Split-Dose Cisplatin Plus Atezolizumab for Patients With Urothelial Carcinoma Who Are Considered Ineligible for Full Doses of Cisplatin (SOGUG-AUREA)

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ABSTRACT

PURPOSE Immune checkpoint inhibitors combined with platinum-based chemotherapy is standard in patients with advanced/metastatic urothelial carcinoma (mUC). Cisplatin has immunomodulatory benefits compared with carboplatin. This study aims to assess the safety and efficacy of atezolizumab and a split-dose cisplatin regimen in patients ineligible for full doses of cisplatin.

PATIENTS/METHODS The phase II single-arm SOGUG-AUREA clinical trial recruited treatment-naïve patients with mUC ineligible for full dose of cisplatin because of elderly, poor performance status, or impaired renal function. Patients received cisplatin (35 mg/m²) and gemcitabine (1,000 mg/m²) on days 1 and 8, up to six cycles, in combination with atezolizumab 1,200 mg intravenously once every 3 weeks until progression, unacceptable toxicity, or absence of clinical benefit. The primary end point was objective response (OR). Secondary end points included duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. A Fleming's two-stage design was used with a total enrollment of 66 patients required (null and alternative hypothesis: OR, 30% *v* 50%; $\alpha = .05$; $\beta = 80\%$).

RESULTS Between January 2021 and March 2022, 66 patients were included. The OR was 48.5% (95% CI, 36 to 61), with seven (10.61%) patients experiencing complete response. The median DoR was 9.2 months (95% CI, 5.5 to 16.8+). After a median follow-up of 11.6 months (range, 0.6-35.3), median PFS was 6.9 months (95% CI, 6.7 to 9.4), with 12-month PFS rate of 31.0% (95% CI, 21.4 to 44.8). The median OS was 12.9 months (95% CI, 10.2 to 20.2), with a 24-month OS rate of 30.1% (95% CI, 20.6 to 44.0). Most frequent grade 3 to 4 toxicities were neutropenia (31.8%), anemia (25.8%), and thrombocytopenia (19.7%).

CONCLUSION Atezolizumab plus split doses of cisplatin and gemcitabine showed durable responses and promising OR in patients with mUC. Safety profile was consistent with previous experience.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Urothelial carcinoma (UC) is the 10th most common cancer worldwide, with an estimated incidence of 549,000 new cases and 200,000 deaths per year worldwide.[1,2]

Recently, the therapeutic scenario in patients with advanced or metastatic UC (mUC) has been revolutionized by the incorporation as first-line treatment of enfortumab vedotin (EV), an antibody-drug conjugate, plus pembrolizumab.[3] Cisplatin-based chemotherapy, for suitable candidates, or carboplatin-based regimens or split doses of cisplatin, for those ineligible for full cisplatin doses, have been the standard background treatment for combinations with immune checkpoint inhibitors (ICIs), which remain an option for selected patients.[4-15]

CONTEXT

Key Objective
Can atezolizumab with a split-dose cisplatin regimen be a treatment option in patients with metastatic urothelial carcinoma ineligible for full doses of cisplatin?

Knowledge Generated
Atezolizumab combination was well tolerated and achieved encouraging activity, with an objective response rate of 48.5% and a median duration of response of 9.2 months (95% CI, 5.5 to 16.8+).

Relevance *(C.H. Marshall)*
This study provides evidence of efficacy of an alternative regimen for patients and providers to consider using split-dose cisplatin in combination with gemcitabine and atezolizumab for patients with advanced urothelial carcinoma.*

Plain Language Summary *(C.H. Marshall)*
Cisplatin is a cancer drug that is commonly used with two other treatments for patients with advanced bladder cancer. However, the full dose of cisplatin can be toxic. In this study, using a smaller dose of cisplatin, given more often with the other treatments, showed promising response rates.†

*Relevance section *JCO Oncology Advances* Associate Editor Catherine Handy Marshall, MD, MPH.
†Plain Language Summary written by *JCO Oncology Advances* Associate Editor Catherine Handy Marshall, MD, MPH.

Maintenance with avelumab or pembrolizumab after induction treatment with chemotherapy significantly prolonged overall survival (OS), regardless of PD-L1 status.[16,17] Moreover, nivolumab or atezolizumab in combination with chemotherapy improved outcomes in patients with treatment-naïve mUC.[18,19] Notably, all combinations showed acceptable toxicity profiles.[16-20]

In the subgroup analysis of the IMvigor130, OS appeared longer in patients receiving atezolizumab + cisplatin (21.5 months) compared with those receiving atezolizumab + carboplatin (14.3 months).[18] This observation together with preclinical and translational studies have demonstrated that cisplatin, but not carboplatin, enhances antigen presentation and promotes T-cell infiltration into the tumor microenvironment, possibly through the upregulation of IFN-γ and NF-κB signaling pathways.[21] These findings highlight the rationale for favoring cisplatin-based regimens in combination with immunotherapy. Two phase II, single-arm trials also explored the role of single-agent ICI in patients with mUC treatment-naïve and cisplatin-ineligible.[22,23] Atezolizumab as a single agent showed an objective response (OR) of 23% and a median OS of 15.9 months,[22] leading to its approval as first-line treatment in patients with mUC who are considered cisplatin-ineligible and whose tumors have a PD-L1 expression ≥5%.

