

Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FR α)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer

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HIGHLIGHTS

- Combining mirvetuximab soravtansine and bevacizumab is a promising approach for platinum-resistant ovarian cancer.
- The combination is well tolerated, with a differentiated safety profile compared to bevacizumab with chemotherapy.
- The efficacy measures compare favorably to reported outcomes for bevacizumab/chemotherapy in similar patient populations.

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ABSTRACT

Purpose. To evaluate the safety and clinical activity of mirvetuximab soravtansine, an antibody-drug conjugate comprising a humanized anti-folate receptor alpha (FR α) monoclonal antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent, in combination with bevacizumab in patients with FR α -positive, platinum-resistant ovarian cancer.

Methods. Patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer were administered mirvetuximab soravtansine (6 mg/kg, adjusted ideal body weight) and bevacizumab (15 mg/kg) once every 3 weeks. Eligibility included FR α positivity by immunochemistry and prior bevacizumab exposure was permitted. Adverse events, tumor response, and progression-free survival (PFS) were determined.

Results. Sixty-six patients, with a median of 3 prior lines of therapy (range, 1–8), received the combination of mirvetuximab soravtansine and bevacizumab at full dosing during the escalation and expansion stages of the study. Adverse events were generally mild-to-moderate (\leq grade 2) with diarrhea, blurred vision, nausea, and fatigue being the most common treatment-related toxicities. Six cases of pneumonitis (9%; all grade 1 or 2), an adverse event of special interest, were observed. The confirmed objective response rate (ORR) was 39%, including 5 complete responses and 21 partial responses, and the median PFS was 6.9 months. The combination was particularly active in the subset of patients ($n = 16$) who were bevacizumab-naïve, less heavily pretreated (1–2 prior

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lines), and whose tumors exhibited medium/high FR α expression (ORR, 56% with a median duration of response of 12 months; PFS, 9.9 months).

Conclusion. The combination of mirvetuximab soravtansine with bevacizumab is well tolerated in patients with platinum-resistant, recurrent ovarian cancer. The encouraging efficacy measures compare favorably to reported outcomes for bevacizumab combined with standard chemotherapy in similar patient populations.

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1. Introduction

The incorporation of molecularly targeted agents into the treatment armamentarium for epithelial ovarian carcinoma (EOC; including epithelial ovarian, fallopian tube, and primary peritoneal cancer) [1,2] has had a meaningful impact in terms of disease control, particularly for individuals in early treatment lines considered at high risk of further relapse [3]. Despite this progress, most women diagnosed with advanced EOC ultimately develop, and succumb to, platinum-resistant recurrences [4]. The dismal prognosis imparted by platinum-resistant disease underscores the substantial unmet need for more effective and tolerable therapeutic agents and innovative approaches to improve outcomes in this clinically challenging population.

The first targeted agent indicated for use in EOC was the angiogenesis inhibitor bevacizumab [5]. Initial approval in the U.S. and E.U. was based on findings from the AURELIA/ENGOT-ov3 trial, which showed that addition of bevacizumab to chemotherapy significantly improved progression-free survival (PFS) over chemotherapy alone in patients with platinum-resistant EOC [6]. Bevacizumab approval was subsequently expanded into the platinum-sensitive, recurrent, and front-line settings, in combination with chemotherapy followed by a maintenance period of single-agent bevacizumab. This occurred in response to additional randomized phase III studies performed in patients with recurrent platinum-sensitive disease (OCEANS and GOG-0213) [7,8] and newly diagnosed, advanced EOC (GOG-218 and ICON7) [9,10], all of which demonstrated prolonged PFS when bevacizumab was combined with chemotherapy.

Another molecular target of interest in EOC is folate receptor alpha (FR α) [11], a transmembrane protein involved in cellular folate transport [12]. FR α expression is highly restricted in normal tissues and absent from normal ovarian epithelium. However, FR α expression has been reported in approximately 80% of EOC tumors; methods to assess FR α expression include immunohistochemistry and imaging with radiolabeled conjugates [13]. This differential distribution pattern makes FR α an attractive candidate for antibody-drug conjugate (ADC)-based therapeutic strategies [14]. ADCs comprise a monoclonal antibody, directed toward tumor-associated antigens, to which a potent cytotoxic agent ('payload') is conjugated via chemical linkage [15]. ADCs are also a clinically validated class of therapeutics, with four currently approved for cancer therapy and >60 others being evaluated in a variety of tumor indications [16].

Mirvetuximab soravtansine is an ADC composed of an anti-FR α antibody coupled via a cleavable disulfide linker to the maytansinoid DM4 [17,18], a potent tubulin-targeting agent [19,20]. Mirvetuximab soravtansine is currently in clinical development for EOC, where it has exhibited encouraging signals of activity and favorable tolerability as monotherapy [21], underscoring its potential as a suitable partnering agent for combination-based strategies. The distinct and complementary mechanisms of action of mirvetuximab soravtansine and bevacizumab, along with nonoverlapping toxicity profiles, provided a rationale for combining the two agents as a novel avenue for therapeutic intervention in EOC. Additional support for this approach was provided by preclinical studies which showed superior antitumor activity for the combination over single-agent regimens, including in patient-derived models of EOC [22]. Here we report results from the Phase Ib combination trial FORWARD II (NCT02606305) designed to evaluate the safety, tolerability, and clinical activity of mirvetuximab

soravtansine when co-administered with bevacizumab to patients with FR α -positive, platinum-resistant EOC.

