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Mirvetuximab soravtansine in folate receptor alpha (FRα)–high platinum-resistant ovarian cancer: final overall survival and post hoc sequence of therapy subgroup results from the SORAYA trial

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ABSTRACT

Objective The single-arm, phase II SORAYA trial (NCT04296890) of mirvetuximab soravtansine-gynx in folate receptor alpha (FRα)–high platinum-resistant ovarian cancer (n=105 (efficacy-evaluable)) met its primary endpoint with an objective response rate of 32.4% (95% CI, 23.6 to 42.2). Here we report final SORAYA trial results for overall survival and post hoc objective response rates in subgroups by sequence and number of prior therapies.

Methods Eligible patients had high-grade serous platinum-resistant ovarian cancer with high FRα expression and one to three prior therapies (prior bevacizumab required). Enrolled participants received 6 mg/kg mirvetuximab soravtansine-gynx adjusted ideal body weight intravenously once every 3 weeks until progressive disease, unacceptable toxicity, withdrawal of consent, or death. Final overall survival and post hoc objective response rates were assessed in efficacy-evaluable participants. The safety population included all patients who received ≥1 dose of mirvetuximab soravtansine-gynx.

Results At data cut-off (December 22, 2022; n=105), final median overall survival was 15.0 months (95% CI, 11.5 to 18.7). Median overall survival in participants with one to two prior therapy lines was 18.7 months (95% CI, 13.8 to not estimable (NE)) and 11.6 months (95% CI, 7.1 to 16.7) with three prior therapy lines. Median overall survival was 15.0 months (95% CI, 11.5 to NE) in participants with prior poly (ADP-ribose) polymerase inhibitor (PARPi) treatment versus 14.0 months (95% CI, 7.1 to NE) in those without. Objective response rate (data cut-off: November 17, 2021) differed among participants who received mirvetuximab soravtansine-gynx as their first treatment in the platinum-resistant setting (34.8%; 95% CI, 23.5 to 47.6) versus a different first treatment (28.2%; 95% CI, 15.0 to 44.9) or had received prior bevacizumab in a platinum-sensitive (34.0%; 95% CI, 24.6 to 44.5) versus platinum-resistant setting (17.6%; 95% CI, 3.8 to 43.4). No new safety signals were observed.

Conclusion These results support the clinically meaningful efficacy of mirvetuximab soravtansine-gynx in FRα-expressing platinum-resistant ovarian cancer, irrespective of prior treatment or sequence.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The current standards of care in platinum-resistant ovarian cancer have limited anticancer activity and high rates of cytotoxicity in this patient population with a historically poor prognosis and survival outcomes. Mirvetuximab soravtansine-gynx is an antibody–drug conjugate targeting folate receptor alpha (FRα), which is highly expressed in ovarian cancer. As previously reported, the single-arm, phase II SORAYA trial (NCT04296890) of mirvetuximab soravtansine-gynx in FRα-expressing, platinum-resistant ovarian cancer met its primary endpoint with an objective response rate of 32.4% (95% CI, 23.6–42.2).

WHAT THIS STUDY ADDS

⇒ Here we report final overall survival and post hoc objective response rate subgroup data from the SORAYA study; clinically relevant subgroups evaluated include participants with one to two, or three, prior lines of therapy, prior poly (ADP-ribose) polymerase inhibitor (PARPi) treatment, participants who received bevacizumab in the platinum-sensitive versus platinum-resistant setting, and participants who received mirvetuximab soravtansine-gynx as their first therapy in the platinum-resistant setting versus a different first therapy.

