original reports

Neoadjuvant Atezolizumab With Gemcitabine and Cisplatin in Patients With Muscle-Invasive Bladder Cancer: A Multicenter, Single-Arm, Phase II Trial

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abstract

PURPOSE Neoadjuvant gemcitabine and cisplatin (GC) followed by radical cystectomy (RC) is standard for patients with muscle-invasive bladder cancer (MIBC). On the basis of the activity of atezolizumab (A) in metastatic BC, we tested neoadjuvant GC plus A for MIBC.

METHODS Eligible patients with MIBC (cT2-T4aN0M0) received a dose of A, followed 2 weeks later by GC plus A every 21 days for four cycles followed 3 weeks later by a dose of A before RC. The primary end point was non–muscle-invasive downstaging to < pT2N0.

RESULTS Of 44 enrolled patients, 39 were evaluable. The primary end point was met, with 27 of 39 patients (69%) < pT2N0, including 16 (41%) pT0N0. No patient with < pT2N0 relapsed and four (11%) with ≥ pT2N0 relapsed with a median follow-up of 16.5 months (range: 7.0-33.7 months). One patient refused RC and two developed metastatic disease before RC; all were considered nonresponders. The most common grade 3-4 adverse event (AE) was neutropenia (n = 16; 36%). Grade 3 immune-related AEs occurred in five (11%) patients with two (5%) requiring systemic steroids. The median time from last dose of chemotherapy to surgery was 7.8 weeks (range: 5.1-17 weeks), and no patient failed to undergo RC because of AEs. Four of 39 (10%) patients had programmed death-ligand 1 (PD-L1)–positive tumors and were all < pT2N0. Of the patients with PD-L1 low or negative tumors, 23 of 34 (68%) achieved < pT2N0 and 11 of 34 (32%) were ≥ pT2N0 ($P = .3$ for association between PD-L1 and < pT2N0).

CONCLUSION Neoadjuvant GC plus A is a promising regimen for MIBC and warrants further study. Patients with < pT2N0 experienced improved relapse-free survival. The PD-L1 positivity rate was low compared with published data, which limits conclusions regarding PD-L1 as a predictive biomarker.

J Clin Oncol 40:1312-1322. © 2022 by American Society of Clinical Oncology

ASSOCIATED CONTENT

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Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 15, 2021 and published at ascopubs.org/journal/jco on January 28, 2022: DOI https://doi.org/10.1200/JCO.21.01485

INTRODUCTION

The majority of patients with muscle-invasive bladder cancer (MIBC) will develop metastases after radical cystectomy and pelvic lymph node dissection (RC-PLND).[1,2] Neoadjuvant cisplatin-based chemotherapy before RC-PLND improves long-term survival compared with RC-PLND alone.[3-5] Although the pivotal phase III neoadjuvant trial used methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC),[4] subsequent efforts include regimens with improved toxicity, such as gemcitabine and cisplatin (GC),[6,7] and dose-dense (dd) administration, such as ddMVAC and ddGC.[8-10] A consistent finding across studies is that non–muscle-invasive downstaging (< pT2) and negative lymph nodes (N0) at the time of RC-PLND correlate with improved survival.[4,7-14] This correlation between pathologic response and clinical benefit from neoadjuvant chemotherapy is similar to observations in other malignancies such as breast cancer and non–small-cell lung cancer.[15-19] However, unlike patients with localized breast cancer in whom pathologic complete response (pCR) after neoadjuvant therapy is the most robust end point,[15-17] pCR and < pT2N0 appear to similarly correlate with improved survival in MIBC.[13,20,21] Unfortunately, only 36%-49% of patients with MIBC will achieve non–muscle-invasive downstaging with GC,[7,12,13,22] which is a widely used neoadjuvant regimen.[12,23]

CONTEXT

Key Objective

In patients with muscle-invasive bladder cancer, neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy is a standard of care. The objective of this phase II trial was to evaluate the efficacy and safety of adding atezolizumab to gemcitabine and cisplatin (GC).

Knowledge Generated

Compared with the historical control of neoadjuvant chemotherapy alone and despite low programmed death-ligand 1 positivity (10%) in the cohort, the addition of atezolizumab to GC resulted in a high rate of non–muscle-invasive downstaging (69%), which correlated with improved relapse-free survival and overall survival. No patients failed to undergo timely radical cystectomy because of toxicity, and no unexpected safety signals were observed during treatment or postoperatively.

Relevance

This trial demonstrated that the addition of atezolizumab to neoadjuvant GC is a promising approach in muscle-invasive bladder cancer. The need for improved biomarkers beyond programmed death-ligand 1 and the association of non–muscle-invasive downstaging and improved outcomes have implications for future trial design.

To improve outcomes in MIBC, a combinatorial approach with GC and immune checkpoint blockade (ICB) of the programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) axis is attractive for several reasons. The absence of clinical cross-resistance is demonstrated by remarkably durable responses in some patients with platinum-resistant metastatic bladder cancer treated with ICB.[24-28] There are also potential immunomodulatory effects of GC that may enhance antitumor immunity.[29-32] Finally, ICB without chemotherapy can result in non–muscle-invasive downstaging at the time of surgery in cisplatin-ineligible patients.[33,34] However, the glucocorticoids given to attenuate chemotherapy-associated nausea and the nontargeted genotoxic effects of GC may suppress an antitumor immune response.[30,35] Therefore, we assessed the efficacy and safety of an atezolizumab lead-in dose followed by four cycles of GC with atezolizumab and one additional dose of atezolizumab after chemotherapy completion and before RC-PLND.

METHODS

Patients

Eligible patients were candidates for RC-PNLD and had cT2N0M0-cT4aN0M0 disease as determined by cystoscopy and transurethral resection of bladder tumor (TURBT) within 60 days of treatment initiation as well as cross-sectional imaging (computed tomography of the chest, abdomen, and pelvis with intravenous [IV] contrast) within 30 days of treatment initiation. TURBT at enrolling sites was not mandated, but pathologic confirmation of MIBC was required. Cisplatin eligibility was defined as an estimated glomerular filtration rate $\geq$ 50 mL/min per 1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration formula); Eastern Cooperative Oncology Group performance status of 0 or 1; no pre-existing grade $\geq$ 2 peripheral neuropathy or hearing impairment; and no New York Heart Association class III or IV heart failure, or recent cardiovascular event. Major exclusion criteria included active infection, prior use of ICB, and autoimmune disease.