2. Patients and methods

2.1. Patient selection and eligibility criteria

Women with histologically-confirmed EOC, primary peritoneal, or fallopian tube cancer who progressed or relapsed within 6 months of completing prior platinum-based therapy were eligible to enroll. Patients needed a minimum requirement of FR α positivity by immunohistochemistry (IHC) on archival tumor samples, generally from initial diagnosis although a fresh biopsy was permitted if archival tumor tissue was not available or sufficient. Following a November 2017 protocol amendment, the threshold was raised from $\geq 25\%$ to $\geq 50\%$ for continuing enrollment into the expansion cohorts due to the evolving understanding of the levels of FR α required for optimal efficacy based on both the current study as well as data from the IMGN853-0401 single agent first in human study. Tumor tissues were analyzed for FR α expression at Ventana Medical Systems, Inc. using a validated assay for sensitivity, specificity, and reproducibility. During escalation, non-measurable disease was permitted and there was no upper limit on the number of previous therapies. For the expansion phase, patients needed at least one lesion measurable by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [23], and up to five prior systemic treatment regimens. All patients were required to be ≥ 18 years of age; 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 platinum refractory disease (defined as disease that has not responded to a platinum-based regimen or progressed while on primary therapy); neuropathy higher than grade 1; history of bowel obstruction (including subocclusive disease) related to underlying disease within 6 months of the start of study treatment; or known hypersensitivity to monoclonal antibody therapy. All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

2.2. Treatment

As part of the dose escalation stage of the Phase Ib combination study FORWARD II, mirvetuximab soravtansine was escalated from 5 to 6 mg/kg (adjusted ideal body weight; 3 and 11 patients, respectively) in combination with 15 mg/kg bevacizumab in patients with FR α -positive, platinum-resistant ovarian cancer. An expansion cohort was subsequently opened to further evaluate the tolerability and clinical activity of the mirvetuximab soravtansine/bevacizumab doublet at full dosing in this patient population. Patients were administered mirvetuximab soravtansine intravenously (IV) at 6 mg/kg (adjusted ideal body weight) followed by 15 mg/kg bevacizumab once every 3 weeks. Patients continued on combination treatment until disease progression, intolerable toxicity or adverse events (AEs), or investigator/patient decision. If bevacizumab treatment was discontinued, patients were permitted to continue participation in the study on mirvetuximab soravtansine as monotherapy. Similarly, if an individual discontinued mirvetuximab soravtansine, bevacizumab monotherapy was allowed until a reason for discontinuation arose. The study was conducted in accordance with US Food and Drug Administration

regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki. The trial was compliant with Institutional Review Board and Independent Ethics Committee requirements and is registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02606305) (NCT02606305).

2.3. Evaluation of toxicity

Baseline assessments included medical history and physical examination, ECOG performance status, blood chemistry and hematology, ophthalmologic exam, pulmonary function tests, and electrocardiogram. Toxicities were 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 dose until 30 days after the patients' last treatment.

2.4. Assessment of clinical activity

During screening, radiological imaging of the chest, abdomen, and pelvis was performed. Overall tumor response was defined by RECIST 1.1 and assessed using computerized tomography (CT) scans or magnetic resonance imaging (MRI). Scans were performed every 6 weeks through week 24, then every 3 months for up to 1 year from randomization, and then every 6 months while on study.

2.5. Statistical considerations

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 April 22, 2019. The median duration of patient follow-up at this time point was 14.8 months (range, 0.76–25.3 months). For safety evaluations, baseline was defined as the last available assessment prior to the first dose of study treatment; 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 assessments, all response-evaluable patients with a post-baseline assessment were included in the objective response rate analyses, along with the corresponding exact 95% CIs based on Clopper-Pearson method. Progression-free survival was analyzed using Kaplan-Meier estimates.

3. Results

3.1. Patient characteristics

Fifty-five patients were enrolled in the expansion cohort and treated with 6 mg/kg mirvetuximab soravtansine and 15 mg/kg bevacizumab. An additional 11 patients received the combination at this full dose level during the escalation stage of the study; these individuals were included in the analyses for a total patient population of 66. The first patient enrolled in December 2015 and, as of the data cutoff date of April 22, 2019, five patients remained on study. Table 1 lists patient demographics for the safety population. The median age was 63 years (range, 39–81) and 58% had an ECOG performance status of 1. The population was heavily pretreated, with a median of three previous systemic treatments (range, 1–8). Forty-one patients (62%) had received prior bevacizumab therapy, with the remaining 25 (38%) being bevacizumab-naïve. A majority (79%) of patients were determined to be either medium or high FRα expressers (50–74% or ≥75% of tumor staining at ≥2+ intensity by IHC, respectively).

3.2. Adverse events

All 66 patients were included in the safety analyses; 65 (98%) had a treatment emergent adverse event (TEAE) deemed related to study drug (either mirvetuximab soravtansine, bevacizumab, or both).

Table 1

Patient demographics and baseline characteristics.

