original reports

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

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abstract

PURPOSE Patients with metastatic urothelial carcinoma (mUC) who progress on platinum-based combination chemotherapy (PLT) and checkpoint inhibitors (CPIs) have limited options that offer objective response rates (ORRs) of approximately 10% with a median overall survival (OS) of 7-8 months. Sacituzumab govitecan (SG) is a TROP-2–directed antibody-drug conjugate with an SN-38 payload that has shown preliminary activity in mUC.

METHODS TROPHY-U-01 (ClinicalTrials.gov identifier: NCT03547973) is a multicohort, open-label, phase II, registrational study. Cohort 1 includes patients with locally advanced or unresectable or mUC who had progressed after prior PLT and CPI. Patients received SG 10 mg/kg on days 1 and 8 of 21-day cycles. The primary outcome was centrally reviewed ORR; secondary outcomes were progression-free survival, OS, duration of response, and safety.

RESULTS Cohort 1 included 113 patients (78% men; median age, 66 years; 66.4% visceral metastases; median of three [range, 1-8] prior therapies). At a median follow-up of 9.1 months, the ORR was 27% (31 of 113; 95% CI, 19.5 to 36.6); 77% had decrease in measurable disease. Median duration of response was 7.2 months (95% CI, 4.7 to 8.6 months), with median progression-free survival and OS of 5.4 months (95% CI, 3.5 to 7.2 months) and 10.9 months (95% CI, 9.0 to 13.8 months), respectively. Key grade ≥ 3 treatment-related adverse events included neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), and febrile neutropenia (10%), with 6% discontinuing treatment because of treatment-related adverse events.

CONCLUSION SG is an active drug with a manageable safety profile with most common toxicities of neutropenia and diarrhea. SG has notable efficacy compared with historical controls in pretreated mUC that has progressed on both prior PLT regimens and CPI. The results from this study supported accelerated approval of SG in this population.

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ASSOCIATED CONTENT

Appendix

Protocol

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

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INTRODUCTION

Patients with metastatic urothelial carcinoma (mUC) with disease progression after combination platinum-based chemotherapy and immune checkpoint inhibitors (CPIs) have limited treatment options.[1] Following progression, the only widely available agents indicated per NCCN and ESMO guidelines have been taxanes and vinflunine (approved in the European Union). These agents have response rates of approximately 10% with a median overall survival (OS) of 7-8 months.[2-7] The therapeutic landscape for mUC in the United States has been expanded by the accelerated US Food and Drug Administration (FDA) approvals of erdafitinib, a pan-fibroblast growth factor receptor inhibitor for patients with tumors harboring FGFR2- or FGFR3-activating mutation or fusion (following platinum-based chemotherapy), and enfortumab vedotin (EV), a nectin-4–directed antibody-drug conjugate (ADC) following platinum-based chemotherapy and CPI.[8-10] Although both EV and erdafitinib have objective response rates (ORRs) of approximately 40%, most patients progress on these therapies. Moreover, erdafitinib is limited to patients with FGFR2/3 mutation or fusion (15%-20% of patients depending on cancer type).[11] Hence, new agents are still needed.

Trophoblast cell surface antigen 2 (Trop-2) is a transmembrane glycoprotein that is highly expressed on the surface of most epithelial cancer cells.[12-16] Elevated Trop-2

CONTEXT

Key Objective

Patients with advanced or metastatic urothelial cancer (mUC) have limited treatment options after progression on platinum or checkpoint inhibitors (CPI). The TROPHY-U-01 study evaluated sacituzumab govitecan (SG), a trophoblast cell surface antigen 2–directed antibody-drug conjugate, in patients with locally advanced or unresectable or mUC who had progressed after prior platinum and CPI.

Knowledge Generated

Of 113 patients who received SG, central review confirmed an objective response rate (ORR) of 27% with six complete responses and 25 partial responses, confirming results from the prior phase I/II study demonstrating that SG is generally well tolerated and has significant anticancer activity in heavily pretreated patients with mUC who had progressed on platinum and CPI.

Relevance

The ORR of 27%, median duration of response of 7.2 months, and median overall survival of 10.9 months compare favorably with single-agent chemotherapy in this population, where ORR is approximately 10% and overall survival is 7 to 8 months.

expression is associated with poor prognosis for several cancer types, including mUC.[12-21] Trop-2 also plays a key role in cell transformation and proliferation.[18,22-24] Sacituzumab govitecan (SG) is a novel Trop-2–directed ADC composed of an anti–Trop-2 humanized monoclonal antibody hRS7 IgG1κ coupled to SN-38, the active metabolite of the topoisomerase 1 inhibitor irinotecan with a high drug-to-antibody ratio (7.6 molecules of SN-38 per antibody).[16,25] This coupling is achieved using a hydrolyzable, proprietary linker, CL2A, that permits a dual mechanism of action.[16,25-29] Internalization of Trop-2–bound SG delivers SN-38 inside tumor cells, thereby killing the tumor cells,[26] while the hydrolyzable linker enables SN-38 to be released into the tumor microenvironment, killing adjacent tumor cells (bystander effect).[16,27,28] The activity of SG, initially assessed in a phase I/II trial (IMMU-132-01; ClinicalTrials.gov identifier: NCT01631552) in patients with advanced epithelial cancers who had received at least one prior therapy for metastatic disease,[28,30] showed encouraging clinical activity across various solid tumors.[31] SG demonstrated clinical activity in patients with relapsed or refractory mUC (ORR, 31%), including a 27% ORR in patients with prior CPI and platinum therapy.[31,32] The TROPHY-U-01 phase II trial was designed to confirm this initial signal in patients with mUC. We hypothesized that SG would have significant antitumor activity, as measured by ORR, comparing favorably to historical controls of cytotoxic chemotherapy. Here, we report the primary results from the full cohort 1 of the TROPHY-U-01 study in patients with mUC who progressed after prior platinum-based and CPI-based therapies.

