitis	
Gastroenteritis	
Haematological infection	
Infected lymphocele	
Infection	
Influenza	
Kidney infection	
Klebsiella bacteraemia	
Osteomyelitis	
Pelvic abscess	
Pelvic infection	
Perineal abscess	
Perinephric abscess	
Peritonitis	
Pneumonia	

Pneumonia aspiration	[redacted]	
Pneumonia bacterial		
Pneumonia mycoplasmal		
Pneumonia parainfluenzae viral		
Post procedural infection		
Postoperative abscess		
Postoperative wound infection		
Pseudomembranous colitis		
Pyelonephritis		
Pyelonephritis acute		
Retroperitoneal abscess		
Sepsis		
Septic shock		
Severe acute respiratory syndrome		
Staphylococcal infection		
Suspected COVID-19		
Upper respiratory tract infection		
Urethritis		
Urinary tract infection		
Urosepsis		
Wound infection		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**67 (12.6)**	**44 (8.4)**
Chronic lymphocytic leukaemia	[redacted]	
Gastric cancer		
Invasive ductal breast carcinoma		

Lung neoplasm malignant	[redacted]	
Neuroendocrine tumour		
Oesophageal carcinoma		
Prostate cancer		
Prostate cancer stage 1		
Prostate cancer stage 11		
Prostate cancer stage 111		
Prostate cancer stage IV		
Rectal cancer		
Squamous cell carcinoma		
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**15 (2.8)**	**32 (6.1)**
Anaemia	[redacted]	
Febrile neutropenia		
Leukocytosis		
Neutropenia		
Thrombocytopenia		
IMMUNE SYSTEM DISORDERS	3 (0.6)	2 (0.4)
Anaphylactic reaction	[redacted]	
Anaphylactic shock		
Drug hypersensitivity		
ENDOCRINE DISORDERS	4 (0.8)	1 (0.2)
Hyperthyroidism	[redacted]	
Hypopituitarism		
Hypothyroidism		
Inappropriate antidiuretic hormone secretion		
Thyroiditis		

METABOLISM AND NUTRITION DISORDERS	18 (3.4)	12 (2.3)	
Acidosis	[redacted]		
Decreased appetite			
Dehydration			
Diabetes mellitus			
Gout			
Hypercalcaemia			
Hyperglycaemia			
Hyperkalaemia			
Hypochloraemia			
Hypoglycaemia			
Hypokalaemia			
Hyponatraemia			
Malnutrition			
Metabolic acidosis			
Type 2 diabetes mellitus			
PSYCHIATRIC DISORDERS	1 (0.2)	1 (0.2)	
Agitation	[redacted]		
Completed suicide			
NERVOUS SYSTEM DISORDERS	**17 (3.2)**	**13 (2.5)**	
Cerebral infarction	[redacted]		
Cerebral venous sinus thrombosis			
Cerebrovascular accident			
Cranial nerve palsies multiple			
Diabetic coma			
Dizziness			

Embolic stroke	[redacted]	
IIIrd nerve paralysis		
Ischaemic stroke		
Seizure		
Subarachnoid haemorrhage		
Syncope		
Transient ischaemic attack		
Uraemic encephalopathy		
CARDIAC DISORDERS	**23 (4.3)**	**10 (1.9)**
Acute coronary syndrome	[redacted]	
Acute myocardial infarction		
Angina pectoris		
Atrial fibrillation		
Cardiac arrest		
Cardiac failure		
Cardio-respiratory arrest		
Cardiogenic shock		
Cardiopulmonary failure		
Myocardial infarction		
Myocardial ischaemia		
Sinus node dysfunction		
Ventricular extrasystoles		
Ventricular fibrillation		
VASCULAR DISORDERS	**21 (0.4)**	**21 (0.4)**
Aortic occlusion	[redacted]	
Arterioenteric fistula		