Characteristic	N = 66 ^a N (%)
Age, years	
Median (range)	63 (39–81)
Race	
White	63 (96)
Black or African American	1 (2)
American Indian or Alaskan Native	1 (2)
Not reported	1 (2)
Primary diagnosis	
Epithelial ovarian cancer	52 (79)
Fallopian tube cancer	12 (18)
Primary peritoneal cancer	2 (3)
Histology	
High grade serous	63 (95.5)
Other serous	3 (4.5)
Performance status	
0	38 (58)
1	28 (42)
No. of prior systemic therapies	
Median (range)	3 (1–8)
1–2	27 (41)
3	11 (17)
4–6	26 (39)
7+	2 (3)
FRα expression ^b	
Low	13 (20)
Medium	24 (36)
High	28 (42)
Prior compound exposure	
Platinum	66 (100)
Taxanes	65 (99)
Bevacizumab	41 (62)
PARP inhibitor	20 (30)

^a Includes escalation stage patients (n = 11) who received the combination of mirvetuximab soravtansine and bevacizumab at full dosing.

^b Low, 25–49%; medium, 50–74%; high ≥75% of tumor cells with ≥2+ staining intensity; data missing for one individual.

Treatment-related TEAEs occurring in >15% of patients are summarized in Table 2. The most common adverse reactions were diarrhea (52%), blurred vision (50%), nausea (45%), and fatigue (41%), the majority of which were mild-to-moderate (≤grade 2) and readily managed with supportive care. Ocular side effects are a known consideration for mirvetuximab soravtansine [24]. In this regard, blurred vision as well as keratopathy (24%, grades 1/2) were managed by proactive mitigation strategies (e.g. lubricating and steroid eye drop use). No long-term ocular sequelae were reported and only one patient discontinued treatment due to blurred vision (grade 3). Hematological toxicities seen with the combination were generally modest (thrombocytopenia, 30% [grade 3, 4.5%], neutropenia, 14% [grade 3, 1.5%]; grade 1/2 anemia, 8%; grade 2 leukopenia and grade 4 febrile neutropenia, one patient each). Hypertension was experienced by 17 patients (26%), with over half the cases being grade 3 in severity. However, none of these events met seriousness criteria and no patients discontinued for this reason. Six cases of pneumonitis (9%; grades 1/2), an AE of special interest in the study, were considered treatment related. With the tubulin-directed payload present in mirvetuximab soravtansine, treatment emergent peripheral neuropathy was observed in 35% of patients (of which 12% of cases were grade 2 and no grade ≥3 events were seen in these heavily pretreated patients) and alopecia (grade 1) was reported in a single patient.

Serious adverse events (SAEs) occurred in 28 patients (42%), the most frequent of which were small intestinal obstruction (four patients, 6%), diarrhea, and gastrointestinal hemorrhage (three patients each, 5%). Nineteen patients (29%) discontinued mirvetuximab soravtansine and/or bevacizumab due to treatment-related AEs. The principal toxicity responsible for study discontinuation was thrombocytopenia (five patients, 8%; one grade 3 and four grade 2 events), followed by grade

Table 2
Treatment-related adverse events reported in >15% of patients.

Adverse event	Grades 1–2		Grade 3		All Grades	
	N	%	N	%	N	%
Diarrhea	33	50	1	1.5	34	51.5
Blurred vision	32	48.5	1	1.5	33	50.0
Nausea	29	43.9	1	1.5	30	45.5
Fatigue	26	39.4	1	1.5	27	40.9
Peripheral neuropathy ^a	23	34.8	0	0	23	34.8
Thrombocytopenia	17	25.8	3	4.5	20	30.3
Dry eye	17	25.8	1	1.5	18	27.3
Hypertension	8	12.1	9	13.6	17	25.8
AST increased	13	19.7	4	6.1	17	25.8
Decreased appetite	17	25.8	0	0	17	25.8
ALT increased	13	19.7	3	4.5	16	24.2
Vomiting	15	22.7	1	1.5	16	24.2
Headache	16	24.2	0	0	16	24.2
Keratopathy ^b	16	24.2	0	0	16	24.2
Epistaxis	10	15.2	2	3.0	12	18.2
Abdominal pain	12	18.2	0	0	12	18.2
Dysphonia	10	15.2	0	0	10	15.2
Myalgia	10	15.2	0	0	10	15.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

^a Grouped term that includes neuropathy peripheral, peripheral sensory neuropathy, paresthesia, and hypoesthesia.

^b Grouped term that includes keratopathy, keratitis, corneal deposits, and corneal epithelial microcysts.

3 gastrointestinal hemorrhage and grade 2 pneumonitis (three patients each, 5%), and grade 2 peripheral neuropathy (two patients, 3%); no other events that prompted drug discontinuations were observed in more than one patient. One death related to bevacizumab (intestinal perforation) was seen on study.

