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ORIGINAL ARTICLE

The efficacy and safety of mirvetuximab soravtansine in FRα-positive, third-line and later, recurrent platinum-sensitive ovarian cancer: the single-arm phase II PICCOLO trial

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Background: Mirvetuximab soravtansine-gynx (MIRV) is a first-in-class, folate receptor alpha (FRα)-targeting antibody—drug conjugate with United States Food and Drug Administration approval for FRα-positive platinum-resistant ovarian cancer. PICCOLO is a phase II, global, open-label, single-arm trial of MIRV as third-line or greater (≥3L) treatment in patients with FRα-positive (≥75% of cells with ≥2+ staining intensity) recurrent platinum-sensitive ovarian cancer (PSOC).

Patients and methods: Participants received MIRV (6 mg/kg adjusted ideal body weight every 3 weeks) until progressive disease (PD), unacceptable toxicity, withdrawal of consent, or death. Primary endpoint was investigator-assessed objective response rate (ORR). Key secondary endpoint was investigator-assessed duration of response (DOR). Additional endpoints included investigator-assessed progression-free survival (PFS), overall survival (OS), and safety. Analyses of subgroups by disease characteristics (e.g. platinum-free interval) and treatment history [e.g. prior bevacizumab and poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi) treatment] were exploratory.

Results: Seventy-nine participants were enrolled and efficacy assessable. The primary endpoint was met; ORR was 51.9% [95% confidence interval (CI) 40.4% to 63.3%]. Median DOR was 8.25 months (95% CI 5.55-10.78 months) and median PFS was 6.93 months (95% CI 5.85-9.59 months). OS was not mature at data cut-off. ORR was 45.8% (95% CI 32.7% to 59.2%) in participants with PD while on/within 30 days of prior PARPi ($n = 59$) and 60.0% (95% CI 14.7% to 94.7%) in those without PD with prior PARPi ($n = 5$). No new safety signals occurred; most common treatment-emergent adverse events (TEAEs) were gastrointestinal, neurosensory, and resolvable ocular events. TEAEs led to discontinuation in 13 participants (16%) and death in 2 participants (3%).

Conclusions: MIRV as ≥3L treatment in heavily pretreated recurrent FRα-positive PSOC demonstrated notable efficacy and tolerable safety, including among those with prior PD on or within 30 days of PARPi (NCT05041257).

Key words: platinum-sensitive ovarian cancer, folate receptor alpha, mirvetuximab soravtansine, antibody—drug conjugate, heavily pretreated

INTRODUCTION

Epithelial ovarian cancer (EOC; includes ovarian, fallopian tube, and primary peritoneal cancer) is the most lethal gynecologic malignancy, with a 5-year relative survival rate of ∼51%.[1,2] In 2022, ∼325 000 new EOC cases and 207 000 EOC-related deaths occurred globally.[3] Most patients are diagnosed with advanced-stage disease, and for these

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patients, first-line therapy typically consists of primary cytoreductive surgery and platinum-based chemotherapy, followed by observation or maintenance treatment with bevacizumab, a poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitor (PARPi), or combination of bevacizumab plus PARPi.[1,2] For patients with advanced-stage disease who are poor surgical candidates, first-line treatment often consists of neoadjuvant chemotherapy treatment before cytoreductive or debulking surgery.[2] Although initial platinum-based chemotherapy yields high response rates, most patients will experience recurrence.[4,5]

Treatment for recurrent EOC is often based on platinum-free interval (PFI), or the time between recurrence and last platinum-based therapy.[6] In patients with a PFI >6 months [traditionally referred to as platinum-sensitive ovarian cancer (PSOC)], the standard of care includes re-treatment with platinum-based chemotherapy—which typically consists of a platinum-based doublet with or without bevacizumab at first recurrence—followed by maintenance therapies (e.g. PARPi or bevacizumab) in select circumstances or by observation.[2] These maintenance therapies may yield additional benefits in patients who have responded to platinum-based chemotherapy.[7,8] However, after each successive disease recurrence, chemotherapy efficacy diminishes in patients with high-grade ovarian cancer [i.e. first-line objective response rate (ORR) of 92% versus fifth-line ORR of 17%],[9] as does a patient's ability to tolerate the accompanying cumulative toxicities associated with treatment, increased risk of platinum hypersensitivity reactions, and concern for cross-resistance to platinum rechallenge after PARPi maintenance.[8,10,11] Further, among patients with later-line PSOC deemed unsuitable for platinum-based chemotherapy, single-agent non-platinum chemotherapies—such as etoposide, topotecan, and pegylated liposomal doxorubicin—have demonstrated modest ORRs in PARPi-naïve patients, with ORRs ranging from 13% to 34%.[12-15]

The mechanisms of resistance to platinum-based chemotherapy and PARPi are complex and multifactorial, with overlapping mechanisms of acquired resistance.[11] This is clinically relevant given the significant use of PARPi therapy in patients with EOC; ∼87% of patients with EOC in the United States were eligible for PARPi treatment in 2023.[16] Several reports have suggested that patients with disease progression on or after PARPi exhibit diminished response to subsequent platinum-based treatments.[17-23] Collectively, these findings highlight the critical need to identify effective and tolerable therapies for patients with PSOC.[17-23]

Mirvetuximab soravtansine-gynx (MIRV) is a first-in-class antibody—drug conjugate (ADC) comprising a folate receptor alpha (FRα)-binding antibody, a cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent.[24,25] MIRV received full United States Food and Drug Administration approval in March 2024 for patients with FRα-positive platinum-resistant EOC (PROC) with 1-3 prior lines of systemic therapy, which was supported by results from the confirmatory, randomized, phase III MIRASOL trial (NCT04209855).[26,27] In the MIRASOL trial of MIRV versus single-agent chemotherapy, MIRV treatment led to significant improvements in progression-free survival (PFS), ORR, and overall survival (OS) and demonstrated a differentiated safety profile consisting primarily of low-grade gastrointestinal, neurosensory, and resolvable ocular adverse events (AEs).[27] Thus, MIRV became the first novel therapy to demonstrate a survival advantage against single-agent chemotherapy in PROC in a phase III trial.[27,28] For patients with FRα-expressing ovarian, fallopian tube, or primary peritoneal cancer, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend MIRV monotherapy as a preferred targeted therapy option in platinum-resistant disease (NCCN category 1); the combination of MIRV plus bevacizumab is also recommended as useful in certain circumstances in platinum-resistant disease (NCCN category 2A) and platinum-sensitive disease (NCCN category 2B).[27,29-33]

Given the decreasing efficacy of chemotherapy and cumulative toxicities that occur with each successive recurrence, there is a need for additional treatment options for patients with PSOC receiving second-line treatment and beyond.[8,9] Given the clinically meaningful benefits observed with MIRV monotherapy in PROC, investigation of MIRV in other ovarian cancer populations is warranted.[27] Here, we report results from the single-arm phase II PICCOLO trial evaluating the efficacy and safety of MIRV monotherapy as third-line or greater treatment in patients with FRα-positive recurrent PSOC, with the objective of assessing the clinical efficacy and safety of MIRV in a patient population not previously studied in a phase II MIRV monotherapy clinical trial.