The SOGUG-AUREA trial investigated the safety and efficacy of combining atezolizumab with a split-dose cisplatin regimen in patients ineligible for full doses of cisplatin.

METHODS

Patient Population

In the SOGUG-AUREA trial, we enrolled patients with histologically confirmed, unresectable, locally advanced, or mUC, stages III and IV (T4B, any N; or any T, N2-3 or M1 according to the American Joint Committee on Cancer 7th edition) that was measurable according to RECIST version 1.1, and patients had not received radiation therapy within 4 weeks before the initiation of first-line chemotherapy. All patients were deemed ineligible for cisplatin, as determined by meeting at least one of the following criteria: (1) impaired renal function (ClCr 30-60 mL/min according to the Cockcroft-Gault formula); (2) Eastern Cooperative Oncology Group performance status (ECOG PS) of 2; (3) significant baseline comorbidities such as New York Heart Association (NYHA) class ≥II heart failure, grade ≥2 peripheral neuropathy, or previous ototoxicity; (4) age ≥70 years, a criterion considered because of its association with increased chemotherapy-related toxicities. Patients were age 18 years or older, treatment-naïve in the advanced setting, and with adequate hematologic and hepatic function. Patients with contraindications for ICIs were excluded. The full eligibility criteria are provided in the Protocol.

Trial Design

SOGUG-AUREA (EudraCT: 2020-001326-65; ClinicalTrials.gov identifier: NCT04602078) is a multicenter, nonrandomized, single-arm, open-label trial. A fixed dose of

1,200 mg/m² atezolizumab was administered to all patients by intravenous (IV) infusion on day 1 of each cycle once every 3 weeks, in combination with a split dose of 1,000 mg/m² gemcitabine plus 35 mg/m² cisplatin IV on days 1 and 8 once every 3 weeks for up to six cycles. After the completion of six cycles, patients received atezolizumab monotherapy until disease progression, unacceptable toxicity, the investigator's decision, or withdrawal of patient consent. Cisplatin and gemcitabine doses could be reduced according to local standard procedures and local criteria for managing treatment-emergent adverse events (AEs). Atezolizumab could be delayed for the management of immune-related AEs (irAEs). The use of corticosteroids was allowed for managing infusion-related reactions or the short-term treatment of irAEs. AEs associated with atezolizumab were managed according to the protocol and the latest version of the atezolizumab investigator's brochure, while AEs related to chemotherapy were managed according to the summary of product characteristics and local standard protocols. Best supportive care was provided as per local practices, including antibiotics, anti-inflammatory drugs, analgesics, hydration, or antiemetics. Local radiotherapy was permitted if administered not concomitantly with gemcitabine.

The trial received approval from the competent authority in Spain, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), and the ethics committee of Hospital Universitario 12 de Octubre (Ref: 20/528). It was conducted in compliance with the Declaration of Helsinki principles and Good Clinical Practice guidelines as defined by the International Council for Harmonisation. Written informed consent was obtained from all participants.

End Points and Assessments

The primary end point was the OR, defined as the percentage of patients with a confirmed complete response (CR) or partial response (PR) as their overall best response according to RECIST v1.1.

Secondary efficacy end points included the duration of response, defined as the time from response confirmation to the date of documented disease progression or death from any cause, whichever occurred first; time to response, defined as the time elapsed until the date of response confirmation; clinical benefit rate (CBR), defined as the percentage of patients with confirmed response or stable disease (SD) maintained for ≥6 months as their overall best response; progression-free survival (PFS), defined as the time from the first dosing date to the date of confirmed disease progression or death; and OS, defined as the time from the first dosing date to the date of death.

Tumors were evaluated using RECIST version 1.1. Imaging by computed tomography or magnetic resonance imaging, preferably with IV contrast, of the neck, chest, abdomen, and pelvis was performed at baseline, weeks 9 and 18, and every 12 weeks thereafter until objective disease progression or death was confirmed. Additional anatomic sites were imaged as indicated by the signs and symptoms. Confirmation of response and radiologic progression (without signs of clinical deterioration) was required at least 4 weeks after the initial assessment. AEs were continuously assessed, coded using the Medical Dictionary for Regulatory Activities and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0.

PDL1 Expression Assessment

PD-L1 expression was centrally assessed by blinded pathologists in formalin-fixed, paraffin-embedded tumor samples. The primary PD-L1 antibody used was clone 22C3 (Agilent/Dako, PharmDx).

The PD-L1 combined positive score (CPS) was calculated as the proportion of PD-L1–staining cells (tumor cells [TCs] and tumor-infiltrating immune cells with positive membranous staining of any intensity) relative to all viable TCs. The PD-L1 tumor proportion score (TPS) was calculated as the percentage of viable TCs showing partial or complete membrane staining at any intensity. Patients were classified as having PD-L1–positive status if the TPS/CPS ratio was >1%.

Statistical Analysis

The null hypothesis (H_0) posited that the OR would be ≤30%, while the alternative hypothesis (H_1) assumed an OR of ≥50%. A Fleming's two-stage design was applied, with an alpha of .05 and a power of 80%. Initially, 46 patients were enrolled; if at least 18 patients achieved a response, the study would proceed with an additional 20 patients. The futility threshold in the interim analysis was surpassed, allowing trial continuation.