3.3. Clinical activity

All 66 patients were evaluable for efficacy analyses. Confirmed tumor responses were observed in 26 patients, consisting of 5 complete responses (CR) and 21 partial responses (PR), for an overall objective response rate (ORR) of 39% (95% CI, 28, 52), and a median duration of response (DOR) of 8.6 months (95% CI, 4.9, 14.9) (Table 3). In an exploratory subset analysis of patients ($n = 16$) that corresponded to the target population enrolled in the pivotal AURELIA study (i.e. bevacizumab-naïve, 1–2 prior therapies [6]), and who also had medium/high FR α levels (i.e., $\geq 50\%$ of cells with at least moderate staining intensity; not a stratification factor in AURELIA), the ORR was 56% (95% CI, 30, 80) and mDOR was 12 months (95% CI, 6.0, 14.9). The median PFS was 6.9 months (95% CI, 4.9, 8.6) for the overall efficacy population (Table 3, Fig. 1) and 9.9 months (95% CI, 4.1, 15.9) for the AURELIA-type patient subset.

Fig. 2A plots changes in target lesion burden as a function of time, based on FR α expression status. Marked disease control at 6 months was seen across all groups with combination treatment. A trend toward

Table 3
Summary of efficacy measures.

Endpoint	Total (N = 66)	AURELIA-type ^a (N = 16)
ORR (confirmed)	39%	56%
95% CI	(28, 52)	(30, 80)
Median DOR (months)	8.6	12.0
95% CI	(4.9, 14.9)	(6.0, 14.9)
Median PFS (months)	6.9	9.9
95% CI	(4.9, 8.6)	(4.1, 15.9)

ORR, objective response rate; DOR, duration of response; PFS, progression-free survival.

^a AURELIA-type patient subset: bevacizumab-naïve and 1–2 prior lines of therapy, plus medium/high FR α expression.

improved duration of response and time on treatment was observed with increasing tumor FR α expression, including 27% of high FR α patients (7/26) having not progressed at 12 months. Within in the AURELIA-type subgroup (Fig. 2B), the majority of patients experienced tumor shrinkage and more consistent, durable responses were seen in high FR α expressers, in agreement with the overall population trend. An example of an objective response in a patient with recurrent, high-grade serous EOC is shown in Fig. 2C. After two cycles, the patient achieved complete clearance of multiple target lesions present in the omentum/peritoneum and lung. The patient remained on study for five treatment cycles before discontinuing due to an AE (grade 4 hyperbilirubinemia; in the context of complementary/alternative medicine use); persistence of non-target lesions at this time resulted in an overall assessment of a partial response.

4. Discussion

Angiogenesis plays a central role in EOC oncogenesis and progression [25]; accordingly, this malignancy has long been considered amenable to the application of antiangiogenic therapeutics [26]. In the pivotal studies that led to approval of bevacizumab alongside chemotherapy, efficacy was consistently demonstrated with regard to PFS; however, less reliable effects were seen with other measures of activity, such as overall survival [27,28]. Thus, an opportunity exists to improve the efficacy of antiangiogenic therapy in EOC, and investigation of alternate strategies with optimized combinatorial partners is warranted for this disease. In this regard, FR α represents a unique and actively pursued molecular target in EOC [13,29]. To date, a number of strategies have been explored to therapeutically exploit expression of this receptor, yet the full potential of this approach for improving patient outcomes in ovarian and other high FR α -expressing cancers remains to be realized [11]. As an ADC, mirvetuximab soravtansine provides site-directed delivery of cytotoxic amounts of its DM4 payload directly to tumors, affording a means to achieve meaningful therapeutic indices [30]. In line with preclinical expectations, this study showed mirvetuximab soravtansine to be a well-tolerated and active partnering agent for bevacizumab in the setting of platinum-resistant EOC.

The study population comprised 66 patients, including all those accrued into the expansion cohort plus eleven from the escalation stage who received full combination dosing of 15 mg/kg bevacizumab with 6 mg/kg AIBW mirvetuximab soravtansine; the latter representing the Phase 3 monotherapy dose [31]. The most frequent treatment-related AEs seen with the combination included predominantly low grade, manageable gastrointestinal or general disorders (diarrhea, nausea, and fatigue). Neuropathy was not a major clinical concern, with no patients experiencing any grade 3 or higher events and only two discontinuations due to persistent grade 2 peripheral neuropathy occurred. Importantly, no new safety signals emerged, nor any clinically significant potentiation of the anticipated toxicities for either agent. For example, low grade and reversible ocular side effects are commonly observed with mirvetuximab soravtansine administration, attributed to off-target effects on the corneal epithelium [32]. Blurred vision and keratopathy were reported at frequencies and grade comparable to those seen in prior monotherapy trials in patients with EOC [24,33,34]. Bevacizumab-associated AEs are well described and include hypertension, thromboembolic events, wound-healing complications, gastrointestinal perforation, bleeding, and proteinuria [25]. In this study, the most common adverse effect related to bevacizumab was hypertension, with all cases being readily managed and none leading to discontinuation. Other serious complications, such as gastrointestinal hemorrhage and perforations, occurred at frequencies similar to that expected with bevacizumab-containing therapy [35].

