Journal for ImmunoTherapy of Cancer

Avelumab-based neoadjuvant therapy in patients with muscle-invasive bladder cancer (AURA Oncodistinct-004): a phase 2 multicenter clinical trial

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To cite: Blanc J, Carnot A, Barthélémy P, *et al*. Avelumab-based neoadjuvant therapy in patients with muscle-invasive bladder cancer (AURA Oncodistinct-004): a phase 2 multicenter clinical trial. *Journal for ImmunoTherapy of Cancer* 2025;**13**:e012045. doi:10.1136/jitc-2025-012045

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2025-012045).

Accepted 07 May 2025

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ABSTRACT

Background Immunotherapy is becoming a standard of care for non-metastatic muscle-invasive bladder cancer (MIBC). The optimal chemotherapy partner for chemo-immunotherapy combinations remains unknown. We evaluated the efficacy and safety of neoadjuvant avelumab-based regimens in patients with MIBC.

Methods The multicenter phase 2 AURA trial (NCT03674424) enrolled patients with non-metastatic MIBC undergoing radical cystectomy. Cisplatin-eligible patients were randomized to receive avelumab with either dose-dense methotrexate-vinblastine-doxorubicin-cisplatin (ddMVAC-A) or gemcitabine-cisplatin (GC-A). Cisplatin-ineligible patients received either avelumab alone (A) or combined with paclitaxel-gemcitabine (PG-A). The primary endpoint was pathological complete response (pCR). Secondary endpoints included safety, event-free survival, and overall survival (OS).

Results Between July 2018 and September 2021, 137 eligible patients were enrolled in the trial. In the cisplatin-eligible cohort (n=79), pCR rates were 58% (95% CI: 42% to 72%) in the ddMVAC-A arm and 53% (95% CI: 37% to 68%) in the GC-A arm. The 36-month OS rates were 87% (95% CI: 76% to 98%) for ddMVAC-A and 67% (95% CI: 53% to 84%) for GC-A. In the cisplatin-ineligible cohort (n=58), pCR rates were 14% (95% CI: 6% to 31%) in the PG-A arm and 32% (95% CI: 18% to 51%) in the A arm. The 36-month OS rates were 48% (95% CI: 33% to 71%) for PG-A and 42% (95% CI: 27% to 65%) for A. Overall, 51 (38%) patients experienced grade 3–4 treatment-related adverse events.

Conclusions Avelumab combined with cisplatin-based neoadjuvant chemotherapy showed promising efficacy in MIBC with a favorable safety profile, also with the ddMVAC regimen. Among cisplatin-ineligible patients, avelumab monotherapy showed encouraging activity, with no additional benefit observed from the PG-A regimen. These results support the use of the ddMVAC regimen as a potential chemotherapy partner for neoadjuvant chemo-immunotherapy combinations in future phase 3 trials, providing an alternative to the GC regimen currently under investigation.

Trial registration number NCT03674424.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Immune checkpoint inhibitors have demonstrated a survival benefit in advanced muscle-invasive bladder cancer and are already approved in the adjuvant setting. Neoadjuvant immunotherapy alone or in combination with chemotherapy has shown promising efficacy in phase 2 trials. Recently, a survival benefit was reported with perioperative durvalumab in combination with neoadjuvant gemcitabine-cisplatin in the phase 3 NIAGARA trial.

WHAT THIS STUDY ADDS

⇒ Avelumab combined with standard cisplatin-based neoadjuvant chemotherapy, including dose-dense methotrexate-vinblastine-doxorubicin-cisplatin (ddMVAC), demonstrated high pathological complete response and survival rates without significant safety concerns. However, adding paclitaxel-gemcitabine to neoadjuvant avelumab in cisplatin-ineligible patients did not provide additional benefit.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results suggest that the ddMVAC-avelumab combination has clinical anti-tumor activity with a favorable safety profile and support further development of phase 3 trials evaluating ddMVAC as a new backbone partner for chemo-immunotherapy combinations.

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INTRODUCTION

Despite recent advancements, muscle-invasive bladder cancer (MIBC) remains a highly aggressive disease with substantial mortality.[1] Immune checkpoint inhibitors (ICI) have become a well-established treatment for advanced MIBC. Maintenance avelumab, an anti-programmed death-ligand 1 (PD-L1) antibody, has demonstrated improved overall survival (OS) when administered after first-line platinum-based chemotherapy.[2] Two other randomized trials have compared ICI-based combinations to standard platinum-based chemotherapy in the first-line treatment of advanced MIBC, showing benefits in progression-free survival and OS.[3 4]

Given the success of ICI in the metastatic setting, their role is being explored in earlier stages of the disease. Nivolumab and pembrolizumab have already been approved in the adjuvant setting for patients with non-metastatic high-risk MIBC.[5 6] These patients underwent radical cystectomy, with cisplatin-based neoadjuvant chemotherapy (NAC) administered before surgery for eligible patients. The most commonly used NAC regimens in clinical practice are gemcitabine-cisplatin (GC) and dose-dense methotrexate-vinblastine-doxorubicin-cisplatin (ddMVAC),[7 8] although the VESPER trial has demonstrated OS benefit with ddMVAC over GC.[9]

Meanwhile, several phase 2 trials have reported promising efficacy with neoadjuvant ICI, showing pathological complete response (pCR) rates ranging from 29.4% to 46%.[10–18] Recently, perioperative durvalumab—administered before and after surgery—in combination with neoadjuvant GC demonstrated a significant survival benefit over NAC alone in a phase 3 trial.[19]

Our investigator-initiated institution-sponsored phase 2 AURA Oncodistinct-004 study seeks to expand current knowledge by assessing, for the first time, the activity and safety of avelumab in the neoadjuvant setting for both cisplatin-eligible and cisplatin-ineligible patients with MIBC. Furthermore, we aim to evaluate its efficacy in combination with both standard NAC regimens, including ddMVAC, which is not currently being investigated in ongoing phase 3 trials[19–21] despite its potential superior immunomodulatory properties.[22–24]

PATIENTS AND METHODS

Study design and patients

AURA is an investigator-initiated institution-sponsored open-label, multicenter, randomized, non-comparative phase 2 study in patients with non-metastatic MIBC. The study design was previously described,[25] and the study is registered on ClinicalTrials.gov (NCT03674424).

