COSMIC-021 Phase Ib Study of Cabozantinib Plus Atezolizumab: Results from the Locally Advanced or Metastatic Urothelial Carcinoma Cohorts

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ABSTRACT

PURPOSE The COSMIC-021 study assessed the safety and efficacy of cabozantinib plus atezolizumab in advanced solid tumors. Presented here are results from the expansion cohorts with advanced urothelial carcinoma (UC).

METHODS This phase Ib study (ClinicalTrials.gov identifier: NCT03170960) enrolled patients with inoperable locally advanced/metastatic UC into four tumor cohorts: first-line cisplatin-eligible (cis-eligible), first-line cisplatin-ineligible (cis-ineligible), previous platinum-containing chemotherapy (previous chemotherapy-treated), and previous immune checkpoint inhibitor (ICI)–treated. Patients received oral cabozantinib 40 mg once daily and intravenous atezolizumab 1,200 mg once every 3 weeks. The primary end point was objective response rate (ORR), as assessed by the investigator per RECIST v1.1 every 6 weeks for 12 months and every 12 weeks thereafter; the secondary end point was safety.

RESULTS A total of 121 patients (previous ICI-treated cohort, n = 31, and each of the other cohorts, n = 30) received study treatment from March 2018 to November 2021. The ORR (95% CI) was 30% (15 to 49) for cis-eligible, 20% (8 to 39) for cis-ineligible, 27% (12 to 46) for previous chemotherapy-treated, and 10% (2 to 26) for previous ICI-treated cohorts. The median progression-free survival (95% CI) was 5.5 (1.6 to 11.6), 5.6 (3.1 to 11.1), 5.4 (1.6 to 7.6), and 3.0 (1.8 to 5.5) months, respectively. Grade 3 or 4 treatment-related adverse events (TRAEs) were experienced by 43%, 67%, 57%, and 45% of patients, respectively. TRAEs led to discontinuation of all treatment components in 17%, 13%, 3%, and 19%, respectively. No grade 5 TRAEs were reported in any cohort.

CONCLUSION The novel combination of cabozantinib plus atezolizumab exhibited clinical activity in advanced UC that is cis-eligible, cis-ineligible, or previously treated with platinum-containing chemotherapy; clinical activity in previous ICI-treated UC was modest. The toxicity profile was consistent with that previously reported for the combination.

ACCOMPANYING CONTENT

Data Sharing Statement

Data Supplement

Protocol

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INTRODUCTION

Standard-of-care first-line therapy for advanced urothelial carcinoma (UC) is pembrolizumab plus enfortumab vedotin regardless of cisplatin eligibility.[1] Other options include gemcitabine and cisplatin combined with nivolumab as first-line therapy and avelumab switch maintenance therapy after no progression on or during platinum-based chemotherapy.[2-5] Second-line treatments include nivolumab monotherapy or pembrolizumab alone or combined with enfortumab vedotin for those who did not receive an immune checkpoint inhibitor (ICI) in first line and had cancer progression.[1,3,6] Subsequent therapies also include chemotherapy, immunotherapies, antibody-drug conjugates, and fibroblast growth factor receptor (FGFR)-2 or FGFR-3 inhibitors depending on previous treatments combined.[6-9] Despite advances in treatment, clinical outcomes for metastatic disease remain poor, with a 5-year survival rate of 8%.[10]

CONTEXT

Key Objective

The COSMIC-021 phase Ib study evaluated cabozantinib plus atezolizumab in four cohorts of patients with advanced urothelial carcinoma (UC): cisplatin-eligible, cisplatin-ineligible, previous chemotherapy-treated, and previous immune checkpoint inhibitor (ICI)–treated.

Knowledge Generated

The combination showed clinical activity across the cohorts with objective response rates (primary end point) ranging from 10% to 30%. The median progression-free survival (PFS) ranged from 3.0 to 5.6 months. The adverse event profile was consistent with that previously reported for this combination. Patients with low C-reactive protein or a high cancer-associated fibroblast signature score had relatively greater PFS and overall survival.

Relevance *(G.K. Schwartz)*

The COSMIC-021 study supports the further development of ICI-tyrosine kinase inhibitor trials in patients with advanced UC, especially among patients who are ICI-naive.*

*Relevance section written by *JCO* Associate Editor Gary K. Schwartz, MD, FASCO.

Single-agent atezolizumab, an anti–PD-L1 antibody, has shown efficacy and is approved for the treatment of non–small cell lung cancer; however, its benefits were limited in advanced UC.[11,12] Cabozantinib inhibits multiple receptor tyrosine kinases involved in tumor growth, angiogenesis, and immunosuppression, including MET, VEGFR, and the TAM kinases (TYRO3, AXL, and MER).[13] It promotes an immune-permissive environment that may enhance the response to ICIs[14] and has demonstrated clinical activity in combination with nivolumab or atezolizumab in various solid tumors.[15-18] Thus, we hypothesized that cabozantinib plus atezolizumab may be efficacious in UC.

The phase Ib COSMIC-021 study evaluated cabozantinib plus atezolizumab in patients with advanced solid tumors. Presented are outcomes for patients with advanced UC who were enrolled into four expansion cohorts: first-line cisplatin-eligible (cis-eligible), first-line cisplatin-ineligible (cis-ineligible), previous treatment with platinum-containing chemotherapy (previous chemotherapy-treated), and previous treatment with ICI (previous ICI-treated).

METHODS

Study Design

COSMIC-021 is a multicenter, open-label, phase Ib study with a dose-escalation stage followed by tumor-specific expansion stages. Oral cabozantinib 40 mg once daily plus atezolizumab 1,200 mg intravenous (IV) infusions once every 3 weeks was administered to expansion cohorts including UC cohorts on the basis of clinical activity and a more favorable safety profile compared with oral cabozantinib 60 mg once daily plus atezolizumab 1,200 mg IV once every 3 weeks observed during dose escalation.[18,19]

Patients in UC expansion cohorts were enrolled across 16 centers in Europe, Australia, and the United States. Eligible patients were 18 years and over, had inoperable locally advanced/metastatic UC, Eastern Cooperative Oncology Group performance status 0-1, and measurable disease per RECIST v1.1.[20]

Patients in the cis-eligible and cis-ineligible cohorts had no previous systemic therapy for locally advanced/metastatic disease. Previous neoadjuvant or adjuvant platinum-based chemotherapy was permitted if disease recurrence took place >12 months from the end of last therapy. Cisplatin ineligibility was determined according to established criteria.[21] Patients enrolled in the previous chemotherapy-treated cohort had radiographically progressed on/after platinum-based chemotherapy, including those with recurrence <12 months after last platinum-based adjuvant/neoadjuvant chemotherapy. Patients in the previous ICI-treated cohort radiographically progressed on/after one previous anti–PD-(L)1 therapy for advanced disease, with two or fewer lines of previous systemic therapy for advanced disease. Previous combination treatment with VEGFR tyrosine kinase inhibitor plus ICI was not allowed.

COSMIC-021 adhered to the Guideline for Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by institutional review boards at participating sites. All patients provided written informed consent. The study is registered with ClinicalTrials.gov (identifier: NCT03170960).