INTRODUCTION

The shortage of effective, targeted treatments for patients with platinum-resistant ovarian cancer represents a significant unmet need.[1] Mirvetuximab soravtansine-gynx is an antibody–drug conjugate that targets folate receptor alpha (FRa) and induces a directed cytotoxic effect through a tubulin-targeting payload (maytansinoid DM4).[2] Recently published

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Results from this updated analysis further demonstrate the clinically meaningful efficacy of mirvetuximab soravtansine-gynx, irrespective of either prior treatment or sequence, and align with previous findings in other studies of mirvetuximab soravtansine-gynx such that no new safety signals were observed. These results, in conjunction with the consistent anticancer activity and safety profile observed with mirvetuximab soravtansine-gynx across other clinical trials, position mirvetuximab soravtansine-gynx as a practice-changing therapeutic option for patients with platinum-resistant ovarian cancer.

results from the single-arm, phase II SORAYA trial (NCT04296890) found that mirvetuximab soravtansine-gynx monotherapy in patients with FRa-high platinum-resistant ovarian cancer (n=105 (efficacy-evaluable)) elicited an investigator-assessed confirmed objective response rate of 32.4% (95% CI, 23.6 to 42.2), including 5 complete and 29 partial responses.[3] The investigator-assessed median duration of response was 6.9 months (95% CI, 5.6 to 9.7). These results supported accelerated approval of mirvetuximab soravtansine-gynx by the US Food and Drug Administration (FDA; November 14, 2022) for adult patients with FRa-positive, platinum-resistant ovarian cancer who received one to three prior systemic treatments.[4 5]

We report updated results from the SORAYA trial for final overall survival and post hoc subgroup analyses to preliminarily evaluate the impact of sequence and number of prior therapies on clinical outcomes with mirvetuximab soravtansine-gynx.

METHODS

The SORAYA trial design, methodology, study protocol, and primary analysis have been published previously.[3] SORAYA was a single-arm, phase II trial that recruited 106 participants from 39 sites in 8 countries (ClinicalTrials.gov ID: NCT04296890).[6] Enrolled participants had a confirmed diagnosis of high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer; were ≥18 years old; platinum-resistant disease; high FRa expression (≥75% of cells with ≥2+ immunohistochemical staining intensity as defined by the FDA-approved VENTANA FOLR1 (FOLR1-2.1) RxDx Assay);[7] and one to three prior lines of systemic anticancer therapy (bevacizumab required). Participants received mirvetuximab soravtansine-gynx monotherapy at 6 mg/kg adjusted ideal body weight once every 3 weeks until progressive disease, unacceptable toxicity, or death. The primary endpoint was investigator-assessed objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. All participants who discontinued mirvetuximab soravtansine-gynx were followed for survival every 3 months (±1 month) until death, loss to follow-up, withdrawal of consent to follow-up, or end of study.[8] Efficacy-evaluable participants had ≥1 measurable lesion (RECIST version 1.1).

Final overall survival was estimated using the Kaplan–Meier method in the overall efficacy-evaluable population and in participants who received one to two versus three prior lines of treatment and those with prior poly (ADP-ribose) polymerase inhibitor (PARPi) treatment versus PARPi-naïve. Post hoc analyses evaluated objective response rate in the following subgroups: participants who had mirvetuximab soravtansine-gynx administered as the first treatment in the platinum-resistant setting versus a different first treatment in the platinum-resistant setting, and participants by timing of prior bevacizumab exposure (ie, in the platinum-sensitive or platinum-resistant setting). Adverse events were evaluated based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) and coded using the Medical Dictionary for Regulatory Activities, version 24.0. Statistical analyses were performed using SAS version 9.4 (Cary, NC, USA).

The study was funded by ImmunoGen, Inc. and performed according to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council for Harmonisation, and local regulatory requirements. A central institutional review board (WCG WIRB; Approval Number: 20200077), along with an independent ethics committee at each investigative site, approved the protocol. All participants (or legally authorized representatives) provided written informed consent.

RESULTS

Participants

Of the 467 patients screened, 106 participants were enrolled from June 2020 to May 2021 (participant flow diagram has been published previously).[3] Baseline characteristics are summarized in Table 1.[3] Of those enrolled, 37% received prior treatment in the platinum-resistant setting. All participants received prior bevacizumab, 48% received one to two prior lines of therapy, 51% received three prior lines of therapy, and 48% received a prior PARPi. At the time of data cut-off for the final overall survival and safety analyses (December 22, 2022), median duration of mirvetuximab soravtansine-gynx treatment was 4.2 (range, 0.7–22.1) months, with 28 participants receiving mirvetuximab soravtansine-gynx for >7 months.