The efficacy end points were assessed in all patients who have been enrolled in the trial. Safety evaluations covered all patients who received at least one dose of the study treatment. Baseline characteristics were depicted using descriptive statistics, with frequencies and percentages for categorical variables, and median values, full ranges, or 95% CIs for continuous variables. Exact two-sided 95% CIs for OR were determined using the Clopper-Pearson method. Comparisons of OR across different subgroups used Fisher's exact test. PFS and OS were estimated via the Kaplan-Meier method. All statistical analyses were conducted using R (version 3.6.3 [2020-02-29] Holding the Windsock, The R Foundation for Statistical Computing, Vienna, Austria). Figures and tables were produced using RStudio (Version 1.2.5033, 2009-2019 RStudio, Inc, Boston, MA).

RESULTS

Patients

Between January 2021 and March 2022, 66 patients were included from 12 sites in Spain (Fig 1) and received at least

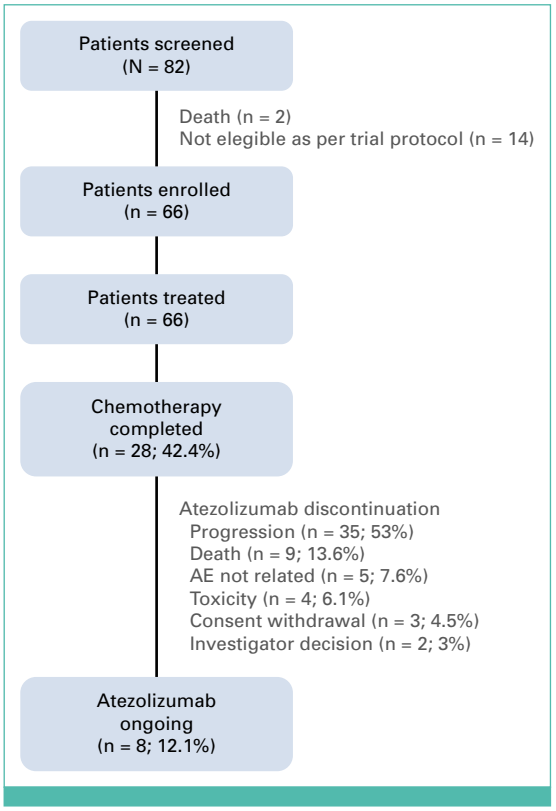

FIG 1. Flow diagram with patient allocation and treatment completion. AE, adverse event.

TABLE 1. Patient Characteristics

Characteristic	Overall Population (N = 66)
Age, years	
Years, median (range)	71 (49-85)
Sex, No. (%)	
Male	57 (86.4)
ECOG PS, No. (%)	
0	17 (25.8)
1	34 (51.5)
2	15 (22.7)
Site of the primary tumor,[a] No. (%)	
Upper tract	11 (16.7)
Lower tract	55 (83.3)
Stage at inclusion, No. (%)	
Locally advanced	8 (12.1)
Metastatic	58 (87.9)
Metastatic locations, No. (%)	
Lymph nodes	44 (66.7)
Lung	36 (54.5)
Bone	20 (30.3)
Liver	12 (18.2)
Reason unfit for full-dose CT, No. (%)	
ECOG 2	15 (22.7)
Age >70 years	36 (54.5)
CrCl 30-60 μmol/L	33 (50.0)
Previous local therapy, No. (%)	
Surgery	58 (87.9)
Radiotherapy	9 (13.6)
PD-L1 status, No. (%)	
Positive	14 (21.2)
Negative	26 (39.4)
Unknown	26 (39.4)

Abbreviations: CrCl, creatinine clearance; CT, cisplatin-based chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a]The upper tract was defined as the renal pelvis or ureter, and the lower tract as the bladder and urethra.

one dose of the study treatment. The median age was 71 years (range, 49-85), and 57 patients (86.4%) were males. The most frequent reasons for classifying patients as cisplatin-ineligible were age >70 years (54.5%), impaired renal function (50%), and an impaired performance status (22.7%). Twenty-two patients (33.3%) fulfilled more than one criterion for being ineligible to receive the full dose of cisplatin. Patient characteristics are described in Table 1.

At the data cutoff on 16 April 2024, eight patients (12.1%) were still receiving atezolizumab treatment. Atezolizumab was discontinued because of disease progression in 35 patients (53%), death in nine (13.6%), AEs in five (7.6%), toxicities in four (6.1%), withdrawal of consent in three (4.5%), and the investigator's decision in two (3%). Chemotherapy was completed as scheduled in 28 (42.4%) patients. The most common reasons for premature discontinuation of chemotherapy were toxicity in 20 patients (30.3%), progressive disease in six (9.1%), death in five (7.6%), AEs in three (4.5%), investigator decision in two (3%), withdrawal of consent in one (1.5%), and other/nonspecified in one (1.5%; Fig 1).

Efficacy

The primary end point of the OR was 48.5% (95% CI, 36 to 61.1), with the lower limit of the CI surpassing the null hypothesis of 30% (Fig 2). Adjusted model accounting for intermediate analysis showed no relevant differences (Data Supplement, Table S1). Seven patients (10.6%) had a confirmed CR, and 25 (37.9%) had a confirmed PR as their best response. Responses were achieved after a median time of 2.1 months (95% CI, 2 to 2.2) and lasted for a median of 9.2 months (95% CI, 5.5 to 16.8+). Five (7.6%) patients had responses that lasted longer than 24 months and were ongoing at the data cutoff (Fig 2B). Most long-lasting responders were male (60%), and all had metastases with lymph node involvement (80%). SD was maintained for over 6 months in 12 patients (18.2%), accounting for a CBR of 66.7% (95% CI, 54 to 77.8).