Trial Oversight

This study was approved by the institutional review boards of participating sites and performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent before study entry.

Study Procedures

This was a nonrandomized, multi-institutional, open-label phase II study (ClinicalTrials.gov identifier: NCT02989584). Patients were treated with an atezolizumab lead-in dose followed 2 weeks later by four 21-day cycles of GC with atezolizumab on day 8 and one additional dose of atezolizumab 3 weeks after chemotherapy completion. Atezolizumab was administered as a flat dose of 1,200 mg IV once every 3 weeks, gemcitabine was administered at a dose of 1,000 mg/m^2 IV once on days 1 and 8, and cisplatin was administered as either 70 mg/m^2 IV once on day 1 or as split-dose at 35 mg/m^2 IV once on days 1 and 8. Split-dose cisplatin was recommended if the estimated glomerular filtration rate was 50 to $<$ 60 or by treating physician's discretion. Hydration, mannitol, and antiemetics were administered in accordance with institutional protocols with the exception of dexamethasone, which was given as either 12 mg IV on day 1 and 4 mg orally on day 2 with cisplatin 70 mg/m^2 dosing or 12 mg IV on days 1 and 8 with split-dose cisplatin. Reductions in dexamethasone dose were allowed at the treating physician's discretion.

Patients underwent a history, physical examination, and toxicity assessment using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 on all treatment days and on a post-treatment follow-up visit

before RC-PLND. Imaging was performed at the completion of protocol therapy and RC-PLND recommended within approximately 4-8 weeks from the last dose of chemotherapy. Postoperative complications up to 90 days after surgery were retrospectively recorded.

PD-L1 immunohistochemical staining on pretreatment TURBT specimens was prospectively assessed centrally (Targos, Kassel, Germany) with the SP142 assay (Ventana, AZ). Staining was performed within 60 days of slides being cut and was defined as ≥ 5% of tumor-infiltrating immune cells staining positive (IC2/3).[34,36]

Statistical Considerations

The primary end point was non–muscle-invasive downstaging, defined as the absence of muscle-invasive disease (< pT2) and lymph node metastases (N0) within the RC-PLND specimen as assessed by institutional pathologists using the American Joint Committee on Cancer 7th edition criteria.[37] We used a Simon's two-stage minimax design with the probabilities of a type I error and type II error set at .05 and .2, respectively. A total of 39 patients were required to detect an improvement in the non–muscle-invasive downstaging rate to 55% from a historical rate of 35% with conventional-dose, cisplatin-based chemotherapy alone.[3,4,7] Twenty-one patients were planned to be accrued in the first stage. If ≥ 9 were < pT2N0, then an additional 18 would be accrued. The combination would be considered promising if at least 19 of 39 patients achieved non–muscle-invasive downstaging. Patients who developed progressive and/or metastatic disease while on neoadjuvant therapy, those who were unable or unwilling to undergo RC-PLND, and those who discontinued protocol therapy because of treatment-related delays and/or treatment-related toxicity were considered nonresponders. Patients who received < 2 cycles of protocol therapy because of withdrawal of consent or unrelated adverse events (AEs) were evaluable for toxicity assessment but were not evaluable for the primary end point and replaced.

Secondary end points included the proportion of patients with a complete pathologic response (pT0N0), safety (Common Terminology Criteria for Adverse Events v4.0), time to cystectomy, overall survival (OS), and relapse-free survival (RFS). RFS was evaluated using the Kaplan-Meier method and measured from treatment initiation until disease recurrence, which was defined as investigator-determined clinical or radiographic progression. Patients without documented recurrence were censored at the last follow-up for the purpose of OS and at the time of last cross-sectional imaging for the purpose of RFS. Association between non–muscle-invasive downstaging and PD-L1 status was analyzed using the Fisher's exact test.

RESULTS

Study Patients

From February 2018 to May 2020, a total of 44 patients were enrolled across five institutions. Five patients came off protocol before completing two cycles of therapy and were evaluable for safety but not for efficacy (Appendix Table A1, online only). Table 1 summarizes the baseline characteristics of the 39 response-evaluable patients. The median age was 65 years and most patients were male (85%), current or former smokers (64%), Eastern Cooperative Oncology Group

TABLE 1. Baseline Patient Characteristics

Baseline Characteristic (N = 39)	No. (%)
Median age, years (IQR)	65 (58-69)
Sex	
Male	33 (84.6)
Female	6 (15.4)
Current or former smoker	25 (64.1)
Clinical TNM stage	
T2	31 (79.5)
T3	7 (17.9)
T4a	1 (2.6)
Prior BCG	2 (5.1)
Histology	
Pure UC, NOS	24 (61.5)
UC with squamous cell carcinoma	9 (23.1)[a]
UC with nested features	2 (5.1)
UC with glandular differentiation	2 (5.1)
UC with micropapillary features	1 (2.6)
UC with focal plasmacytoid features	1 (2.6)
Hydronephrosis	12 (30.8)
eGFR categorized[b]	
≥ 60 mL/min/1.73 m^2	33 (84.6)
50 ≤ to < 60 mL/min/1.73 m^2	6 (15.4)
ECOG	
0	23 (59.0)
1	16 (41.0)
Median hemoglobin (IQR)	13.90 (12.50-14.60)
Median albumin (IQR)	4.20 (4.00-4.45)
PD-L1 (%)	
< 5	35 (89.7)[c]
≥ 5	4 (10.3)

Abbreviations: BCG, Bacillus Calmette-Guérin; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration formula; ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NOS, not otherwise specified; PD-L1, programmed death-ligand 1; UC, urothelial carcinoma.

[a]Four patients with predominant (> 50%) squamous differentiation.

[b]Calculated using the CKD-EPI equation.

[c]One patient with a PD-L1–negative tumor declined cystectomy and received radiation to the bladder with concurrent gemcitabine. This patient was considered a nonresponder for the primary end point but has not relapsed (36-month follow-up from start of protocol therapy). This patient was excluded from the PD-L1 and response analysis.

0 (59%), and clinical T2N0M0 (80%). Six patients (15%) had an estimated pretreatment glomerular filtration rate < 60 mL/min. Hydronephrosis was present in 12 (31%) patients. Tumors were predominantly histologically pure urothelial carcinoma, not otherwise specified (n = 24, 62%). Only four (10%) pretreatment tumors were PD-L1–positive.

