Gynecologic Oncology 170 (2023) 241–247

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer

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HIGHLIGHTS

- Mirvetuximab soravtansine (MIRV) is a biomarker-driven antibody-drug conjugate targeting folate receptor alpha (FRα).
- In platinum-resistant ovarian cancer (PROC), objective response rate was 44% (N = 94; 5 complete and 36 partial responses).
- Treatment was efficacious across all FRα expression levels, but further improved with higher FRα expression.
- These data support MIRV as a promising and novel combination partner of choice for bevacizumab in patients with PROC.

ARTICLE INFO

Article history:
Received 3 October 2022
Received in revised form 21 December 2022
Accepted 17 January 2023
Available online xxxx

Keywords:
Antibody-drug conjugate
Mirvetuximab soravtansine
Folate receptor alpha
Biomarker
Bevacizumab
Platinum-resistant ovarian cancer

ABSTRACT

Purpose. Evaluate the antitumor activity and safety profile of the combination of mirvetuximab soravtansine and bevacizumab in patients with platinum-resistant ovarian cancer.

Methods. Patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, whose most recent platinum-free interval was ≤6 months, were administered mirvetuximab soravtansine (6 mg/kg adjusted ideal body weight) and bevacizumab (15 mg/kg), intravenously, once every 3 weeks. Eligibility included FRα expression by immunohistochemistry (IHC; ≥25% of cells with ≥2+ intensity). Prior bevacizumab and/or PARP inhibitor (PARPi) treatment were permitted. The primary endpoint was confirmed objective response rate (ORR). Secondary endpoints included duration of response (DOR), progression-free survival (PFS), and safety.

Results. Ninety-four patients received combination treatment with mirvetuximab soravtansine and bevacizumab. Median age was 62 years (range, 39–81). Fifty-two percent had ≥3 prior therapies; 59% had prior bevacizumab; and 27% had prior PARPi. ORR was 44% (95% CI 33, 54) with 5 complete responses, median DOR 9.7 months (95% CI 6.9, 14.1), and median PFS 8.2 months (95% CI 6.8, 10.0). Treatment-related adverse events were consistent with the profiles of each agent, with the most common being blurred vision (all grades 57%; grade 3, 1%), diarrhea (54%; grade 3, 1%), and nausea (51%; grade 3, 1%).

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https://doi.org/10.1016/j.ygyno.2023.01.020

Conclusion. The mirvetuximab soravtansine plus bevacizumab doublet is an active and well-tolerated regimen in patients with FRα-expressing platinum-resistant ovarian cancer. Promising activity was observed for patients regardless of level of FRα expression or prior bevacizumab. These data underscore the potential for mirvetuximab soravtansine as the combination partner of choice for bevacizumab in this setting.

1. Introduction

Despite recent therapeutic advances [1], most patients diagnosed with ovarian cancer [2] eventually develop and succumb to platinum-resistant ovarian cancer (PROC). Current standard-of-care options for PROC consist primarily of non-platinum chemotherapy, either as a single agent or in combination with bevacizumab. Single-agent chemotherapies are typically associated with low response rates, while toxicities can be considerable [3,4]. Bevacizumab, the first targeted agent indicated for use in ovarian cancer [5], is approved in the frontline, maintenance, and recurrent (both platinum-sensitive and platinum-resistant) disease settings [5]. Initial approval of this agent in the United States was granted in 2014 for patients with PROC based on the findings of the AURELIA trial, which showed that the addition of bevacizumab to single-agent chemotherapy significantly improved progression-free survival (PFS) over chemotherapy alone in a primarily antiangiogenic-naïve population [6]. Current National Comprehensive Cancer Network (NCCN) guidelines include bevacizumab combined with paclitaxel, pegylated liposomal doxorubicin (PLD), topotecan, or cyclophosphamide as preferred regimens for PROC. However, treatment options for patients with PROC who are ineligible for, or have received prior bevacizumab, are limited to single-agent chemotherapy.

Bevacizumab was subsequently approved with platinum-doublet chemotherapy followed by single agent bevacizumab until progression for patients with recurrent, platinum-sensitive ovarian cancer (PSOC) [5]. This was based on the results of the OCEANS and GOG-0213 trials conducted in patients with recurrent, platinum-sensitive disease [7,8]. Frontline approvals followed, based on the GOG-0218 and ICON7 trials in newly diagnosed, advanced ovarian cancer [9,10]. Each of these randomized phase III studies demonstrated significantly improved PFS and superior response rates when bevacizumab was combined with chemotherapy compared to chemotherapy alone. Recently, findings were reported for the MITO16b/MANGO OV2b/ENGOT OV17 trial that evaluated bevacizumab in combination with a platinum-containing chemotherapy doublet versus chemotherapy alone in a recurrent PSOC population that had received bevacizumab as part of first-line therapy [11]. The study showed that rechallenge with bevacizumab alongside platinum-based chemotherapy in the platinum-sensitive setting could prolong PFS when compared to chemotherapy alone (11.8 vs 8.8 months, $p < 0.0001$), a similar size treatment effect obtained with second-line bevacizumab to that seen with use as first-line therapy.