The OR was reduced to 25% in patients with liver metastases. Patients with lymph-node-only metastases had a higher OR

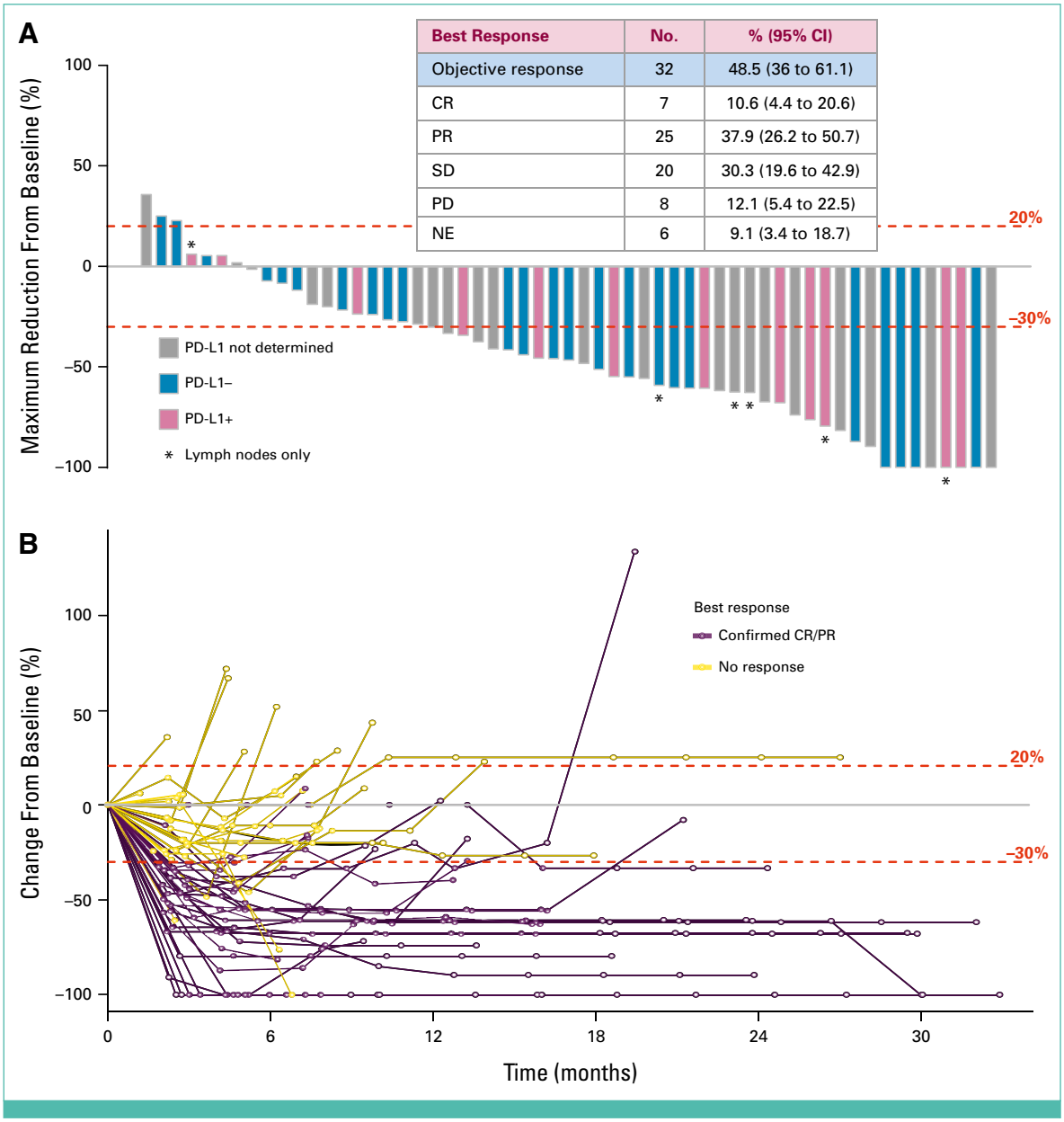

FIG 2. Changes in tumor size. (A) Waterfall plot showing the maximum reduction of the target lesions from baseline, as surrogate of the depth of the tumor reduction. Appearance of new lesions or growth of nonmeasurable lesions and nontarget lesions is not included for tumor size reduction. (B) Spider plot showing the changes from baseline tumor burden, defined as the sum of target lesion diameters, throughout the study period. Patients with confirmed responses are colored in dark blue and patients without confirmed responses are colored in yellow. CR, complete response; NE, not evaluable; OR, objective response; PD, progressive disease; PR, partial response; SD, stable disease.

(77.8%). Response rates were similar regardless of age (50% *v* 47.2% in patients ≤70 and >70 years, respectively; $P = 1.000$), renal function (51.5% *v* 45.5% in patients with adequate and mild impairment, respectively; $P = .806$), or performance status (49% *v* 46.7% in patients with ECOG 0-1 and 2, respectively; $P = 1.000$). PD-L1–positive patients exhibited an OR of 57.1% versus 38.5% in PD-L1–negative ($P = .414$).