METHODS

Study Participants

TROPHY-U-01 is a phase II study assessing the activity of SG in patients with locally advanced unresectable or mUC (Appendix Fig A1, online only). In cohort 1, eligible patients included adults with histologically confirmed, locally advanced UC or mUC who had disease progression following a platinum-containing regimen and CPI therapy. Patients who recurred within 12 months after completion of platinum therapy in the neoadjuvant or adjuvant setting were considered refractory to platinum therapy and permitted to enroll if they progressed after subsequent CPI therapy. All patients also were required to have measurable disease by RECIST v1.1,[33] an Eastern Cooperative Oncology Group performance status of 0 to 1, adequate hepatic, renal, and hematologic function, and no known Gilbert syndrome. Patients must have recovered from all acute toxicities (except grade ≤ 2 neuropathy or alopecia) from prior therapy with a minimum washout period of 4 weeks from prior monoclonal antibody therapy and 2 weeks from prior chemotherapy, small-molecule therapy, or radiotherapy, and patients with treated, nonprogressive brain metastases were allowed to enroll. There was no requirement for tumor Trop-2 expression for enrollment (Appendix, online only).

Treatment

SG 10 mg/kg was administered intravenously on days 1 and 8 in a 21-day treatment cycle, until unacceptable toxicity, loss of clinical benefit, or withdrawal of consent. Hematopoietic growth factors or blood transfusions were allowed as clinically indicated. Pre-medication with a 2-drug antiemetic was recommended (followed by a 3-drug antiemetic for persistent nausea and vomiting), with premedication for infusion-related reactions and other supportive or palliative care recommended based on institution policy. The scheduled day 1 and day 8 infusions may have been delayed for up to 1 week for recovery of treatment-related toxicities with a maximum dose delay of 5 weeks permitted for any reason.

Assessments

For efficacy evaluations, computed tomography or magnetic resonance imaging scans were obtained at baseline

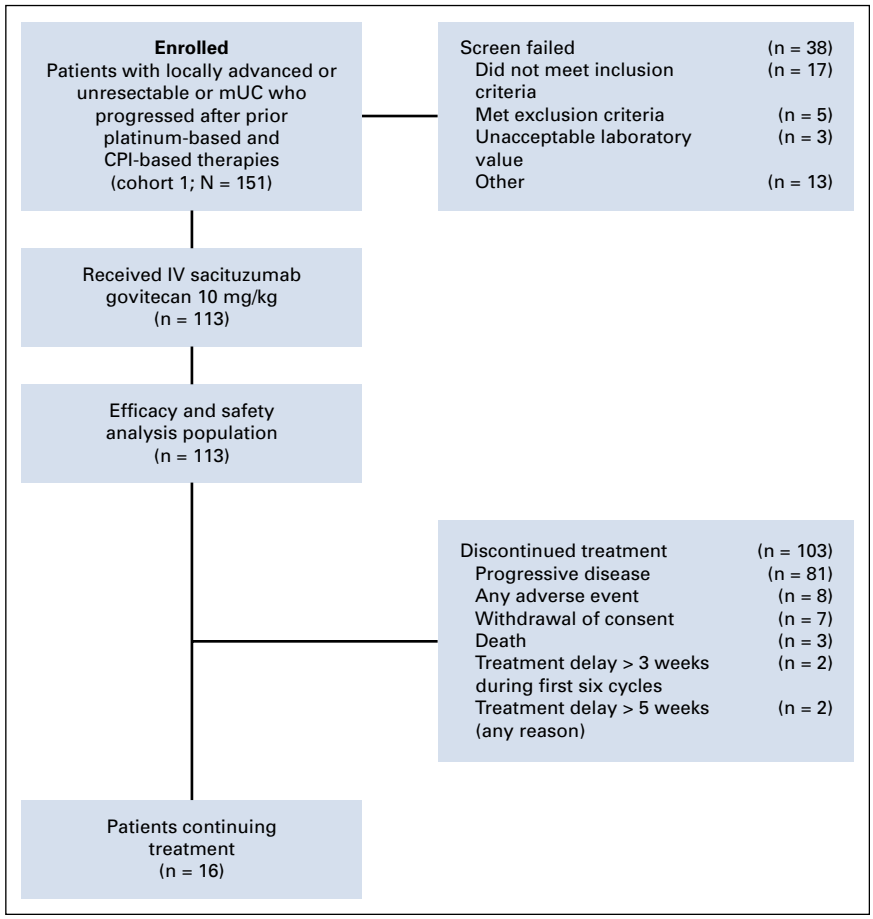

FIG 1. CONSORT diagram. CPI, checkpoint inhibitor; IV, intravenous; mUC, metastatic urothelial cancer.

and at 6-week intervals from the initiation of treatment until completion of 12 cycles of therapy, after which the interval could be lengthened to every 9 weeks. Confirmatory computed tomography or magnetic resonance imaging scans were to be obtained 4 to 6 weeks after first evidence of response. Response was evaluated by blinded independent central review (BICR) using RECIST v1.1.

Safety evaluations included adverse events (AEs), standard laboratory safety evaluations, physical examinations, and vital signs. AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0. Additional safety analyses examined the impact of *UGT1A1* genotype status on the incidence of AEs in evaluable patients.

End Points

The primary objective of this phase II study was to determine the ORR per BICR. Secondary objectives included assessments of duration of response (DOR) and progression-free survival (PFS), both centrally reviewed, investigator-assessed ORR, OS, and safety.

Trial Oversight

All patients provided written informed consent. The Protocol (online only) was approved by the institutional review boards or independent ethics committees at the participating institutions and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and other applicable local regulatory requirements and laws.