Mirvetuximab soravtansine is an antibody-drug conjugate comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and maytansinoid DM4 payload, a potent tubulin-targeting antimitotic agent [12]. FRα is a membrane protein that binds to and transports folate into cells. In contrast to normal adult tissues that generally exhibit restricted FRα expression, epithelial tumors, particularly high-grade serous ovarian cancers, overexpress the receptor [13,14]. As monotherapy, mirvetuximab soravtansine has demonstrated encouraging antitumor activity in the setting of platinum-resistant disease [15–17], including in post-bevacizumab PROC with an ORR of 32% and duration of response of 6.9 months [18]. Mirvetuximab soravtansine exhibits a differentiated and favorable safety profile in patients with advanced ovarian cancer [16] with low treatment-related discontinuation rates (<10%) [17].

Preclinical studies showed that the combination of mirvetuximab soravtansine and bevacizumab was highly efficacious in platinum-resistant (including patient-derived) ovarian cancer xenograft models [19]. As monotherapy, in a xenograph model with FRα PS2+ expression of 10%, each agent showed comparable antitumor activity; however, neither resulted in sustained tumor growth inhibition. In contrast, the combination elicited robust tumor regressions, using a range of dose levels and fractionated dosing regimens [19]. Together, the clinical activity and non-overlapping toxicity profile of mirvetuximab soravtansine with bevacizumab underscored its suitability as a partnering agent of choice for combination-based therapeutic approaches. We have previously reported dose finding results for the mirvetuximab soravtansine plus bevacizumab doublet as part of the Phase Ib/II FORWARD II trial (NCT02606305) [20]. Here we present findings of combined expansion cohorts opened as part of the same study further evaluating the mirvetuximab soravtansine and bevacizumab combination as a novel, targeted regimen for the treatment of patients with FRα-expressing PROC.

2. Patients and methods

2.1. Trial status

NCT02606305 is a multi-arm, Phase 1b/2 study evaluating the safety and tolerability of mirvetuximab soravtansine in combination with bevacizumab, carboplatin, pegylated liposomal doxorubicin, pembrolizumab, or bevacizumab plus carboplatin, in adults with FRα-expressing, advanced epithelial ovarian, primary peritoneal, or fallopian tube cancer. This report is the final analysis of patients treated with the mirvetuximab soravtansine plus bevacizumab regimen. All other cohorts have been completed and will be reported elsewhere.

2.2. Patient selection and eligibility criteria

Eligible patients were 18 years of age or older with histologically confirmed epithelial ovarian, primary peritoneal, or fallopian tube cancer, which was platinum-resistant (recurrence within 6 months of last platinum dose). Patients within the reported cohorts must have received at least one but not more than three prior systemic treatment regimens, and prior regimens may have included bevacizumab and/or poly (ADP-ribose) polymerase inhibitors (PARPi). Maintenance therapy with either bevacizumab or PARPi were considered part of the prior line of treatment, and not counted as a separate line of therapy. Patients were required to have at least one lesion that met the definition of measurable disease by Response Evaluation Criteria in Solid Tumors [RECIST], version 1.1 [21], with confirmation of threshold FRα expression. The threshold of FRα expression was determined by central immunohistochemistry (IHC) testing using the anti-FOLR1 2.1 antibody developed by Ventana Medical Systems and using the PS2 scoring methodology of ≥25% of tumor staining at ≥2+ intensity. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 and have adequate hematologic, renal, and hepatic function. Key exclusion criteria included primary refractory disease (defined as disease that did not respond to, or

progressed within 30 days after, first-line platinum therapy); neuropathy greater than grade 1; any active or chronic corneal disorder; history of bowel obstruction, abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess; uncontrolled hypertension (≥grade 3); or known hypersensitivity to monoclonal antibody therapy. All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