Procedures and Assessments

Patients received oral cabozantinib 40 mg once daily and atezolizumab 1,200 mg IV once every 3 weeks. Treatment beyond radiographic progression was allowed if there was clinical benefit per the investigator. Cabozantinib could be dose-reduced or held to manage adverse events (AEs); atezolizumab could be delayed.

Tumor assessments by computed tomography/magnetic resonance imaging were conducted at screening, every 6 weeks for the first 12 months, and every 12 weeks thereafter. AEs were graded by investigators per the National Cancer Institute's Common Terminology Criteria for Adverse Events, v4.0.

End Points

The primary end point was investigator-assessed objective response rate (ORR), defined as proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1. The secondary end point was safety, including AEs of special interest (AESI) defined as potential immune-related AEs for atezolizumab provided by the sponsor and summarized as grouped Medical Dictionary for Regulatory Activities terms irrespective of causality. Exploratory end points included duration of response (DOR), progression-free survival (PFS), disease control rate (DCR; percentage of patients with a CR, PR, or stable disease [SD] as best response) per investigator and RECIST v1.1, and overall survival (OS).

Biomarker Assessments

Immunohistochemistry (IHC) with formalin-fixed paraffin-embedded (FFPE) tissues was performed at Labcorp (Morrisville, NC, and Los Angeles, CA) for PD-L1 to determine combined positive score (CPS) and tumor proportion score (TPS) by clone SP263. H-score or density was determined for biomarker analyses using specific antibodies for AXL (clone C89E7), CD8 (clone SP57), C-MET (clone SP44), VEGFR-2 (clone 55B11), and CD31 (clone JC70).

Blood was collected before the first dose (day 1 of treatment), and plasma was prepared. C-reactive protein (CRP) levels from plasma were determined by enzyme-linked immunosorbent assay (ELISA), developed by AssayGate and on the basis of DuoSet ELISA kits of R&D systems, Minneapolis, MN, and tested by AssayGate, Ijamsville, MD.

FFPE tumor tissue was analyzed by IHC, and patient-matched blood samples were used for whole-exome sequencing and RNA sequencing. For details on sample preparation and sequencing, see the Data Supplement (online only). Immune subsets were determined per the study by Wang et al,[22] X-cell,[23] the study by McDermott et al,[24] and MCP-counter.[25] Molecular subtypes were determined by k-means clustering[26] and single sample classifier consensus classes.[27]

Clinical Data Statistical Analysis

No prespecified target ORR and statistical comparisons between cohorts were planned. Time-to-event end points and associated 95% CIs were estimated using the Kaplan-Meier method. Follow-up duration was calculated using the following formula: (cutoff date – treatment initiation date + 1) ÷ 30.4375. Statistical analyses were performed using SAS software (v9.4, SAS Institute Inc, Cary, NC). Statistical analyses of biomarker data are described in the Data Supplement.

RESULTS

Patients

From March 2018 to November 2021, 31 patients in the previous ICI-treated cohort and 30 patients each in the cis-eligible, cis-ineligible, and previous chemotherapy cohorts were enrolled (Fig 1). Most patients had metastatic disease and a Bellmunt risk score of ≥1 (Table 1).[28] The responses to previous ICI in the previous ICI-treated cohort were low (best overall response to previous ICI: one [3%] CR, two [6%] PR, 14 [45%] SD, and 11 [35%] progressive disease [PD], with three [10%] unknown).

The median follow-up (range) was 22.2 months (10.5-45.1) for cis-eligible, 31.0 months (18.3-46.9) for cis-ineligible, 42.6 months (38.1-46.7) for previous chemotherapy-treated, and 36.0 months (26.1-44.3) for previous ICI-treated patients. Four patients in the cis-eligible cohort and one each in the other three cohorts were on study treatment at last follow-up. The most common reason for study discontinuation was disease progression (40%-60%; Fig 1).

Clinical Activity

In the cis-eligible cohort, the ORR was 30% (95% CI, 15 to 49) and the DCR was 63% (Table 2). The median time to response (TTR) was 2.9 months, and the median DOR was 23.5 months (95% CI, 7.2 to not estimable [NE]). One of four patients continuing treatment had an ongoing CR with a DOR of 25 months (Data Supplement, Fig S1). Any reduction in sum of target lesion diameters was observed in 57% (17 of 30) of evaluable patients (Fig 2). The median PFS was 5.5 months (95% CI, 1.6 to 11.6), and the median OS was 15.1 months (95% CI, 8.0 to 23.2; Fig 3).

In the cis-ineligible cohort, the ORR was 20% (95% CI, 8 to 39) and the DCR was 80% (Table 2). The median TTR was 1.4 months, and the median DOR was 7.1 months (95% CI, 2.8 to NE). The one patient still receiving treatment had an ongoing CR with a DOR of 22 months (Data Supplement, Fig S1). Any reduction in sum of target lesion diameters

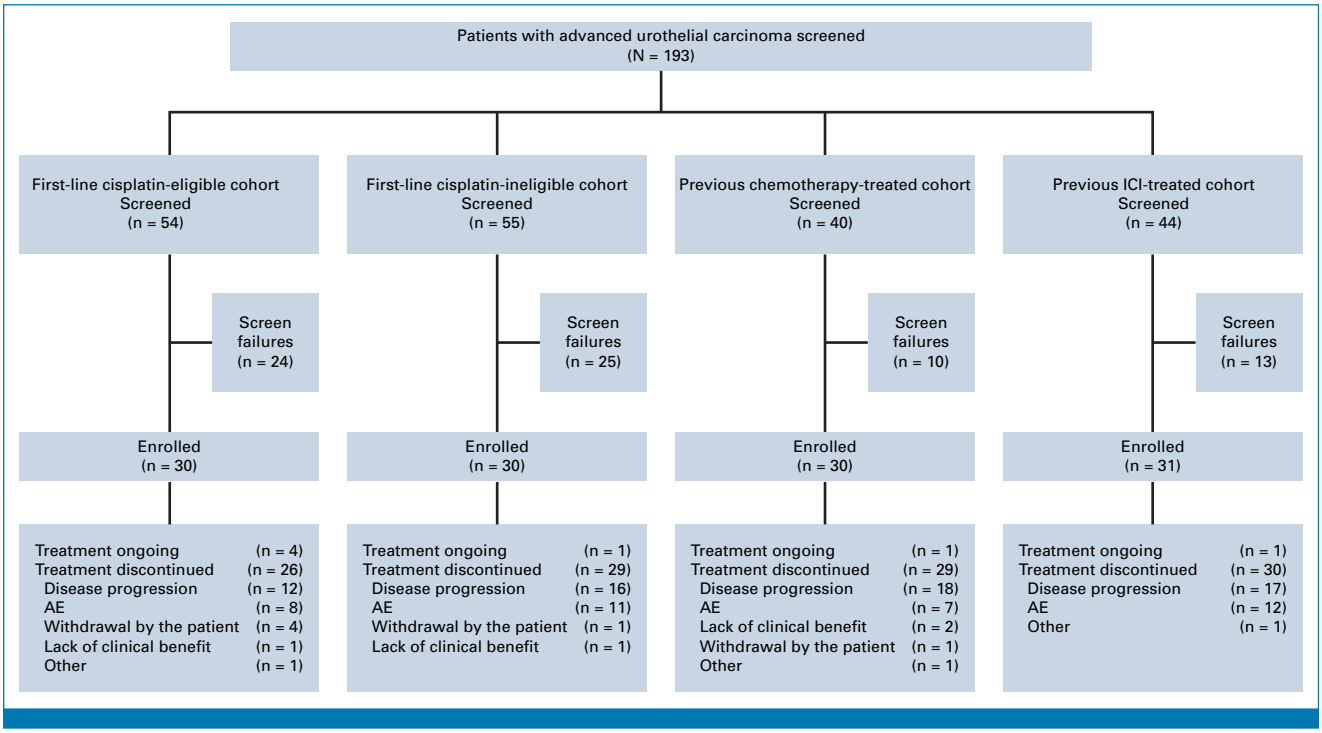

FIG 1. Flow diagram. AE, adverse event; ICI, immune checkpoint inhibitor.