Efficacy

The final median overall survival in the efficacy-evaluable population (n=105) was 15.0 months (95% CI, 11.5 to 18.7), with 37% of participants alive at year 2 and a median follow-up of 20.0 months (95% CI, 19.0 to 20.6) (Figure 1A). In participants with one to two prior lines of therapy (n=51), median overall survival was 18.7 months (95% CI, 13.8 to not estimable (NE)) versus 11.6 months (95% CI, 7.1 to 16.7) in participants with three prior lines of therapy (n=53) (Figure 1B). In participants who received prior PARPi (n=50), median overall survival was 15.0 months (95% CI, 11.5 to NE) versus 14.0 months (95% CI, 7.1 to NE) in PARPi-naïve participants (n=51).

As reported previously, investigator-assessed objective response rate was 32.4% (95% CI, 23.6 to 42.2) in the efficacy-evaluable population (n=105).[3] Post hoc subgroup analyses (data cut-off: November 17, 2021) (Figure 1C) demonstrated that participants who received mirvetuximab soravtansine-gynx as their first treatment in the platinum-resistant setting (n=66) had an objective response rate of 34.8% (95% CI, 23.5 to 47.6), and those who received prior treatment in the platinum-resistant setting (n=39) had an objective response rate of 28.2% (95% CI, 15.0 to 44.9). Participants who received bevacizumab in the platinum-sensitive setting (n=94) had an objective response rate of 34.0% (95% CI,

Table 1 Patients' baseline demographics and clinical characteristics[3]

Characteristic	Value (N=106)
Age, years	
Median	62.0
Range	35–85
Race, n (%)	
White	102 (96)
Asian	2 (2)
Not reported	2 (2)
Ethnicity, n (%)	
Hispanic or Latino	2 (2)
Not Hispanic or Latino	99 (93)
Not reported	4 (4)
Unknown	1 (1)
Primary diagnosis, n (%)	
Epithelial ovarian	85 (80)
Fallopian tube*	8 (8)
Primary peritoneal*	12 (11)
Other†	1 (1)
Histology, n (%)	
High-grade serous	106 (100)
Stage at initial diagnosis, n (%)	
I	2 (2)
II	0 (0)
III	63 (59)
IV	40 (38)
Missing	1 (1)
Eastern Cooperative Oncology Group performance status, n (%)	
0	60 (57)
1	46 (43)
BReast CAncer gene (BRCA) mutations‡	
Yes	21 (20)
BRCA1	15 (14)
BRCA2	6 (6)
No/unknown	85 (80)
Prior systemic therapy, n (%)§	
1	10 (9)
2	41 (39)
3	54 (51)
Prior exposure, n (%)	
Platinum-containing regimen	106 (100)
Bevacizumab	106 (100)
Taxanes	105 (99)
Liposomal doxorubicin	75 (71)
Poly (ADP-ribose) polymerase inhibitor (PARPi)	51 (48)
Topotecan	0 (0)
Primary platinum-free interval, n (%)¶	
0–12 months	63 (59)
>12 months	43 (41)
Platinum-free interval, n (%)**, ††	
0–3 months	39 (37)
3–6 months	64 (60)

Table used with permission from Matulonis UA *et al*[3] 2023, Wolters Kluwer Health.
*The term epithelial ovarian cancer often includes fallopian tube carcinoma and primary peritoneal carcinoma, as they have the same prognosis and treatment.
†One patient with primary diagnosis categorized as other had histopathology consistent with the inclusion/exclusion criteria, intraepithelial tubo-ovarian carcinoma.
‡The BReast CAncer gene (*BRCA*) mutation status from prior testing was recorded from the source record. Patients with a germline or somatic *BRCA* mutation in the tumor tissue were classified as positive, patients who were tested and had no *BRCA* mutation were classified as negative, and patients without known *BRCA* mutation status were classified as unknown. The no and unknown fields were grouped in the database.
§One patient had received four prior lines of therapy.
¶Time from last dose of the first-line platinum therapy to the date of disease progression and/or relapse following the first-line therapy.
**Time from last dose of the latest-line platinum therapy (most recent line prior to trial entry) to the date of disease progression and/or relapse following that line of therapy.
††Three patients were enrolled with a platinum-free interval of >6 months, of which 2 patients had a platinum-free interval of 6.01 months and 1 patient had a platinum-free interval of 18.07 months.