PATIENTS AND METHODS

Participants

Patients eligible for the PICCOLO trial were aged ≥18 years with confirmed high-grade serous EOC that was platinum sensitive, defined as radiographic progression >6 months from the last dose of most recent platinum therapy. Patients were required to have radiographic progressive disease (PD) on or after their most recent line of anticancer therapy and to have received ≥2 prior lines of platinum-containing therapy (or 1 line, with a documented platinum allergy), and to be determined by the investigator as appropriate for single-agent non-platinum therapy (e.g. high risk of hypersensitivity reaction, risk of further cumulative toxicity with additional platinum, including but not limited to myelosuppression, neuropathy, renal insufficiency, or other). Positive FRα tumor expression was required, as determined using the positive staining 2+ (PS2+) scoring method (i.e. ≥75% of cells with ≥2+ staining intensity) with the VENTANA FOLR1 (FOLR1-2.1) RxDx Assay (Roche Tissue Diagnostics, Roche, Basel, Switzerland) using a fresh/recent biopsy or archival tissue.[34] All patients had ≥1 lesion that met the definition of measurable disease according to Response Evaluation

Criteria in Solid Tumors (RECIST) version 1.1 and had an Eastern Cooperative Oncology Group performance status score of 0 or 1. Patients with grade >1 peripheral neuropathy, active or chronic corneal disorders, history of corneal transplantation, or active ocular conditions requiring ongoing treatment or monitoring were excluded. Full eligibility criteria are provided in the protocol.

Trial design and treatment

PICCOLO (NCT05041257) is a global, open-label, single-arm, phase II trial. Full investigator list is provided in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2024.11.011. The trial was conducted in compliance with the principles of the Declaration of Helsinki, the Good Clinical Practice Guidelines of the International Conference for Harmonisation, and local regulatory requirements. The protocol was approved by the institutional review board or independent ethics committee at each trial site. Written consent was obtained from all participants.

Participants received MIRV monotherapy at 6 mg/kg using adjusted ideal body weight, administered intravenously once every 3 weeks until PD, unacceptable toxicity, withdrawal of consent, or death. Participants were premedicated with acetaminophen/paracetamol, dexamethasone, and diphenhydramine ∼30 min before each MIRV infusion. Self-administration of 1% prednisolone eye drops was mandated 6 times daily on days −1 through 4 and 4 times daily on days 5 through 8 of each 3-week treatment cycle. Daily use of lubricating eye drops was also required. Further information on ocular prophylaxis and examinations is provided in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2024.11.011.

Trial endpoints and assessments

The primary endpoint was investigator-assessed ORR, defined as the percentage of participants with a confirmed complete response (CR) or partial response (PR) as per RECIST version 1.1. The key secondary endpoint was investigator-assessed duration of response (DOR), defined as the time from CR or PR until PD. Additional secondary endpoints included investigator-assessed PFS, defined as the time from the first MIRV dose until PD or death, whichever occurred first; OS, defined as the time from the first MIRV dose until death; cancer antigen 125 (CA-125) response rate as determined by the Gynecologic Cancer Intergroup criteria[35]; and safety [treatment-emergent AEs (TEAEs)]. Treatment-related AEs (TRAEs) and serious AEs (SAEs) are also reported. Blinded independent central review (BICR) was carried out as a sensitivity analysis for ORR, DOR, and PFS. Exploratory analyses of efficacy endpoints were also carried out in subgroups of interest (e.g. prior lines of therapy, *BRCA* status, prior bevacizumab, prior PARPi, and most recent PFI).

Statistical analysis

Safety analyses were carried out in the safety population (participants who received ≥1 dose of MIRV). Efficacy analyses were carried out in the efficacy-assessable population, which consisted of all participants who received ≥1 dose of MIRV and had ≥1 measurable lesion (as per RECIST version 1.1) at baseline. The CA-125-assessable population included all participants in the safety population with a pretreatment CA-125 level ≥2.0 times the upper limit of normal ≤2 weeks before first MIRV dose and ≥1 post-baseline CA-125 assessment.

Using an optimal Simon's two-stage design, the trial was designed to test the null hypothesis that the ORR was ≤28% versus the alternative that the ORR was ≥48% with no planned pause in enrollment given the preliminary efficacy and established safety of MIRV.[36] Expected sample sizes and probabilities of early termination are provided in Supplementary Methods, available at https://doi.org/10.1016/j.annonc.2024.11.011. Approximately 75 participants were planned such that a minimum of 69 participants would be assessable for efficacy.

The primary endpoint of ORR was estimated along with a two-sided 95% confidence interval (CI) using the Clopper—Pearson method[37]; the null hypothesis was rejected if the lower bound of the 95% CI exceeded 28%. DOR, PFS, and OS were estimated using the Kaplan—Meier method. The 95% CI associated with the CA-125 response rate was estimated using the Clopper—Pearson method. No formal hypothesis testing was carried out on secondary endpoints. All statistical analyses were carried out using SAS version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Patients

Screening and enrollment occurred between August 2021 and February 2023, with 302 patients screened across 78 centers. Of the 302 screened patients, ∼43.5% ($n = 124$) of tumors were FRα positive. In total, 79 patients with FRα-positive recurrent PSOC were enrolled in North America, Europe, and Australia (Figure 1).