Statistical Analysis

Target enrollment was approximately 100 patients, based on a Simon two-stage design for 90% power to reject the null hypothesis of ORR $\leq$ 12%. A sample size of 100 provided sufficient power to ensure the lower boundary of the 95% CI calculated from the Clopper-Pearson exact method would exclude an ORR of $\leq$ 15%, assuming a 24% ORR (24 out of 100 responders). There was a preplanned interim analysis based on investigator assessment of data per RECIST v1.1 from cohort 1 after 35 response-evaluable patients were enrolled, with continued enrollment if four or more responses were observed. The initial stage demonstrated that 10 of 35 evaluable patients responded, which surpassed futility criteria to continue enrollment.[34] Final analysis was based on BICR assessment of data per RECIST v1.1 from cohort 1. ORR, defined as a best overall response of complete response (CR) or partial response (PR), was calculated with 95% CI estimated by the Clopper-Pearson method.[35] DOR, PFS, and OS were analyzed by

TABLE 1. Patient Demographics and Baseline Characteristics

Characteristic	N = 113
Age, median (range), years	66 (33-90)
≥ 75, No. (%)	26 (23)
Male, No. (%)	88 (78)
Race, No. (%)	
White	84 (74)
Black	3 (3)
Asian	3 (3)
Other	1 (1)
Not reported	22 (20)
ECOG PS, No. (%)	
0	32 (28)
1	81 (72)
Type of disease, No. (%)	
Metastatic urothelial cancer	108 (96)
Locally advanced unresectable	4 (3.5)
Missing	1 (0.09)
Visceral metastatic sites, No. (%)[a]	75 (66)
Lung	49 (43)
Liver	38 (34)
Other	15 (13)
Setting of prior systemic therapy, No. (%)	
Adjuvant	22 (19.5)
Metastatic	108 (95.6)
Neoadjuvant	36 (31.9)
Prior CPIs, No. %	112 (99)[b]
Prior platinum anticancer therapy, No. (%)	113 (100)
Cisplatin	89 (79)
Carboplatin	24 (21)
Prior enfortumab vedotin, No. (%)	10 (8.8)
Prior erdafitinib, No. (%)	2 (1.8)
Prior anticancer regimens, median, No. (range)	3.0 (1-8)
Median duration of last anticancer regimen, months (range)	2.8 (0-36)
Lines of prior metastatic regimens, No. (%)	
1	22 (20)
2	30 (27)
≥ 3	56 (50)
Median time since diagnosis of metastatic cancer, months (range)	24.1 (4-144)
Bellmunt risk factors[c], No. (%)	
0	18 (16)
1	54 (48)
2	32 (28)
3	9 (8)
UGT1A1 status, No. (%)	
Wild-type *1/*1	45 (39.8)
Heterozygous *1/*28	47 (41.6)
Homozygous *28/*28	13 (11.5)
Missing	8 (7.1)

Abbreviations: CPI, checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status.

[a]Sites identified based on target and nontarget lesions as identified and assessed by investigators and blinded independent central review at baseline.

[b]One patient was enrolled who did not have prior CPI.

[c]Risk factors are ECOG PS > 0, presence of liver metastases, and hemoglobin < 10 g/dL.

the Kaplan-Meier method with medians and corresponding 95% CIs determined according to the Brookmeyer and Crowley formula with log-log transformation. Descriptive statistics were used to characterize and present treatment-related AEs (TRAEs).

RESULTS

Study Participants

From August 2018 to November 2019, 113 patients were enrolled and treated in cohort 1 (Fig 1); these patients form the population for all analyses with a data cutoff of September 18, 2020. Patients were predominantly men (78%), with a median age of 66 years (range, 33-90 years) (Table 1). Visceral disease was present in 75 patients (66.4%) and 38 (33.6%) patients had liver metastases. Of the 113 patients enrolled, 112 previously received CPI therapy. Patients received a median of three prior anticancer regimens (range, 1-8), with 21% (n = 24) receiving combination chemotherapy with carboplatin or 79% (n = 89) with cisplatin. The majority (84%) had at least one adverse Bellmunt prognostic risk factor (including performance status, hemoglobin < 10 g/dL, and the presence of liver metastases).[36] Patients received a median of 6 cycles of SG (11 doses; range, 1-56 doses), with median treatment duration of 3.7 months (range, 0-20 months). The median relative dose intensity was 96.9% despite 31.0% requiring a single dose reduction. Only four (3.5%) patients required an infusion interruption. Most patients (n = 103) discontinued treatment, primarily because of cancer progression (n = 81) (Fig 1). As of the data cutoff date, 16 patients continued to receive study therapy.

Efficacy

Clinical activity (based on BICR) was observed with an ORR of 27.4% (31 of 113) (95% CI, 19.5 to 36.6; Table 2) including six confirmed CR (5.3%) and 25 confirmed PR (22.1%) in an intent-to-treat analysis. The clinical benefit rate (defined as CR plus PR plus stable disease ≥ 6 months)

was 37.2% (95% CI, 28.3 to 46.8; Table 2). Stable disease as best response was observed in 33.6% (38 of 113) of patients and 18.6% (21 of 113) had progressive disease as best response at data cutoff. SG showed efficacy in all evaluated subgroups, including patients with ≥ 2 prior lines of therapy, visceral and liver metastases at baseline, and by Bellmunt risk factor (Appendix Fig A2, online only). Interestingly, in the small subgroup of patients who received prior EV therapy (n = 10), three patients achieved PR, with 30% ORR (95% CI, 6.7 to 65.3). Of those three patients with PR, two had a best response of progressive disease with prior EV.