Circulatory collapse	[redacted]	
Deep vein thrombosis		
Distributive shock		
Embolism		
Femoral artery embolism		
Hypertension		
Hypotension		
Lymphocele		
Peripheral ischaemia		
Shock haemorrhagic		
Superficial vein thrombosis		
Thrombophlebitis		
Thrombosis		
Venous thrombosis limb		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**30 (5.7)**	**14 (2.7)**
Acute respiratory distress syndrome	[redacted]	
Acute respiratory failure		
Aspiration		
Autoimmune lung disease		
Bronchospasm		
Chronic obstructive pulmonary disease		
Dyspnoea		
Epistaxis		
Immune-mediated lung disease		
Interstitial lung disease		

Pleural effusion	[redacted]	
Pneumonitis		
Pulmonary embolism		
Pulmonary oedema		
Respiratory failure		
GASTROINTESTINAL DISORDERS	**53 (10.0)**	**35 (6.7)**
Abdominal distension	[redacted]	
Abdominal hernia		
Abdominal hernia obstructive		
Abdominal pain		
Abdominal pain upper		
Colitis		
Colitis ischaemic		
Constipation		
Diarrhoea		
Dyspepsia		
Enterocolitis		
Enterocutaneous fistula		
Fistula of small intestine		
Gastrointestinal haemorrhage		
Gastrointestinal hypomotility		
Gastrointestinal necrosis		
Gastrointestinal obstruction		
Gastrointestinal perforation		
Hernial eventration		
Ileal perforation		

Ileus	[redacted]	
Ileus paralytic		
Immune-mediated enterocolitis		
Inguinal hernia		
Inguinal hernia strangulated		
Intestinal fistula		
Intestinal obstruction		
Intestinal perforation		
Intestinal strangulation		
Large intestine poll)		
Mechanical ileus		
Nausea		
Pancreatitis		
Small intestinal obstruction		
Small intestinal perforation		
Umbilical hernia		
Volvulus of small bowel		
Vomiting		
HEPATOBILIARY DISORDERS	**3 (0.6)**	**2 (0.4)**
Cholangitis	[redacted]	
Cholangitis acute		
Chronic hepatic failure		
Hepatic failure		
Hepatitis acute		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**1 (0.2)**	**1 (0.2)**
Eczema	[redacted]	

Rash	[redacted]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**5 (0.9)**	**4 (0.8)**
Arthralgia	[redacted]	
Back pain		
Groin pain		
Intervertebral disc protrusion		
Myositis		
Osteitis		
Pathological fracture		
Polymyalgia rheumatica		
RENAL AND URNARY DISORDERS	**66 (12.5)**	**58 (11.0)**
Acute kidney injury	[redacted]	
Anuria		
Bladder wall calcification		
Chronic kidney disease		
Cystitis noninfective		
Haematuria		
Hydronephrosis		
Immune-mediated nephritis		
Nephritis		
Nephrolithiasis		
Obstructive nephropathy		
Perinephric collection		
Renal failure		
Renal impairment		

Renal pelvis fistula	[redacted]	
Ureteric stenosis		
Ureterolithiasis		
Urethral stenosis		
Urinary fistula		
Urinary incontinence		
Urinary retention		
Urinary tract disorder		
Urinary tract inflammation		
Urinary tract obstruction		
Vesicourethral fistula		
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**3 (0.6)**	**6 (1.1)**
Benign prostatic hyperplasia	[redacted]	
Orchitis noninfective		
Pelvic fluid collection		
Prostatic dysplasia		
Prostatitis		
Vaginal fistula		
Vaginal prolapse		
CONGENITAL, FAMILIAL AND GENETIC DISORDERS	**1 (0.2)**	**0**
Hamartoma	[redacted]	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**14 (2.6)**	**18 (3.4)**
Asthenia	[redacted]	
Death		
Dehiscence		

