Gynecologic Oncology 151 (2018) 46–52

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Safety and activity findings from a phase 1b escalation study of mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with carboplatin in patients with platinum-sensitive ovarian cancer

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HIGHLIGHTS

- Combining mirvetuximab soravtansine and carboplatin is a promising approach for platinum-sensitive ovarian cancer.
- The combination was well tolerated; low incidence of severe hematologic/neuropathic toxicities, and no new safety signals.
- A highly active regimen, with a confirmed objective response rate of 71%.
- Better median PFS (15 months) compared to historical carboplatin plus chemotherapy phase III trials.

ARTICLE INFO

Article history:
Received 25 May 2018
Received in revised form 18 July 2018
Accepted 21 July 2018
Available online 6 August 2018

Keywords:
Antibody-drug conjugate
Combination therapy
Clinical trial
Ovarian cancer

ABSTRACT

Purpose. To evaluate the safety profile and preliminary antitumor activity of mirvetuximab soravtansine when administered in combination with carboplatin to relapsed ovarian cancer patients.

Methods. Patients with recurrent, platinum-sensitive epithelial ovarian or fallopian tube cancer were enrolled. Eligibility included a minimum requirement of tumor FRα positivity (≥25% of cells with ≥2+ staining intensity). Patients received escalating doses of mirvetuximab soravtansine and carboplatin on day 1 of a 21-day cycle (once every 3 weeks). Mirvetuximab soravtansine maintenance therapy was permitted, at the investigators discretion, following cessation of carboplatin treatment. Adverse events, tumor response, and progression-free survival (PFS) were determined.

Results. Eighteen patients were enrolled and dosed with combination therapy; thirteen continued with mirvetuximab soravtansine maintenance following carboplatin discontinuation. Mirvetuximab soravtansine dosing was escalated from 5 to 6 mg/kg (adjusted ideal body weight) and carboplatin from AUC4 to AUC5. Adverse events were generally mild (≤ grade 2) with nausea, diarrhea, thrombocytopenia, blurred vision, and fatigue being the most common treatment-emergent toxicities. For all evaluable patients ($n = 17$), the confirmed objective response rate (ORR) was 71%, including three complete responses and nine partial responses, and the median PFS was 15 months. A median duration of response was not reached.

Conclusion. These data demonstrate that mirvetuximab soravtansine combined with carboplatin is a well-tolerated and highly active regimen in recurrent, platinum-sensitive ovarian cancer. Further evaluation of this combination in a randomized fashion is warranted.

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https://doi.org/10.1016/j.ygyno.2018.07.017
0090-8258/

1. Introduction

The foundation of standard-of-care treatment for women diagnosed with epithelial ovarian cancer (EOC) is cytoreductive surgery and chemotherapy using a platinum-based combination regimen, most commonly the carboplatin-paclitaxel doublet [1]. Despite the highly chemosensitive nature of EOC, and multiple attempts to improve upon this doublet with changes in administration frequency and route [2,3], this approach has reached a plateau of effectiveness with respect to patient survival [4,5] and the vast majority of women still relapse with eventual development of platinum-resistant disease, classified based on the time to relapse from the last dose of a platinum agent (the platinum-treatment free interval, TFIp). Relapse within six months of completing initial therapy is classified as primary platinum-resistant. Relapse beyond six months is considered platinum-sensitive disease and these patients have a high likelihood of responding to additional platinum-based therapy [6]. In this setting, carboplatin is generally administered as part of another platinum-chemotherapy combination, typically alongside pegylated liposomal doxoribucin (PLD), gemcitabine, or a taxane [7–10]. More recently, the integration of molecularly targeted agents, such as bevacizumab and PARP inhibitors, into management paradigms for platinum-sensitive patients have resulted in meaningful improvements in progression-free, and in the case of bevacizumab, overall survival [11–15]. Despite this, survival outcomes and durations of response in this population remain disappointingly poor. Moreover, for some patients, re-challenge with taxanes is not an option due to residual neuropathy, history of taxane allergies, and/or an aversion to repeat alopecia. While combinations of carboplatin with gemcitabine or PLD appear as effective as paclitaxel and carboplatin, they do exhibit higher levels of hematologic toxicity and, in the case of gemcitabine combinations, the schedule can be less convenient. Alterative platinum-based combinations that are highly effective and reduce toxicity – both hematologic and neuropathic - are urgently required.