A key finding of the safety analyses was that the mirvetuximab soravtansine/bevacizumab combination was characterized by a low incidence of myelosuppressive toxicities typically seen when bevacizumab is administered together with chemotherapy. Specifically,

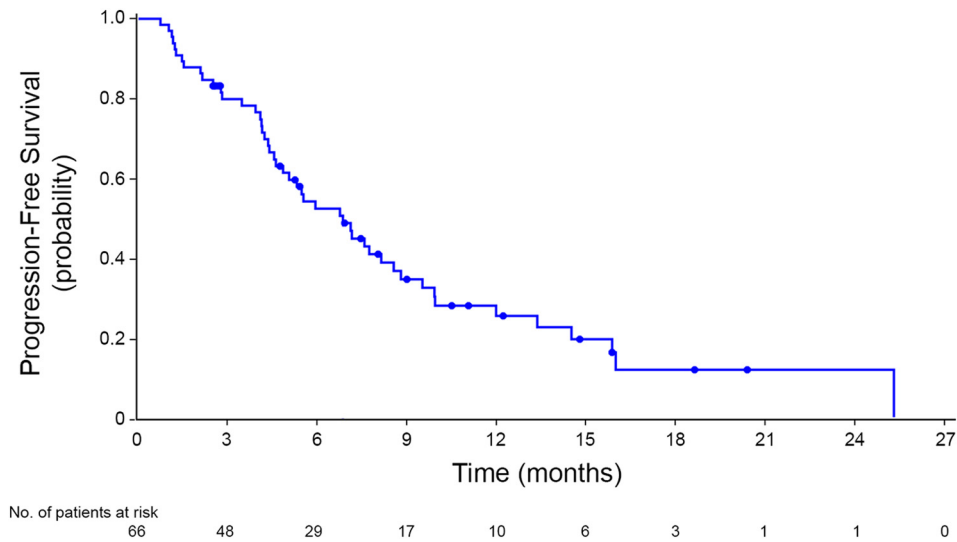


Fig. 1. Kaplan-Meier analysis of progression-free survival (PFS) in all patients (median 6.9 months).

moderate or severe cytopenias (neutropenia, leukopenia) were less common than those reported for bevacizumab with standard chemotherapy in the AURELIA study [6]. Thrombocytopenia, a potentially overlapping toxicity for mirvetuximab soravtansine and bevacizumab [36], was the primary cytopenia seen with combination treatment and also the leading individual cause of AE-related discontinuations (five

patients in total). Of note, four of these cases involved persistent grade 2 thrombocytopenia, and only one was due to a grade 3 event. Moreover, none of the thrombocytopenias seen in any patient on study met seriousness criteria, even in those who discontinued due to this toxicity.

The combination of mirvetuximab soravtansine/bevacizumab is an active regimen in heavily pretreated, platinum-resistant EOC. Indeed,