Fatigue	[redacted]	
General physical health deterioration		
Hyperpyrexia		
Inflammation		
Malaise		
Multiple organ dysfunction syndrome		
Oedema peripheral		
Pyrexia		
Sudden cardiac death		
INVESTIGATIONS	**19 (3.6)**	**11 (2.1)**
Blood creatinine increased	[redacted]	
C-reactive protein increased		
Candida test positive		
Gastrointestinal stoma output increased		
Hepatic enzyme increased		
Lymphocyte count decreased		
Neutrophil count decreased		
Pancreatic enzymes increased		
Platelet count decreased		
SARS-CoV-2 test positive		
White blood cell count decreased		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**28 (5.3)**	**23 (4.4)**
Abdominal injury	[redacted]	
Abdominal wound dehiscence		
Anastomotic fistula		

Anastomotic leak	[redacted]	
Femur fracture		
Gastrointestinal anastomotic leak		
Incisional hernia		
Limb traumatic amputation		
Post procedural complication		
Post procedural fever		
Post procedural haematoma		
Post procedural haemorrhage		
Post procedural urine leak		
Postoperative ileus		
Postoperative wound complication		
Procedural haemorrhage		
Rectal injury		
Stenosis of vesicourethral anastomosis		
Stomal hernia		
Subdural haematoma		
Subdural haemorrhage		
Suture related complication		
Ureteric anastomosis complication		
Urethral injury		
Urinary tract injury		
Urostomy complication		
Wound dehiscence		
Wound evisceration		
PRODUCT ISSUES	**5 (0.9)**	**3 (0.6)**

Device dislocation	[redacted]
Device occlusion	

Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

N/A

Table 53. Overview of parameters in the PSA N/A

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Probabilities				
Efficacy Outcome A	0.72			Beta
HSUV				
State A	0.79			Beta
Costs				
Hospitalization	20000			Gamma

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 54 Bibliographic databases included in the literature search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

Table 55 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
N/A			

Abbreviations:

Table 56 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

H.1.1 Search strategies

N/A

Table 57 of search strategy table for [name of database] N/A

No.	Query	Results
#1	N/A	
#2		

No.	Query	Results
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

H.1.2 Systematic selection of studies

N/A

Table 58 Inclusion and exclusion criteria used for assessment of studies N/A

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	N/A		
Intervention			
Comparators			
Outcomes			
Study design/publication type			
Language restrictions			

Table 59 Overview of study design for studies included in the analyses N/A

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
Study 1	N/A					
Study 2						

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

N/A

Table 60 Bibliographic databases included in the literature search N/A

Database	Platform	Relevant period for the search	Date of search completion
N/A			

Abbreviations:

Table 61 Other sources included in the literature search N/A

Source name	Location/source	Search strategy	Date of search
N/A			

Table 62 Conference material included in the literature search N/A

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
N/A				

I.1.1 Search strategies

N/A

Table 63 Search strategy for [name of database] N/A

No.	Query	Results
#1	N/A	
#2		

No.	Query	Results
#3		
#4		
#5		
#6		
#7		
#8		
#9		
#10		

Literature search results included in the model/analysis:

N/A

I.1.2 Quality assessment and generalizability of estimates

N/A

I.1.3 Unpublished data

N/A

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

N/A

J.1.1 Example: Systematic search for […]

N/A

Table 51 Sources included in the search N/A

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	e.g. Embase.com	e.g. 1970 until today	dd.mm.yyyy
Medline			dd.mm. yyyy
CENTRAL	Wiley platform		dd.mm. yyyy

Abbreviations:

J.1.2 Example: Targeted literature search for [estimates]