Folate receptor alpha (FRα) is a transmembrane glycoprotein that facilitates the unidirectional transport of folates into cells [16]. Although absent from normal ovarian epithelium, aberrant overexpression of FRα is seen in approximately 80% of EOC tumors [17,18], and elevated receptor expression may be a negative prognostic factor with respect to chemotherapeutic response in this malignancy [19]. Accordingly, FRα is an attractive candidate for molecularly targeted approaches in EOC designed to exploit this differential distribution pattern as a means of therapeutic intervention [20]. In this regard, as a cell surface molecule and through its ability to internalize large molecules, FRα is an ideal target for antibody-drug conjugate (ADC)-based therapeutic strategies. ADCs are a clinically validated class of therapeutic agents, comprising a monoclonal antibody that recognizes tumor-associated antigens to which a potent cytotoxic agent is conjugated *via* stable linkage [21]. In this manner, ADCs provide a mechanism for site-directed delivery of cytocidal amounts of therapeutic agents directly to tumors, thus affording an opportunity to achieve meaningful therapeutic indices while minimizing systemic toxicities [22].

Mirvetuximab soravtansine (IMGN853) is an ADC consisting of a humanized FRα-targeting antibody coupled to the maytansinoid DM4 [23]. High affinity binding to FRα and internalization of the conjugate molecule results in intracellular accumulation of DM4 - which subsequently acts as a potent antimitotic agent *via* its ability to suppress microtubule dynamics [24,25]. In addition, mirvetuximab soravtansine contains a cleavable linker which allows active DM4 metabolites to diffuse into and kill proximal tumor cells, an effect known as bystander killing [26]. The potential for mirvetuximab soravtansine to substitute for paclitaxel, based on their similar modes of action as microtubule inhibitors, as part of a combinatorial strategy alongside carboplatin within the context of platinum sensitivity has been examined preclinically [27]. The combination was highly synergistic *in vitro* and displayed superior antitumor activity *in vivo* compared to single-agent exposure and, importantly, was more efficacious than corresponding carboplatin/paclitaxel and carboplatin/PLD doublets in patient-derived xenograft models [27]. These findings provided a rationale for combining mirvetuximab soravtansine with carboplatin as a novel approach for optimizing response to platinum therapy in EOC.

The maturing clinical profile of mirvetuximab soravtansine has revealed favorable tolerability when administered as monotherapy to patients with advanced ovarian cancer, consisting primarily of low grade and manageable gastrointestinal events, as well as reversible blurred vision that can be mitigated by appropriate ocular management procedures [28]. Importantly, mirvetuximab soravtansine is also characterized by a low incidence of toxicities commonly seen with chemotherapy, including bone marrow suppression and alopecia [29,30], further identifying this agent as an attractive candidate for combination-based therapeutic approaches. Here we report the findings of an escalation cohort study, opened as part of a Phase Ib combination trial (FORWARD II; NCT02606305), designed to evaluate the safety, tolerability, and preliminary activity of mirvetuximab soravtansine when administered in combination with carboplatin to patients with platinum-sensitive EOC.

2. Patients and methods

2.1. Patient selection and eligibility criteria

Adults with relapsed EOC, primary peritoneal, or fallopian tube cancer were eligible to enroll. Patients were required to have potentially platinum-sensitive disease, defined as disease that responded to platinum therapy and did not progress within 6 months of completing the treatment. There was no upper limit on the number of prior treatment regimens received. Patients could have measurable or non-measureable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [31], with tumors having met the minimum requirement of FRα positivity by immunohistochemistry (IHC; ≥25% of tumor staining at ≥2+ intensity). Patients were also 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; neuropathy greater than grade 1; any active or chronic corneal disorder; or known hypersensitivity to monoclonal antibody therapy. All patients provided written informed consent in accordance with federal, local and institutional guidelines.