Enrollment was performed across eight centers in Belgium and France (online supplemental table 1). Eligible patients were adults aged 18 years or older with histologically confirmed urothelial carcinoma or presenting histological subtype with a predominant urothelial component (>50%). All participants were candidates for radical cystectomy with tumor stages cT2-cT4a, with or without lymph node involvement (cN0-cN1), and had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1. Patients with evidence of distant metastases were excluded. Full eligibility criteria are provided in the supplementary material (online supplemental tables 2 and 3).

Randomization and procedures

Patients were divided into two cohorts based on their cisplatin eligibility,[26] which required a creatinine clearance ≥60 mL/min, peripheral neuropathy ≤grade 1, hearing impairment ≤grade 1 and adequate cardiac function (left ventricular ejection fraction ≥55%). Unblinded randomization was conducted via a web-based registration tool and used the study site and the clinical lymph node status (cN0 or cN1) as stratification factors.

In the cisplatin-eligible cohort, patients were randomized (1:1) to receive either avelumab combined with GC (GC-A) or ddMVAC (ddMVAC-A). In the cisplatin-ineligible cohort, patients were randomized (1:1) to receive either avelumab alone (A) or in combination with paclitaxel-gemcitabine (PG-A). Avelumab (10 mg/kg) was administered intravenously every 2 weeks for a total of four to six cycles in all treatment arms. The GC regimen included gemcitabine (1,000 mg/m^2 intravenously on day 1 and day 8) and cisplatin (70 mg/m^2 intravenously, day 1) every 3 weeks up to four cycles. The ddMVAC regimen included methotrexate (30 mg/m^2 intravenously, day 1), vinblastine (3 mg/m^2 intravenously, day 2), doxorubicin (30 mg/m^2 intravenously, day 2) and cisplatin (70 mg/m^2 intravenously, day 2), administered every 2 weeks for up to four cycles. Subcutaneous pegfilgrastim (6 mg) was given 24–48 hours after ddMVAC (mandatory), and after GC according to the investigator's choice. In the cisplatin-ineligible cohort, patients received avelumab alone up to four cycles or combined with paclitaxel (80 mg/m^2 intravenously, day 1 and day 15) and gemcitabine (1,000 mg/m^2 intravenously, day 1 and day 15) every 4 weeks up to two cycles. Pre-medication was performed as per manufacturer's recommendations and local practice.

Standard radical cystectomy with bilateral pelvic lymph node dissection was performed 3–6 weeks after the last administration of neoadjuvant therapy by experienced surgeons. In cases of delayed surgery, an additional cycle of avelumab was permitted.

Outcomes

The primary endpoint was pCR, defined as the absence of invasive residual disease (ypT0/Tis) and no microscopic lymph node involvement (ypN0) in the surgical specimen of evaluable patients. Patients who received at least one dose of each medication in their respective treatment arm and underwent cystectomy were considered evaluable. Patients experiencing early progression that precluded surgery were considered evaluable and assessed as therapeutic failures.

Secondary endpoints included non-muscle-invasive downstaging (<ypT2 N0), adverse events graded

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according to the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.03, event-free survival (EFS) and OS rates at 12 and 36 months after randomization. EFS rate was defined as the proportion of patients alive without progression precluding surgery, local or distant recurrence, or second primary cancer, and OS rate as the proportion of patients alive at the prespecified time points. An exploratory survival analysis was performed for patients achieving pCR in each treatment arm.

Pretreated tumor, surgical specimens, and biological samples—including blood, urine and stools—were collected at each cycle of neoadjuvant treatment for exploratory biomarker analyses (online supplemental figure 1). PD-L1 expression was explored by immunohistochemistry on available baseline formalin-fixed paraffin-embedded tumor samples, using the 22C3 antibody clone (Agilent Dako, Santa Clara, California, USA). PD-L1 expression was classified using the combined positive score (CPS) with a cut-off value of 10, calculated as the number of stained tumor and immune cells divided by the total number of viable tumor cells, multiplied by 100.

Statistical analysis

The sample size calculation aimed to assess the pCR rate in each arm independently, as the trial was not designed to compare the arms within a cohort.

We assumed a 25% pCR rate with NAC alone in each arm of the cisplatin-eligible cohort. With a one-sided alpha level of 5% and 90% power, the null hypothesis should be rejected if the true pCR rate was ≥45%. A two-stage Fleming's design was applied for each treatment regimen, requiring enrollment of a maximum of 108 patients to obtain 98 evaluable patients in this cohort. An interim analysis of the primary endpoint was conducted on the first 28 evaluable patients randomized in each arm. The prespecified boundary for futility was not crossed, but the pCR rates in both arms exceeded the 45% threshold required to reject the null hypothesis. Data were reviewed by an Independent Data Monitoring Committee (IDMC), and further recruitment was stopped in both arms on April 16, 2021, for early efficacy assessment. As the decision to stop recruitment was not related to safety or futility, all patients enrolled up to the date of the IDMC's conclusion were allowed to continue their participation in the clinical trial.