Efficacy

The study met its primary end point with 27 of 39 response-evaluable patients achieving < pT2N0 disease for an overall non–muscle-invasive downstaging rate of 69% (95% CI, 55 to 79), including 16 (41%) patients with a pCR (Table 2). Two patients (5%) exhibited pT2N0 disease at RC-PLND, and seven (18%) nonresponders had node-positive disease at RC-PLND. Two patients (5%) developed metastatic disease prior to RC-PLND and were considered nonresponders. A single patient refused RC-PLND and instead received radiotherapy to the bladder with concurrent gemcitabine. This patient was considered a nonresponder but has not relapsed (36-month follow-up from the start of protocol therapy).

Among the 39 response-evaluable patients, four have died from disease and six have experienced disease progression (including the two who progressed before RC-PLND). Median follow-up from time of treatment start was 23.6 months (range: 12.0-38.2 months). Median RFS and OS were not reached (Fig 1; data cutoff May 1, 2021). Thirty-six patients underwent RC-PLND with a median follow-up of 16.5 months (range: 7.0-33.7 months) from the time of RC-PLND to last follow-up among those alive at the end of study. Among these 36 patients, no responding patient (< pT2N0) has relapsed, and four nonresponding patients (≥ pT2N0) subsequently relapsed. Responders had significantly better RFS compared with nonresponders (log-rank $P < .001$; Fig 2).

All patients with PD-L1–positive tumors achieved < pT2N0 (4 of 4; 100%). Of the patients with PD-L1 low and negative tumors (excluding the one patient who refused surgery), 23 of 34 (68%) achieved < pT2N0 and 11 of 34 (32%) were ≥ pT2N0 ($P = .3$ for association between PD-L1 and < pT2N0).

TABLE 2. Pathologic Response at the Time of RC

Pathologic Response	No. (%)
Responders (< pT2N0)	27 (69.2; 95% CI, 55.0 to 79.0)
pT0N0/pT0NX[a]	16 (41.0)
pTaN0	2 (5.1)
pTisN0	7 (17.9)
pT1N0	2 (5.1)
Nonresponders (≥ pT2N0)	9 (23.1)
pT2N0	2 (5.1)
pTxN1	3 (7.7)
pTxN2	3 (7.7)
pTxN3	1 (2.6)
No surgery	3 (7.7)
Refused surgery	1 (2.6)
Developed metastatic disease before surgery	2 (5.1)

Abbreviation: RC, radical cystectomy.

[a]One patient was unable to have a lymph node dissection because of adhesions from prior abdominal surgeries.

Safety

Among the 44 patients evaluable for safety, 98% experienced treatment-related AEs (TRAEs; Table 3; Appendix Tables A2 and A3, online only). The most common TRAEs of any grade were neutropenia (n = 26; 59%), fatigue (n = 24; 55%), anemia (n = 24; 55%), and nausea (n = 22; 50%). A total of 26 patients (59%) experienced a grade ≥ 3 TRAE. The most common grade 3-4 TRAE was neutropenia (n = 16, 36%), although no patients developed neutropenic fever. Three patients experienced treatment-related venous thromboembolic events (grade 2 upper-extremity deep venous thrombosis; n = 1; grade 3 pulmonary embolus; n = 2) and two experienced a treatment-related arterial thromboembolic event (grade 2 stroke; n = 2). Grade 3 immune-related AEs (irAEs) occurred in five (11%) patients including hepatitis (n = 1), asymptomatic elevation in lipase during treatment and nephritis after RC-PLND (n = 1), pancreatitis (n = 1), rash (n = 1), and asymptomatic elevations in amylase/lipase (n = 1). The patient with hepatitis and the patient with nephritis required high-dose systemic steroids (≥ 40 mg of prednisone or the equivalent).

Among the 39 response-evaluable patients, 26 (67%) required dose modifications (Appendix Table A4, online only). The most common reasons for dose modifications were chemotherapy-related and included neutropenia (n = 12), creatinine increase (n = 6), and thrombocytopenia (n = 4). Thirty-six (92%) patients received four cycles of cisplatin-based chemotherapy and 29 (74%) received all six planned doses of atezolizumab. Two patients discontinued chemotherapy after experiencing grade 2 stroke and one patient discontinued chemotherapy after experiencing a grade 2 creatinine increase; all patients underwent RC-PLND.

None of the 39 response-evaluable patients failed to undergo surgery owing to AEs and the median number of weeks from last chemotherapy to RC was 7.8 (range, 5.1-17.0). Two patients had delays in surgery beyond 12 weeks from chemotherapy, and neither was because of AEs. The quality of surgery as well as postoperative complications are listed in Table 4.

DISCUSSION

In this single-arm multicenter phase II study, neoadjuvant GC with atezolizumab demonstrated promising activity in MIBC, with 27 patients (69%) found to be < pT2N0 and 16 (41%) found to be pT0N0 at the time of RC-PLND. Based

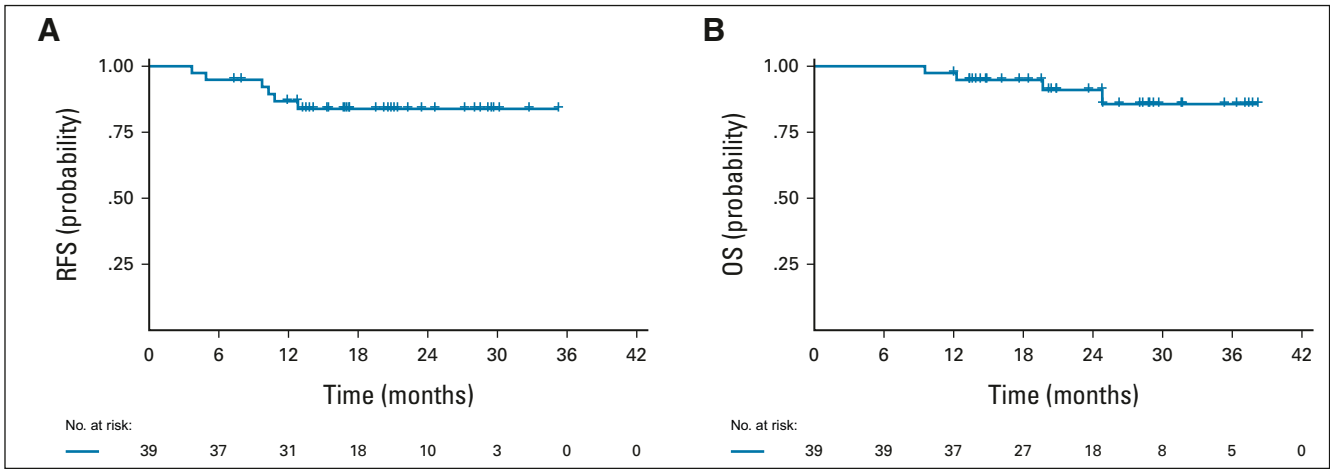

FIG 1. (A) RFS and (B) OS in 39 response-evaluable patients who were treated with neoadjuvant GC with atezolizumab. GC, gemcitabine and cisplatin; OS, overall survival; RFS, relapse-free survival.

upon these results, the study met its primary end point of at least 19 of 39 patients achieving < pT2N0 to consider GC with atezolizumab worthy of further investigation. Grade 3-4 TRAEs were observed in 59% of patients and were primarily because of chemotherapy. No patient experienced AE-related delays to RC-PLND.