2.3. Treatment

Patients were dosed with mirvetuximab soravtansine 6 mg/kg adjusted ideal body weight (AIBW) followed by bevacizumab 15 mg/kg, intravenously (IV), on day 1 of a 21-day cycle (Q3W dosing). All patients had an ophthalmic exam performed at screening. As a prophylactic measure for ocular symptoms, patients were required to use preservative-free lubricating artificial tears daily and corticosteroid eye drops starting the day of their dose and continuing through day 8 of each cycle. Patients reporting ocular symptoms were evaluated by an ophthalmologist and subsequently underwent ophthalmic exams every other cycle and at either the end of treatment or at the 30-day follow-up visit. Patients received study treatment until disease progression, intolerable toxicity, or withdrawal of consent. If mirvetuximab soravtansine treatment was discontinued, patients were permitted to continue participation in the study with bevacizumab as monotherapy. Similarly, if bevacizumab was discontinued, mirvetuximab soravtansine monotherapy was allowed until a reason for discontinuation occurred. The study was conducted in accordance with the US Food and Drug Administration regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study was compliant with all Institutional Review Board and Independent Ethics Committee requirements. This trial is registered at ClinicalTrials.gov (NCT02606305).

2.4. Endpoints and assessments

The primary efficacy endpoint was objective response rate (ORR), defined by the percentage of patients with a confirmed complete or partial response according to RECIST v1.1. During screening, radiological imaging of the chest, abdomen, and pelvis was performed. Objective tumor response was investigator-assessed per RECIST v1.1 using computerized tomography (CT) scans or magnetic resonance imaging (MRI). Scans were performed using the same method every 6 weeks through week 24, then every 3 months for up to one year from randomization, and then every six months while on study. Secondary objectives included duration of response, safety and tolerability, and PFS. The clinical response of sub-groups was an exploratory endpoint.

Baseline assessments included medical history and physical examination, ocular assessment, ECOG performance status, blood chemistry and hematology, pulmonary function tests, and electrocardiogram. Adverse events were defined and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 and monitored continuously throughout the study from the time of the first study dose until 30 days after the patients' last dose.

2.5. Statistical considerations

The study population included all patients enrolled in FORWARD II that received mirvetuximab soravtansine 6 mg/kg AIBW and bevacizumab 15 mg/kg across escalation and expansion cohorts who were defined as platinum-resistant. Descriptive statistics were used to summarize demographic and baseline characteristics and additional analyses were performed using SAS statistical software (version 9.4), with a cutoff date of June 21, 2021. The median duration of follow-up was 8.7 months (range, 0.8 to 25.3). For safety assessments, any adverse event with the same onset date as the start of study treatment or later (including the 30-day follow up period) was reported as treatment-emergent. For efficacy evaluations, the baseline was defined as the last available evaluation prior to the first dose of study treatment. All patients who had a post-baseline assessment were considered response-evaluable and were included in the objective response rate analyses, along with the corresponding exact 95% CIs based on Clopper-Pearson method. Progression-free survival was estimated using Kaplan-Meier estimates for the intent-to-treat (ITT) population.

3. Results

3.1. Patient characteristics

Ninety-four patients with platinum-resistant disease enrolled and received combination treatment with mirvetuximab soravtansine plus bevacizumab and constituted the ITT population. Patient demographics and baseline characteristics are summarized in Table 1. The median age was 62 years (range 39–81) and 64% had an ECOG performance status of 0. Patients were diagnosed with epithelial ovarian (77%), fallopian tube cancer (18%), or primary peritoneal cancer (5%). Patients had tumors with a range of FRα expression: 47% (≥75%), 42% (50–74%), and 12% (25–49%). More than half the population had received 3 prior systemic therapies. Fifty-five patients (59%) had prior bevacizumab and 25 (27%) had received prior PARPi. Patients on study received a median of 7.5 cycles (range, 1, 35) of mirvetuximab soravtansine and 7 cycles (range, 1, 35) of bevacizumab. As part of the same trial, an additional 31 patients with platinum-sensitive disease were treated with the mirvetuximab soravtansine plus bevacizumab combination; patient demographics and baseline characteristics are shown in Supplementary Table S1.

3.2. Clinical activity

All 94 patients were evaluable for efficacy analyses and the confirmed ORR in the ITT population was 44% (95% CI, 33, 54; Table 2), which included 5 complete responses (CR) and 36 partial responses (PR). Best percentage change in target lesion size for all patients (and changes in tumor burden as a function of time for responders) are shown in Fig. 1. The median duration of response (mDOR) was 9.7 months (95% CI, 6.9, 14.1). Median progression free survival (mPFS) was 8.2 months (95% CI, 6.8, 10.0; Fig. 2A).

Table 1
Patient demographics and baseline characteristics.