Demographics and baseline clinical characteristics are summarized in Table 1. It is important to note that the lack of racial and ethnic diversity among trial participants may undermine the generalizability of the study results. Median age was 66.0 years (range 41-84 years). *BRCA* mutations were present in 27.8% of participants ($n = 22$). Baseline clinical characteristics showed that 60.8% of participants ($n = 48$) had received 2 prior lines of systemic therapy, 30.4% ($n = 24$) had received 3 prior lines, and 7.6% ($n = 6$) had received ≥4 prior lines. The majority of patients had received prior taxane treatment [97.5%, $n = 77$ (25.3%, $n = 20$ received taxanes in multiple prior lines)], prior bevacizumab treatment [64.6%, $n = 51$ (8.9%, $n = 7$ received bevacizumab in multiple prior lines)], or prior PARPi treatment (81.0%, $n = 64$); 53.9% of participants ($n = 41/76$; excluding $n = 3$ with prior PARPi unknown) had

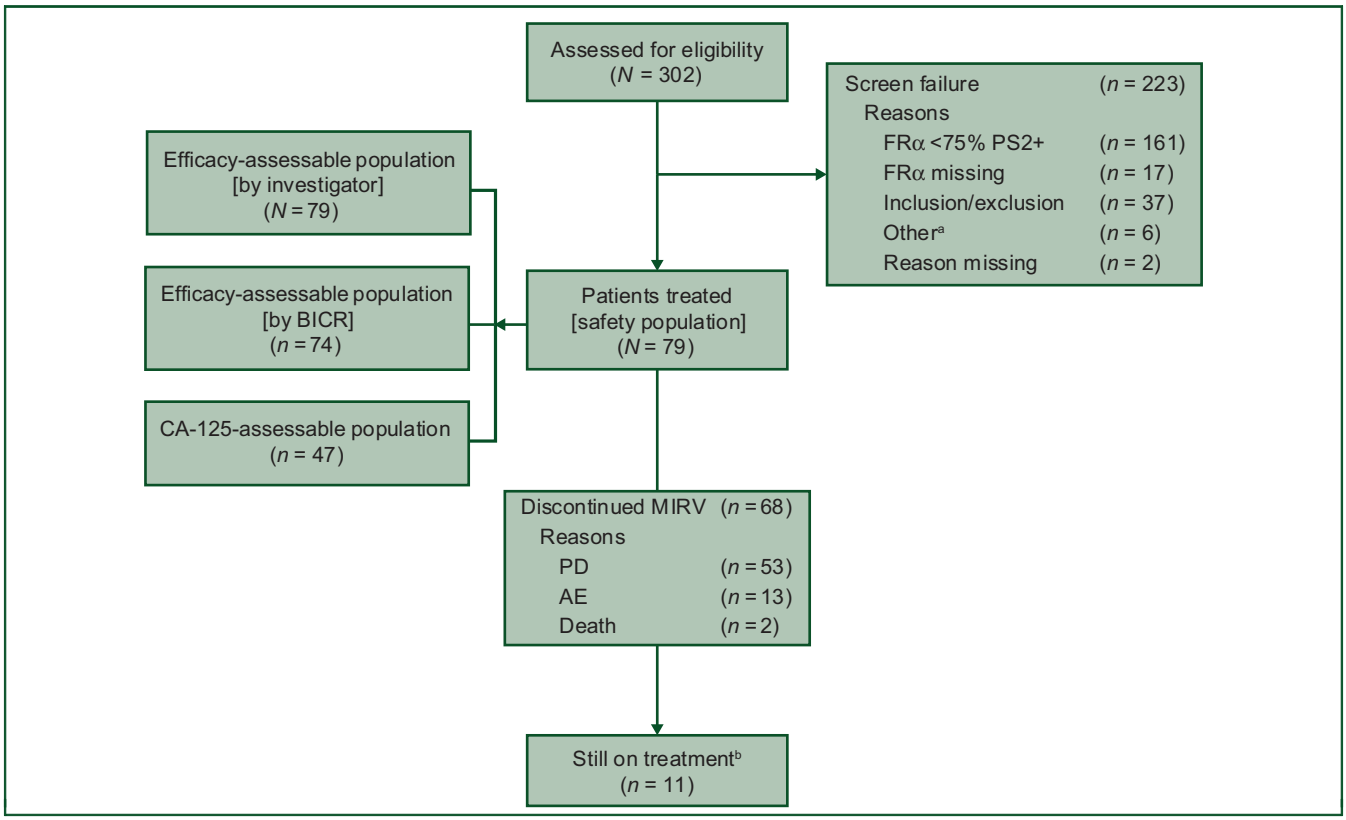

Figure 1. Participant disposition.
AE, adverse event; BICR, blinded independent central review; CA-125, cancer antigen 125; FRα, folate receptor alpha; MIRV, mirvetuximab soravtansine-gynx; PD, progressive disease; PS2+, positive staining 2+; PSOC, platinum-sensitive ovarian cancer.
[a]Free text reasons for 'other' included patient withdrawal of consent ($n = 4$) or did not meet the eligibility criteria (not PSOC $n = 1$; no radiographic PD $n = 1$).
[b]As of data cut-off 17 January 2024.

received both prior PARPi and prior bevacizumab. Among all participants ($N = 79$), 74.7% ($n = 59$) had PD while on prior PARPi or within 30 days of PARPi; 6.3% ($n = 5$) discontinued prior PARPi therapy without PD recorded. Evaluation of most recent PFI showed that 54.4% of participants ($n = 43$) had a PFI of $\leq$12 months, and 43.0% ($n = 34$) had a PFI of >12 months (missing data in two participants). Among participants, 19.0% ($n = 15$) were considered appropriate for single-agent non-platinum therapy due to a platinum allergy, while 51.9% ($n = 41$) were considered at risk of further cumulative toxicity with additional platinum.

At the time of data cut-off (17 January 2024), participants had received a median of 9 MIRV cycles (range 1-27), the median exposure duration was 6.9 months (range 0.7-21.7 months), and 14% of participants ($n = 11$) continued to receive MIRV.

Efficacy

All 79 participants were assessable for investigator-assessed efficacy endpoints. Table 2 reports primary and secondary efficacy findings. The primary endpoint was met, with a confirmed investigator-assessed ORR of 51.9% (95% CI 40.4% to 63.3%), which included 6 CRs (7.6%) and 35 PRs (44.3%). Stable disease occurred in 36.7% of participants ($n = 29$); overall 85.5% of the participants with post-baseline tumor measurements showed a reduction in tumor volume. Figure 2 represents the maximum tumor percentage change from baseline with MIRV. The median DOR among responders was 8.25 months (95% CI 5.55-10.78 months). Median PFS was 6.93 months (95% CI 5.85-9.59 months), and OS was not mature at time of data cut-off. The CA-125 response rate among the 47 assessable participants was 74.5% ($n = 35$, 95% CI 59.7% to 86.1%). The concordance rate of investigator-assessed best overall response versus BICR-assessed best overall response was 73.4% (95% CI 62.3% to 82.7%).