The 69% < pT2N0 and 41% pT0N0 rates observed with GC plus atezolizumab compare favorably to those reported for GC and dd-MVAC, which are the neoadjuvant regimens preferred by the National Comprehensive Cancer Network.[38] Several large retrospective analyses of neoadjuvant GC have reported < pT2N0 rates of 36%-46% and pT0N0 rates of 21%-31%.[7,12,13,39] Two prospective single-arm trials of ddMVAC found < pT2N0 rates of 49%-53%, including a pT0N0 rate of 26%-38%.[8,9] A recent randomized phase III study (VESPER) prospectively compared neoadjuvant ddMVAC with GC.[22] This study reported < pT2N0 rates among patients treated with ddMVAC and GC of 63% and 49% (P = .007), respectively, as well as pCR rates of 42% and 36% (P = .2), respectively. Patients who underwent RC-PLND and achieved < pT2N0 after GC with atezolizumab experienced excellent RFS and OS, which is consistent with the neoadjuvant cisplatin-based chemotherapy experience in patients with MIBC.[4,7-14]

The future of combination anti–PD-1/L1 immunotherapy with GC in patients with metastatic bladder cancer remains uncertain. Two randomized phase III trials were conducted to test the combination of pembrolizumab (KEYNOTE-361) or atezolizumab (IMvigor130) with platinum doublet chemotherapy in the frontline setting.[40,41] In KEYNOTE-361, the progression-free survival and OS benefits of chemotherapy with pembrolizumab versus chemotherapy alone did not reach statistical significance.[40] In IMvigor130, chemotherapy with atezolizumab demonstrated a statistically significant improvement in progression-free survival compared with chemotherapy alone (8.2 months *v* 6.3 months, HR 0.82,

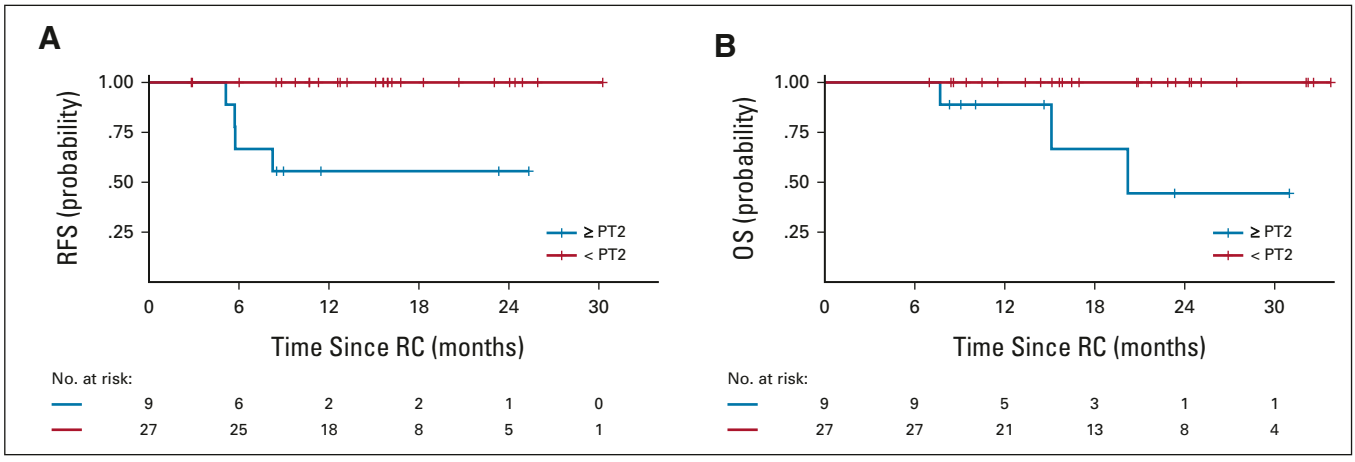

FIG 2. (A) RFS and (B) OS stratified by pathologic response (< pT2 *v* ≥ pT2N0) for 36 patients who underwent RC. OS, overall survival; RC, radical cystectomy; RFS, relapse-free survival.

TABLE 3. Summary of TRAEs[a]

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Hematologic					
Neutropenia	26 (59)	1 (2)	9 (20)	13 (30)	3 (7)
Anemia	24 (55)	12 (27)	7 (16)	5 (11)	0 (0)
Thrombocytopenia	19 (43)	16 (36)	2 (5)	1 (2)	0 (0)
Lymphopenia	16 (36)	5 (11)	4 (9)	5 (11)	2 (5)
Nonhematologic					
Fatigue	24 (55)	17 (39)	6 (14)	1 (2)	0 (0)
Nausea	22 (50)	18 (41)	4 (9)	0 (0)	0 (0)
Creatinine increased	9 (20)	8 (18)	1 (2)	0 (0)	0 (0)
Dysgeusia	9 (20)	9 (20)	0 (0)	0 (0)	0 (0)
Hypomagnesemia	9 (20)	9 (20)	0 (0)	0 (0)	0 (0)
Anorexia	8 (18)	6 (14)	2 (5)	0 (0)	0 (0)
Constipation	8 (18)	8 (18)	0 (0)	0 (0)	0 (0)
Hyponatremia	8 (18)	5 (11)	0 (0)	3 (7)	0 (0)
Alopecia	7 (16)	6 (14)	1 (2)	0 (0)	0 (0)
Vomiting	7 (16)	4 (9)	3 (7)	0 (0)	0 (0)
Peripheral sensory neuropathy	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)
Diarrhea	5 (11)	4 (9)	1 (2)	0 (0)	0 (0)
Hyperkalemia	5 (11)	5 (11)	0 (0)	0 (0)	0 (0)
Tinnitus	5 (11)	5 (11)	0 (0)	0 (0)	0 (0)
Thromboembolic event[b]	5 (11)	0 (0)	3 (7)	2 (5)	0 (0)
irAEs[c]					
Hepatitis	1 (2)	0 (0)	0 (0)	1 (2)[d]	0 (0)
Nephritis	1 (2)	0 (0)	0 (0)	1 (2)[e]	0 (0)
Pancreatitis	1 (2)	0 (0)	0 (0)	1 (2)[f]	0 (0)
Arthritis	2 (5)	0 (0)	2 (5)	0 (0)	0 (0)
Hypothyroidism	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Rash	7 (16)	5 (11)	1 (2)	1 (2)[g]	0 (0)
Pruritus	3 (7)	3 (7)	0 (0)	0 (0)	0 (0)
Fever	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Infusion reaction	2 (5)	1 (2)	1 (2)	0 (0)	0 (0)
Amylase increased[h]	9 (20)	7 (16)	1 (2)	1 (2)	0 (0)
Lipase increased[h]	5 (11)	2 (5)	1 (2)	2 (5)	0 (0)
Alanine aminotransferase increased[h]	8 (18)	6 (14)	2 (5)	0 (0)	0 (0)
Aspartate aminotransferase increased[h]	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)