With a median follow-up duration of 9.1 months (range, 0-19.9 months), the median DOR was 7.2 months (95% CI, 4.7 to 8.6 months) (Table 2). The median time to objective response was 1.6 months (range, 1.2-5.5 months). Six (5.3%) patients achieved CR with DOR ranging from 1.4 to 13.7 months. A reduction in the size of target lesions was achieved by 77% (72 of 94) of patients with at least 1 post-baseline target lesion measurement by BICR (Fig 2A). The spider plot by BICR of best percent change from baseline in the sum of the diameters of the target lesions (Fig 2B) shows the reduction in the size of target lesions was durable in most patients, including many of those who did not have a documented confirmed response. The onset of response and DOR for responders (CR or PR) is summarized in the swimmer plot by BICR (Fig 2C), with 30 of 31 patients still alive at the time of data cutoff and four patients with ongoing response at the time of data cutoff. Median PFS was 5.4 months (95% CI, 3.5 to 7.2 months; range, 2.4-8.9 months), and median OS was 10.9 months (95% CI, 9.0 to 13.8 months; range, 3.8-19.8 months) (Fig 3).

TABLE 2. Summary of Treatment Efficacy

Variable	(N = 113)
Best response, No. (%)	
CR	6 (5)
PR	25 (22)
SD	38 (34)
PD	21 (19)
Not evaluable	8 (7)
Not assessed[a]	15 (13)
ORR	
No. of patients	31
% patients (95% CI)	27 (19 to 37)
CBR[b]	
No. of patients	42
% patients (95% CI)	37 (28 to 47)
Time to onset of response (months)	
Median	1.6
Range	1.2-2.9
Median DOR (months)	
Median	7.2
95% CI	4.7 to 8.6
Range	1.4-13.7

Abbreviations: AEs, adverse events; CBR, clinical benefit rate; CR, complete response; DOR, duration of response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]These patients had no post-baseline radiologic tumor assessments because of cancer progression or AEs because of progression (n = 11), AEs not related to disease progression (n = 2), lost to follow-up (n = 1), and withdrawal of consent before disease assessment (n = 1).

[b]CBR defined as CR + PR + SD ≥ 6 months.

Safety

Almost all patients (111 of 113; 98.2%) experienced at least 1 AE during the study, and 107 of 113 (94.7%) experienced a TRAE. The most common any-grade TRAEs that occurred in ≥ 20% of patients included diarrhea (65%), nausea (60%), fatigue (52%), alopecia (47%), neutropenia (46%), decreased appetite (36%), anemia (33%), vomiting (30%), and leukopenia (25%) (Table 3). These AEs were primarily managed with routine supportive care, including antidiarrheal, antiemetics, hydration, and growth factor support, and/or dose reduction or delay. There was a low rate of treatment-related skin rash (6%), maculopapular rash (7%), ocular disorders (4%), peripheral neuropathy (4%; grade ≤ 2), and hyperglycemia (< 1%; grade ≤ 2). About a third (39%) of patients had dose reduction because of TRAEs primarily for neutropenia, diarrhea, and fatigue. Dose interruption or delay because of TRAEs occurred in 45% of patients, most commonly because of neutropenia, leukopenia, and anemia. TRAEs led to discontinuations in 6% (n = 7) of patients primarily due to neutropenia or associated complications (ie, febrile neutropenia and sepsis).

Most common grade ≥ 3 TRAEs that occurred in ≥ 5% of patients included neutropenia (35%), leukopenia (18%), anemia (14%), diarrhea (10%), febrile neutropenia (10%), lymphopenia (7%), and urinary tract infection (6%) (Table 3). Notably, although treatment-related neutropenia of any grade occurred in almost half of the patients (46%), febrile neutropenia was relatively infrequent (n = 11; 10%). Neutropenia was managed through use of dose reductions or interruptions, while 30.1% of patients received growth factor support (18% received granulocyte colony-stimulating factor [G-CSF] in cycle 1 and the remainder received G-CSF in cycle 2 or later). Most cases of treatment-related diarrhea were grade 1 (n = 45; 40%), with 15% (n = 17) grade 2, 9% (n = 10) grade 3, and < 1% (n = 1) grade 4.

Grade ≥ 3 serious TRAEs that occurred in more than 1 patient included febrile neutropenia (n = 10), diarrhea (n = 4), urinary tract infection (n = 4), sepsis (n = 2), and thrombocytopenia (n = 2). A single case of grade 2 interstitial lung disease occurred in a 76-year-old woman with