Results for investigator-assessed ORR and median DOR in participant subgroups by *BRCA* mutation status, number of prior lines of therapy, prior bevacizumab and/or PARPi treatment, and most recent PFI can be found in Table 3 (investigator-assessed PFS among subgroups is reported in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2024.11.011). ORR was 55.1% ($n = 27/49$, 95% CI 40.2% to 69.3%) in participants with one or two prior lines of therapy and 50.0% ($n = 12/24$, 95% CI 29.1% to 70.9%) in those with three prior lines. One participant had only one prior line of therapy, and best overall response was stable disease for that participant. In bevacizumab-naïve participants, the ORR was 57.1% ($n = 16/28$, 95% CI 37.2% to 75.5%) versus 49.0% ($n = 25/51$, 95% CI 34.8% to 63.4%) in participants with prior bevacizumab. ORR was

Table 1. Participant demographics and baseline clinical characteristics

Characteristic	N = 79
Age, median (range), years	66 (41-84)
Race,[a] *n* (%)	
Asian	1 (1.3)
Black or African American	4 (5.1)
Not reported	8 (10.1)
Other	1 (1.3)
White	65 (82.3)
Ethnicity,[a] *n* (%)	
Hispanic or Latino	2 (2.5)
Not Hispanic or Latino	68 (86.1)
Not reported	7 (8.9)
Unknown	2 (2.5)
Primary diagnosis, *n* (%)	
Epithelial ovarian cancer	67 (84.8)
Fallopian tube cancer	5 (6.3)
Primary peritoneal cancer	4 (5.1)
Other	3 (3.8)
Stage at initial diagnosis, *n* (%)	
I	4 (5.1)
II	5 (6.3)
III	51 (64.6)
IV	18 (22.8)
Missing	1 (1.3)
ECOG performance status, *n* (%)	
0	57 (72.2)
1	22 (27.8)
BRCA mutations, *n* (%)	
Positive[b]	22 (27.8)
BRCA1	18 (22.8)
BRCA2	6 (7.6)
Negative/unknown	57 (72.2)
No. of prior systemic therapies, *n* (%)	
1	1 (1.3)
2	48 (60.8)
3	24 (30.4)
≥4	6 (7.6)
Prior exposure, *n* (%)	
Taxanes	77 (97.5)
Exposed in multiple lines	20 (25.3)
PARPis[c]	64 (81.0)
Progression on PARPi[d]	59 (74.7)
Without progression on PARPi	5 (6.3)
Bevacizumab	51 (64.6)
Exposed in multiple lines	7 (8.9)
PARPis and bevacizumab	41 (53.9)[d]
Platinum-free interval,[e] *n* (%)	
≤12 months	43 (54.4)
>12 months	34 (43.0)
Missing	2 (2.5)
Reason for single-agent non-platinum therapy, *n* (%)	
Documented platinum allergy	15 (19.0)
High risk of hypersensitivity reaction	15 (19.0)
Risk of further cumulative toxicity	41 (51.9)
Other	8 (10.1)
FRα expression,[f] *n* (%)	
≥75%	79 (100)

BRCA, BReast CAncer gene; ECOG, Eastern Cooperative Oncology Group; FRα, folate receptor alpha; PARPis, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors; PD, progressive disease; PS2+, positive staining 2+.
[a]Race and ethnic group were reported by the participants.
[b]Two participants were positive for both *BRCA1* and *BRCA2* mutations.
[c]Exposure to prior PARPi was uncertain in three participants (3.8%) who participated in double-blind trials evaluating PARPi versus placebo (actual treatment not known).
[d]If the participant had progression of disease within 30 days after the last dosing of a PARPi or progression was listed as the reason for treatment discontinuation of a PARPi, the participant was defined as having PD on prior PARPi and was included in this category.
[e]Platinum-free interval is defined as time from the last dose of the latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy (time rounded to whole number).
[f]≥75% of tumor cells with FRα membrane staining of ≥2+ intensity using PS2+ scoring methodology.

75.0% ($n = 9/12$, 95% CI 42.8% to 94.5%) in PARPi-naïve participants and 46.9% ($n = 30/64$, 95% CI 34.3% to 59.8%) in participants with prior PARPi treatment. Participants with both prior PARPi and prior bevacizumab demonstrated an ORR of 43.9% ($n = 18/41$, 95% CI 28.5% to 60.3%). Among participants with PD while on PARPi or within 30 days after the last dose of PARPi, ORR was 45.8% ($n = 27/59$, 95% CI 32.7% to 59.2%) versus 60.0% ($n = 3/5$, 95% CI 14.7% to 94.7%) in those who did not have PD with prior PARPi treatment. ORR was 49.1% ($n = 28/57$, 95% CI 35.6% to 62.7%) in participants with prior exposure to taxanes in one line only, compared with 60.0% ($n = 12/20$, 95% CI 36.1% to 80.9%) in participants with exposure to taxanes in multiple lines.

Safety

Safety analyses included all 79 participants (safety findings are reported in Table 4). Ninety-nine percent of participants ($n = 78$) experienced ≥1 TEAE; 51% of participants ($n = 40$) experienced ≥1 TEAE of grade ≥3. Thirty-five percent of participants ($n = 28$) experienced ≥1 TRAE of grade ≥3 (TRAEs are summarized in Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2024.11.011). The most common (≥30%) TEAEs (all grades) included blurred vision (63%, $n = 50$), dry eye (37%, $n = 29$), nausea (37%, $n = 29$), keratopathy (33%, $n = 26$), and diarrhea (30%, $n = 24$) (TEAEs occurring in ≥10% of participants are provided in Table 4). The most common grade ≥3 TEAEs included blurred vision (10%, $n = 8$), cataract (8%, $n = 6$), keratopathy (4%, $n = 3$), peripheral neuropathy (4%, $n = 3$), and pneumonitis (4%, $n = 3$). SAEs occurred in 19% of participants ($n = 15$), and treatment-related SAEs occurred in 9% of participants ($n = 7$; details are provided in Supplementary Results, available at https://doi.org/10.1016/j.annonc.2024.11.011).

Table 2. Summary of efficacy measures

Endpoint	
ORR[a]	N = 79
n (%)	41 (51.9)
95% CI	40.4-63.3
Best overall response, *n* (%)[a]	N = 79
Complete response	6 (7.6)
Partial response	35 (44.3)
Stable disease	29 (36.7)
Progressive disease	7 (8.9)
Not evaluable	2 (2.5)
Median DOR[a,b]	*n* = 41
Months (95% CI)	8.25 (5.55-10.78)
Median PFS[a]	N = 79
Months (95% CI)	6.93 (5.85-9.59)
CA-125 response[c]	*n* = 47
n (%)	35 (74.5)
95% CI	59.7-86.1

CA-125, cancer antigen 125; CI, confidence interval; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival.
[a]Investigator assessed.
[b]Calculated among participants who had a complete or partial response.
[c]Analysis carried out on the CA-125-assessable population.