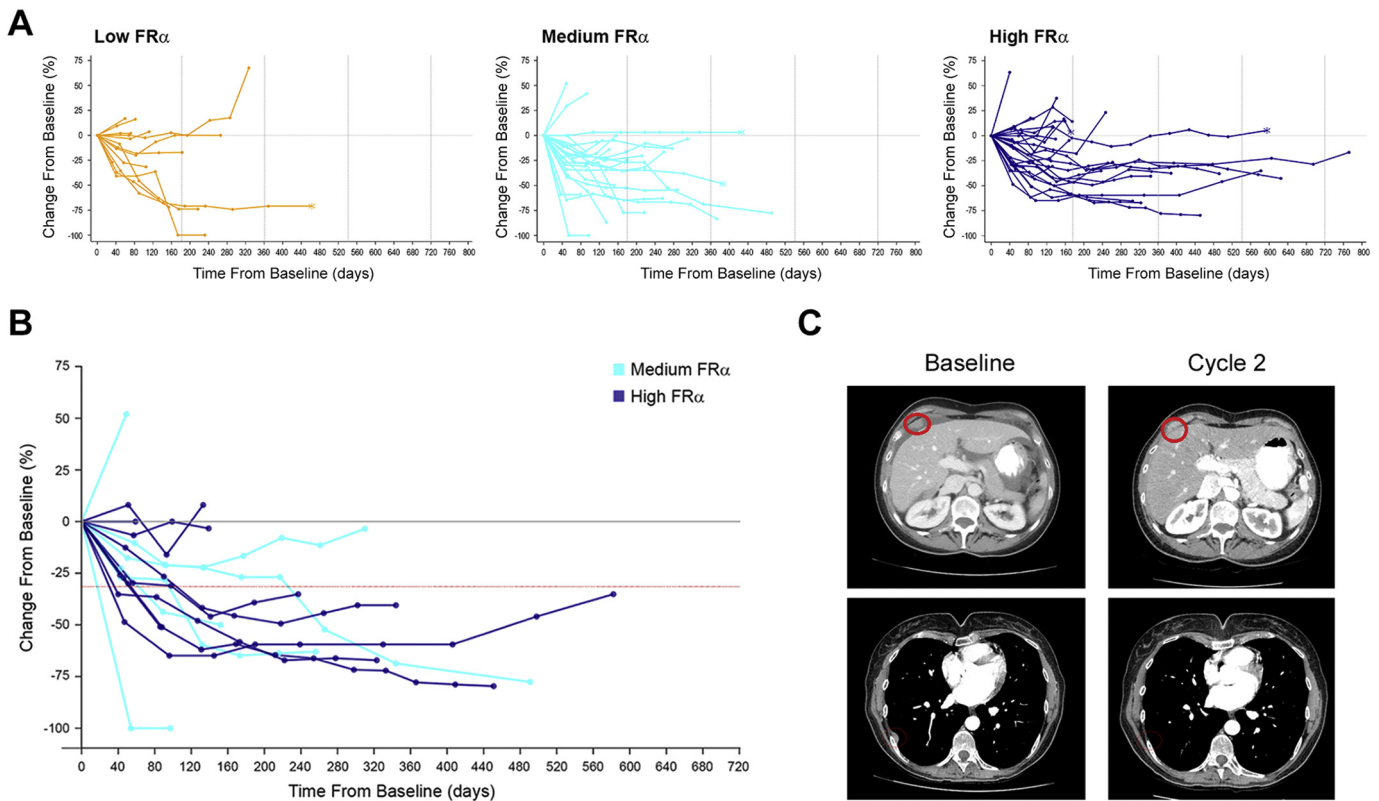


Fig. 2. (A) Percent tumor change in target lesions from baseline in patients with platinum-resistant ovarian cancer grouped by folate receptor alpha (FR α) expression. Two high FR α patients are not presented in the plot; target lesion measurements were not available for these individuals. Dashed vertical lines represent 6, 12, 18, and 24-month intervals from baseline. (B) Percent tumor change in target lesions in the AURELIA-type subpopulation grouped by FR α expression. Dashed red line in plot corresponds to 30% decrease in tumor size. (C) Activity of the mirvetuximab soravtansine/bevacizumab combination in a patient with platinum-resistant EOC with an overall partial response to therapy. Results are shown for a recurrent serous ovarian cancer patient with large, measurable metastases present in the omentum/peritoneum (upper panels) and lung (lower panels). Red circles show complete regression and clearance of target lesions by computed tomography after two cycles of treatment.

given that the majority of patients (~60%) in the present study had received three or more previous lines of systemic therapy, the ORR and median PFS measures of 39% and 6.9 months, respectively, compare favorably with the benchmark values of 27% and 6.7 months seen with bevacizumab/chemotherapy in the AURELIA trial [6]. Three different chemotherapeutics were evaluated as part of AURELIA (paclitaxel, pegylated liposomal doxorubicin [PLD], and topotecan) and, while superiority could not be assessed since the trial design did not randomize the individual agents, highest activity was seen in the paclitaxel/bevacizumab cohort (53% ORR and median PFS 10.4 months) [37]. Interestingly, comparable efficacy measures – 56% ORR (with a 12-month duration of response) and 9.9-month median PFS – were seen in the 'AURELIA-type' subgroup analysis undertaken here. With the caveat of low numbers, this finding suggests that combining mirvetuximab soravtansine and bevacizumab may be similarly effective as paclitaxel/bevacizumab therapy in a similar patient population, and with a differentiated safety profile that includes potentially more manageable neuropathy and negligible alopecia.

In the real-world clinical setting the optimal partner for bevacizumab in EOC has not yet been established, with the choice of cytotoxic agent used for recurrent, platinum-resistant disease typically based on prior treatment history and the ability of the patient to tolerate further anticipated toxicities [38]. Of relevance, results from a multicenter observational study conducted in Korean patients with platinum-resistant EOC (REBECA; Real-world effectiveness of bevacizumab based on AURELIA) were recently reported [39]. Consistent with AURELIA, patients who received the paclitaxel/bevacizumab regimen showed superior response rates and PFS intervals over those that received PLD/bevacizumab (48.6% vs. 30.6% and 8.3 vs. 5.4 months, respectively). However, the majority of patients (66%) were treated with the PLD/bevacizumab doublet, compared to fewer than 10% who received paclitaxel/bevacizumab [39]. This is because PLD/bevacizumab therapy was characterized by a lower incidence of high-grade adverse events, especially hematologic toxicities, compared to paclitaxel/bevacizumab. In this context, it is reasonable to suggest that the early evidence of tolerability and antitumor activity afforded by the addition of mirvetuximab soravtansine to bevacizumab reported here has potential for improving outcomes as part of general oncology practice.

Overall, the current findings confirm the feasibility of combining mirvetuximab soravtansine with bevacizumab for the treatment of patients with platinum-resistant recurrences of EOC. The encouraging clinical activity and differentiated safety profile compared to chemotherapy suggests that the combination may yield benefit for this difficult-to-treat population and further evaluation of this novel doublet in a randomized study is warranted. Accordingly, an ongoing FORWARD II expansion cohort is assessing the combination in 'platinum-agnostic', less heavily pre-treated patients (1–3 therapies, irrespective of platinum sensitivity or prior bevacizumab exposure). Together, the results will define a framework for continued evaluation and application of mirvetuximab soravtansine/bevacizumab-based therapy in relapsed EOC.

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Author contribution

D.M.O., U.A.M., M.J.B., I.V., L.P.M., A.G.M., and K.N.M. contributed to the study design.

D.M.O., U.A.M., M.J.B., C.M.C., L.G., I.V., L.P.M., G.M.M.S., A.G.M., R.B., R.T.P., and K.N.M. contributed patients to the trial.

All authors contributed to the collection and assembly of data.