Abbreviations: AE, adverse event; irAEs, immune-related AEs; TRAEs, treatment-related AEs.

[a]> 10% grade 1 and 2 or any grade 3-4.

[b]Three patients had treatment-related venous thromboembolic events (grade 2 upper-extremity deep venous thrombosis; n = 1; grade 3 pulmonary embolus; n = 2) and two had treatment-related arterial thromboembolic events (both grade 2 stroke). Two patients had unrelated grade 3 venous thromboembolic events.

[c]All reported.

[d]Required high-dose steroids (≥ 40 mg of prednisone or the equivalent).

[e]Diagnosed after radical cystectomy and required high-dose steroids (≥ 40 mg of prednisone or the equivalent).

[f]Symptomatic and with radiographic findings but resolved without steroids.

[g]Resolved without systemic steroids.

[h]All instances asymptomatic and resolved without steroids.

TABLE 4. Postcystectomy Complications (N = 36)

Characteristic	No. (%)	Median (IQR)
Surgical approach		
Open	23 (63.9)	
Robot	13 (36.1)	
Urinary diversion		
Conduit	17 (47.2)	
Continent	19 (52.8)	
Median length of hospital stay, days		6 (5.0-8.2)
Intraoperative blood loss, mL		425 (287.5-762.5)
30-day readmission	6 (16.7)	
30-day surgical reintervention	1 (2.8)	
Lymph node yield[a]		28.5 (20.5-46.3)
Standard lymph node dissection	9 (25.0)	
Extended lymph node dissection	26 (72.2)	
Positive margin status	0	0 (0)
Postoperative complications (Clavien Dindo) within 90 days		
Low grade (Clavien I-II)	25 (69)	
High grade (Clavien ≥ III)	7 (19)	
Types of Clavien Dindo grade ≥ 3 postoperative complications[b]		
Small bowel obstruction	1 (2.8)	
Hypotension	2 (5.6)	
Anemia	1 (2.8)	
Hydronephrosis	1 (2.8)	
Seroma	2 (5.6)	
Ureteroenteric anastomotic leak	1 (2.8)	
Pulmonary embolism	1 (2.8)	

Abbreviation: IQR, interquartile range.

[a]One patient did not undergo lymph node dissection because of adhesions from previous surgery.

[b]Two patients had two Clavien Dindo grade ≥ 3 postoperative complications.

$P = .007$), although OS data are not yet mature.[41] Importantly, these trials included both cisplatin-ineligible and cisplatin-eligible patients, and the majority in both studies were treated with carboplatin-based therapy. Thus, these results cannot necessarily be extrapolated to the treatment of cisplatin-eligible patients with MIBC. Indeed, a subgroup analysis of IMvigor130 revealed a larger effect size with the addition of atezolizumab in the subset of patients who received cisplatin (hazard ratio for OS, 0.73; 95% CI, 0.55 to 0.97).[41] Furthermore, in addition to our study of GC with atezolizumab, other trials of neoadjuvant GC with anti–PD-1/L1 ICB for patients with MIBC have reported < pT2N0 rates of 56%-66% and pT0N0 rates of 34%-44%, which also compare favorably to historical data with GC alone.[42-45] Finally, the administration of atezolizumab before and after GC is unique to this study and may have facilitated enhanced antitumor immunity.

The toxicity of GC with atezolizumab observed in our study is consistent with prior chemotherapy with ICB studies in that no new safety signals emerged and the combination AE profile was consistent with those of the individual therapeutic modalities.[41,42,46-49] Grade 3 treatment-related venous thromboembolic events occurred in three (7%) patients and stroke occurred in two (5%) patients, which are consistent with rates reported with cisplatin-based chemotherapy across multiple malignancies.[50] Two patients (5%) required high-dose systemic steroids (≥ 40 mg of prednisone or the equivalent) for irAEs, one with hepatitis and the other with nephritis. The nephritis manifested after RC-PLND, underscoring the need for continued vigilance for irAEs in the postoperative period. We found GC with atezolizumab to be associated with moderate rates of grade ≥ 3 cytopenias (36% neutropenia, 11% anemia, and 2% thrombocytopenia), no neutropenic fever, only 2% grade 3 fatigue, and 0% grade ≥ 3 nausea. The VESPER trial demonstrated ddMVAC is associated with more grade ≥ 3 anemia (22% *v* 8%), nausea (10% *v* 3%), and fatigue (14% *v* 4%) than GC.[22] Both ddMVAC and GC were

associated with moderate rates of grade ≥ 3 neutropenia (39% and 46%) and thrombocytopenia (20% and 17%) with neutropenic fever occurring in 7% and 2% of patients receiving ddMVAC and GC, respectively.[22] Although larger comparative trials are needed, the < pT2N0 rate of 69% observed in this study with GC with atezolizumab mirrors the higher < pT2N0 rate of ddMVAC versus GC (63% and 49%; $P = .007$) in the VESPER trial but with a toxicity profile more similar to GC, with the exception of uncommon irAEs.