2.2. Treatment

Mirvetuximab soravtansine was delivered intravenously (IV) on day 1 of each 21-day cycle; carboplatin was administered IV following completion of the mirvetuximab soravtansine infusion. Dose escalation followed a standard 3 + 3 design, and was determined by the lead investigators in collaboration with the sponsor. The starting dose of mirvetuximab soravtansine was 5 mg/kg, calculated using adjusted ideal body weight (AIBW), which is one dose level lower than the monotherapy dose of 6 mg/kg AIBW chosen for further development during the first-in-human trial of this agent [29]. Carboplatin dosing was escalated from an AUC4 to AUC5 after the initial patient cohort was treated. Carboplatin treatment was discontinued after 6 or more cycles at the discretion of the investigator based on the risk/benefit profile for the patient. Patients were permitted to continue on mirvetuximab soravtansine if they met treatment criteria and had at least stable disease per RECIST v1.1, until intolerable toxicity or adverse events (AEs), disease progression, or investigator/patient decision. 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 Institutional Review Board and Independent Ethics Committee requirements. This trial is registered at Clinicaltrials.gov (NCT02606305).

2.3. Evaluation of toxicity

Baseline assessments included medical history and physical examination, ECOG performance status, blood chemistry and hematology, 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 study dose until 30 days after the patients' last dose. Because ocular adverse events are an important clinical consideration for patients receiving mirvetuximab soravtansine, baseline ophthalmologic exams were performed that included indirect fundoscopy, slit-lamp examination under dilatation, intraocular pressure measurement, and corneal photography. Ocular symptom assessment was performed prior to the start of each cycle by the treating physician. Patients who experienced ocular symptoms had a complete ophthalmologic exam performed every other cycle from the point where toxicity was first reported, including patients with blurred vision but normal eye examinations. All patients received a complete ophthalmologic exam at the end of treatment or 30-day follow up visit.

2.4. Assessment of clinical activity

During screening, radiological imaging of the chest, abdomen, and pelvis was performed. For patients with measureable disease, overall tumor response was defined by RECIST 1.1 and assessed using computerized tomography scans performed every 6 weeks.

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 February 1, 2018. The median duration of patient follow-up at this time point was 15.9 months. For the safety evaluations, baseline was defined as the last available assessment prior to the first dose of study treatment and 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 the efficacy assessments, all response-evaluable patients who had 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

Between December 2015 and November 2016 eighteen patients with relapsed, platinum-sensitive ovarian cancer were enrolled in the escalation cohort and received combination treatment using the once every three weeks dosing schedule. Patient demographics and baseline characteristics are summarized in Table 1. The median age was 66 years (range, 47–82) and patients were diagnosed with either epithelial ovarian (89%) or fallopian tube cancer (11%). A majority of individuals had a platinum-treatment free interval of 12 months or less (61%). All patients were white and most had an ECOG performance status of 1 (61%). The population received a median of 2.5 prior systemic therapies (range, 1–6), with all individuals having prior platinum and taxane exposure.

3.2. Dose escalation and treatment administered

Dose escalation is summarized in Table 2. The first four patients received mirvetuximab soravtansine at 5 mg/kg (AIBW) and carboplatin at AUC4; carboplatin dosing was escalated to AUC5 for the next 4 patients. Ten patients were subsequently treated at a dose of 6 mg/kg mirvetuximab soravtansine with carboplatin at AUC5, the highest prespecified dose level as per protocol. At this level, one dose limiting toxicity (DLT; Grade 3 vasculitis) was observed. Overall, patients received a median of seven cycles of carboplatin (range 2–17), and 72% ($n = 13$) continued with mirvetuximab soravtansine maintenance therapy. As of February 2018, six individuals (33%) remained on treatment.

3.3. Adverse events

All 18 patients were included in the safety analyses. Treatment emergent adverse events (TEAEs) occurring in ≥20% of patients, across all dose cohorts, are summarized in Table 3. The major adverse reactions observed were nausea (67%), diarrhea, thrombocytopenia, and blurred vision (each 61%). In the majority of cases, these were mild-to-moderate (≤grade 2) and managed with appropriate supportive care. Ocular effects were previously identified as AEs of interest for mirvetuximab soravtansine [29]; both the blurred vision (grade 1 and 2 incidence of 28% and 33%, respectively) and keratopathy (6% and 17% grade 1/2), were completely reversible. Fatigue and neutropenia were also seen at a high frequency (56%), with the latter event accounting for the only grade 4 toxicity observed (one patient, 6%) and with no cases of febrile neutropenia seen. The prevalence of peripheral neuropathy (grouped term that included occurrences of neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and hypoesthesia) consisted predominantly of grade 1 events (28%). Five cases of pneumonitis (four grade 1 and one grade 2), considered an adverse event of special interest in the current study, were reported across all dose levels.