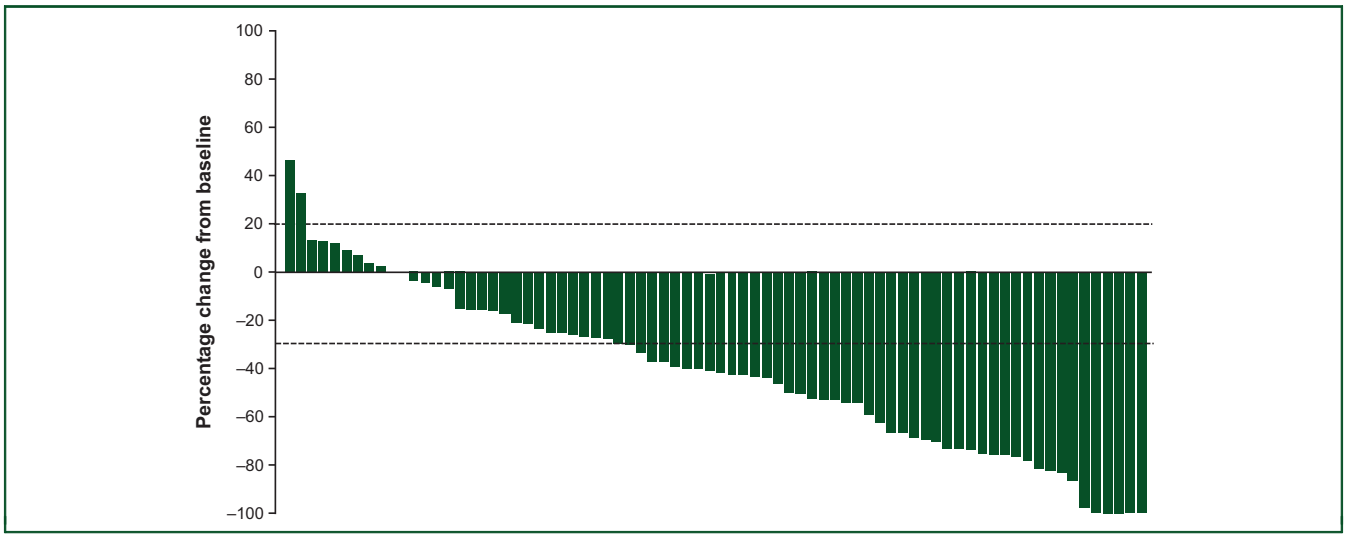

Figure 2. Maximum tumor percentage change from baseline among 79 efficacy-assessable participants treated with MIRV as assessed by the investigator (85.5% of participants demonstrated tumor reduction).
MIRV, mirvetuximab soravtansine-gynx.

MIRV dose modifications (including dose reduction and dose delay) due to TEAEs occurred in 66% of participants ($n = 52$). Dose delay/hold occurred in 61% of participants ($n = 48$), dose reduction occurred in 42% ($n = 33$), and discontinuation in 16% ($n = 13$). TEAEs responsible for discontinuation in >1 participant were (preferred terms) pneumonitis (4%, $n = 3$), cataract, corneal epithelial microcysts, peripheral neuropathy, and blurred vision [each occurring in two participants (3%), respectively]. The median number of MIRV cycles administered before discontinuation due to toxicity was 10 (range 2-21).

TEAEs led to death in two participants (3%), one of which was determined to be MIRV-related (pneumonitis; further details in Supplementary Results, available at https://doi.

Table 3. Investigator-assessed ORR and DOR[a] in participant subgroups

Subgroup	ORR subgroup, *n*	ORR, *n* (%) [95% CI]	DOR subgroup, *n*	Median DOR, months [95% CI]
Prior lines of therapy				
1 or 2	49	27 (55.1) [40.2-69.3]	27	7.44 [4.63-9.66]
3	24	12 (50.0) [29.1-70.9]	12	8.41 [4.63-NR]
≥4	6	2 (33.3) [4.3-77.7]	2	NR [2.69-NR]
Exposure to PARPis				
Yes	64	30 (46.9) [34.3-59.8]	30	8.25 [5.45-10.78]
Progression on PARPi[b]	59	27 (45.8) [32.7-59.2]	27	7.33 [5.03-10.78]
Without progression on PARPi	5	3 (60.0) [14.7-94.7]	3	8.41 [6.97-NR]
No	12	9 (75.0) [42.8-94.5]	9	8.77 [3.52-NR]
Unknown[c]	3	2 (66.7) [9.4-99.2]	2	4.21 [NR-NR]
Exposure to bevacizumab				
Yes	51	25 (49.0) [34.8-63.4]	25	8.41 [4.63-NR]
No	28	16 (57.1) [37.2-75.5]	16	7.01 [4.40-NR]
Exposure to both PARPis and bevacizumab	41	18 (43.9) [28.5-60.3]	18	8.41 [4.63-NR]
Exposure to taxanes				
1 line only	57	28 (49.1) [35.6-62.7]	28	8.41 [5.65-NR]
Multiple lines	20	12 (60.0) [36.1-80.9]	12	6.13 [4.21-9.66]
BRCA mutation status				
Positive	22	16 (72.7) [49.8-89.3]	16	4.63 [4.34-6.97]
Negative/Unknown	57	25 (43.9) [30.7-57.6]	25	9.07 [7.33-NR]
Most recent PFI[d]				
≤12 months	43	18 (41.9) [27.0-57.9]	18	7.33 [4.27-10.78]
>12 months	34	22 (64.7) [46.5-80.3]	22	8.33 [4.63-NR]
Missing	2	1 (50.0) [1.3-98.7]	1	NR

BRCA, BReast CAncer gene; CI, confidence interval; DOR, duration of response; NR, not reached; ORR, objective response rate; PARPis, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors; PFI, platinum-free interval.
[a]Calculated among participants who had a complete or partial response.
[b]If the participant had progression of disease within 30 days after the last dosing of a PARPi or progression was listed as the reason for treatment discontinuation of a PARPi, the participant was defined as having progressive disease on prior PARPi and was included in this category.
[c]For participants who participated in double-blind trials evaluating PARPi versus placebo and the actual treatment was not known.
[d]Platinum-free interval is defined as time from the last dose of the latest line platinum therapy to the date of disease progression and/or relapse following that line of therapy (time rounded to whole number).