After a median follow-up of 11.6 months (95% CI, 8.9 to 18.5), the median PFS was 6.9 months (95% CI, 6.7 to 9.4), and the 12-month PFS rate was 31% (95% CI, 21.4 to 44.8; Fig 3). No differences were observed in PFS with respect to cisplatin ineligibility criteria or PD-L1 status. The median PFS was 9 months (95% CI, 5.8 to 16.5), 6.9 months (95% CI, 5.4 to 15), and 6.2 months (95% CI, 3.6 to not reached [NR]) in older adult patients (>70 years), those with impaired renal function, and in patients with ECOG 2, respectively (Data Supplement, Fig S1). The median PFS for patients with exclusively lymph-node-only metastasis was 15 months (95% CI, 12.3 to NR; Data Supplement, Fig S2).

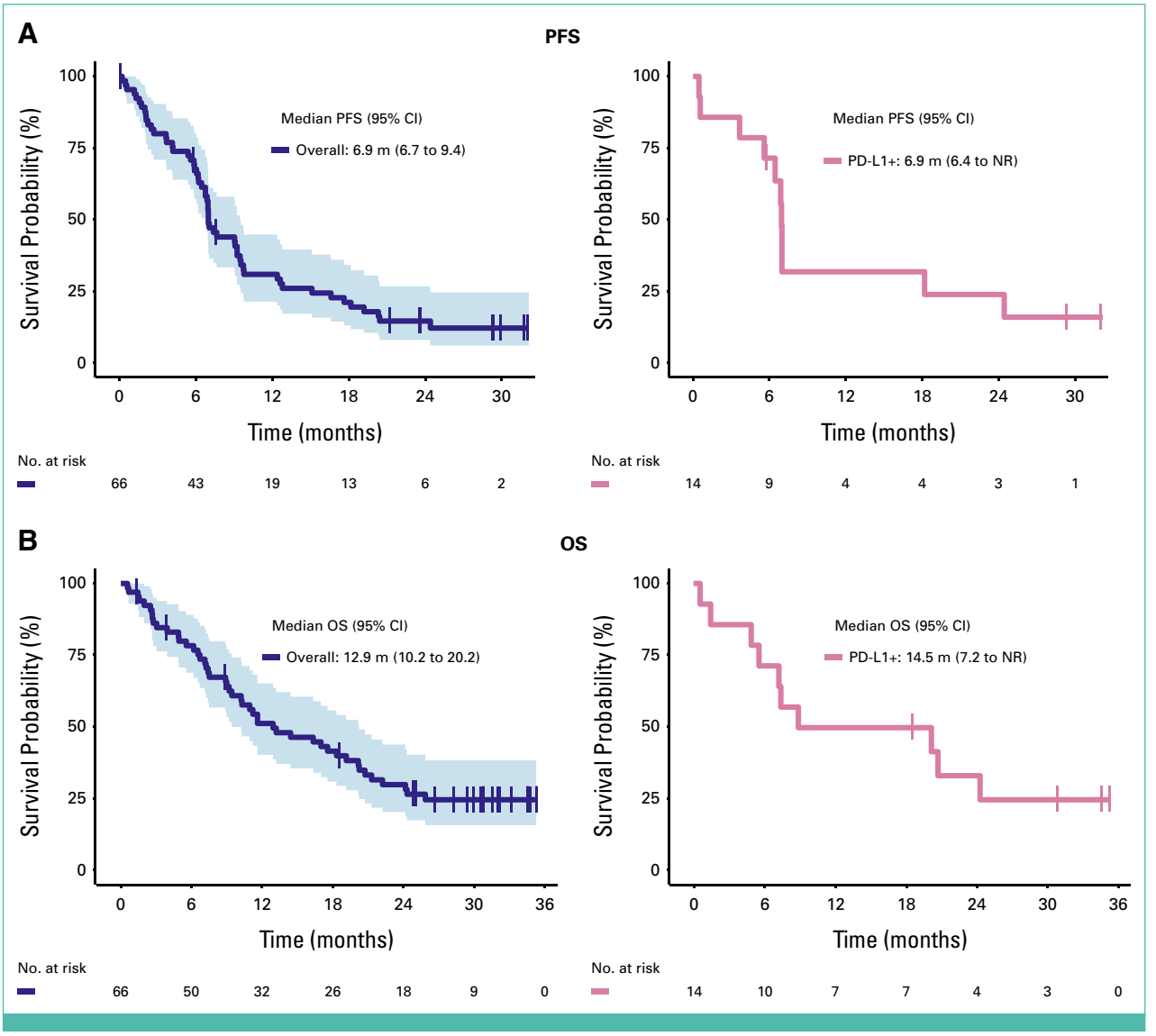

FIG 3. Survival outcomes. (A) PFS in the full analysis set (blue) and in the PD-L1–positive population (purple). PFS was assessed by the local investigator according to RECIST v1.1 criteria. (B) OS in the full analysis set and in the PD-L1–positive population. The shaded area represents the 95% CI in the full data set. NR, not reached; OS, overall survival; PFS, progression-free survival.