In each arm of the cisplatin-ineligible cohort, a pCR rate of 5% was expected. With a one-sided alpha level of 5% and 90% power, the null hypothesis would be rejected if the true pCR rate was ≥25%. A two-stage Simon design was applied for each treatment regimen, requiring up to 58 patients to obtain 52 evaluable patients in this cohort. An interim analysis was performed on the first 12 patients randomized in each arm. As no futility was observed, recruitment was allowed to continue.

Pathological response rates were estimated with 95% CIs using the Wilson method. Time-to-event endpoints, including EFS and OS, were analyzed using the Kaplan-Meier method, with censoring for patients without predefined events or lost to follow-up at the data cut-off.

The association of PD-L1 expression with outcomes was assessed using the Kaplan-Meier method and Fisher's exact test, with significance defined as a p value≤0.05. All analyses were performed using SAS software (V.9.4, SAS Institute, Cary, North Carolina, USA) and R programming software (V.4.3.0).

RESULTS

Patients and treatment

A total of 154 patients were assessed for eligibility from July 1, 2018, through September 30, 2021. In the cisplatin-eligible cohort, 79 patients were randomly assigned to the ddMVAC-A (n=39) or GC-A (n=40) arms, all initiating systemic treatment. In the cisplatin-ineligible cohort, 58 patients were randomly assigned to the PG-A (n=29) or A (n=29) arms, with 1 patient in each arm not receiving any systemic treatment due to withdrawal and medical decision (figure 1). The reasons for cisplatin ineligibility were renal alteration (n=31, 53%), cardiac impairment (n=20, 34%), hearing loss (n=17, 29%), and/or peripheral neuropathy (n=3, 5%).

The baseline patients' characteristics are summarized in table 1. Most patients were male (n=112, 82%), with an ECOG performance status of 0 (n=94, 69%), with cT2 tumorous stage (n=113, 82%) and without locoregional lymph node involvement (n=115, 84%).

The majority of the patients received the full planned cycles of chemotherapy and/or avelumab and underwent radical cystectomy. Detailed data are illustrated in the online supplemental table 4. The median treatment period was 43 (IQR: 43–48) days for ddMVAC-A and 70 (IQR: 69–74) days for GC-A, with a median time from last avelumab administration to surgery of 37 (IQR: 30–43) and 34 (IQR: 27–40) days, respectively. The median treatment period was 42 (IQR: 42–43) days for PG-A and 42 (IQR: 42–42) days for A, with a median time from last avelumab administration to surgery of 38 (IQR: 31–49) and 23 (IQR: 19–31) days, respectively.

Efficacy

Among the evaluable patients in the cisplatin-eligible cohort, pCR was achieved in 41 patients (55%, 95% CI: 44% to 66%), including 33 (45%, 95% CI: 34% to 56%) patients with ypT0N0. In particular, pCR rates were 58% (95% CI: 42% to 72%) in the ddMVAC-A arm and 53% (95% CI: 37% to 68%) in the GC-A arm. In the cisplatin-ineligible cohort, pCR was observed in 13 evaluable patients (23%, 95% CI: 14% to 36%), including 7 patients (13%, 95% CI: 6% to 24%) with ypT0N0. Detailed pathological responses for each treatment arm are reported in table 2.

At the data cut-off (October 20, 2024), all patients reached at least 36 months of follow-up with 51 deaths reported. In the cisplatin-eligible cohort, the 12-month

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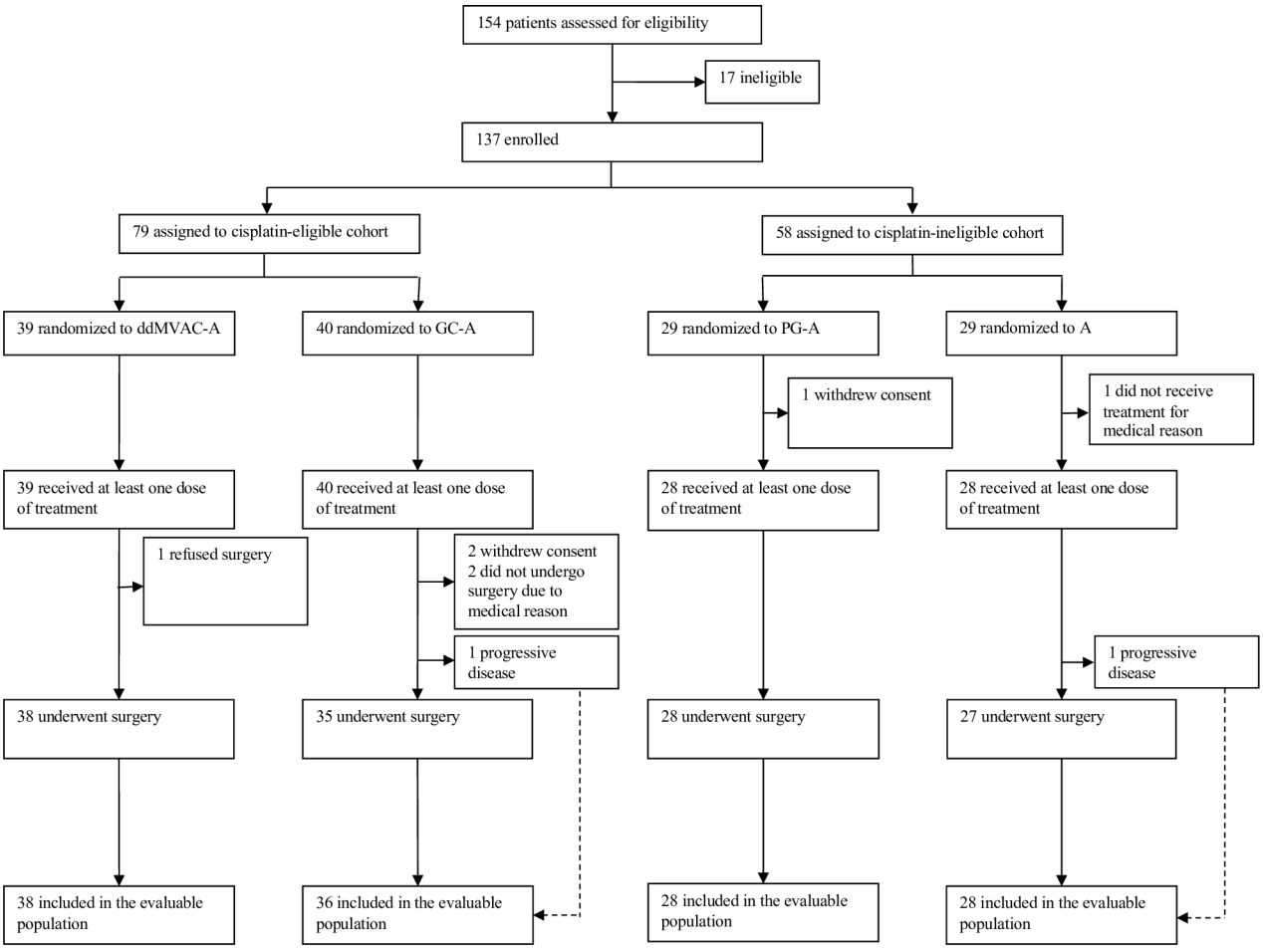