Table 4. Overview of TEAEs

TEAEs, *n* (%)	*N* = 79			
Any TEAE	78 (99)			
Grade 3	37 (47)			
Grade 4	1 (1)			
Grade 5	2 (3)			
SAEs	15 (19)			
Treatment-related SAEs	7 (9)			
TEAEs leading to dose modification[a]	52 (66)			
TEAEs leading to dose reduction	33 (42)			
TEAEs leading to dose delay/hold	48 (61)			
TEAEs leading to discontinuation	13 (16)			
TEAEs leading to death[b]	2 (3)			
TRAEs leading to death	1 (1)			
TEAEs ≥10%,[c] *n* (%)	**All grades**	**Grade 3**	**Grade 4**	**Grade 5**
Participants with any TEAE	78 (99)	37 (47)	1 (1)	2 (3)
Blurred vision	50 (63)	8 (10)	0	0
Dry eye	29 (37)	2 (3)	0	0
Nausea	29 (37)	1 (1)	0	0
Keratopathy	26 (33)	3 (4)	0	0
Diarrhea	24 (30)	2 (3)	0	0
Asthenia	23 (29)	2 (3)	0	0
Peripheral neuropathy	22 (28)	3 (4)	0	0
Cataract	19 (24)	6 (8)	0	0
Arthralgia[d]	16 (20)	1 (1)	0	0
Aspartate aminotransferase increase	16 (20)	0	0	0
Vomiting	15 (19)	1 (1)	0	0
Fatigue	14 (18)	0	0	0
Alanine aminotransferase increase	14 (18)	0	0	0
Constipation	13 (16)	0	0	0
Headache	13 (16)	0	0	0
Photophobia	12 (15)	0	0	0
COVID-19	12 (15)	0	0	0
Neutropenia	11 (14)	1 (1)	1 (1)	0
Abdominal pain	11 (14)	0	0	0
Neurotoxicity	10 (13)	2 (3)	0	0
Dysgeusia	9 (11)	0	0	0
Pneumonitis	8 (10)	2 (3)	0	1 (1)

COVID-19, coronavirus disease 2019; MIRV, mirvetuximab soravtansine-gynx; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events.
[a]Dose modifications include dose reduction and dose delay. Treatment discontinuation is not included.
[b]Adverse events led to death in two participants. One was deemed related to MIRV (TRAE of pneumonitis), and the other was deemed unrelated (septic shock).
[c]Preferred terms.
[d]One participant had a missing grade.

org/10.1016/j.annonc.2024.11.011); the other was deemed unrelated (septic shock).

Ocular TEAEs (all grades) occurred in 81% of participants ($n = 64$). Grade 3 ocular TEAEs occurred in 22% of participants ($n = 17$; summarized in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2024.11.011); no grade ≥4 ocular TEAEs occurred. Median time to first onset of any ocular TEAE was 6.1 weeks (range 0.3-51.9 weeks). Six participants (8%) discontinued MIRV due to ocular TEAEs. No corneal ulcers or corneal perforations were reported.

Supplementary Results, available at https://doi.org/10.1016/j.annonc.2024.11.011, provide additional ocular TEAE data (dose modifications and resolution) and further information on TEAEs of pneumonitis and peripheral neuropathy and hematologic TEAEs.

DISCUSSION

Here we report results from the phase II PICCOLO trial, which evaluated the efficacy and safety of MIRV in third-line and later PSOC. These results build upon the clinical benefit observed with MIRV in other populations of patients with ovarian cancer and further demonstrate that MIRV is efficacious in a variety of patients with FRα-positive ovarian cancer. While the efficacy of MIRV monotherapy has been studied (including a confirmatory trial)[27,30,38] in patients with PROC, the PICCOLO trial provides results from the first completed, phase II trial of MIRV monotherapy focused solely on patients with PSOC. This is of importance, given the distinguishing factors between PSOC and PROC patient populations.[39,40] The efficacy of MIRV in PSOC is further being evaluated in the phase III, randomized GLORIOSA trial (NCT05445778) in combination with bevacizumab versus bevacizumab alone as maintenance therapy for patients with FRα-high, recurrent PSOC.[41] The PICCOLO trial met its primary endpoint, with an investigator-assessed ORR of 51.9% (95% CI 40.4% to 63.3%) in the overall population, including a 7.6% CR rate and a 44.3% PR rate. These responses were durable, as demonstrated by the key secondary endpoint of DOR [median DOR 8.25 months (95% CI, 5.55-10.78 months)] and further supported by the investigator-assessed median PFS of 6.93 months (95% CI 5.85-9.59 months). Additionally, 11 participants were still on treatment at time of data cut-off. The safety profile of MIRV was consistent with that of previous trials, and no new safety signals were observed.[25,27,30,38] Furthermore, 43.5% of screened participants demonstrated positive FRα tumor expression (≥75% of cells with ≥2+ staining intensity), which differs marginally from the rates of positive FRα tumor expression in patients with PROC (32% to 36%).[27,30] The findings underscore the utility of MIRV as a viable treatment option in a substantial proportion of patients with PSOC.

Multiple courses of platinum-based chemotherapy put patients at risk for concerns such as cumulative toxicities that are detrimental to quality of life,[8,42] diminished clinical responses to chemotherapy,[8,9] and platinum hypersensitivity.[10] Thus, non-platinum-based, novel treatment options could be of potential benefit for heavily pretreated patients with PSOC. The efficacy benefits seen among subgroups in PICCOLO suggest that MIRV may be a potentially effective treatment option for patients with recurrent PSOC who are heavily pretreated and have experienced disease progression with other treatments. This includes participants with three prior lines of therapy [ORR 50.0% (95% CI 29.1% to 70.9%)], prior bevacizumab treatment [49.0% (95% CI 34.8% to 63.4%)], prior PARPi treatment [46.9% (95% CI 34.3% to 59.8%)], and prior taxane treatment in multiple lines [60.0%

(95% CI 36.1% to 80.9%)]; however, these subgroup results are exploratory only.