occurred in 74% (20 of 27) of evaluable patients (Fig 2). The median PFS was 5.6 months (95% CI, 3.1 to 11.1), and the median OS was 15.9 months (95% CI, 8.6 to 35.9; Fig 3).

In the previous chemotherapy-treated cohort, the ORR was 27% (95% CI, 12 to 46) and the DCR was 63% (Table 2). The median TTR was 3.0 months, and the median DOR was 15.3 months (95% CI, 2.9 to NE). The one patient still receiving treatment had an ongoing CR with a DOR of 32 months (Data Supplement, Fig S1). Regression of target lesions occurred in 53% (16 of 30) of evaluable patients (Fig 2). The median PFS was 5.4 months (95% CI, 1.6 to 7.6), and the median OS was 10.3 months (95% CI, 3.3 to 12.8; Fig 3).

In the previous ICI-treated cohort, the ORR was 10% (95% CI, 2 to 26) and the DCR was 61% (Table 2). The median TTR was 5.5 months, and the median DOR was 4.1 months (95% CI, 2.6 to NE). The one patient still receiving treatment had an ongoing PR with a DOR of 17 months (Data Supplement, Fig S1). Regression of target lesions occurred in 55% (17 of 31) of evaluable patients (Fig 2). The median PFS was 3.0 months (95% CI, 1.8 to 5.5), and the median OS was 8.2 months (95% CI, 5.5 to 9.8; Fig 3).

Treatment Exposure and Safety

The median duration of treatment (range) was 4.2 months (0.5-45.1) for cis-eligible, 5.3 months (0.7-29.9) for cis-ineligible, 4.3 months (0.6-38.7) for previous chemotherapy-treated, and 2.8 months (0.3-33.3) for previous ICI-treated patients. Cabozantinib dose reductions because of treatment-emergent AEs (TEAEs) were required in 27%-43% of patients (Data Supplement, Table S1); the median (range) average once daily oral cabozantinib doses were 28.2 mg (6-40), 30.1 mg (1-40), 22.3 mg (7-40), and 25.4 mg (11-40), respectively. Atezolizumab dose delays because of TEAEs occurred in 40%-63% of patients (Data Supplement, Table S1).

Treatment-related AEs (TRAEs) of any grade occurred in ≥90% of patients in all cohorts, with 43%-67% experiencing grade 3/4 TRAEs (Table 3). The most common any-grade TRAEs across cohorts were diarrhea (range, 30%-43%), decreased appetite (23%-39%), and fatigue (13%-48%). TRAEs leading to discontinuation of both drugs occurred in 3%-19% of patients (Data Supplement, Table S1). There were no grade 5 TRAEs. Any-grade immune-related AESIs, irrespective of causality, were experienced by 52%-87%; grade 3/4 AESIs occurred in 20%-30% (Data Supplement, Table S2).

Correlative Biomarker Analysis

Biomarker analyses included all cohorts except for the previous ICI-treated cohort (unless noted) because of the distinct biology of previous ICI-treated tumors, and data were analyzed together regardless of the cohort. TMB data were available for 44 patients across the three cohorts (12 previous chemotherapy-treated, 18 cis-ineligible, 14 cis-eligible) and showed no association with TMB in responders versus nonresponders (Fig 4A). In patients with TMB ≥median versus <median, there was no statistically significant difference in PFS or OS (Figs 4B and 4C). Among patients with

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristic	Cis-Eligible (n = 30)	Cis-Ineligible[a,b] (n = 30)	Received Previous Chemotherapy (n = 30)	Received Previous ICI (n = 31)
Age, years, median (range)	66 (49-87)	74 (55-93)	66 (44-84)	68 (46-81)
Male, No. (%)	22 (73)	20 (67)	22 (73)	17 (55)
Race, No. (%)				
White	16 (53)	25 (83)	24 (80)	23 (74)
Other	4 (13)	2 (7)	0	0
Not reported	10 (33)	3 (10)	6 (20)	8 (26)
ECOG PS, No. (%)				
0	13 (43)	10 (33)	12 (40)	8 (26)
1	17 (57)	19 (63)	18 (60)	23 (74)
Smoking history, No. (%)				
Current	2 (7)	6 (20)	3 (10)	3 (10)
Former	19 (63)	13 (43)	17 (57)	14 (45)
Never	9 (30)	10 (33)	10 (33)	14 (45)
Histology, No. (%)				
Pure transitional cell type	20 (67)	20 (67)	12 (40)	23 (74)
Mixed cell type	6 (20)	6 (20)	13 (43)	4 (13)
Not reported	4 (13)	4 (13)	5 (17)	4 (13)
Disease stage, No. (%)				
Locally advanced	4 (13)	1 (3)	0	2 (6)
Recurrent	0	0	0	0
Metastatic	26 (87)	29 (97)	30 (100)	29 (94)
No. of tumor sites, No. (%)				
1	14 (47)	11 (37)	8 (27)	9 (29)
2	3 (10)	10 (33)	7 (23)	8 (26)
≥3	13 (43)	9 (30)	15 (50)	14 (45)
Sites of the primary tumor, No. (%)				
Bladder	21 (70)	20 (67)	23 (77)	22 (71)
Renal pelvis	4 (13)	4 (13)	4 (13)	4 (13)
Ureter	4 (13)	6 (20)	3 (10)	5 (16)
Urethra	1 (3)	0	0	0
Metastatic tumor sites, No. (%)				
Lung	12 (40)	10 (33)	13 (43)	18 (58)
Liver	6 (20)	5 (17)	8 (27)	7 (23)
Bone	9 (30)	8 (27)	6 (20)	10 (32)
Lymph node	14 (47)	17 (57)	23 (77)	19 (61)

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TABLE 1. Baseline Demographics and Clinical Characteristics (continued)

Characteristic	Cis-Eligible (n = 30)	Cis-Ineligible[a,b] (n = 30)	Received Previous Chemotherapy (n = 30)	Received Previous ICI (n = 31)
Bellmunt risk score, No. (%)				
0	12 (40)	9 (30)	8 (27)	5 (16)
1	9 (30)	16 (53)	11 (37)	17 (55)
2	9 (30)	4 (13)	8 (27)	7 (23)
3	0	0	3 (10)	2 (6)
Received previous systemic therapy in any setting, No. (%)	6 (20)	6 (20)	30 (100)	31 (100)
Previous lines of systemic therapy in any setting, %				
0	0	0	0	0
1	0	0	43	32
2	0	0	20	65
≥3	0	0	3	3
Missing	20	20	33	0
Received previous chemotherapy for locally advanced or metastatic disease, No. (%)	0	0	20 (67)	20 (65)
Received previous PD-1/PD-L1 ICI for locally advanced or metastatic disease, No. (%)	0	0	0	31 (100)
Time from most recent systemic therapy to enrollment, weeks, median (range)	12 (8-15)	8 (4-31)	6 (1-37)	6 (2-421)
Previous radiation therapy, No. (%)	4 (13)	6 (20)	9 (30)	13 (42)
Previous cystectomy, No. (%)	8 (27)	6 (20)	9 (30)	10 (32)

Abbreviations: cis, cisplatin; dB, decibel; ECOG PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; NCI-CTCAE, National Cancer Institute's Common Terminology Criteria for Adverse Events.