24.6 to 44.5) versus 17.6% (95% CI, 3.8 to 43.4) in the platinum-resistant setting (n=17).

Safety

Analyses of safety data (data cut-off: December 22, 2022) identified no new safety signals (Table 2).[3] Treatment-related adverse events occurred in 86% of the safety population (n=106), with 30% having a grade 3–4 event. The most common (≥20% of participants) treatment-related adverse events (all grades, grade 3–4) were visual impairment (43%, 6%), fatigue (37%, 2%), keratopathy (36%, 9%), nausea (29%, 0%), peripheral neuropathy (27%, 3%), dry eye (25%, 2%), and diarrhea (22%, 2%).

DISCUSSION

Summary of main results

The final median overall survival of 15.0 months and lack of new safety signals from the SORAYA trial further support the clinical benefit of mirvetuximab soravtansine-gynx in patients with FRα-expressing, platinum-resistant ovarian cancer. Although no formal statistical comparisons were performed, and therefore all descriptive findings in this article are restricted by this inherent

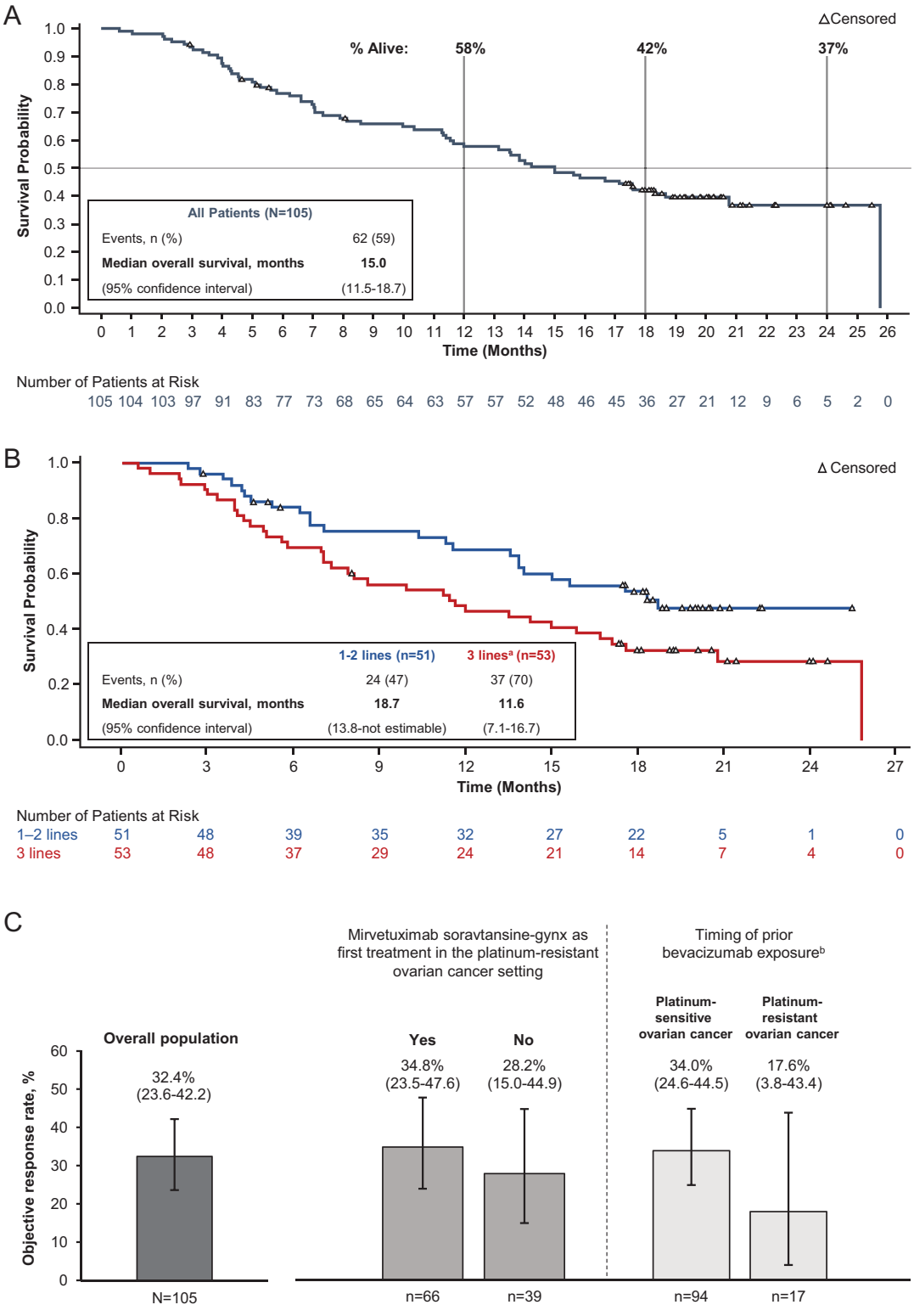

Figure 1 Final overall survival and post hoc subgroup analyses by sequence and number of prior therapies. Shown are Kaplan–Meier plots (data cut-off: December 22, 2022) of final overall survival in (A) the efficacy-evaluable population and (B) in participants who had one to two prior lines of therapy (blue) versus three prior lines of therapy (red). (C) Shows objective response rate (data cut-off: November 17, 2021) in the overall population and post hoc analysis results for objective response rate in participants who received mirvetuximab soravtansine-gynx as their first treatment in the platinum-resistant setting versus a different first treatment in the platinum-resistant setting and in participants who were first exposed to bevacizumab in the platinum-sensitive versus platinum-resistant setting. [a]One patient in the efficacy-evaluable population had four prior lines of