Characteristic	$N = 94$
Age, years	
Median (range)	62 (39–81)
Primary diagnosis, n (%)	
Epithelial ovarian cancer	72 (77)
Fallopian tube cancer	17 (18)
Primary peritoneal cancer	5 (5)
ECOG PS, n (%)	
0	60 (64)
1	34 (36)
No. of prior systemic therapies, n (%)	
1–2	45 (48)
≥3[a]	49 (52)
FRα expression,[b] n (%)	
≥75%	44 (47)
50–74%	39 (42)
25–49%	11 (12)
Prior exposure, n (%)	
Taxane	91 (97)
Bevacizumab	55 (59)
PARP inhibitor	25 (27)

ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; PARP, poly (ADP-ribose) polymerase; PS2+, positive staining 2 +.
[a] One patient had 4 prior lines of therapy.
[b] ≥75%, 50–74%, 25–49% of tumor cells with FRα membrane staining of ≥2+ intensity using PS2+ scoring methodology.

Table 2
Summary of efficacy measures.

Endpoint	N = 94
Confirmed objective response rate, n (%)	41 (44)
95% CI	(33, 54)
Best overall response, n (%)	
Complete response	5 (5)
Partial response	36 (38)
Stable disease	44 (47)
Progressive disease	8 (9)
Not evaluable	1 (1)
Median duration of response, (months)	9.7
95% CI	(6.9, 14.1)
Median progression-free survival, (months)	8.2
95% CI	(6.8, 10.0)

Exploratory analyses examined the impact of tumor FRα expression level as well as prior bevacizumab exposure on the activity of the combination. Activity was seen across all FRα expression levels (Table 3). Patients with tumors demonstrating FRα expression of ≥75% had a higher ORR and longer mPFS interval (Fig. 2B) relative to patients whose tumors had 50–74% expression level. The duration of response was similar between the two subgroups. Despite the caveat of small numbers, meaningful antitumor activity was observed for the combination even in the subset of patients with 25–49% FRα expression.

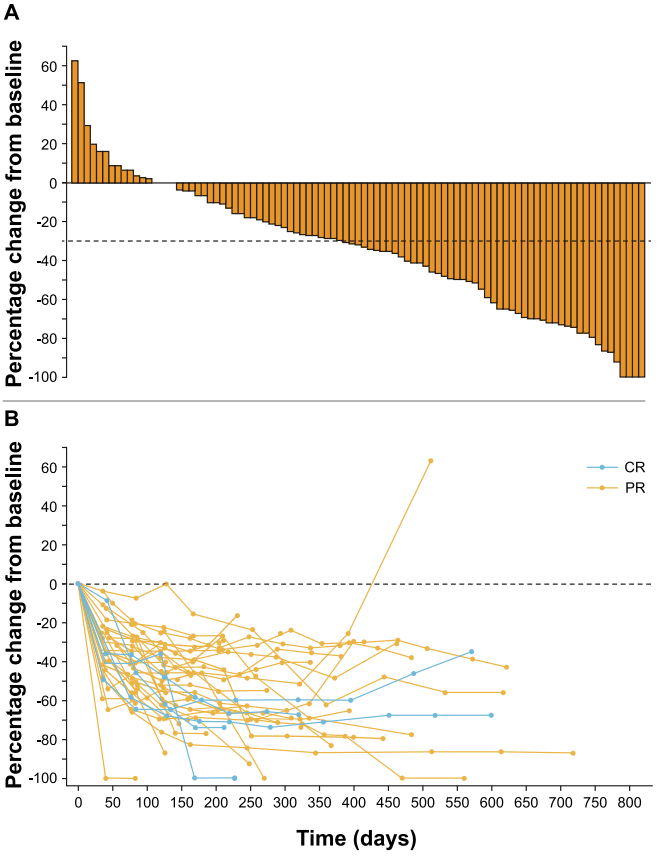

Fig. 1. (A) Maximum percentage change in tumor lesion size from baseline for individual patients in the ITT. The dashed gray line (−30%) indicates the partial response boundary according to RECIST guidelines. (B) Kinetics of tumor burden over time presented as percentage change in RECIST sum of longest diameters in patients with confirmed responses to combination treatment. For those patients who achieved a CR with ~60–80% changes from baseline, target lesions were lymph nodes that showed a reduction in the short-axis measurement to <10 mm. CR, complete response; ITT, intent-to-treat; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