[a]Cis-ineligibility because of glomerular filtration rate <60 mL/min/1.73 m^2, hearing loss ≥25 dB at two contiguous frequencies, and grade ≥2 peripheral neuropathy per NCI-CTCAE.

[b]In the cis-ineligible cohort, n = 1 missing data each for ECOG PS, smoking history, and Bellmunt risk score.

TABLE 2. Tumor Response per Investigator per RECIST v1.1

Clinical Outcome	Cis-Eligible[a] (n = 30)	Cis-Ineligible (n = 30)	Received Previous Chemotherapy (n = 30)	Received Previous ICI (n = 31)
ORR, % (95% CI)	30 (15 to 49)	20 (8 to 39)	27 (12 to 46)	10 (2 to 26)
Best overall response, No. (%)				
CR	2 (7)	1 (3)	3 (10)	0
PR	7 (23)	5 (17)	5 (17)	3 (10)
SD	10 (33)	18 (60)	11 (37)	16 (52)
PD	7 (23)	3 (10)	7 (23)	8 (26)
Not evaluable	1 (3)	0	0	0
No postbaseline assessments	2 (7)	3 (10)	4 (13)	4 (13)
Disease control rate, % (95% CI)	63 (44 to 80)	80 (61 to 92)	63 (44 to 80)	61 (42 to 78)
TTR, months, median (range)	2.9 (1.3-13.7)	1.4 (1.2-9.5)	3.0 (1.2-5.9)	5.5 (2.7-11.3)
DOR, months, median (95% CI)	23.5 (7.2 to NE)	7.1 (2.8 to NE)	15.3 (2.9 to NE)	4.1 (2.6 to NE)
Patients with ongoing treatment at cutoff, No. (%)	4 (13)	1 (3)	1 (3)	1 (3)

Abbreviations: cis, cisplatin; CR, complete response; DOR, duration of response; ICI, immune checkpoint inhibitor; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.
[a]One patient in the cis-eligible cohort is missing the best overall response because no assessments met the minimum SD criteria.

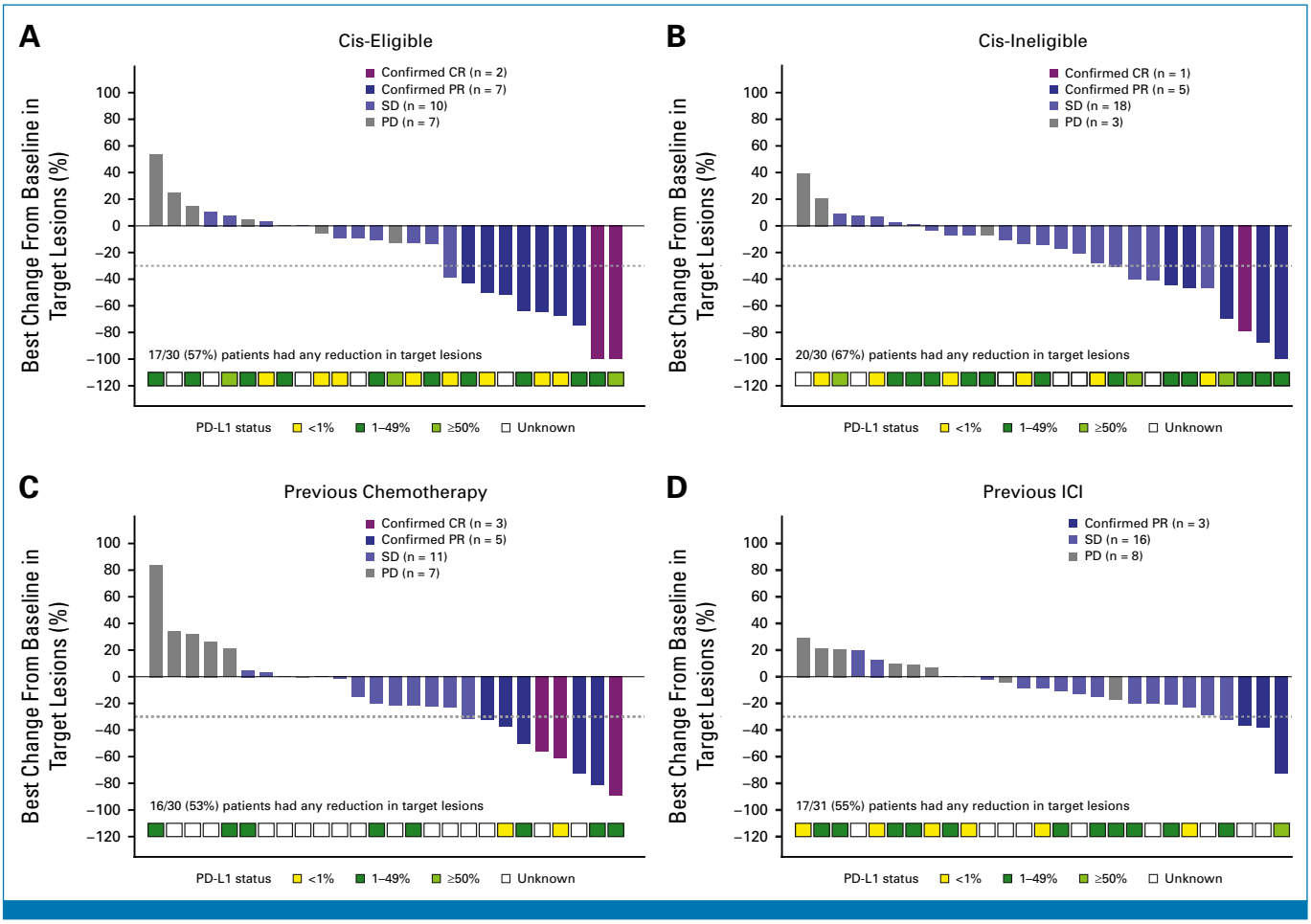

FIG 2. Best change from baseline in the sum of diameters of tumor lesions in patients with UC receiving cabozantinib plus atezolizumab who (A) are cis-eligible, (B) are cis-ineligible, (C) received previous chemotherapy, and (D) received previous ICI. Only patients with at least one measurable baseline and postbaseline assessment are shown; the percentages of patients with any reduction are based on the overall safety population. Confirmed CR and PR are shown. cis, cisplatin; CR, complete response; ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease; UC, urothelial carcinoma.