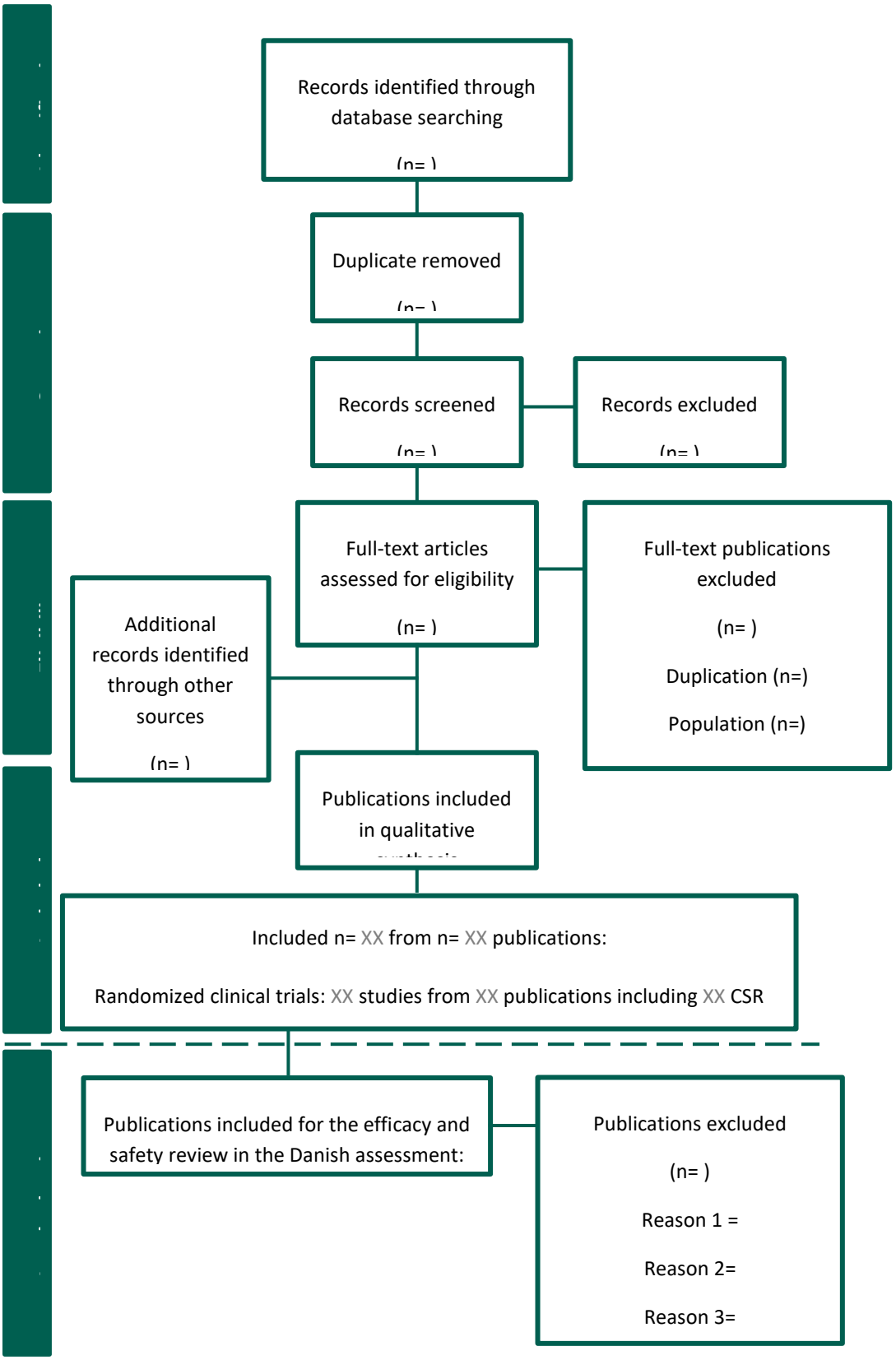
N/A

Table 52 Sources included in the targeted literature search N/A

Source name/ database	Location/source	Search strategy	Date of search
e.g. NICE	www.nice.org.uk		dd.mm.yyyy
			dd.mm.yyyy

Abbreviations:

Example of PRISMA diagram. The diagram is editable and may be used for recording the records flow for the literature searches and for the adaptation of existing SLRs.



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