Figure 1 Trial profile. A, avelumab; ddMVAC, dose-dense methotrexate-vinblastine-doxorubicin-cisplatin; GC, gemcitabine-cisplatin; PG, paclitaxel-gemcitabine.

and 36-month EFS rates were 88% (95% CI: 81% to 96%) and 73% (95% CI: 63% to 84%), respectively. OS rates were 93% (95% CI: 88% to 99%) at 12 months and 77% (95% CI: 68% to 87%) at 36 months, disease progression was the main cause of death (n=10, 53%). 36-month OS was 87% (95% CI: 76% to 98%) in the ddMVAC-A arm and 67% (95% CI: 53% to 84%) in the GC-A arm.

In the cisplatin-ineligible cohort, the 12-month and 36-month EFS rates were 62% (95% CI: 51% to 76%) and 42% (95% CI: 31% to 57%), respectively. The OS rates were 80% (95% CI: 70% to 91%) at 12 months and 45% (95% CI: 34% to 61%) at 36 months, with disease progression as the primary cause of death (n=29, 91%). Survival analyses for each treatment arm are shown in figure 2.

An exploratory survival analysis for patients who achieved pCR demonstrated a significant OS benefit compared with those with residual disease across all treatment arms, as illustrated in online supplemental figure 2.

Safety

The most frequent all-grade treatment-related adverse events (trAEs) in the cisplatin-eligible cohort included asthenia (n=58, 73%), nausea (n=37, 47%) and anorexia (n=28, 35%). Grade 3–4 trAEs were reported in 44 patients (56%), mostly hematological and related to the chemotherapy. In the cisplatin-ineligible cohort, asthenia (n=29, 52%), skin disorder (n=10, 18%) and diarrhea (n=9, 16%) were the most frequent trAEs, with seven patients experiencing grade 3-4 trAEs. A full list of trAEs occurring in more than 10% of participants is provided in table 3.

Overall, grade 3–4 immune-related adverse events (irAEs) were observed in 4 (3%) patients. Notably, one cisplatin-eligible patient treated with ddMVAC-A developed grade 3 immuno-mediated thrombocytopenia, not requiring systemic corticosteroids. In the cisplatin-ineligible cohort, two patients treated with PG-A developed grade 3 immune-related hepatotoxicity and pneumonitis, respectively, leading to the discontinuation of avelumab and requiring systemic corticosteroid treatment in one patient. One patient treated with avelumab alone experienced a grade 3 infusion site reaction. A detailed list of irAEs is provided in online supplemental table 5.

No treatment-related deaths occurred, and no patients failed to undergo surgery due to adverse events.

Exploratory PD-L1 expression analysis

PD-L1 expression was assessed in 119 available baseline tumor samples, with 40 samples (35%) showing a CPS≥10

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Table 1 Baseline patient characteristics reported by neoadjuvant treatment arm