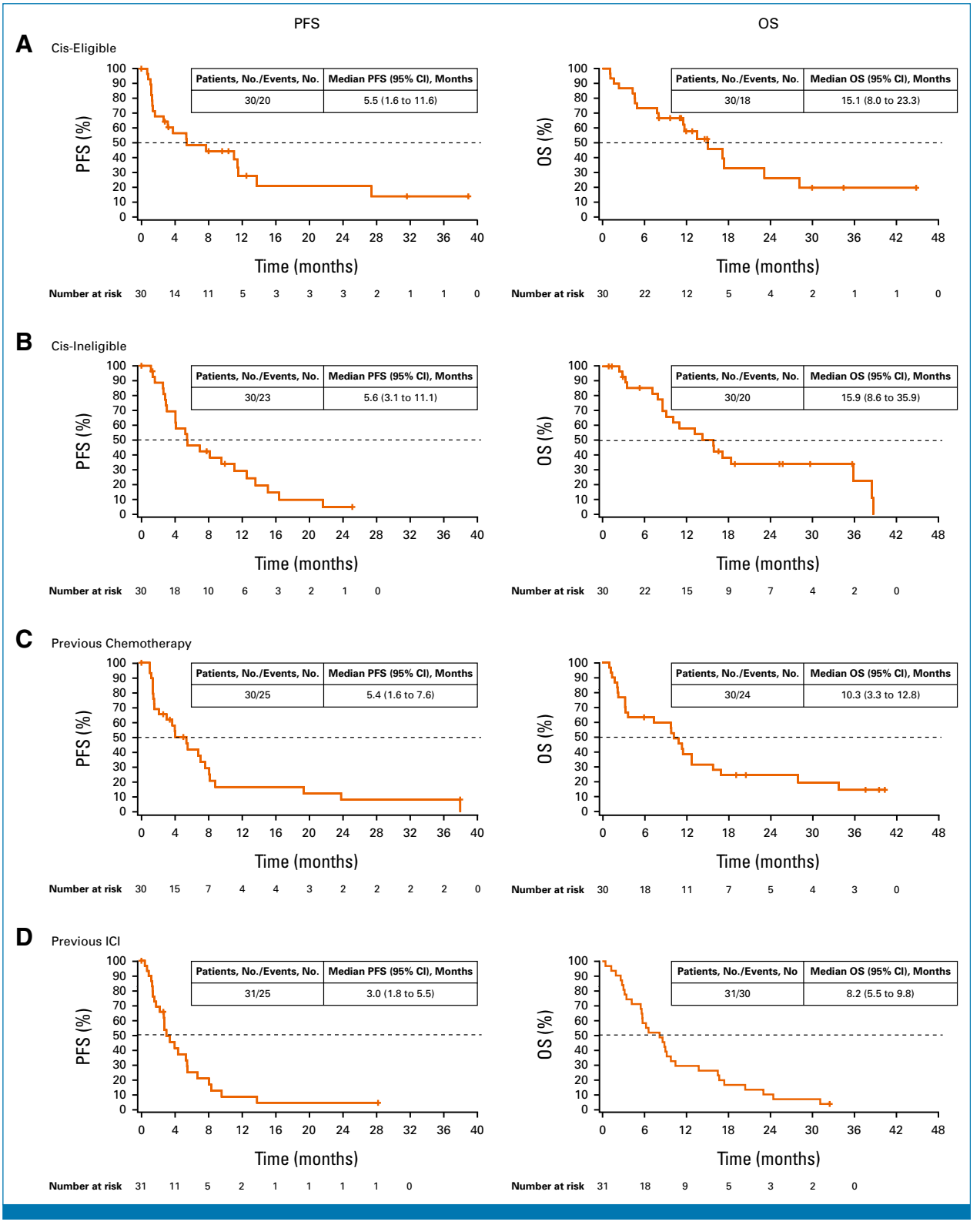

FIG 3. PFS and OS for patients with UC receiving cabozantinib plus atezolizumab who (A) are cis-eligible, (B) are cis-ineligible, (C) received previous chemotherapy, and (D) received previous ICI. cis, cisplatin; ICI, immune checkpoint inhibitor; OS, overall survival; PFS, progression-free survival; UC, urothelial carcinoma.

TABLE 3. Treatment-Related AEs in ≥20% of Patients in Any Cohort

	Cis-Eligible (n = 30), No. (%)		Cis-Ineligible (n = 30), No. (%)		Received Previous Chemotherapy (n = 30), No. (%)		Received Previous ICI (n = 31), No. (%)	
AE	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Any AE	28 (93)	13 (43)	29 (97)	20 (67)	27 (90)	17 (57)	28 (90)	14 (45)
Diarrhea	10 (33)	1 (3)	13 (43)	0	9 (30)	0	11 (35)	0
Decreased appetite	8 (27)	2 (7)	10 (33)	0	7 (23)	1 (3)	12 (39)	1 (3)
Fatigue	8 (27)	1 (3)	8 (27)	1 (3)	4 (13)	1 (3)	15 (48)	2 (6)
AST increased	6 (20)	2 (7)	12 (40)	1 (3)	2 (7)	1 (3)	6 (19)	0
PPE	6 (20)	0	6 (20)	0	4 (13)	0	3 (10)	0
Stomatitis	6 (20)	0	4 (13)	0	4 (13)	0	5 (16)	1 (3)
ALT increased	5 (17)	3 (10)	10 (33)	1 (3)	2 (7)	0	5 (16)	1 (3)
Nausea	5 (17)	0	8 (27)	0	4 (13)	0	8 (26)	0
Asthenia	3 (10)	0	6 (20)	1 (3)	11 (37)	1 (3)	5 (16)	1 (3)
Amylase increased	2 (7)	0	6 (20)	2 (7)	1 (3)	0	2 (6)	2 (6)
Hypertension	2 (7)	2 (7)	4 (13)	2 (7)	6 (20)	1 (3)	4 (13)	3 (10)
Mucosal inflammation	1 (3)	0	2 (7)	1 (3)	6 (20)	0	4 (13)	0
Transaminases increased	0	0	2 (7)	0	7 (23)	1 (3)	0	0

Abbreviations: AE, adverse event; cis, cisplatin; ICI, immune checkpoint inhibitor; PPE, palmar-plantar erythrodysesthesia.

evaluable tissue, six had a mutation in *FGFR3* with no mutations in *FGFR2*. Four patients with *FGFR3* mutations had SD as best response, and two had PD. PD-L1 TPS and CPS scores were not different between responders versus nonresponders (Figs 4D and 4E, respectively) and showed no clear relationship with TMB (Figs 4F and 4G, respectively). Notably, the one responder in the previous ICI-treated cohort had a PD-L1 score of 100% on the basis of TPS and CPS.