D.M.O., U.A.M., M.J.B., C.M.C., L.G., I.V., L.P.M., A.G.M., and K.N.M. contributed to data analysis and interpretation.

All authors contributed to writing and approval of the final manuscript.

Declaration of competing interest

This study was supported by ImmunoGen, Inc. Karim Malek is an employee of ImmunoGen. There are no other conflicts of interest to declare.

References

- [1] U.A. Matulonis, Management of newly diagnosed or recurrent ovarian cancer, *Clin. Adv. Hematol. Oncol.* 16 (2018) 426–437.
- [2] S. Pignata, C.C. S, A. Du Bois, P. Harter, F. Heitz, Treatment of recurrent ovarian cancer, *Ann. Oncol.* 28 (2017) viii51–viii56.
- [3] C. Marth, D. Reimer, A.G. Zeimet, Front-line therapy of advanced epithelial ovarian cancer: standard treatment, *Ann. Oncol.* 28 (2017) viii36–viii39.
- [4] A. Davis, A.V. Tinker, M. Friedlander, "Platinum resistant" ovarian cancer: what is it, who to treat and how to measure benefit? *Gynecol. Oncol.* 133 (2014) 624–631.
- [5] L. Rossi, M. Verrico, E. Zaccarelli, A. Papa, M. Colonna, M. Strudel, et al., Bevacizumab in ovarian cancer: a critical review of phase III studies, *Oncotarget* 8 (2017) 12389–12405.
- [6] E. Pujade-Lauraine, F. Hilpert, B. Weber, A. Reuss, A. Poveda, G. Kristensen, et al., Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial, *J. Clin. Oncol.* 32 (2014) 1302–1308.
- [7] C. Aghajanian, S.V. Blank, B.A. Goff, P.L. Judson, M.G. Teneriello, A. Husain, et al., OCEANS: a randomized, double-blind, placebo-controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, *J. Clin. Oncol.* 30 (2012) 2039–2045.
- [8] R.L. Coleman, M.F. Brady, T.J. Herzog, P. Sabbatini, D.K. Armstrong, J.L. Walker, et al., Bevacizumab and paclitaxel-carboplatin chemotherapy and secondary cytoreduction in recurrent, platinum-sensitive ovarian cancer (NRG Oncology/Gynecologic Oncology Group study GOG-0213): a multicentre, open-label, randomised, phase 3 trial, *Lancet Oncol.* 18 (2017) 779–791.
- [9] R.A. Burger, M.F. Brady, M.A. Bookman, G.F. Fleming, B.J. Monk, H. Huang, et al., Incorporation of bevacizumab in the primary treatment of ovarian cancer, *N. Engl. J. Med.* 365 (2011) 2473–2483.
- [10] T.J. Perren, A.M. Swart, J. Pfisterer, J.A. Ledermann, E. Pujade-Lauraine, G. Kristensen, et al., A phase 3 trial of bevacizumab in ovarian cancer, *N. Engl. J. Med.* 365 (2011) 2484–2496.
- [11] M.J. Birrer, I. Betella, L.P. Martin, K.N. Moore, Is targeting the folate receptor in ovarian cancer coming of age? *Oncologist* 24 (2019) 425–429.
- [12] H. Elnakat, M. Ratnam, Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy, *Adv. Drug Deliv. Rev.* 56 (2004) 1067–1084.
- [13] I.B. Vergote, C. Marth, R.L. Coleman, Role of the folate receptor in ovarian cancer treatment: evidence, mechanism, and clinical implications, *Cancer Metastasis Rev.* 34 (2015) 41–52.
- [14] C. Marchetti, I. Palaia, M. Giorgini, C. De Medici, R. Iadarola, L. Verdecchia, et al., Targeted drug delivery via folate receptors in recurrent ovarian cancer: a review, *Onco. Targets Ther.* 7 (2014) 1223–1236.
- [15] R.V. Chari, M.L. Miller, W.C. Widdison, Antibody-drug conjugates: an emerging concept in cancer therapy, *Angew. Chem.* 53 (2014) 3796–3827.
- [16] M.J. Birrer, K.N. Moore, I. Betella, R.C. Bates, Antibody-drug conjugate-based therapeutics: state of the science, *J. Natl. Cancer Inst.* 111 (2019) 538–549.
- [17] C.C. Gunderson, K.N. Moore, Mirvetuximab soravtansine, FR α -targeting ADC; treatment of epithelial ovarian cancer, *Drugs Future* 41 (2016) 539–545.
- [18] O. Ab, K.R. Whiteman, L.M. Bartle, X. Sun, R. Singh, D. Tavares, et al., IMGN853, a folate receptor-alpha (FR α)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against FR α -expressing tumors, *Mol. Cancer Ther.* 14 (2015) 1605–1613.
- [19] E. Orudjev, M. Lopus, L. Wilson, C. Audette, C. Provenzano, H. Erickson, et al., Maytansinoid-antibody conjugates induce mitotic arrest by suppressing microtubule dynamic instability, *Mol. Cancer Ther.* 9 (2010) 2700–2713.
- [20] V.S. Goldmacher, C.A. Audette, Y. Guan, E.H. Sidhom, J.V. Shah, K.R. Whiteman, et al., High-affinity accumulation of a maytansinoid in cells via weak tubulin interaction, *PLoS One* 10 (2015), e0117523.
- [21] K.N. Moore, L.P. Martin, D.M. O'Malley, U.A. Matulonis, J.A. Konner, I. Vergote, et al., A review of mirvetuximab soravtansine in the treatment of platinum-resistant ovarian cancer, *Future Oncol.* 14 (2018) 123–136.
- [22] J.F. Ponte, O. Ab, L. Lanieri, J. Lee, J. Coccia, L.M. Bartle, et al., Mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, potentiates the activity of standard of care therapeutics in ovarian cancer models, *Neoplasia* 18 (2016) 775–784.
- [23] E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, et al., New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1), *Eur. J. Cancer* 45 (2009) 228–247.