One patient in the full dose cohort experienced a serious adverse event (SAE) considered related to treatment (grade 3 diarrhea; Table 2). One patient who received full dosing developed grade 2 motor neuropathy which led to study discontinuation but resolved after withdrawal. Grade 2 infusion reactions seen in two additional patients treated at the initial 5 mg/kg mirvetuximab soravtansine/carboplatin AUC4 level resulted in discontinuation of carboplatin after

Table 1
Patient demographics and baseline characteristics.

Characteristic	$n = 18$ N (%)
Age, years	
Median (range)	66 (47–82)
Race	
White	18 (100)
Primary diagnosis	
Epithelial ovarian cancer	16 (89)
Fallopian tube cancer	2 (11)
Performance status	
0	7 (39)
1	11 (61)
No. of prior systemic therapies	
Median (range)	2.5 (1–6)
1–2	9 (50)
3	5 (28)
4–6	4 (22)
Platinum-free treatment interval[a]	
< 6 months	1 (6)
6–12 months	10 (56)
> 12 months	5 (28)
FRα expression[b]	
Low	7 (39)
Medium	4 (22)
High	7 (39)
Prior compound exposure	
Platinum	18 (100)
Taxane	18 (100)
Bevacizumab	5 (28)
PARP inhibitor	9 (50)

[a] Data not available for 2 individuals.
[b] Low, 25–49%; Medium, 50–74%; High ≥75% of tumor cells with ≥2 + staining intensity.

Table 2
Summary of dose escalation.

Mirvetuximab soravtansine dose	Carboplatin dose	No. of patients	Treatment-related SAEs and DLTs
5 mg/kg	AUC4	4	None
5 mg/kg	AUC5	4	None
6 mg/kg	AUC5	10	SAE: Diarrhea (grade 3) DLT: Vasculitis (grade 3)

3 and 7 cycles, respectively; both patients continued with mirvetuximab soravtansine maintenance therapy. Dose reductions of mirvetuximab soravtansine due to a TEAE occurred in three patients (16.7%), with blurred vision responsible for two of these cases. Carboplatin dose reductions due to TEAE occurred in four patients (22%) with thrombocytopenia as the primary reason (three cases). Indeed, thrombocytopenia was the principal adverse event responsible for dose modifications across the study, additionally prompting dose delays of the combination in seven patients (39%). No deaths related to either drug were seen during the course of the study.

3.4. Clinical activity

Seventeen patients were evaluable for efficacy analyses, as one individual withdrew from study prior to their first post-treatment assessment. Confirmed tumor responses were observed in 12 individuals (all with measurable disease), consisting of three complete responses (CR) and nine partial responses (PR), for an overall objective response rate (ORR) of 71% (Table 4). Fig. 1 displays the change in patient target lesion burden as a function of time, with individuals grouped according to FRα levels. It has previously been demonstrated that higher tumor receptor expression is associated with greater antitumor activity when mirvetuximab soravtansine is administered as monotherapy [32]. Consistent with this, eight of the responses occurred in the subset of patients with medium/high FRα expression ($n = 10$), resulting in an ORR of 80%. The median PFS for the overall population was 15 months (95% CI, 9.9, —) and, at time of analyses, median duration of response (DOR) was not reached (Fig. 2, Table 4) with five responders and one patient with prolonged stable disease still receiving mirvetuximab soravtansine monotherapy.

Table 3
Treatment emergent adverse events reported in >20% of patients.

	Grades 1–2		Grade 3		Grade 4		All grades	
Adverse event	N	%	N	%	N	%	N	%
Nausea	12	66.7	0	0	0	0	12	66.7
Diarrhea	10	55.6	1	5.6	0	0	11	61.1
Thrombocytopenia	8	44.4	3	16.7	0	0	11	61.1
Vision blurred	11	61.1	0	0	0	0	11	61.1
Fatigue	9	50.0	1	5.6	0	0	10	55.6
Neutropenia	5	27.8	4	22.2	1	5.6	10	55.6
Vomiting	9	50.0	0	0	0	0	9	50.0
Hypokalemia	6	33.3	2	11.1	0	0	8	44.4
Peripheral neuropathy[a]	8	44.4	0	0	0	0	8	44.4
Anemia	5	27.8	2	11.1	0	0	7	38.9
Hypomagnesemia	7	38.9	0	0	0	0	7	38.9
Decreased appetite	6	33.3	0	0	0	0	6	33.3
Dyspnea	5	27.8	1	5.6	0	0	6	33.3
Headache	5	27.8	0	0	0	0	5	27.8
Pneumonitis	5	27.8	0	0	0	0	5	27.8
ALT increased	4	22.2	0	0	0	0	4	22.2
AST increased	4	22.2	0	0	0	0	4	22.2
Constipation	4	22.2	0	0	0	0	4	22.2
Keratopathy[b]	4	22.2	0	0	0	0	4	22.2
Myalgia	4	22.2	0	0	0	0	4	22.2
Pneumonia	4	22.2	0	0	0	0	4	22.2
Pyrexia	4	22.2	0	0	0	0	4	22.2
Upper respiratory tract infection	4	22.2	0	0	0	0	4	22.2

ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[a] Grouped term that includes neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and hypoesthesia.
[b] Grouped term that includes keratopathy, corneal epithelial microcysts, and keratitis.

4. Discussion

Treatment of platinum-sensitive ovarian cancer is an evolving therapeutic landscape, as evidenced by the recent approval of molecularly targeted agents like bevacizumab and the PARP inhibitors olaparib, rucaparib, and niraparib alongside traditional chemotherapy and/or in the maintenance setting for recurrent platinum-sensitive disease [33,34]. This tailored approach has had a significant impact in prolonging progression-free survival, including for patients in the first-line setting considered at high risk of further relapse [35], and serves as a paradigm for the application for new, effective strategies designed to additionally improve patient outcomes. EOC is a malignancy considered amenable to the application of FRα-targeting therapeutics [20]. The maturing clinical profile of mirvetuximab soravtansine, the first FRα-targeting ADC, has been characterized by good tolerability and encouraging signs of single-agent antitumor activity, initially in platinum-resistant EOC [28,30]. In preclinical models, mirvetuximab soravtansine was shown to potentiate the antitumor activity of carboplatin, with the combination being more active than other clinically relevant modalities (carboplatin/paclitaxel and carboplatin/PLD) [27]. Moreover, as an ADC, the tumor-directed drug delivery mechanism of action for mirvetuximab soravtansine affords a means to reduce off-target toxicities by limiting the exposure of normal tissues to the payload [36]; further underscoring the potential for this agent as a combinatorial partner with platinum-based therapy. In light of these considerations, this escalation cohort was opened as part of a Phase Ib combination study in order to evaluate the mirvetuximab soravtansine/carboplatin combination in patients with platinum-sensitive EOC.

The study accrued 18 patients, and achieved the goal of treating ten individuals with the pre-specified full combination doses of carboplatin AUC5 with 6 mg/kg AIBW mirvetuximab soravtansine; the latter representing the Phase 3 monotherapy dose currently under evaluation [37]. Confirming preclinical expectations, mirvetuximab soravtansine was shown to be a safe and highly active partnering agent for carboplatin for the treatment of platinum-sensitive EOC. The only DLT to emerge during dose-finding was Grade 3 vasculitis which occurred in one patient who received full dosing of the combination. The TEAEs observed were expected based on the known profiles of each of the individual agents and, importantly, no new safety signals were seen. The principal AEs included gastrointestinal or general disorders (nausea, diarrhea, vomiting, and fatigue), with the majority of cases being mild (≤grade 2) and readily managed by appropriate supportive measures. Blurred vision, and to a lesser extent corneal keratopathy, were treatment-emergent ocular disorders observed during the study. This ocular adverse event profile is a known consideration for single-agent mirvetuximab soravtansine treatment [29] and is consistent with that seen for a variety of ADCs undergoing clinical trials [38]. Similar to the monotherapy experience, all events were low grade and completely reversible. Myelosuppression is an established toxicity of carboplatin exposure, sufficient to account for the high incidence of both thrombocytopenia and neutropenia observed in patients

Table 4
Summary of efficacy measures.

Endpoint	$n = 17$
ORR (confirmed)	71%
95% CI	(44, 90)
Median PFS (months)	15
95% CI	(9.9, —)
Median DOR (months)	NR
95%CI	(5.7, —)

ORR, objective response rate; PFS, progression-free survival; DOR, duration of response; NR, not reached.