therapy. [b]Of the 17 participants who received bevacizumab in the platinum-resistant setting (16% of all participants), 8 (47%) had stage IV disease at diagnosis and 10 (59%) received mirvetuximab soravtansine-gynx as fourth-line therapy. Six participants (6% of all participants) received bevacizumab in both the platinum-sensitive and platinum-resistant settings.

Table 2 Most common (≥10%) treatment-related adverse events in the safety population (N=106)

Treatment-related adverse event	All grades, n (%)	Grades 3–4, n %
Patients with any event	91 (86)	32 (30)
Visual impairment	46 (43)	6 (6)
Fatigue	39 (37)	2 (2)
Keratopathy*	38 (36)	9 (9)
Nausea	31 (29)	0
Peripheral neuropathy	29 (27)	3 (3)
Dry eye	26 (25)	2 (2)
Diarrhea	23 (22)	2 (2)
Photophobia	15 (14)	0
Decreased appetite	14 (13)	1 (1)
Neutropenia	14 (13)	2 (2)
Abdominal pain	12 (11)	2 (2)
Vomiting	12 (11)	0
Cataract	11 (10)	0
Pneumonitis	11 (10)	2 (2)

Data cut-off: December 22, 2022.
NOTE: Adverse events were evaluated on the basis of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Adverse events were linked to system organ class and preferred term (group and list terms included) using the Medical Dictionary for Regulatory Activities, version 24.0. When counting events, each record is counted once for each adverse event entered in the electronic case report form. For the remaining frequencies, each patient is counted once, with the worst grade for each preferred term, system organ class, or overall. Related events include those with a drug relationship of possibly related, probably related, or definitely related.
*The grouped preferred term 'keratopathy' includes all with the following preferred terms: corneal cyst, corneal disorder, corneal epithelial microcysts, keratitis, keratopathy, limbal stem-cell deficiency, corneal opacity, corneal erosion, corneal pigmentation, corneal deposits, keratitis interstitial, punctate keratitis, and corneal epithelial defect.