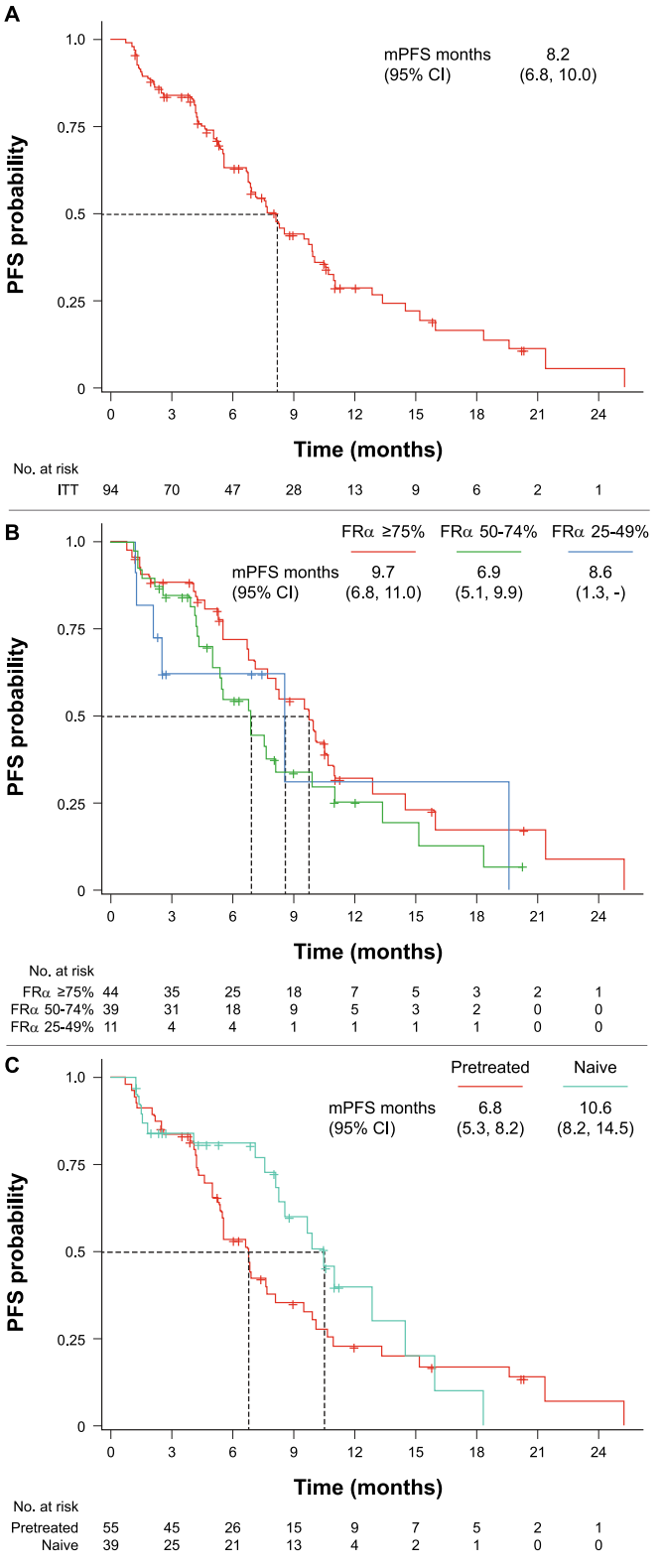

Fig. 2. (A) Kaplan-Meier analysis of progression-free survival (PFS) in the ITT population. (B) Kaplan-Meier analysis of PFS grouped by FRα expression. (C) Kaplan-Meier analysis of PFS grouped by prior bevacizumab exposure. FRα, folate receptor alpha; ITT, intent-to-treat; mPFS, median progression free survival.

Previous bevacizumab treatment also resulted in outcome differences (Table 3; Fig. 2C). Patients who were bevacizumab-naïve responded better to combination treatment (ORR 56%, mDOR 10.4 months, mPFS 10.6 months) compared with those who had received

Table 3
Summary of efficacy in patients by subgroups.

Endpoint	FRα ≥ 75% (*n = 44*)	FRα 50–74% (*n = 39*)	FRα 25–49% (*n = 11*)	BEV-naïve (*n = 39*)	BEV-pretreated (*n = 55*)
Confirmed objective response rate, n (%)	21 (48)	16 (41)	4 (36)	22 (56)	19 (35)
95% CI	(33, 63)	(26, 58)	(11, 69)	(40, 72)	(22, 49)
Median duration of response, (months)	9.7	9.7	18.5	10.4	9.7
95% CI	(6.0, 12.0)	(3.0, NR)	(NE)	(6.9, 14.5)	(4.2, NR)
Median progression-free survival, (months)	9.7	6.9	8.6	10.6	6.8
95% CI	(6.8, 11.0)	(5.1, 9.9)	(1.3, NR)	(8.2, 14.5)	(5.3, 8.2)

BEV, bevacizumab; FRα, folate receptor alpha; NE, not evaluable; NR, not reached.

bevacizumab as part of earlier lines of therapy (ORR 35%, mDOR 9.7 months, mPFS 6.8 months).

In the subset of PSOC patients, the confirmed ORR was 48% (95% CI, 30, 67), mDOR was 12.7 months (95% CI, 5.0, 14.5), and mPFS was 9.6 months (95% CI, 5.4, 14.1) (Supplementary Table S2).