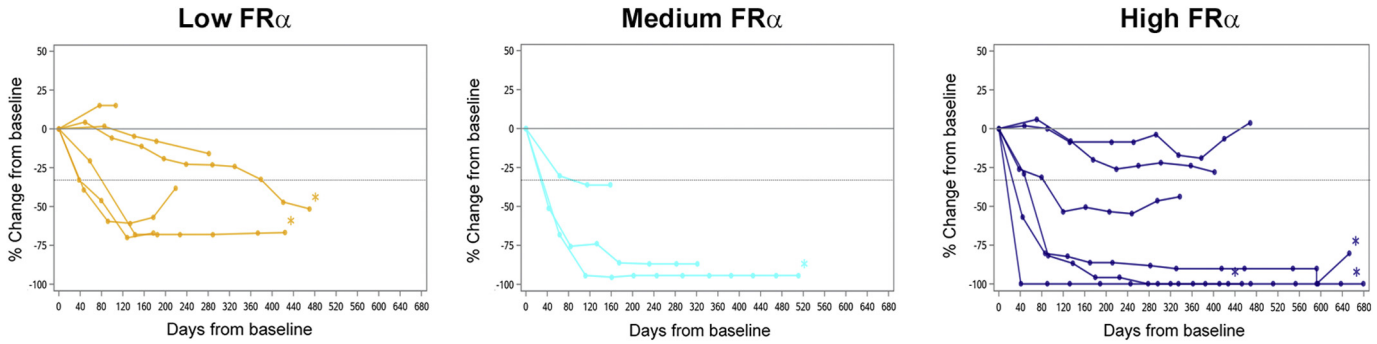

Fig. 1. Percent tumor change in target lesions by FRα expression. Data are presented from 15 patients as individuals with non-measurable disease were enrolled in the study. Asterix denotes patient still on study at time of final analyses. Dotted line in plots corresponds to 30% decrease in tumor size.

while on study. Despite an increased frequency of grade 3 events, however, the carboplatin/mirvetuximab soravtansine combination shows a comparative reduction in moderate or severe hematological toxicities when compared to that reported for the carboplatin/paclitaxel doublet [7,11].

Indeed a key finding of the safety analyses was that the tolerability of the carboplatin/mirvetuximab soravtansine combination was at least equivalent to current standard-of-care platinum-based chemotherapy. For some patients, subsequent re-challenge with carboplatin/paclitaxel is hampered by the risk of cumulative toxicities, principally hematologic and neuropathic in nature, that can limit further therapy and diminish quality of life [6]. Accordingly gemcitabine and, more commonly, PLD are also used along with carboplatin to treat platinum-sensitive recurrences. Specifically, patients treated with the carboplatin/PLD regimen exhibit a lower frequency of alopecia, hypersensitivity reactions, and neuropathies [9,39]. Alopecia is an undesirable side-effect that occurs in over 80% of patients receiving carboplatin/paclitaxel therapy [9,11], and in almost half of those treated with carboplatin/gemcitabine [8]. Although grade 2 events (total hair loss) seen with carboplatin/PLD were reduced to 7% in the pivotal CALYPSO trial, the overall incidence of alopecia remained above 30% [9]. In stark contrast, no alopecia was observed in any patients receiving carboplatin/mirvetuximab soravtansine in the present study. Importantly, the combination was also characterized by a low incidence of potentially dose-limiting toxicities, including hypersensitivity reactions and peripheral neuropathy, which were similar in frequency and severity to the profiles seen with either carboplatin/gemcitabine or carboplatin/PLD therapy, and well below levels observed with carboplatin/paclitaxel treatment [8,9,11]. With specific respect to hypersensitivity, only three patients overall (17%) experienced infusion related reactions in the current study, all of which were mild (grade 2). Importantly, none of these events were considered dose-limiting or reached seriousness criteria, even in the two instances where they led to carboplatin discontinuation.

Even with the caveat of low patient numbers, the preliminary signs of clinical activity for the combination are particularly encouraging. In a single-arm combination study, it is difficult to determine the contribution of each individual agent, however it is informative to examine the observed activity of the carboplatin/mirvetuximab soravtansine doublet in relation to other carboplatin-based combinations used in the management of ovarian cancer. PFS is considered a valid endpoint for second-line treatment of platinum-sensitive ovarian cancer [40] and, at the time of analysis, the median PFS observed for all evaluable patients was 15 months. This compares favorably with benchmark values of 9.4 and 10.4 months for conventional carboplatin/paclitaxel therapy reported in the large phase 3 CALYPSO and GOG-0213 trials conducted in similar patient populations [9,11], and is also well above the 8.4 months seen with the carboplatin/gemcitabine doublet in the OCEANS study [12]. Of interest, the majority of patients in our study had a TFIp of 6–12 months, traditionally referred to as 'partially' platinum-sensitive and characterized by inferior responses to chemotherapy when compared to 'fully' platinum-sensitive individuals (TFIp >12 months) [41]. In this regard, the PFS value seen here is superior to the 8.8 months reported in a subset analysis of the CALYPSO trial evaluating the 6–12 month TFIp population [39]. In addition, it is important to