The median OS was 12.9 months (95% CI, 10.2 to 20.2), with 12-month and 24-month OS rates of 51.4% (95% CI, 40.4 to 65.3) and 30.1% (95% CI, 20.6 to 44.0), respectively (Fig 3). At the time of data cutoff, 47 patients (71.2%) had died. The principal causes of death were disease progression in 34 patients (51.5%), AEs in 11 (16.7%), and two (3%) deaths were attributable to the study treatment (Data Supplement, Table S2). One patient died of sepsis secondary to neutropenia, related to gemcitabine and cisplatin, while another patient passed away owing to cardiac failure, where the involvement of atezolizumab could not be excluded. The latter patient experienced a cardiac arrest at home, with no further details available.

No variances in OS were observed on the basis of criteria for cisplatin eligibility or PD-L1 status (Data Supplement, Fig S1). Patients with liver metastases exhibited a significantly poorer prognosis than did those without liver involvement, demonstrating a median OS of 6.7 months (95% CI, 4.93 to NR) versus 17 months (95% CI, 10.9 to 24.2; $P = .043$; Fig 4). The median OS for patients with exclusive lymph-node-only metastasis was 25.9 months (95% CI, 18.3 to NR).

Safety

Among all treated patients, the median duration of atezolizumab treatment was 7.2 months (95% CI, 6.3 to 9.5). AEs led to delays in the atezolizumab dosage for 41 patients (62.1%) during the concomitant phase with chemotherapy, and for 24 patients (36.4%) during the maintenance phase as a single agent. Cisplatin and gemcitabine were administered

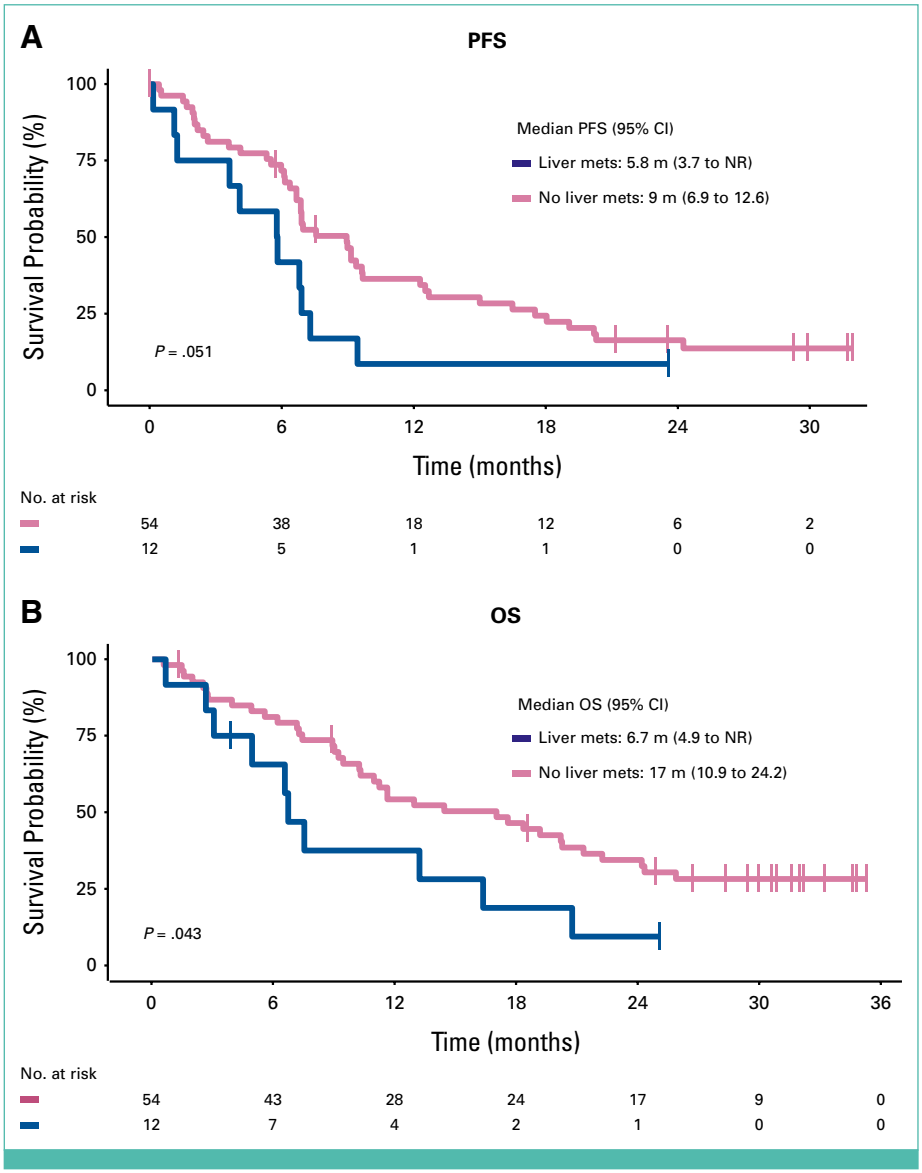

FIG 4. Survival outcomes in patients stratified according to the presence of liver disease. (A) PFS stratified by presence of liver involvement at baseline. PFS was assessed by the local investigator according to RECIST v1.1 criteria. (B) OS stratified by presence of liver involvement at baseline. NR, not reached; OS, overall survival; PFS, progression-free survival.

for a median of five cycles (95% CI, 4 to 6). Thirty (45.5%) patients received six scheduled cycles of chemotherapy. Chemotherapy was delayed for 39 (59.1%) patients because of AEs. The doses of cisplatin and gemcitabine were reduced to manage AEs in 18 (27.3%) and 20 (30.3%) patients, respectively. Dosing on day 8 was omitted in at least one cycle for 34 patients (51.5%).