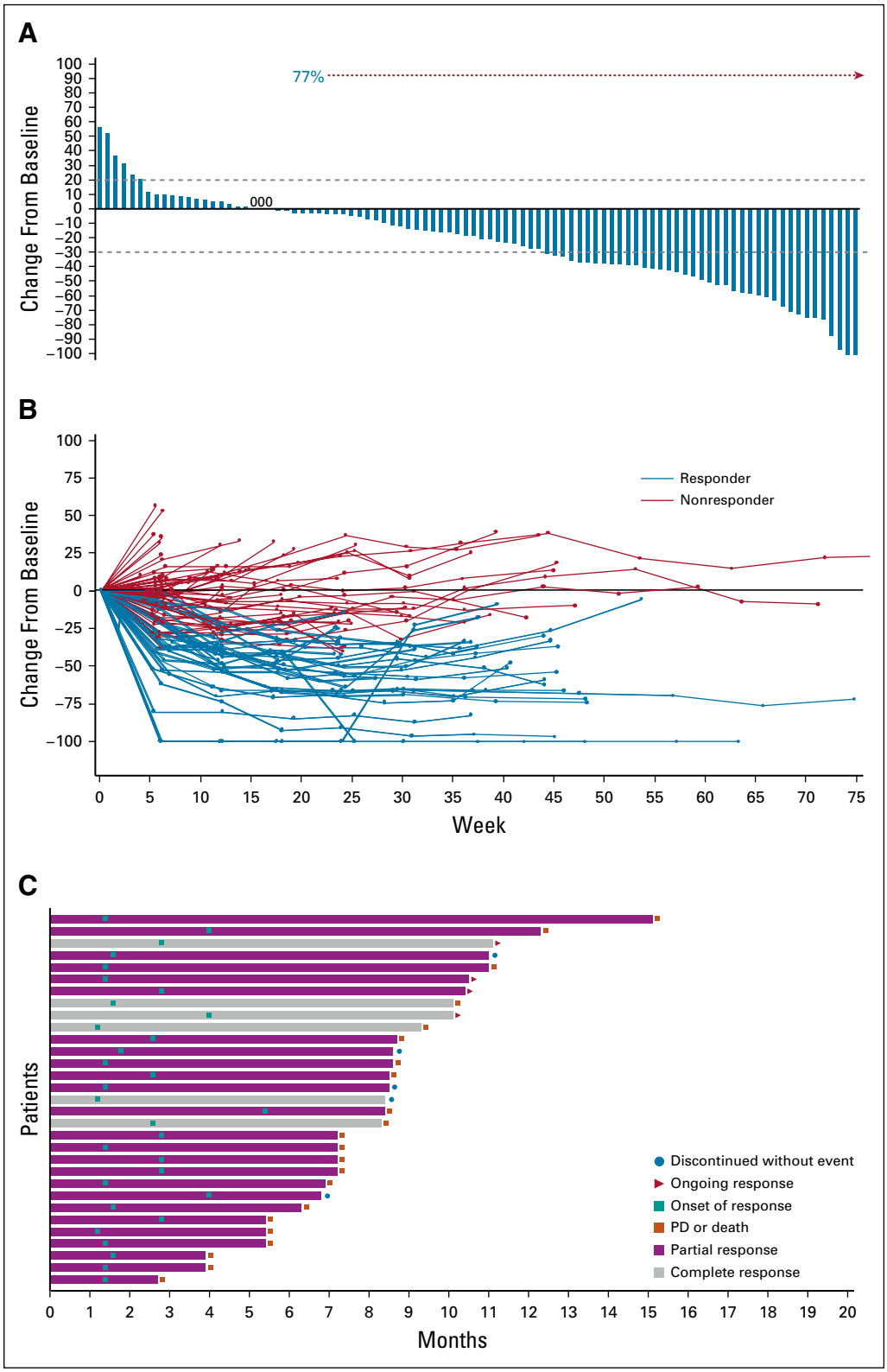

FIG 2. Tumor response to sacituzumab govitecan. (A) Waterfall plot showing best percent change from baseline in the sum of the diameters of the target lesions (longest for non-nodal and short axis for nodal lesions) in 94 patients (excludes 19 patients; 15 patients did not have post-baseline radiologic assessments and four patients lacked or had unevaluable target lesions at baseline or post-baseline). The dashed lines at +20% and −30% indicate thresholds for PD and partial response, respectively, according to RECIST v1.1. Target lesions were reduced in 77% of patients (72 of 94) with at least 1 post-baseline target lesion measurement. (B) Spider plot of tumor response by week. (C) Swimmer plot of response and duration. PD, progressive disease.

ischemic cardiomyopathy who had discontinued avelumab 2 months before enrolling in the trial; the patient recovered, and her condition resolved. There was one treatment-related death because of sepsis as a result of febrile neutropenia in a 65-year-old man with mUC, stage III chronic kidney disease, and medical history of lung cancer. Four days after receiving the last dose (cycle 3, day 1) of SG, the patient developed severe sepsis, with grade 4 febrile neutropenia and grade 3 thrombocytopenia. The patient was treated with broad-spectrum antibiotics and G-CSF; however, he was transitioned to inpatient hospice and subsequently died.

There were 105 (93%) evaluable patients for whom *UGT1A1* genotype analysis was performed (Table 1). Neutropenia (all grade) was numerically more frequent in homozygous (*28/*28) patients (54%) and heterozygous (*1/*28) patients (51%) compared with wild-type (*1/*1) patients (38%). Similarly, grade ≥ 3 neutropenia occurred more frequently in homozygous patients (54%) compared with heterozygous (34%) and wild-type (31%) patients. The frequency of diarrhea was generally not higher in homozygous patients versus the other groups (69%, 75%, and 53%, for homozygous, heterozygous, and wild-type patients, respectively). The incidence of discontinuation was similar across homozygous, heterozygous, and wild-type patients (8%, 6%, and 7%, respectively); however, treatment interruption was more common numerically in homozygous patients compared with heterozygous or wild-type patients (69%, 36%, and 42%, respectively).

DISCUSSION

In this study, SG has demonstrated a clinically and statistically significant ORR (27%) in patients with pretreated locally advanced unresectable or mUC when administered after progression on platinum-based chemotherapy and immunotherapy compared with historical controls.[6] The ORR reported here is also consistent with the 27% ORR seen in the earlier phase I/II study in the cohorts of patients with mUC who were treated with both CPI and platinum (n = 15).[31] Responses lasted for a median of 7.2 months, with the longest ongoing response of 9.5 months at the time of data cutoff (September 18, 2020). The median PFS (5.4 months) and median OS (10.9 months) observed with SG compare favorably to that of single-agent chemotherapy (median 2.7-3.3 months PFS and approximately 7 months OS).[3,5] Benefit with SG was also seen across multiple subgroups (including the small subgroup with prior exposure to EV), although some subgroups were small and warrant further investigation. Although the numbers are very small, responses in patients previously treated with EV highlight the different antigen target, linker, and payload delivered by SG, and support the hypothesis of nonoverlapping mechanisms of action and resistance.