3.3. Adverse events

All 94 patients were included in the safety analyses and 93 (99%) experienced at least one treatment-related adverse event (TRAE) deemed related to the study drug (either mirvetuximab soravtansine, bevacizumab, or both). TRAEs occurring in >20% of patients are summarized in Table 4. The most common events of any grade were blurred vision (57%), diarrhea (54%), nausea (51%), and fatigue (43%). However, most cases were grade ≤ 2 and managed with appropriate supportive care. Keratopathy was another ocular side effect (34%) that was expected based on the known safety profile of mirvetuximab soravtansine [22]. All cases were grade ≤ 2, reversible, and no long-term sequelae were reported. Of note, despite the corneal nature of this event, no corneal ulcers or perforations were seen in any patients. Per protocol, ocular events were managed by proactive mitigation strategies, including lubricating and steroid eye drop use, and, if needed, dose modifications. Peripheral neuropathy occurred in 38% of patients, of which all events except one were grade ≤ 2. Treatment-related adverse events occurring in >20% of both PROC and PSOC patients are shown in Supplementary Table S3.

With respect to hematological toxicity, 30% of patients experienced thrombocytopenia (grade ≥ 3, 4%) and neutropenia was seen in 17% of patients (grade ≥ 3, 7%). Hypertension, a bevacizumab-associated AE, occurred in 26 patients (28%), with 14 cases being grade 3 in severity. Serious adverse events occurred in 36 patients (38%), the most frequent of which were small intestinal obstruction (four patients, 4%), diarrhea, and gastrointestinal hemorrhage (three patients each, 3%). Thirty patients (32%) discontinued mirvetuximab soravtansine and/or bevacizumab due to TRAEs. The most common events responsible for study discontinuation were thrombocytopenia (7%), peripheral neuropathy (3%), gastrointestinal hemorrhage (3%), and pneumonitis (2%). One death related to bevacizumab (intestinal perforation) was seen on study.

Table 4
Treatment-related adverse events reported in >20% of patients.

	Grades 1–2	Grade 3	Grade 4	All Grades
Adverse event	n (%)	n (%)	n (%)	n (%)
Vision blurred	53 (56)	1 (1)	0 (0)	54 (57)
Diarrhea	50 (53)	1 (1)	0 (0)	51 (54)
Nausea	47 (50)	1 (1)	0 (0)	48 (51)
Fatigue	37 (39)	3 (3)	0 (0)	40 (43)
Peripheral neuropathy	35 (37)	1 (1)	0 (0)	36 (38)
Keratopathy	32 (34)	0 (0)	0 (0)	32 (34)
Thrombocytopenia	24 (26)	4 (4)	0 (0)	28 (30)
Decreased appetite	26 (28)	0 (0)	0 (0)	26 (28)
Dry eye	24 (26)	2 (2)	0 (0)	26 (28)
Hypertension	12 (13)	14 (15)	0 (0)	26 (28)
AST increased	21 (22)	4 (4)	0 (0)	25 (27)
Headache	25 (27)	0 (0)	0 (0)	25 (27)
Vomiting	24 (26)	1 (1)	0 (0)	25 (27)
ALT increased	19 (20)	3 (3)	0 (0)	22 (23)
Epistaxis	20 (21)	1 (1)	0 (0)	21 (22)
Abdominal pain	19 (20)	0 (0)	0 (0)	19 (20)

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

4. Discussion

Outcomes for ovarian cancer patients have improved over the last decade with incorporation of targeted therapies and maintenance treatment (bevacizumab and PARPi) [5,23]. However, disease recurrence remains incurable and, as the number of patients living with ovarian cancer continues to grow, effective treatments for those with relapsed disease remain a clinical challenge [24]. Bevacizumab is used in the front-line and recurrent settings, yet opportunity exists to improve outcomes with antiangiogenic therapy in ovarian cancer, and investigation of alternate strategies with partners that improve efficacy or have improved tolerability is warranted. Here we show that mirvetuximab soravtansine is an active and well-tolerated partnering agent for bevacizumab in patients with PROC.