Toxicities of any grade were reported in 62 patients (93.9%), and grade ≥3 toxicities occurred in 44 patients (66.7%). Serious AEs are summarized in the Data Supplement (Table S3). The most frequent grade ≥3 toxicities were neutropenia (31.8%), anemia (25.8%), thrombocytopenia (19.7%), and fatigue (6.1%; Fig 5). Renal toxicity was infrequent; grade ≥3 renal toxicities included nephritis in two patients (3%), acute kidney injury in one (1.5%), and hematuria in one (1.5%).

In total, 15 patients (22.7%) experienced grade 3 to 4 toxicity related to atezolizumab. The addition of atezolizumab to split-dose cisplatin and gemcitabine resulted in a low frequency of irAEs, the most frequent (any grade) being hypothyroidism (10.6%), anemia (9.1%), and thrombocytopenia (7.6%; Fig 5 and Data Supplement, Table S4). Cocausality with chemotherapy for these hematologic events was not discarded. AEs of special interest requiring the use of systemic corticosteroids occurred in 22 (33.3%) patients.

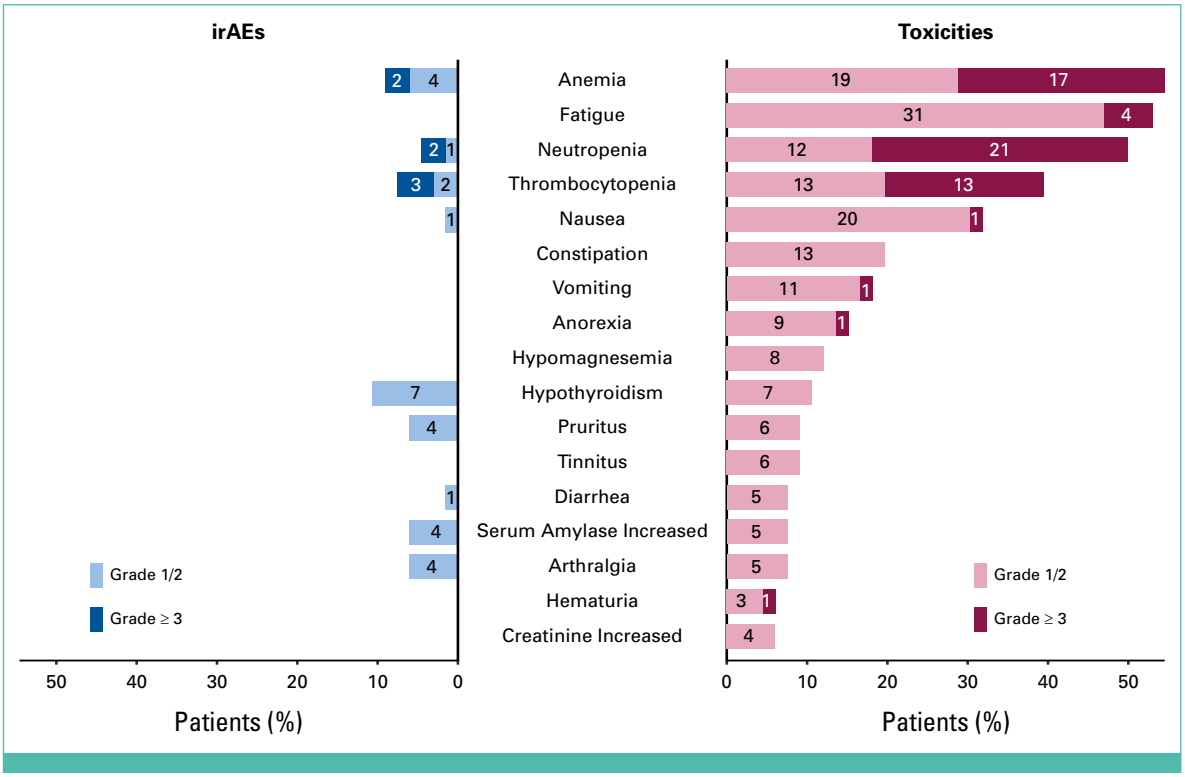

FIG 5. Safety profile. Treatment-related AEs (purple, right panel) and irAEs (blue, left panel). The safety population included all patients who received at least one dose of study treatment. Shown are the toxicities of any grade that occurred in at least 5% of these patients. AEs, adverse events; ir-AEs, immune-related AEs.