Characteristic	Cisplatin-eligible cohort (n=79)		Cisplatin-ineligible cohort (n=58)	
	ddMVAC-A (n=39)	GC-A (n=40)	PG-A (n=29)	A (n=29)
Age*				
Median (range), years	63 (57–70)	68 (59–72)	72 (67–77)	74 (69–77)
Category, n (%)				
<65 years	24 (62)	17 (43)	3 (10)	4 (14)
≥65 years	15 (38)	23 (57)	26 (90)	25 (86)
Sex, n (%)				
Female	9 (23)	11 (28)	2 (7)	3 (10)
Male	30 (77)	29 (72)	27 (93)	26 (90)
ECOG performance status score*, n (%)				
0	36 (92)	32 (80)	15 (52)	11 (38)
1	3 (8)	8 (20)	14 (48)	18 (62)
BMI*, kg/m^2				
Median (range)	26.7 (23.4–29.7)	26.5 (24.5–30.4)	25.9 (22.2–29.4)	27.7 (24.9–31.8)
Category ≥25, n (%)	25 (64)	26 (65)	16 (55)	19 (65)
Cisplatin ineligibility criteria†, n (%)				
Creatinine clearance <60 mL/min	NA	NA	15 (52)	16 (55)
LVEF<55%	NA	NA	13 (45)	7 (24)
Hearing loss grade ≥2	NA	NA	6 (21)	11 (38)
Peripheral neuropathy grade ≥2	NA	NA	3 (10)	0
Clinical tumor stage, n (%)				
cT2Nany	32 (82)	35 (88)	22 (76)	24 (83)
cT2N0	30 (77)	28 (70)	18 (62)	23 (79)
cT2N1	2 (5)	7 (18)	4 (14)	1 (3)
cT3Nany	4 (10)	1 (3)	1 (3)	2 (7)
cT3N0	0	1 (3)	1 (3)	1 (3)
cT3N1	4 (10)	0	0	1 (3)
cT4Nany	3 (8)	4 (10)	5 (17)	3 (10)
cT4N0	2 (5)	4 (10)	5 (17)	2 (7)
cT4N1	1 (3)	0	0	1 (3)
cTanyN0	32 (82)	33 (82)	24 (83)	26 (90)
cTanyN1	7 (18)	7 (18)	5 (17)	3 (10)
Histological type, n (%)				
Pure UC	32 (82)	38 (95)	23 (79)	25 (86)
Mixed histology‡	7 (18)	2 (5)	6 (21)	4 (14)
Previous intravesical therapy§, n (%)				
Yes	4 (10)	4 (10)	3 (10)	1 (3)
No	35 (90)	36 (90)	26 (90)	28 (97)

Percentages might not sum to 100 because of rounding.
*At randomization.
†More than one criterion per patient may be included if present.
‡Mixed histology: presence of histological subtypes but the predominant component remains urothelial (>50%).
§All patients with previous intravesical therapy received BCG therapy except one patient in the GC-A and one in the PG-A arms for whom the intravesical treatment was mitomycin.
A, avelumab; BMI, body mass index; CPS, combined positive score; ddMVAC, dose-dense methotrexate-vinblastine-doxorubicin-cisplatin; ECOG, Eastern Cooperative Oncology Group; GC, gemcitabine-cisplatin; LVEF, left ventricular ejection fraction; NA, not applicable; PG, paclitaxel-gemcitabine; UC, urothelial carcinoma.

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Table 2 Pathological responses by neoadjuvant treatment arm in evaluable patients

	Cisplatin-eligible cohort (n=74)		Cisplatin-ineligible cohort (n=56)	
Response, n (%; 95% CI)	ddMVAC-A (n=38)	GC-A (n=36)	PG-A (n=28)	A (n=28)
Pathological complete response				
ypT0/TisN0	22 (58; 42 to 72)	19 (53; 37 to 68)	4 (14; 6 to 31)	9 (32; 18 to 51)
ypT0N0	20 (53; 37 to 68)	13 (36; 22 to 52)	1 (4; 1 to 18)	6 (21; 10 to 40)
ypTisN0	2 (5; 1 to 17)	6 (17; 8 to 32)	3 (11; 4 to 27)	3 (11; 4 to 27)
Non-muscle-invasive downstaging				
<ypT2 N0	26 (68; 53 to 81)	23 (64; 48 to 78)	5 (18; 8 to 36)	11 (39; 24 to 58)
ypT0/Tis/TaN0	24 (63; 47 to 77)	20 (56; 40 to 70)	4 (14; 6 to 31)	10 (36; 21 to 54)
ypT1N0	2 (5; 1 to 17)	3 (8; 3 to 22)	1 (4; 1 to 18)	1 (4; 1 to 18)
Muscle-invasive status or positive lymph nodes				
ypT2N0	3 (8; 3 to 21)	6 (17; 8 to 32)	7 (25; 13 to 43)	5 (18; 8 to 36)
ypT3-T4N0	5 (13; 6 to 27)	2 (6; 2 to 18)	5 (18; 8 to 36)	4 (14; 6 to 31)
ypTanyN+	4 (11; 4 to 24)	4 (11; 5 to 25)	11 (39; 24 to 58)	7 (25; 13 to 43)

A, avelumab; ddMVAC, dose-dense methotrexate-vinblastine-doxorubicin-cisplatin; GC, gemcitabine-cisplatin; PG, paclitaxel-gemcitabine.

(online supplemental table 6). High PD-L1 expression in evaluable patients was statistically correlated (p=0.047) to pCR in the overall population, but subgroup analyses per cohort and treatment arm did not show any significant correlation (online supplemental figures 3 and 4). Additionally, PD-L1 expression was not associated with survival outcomes in the overall population, neither in any treatment arm (online supplemental figure 5).

DISCUSSION

In cisplatin-eligible patients with non-metastatic MIBC, neoadjuvant avelumab combined with cisplatin-based NAC showed promising antitumor activity with high pCR rates of 53% and 58%, and 3-year OS rates of 67% and 87% for GC-A and ddMVAC-A, respectively. Here, we report for the first time the feasibility and safety of ICI in combination with both standard cisplatin-based NAC regimens including ddMVAC, which showed a survival benefit in the VESPER trial.[9]