Available biomarker data for all cohorts except for ICI-treated were pooled to evaluate the association of outcomes with immune cell signatures. When corrected for multiple testing, there was no significant association of response or survival with any immune cell signature (Data Supplement, Fig S2A). Patients with a cancer-associated fibroblast (CAF) score (part of X-cell) >median (n = 19) had longer PFS (hazard ratio [HR], 0.60 [95% CI, 0.38 to 0.93]; P = .02) and OS (HR, 0.61 [95% CI, 0.39 to 0.97]; P = .04) compared with those with a score of ≤median (n = 20; Data Supplement, Figs S2B and S2D). The median PFS (HR, 0.65 [95% CI, 0.42 to 1.00]; P = .05) and OS (HR, 0.65 [95% CI, 0.42 to 1.02]; P = .06) were similar for patients with a stroma score (part of X-cell) >median (n = 19) versus ≤median (n = 20; Data Supplement, Figs S2C and S2E).

In a pooled analysis across the ICI-naïve cohorts, mean soluble blood CRP levels at baseline were lower in responders versus nonresponders (CR/PR *v* SD; P = .0009 and CR/PR *v* PD; P = .0029; Data Supplement, Fig S2F); patients with CRP levels >median (n = 44) had a shorter PFS (HR, 3.19 [95% CI, 1.91 to 5.33]; $P = 9.02 \times 10^{-6}$) and OS (HR, 4.92 [95% CI, 2.77 to 8.72]; $P = 5.2 \times 10^{-8}$) versus those with levels ≤median (n = 45; Data Supplement, Figs S2G and S2H). Four molecular subtypes by k-means[26] (Data Supplement, Figs S3A-S3C) and four molecular subtypes by single sample classifier consensus classes[27] were identified (Data Supplement, Figs S4A-S4C), but none of these molecular clusters were associated with response, PFS, or OS (Data Supplement, Figs S3D-S3F and Figs S4D-S4F). Finally, levels of tumor staining for AXL, CD8, C-MET, VEGFR-2, CD68, and tumor-associated vasculature density were not associated with PFS or OS (Data Supplement, Fig S5).

DISCUSSION

Cabozantinib plus atezolizumab demonstrated clinical activity in patients with advanced UC who were cis-eligible, cis-ineligible, or previously treated with chemotherapy; modest clinical activity was observed in previous ICI-treated patients. Safety with the combination was consistent with previous reports with no new safety signals detected.[16,17]

The frontline standard of care for locally advanced/metastatic untreated UC has been changed since the phase III EV-302/KEYNOTE A-39 study showed a significant improvement in OS with enfortumab vedotin and pembrolizumab versus gemcitabine plus cisplatin or carboplatin.[1] However, only a minority receive subsequent therapy on progression, underscoring the need for efficacious treatments with durable responses. Although ICI combination therapies showed clinical benefit versus chemotherapy in chemotherapy-eligible patients with advanced/metastatic UC, ICI monotherapy failed to show superiority over chemotherapy.[29] Similarly, therapies targeting angiogenesis primarily through the VEGF pathway have been unsuccessful as monotherapy or when

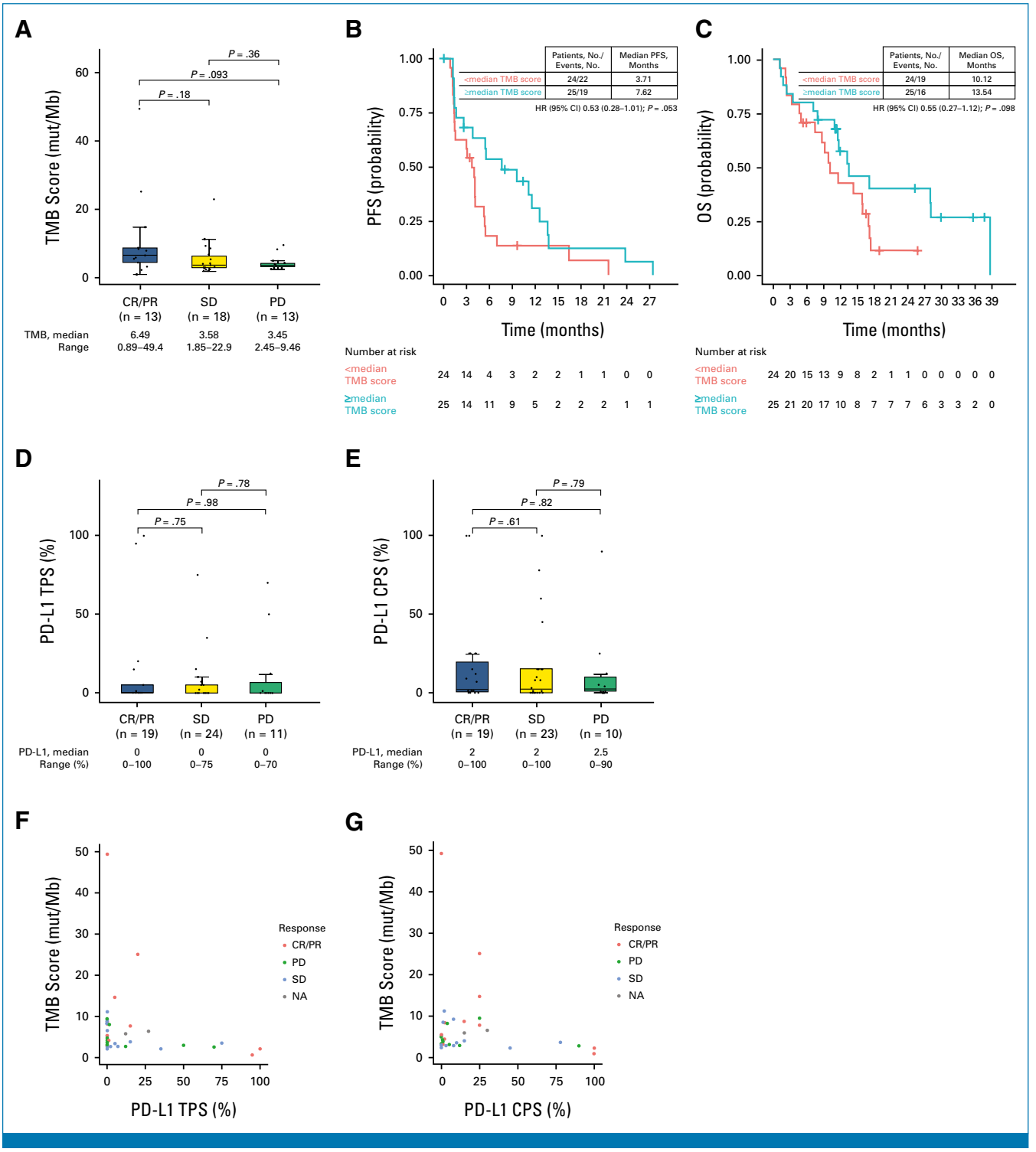

FIG 4. Association of TMB and PD-L1 scores with clinical outcomes in previous chemotherapy-treated, cis-ineligible, and cis-eligible cohorts of patients with UC receiving cabozantinib plus atezolizumab. Association of median TMB score with (A) response, (B) PFS, and (C) OS. Association of (D) median PD-L1 TPS and (E) median PD-L1 CPS with response. Correlation between TMB score and (F) PD-L1 TPS and (G) PD-L1 CPS. In (A), (D), and (E), the line inside the box represents the median, and lower and upper boundaries of the boxes represent the first and third quartiles, respectively; the whiskers extend from the first or third quartile to the most extreme values within 1.5 times the IQR of the quartiles. In (A), the significance of the difference between the medians of the groups was assessed using a Welch *t*-test. In (B) and (C), the association between survival and TMB grouping on the basis of the median was assessed using Cox proportional hazards regression. In (D) and (E), the significance of the difference between the medians of the groups was assessed using a Wilcoxon rank-sum test. (F) and (G) evaluate the relationship between TMB and PD-L1 expression on the basis of TPS and CPS scores, respectively. cis, cisplatin; CPS, combined positive score; CR, complete response; HR, hazard ratio; NA, not available; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TMB, tumor mutational burden; TPS, tumor proportion score; UC, urothelial carcinoma.