There are limitations to this study. The median follow-up may be insufficient to capture all recurrences. In particular, the correlation between pathologic response and long-term OS needs further study in the context of neoadjuvant ICB for MIBC, although initial data from single-arm, phase II trials of neoadjuvant chemotherapy plus PD-1/L1 blockade in non–small-cell lung cancer as well as pembrolizumab in MIBC suggest that the correlation is maintained.[42,46,51-53] Furthermore, the 15% rate of pCR with TURBT alone presents challenges to the interpretation of response rates in all single-arm MIBC trials.[4] In addition, the higher proportion of cT2 cases and variant histology as well as the low rate of PD-L1 positivity may limit generalizability. However, the rate of cT2N0 (80%) is similar to the 65% and 72% rates reported in the neoadjuvant ddGC and GC with pembrolizumab studies, respectively, and less than the > 90% rate reported in VESPER.[13,22,42] Among the eight patients who were ≥ cT3 in our study, five achieved non–muscle-invasive downstaging (pTisN0, n = 3; pT0N0, n = 2), which is not markedly different from the overall cohort. Finally, in single-arm phase II trials reported to date of neoadjuvant GC with anti–PD-1/L1 ICB for patients with MIBC,[42-45] PD-L1 positivity was not predictive of non–muscle-invasive downstaging. Thus, additional interrogation of the genomic and host immune factors mediating response and resistance to GC with atezolizumab is ongoing.

In summary, the addition of atezolizumab to neoadjuvant GC was safe and associated with a 69% non–muscle-invasive downstaging rate and a 41% complete response rate in patients with MIBC. The combination of GC and ICB, therefore, compares favorably with historical data and warrants additional investigation. Indeed, there are ongoing phase III trials evaluating GC versus GC combined with pembrolizumab (anti–PD-1),[54] nivolumab (anti–PD-1) with or without the indoleamine 2,3-dioxygenase inhibitor linrodostat,[55] and durvalumab (anti–PD-L1).[56] In addition, enfortumab vedotin, an antibody-drug conjugate targeting nectin-4 that is approved for patients with metastatic bladder cancer who previously received platinum-based treatment and a PD-1 or PD-L1 inhibitor,[57,58] is being investigated in phase III trials as neoadjuvant therapy for patients with MIBC.[59,60] Of note, these phase III trials include adjuvant therapy irrespective of the pathologic response at the time of RC-PLND, which data from our study and from studies of neoadjuvant cisplatin-based chemotherapy suggest may be overtreatment for those patients with non–muscle-invasive downstaging. Furthermore, as novel therapies become incorporated into the perioperative treatment armamentarium for patients with MIBC, a prospective biomarker-based approach to identify those patients most likely to benefit from these therapies is crucial. For example, the RETAIN (NCT02710734) and HCRN GU16-257 (NCT03558087) trials[61,62] and the ongoing A031701 (NCT03609216) trial incorporate assessment for tumor DNA damage repair mutations as part of the qualifying criteria for pursing active surveillance instead of RC-PLND following neoadjuvant therapy. Additional coordinated efforts will be needed apply both immune-profiling and genomic-profiling technologies to personalize therapeutic combinations while preserving efficacy and minimizing toxicity.

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SUPPORT

Supported by Genentech/Roche, the NIH/NCI Cancer Center Support Grant P30 CA008748, and the NIH/NCI P50 CA221745 SPORE in Bladder Cancer.

CLINICAL TRIAL INFORMATION

NCT02989584

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/jco.21.01485.

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ACKNOWLEDGMENT

The clinical trial protocol was designed, in part, at the 2015 ASCO/AACR Methods in Clinical Cancer Research Workshop supported by the National Cancer Institute of the National Institutes of Health under Award Number R25CA068647.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Neoadjuvant Atezolizumab With Gemcitabine and Cisplatin in Patients With Muscle-Invasive Bladder Cancer: A Multicenter, Single-Arm, Phase II Trial

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Patents, Royalties, Other Intellectual Property: Predictor of platinum sensitivity (Inst)

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Nonevaluable Patient Characteristics and Reasons for Protocol Discontinuation

	Age, years	Sex	Smoking Status	Clinical T Stage	ECOG	Baseline eGFR	Hydronephrosis	PD-L1 Status	Reason for Protocol Discontinuation
Patient 16	61	Male	Former	T2	0	50-60	No	Not available	Patient relocated internationally and was therefore taken off-protocol for noncompliance with study procedures.
Patient 17	63	Male	Current	T2	1	≥ 60	No	Not available	Patient taken off-protocol at investigator discretion for noncompliance with study procedures.
Patient 19	63	Male	Current	T2	1	≥ 60	Yes	Not available	Patient withdrew consent because of excessive travel time to study site.
Patient 28	79	Male	Never	T2	1	≥ 60	Yes	Not available	Patient developed non-neutropenic, urinary sepsis on C1D8 complicated by acute kidney injury and hypotension requiring hospitalization. His renal function did not sufficiently recover to receive further cisplatin and he was taken off-protocol.
Patient 30	78	Female	Never	T2	1	50-60	Yes	< 5%	Patient withdrew consent, preferring to proceed directly to surgery without neoadjuvant therapy

Abbreviations: ECOG, Eastern Cooperative Oncology Group; eGFR, estimated glomerular filtration rate; PD-L1, programmed death-ligand 1.