DISCUSSION

To our knowledge, the SOGUG-AUREA trial showed for the first time that the combination of atezolizumab with split doses of cisplatin and gemcitabine was effective and safe for patients with mUC. The addition of atezolizumab achieved an OR of 48.5%, which was greater than that of split-dose cisplatin/gemcitabine alone (approximately 39% in previous trials).[10] The OR was comparable with that achieved in the first-line treatment of mUC with a combination of ICI plus chemotherapy at full doses.[18-20] The responses were significant, with 11% (7) of patients achieving a CR, which was long-lasting and maintained for longer than 2 years in five patients, consistent with full chemotherapy dosing schemes.[18-20]

The results were comparable with those of other regimens assessed in the non–cisplatin-evaluable population. However, the benefit in OS was limited in this study, especially if compared with novel combinations in this setting including EV plus pembrolizumab that has a noteworthy activity, prolonged survival (median OS 26.1 months), and is approved as standard of care in the first-line of treatment.[3] EV was well tolerated and efficacy was greater than our combination, so it should be considered for the majority of patients. Even in subgroups for which our combination reported better efficacy outcomes, such as patients with lymph-node-only metastasis and no liver metastasis, these are yet below those reported with EV plus pembrolizumab. In general, our treatment strategy should not be prioritized over EV/pembrolizumab. Nevertheless, our approach might still be a valid alternative in certain settings, particularly where EV/pembrolizumab is not accessible. This includes frail patients for whom a time-limited chemotherapy scheme may be preferable to long-term EV exposure. The EV-302 trial reported limited data specifically for patients with ECOG 2, who represented a small and highly selected subgroup. This highlights the need for further real-world data to assess the performance of the EV/pembrolizumab combination in this population, and provides a rationale for comparing such findings with the results we observed in our less selected ECOG 2 cohort.

Survival was similar to that of previous trials combining ICI with carboplatin-based chemotherapy.[18-20] Therefore, the limited benefit observed with carboplatin schemes is more likely attributable to patient frailty than to the differential potential of cisplatin to induce immunomodulatory effects.[21] Other randomized trials using ICIs as first-line treatment also failed to demonstrate an improvement in survival, which seems more limited to patients eligible for cisplatin.[20-24] Caution should be exercised owing to the indirect nature of the comparisons. For instance, our study included patients with a high proportion of visceral metastases, while only 13.6% of patients had distal disease exclusively circumscribed to the regional lymph nodes.

Response rates varied significantly on the basis of metastatic locations, from an OR of 77.8% to 25% in patients with lymph-node-only and liver metastases, respectively. These findings are consistent with previous studies indicating that liver metastases correlate with poorer response to ICIs, likely because of an immunosuppressive microenvironment characterized by increased infiltration of myeloid-derived suppressor cells and a reduced T-cell response.[25] By contrast, lymph node metastases have been associated with a more immunogenic tumor microenvironment.[26] The response rate and prognosis remained independent of age, ECOG performance status, renal function, and PD-L1 status. Interestingly, the addition of perioperative durvalumab (another PD-L1 agent) to cisplatin-based chemotherapy has demonstrated, in a phase III trial, significant impact in OS. Of note, 20% of patients included had mild renal function impairment (creatinine clearance 40-60 mL/min) and were treated during the neoadjuvant period with split-dose cisplatin-gemcitabine and durvalumab. The subgroup analysis of this study showed that this preestablished subset of patients also benefited from adding ICI in terms of OR, event-free survival, and OS.[27]

The administration of atezolizumab did not induce irAEs that affected the chemotherapy dose intensity. The safety profile of atezolizumab was consistent with previous reports.[13,14,18,22,28-30] Most AEs were attributed to the chemotherapy, and the addition of atezolizumab did not lead to a clinically meaningful increase in toxicity. Hematologic and renal toxicities remained within the expected range for platinum-based regimens without ICI. This level of toxicity resulted in a low rate of atezolizumab discontinuation (6%). Chemotherapy discontinuation because of toxicities occurred in a proportion of patients similar to that reported in previous studies.[10,18]

Single-agent ICI represents an alternative strategy to mitigate toxicity in frail patients, but a substantial proportion of patients experience early disease progression and only a few proceeded to second-line treatments.[21,22,31] Another matter of debate is the sequential use of chemotherapy and ICIs to avoid the emergence of concomitant toxicities and the concurrent use of corticosteroids. The incidence of hematologic or renal events with maintenance treatment after achieving disease control with platinum-based chemotherapy is low, with anemia ranging from 11.3% for avelumab.[16] This strategy resulted in additional ORs and significantly prolonged the median PFS to 3.7 months.[16] The median OS with ICI maintenance ranged from 21.4 to 22 months.[16,17] Nevertheless, the populations in these trials did not include early progressors, who accounted for a substantial number of patients, and the toxicity rates did not account for patients with resolved toxicities from chemotherapy. In this scenario, the combination of atezolizumab and split-dose cisplatin seems still a valid approach for selected populations.

The primary limitation of the trial was the absence of a control group, which would have strengthened the internal validity through direct treatment comparisons. The use of age as a criterion to determine cisplatin eligibility approached our population to real practice, but limited comparisons with previous trials using classical Galsky criteria. Furthermore, comparing survival outcomes with first-line alternatives was also constrained by the brief follow-up period and limited sample size.

In conclusion, the combination of atezolizumab with split-dose cisplatin/gemcitabine provided encouraging and durable response rates that did not result in a significant improvement in OS among patients with mUC deemed ineligible for full-dose cisplatin.

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DISCLAIMER

The funder did not have a role in designing or conducting the study, and was not involved in the analysis and interpretation of study results.

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Deidentified data (patient characteristics and outcome) will be made available to other researchers on request to the corresponding author, subject to the approval of the Sponsor. Requests need a formal data sharing agreement that describes the conditions for release and requirements for data transfer, storage, archiving, publication, and intellectual property. Requests are reviewed by the sponsor to ensure their scientific merit and ethical considerations including patient consent. The ethics committee that initially approved the trial should also approve any data transfer not covered by already collected informed consent forms and might request new evaluation or reconsent.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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