combined with chemotherapy for advanced UC because of the lack of clinical activity or concerns about toxicity.[30] Single-agent cabozantinib, which targets multiple receptor tyrosine kinases, including VEGFR, has also shown limited efficacy in advanced UC as maintenance therapy.[31] Cabozantinib plus atezolizumab was evaluated in the COSMIC-021 study because cabozantinib has been shown to promote an immune-permissive environment that may enhance response to ICIs and has shown efficacy in other tumors.[14,17,18] In the cis-eligible cohort of the COSMIC-021, although cabozantinib plus atezolizumab demonstrated clinical activity (ORR, 30%), the response rates were relatively low compared with those with enfortumab vedotin plus pembrolizumab (68%) or chemotherapy (46%-49%).[1,32] The median OS with cabozantinib plus atezolizumab was also low compared with that with enfortumab vedotin plus pembrolizumab (15.1 *v* 31.5 months), indicating that the combination is unfavorable compared with the standard of care in the front-line setting. The response rate with cabozantinib plus atezolizumab in the cis-eligible cohort (30%) was comparable with that with single-agent atezolizumab in the phase III IMvigor130 study (23%), suggesting that the combination has a limited additive effect.[12]

Up to 50% of patients with UC are cis-ineligible.[33] Non-cisplatin chemotherapy-based regimens have been the standard of care for these patients, but are associated with low DCRs and intolerability.[34,35] While efficacy outcomes were encouraging with cabozantinib plus atezolizumab, the ORR did not appear to be improved with the combination relative to chemotherapy (20% *v* 41%).[34]

Patients who experience disease progression on platinum-based chemotherapy generally receive pembrolizumab as subsequent therapy.[32] Single-agent atezolizumab did not significantly improve OS or ORR versus chemotherapy after platinum-based chemotherapy in the phase III IMvigor211 study.[36] Although efficacy outcomes of cabozantinib plus atezolizumab in the previous chemotherapy-treated cohort of COSMIC-021 are comparable with those of the single-agent atezolizumab and chemotherapy arms of IMvigor211, DOR was longer with cabozantinib plus atezolizumab (15.3 months) and with single-agent atezolizumab in IMvigor211 (21.7 months) versus chemotherapy in IMvigor 211 (7.4 months).[37]

At the time COSMIC-021 was initiated, prospective studies in previous ICI-treated patients were lacking. Generally, these patients were treated with platinum-based chemotherapy, but this was supported only by retrospective data,[38] highlighting the need for new treatments. In COSMIC-021, cabozantinib plus atezolizumab demonstrated only modest clinical activity in previous ICI-treated patients. Similarly, cabozantinib plus atezolizumab did not improve clinical outcomes in patients with advanced renal cell carcinoma who have disease progression on a previous ICI, suggesting that rechallenging with ICI-based therapies in genitourinary tumors shows limited benefits.[39]

Biomarker analyses were performed in the previous chemotherapy-treated, cis-ineligible, and cis-eligible cohorts. Increased PFS and OS were observed with lower CRP levels. Although CRP has been previously reported to be associated with outcomes, its clinical applications are yet to be elucidated.[40] Of the cell signatures evaluated, patients with a CAF score[23] >median had improved PFS and OS; CAFs are associated with immunosuppression in the tumor microenvironment, and these results indicate that patients with higher CAF scores may be more sensitive to the immunomodulatory properties of cabozantinib.[41,42] Interesting trends, such as an association of TMB and some immune signatures with certain efficacy outcomes, were also observed. Notably, improved outcomes were not observed with some established biomarkers of ICIs like PD-L1 expression.[43] The authors suspect that this results from small sample sizes and other challenges with PD-L1 staining, which have been widely described as opposed to the mechanism of action of the combination. Another limitation of the biomarker analysis was that patient cohorts were pooled; thus, known prognostic biomarkers such as treatment history might have had an impact on the results. Further investigation of these biomarkers in larger studies is warranted.

This study has several limitations, including a non-randomized study design, small expansion cohorts, and differences in baseline characteristics and median follow-up times among cohorts. Another limitation was the lack of data on previous ICI treatment, such as type, if it was used in a maintenance or refractory setting, and associated responses.

Our results for cabozantinib plus atezolizumab in ICI-naïve patients in COSMIC-021 support ongoing explorations of cabozantinib plus anti–PD-1/PD-L1 ICIs for UC. Cabozantinib plus durvalumab is being evaluated in previous platinum chemotherapy-treated advanced UC and non-UC variants in the phase II ARCADIA study (ClinicalTrials.gov identifier: NCT03824691); interim results showed preliminary activity.[44] Thus, further evaluation may inform the optimal use of cabozantinib-ICI combinations in advanced UC.