TABLE A2. All TRAEs

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Neutropenia	26 (59)	1 (2)	9 (20)	13 (30)	3 (7)
Anemia	24 (55)	12 (27)	7 (16)	5 (11)	0 (0)
Fatigue	24 (55)	17 (39)	6 (14)	1 (2)	0 (0)
White blood cell decreased	23 (52)	6 (14)	9 (20)	7 (16)	1 (2)
Nausea	22 (50)	18 (41)	4 (9)	0 (0)	0 (0)
Platelet count decreased	19 (43)	16 (36)	2 (5)	1 (2)	0 (0)
Lymphopenia	16 (36)	5 (11)	4 (9)	5 (11)	2 (5)
Creatinine increased	9 (20)	8 (18)	1 (2)	0 (0)	0 (0)
Dysgeusia	9 (20)	9 (20)	0 (0)	0 (0)	0 (0)
Hypomagnesemia	9 (20)	9 (20)	0 (0)	0 (0)	0 (0)
Serum amylase increased	9 (20)	7 (16)	1 (2)	1 (2)	0 (0)
Alanine aminotransferase increased	8 (18)	6 (14)	2 (5)	0 (0)	0 (0)
Anorexia	8 (18)	6 (14)	2 (5)	0 (0)	0 (0)
Constipation	8 (18)	8 (18)	0 (0)	0 (0)	0 (0)
Hyponatremia	8 (18)	5 (11)	0 (0)	3 (7)	0 (0)
Alopecia	7 (16)	6 (14)	1 (2)	0 (0)	0 (0)
Rash	7 (16)	5 (11)	1 (2)	1 (2)	0 (0)
Vomiting	7 (16)	4 (9)	3 (7)	0 (0)	0 (0)
Aspartate aminotransferase increased	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)
Peripheral sensory neuropathy	6 (14)	6 (14)	0 (0)	0 (0)	0 (0)
Diarrhea	5 (11)	4 (9)	1 (2)	0 (0)	0 (0)
Hyperkalemia	5 (11)	5 (11)	0 (0)	0 (0)	0 (0)
Lipase increased	5 (11)	2 (5)	1 (2)	2 (5)	0 (0)
Tinnitus	5 (11)	5 (11)	0 (0)	0 (0)	0 (0)
Thromboembolic event[a]	5 (11)	0 (0)	3 (7)	2 (5)	0 (0)
Dyspnea	4 (9)	2 (5)	2 (5)	0 (0)	0 (0)
Fever[b]	4 (9)	2 (5)	2 (5)	0 (0)	0 (0)
Hypocalcemia	4 (9)	4 (9)	0 (0)	0 (0)	0 (0)
Superficial thrombophlebitis	4 (9)	0 (0)	4 (9)	0 (0)	0 (0)
Alkaline phosphatase increased	3 (7)	3 (7)	0 (0)	0 (0)	0 (0)
Gastroesophageal reflux disease	3 (7)	2 (5)	1 (2)	0 (0)	0 (0)
Headache	3 (7)	3 (7)	0 (0)	0 (0)	0 (0)
Malaise	3 (7)	2 (5)	1 (2)	0 (0)	0 (0)
Mucositis oral	3 (7)	2 (5)	1 (2)	0 (0)	0 (0)
Pruritus	3 (7)	3 (7)	0 (0)	0 (0)	0 (0)
Arthritis	2 (5)	0 (0)	2 (5)	0 (0)	0 (0)
Chills	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Dry mouth	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Dry skin	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Edema limbs	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Hiccups	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Hypernatremia	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Hypokalemia	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)

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TABLE A2. All TRAEs (continued)

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
Infusion reaction	2 (5)	1 (2)	1 (2)	0 (0)	0 (0)
Insomnia	2 (5)	1 (2)	1 (2)	0 (0)	0 (0)
Loose stool	2 (5)	2 (5)	0 (0)	0 (0)	0 (0)
Autoimmune hepatitis	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)
Autoimmune nephritis	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)
Autoimmune pancreatitis	1 (2)	0 (0)	0 (0)	1 (2)	0 (0)
Atrial fibrillation	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Back pain	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Bloating	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Blood bilirubin increased	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Blotchy skin back of right hand	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Bruising	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Cellulitis	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Chest pain—cardiac	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Cough	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Discoloration of the tongue	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Dry eye	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Dyspepsia	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Edema face	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Flu-like symptoms	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Hearing impaired	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Hematuria	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Hives	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Hypertension	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Hypothyroidism	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Increased TSH	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Infusion site extravasation	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Infusion site reaction	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Mass on right under ear lobe	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Pain in extremity	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Paresthesia	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Sweating	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Urinary tract pain	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Vertigo	1 (2)	0 (0)	1 (2)	0 (0)	0 (0)
Watering eyes	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)
Weight loss	1 (2)	1 (2)	0 (0)	0 (0)	0 (0)

Abbreviations: AE, adverse event; TRAEs, treatment-related AEs; TSH, thyroid stimulating hormone.

[a]One fever was felt to be immune-related.

[b]Three patients had treatment-related venous thromboembolic events (grade 2 upper-extremity deep venous thrombosis; n = 1; grade 3 pulmonary embolus; n = 2) and two had treatment-related arterial thromboembolic events (both grade 2 stroke). Two patients had unrelated grade 3 venous thromboembolic events.

TABLE A3. All Treatment-Unrelated AEs[a]

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)
Hyperglycemia	17 (39)	9 (20)	5 (11)	3 (7)
Hypoalbuminemia	9 (20)	8 (18)	1 (2)	0 (0)
Headache	8 (18)	8 (18)	0 (0)	0 (0)
Cough	6 (14)	5 (11)	1 (2)	0 (0)
Insomnia	6 (14)	6 (14)	0 (0)	0 (0)
Constipation	5 (11)	5 (11)	0 (0)	0 (0)
Creatinine increased	5 (11)	4 (9)	0 (0)	1 (2)
Dyspnea	5 (11)	3 (7%)	0 (0)	2 (5)
Hematuria	5 (11)	5 (11)	0 (0)	0 (0)
Hypertension	5 (11)	1 (2)	3 (7)	1 (2)
Nasal congestion	5 (11)	5 (11)	0 (0)	0 (0)
Urinary tract pain	5 (11)	4 (9)	1 (2)	0 (0)
Diarrhea	4 (9)	4 (9)	0 (0)	0 (0)
Fatigue	4 (9)	1 (2)	3 (7)	0 (0)
Hyponatremia	4 (9)	2 (5)	0 (0)	2 (5)
Pain	4 (9)	4 (9)	0 (0)	0 (0)
Urinary tract infection	4 (9)	0 (0)	1 (2)	3 (7)
Arthralgia	3 (7)	2 (5)	1 (2)	0 (0)
Back pain	3 (7)	1 (2)	2 (5)	0 (0)
Edema limbs	3 (7)	3 (7)	0 (0)	0 (0)
Fever	3 (7)	2 (5)	1 (2)	0 (0)
Hypoglycemia	3 (7)	3 (7)	0 (0)	0 (0)
Nausea	3 (7)	3 (7)	0 (0)	0 (0)
Pain in extremity	3 (7)	2 (5)	1 (2)	0 (0)
Tinnitus	3 (7)	3 (7)	0 (0)	0 (0)
Urinary frequency	3 (7)	3 (7)	0 (0)	0 (0)
Activated PTT prolonged	2 (5)	1 (2)	0 (0)	1 (2)
Alkaline phosphatase increased	2 (5)	2 (5)	0 (0)	0 (0)
Allergic rhinitis	2 (5)	2 (5)	0 (0)	0 (0)
Anxiety	2 (5)	1 (2)	1 (2)	0 (0)
Bruising	2 (5)	2 (5)	0 (0)	0 (0)
Dehydration	2 (5)	0 (0)	1 (2)	1 (2)
Dizziness	2 (5)	2 (5)	0 (0)	0 (0)
Flu-like symptoms	2 (5)	1 (2)	1 (2)	0 (0)
INR increased	2 (5)	2 (5)	0 (0)	0 (0)
Lymphopenia	2 (5)	1 (2)	1 (2)	0 (0)
Pelvic pain	2 (5)	1 (2)	1 (2)	0 (0)
Peripheral sensory neuropathy	2 (5)	1 (2)	1 (2)	0 (0)
Thromboembolic event	2 (5)	0 (0)	0 (0)	2 (5)
Vomiting	2 (5)	2 (5)	0 (0)	0 (0)
Acute COPD exacerbation	1 (2)	0 (0)	0 (0)	1 (2)
Anemia	1 (2)	1 (2)	0 (0)	0 (0)
Anorexia	1 (2)	1 (2)	0 (0)	0 (0)