The combination of mirvetuximab soravtansine plus bevacizumab elicited high response rates and achieved durable antitumor activity with a favorable toxicity profile in patients with relapsed, FRα-expressing ovarian cancer. Results from the Phase III SORAYA study (NCT04296890) evaluating mirvetuximab soravtansine as monotherapy in bevacizumab-pretreated FRα-high platinum-resistant disease included a confirmed ORR of 32.4% with mDOR of 6.9 months [17]. In the current study, in a population with a range of FRα expression and mixed exposure to prior bevacizumab, combination treatment resulted in a confirmed ORR of 44%, mDOR of 9.7 months, and a mPFS interval of 8.2 months. In addition, exploratory analyses revealed meaningful antitumor activity across all FRα levels, with higher response rates with increasing FRα expression. Of note, the duration of response was similar across all levels of FRα expression. Higher response rates and slightly longer duration of response were observed in patients who were bevacizumab-naive compared to those who had received prior bevacizumab (ORR: 56% and 35%; DOR 10.4 and 9.7 months, respectively). Further, and confirming preclinical expectations [19], the almost 3-month improvement in DOR seen with the combination in bevacizumab-pretreated patients (regardless of FRα expression level) compared to that reported for monotherapy in the SORAYA study suggests that the addition of bevacizumab to mirvetuximab soravtansine has additive clinical benefit for patients with PROC.

The clinical activity of mirvetuximab soravtansine plus bevacizumab (ORR, durability of response, and PFS) is encouraging, regardless of prior bevacizumab treatment. The notable activity of the doublet compares favorably to bevacizumab plus chemotherapy regimens used in patients with PROC and, with the caveats of cross-trial comparisons, it is informative to consider the results from this study in the context of other studies in similar platinum-resistant patient populations. The historical benchmarks for a bevacizumab-naïve, PROC population are an ORR of 27%, DOR of 9.4 months, and PFS of 6.7 months seen with bevacizumab plus single-agent chemotherapy in AURELIA [6,25]. Here, in the bevacizumab-naïve sub-population of PROC, the mirvetuximab soravtansine plus bevacizumab combination elicited an ORR of 56%,

DOR of 10.4 months, and PFS of 10.6 months, irrespective of tumor FRα expression level.

Recent findings from the MITO16b/MANGO-OV2/ENGOT-ov17 trial demonstrated that rechallenge with bevacizumab following prior bevacizumab exposure can confer therapeutic benefit for patients with PSOC [11]. Here, in the PROC setting, almost two-thirds of patients had received bevacizumab as part of earlier lines of therapy. Within this patient subset, combination treatment elicited meaningful clinical activity, as evidenced by an ORR of 35%, DOR of 9.7 months, and mPFS of 6.8 months. It is reasonable to suggest, therefore, that bevacizumab rechallenge may be clinically relevant in the platinum-resistant setting as well.

Combination treatment was well tolerated with adverse events as expected based on the side effect profiles of each agent and no new safety signals. Notably, the doublet was characterized by a low incidence of myelosuppressive toxicities [6,7]. The most frequent mirvetuximab soravtansine-related events consisted of predominantly low-grade gastrointestinal and ocular disorders with grade ≥ 3 toxicity reported in ≤4%. Of note, ocular adverse events were reversible, without an inflammatory component, and no permanent sequelae occurred, consistent with earlier monotherapy findings [26]. The most frequent bevacizumab-associated AE was hypertension. Other established bevacizumab-related toxicities including proteinuria and bleeding occurred at low frequencies similar to that expected with bevacizumab-containing therapy [27].

In summary, the combination of mirvetuximab soravtansine with bevacizumab is highly active, with durable responses, and a manageable safety profile in patients with platinum-resistant ovarian cancer. Promising activity was seen across all FRα expression levels studied and in patients with and without prior bevacizumab exposure. The findings presented here suggest that this regimen may provide meaningful clinical benefit for a broad population of patients with PROC and warrant further evaluation of the combination as an alternative to current treatments.

Funding

This study was supported by ImmunoGen, Inc.

Declaration of Competing Interest

LG reports personal fees from Merck and GSK; advisory board participation with AstraZeneca, Alkermes, Merck, Eisai, Eisai-Merck, GSK, and Novocure; institutional funding from OncoQuest Pharmaceuticals, Novocure GmbH, Alkermes Inc., ImmunoGen Inc., AstraZeneca, Esperas Pharma Inc., K-Group Beta Inc., Merck Sharp & Dohme, Roche, Karyopharm, Tesaro, and IMV Inc.