Cisplatin has shown immune-enhancing effects in both preclinical and clinical studies by recruiting cytotoxic effectors and downregulating the immunosuppressive tumor microenvironment.[27] The GC regimen is currently used as the backbone NAC in all ongoing phase 3 trials investigating perioperative ICI, for which survival benefits have already been demonstrated in combination with durvalumab in the NIAGARA trial.[19–21] Anthracyclines, a key component of the ddMVAC regimen, have also demonstrated immunomodulatory properties by inducing immunogenic tumor cell death, which is mediated by dendritic cell activation, cytotoxic lymphocyte stimulation, and antigen-specific interferon-gamma production.[22–24] The synergistic potential between immunotherapy and anthracyclines has been highlighted in phase 1 and 2 trials in solid tumors, such as triple-negative breast cancer, where doxorubicin combined with ICI demonstrated clinical efficacy.[28–30] Although our trial was not powered to compare the two regimens within the cisplatin-eligible cohort, we observed a trend toward improved 3-year OS with ddMVAC-A (87% vs 67%), which aligns with the survival analysis from the VESPER trial.[9] However, long-term survival data from the AURA trial are not yet available. The impact of adding immunotherapy to standard NAC remains uncertain, whether their combination will amplify or attenuate the outcome differences between the two NAC regimens is still to be determined. Despite its limited sample size, the AURA trial provides valuable insights and generates promising hypotheses, particularly regarding the feasibility and safety of ddMVAC in combination with immunotherapy as a potential alternative to GC, with robust activity, manageable toxicity, and a shorter treatment duration facilitating rapid access to surgery.

Of note, patients enrolled in the AURA trial did not receive any postoperative therapy, as adjuvant immunotherapy had not yet been approved at the time of the study. This may have contributed to the lower OS rates in the GC-A arm compared with the 2-year OS rate of 82.2% reported in the NIAGARA trial, where all patients randomized to the investigational arm received eight cycles of adjuvant durvalumab.[19] However, the benefit of continuing adjuvant immunotherapy in patients who achieved pCR remains uncertain. In our trial, this specific population experienced longer survival than patients with residual disease, despite the absence of adjuvant immunotherapy. In contrast, the optimal systemic treatment approach for patients with residual disease remains challenging. The key question is whether immunotherapy is still necessary or if a drug with a different mechanism of action would be more effective, such as enfortumab-vedotin,

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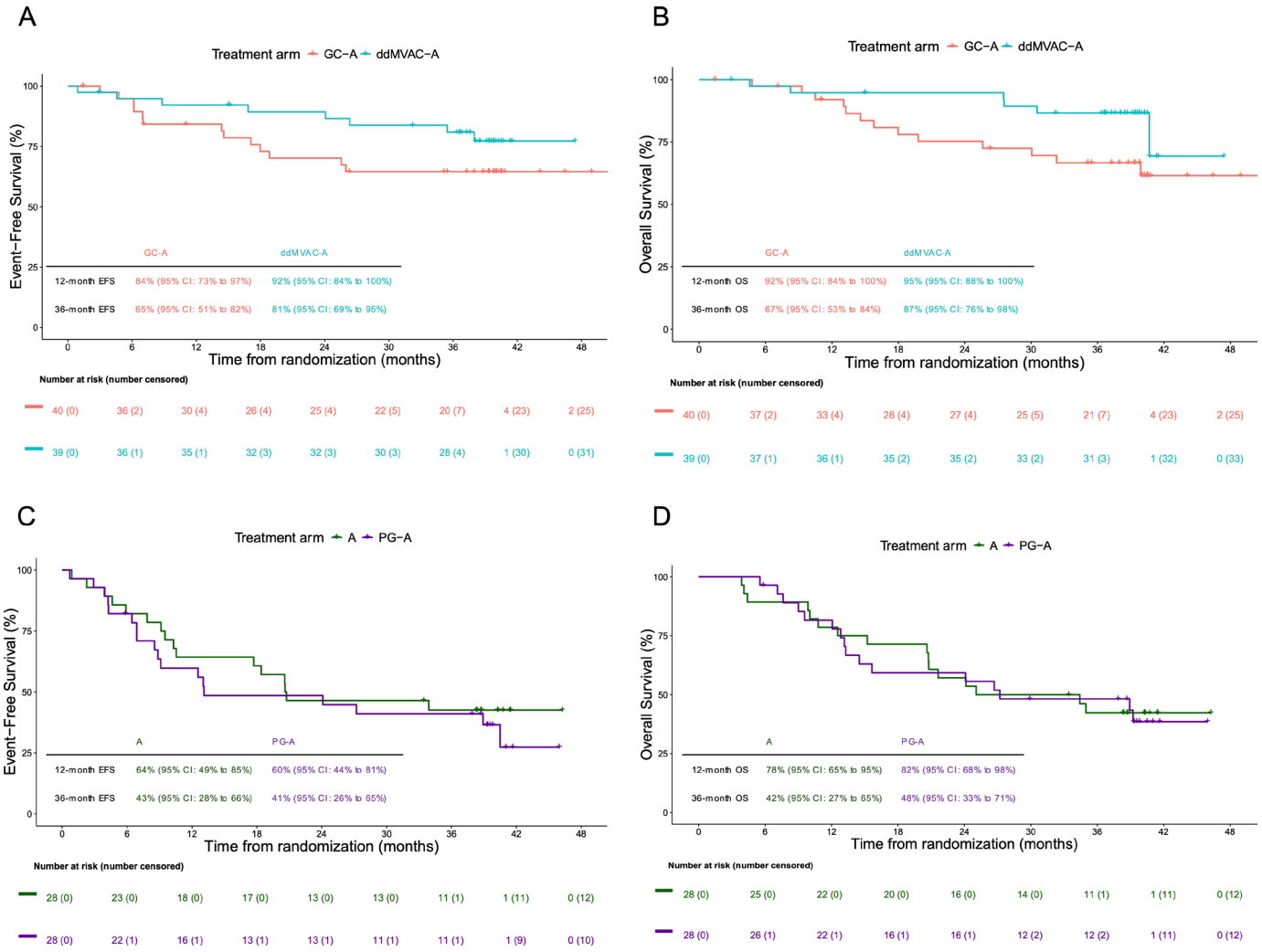