Patients with mUC who have had disease progression after platinum-based chemotherapy and CPI therapy have poor outcomes and limited treatment options.[6,7,37] Several single and combination therapies have been investigated to improve the safety and efficacy of currently available options. Single and combination chemotherapy (pemetrexed, vinflunine, nab-paclitaxel, docetaxel, and ifosfamide) have resulted in ORRs of approximately 5.0%-25.0% and median OS of only 4.0-7.5 months.[38-41] Novel agents, such as oral mocetinostat (class I/IV histone deacetylase inhibitor) and rucaparib (PARP inhibitor) did not have notable clinical activity,[42,43] whereas erdafitinib, the first FGFR2/3-targeting agent, achieved a 40% ORR in a single-arm phase II trial, and significantly exceeded historical controls in a biomarker-selected platinum refractory population.[10]

For those who do not receive maintenance immunotherapy, a CPI is now standard second-line treatment with a significant OS advantage over single-agent chemotherapy, such as taxane or vinflunine; however, only about 13%-21% of patients exhibit a response.[5,44-47] Recent data indicate that the combination of the CPIs nivolumab and ipilimumab resulted in improved ORR compared with nivolumab alone in a nonrandomized trial; however, this combination remains investigational in UC.[48] Furthermore, outcomes with single-agent chemotherapy after progression on CPI therapy remain short with no apparent difference compared with historic pre-CPI era data.[49] ADCs represent a promising therapeutic modality for patients with refractory UC.[7,28,37,50] One such ADC, EV, received accelerated FDA approval in patients who have received prior platinum-based chemotherapy and CPI therapy based on the EV-201 phase II trial, and most recently demonstrated OS survival benefit over single-agent taxane or vinflunine in the EV-301 trial.[51] EV was associated with fatigue, skin toxicities, peripheral neuropathy, and hyperglycemia, among other toxicities, and cannot be used in those with baseline uncontrolled hyperglycemia and neuropathy.[37,51] Erdafitinib has accelerated approval in the United States, but is appropriate only for patients harboring activating mutation or fusion in FGFR2 or FGFR3 genes.[10]

SG was found to be tolerable, and despite dose interruptions and delays, the dose intensity remained 96%. The AEs most commonly associated with SG were neutropenia and diarrhea, consistent with its SN-38 payload (irinotecan metabolite). These AEs are predictable and manageable, resulting in a low rate of treatment discontinuation (6%; n = 7). Few patients discontinued because of TRAEs (n = 7); very few discontinued because of neutropenia (n = 4) and no patients discontinued because of diarrhea, possibly because of the systemic rather than localized release of SN-38 metabolite. Proactive management using established guidelines is recommended for both neutropenia and diarrhea as well as common AEs such as nausea and vomiting.[52] Other common toxicities associated with ADC therapy were quite low. AEs of rash, ocular toxicity, and peripheral neuropathy were infrequent and all were grade ≤ 2. Patients with known *UGT1A1* homozygous *28/*28 genotype are at increased risk of neutropenia, and while prescreening is

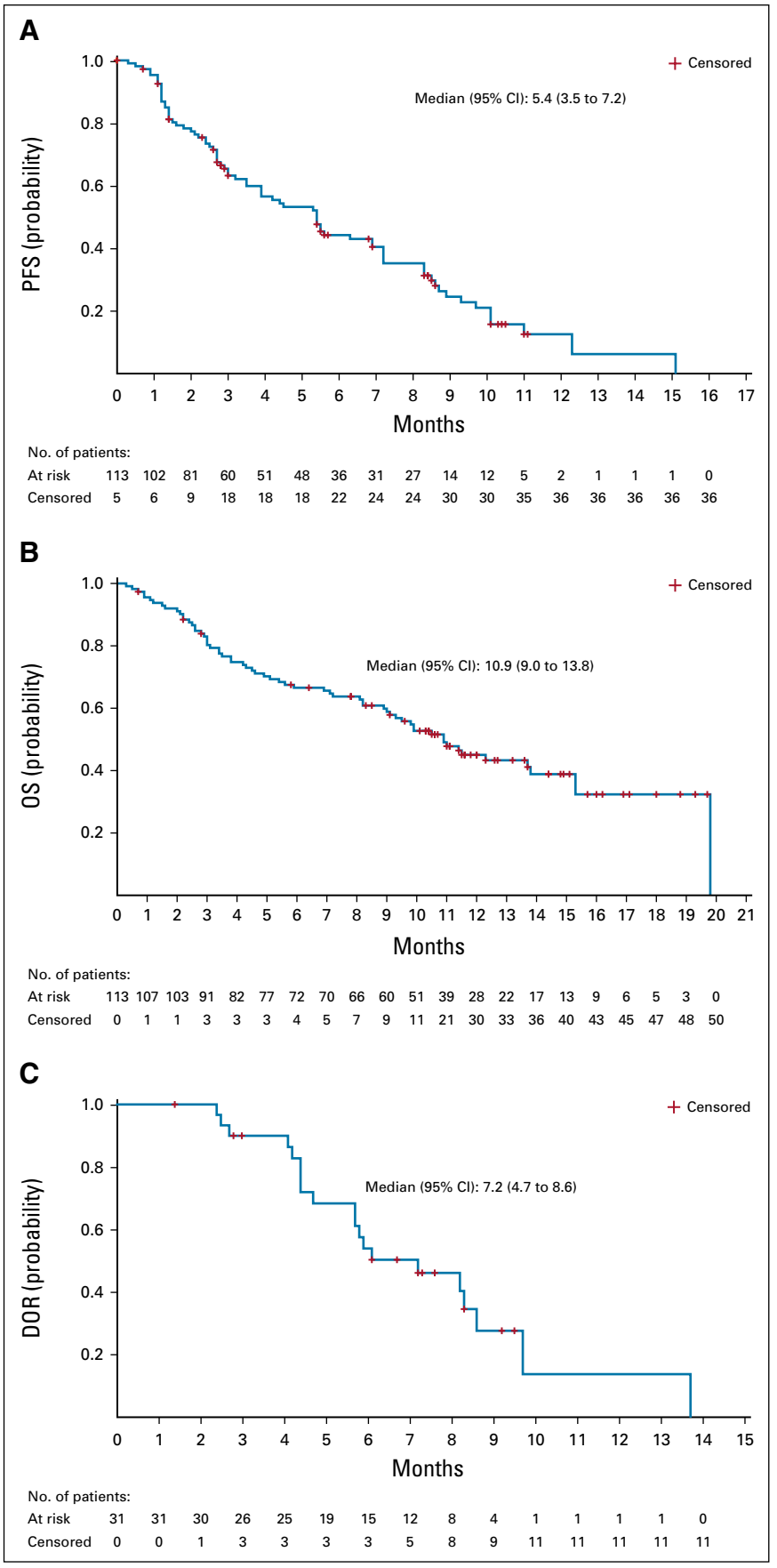

FIG 3. Kaplan-Meier analysis of (A) PFS, (B) OS, and (C) DOR. DOR, duration of response; OS, overall survival; PFS, progression-free survival.