- [24] K.N. Moore, H. Borghaei, D.M. O'Malley, W. Jeong, S.M. Seward, T.M. Bauer, et al., Phase 1 dose-escalation study of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in patients with solid tumors, *Cancer* 123 (2017) 3080–3087.
- [25] D.K. Chellappan, K.H. Leng, L.J. Jia, N. Aziz, W.C. Hoong, Y.C. Qian, et al., The role of bevacizumab on tumour angiogenesis and in the management of gynaecological cancers: a review, *Biomed. Pharmacother.* 102 (2018) 1127–1144.
- [26] J.A. Ledermann, C. Marth, M.S. Carey, M. Birrer, D.D. Bowtell, S. Kaye, et al., Role of molecular agents and targeted therapy in clinical trials for women with ovarian cancer, *Int. J. Gynecol. Cancer* 21 (2011) 763–770.
- [27] A.M. Oza, A.D. Cook, J. Pfisterer, A. Embleton, J.A. Ledermann, E. Pujade-Lauraine, et al., Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial, *Lancet Oncol.* 16 (2015) 928–936.
- [28] J. Liu, U.A. Matulonis, New strategies in ovarian cancer: translating the molecular complexity of ovarian cancer into treatment advances, *Clin. Cancer Res.* 20 (2014) 5150–5156.
- [29] R.J. Lutz, Targeting the folate receptor for the treatment of ovarian cancer, *Transl. Cancer Res.* 4 (2015) 118–126.
- [30] A.C. Parslow, S. Parakh, F.T. Lee, H.K. Gan, A.M. Scott, Antibody-drug conjugates for cancer therapy, *Biomedicines* 4 (2016) 14.
- [31] K.N. Moore, I. Vergote, A. Oaknin, N. Colombo, S. Banerjee, A. Oza, et al., FORWARD 1: a phase III study of mirvetuximab soravtansine versus chemotherapy in platinum-resistant ovarian cancer, *Future Oncol.* 14 (2018) 1669–1678.
- [32] U.A. Matulonis, M.J. Birrer, D.M. O'Malley, K.N. Moore, J. Konner, L. Gilbert, et al., Evaluation of prophylactic corticosteroid eye drop use in the management of corneal abnormalities induced by the antibody-drug conjugate mirvetuximab soravtansine, *Clin. Cancer Res.* 25 (2018) 1727–1736.
- [33] K.N. Moore, L.P. Martin, D.M. O'Malley, U.A. Matulonis, J.A. Konner, R.P. Perez, et al., Safety and activity of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a phase I expansion study, *J. Clin. Oncol.* 35 (2017) 1112–1118.
- [34] L.P. Martin, J.A. Konner, K.N. Moore, S.M. Seward, U.A. Matulonis, R.P. Perez, et al., Characterization of folate receptor alpha (FRalpha) expression in archival tumor and biopsy samples from relapsed epithelial ovarian cancer patients: a phase I expansion study of the FRalpha-targeting antibody-drug conjugate mirvetuximab soravtansine, *Gynecol. Oncol.* 147 (2017) 402–407.
- [35] M.C. Liu, K.S. Tewari, Anti-angiogenesis therapy, synthetic lethality, and checkpoint inhibition in ovarian cancer: state of the science and novel combinations, *Drugs Context* 7 (2018) 212558.
- [36] F.A. Schutz, D.L. Jardim, Y. Je, T.K. Choueiri, Haematologic toxicities associated with the addition of bevacizumab in cancer patients, *Eur. J. Cancer* 47 (2011) 1161–1174.
- [37] A.M. Poveda, F. Selle, F. Hilpert, A. Reuss, A. Savarese, I. Vergote, et al., Bevacizumab combined with weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan in platinum-resistant recurrent ovarian cancer: analysis by chemotherapy cohort of the randomized phase III AURELIA trial, *J. Clin. Oncol.* 33 (2015) 3836–3838.
- [38] E.C. McClung, R.M. Wenham, Profile of bevacizumab in the treatment of platinum-resistant ovarian cancer: current perspectives, *Int. J. Women's Health* 8 (2016) 59–75.
- [39] J.Y. Lee, J.Y. Park, S.Y. Park, J.W. Lee, J.W. Kim, Y.B. Kim, et al., Real-world effectiveness of bevacizumab based on AURELIA in platinum-resistant recurrent ovarian cancer (REBECA): a Korean Gynecologic Oncology Group study (KGOG 3041), *Gynecol. Oncol.* 152 (2019) 61–67.