AO reports personal fees from AstraZeneca, Doctaforum Servicios S. L, Edizioni Minerva Medica SpA, ESMO, PharmaMar, and Roche; advisory board participation with Agenus, AstraZeneca, Clovis Oncology, Inc., Corcept Therapeutics, Deciphera Pharmaceutical, Eisai Europe Limited, EMD Serono, Inc., F. Hoffmann-La Roche, GlaxoSmithKline, ImmunoGen, KL Logistics, Medison Pharma, Merck Sharp & Dohme de España, Mersana Therapeutics, Novocure GmbH, PharmaMar, prIME Oncology, ROCHE FARMA, Sattucklabs, and Sutro Biopharma, Inc.; funding from AbbVie Deutschland Gmbh & Co Hg, Ability Pharmaceuticals, Advaxis, Agenus, Aprea Therapeutics AB, AstraZeneca AB, Beigene USA, Inc., Belgian Gynaecological Oncology Group (BGOG), Bristol-Myers Squibb International Corporation, Clovis Oncology, Corcept Therapeutics, Eisai, Eli Lilly and Company, F. Hoffmann-La Roche, Grupo Español de Investigación en Cáncer de Ovario (GEICO), ImmunoGen, Iovance Biotherapeutics, Medimmune, Merck Healthcare, Merck Sharp & Dohme, Millennium Pharmaceuticals, Mundipharma Research, Novartis Farmacéutica, Regeneron Pharmaceuticals, Seagen, Seattle Genetics, Sutro Biopharma, Tesaro, University Health Network, and Verastem.

UAM reports consulting fees from Merck, GSK, and AstraZeneca; personal fees from Med Learning Group; advisory board participation with 2× Oncology, NextCure, Trillium, Agenus, ImmunoGen, Novartis, Boehringer Ingelheim, Rivkin Foundation, Ovarian Cancer Research Alliance, Clearity Foundation, and Morphosys; data safety monitoring board participation with Alkermes and Symphogen.

GMMS reports advisory board participation with ImmunoGen.

PCL reports no disclosures.

CMC reports personal fees from Qiagen, Inc., Teladoc Health, and InfiniteMD.

DP reports no disclosures.

SM reports no disclosures.

MM reports employment and stock options with ImmunoGen Inc.

JW reports employment and stock options with ImmunoGen Inc.

KNM reports personal fees from AbbVie, Alkemeres, Aravive, AstraZeneca, Blueprint Pharma, Bristol Myers Squibb, Eisai, Elevar, GSK/Tesaro, Genentech/Roche, iMab, ImmunoGen, Merck, Mereo, Mersana, Myriad, OncXerna, Oncomed, Rubius, Sorrento, Tarveda, Vavotar, and VBL Therapeutics; advisory board participation with Abbvie, Alkemeres, Aravive, AstraZeneca, Blueprint Pharmaceuticals, Eisai, Elevar, Genetech/Roche, GSK/Tesaro, ImmunoGen, Merck, Mereo, Mersana, Myriad, Onco Med, OncXerna, Rubius, Sorrento, Tarveda, Vavotar, VBL Therapeutics; funding from Genentech/Roche, GSK/Tesaro, ImmunoGen, Lilly, Merck, and PTC Therapeutics.

DMO reports receiving grants or contracts from AbbVie Inc., Agenus Inc., Ajinomoto Co Inc., Amgen Inc., Array BioPharma Inc., AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Clovis Oncology, Dare Bioscience, Eisai Inc., EMD Serono Inc., Ergomed Plc, Genentech, Genmab, GOG Foundation Inc., ImmunoGen Inc., Iovance Biotherapeutics, Janssen Biotech Inc., Johnson & Johnson Pharmaceuticals, Ludwig Institute for Cancer Research Ltd., Merck, Merck Serono, Mersana Therapeutics, New Mexico Cancer Care Alliance, Novocure Inc., PRA Health Sciences, Regeneron Pharmaceuticals Inc., Seagen Inc., Stemcentrx, Sumitomo, Dainippon Pharma Oncology Inc., Syneos Health, Tesaro, TRACON Pharmaceuticals, VentiRX Pharmaceuticals Inc., and Yale University; data safety monitoring board and/or advisory board participation with AbbVie Inc., Ambry Genetics, Amgen Inc., Arquer Diagnostics, AstraZeneca Pharmacueticals LP, Celsion Corporation, Clovis Oncology, Corcept Therapeutics, Eisai Inc., Elevar Therapeutics, Genentech, GOG Foundation Inc., ImmunoGen Inc., InxMed, Iovance Biotherapeutics, Janssen Biotech Inc., Johnson and Johnson Pharmaceuticals, Merck, Mersana Therapeutics Inc., Novartis, Novocure Inc., Regeneron Pharmaceuticals Inc., Roche Diagnostics MSA, Seagen Inc., Sorrento Therapeutics, Sumitomo Danippon Pharma Oncology Inc., Takeda Pharmaceuticals USA Inc., Tesaro, and Tora; other financial or nonfinancial interests with Agenus Inc., Myriad Genetic Laboratories Inc., Rubis, and Tarveda Therapeutics.

Acknowledgments

We wish to thank all the patients who participated and their families, as well as co-investigators, nurses, study coordinators, and operations staff at each of the clinical sites. We also thank Dr. Richard Bates who provided drafts and editorial assistance during the production of this manuscript. This study was funded by ImmunoGen, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2023.01.020.

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