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TABLE A3. All Treatment-Unrelated AEs[a] (continued)

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)
Atrial fibrillation	1 (2)	0 (0)	1 (2)	0 (0)
Bacteremia	1 (2)	0 (0)	0 (0)	1 (2)
Bladder spasm	1 (2)	1 (2)	0 (0)	0 (0)
Bloating	1 (2)	1 (2)	0 (0)	0 (0)
Bilirubin increased	1 (2)	1 (2)	0 (0)	0 (0)
Blood LDH Increased	1 (2)	1 (2)	0 (0)	0 (0)
Blurred vision	1 (2)	1 (2)	0 (0)	0 (0)
Bone pain	1 (2)	1 (2)	0 (0)	0 (0)
Bronchial infection	1 (2)	0 (0)	1 (2)	0 (0)
Cataract	1 (2)	1 (2)	0 (0)	0 (0)
Chest pain—cardiac	1 (2)	0 (0)	0 (0)	1 (2)
Chills	1 (2)	1 (2)	0 (0)	0 (0)
Confusion	1 (2)	1 (2)	0 (0)	0 (0)
Dry skin	1 (2)	1 (2)	0 (0)	0 (0)
Dyspepsia	1 (2)	1 (2)	0 (0)	0 (0)
Dysuria	1 (2)	1 (2)	0 (0)	0 (0)
Folic acid decreased	1 (2)	0 (0)	1 (2)	0 (0)
Gastroesophageal reflux disease	1 (2)	0 (0)	1 (2)	0 (0)
Generalized muscle weakness	1 (2)	0 (0)	0 (0)	1 (2)
Hypercalcemia	1 (2)	1 (2)	0 (0)	0 (0)
Hyperkalemia	1 (2)	0 (0)	1 (2)	0 (0)
Hypertriglyceridemia	1 (2)	0 (0)	1 (2)	0 (0)
Hypocalcemia	1 (2)	1 (2)	0 (0)	0 (0)
Hypophosphatemia	1 (2)	0 (0)	1 (2)	0 (0)
Hypotension	1 (2)	1 (2)	0 (0)	0 (0)
Infusion site extravasation	1 (2)	0 (0)	1 (2)	0 (0)
Irritation	1 (2)	1 (2)	0 (0)	0 (0)
Light sensitivity	1 (2)	1 (2)	0 (0)	0 (0)
Lip pain	1 (2)	1 (2)	0 (0)	0 (0)
Lymph node pain	1 (2)	1 (2)	0 (0)	0 (0)
Neck pain	1 (2)	1 (2)	0 (0)	0 (0)
Chest pain—noncardiac	1 (2)	1 (2)	0 (0)	0 (0)
Paresthesia	1 (2)	0 (0)	1 (2)	0 (0)
Phlebitis	1 (2)	0 (0)	1 (2)	0 (0)
Thrombocytopenia	1 (2)	1 (2)	0 (0)	0 (0)
Postnasal drip	1 (2)	1 (2)	0 (0)	0 (0)
Productive cough	1 (2)	1 (2)	0 (0)	0 (0)
Rash	1 (2)	1 (2)	0 (0)	0 (0)
Sinusitis	1 (2)	0 (0)	1 (2)	0 (0)
Skin infection	1 (2)	0 (0)	1 (2)	0 (0)
Stomach pain	1 (2)	1 (2)	0 (0)	0 (0)
Tendonitis of elbow	1 (2)	0 (0)	1 (2)	0 (0)
Tremor	1 (2)	1 (2)	0 (0)	0 (0)

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TABLE A3. All Treatment-Unrelated AEs[a] (continued)

AE	All Grades, No. (%)	Grade 1, No. (%)	Grade 2, No. (%)	Grade 3, No. (%)
Upper respiratory infection	1 (2)	0 (0)	1 (2)	0 (0)
Urinary retention	1 (2)	0 (0)	1 (2)	0 (0)
Urinary urgency	1 (2)	1 (2)	0 (0)	0 (0)
Vaginal discharge	1 (2)	1 (2)	0 (0)	0 (0)
Vaginal pain	1 (2)	1 (2)	0 (0)	0 (0)
Watering eyes	1 (2)	1 (2)	0 (0)	0 (0)
Weight gain	1 (2)	1 (2)	0 (0)	0 (0)

Abbreviations: AE, adverse event; COPD, chronic obstructive pulmonary disease; INR, international normalized ratio; LDH, lactate dehydrogenase; PTT, partial thromboplastin time.

[a]These events were recorded up until the day of surgery. There were no grade 4 or 5 events. For postoperative complications, see Table 4.

TABLE A4. Dose Modifications and Delivery[a]

Characteristic	No. (%)
Patients requiring toxicity-related dose modification	26 (66.7)
AEs leading to dose modification	
Neutropenia	12 (30.8)
Creatinine increased	6 (15.4)
Thrombocytopenia	4 (10.3)
Immune-related pancreatic enzyme elevation	3 (7.7)
Stroke	2 (5.1)
Immune-related rash	2 (5.1)
Immune-related hepatitis	1 (2.6)
Total No. of chemotherapy cycles, median (range)	4 (2-4)
Total No. of atezolizumab doses, median (range)	6 (1-6)
Weeks from chemotherapy completion to surgery, median (range)[b]	7.8 (5.1-17)

Abbreviation: AE, adverse event.

[a]A single patient may have had multiple dose modifications and multiple reasons for dose modification.

[b]Two patients were delayed beyond 12 weeks, both for surgical planning issues and not for AEs.