TABLE 3. Most Common TRAEs of Any Grade (Observed in ≥ 20% of Patients) orTRAEs Grade ≥ 3 (Observed in ≥ 5% of Patients) (N = 113)

Category	Event	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic[a]	Neutropenia	46	22	12
	Leukopenia	25	12	5
	Anemia	33	14	0
	Lymphopenia	11	5	2
	Febrile neutropenia	10	7	3
GI	Diarrhea	65	9	1
	Nausea	60	4	0
	Vomiting	30	1	0
General disorders and administrative site conditions	Fatigue	52	4	0
Skin and subcutaneous tissue	Alopecia	47	0	0
Metabolism and nutrition	Decreased appetite	36	3	0
Infections and infestations	Urinary tract infection	8	6	0

Abbreviation: TRAEs, treatment-related adverse events.

[a]Neutrophil count decreased, WBC count decreased, lymphocyte count decreased, and hemoglobin decreased have been recoded to neutropenia, leukopenia, lymphopenia, and anemia, respectively, for summary purposes.

not required, close monitoring is advised. It is theoretically possible that heterozygotes have lower enzymatic activity and higher risk of neutropenia, but this small, nonrandomized data set is not able to address this question.

Study limitations include moderate sample size, lack of biomarker analysis, and single-arm, open-label study design. While there were a limited number of *UGT1A1* *28 homozygous patients to make any statistically valid observations, and despite the lack of a comparator arm, the final results for cohort 1 of this study confirm the interim findings and prior phase I/II results of SG as a tolerable and clinically active agent in patients with mUC.[31,34] The safety results reported here are also consistent with previous reports in other cancers.[28,30,53-55]

SG (Trodelvy) has recently been approved by the FDA for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer who have received two or more prior systemic therapies, at least one of them for metastatic disease.[56] The phase III confirmatory ASCENT trial that compared SG with chemotherapy of physician's choice in triple-negative breast cancer reported a highly significant benefit for SG in all end points including ORR (35% *v* 5%), PFS (5.6 *v* 1.7 months), and OS (12.1 *v* 6.7 months).[57] The clinically meaningful activity and safety profile of SG demonstrated in cohort 1 of the TROPHY-U-01 mUC trial led to the accelerated FDA approval of SG[58] for patients with locally advanced or mUC who previously received a platinum-containing chemotherapy and either a programmed death-1 or a programmed death-ligand 1 inhibitor. The results will be corroborated in the ongoing phase III confirmatory trial of SG versus taxane or vinflunine in mUC (TROPiCS-04; ClinicalTrials.govidentifier: NCT04527991). Additional cohorts of TROPHY-U-01 continue to evaluate the role of SG in mUC. Cohort 2 is investigating the role of SG in platinum-ineligible patients with mUC who progressed after CPI therapy. Cohort 3 is evaluating SG in combination with pembrolizumab in patients with mUC who are CPI-naive and progressed after prior platinum-based chemotherapies. Both cohorts 4 and 5 are evaluating SG as induction and maintenance therapy in platinum-naïve patients with mUC who are not refractory to platinum-based therapy in the neoadjuvant setting either as a cisplatin combination (cohort 4) or in addition to both cisplatin and avelumab (cohort 5) during induction. Both cohorts 4 and 5 will also receive SG in addition to avelumab as maintenance therapy. In conclusion, the results of cohort 1 of the TROPHY-U-01 trial supported fast-track designation and accelerated FDA approval of SG for the treatment of mUC previously treated with platinum-based chemotherapy and CPI by the FDA.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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APPENDIX

List of TROPHY cohort 1 investigators

The following investigators (listed by country) participated in the TROPHY-U-01 Cohort 1 study:

United States: Clarence Adoo, Neeraj Agarwal, Arjun V. Balar, Pranshu Bansal, Manojkumar Bupathi, Bradley Carthon, Christopher Chen, Mary Crow, Jorge Darcourt, Saby George, Petros Grivas, Elisabeth Heath, Rohit K. Jain, Christos E. Kyriakopoulos, Luke Nordquist, Rami Owera, Phillip Palmbos, Chandler Park, Daniel Petrylak, Joseph Pizzalato, Arash Rezazedeh, Scott Tagawa, Eddie Thara, Nicholas Vogelzang, and Shenhong Wu. France: Philippe Barthelemy, Philippe Beuzeboc, Aude Fléchon, Yohann Loriot, and Damien Pouessel.

SUPPLEMENTARY RESULTS

Efficacy by Investigator Assessment

Clinical activity (based on investigator's assessment) was demonstrated with an objective response rate of 23% (26 of 113) (95% CI, 15.6 to 31.9) including six confirmed complete responses (CRs) (5.3%) and 20 confirmed partial responses (PRs) (17.7%). The clinical benefit rate (defined as CR plus PR plus stable disease [SD] ≥ 6 months) was 38.9% (95% CI, 29.9 to 48.6). SD as best response was observed in 43.4% (49 of 113) of patients and 20.4% (23 of 113) had progressive disease at data cutoff. Sacituzumab govitecan demonstrated efficacy in all subgroups evaluated, including patients with ≥ 2 prior lines of therapy, visceral and liver metastases at baseline, and by Bellmunt risk factor. Interestingly, in the small subgroup of patients who received prior therapy with enfortumab vedotin (n = 10), there was 1 responder who achieved a PR, with an objective response rate of 10% (95% CI, 0.25 to 44.5), six who had SD, and three who had a best response of progressive disease with sacituzumab govitecan.