limitation, subgroup analyses identified potential differences in clinical outcomes among participants based on sequence and/or number of prior lines of therapy. Participants with one to two prior lines of therapy demonstrated slightly longer median overall survival (18.7 months) versus participants with three prior lines of therapy (11.6 months), though no statistical comparison was performed. The median overall survival in subgroups by previous PARPi exposure was similar to the median overall survival in the total population (overall, 15.0 months; prior PARPi, 15.0 months; PARPi-naïve, 14.0 months) suggesting limited impact of prior PARPi treatment on mirvetuximab soravtansine-gynx efficacy. Additionally, participants who received mirvetuximab soravtansine-gynx as their first treatment in the platinum-resistant setting had a moderately higher objective response rate versus participants who did not (34.8% vs 28.2%), though no statistical comparison was performed.

Follow-up safety data provided from this study showed no new safety signals with mirvetuximab soravtansine-gynx. The most common adverse events (visual impairment, fatigue, keratopathy, nausea, peripheral neuropathy, dry eye, and diarrhea) and overall rate of grade 3–4 treatment-related adverse events (30%) were consistent with initial reports from the SORAYA trial and other trials of mirvetuximab soravtansine-gynx monotherapy.[3 9 10] Further, grade 3–4 ocular treatment-related adverse events were limited (visual impairment, 6%; keratopathy, 9%; and dry eye, 2%), indicating that prophylactic and mitigative procedures for ocular adverse events continued to be effective in the vast majority of patients despite continued mirvetuximab soravtansine-gynx exposure.

Results in the context of published literature

Minimal or no improvements in overall survival have been observed in trials among patients with platinum-resistant ovarian cancer, which underscores the challenge of identifying effective treatments for this population. In recent phase III randomized trials of monotherapy in platinum-resistant ovarian cancer, median overall survival was 11.4 months versus 10.9 months with lurbinectedin versus chemotherapy (CORAIL trial; HR, 0.96; 95% CI, 0.77 to 1.18; p=0.679)[11] and 10.1 months versus 12.1 months with nivolumab versus chemotherapy (NINJA trial; HR, 1.0; 95% CI, 0.8 to 1.3; p=0.808).[12] While trials of combination therapy in platinum-resistant ovarian cancer have demonstrated numerically longer median overall survival with various therapies plus chemotherapy, improvements in overall survival have not been statistically significant compared with chemotherapy alone (AURELIA trial (bevacizumab plus chemotherapy) overall survival HR, 0.85; 95% CI, 0.66 to 1.08; p<0.174; JAVELIN 2000 trial (avelumab plus chemotherapy) overall survival HR, 0.89; repeated 88.85% CI, 0.74 to 1.24; p=0.21).[13 14]

Crucially, the final SORAYA trial results for overall survival in the current report are notable and further corroborate the results from the confirmatory, randomized, phase III MIRASOL trial (NCT04209855) in FRa-expressing, platinum-resistant ovarian cancer (data cut-off: March 6, 2023), which showed statistically significant improvements in the key secondary endpoint of overall survival with mirvetuximab soravtansine-gynx monotherapy versus single-agent chemotherapy (median, 16.46 months vs 12.75 months; HR, 0.67; 95% CI, 0.50 to 0.89; p=0.005).[9] Results from the MIRASOL trial also demonstrated significant improvement with mirvetuximab soravtansine-gynx versus chemotherapy in investigator-assessed progression-free survival (primary endpoint; median, 5.62 months vs 3.98 months; HR, 0.65; 95% CI, 0.52 to 0.81; p<0.001) and objective response rate (key secondary endpoint; 42.3% vs 15.9%; OR, 3.81; 95% CI, 2.44 to 5.94; p<0.001).[9 15] Altogether, these results are unprecedented as mirvetuximab soravtansine-gynx is the first novel therapy to demonstrate a survival benefit over chemotherapy in a phase III trial of platinum-resistant ovarian cancer.[11–13]