Figure 2 Event-free survival and overall survival according to the treatment arm in the cisplatin-eligible cohort (A–B) and in the cisplatin-ineligible cohort (C–D). Censored events are indicated with a+symbol. A, avelumab; ddMVAC, dose-dense methotrexate-vinblastine-doxorubicin-cisplatin; EFS, event-free survival; GC, gemcitabine-cisplatin; OS, overall survival; PG, paclitaxel-gemcitabine.

which is currently being investigated in the perioperative setting.[20 31] In addition, circulating tumor DNA-driven strategies to select patients who will benefit from adjuvant immunotherapy are also ongoing, opening new avenues for personalized treatment options.[32]

Unfortunately, nearly half of the patients diagnosed with non-metastatic MIBC are ineligible for cisplatin-based chemotherapy, and no alternative neoadjuvant options are currently available for this population.[7 8] This unmet medical need highlights the relevance of the cisplatin-ineligible cohort in our study, in which a promising pCR rate of 32% was achieved in patients treated with avelumab monotherapy. This result aligns with previously reported pCR rates of 29.4%, 42% and 31% in phase 2 trials evaluating neoadjuvant ICI monotherapy.[10 13 18] However, in our study, the addition of the PG regimen to avelumab did not confer any additional benefit. Taxane-based chemo-immunotherapy combinations have been investigated across different solid tumors with discordant results regarding pCR and survival.[33–37] Notably, most of these studies involved taxanes combined with platinum or anthracyclines, which may have contributed to the observed efficacy. In our cohort, disparities in baseline characteristics, including a higher prevalence of cN1 and cT4 stages in the PG-A arm, may have influenced the difference in pCR rates between the two arms of the cisplatin-ineligible cohort. Additionally, the routine use of systemic corticosteroids for taxane pre-medication may also have impacted ICI efficacy, as previously hypothesized in patients with breast cancer. Investigators observed a clinical benefit with atezolizumab combined with nab-paclitaxel but not with the combination of atezolizumab and paclitaxel, which requires corticosteroids premedication.[33 34] Furthermore, a phase 2 trial evaluating neoadjuvant pembrolizumab combined with gemcitabine reported a pCR rate of 41%,[38] comparable to the 29.4–42% achieved with pembrolizumab monotherapy in separate studies.[10 13] Altogether, these findings raise questions about the added value of chemotherapy in neoadjuvant immunotherapy regimens for cisplatin-ineligible patients

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Table 3 Most common treatment-related adverse events (trAEs)

	Cisplatin-eligible cohort (n=79)				Cisplatin-ineligible cohort (n=56)			
	ddMVAC-A (n=39)		GC-A (n=40)		PG-A (n=28)		A (n=28)	
trAEs, n (%)	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4	Any grade	Grade 3–4
Hematologic								
Anemia	13 (33)	5 (13)	13 (33)	3 (8)	5 (18)	0	0	0
Thrombocytopenia	10 (26)	3 (8)	22 (55)	14 (35)	0	0	0	0
Neutropenia	7 (18)	7 (18)	11 (28)	8 (20)	1 (4)	1 (4)	0	0
Non-hematologic								
Asthenia	30 (77)	2 (5)	28 (70)	3 (8)	18 (64)	0	11 (39)	0
Nausea	17 (44)	1 (3)	20 (50)	0	5 (18)	1 (4)	1 (4)	0
Anorexia	13 (33)	1 (3)	15 (38)	0	4 (14)	0	2 (7)	0
Constipation	7 (18)	0	7 (18)	0	1 (4)	1 (4)	0	0
Acute kidney injury	8 (21)	5 (13)	8 (20)	3 (8)	0	0	0	0
Diarrhea	5 (13)	1 (3)	11 (28)	0	6 (21)	0	3 (11)	0
Skin disorder*	7 (18)	0	0	0	6 (21)	0	4 (14)	0
Stomatitis	9 (23)	3 (8)	3 (8)	0	1 (4)	0	1 (4)	0
Dysgeusia	5 (13)	0	7 (18)	0	1 (4)	0	0	0
Headache	1 (3)	0	4 (10)	0	0	0	1 (4)	0
Alopecia	9 (23)	1 (3)	2 (5)	0	7 (25)	0	0	0
Vomiting	5 (13)	0	5 (13)	1 (3)	2 (7)	0	1 (4)	0
Abdominal pain	3 (8)	0	4 (10)	0	0	0	1 (4)	0
Gastroesophageal reflux	1 (3)	0	4 (10)	0	0	0	0	0
Epistaxis	2 (5)	0	2 (5)	0	3 (11)	0	0	0
Myalgia	2 (5)	0	3 (8)	0	3 (11)	0	3 (11)	0
Tinnitus	0	0	4 (10)	0	0	0	0	0
Fever	1 (3)	0	2 (5)	0	4 (14)	0	1 (4)	0
Arthralgia	0	0	1 (3)	0	3 (11)	0	1 (4)	0
Pruritus	0	0	1 (3)	0	3 (11)	0	1 (4)	0
Chills	0	0	0	0	1 (4)	0	3 (11)	0
Infusion-related reaction	0	0	3 (8)	0	0	0	3 (11)	1 (4)

trAEs occurring in 10% or more of participants and in at least one arm of treatment according to Common Terminology Criteria for Adverse Events (V.4.03) assessed by the investigator. Patients with multiple events in the same category are counted only once in that group. Patients with events in more than one category are counted in each of those categories. No grade 5 trAEs were reported.
*Skin disorder represented any skin lesion including rash, skin infection and xerodermia.
A, avelumab; ddMVAC, dose-dense methotrexate-vinblastine-doxorubicin-cisplatin; GC, gemcitabine-cisplatin; PG, paclitaxel-gemcitabine.

with MIBC, while the survival benefit of neoadjuvant immunotherapy alone in this population remains uncertain. Given the outstanding survival benefit observed with the enfortumab-vedotin and pembrolizumab combination in the first-line treatment of metastatic disease, its use is currently being investigated in the perioperative setting in a phase 3 trial.[20] Encouraging results in terms of pCR and EFS have already been reported with neoadjuvant enfortumab-vedotin in a phase 2 trial.[39] However, survival benefits from neoadjuvant immunotherapy in cisplatin-ineligible patients with MIBC are still awaited.