With a median follow-up duration of 9.1 months, the median duration of response was 7.7 months (95% CI, 4.4 to 9.0 months). The median time to objective response was 1.6 months (range, 1.2-2.9 months). Six subjects achieved a CR with a duration of response ranging from 2.7 to 15.8 months. A reduction in the size of target lesions was achieved by 71% (70 of 99) of patients with at least one post-baseline target lesion measurement by investigator assessment. The median progression-free survival and median overall survival were 4.4 months (95% CI, 2.9 to 5.7 months) and 10.9 months (95% CI, 9.0 to 13.8 months), respectively.

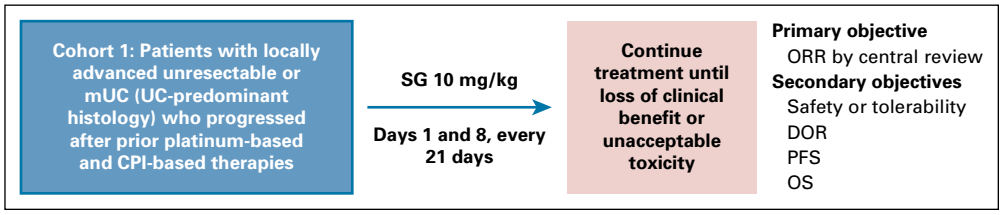

FIG A1. TROPHY-U-01 study design. EudraCT Number: 2018-001167-23; ClinicalTrials.gov identifier: NCT03547973; IMMU-132-06 study. CPI, checkpoint inhibitor; DOR, duration of response; mUC, metastatic urothelial cancer; ORR, objective response rate; OS, overall survival; PD-1, programmed death-1; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SG, sacituzumab govitecan.

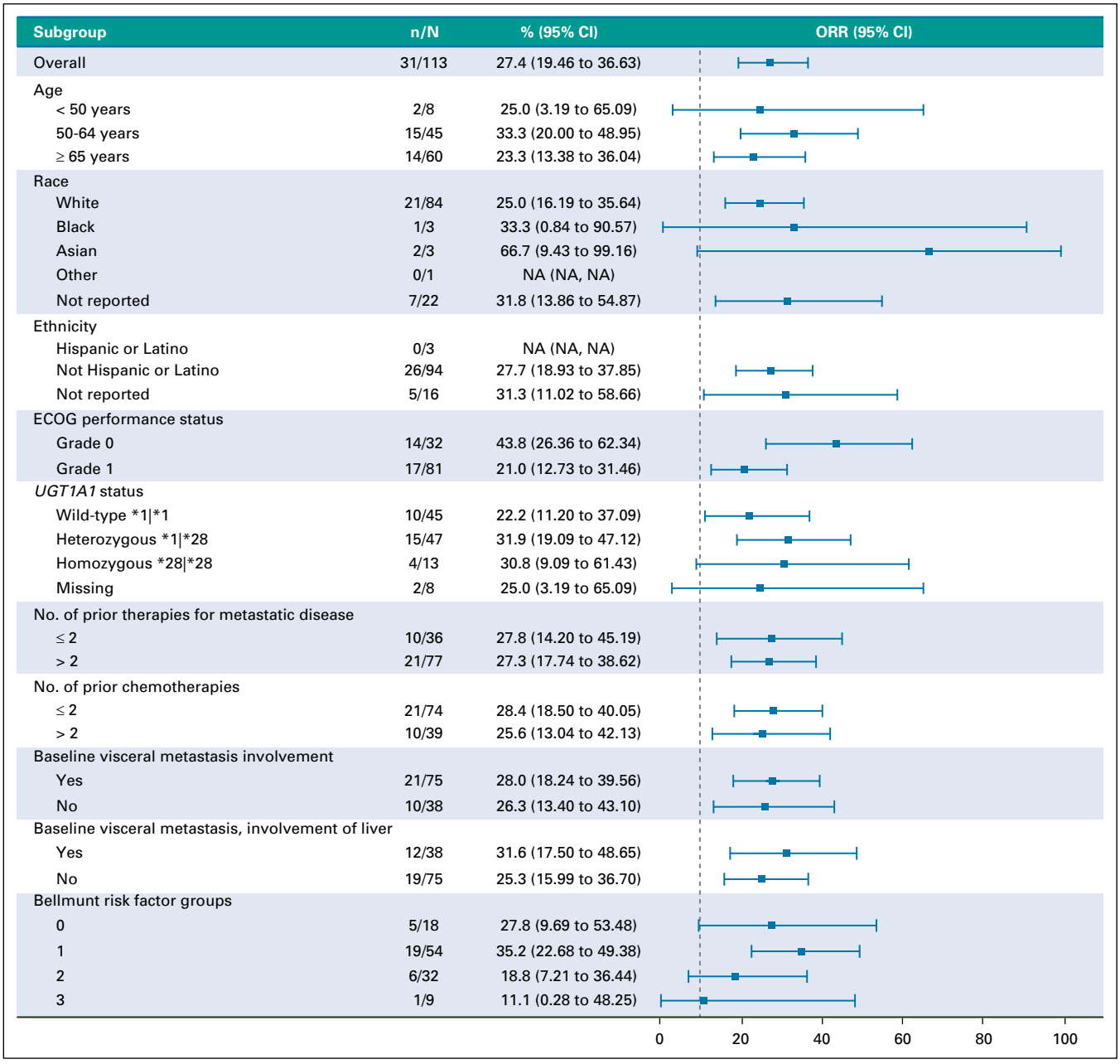

FIG A2. Forest plot showing ORR in different subgroups. Horizontal line represents CI. ECOG, Eastern Cooperative Oncology Group; NA, not available; ORR, objective response rate.