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REFERENCES

1. Powles T, Valderrama BP, Gupta S, et al: Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. N Engl J Med 390:875-888, 2024
2. Mansinho A, Cruz A, Marconi L, et al: Avelumab as first-line maintenance treatment in locally advanced or metastatic urothelial carcinoma. Adv Ther 40:4134-4150, 2023
3. Powles T, Bellmunt J, Comperat E, et al: ESMO Clinical Practice Guideline interim update on first-line therapy in advanced urothelial carcinoma. Ann Oncol 13:485-490, 2024
4. van der Heijden MS, Sonpavde G, Powles T, et al: Nivolumab plus gemcitabine–cisplatin in advanced urothelial carcinoma. N Engl J Med 389:1778-1789, 2023
5. Powles T, Park SE, Caserta C, et al: Avelumab first-line maintenance for advanced urothelial carcinoma: Results from the JAVELIN bladder 100 trial after ≥2 years of follow-up. J Clin Oncol 41: 3486-3492, 2023
6. Fradet Y, Bellmunt J, Vaughn DJ, et al: Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: Results of >2 years of follow-up. Ann Oncol 30:970-976, 2019
7. Loriot Y, Matsubara N, Park SH, et al: Erdafitinib or chemotherapy in advanced or metastatic urothelial carcinoma. N Engl J Med 389:1961-1971, 2023
8. Loriot Y, Petrylak DP, Rezazadeh Kalebasty A, et al: TROPHY-U-01, a phase II open-label study of sacituzumab govitecan in patients with metastatic urothelial carcinoma progressing after platinum-based chemotherapy and checkpoint inhibitors: Updated safety and efficacy outcomes. Ann Oncol 35:392-401, 2024
9. Rosenberg JE, Powles T, Sonpavde GP, et al: EV-301 long-term outcomes: 24-month findings from the phase III trial of enfortumab vedotin versus chemotherapy in patients with previously treated advanced urothelial carcinoma. Ann Oncol 34:1047-1054, 2023
10. National Cancer Institute: Surveillance epidemiology and end results (SEER) program, cancer stat facts: Bladder cancer, 2018. https://seer.cancer.gov/statfacts/html/urinb.html
11. Balar AV, Galsky MD, Rosenberg JE, et al: Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: A single-arm, multicentre, phase 2 trial. Lancet 389:67-76, 2017
12. Galsky MD, Arija JAA, Bamias A, et al: Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): A multicentre, randomised, placebo-controlled phase 3 trial. Lancet 395:1547-1557, 2020
13. Yakes FM, Chen J, Tan J, et al: Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 10:2298-2308, 2011
14. Bergerot P, Lamb P, Wang E, et al: Cabozantinib in combination with immunotherapy for advanced renal cell carcinoma and urothelial carcinoma: Rationale and clinical evidence. Mol Cancer Ther 18:2185-2193, 2019
15. Choueiri TK, Powles T, Burotto M, et al: Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 384:829-841, 2021
16. Agarwal N, McGregor B, Maughan BL, et al: Cabozantinib in combination with atezolizumab in patients with metastatic castration-resistant prostate cancer: Results from an expansion cohort of a multicentre, open-label, phase 1b trial (COSMIC-021). Lancet Oncol 23:899-909, 2022
17. Kelley RK, Rimassa L, Cheng AL, et al: Cabozantinib plus atezolizumab versus sorafenib for advanced hepatocellular carcinoma (COSMIC-312): A multicentre, open-label, randomised, phase 3 trial. Lancet Oncol 23:995-1008, 2022
18. Pal SK, McGregor B, Suarez C, et al: Cabozantinib in combination with atezolizumab for advanced renal cell carcinoma: Results from the COSMIC-021 study. J Clin Oncol 39:3725-3736, 2021
19. Agarwal N, Vaishampayan U, Green M, et al: Phase Ib study (COSMIC-021) of cabozantinib in combination with atezolizumab: Results of the dose escalation stage in patients (pts) with treatment-naïve advanced renal cell carcinoma (RCC). Ann Oncol 29, 2018 (abstr 872P)
20. Eisenhauer EA, Therasse P, Bogaerts J, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45:228-247, 2009
21. Galsky MD, Hahn NM, Rosenberg J, et al: Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 29:2432-2438, 2011

22. Wang L, Sfakianos JP, Beaumont KG, et al: Myeloid cell-associated resistance to PD-1/PD-L1 blockade in urothelial cancer revealed through bulk and single-cell RNA sequencing. Clin Cancer Res 27:4287-4300, 2021
23. Aran D, Hu Z, Butte AJ: xCell: digitally portraying the tissue cellular heterogeneity landscape. Genome Biol 18:220, 2017
24. McDermott DF, Huseni MA, Atkins MB, et al: Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. Nat Med 24:749-757, 2018
25. Becht E, Giraldo NA, Lacroix L, et al: Estimating the population abundance of tissue-infiltrating immune and stromal cell populations using gene expression. Genome Biol 17:218, 2016
26. Guo CC, Bondaruk J, Yao H, et al: Assessment of luminal and basal phenotypes in bladder cancer. Sci Rep 10:9743, 2020
27. Kamoun A, de Reynies A, Allory Y, et al: A consensus molecular classification of muscle-invasive bladder cancer. Eur Urol 77:420-433, 2020
28. Bellmunt J, Choueiri TK, Fougeray R, et al: Prognostic factors in patients with advanced transitional cell carcinoma of the urothelial tract experiencing treatment failure with platinum-containing regimens. J Clin Oncol 28:1850-1855, 2010
29. Mori K, Pradere B, Moschini M, et al: First-line immune-checkpoint inhibitor combination therapy for chemotherapy-eligible patients with metastatic urothelial carcinoma: A systematic review and meta-analysis. Eur J Cancer 151:35-48, 2021
30. Torres-Jiménez J, Albarran-Fernandez V, Pozas J, et al: Novel tyrosine kinase targets in urothelial carcinoma. Int J Mol Sci 22:747, 2021
31. Jones RJ, Hussain SA, Birtle AJ, et al: A randomised, double blind, phase II clinical trial of maintenance cabozantinib following chemotherapy for metastatic urothelial carcinoma (mUC): Final analysis of the ATLANTIS cabozantinib comparison. J Clin Oncol 40, 2022 (suppl 17; abstr LBA4505)
32. von der Maase H, Hansen SW, Roberts JT, et al: Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: Results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068-3077, 2000
33. Hepp Z, Shah SN, Smoyer K, et al: Epidemiology and treatment patterns for locally advanced or metastatic urothelial carcinoma: A systematic literature review and gap analysis. J Manag Care Spec Pharm 27:240-255, 2021
34. De Santis M, Bellmunt J, Mead G, et al: Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 30:191-199, 2012
35. Malangone-Monaco E, Wilson K, Varker H, et al: A real-world study of chemotherapy treatment and costs in metastatic urothelial cancer (mUC) patients in the United States. J Clin Oncol 35, 2017 (suppl 15; abstr e16009)
36. van der Heijden MS, Loriot Y, Duran I, et al: Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: A long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. Eur Urol 80:7-11, 2021
37. Powles T, Duran I, van der Heijden MS, et al: Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma (IMvigor211): A multicentre, open-label, phase 3 randomised controlled trial. Lancet 391:748-757, 2018
38. Gomez de Liano Lista A, van Dijk N, de Velasco Oria de Rueda G, et al: Clinical outcome after progressing to frontline and second-line anti-PD-1/PD-L1 in advanced urothelial cancer. Eur Urol 77: 269-276, 2020
39. Pal SK, Albiges L, Tomczak P, et al: Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): A multicentre, randomised, open-label, phase 3 trial. Lancet 402:185-195, 2023
40. O'Brian D, Prunty M, Hill A, et al: The role of C-reactive protein in kidney, bladder, and prostate cancers. Front Immunol 12:721989, 2021
41. Duran I, Castellano D, Puente J, et al: Exploring the synergistic effects of cabozantinib and a programmed cell death protein 1 inhibitor in metastatic renal cell carcinoma with machine learning. Oncotarget 13:237-256, 2022
42. Zhang C, Fei Y, Wang H, et al: CAFs orchestrates tumor immune microenvironment—A new target in cancer therapy? Front Pharmacol 14:1113378, 2023
43. Eckstein M, Cimadamore A, Hartmann A, et al: PD-L1 assessment in urothelial carcinoma: A practical approach. Ann Transl Med 7:690, 2019
44. Giannatempo P, Guadalupi V, Marandino L, et al: Activity of cabozantinib (CABO) plus durvalumab (DURVA) in patients (pts) with advanced urothelial carcinoma (UC) or non-UC variant histologies (VH) after platinum chemotherapy: Interim results from the phase 2 ARCADIA trial. J Clin Oncol 41:4578, 2023

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COSMIC-021 Phase Ib Study of Cabozantinib Plus Atezolizumab: Results From the Locally Advanced or Metastatic Urothelial Carcinoma Cohorts

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