The current analyses from the SORAYA trial showed that the demonstrated overall survival benefit of mirvetuximab soravtansine-gynx persists regardless of prior lines of therapy and previous PARPi exposure. However, participants who had received one to two prior lines of therapy demonstrated slightly longer overall survival than those who had received three prior lines of therapy (median overall survival, 18.7 months vs 11.6 months). This finding is in line with the well-documented observation that survival outcomes decrease with each additional line of therapy,[16 17] which may be due to treatment resistance as well as diminished ability of a patient to withstand treatment due to cumulative toxicity. Conversely, mirvetuximab

soravtansine-gynx demonstrated similar median overall survival regardless of prior PARPi exposure, which suggests that mirvetuximab soravtansine-gynx's mechanism of action succeeds in patients who were previously selected for a PARPi. Future studies should investigate the efficacy of mirvetuximab soravtansine-gynx in patients who progress on PARPi to better understand the clinical benefit of mirvetuximab soravtansine-gynx in these patients, as well as the underlying molecular/clinical features of these patients.

Of note, previously observed objective response rates with third- or fourth-line chemotherapy in heavily pre-treated patients with platinum-resistant or platinum-refractory ovarian cancer have been low (3.1% or 1.6%, respectively).[18] Thus, the objective response rate of 17.6% among participants in the current study who had been treated with bevacizumab in the platinum-resistant setting (n=17; 16% of all participants) is notable given 59% (n=10/17) received mirvetuximab soravtansine-gynx as fourth-line therapy and 35% (n=6/17) received bevacizumab in both the platinum-sensitive and platinum-resistant settings.

Lastly, in other phase III platinum-resistant ovarian cancer monotherapy trials previously described, patients receiving chemotherapy had grade ≥3 treatment-related adverse events at rates of 59%–65% (compared with 30% reported here with mirvetuximab soravtansine-gynx).[11–13] Thus, the final follow-up safety results from the SORAYA trial further demonstrate the favorable and differentiated tolerability profile of mirvetuximab soravtansine-gynx.

Strengths and weaknesses

An important strength of this trial is that it included a more heavily pre-treated population than recent phase III clinical trials in platinum-resistant ovarian cancer.[11–14] The differentiated safety profile and demonstrated anticancer activity even in heavily pre-treated patients underscores the potential for mirvetuximab soravtansine-gynx to meet an unmet clinical need in this patient population. Limitations of this trial include its nonrandomized design, eligibility criteria that limited enrollment to participants who received one to three prior lines of therapy, and lack of formal statistical comparisons for the subgroup analyses due to insufficient power to detect differences in the small sample sizes. The generalizability of these results is therefore limited by the hypothesis-generating nature of the analyses.

Implications for practice and future research

Although additional investigation is warranted to confirm these observations, it is reasonable to consider initiating mirvetuximab soravtansine-gynx therapy earlier in the treatment journey for patients in the platinum-resistant setting, with or without bevacizumab (as studied in the FORWARD II trial (NCT02606305) of mirvetuximab soravtansine-gynx plus bevacizumab).[19] These data underscore the clinical benefit of mirvetuximab soravtansine-gynx as an effective treatment option with a tolerable safety profile for patients with platinum-resistant ovarian cancer irrespective of whether a patient received up to three lines of prior therapy or bevacizumab in either the platinum-sensitive or platinum-resistant setting. Understanding the use of mirvetuximab soravtansine-gynx in this patient population with a historically poor prognosis represents a crucial advancement in identifying patients who may benefit from this therapy.

CONCLUSIONS

These results, in conjunction with the consistent anticancer activity and safety profile observed with mirvetuximab soravtansine-gynx across other clinical trials, provide important insights and position mirvetuximab soravtansine-gynx as a practice-changing therapeutic option for individuals living with platinum-resistant ovarian cancer.

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Ethics approval This study involves human participants and was performed according to the principles of the Declaration of Helsinki, Good Clinical Practice guidelines of the International Council for Harmonisation, and local regulatory requirements. The institutional review board or independent ethics committee at each investigative site approved the protocol. All participants (or legally authorized representatives) provided written informed consent. Participants gave informed consent to participate in the study before taking part.

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Data availability statement Data are available upon reasonable request. The study sponsor, ImmunoGen, Inc., is committed to the responsible sharing of clinical trial data. The research protocol has been published previously and data from this clinical trial can be requested by any qualified investigator who engages in relevant research. In accordance with the Journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

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