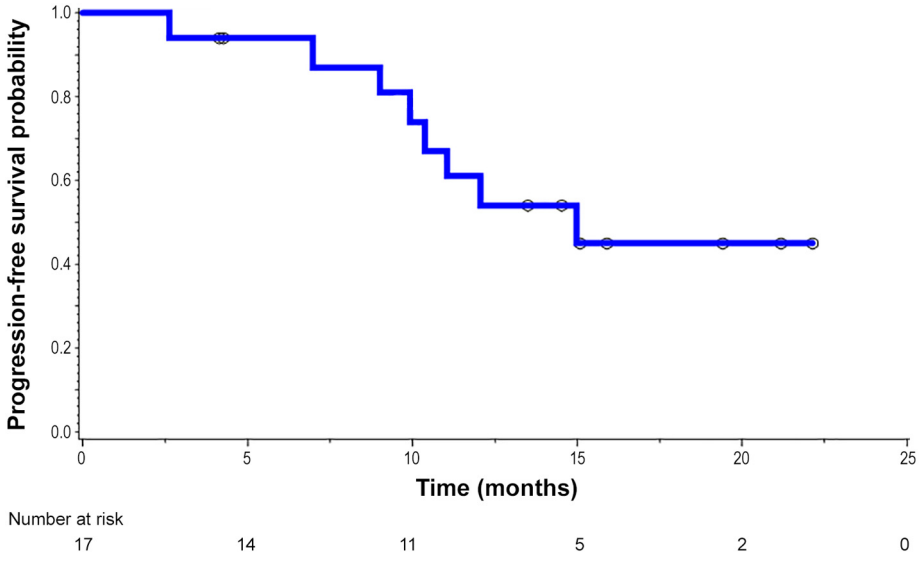

Fig. 2. Kaplan-Meier analysis of progression-free survival (PFS).

note that half of the patients treated during dose-escalation had received three or more previous lines of systemic therapy, making this a more heavily pretreated population than those evaluated in these other trials (who received only one or two priors). While caution must be exercised when comparing response rates across trials in recurrent platinum-sensitive disease, due to the difficulty in measuring accurately and reproducibly [42], the confirmed ORR of 71% observed with carboplatin/mirvetuximab soravtansine suggests that this is a highly active regimen, in light of the 45–59% ORRs seen in the same three trials above [11,12,39]. This response rate included three confirmed CRs, all of which occurred in patients with high FRα expression, consistent with earlier findings of a relationship between superior efficacy outcomes and higher levels of tumor receptor expression for mirvetuximab soravtansine when administered as monotherapy [32].

Overall, the findings presented here confirm the feasibility of combining mirvetuximab soravtansine with carboplatin for the treatment of women with platinum-sensitive recurrences of EOC. Together with preliminary clinical evidence of tolerability and antitumor activity afforded by the addition of mirvetuximab soravtansine to bevacizumab therapy [43], these results helped define the dose and target population of an expansion cohort now underway, opened as part of FORWARD II, designed to evaluate a triplet combination of carboplatin/mirvetuximab soravtansine with bevacizumab in the setting of recurrent platinum-sensitive disease. The results of that study will be informative as to the promise of mirvetuximab soravtansine-based combination therapy as a potentially more tolerable and effective alternative treatment option for the management of patients with relapsed EOC.

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, Assoc. Director of Medical Affairs at ImmunoGen, who provided drafts and editorial assistance during the production of this manuscript.

Disclosure statement

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

Author contribution

Conception and design: K.N.M., D.M.O., K.M., and M.J.B.

Provision of study materials or patients: K.N.M, D.M.O., I.V., L.P.M, A.G.M., and M.J.B.

Collection and assembly of data: All authors.

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Manuscript writing and final approval: All authors.

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