A large proportion of participants in the PICCOLO trial (74.7%, $n = 59$) had prior documented PD while on or within 30 days of PARPi treatment; these participants demonstrated an ORR of 45.8% (95% CI 32.7% to 59.2%) with MIRV. This response is notable given the significant use of PARPi therapy in EOC and limited randomized prospective trials for platinum-based therapy after PD with PARPi.[17,43] Treatment for later-line PSOC following prior PARPi typically consists of re-treatment with platinum-based chemotherapy with or without bevacizumab, followed by bevacizumab as maintenance therapy.[43] Diminished efficacy with subsequent therapies (including platinum-based chemotherapy re-treatment) following disease progression on PARPi treatment has been observed.[18-23] *Post hoc* analysis of the SOLO-2 trial found that median time to second progression on subsequent chemotherapy was significantly longer in patients who previously received placebo versus PARPi [12.1 months with placebo versus 6.9 months with olaparib; hazard ratio 2.17 (95% CI 1.47-3.19)].[18] Similar findings were observed in *post hoc* analyses of the PAOLA-1 study; time from first subsequent therapy to second subsequent therapy was shortest in patients who progressed during PARPi maintenance therapy (6.1 months), compared with those who progressed afterward (11.4 months) or who were treated with bevacizumab plus placebo (11.9 months).[21] Further, a retrospective real-world analysis of patients who received platinum-based chemotherapy with or without bevacizumab following disease progression after PARPi found that ORR was 41.9%, median PFS was 6.6 months (95% CI 6.0-9.2 months), and median OS was 20.6 months (95% CI 13.6-28.9 months).[20] Other retrospective analyses, real-world data, and meta-analyses of PARPi-treated patients have corroborated these findings and highlighted the unmet need in this population.[19,22,23]

No new MIRV safety signals were observed in the PICCOLO trial, as the most common TEAEs were generally low-grade gastrointestinal, neurosensory, and resolvable ocular events.[44] Notable differences from prior MIRV clinical experience include higher rates of discontinuation for TEAEs (16% in PICCOLO versus 12% in previous MIRV trials), including discontinuation for ocular TEAEs (8% versus 1%).[44] This may be related to longer median time on therapy [median of 9 (range 1-27) MIRV cycles in the PICCOLO trial compared with 6 (range 1-44) in previous MIRV trials].[44] Subjects who discontinued MIRV for TEAEs had a median duration of treatment of 10 cycles (range 2-21 cycles).[44] Specifically, two participants discontinued MIRV treatment after receiving 13 cycles of MIRV and undergoing cataract surgery, after which the investigator could have elected to resume treatment. Slightly higher rates of keratopathy occurred in the PICCOLO trial compared with previous trials of MIRV (33% versus 29%); however, there was no difference in grade $\geq$3 keratopathy (4% versus 5%).[44] Additionally, no progression to SAEs of corneal ulcer or perforation was reported in this trial.

Overall, grade $\geq$3 TEAEs occurred in 51% of participants (including one grade 4 and two grade 5 events), and grade $\geq$3 TRAEs occurred in 35% of participants. Pneumonitis, an AE of concern for ADCs, occurred in 8 participants (10%), and peripheral neuropathy, a common issue with tubulin-targeting agents, occurred in 22 participants (28%), consistent with previous MIRV trials.[44] Grade $\geq$3 pneumonitis occurred in three participants (4%) in the PICCOLO trial, slightly higher than the rates seen in previous trials [$n = 9$/682 participants (1%)].[44] Conversely, grade $\geq$3 peripheral neuropathy occurred in three participants (4%) in the PICCOLO trial, consistent with previous trials [$n = 18$/682 participants (3%)].[44] One participant in the PICCOLO trial experienced grade 5 pneumonitis (further details in Supplementary Results, available at https://doi.org/10.1016/j.annonc.2024.11.011) and this patient had a history of grade 3 pneumonia considered unrelated to MIRV.[44]

While definitive conclusions cannot be made from a single-arm trial without a comparator arm, PICCOLO demonstrated notable efficacy in a heavily pretreated population of participants with PSOC, including 81% of participants who had prior PARPi therapy. The generalizability of these results may be limited by the lack of racial and ethnic diversity among trial participants and the FRα eligibility criterion.

In conclusion, the PICCOLO trial demonstrated that MIRV monotherapy elicited high ORRs, durable responses, and a tolerable safety profile in heavily pretreated patients with third-line and later FRα-positive PSOC. This trial provides results from the first completed, phase II trial of MIRV monotherapy focused solely on patients with PSOC. Given the need for effective and tolerable therapeutic options for these patients, these findings suggest that MIRV provides a potential efficacious choice in later-line, FRα-positive PSOC.

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DATA SHARING

The study sponsor, ImmunoGen, Inc, is committed to responsible sharing of clinical trial data. Data from this clinical trial can be requested by any qualified investigator who engages in relevant research. Data requests can be submitted at any time via medicalinformation@immunogen.com.

REFERENCES

1. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Ovarian Cancer. Available at https://seer.cancer.gov/statfacts/html/ovary.html. Accessed April 4, 2023.
2. Kuroki L, Guntupalli SR. Treatment of epithelial ovarian cancer. *Br Med J*. 2020;371:m3773.
3. International Agency for Research on Cancer; World Health Organization. Ovary. Available at https://gco.iarc.who.int/media/globocan/factsheets/cancers/25-ovary-fact-sheet.pdf. Accessed April 15, 2024.
4. Chien J, Kuang R, Landen C, Shridhar V. Platinum-sensitive recurrence in ovarian cancer: the role of tumor microenvironment. *Front Oncol*. 2013;3:251.
5. Salani R, Khanna N, Frimer M, Bristow RE, Chen LM. An update on post-treatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncology (SGO) recommendations. *Gynecol Oncol*. 2017;146(1):3-10.
6. Luvero D, Milani A, Ledermann JA. Treatment options in recurrent ovarian cancer: latest evidence and clinical potential. *Ther Adv Med Oncol*. 2014;6(5):229-239.
7. Arnaoutoglou C, Dampala K, Anthoulakis C, et al. Epithelial ovarian cancer: a five year review. *Medicina (Kaunas)*. 2023;59(7):1183.
8. Gupta S, Nag S, Aggarwal S, Rauthan A, Warrier N. Maintenance therapy for recurrent epithelial ovarian cancer: current therapies and future perspectives – a review. *J Ovarian Res*. 2019;12(1):103.