Importantly, no unexpected safety signals were reported in our trial, and no patient failed to undergo surgery due to trAEs. Toxicity was manageable, and the safety profile of avelumab was consistent with previous studies.[2 40] These findings align with results from other phase 2 trials, which have also demonstrated the feasibility of neoadjuvant immunotherapy with no major safety concerns or treatment-related surgical delays.[10–18]

The exploratory analysis of PD-L1 expression showed a correlation between high expression and pCR when assessed in the overall population, but this association

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was not observed in subgroup analyses. Additionally, no correlation with survival was found, underlining the need for further biomarker investigation. To date, no validated predictive biomarkers have been identified for clinical practice, with discordant results across studies.[12–16] Integrating translational research with pretreatment and on-treatment biomarkers may help develop personalized management strategies for MIBC, with the ultimate goal of improving patient care.

Limitations of this study include its small sample size and its non-comparative, non-controlled single-arm design, which precludes comparison between treatment arms within each cohort. The lack of central pathological and radiological review could have impacted eligibility assessment and efficacy evaluation. Additionally, since the trial was not designed to evaluate perioperative ICI, the impact of adjuvant avelumab on survival remains uncertain. Finally, biomarker analyses using prospectively collected samples are still ongoing, except for PD-L1 expression, and no biomarker-driven conclusions can be drawn at this stage.

CONCLUSIONS

In summary, avelumab combined with cisplatin-based chemotherapy shows promising efficacy in the neoadjuvant treatment for patients with MIBC. Both ddMVAC-A and GC-A combinations demonstrate antitumor activity with high complete pathological response and survival rates. The ddMVAC-A regimen exhibits a manageable toxicity profile and shorter time to surgery, supporting the suitability of both regimens as chemotherapy partners in future phase 3 neoadjuvant chemo-immunotherapy trials. In the cisplatin-ineligible population with currently no standard neoadjuvant treatment, avelumab monotherapy shows encouraging activity so far, but the addition of PG chemotherapy in this subgroup does not provide any additional benefit.

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Acknowledgements The authors thank all patients, their families and caregivers for participating in the AURA trial. We thank the Jules Bordet Institute as sponsor of the study and Merck for funding contribution to the trial. The authors express their gratitude to the investigators, site staff, the Oncodistinct network for their support, and the CTSU department from the Jules Bordet Institute for the assistance in clinical trial running and the previous fellows. We are grateful to the BCTL team of the Jules Bordet Institute for the central bio-banking of biological samples and for conducting translational analysis. We also thank the IMDC committee who reviewed the interim analysis.

Contributors JB: Formal Analysis, Writing—Original Draft, Visualization. AC: Investigation, Writing Review. PB: Investigation, Writing Review. VC: Investigation, Writing Review. BS: Investigation, Writing Review. JVdB: Investigation, Writing Review. VV: Investigation, Writing Review. LS: Investigation, Writing Review. ES: Investigation, Writing Review. VD: Data Curation, Writing Review. LA: Formal Analysis, Writing Review. NK: Writing Review. FR: Resources, Supervision, Writing Review. SR: Resources, Writing Review. J-CF: Investigation, Writing Review. TT: Investigation, Writing Review. TR: Investigation, Writing Review. AA: Conceptualization, Methodology, Funding Acquisition, Writing Review. NMC: Guarantor, Conceptualization, Investigation, Methodology, Writing—Original Draft, Writing Review, Visualization, Supervision, Project administration, Funding acquisition. NMC had full access to all the data in the study and had final responsibility for the decision to submit for publication. All authors have critically reviewed the manuscript and approved the final version for the submission.

Funding This work is an investigator-initiated, institution-sponsored study, with the Jules Bordet Institute, an academic hospital affiliated with the Free University of Brussels (Université Libre de Bruxelles), Brussels, Belgium, serving as the sponsor. Funding to conduct the trial and drug (avelumab) supply were provided by the healthcare business of Merck KGaA, Darmstadt, Germany (no grant number), which had no role in study design, data collection, data analysis, data interpretation or report writing.

Competing interests JB: FNRS funded PhD student, medical advisory (institutional) from Merck, travel support for medical congresses from Ipsen, Recordati, Merck and AstraZeneca. AC: honoraria for educational events from Astellas. LS: travel support by Merck. BS: honoraria from MSD and Janssen, consulting or advisory role for Astellas pharma, Janssen, BMS Belgium, Merck, Bayer, Johnson & Johnson/Janssen. NMC: research travel from Pfizer and Ipsen, consulting fees (institutional) from BMS, Bayer and Merck.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Ethics Committee 021/406 (Hospital Erasme) with internal reference: CE 2716, with approval by the Federal Agency for Medicines and Health Products (FAMHP). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The AURA clinical trial data are not available because of ethical and data protection constraints. The anonymous data generated in this study have been deposited at the Data Centre at Jules Bordet Institute (Belgium) and cannot be sent without the agreement of the study sponsor. Proposals for possible collaborations in further analysis of the data should be addressed to the corresponding author NMC (n.martinezchanza@hubruxelles.be).

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