9. Kessous R, Wissing MD, Laskov I, et al. Multiple lines of chemotherapy for patients with high-grade ovarian cancer: predictors for response and effect on survival. *Int J Cancer.* 2021;148(9):2304-2312.
10. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. *Clin Rev Allergy Immunol*. 2022;62(3):432-448.
11. McMullen M, Karakasis K, Madariaga A, Oza AM. Overcoming platinum and PARP-inhibitor resistance in ovarian cancer. *Cancers (Basel)*. 2020;12(6):1607.
12. Ozols RF. Oral etoposide for the treatment of recurrent ovarian cancer. *Drugs*. 1999;58(suppl 3):43-49.
13. Morris R, Alvarez RD, Andrews S, et al. Topotecan weekly bolus chemotherapy for relapsed platinum-sensitive ovarian and peritoneal cancers. *Gynecol Oncol*. 2008;109(3):346-352.
14. ten Bokkel Huinink W, Gore M, Carmichael J, et al. Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol*. 1997;15(6):2183-2193.
15. Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. *J Clin Oncol*. 2010;28(19):3107-3114.
16. Carballo EV, Kim KH, Penn CA. Trends in estimated PARP inhibitor eligibility and benefit among US epithelial ovarian cancer patients. *Gynecol Oncol*. 2024;187:204-211.
17. Lele S, editor. *Ovarian Cancer.* Brisbane (AU): Exon Publications; 2022.
18. Frenel JS, Kim JW, Aryal N, et al. Efficacy of subsequent chemotherapy for patients with BRCA1/2-mutated recurrent epithelial ovarian cancer progressing on olaparib versus placebo maintenance: post-hoc analyses of the SOLO2/ENGOT Ov-21 trial. *Ann Oncol*. 2022;33(10):1021-1028.
19. Cecere SC, Giannone G, Salutari V, et al. Olaparib as maintenance therapy in patients with BRCA 1-2 mutated recurrent platinum sensitive ovarian cancer: real world data and post progression outcome. *Gynecol Oncol*. 2020;156(1):38-44.
20. Romeo M, Gil-Martin M, Gaba L, et al. Multicenter real-world data of subsequent chemotherapy after progression to PARP inhibitors in a maintenance relapse setting. *Cancers (Basel)*. 2022;14(18):4414.
21. Harter P, Mouret-Reynier M-A, Lorusso D, et al. Presented at: 2023 American Society of Clinical Oncology; June 2-6, 2023; Chicago, IL. Abstract 5550.
22. Park J, Kim SI, Jeong SY, et al. Second-line olaparib maintenance therapy is associated with poor response to subsequent chemotherapy in BRCA1/2-mutated epithelial ovarian cancer: a multicentre retrospective study. *Gynecol Oncol*. 2022;165(1):97-104.
23. Rose PG, Yao M, Chambers LM, et al. PARP inhibitors decrease response to subsequent platinum-based chemotherapy in patients with BRCA mutated ovarian cancer. *Anticancer Drugs*. 2021;32(10):1086-1092.
24. Ab O, Whiteman KR, Bartle LM, et al. IMGN853, a folate receptor-α (FRα)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against FRα-expressing tumors. *Mol Cancer Ther.* 2015;14(7):1605-1613.
25. Moore KN, Martin LP, O'Malley DM, 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*. 2017;35(10):1112-1118.
26. ELAHERE (mirvetuximab soravtansine-gynx) [prescribing information]. ImmunoGen, Inc.; Waltham, MA.; 2024.
27. Moore KN, Angelergues A, Konecny GE, et al. Mirvetuximab soravtansine in FRα-positive, platinum-resistant ovarian cancer. *N Engl J Med*. 2023;389(23):2162-2174.
28. Pujade-Lauraine E, Hilpert F, Weber B, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol*. 2014;32(13):1302-1308.
29. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer V.3.2024. © National Comprehensive Cancer Network, Inc. 2024. Available at: NCCN.org. Accessed August 1, 2024. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
30. Matulonis UA, Lorusso D, Oaknin A, et al. Efficacy and safety of mirvetuximab soravtansine in patients with platinum-resistant ovarian cancer with high folate receptor alpha expression: results from the SORAYA study. *J Clin Oncol*. 2023;41(13):2436-2445.
31. Gilbert L, Oaknin A, Matulonis UA, et al. Safety and efficacy of mirvetuximab soravtansine, a folate receptor alpha (FRalpha)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol*. 2023;170:241-247.
32. O'Malley DM, Matulonis UA, Birrer MJ, et al. Phase Ib study of mirvetuximab soravtansine, a folate receptor alpha (FRalpha)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients with platinum-resistant ovarian cancer. *Gynecol Oncol*. 2020;157(2):379-385.
33. O'Malley D, Oaknin A, Matulonis U, et al. Mirvetuximab soravtansine and bevacizumab in folate receptor alpha-positive ovarian cancer: efficacy in patients with and without prior bevacizumab [abstract]. Presented at International Gynecologic Cancer Society Annual Meeting. September 29-October 1, 2022; New York City, New York; Abstract 496.
34. U.S. Food and Drug Administration. VENTANA FOLR1 (FOLR1-2.1) RxDx assay. Tucson, AZ: Ventana Medical Systems. Available at https://www.accessdata.fda.gov/cdrh_docs/pdf22/P220006A.pdf; 2022. Accessed October 7, 2022.
35. Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst*. 2004;96(6):487-488.
36. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989;10(1):1-10.
37. Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika*. 1934;26(4):404-413.
38. Moore KN, Oza AM, Colombo N, et al. Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I. *Ann Oncol*. 2021;32(6):757-765.
39. Wu X, Zhu J, Wang J, et al. Pamiparib monotherapy for patients with germline BRCA1/2-mutated ovarian cancer previously treated with at least two lines of chemotherapy: a multicenter, open-label, phase II study. *Clin Cancer Res*. 2022;28(4):653-661.
40. Havasi A, Cainap SS, Havasi AT, Cainap C. Ovarian cancer-insights into platinum resistance and overcoming it. *Medicina (Kaunas)*. 2023;59(3):544.
41. Mirvetuximab Soravtansine With Bevacizumab Versus Bevacizumab as Maintenance in Platinum-sensitive Ovarian, Fallopian Tube, or Peritoneal Cancer (GLORIOSA). ClinicalTrials.gov identifier: NCT05445778. Updated October 28, 2024. Available at https://clinicaltrials.gov/ct2/show/NCT05445778. Accessed October 31, 2024.
42. Dunton CJ. Management of treatment-related toxicity in advanced ovarian cancer. *Oncologist*. 2002;7(suppl 5):11-19.
43. O'Malley DM, Krivak TC, Kabil N, Munley J, Moore KN. PARP inhibitors in ovarian cancer: a review. *Target Oncol*. 2023;18(4):471-503.
44. Moore KN, Lorusso D, Oaknin A, et al. Safety and tolerability of mirvetuximab soravtansine monotherapy for folate receptor alpha-expressing recurrent ovarian cancer: an integrated safety summary. *Gynecol Oncol*. 2024;191:249-258.