original reports

# Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study

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abstract

**PURPOSE** Single-agent chemotherapies have limited activity and considerable toxicity in patients with platinum-resistant epithelial ovarian cancer (PROC). Mirvetuximab soravtansine (MIRV) is an antibody-drug conjugate targeting folate receptor α (FRα). SORAYA is a single-arm, phase II study evaluating efficacy and safety of MIRV in patients with PROC.

**METHODS** SORAYA enrolled FRα-high patients with PROC who had received one to three prior therapies, including required bevacizumab. The primary end point was confirmed objective response rate (ORR) by investigator; duration of response was the key secondary end point.

**RESULTS** One hundred six patients were enrolled; 105 were evaluable for efficacy. All patients had received prior bevacizumab, 51% had three prior lines of therapy, and 48% received a prior poly ADP-ribose polymerase inhibitor. Median follow-up was 13.4 months. ORR was 32.4% (95% CI, 23.6 to 42.2), including five complete and 29 partial responses. The median duration of response was 6.9 months (95% CI, 5.6 to 9.7). In patients with one to two priors, the ORR by investigator was 35.3% (95% CI, 22.4 to 49.9) and in patients with three priors was 30.2% (95% CI, 18.3 to 44.3). The ORR by investigator was 38.0% (95% CI, 24.7 to 52.8) in patients with prior poly ADP-ribose polymerase inhibitor exposure and 27.5% (95% CI, 15.9 to 41.7) in those without. The most common treatment-related adverse events (all grade and grade 3-4) were blurred vision (41% and 6%), keratopathy (29% and 9%), and nausea (29% and 0%). Treatment-related adverse events led to dose delays, reductions, and discontinuations in 33%, 20%, and 9% of patients, respectively.

**CONCLUSION** MIRV demonstrated consistent clinically meaningful antitumor activity and favorable tolerability and safety in patients with FRα-high PROC who had received up to three prior therapies, including bevacizumab, representing an important advance for this biomarker-selected population.

J Clin Oncol 41:2436-2445. © 2023 by American Society of Clinical Oncology



ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on December 8, 2022 and published at ascopubs.org/journal/jco on January 30, 2023: DOI https://doi.org/10.1200/JCO.22.01900

## INTRODUCTION

Although ovarian cancer in most patients will initially respond to platinum-based chemotherapy, up to 80% of patients will experience recurrence, with subsequent treatment determined by the duration of response (DOR) following platinum therapy.[1,2] Unfortunately, nearly all patients with recurrent disease will eventually develop platinum-resistant ovarian cancer (PROC; progression within 6 months of last platinum treatment). Current therapies in PROC consist primarily of nonplatinum chemotherapy, either as a single agent or in combination with bevacizumab; approved cytotoxic regimens in the platinum-resistant setting are associated with low response rates and considerable toxicities.[3-10] Each successive line of therapy in PROC is associated with progressively lower response rates, and unfortunately, fewer patients are healthy enough to tolerate further rounds of treatment.[11] Approval of bevacizumab in combination with chemotherapy for patients with PROC was based on the AURELIA study, in which the control arm of single-agent chemotherapy was associated with an objective response rate (ORR) of 11.8% and a median DOR of 5.4 months.[12,13] Four other recent phase III studies (CORAIL, NINJA, FORWARD I, and JAVELIN Ovarian 200) conducted in patients with PROC have reported similar outcomes for chemotherapy in this setting (ORR range, 4%-13%; DOR range, 3.7-13.1 months).[14-17] Since the 2014 approval of bevacizumab

## CONTEXT

**Key Objective**

What is the potential of mirvetuximab soravtansine in folate receptor α–positive platinum-resistant ovarian cancer?

**Knowledge Generated**

To our knowledge, this is the first trial of an antibody-drug conjugate that demonstrated a meaningful therapeutic benefit in a biomarker-selected platinum-resistant ovarian cancer population who had previously received up to three prior lines of therapy including bevacizumab and in patients who had received a prior poly ADP-ribose polymerase inhibitor. Folate receptor α is a promising biomarker for targeted therapy for patients with ovarian cancer.

**Relevance**

Mirvetuximab soravtansine offers real benefit to patients with platinum-resistant ovarian cancer, but selection on the basis of folate receptor α expression is required.

combined with chemotherapy in the United States and Europe, there have been no new agents specifically indicated for PROC.[14,15,17] Treatment options for patients with PROC who have received prior bevacizumab or are ineligible for bevacizumab are limited to single-agent chemotherapy.

Moreover, although biomarker-based patient selection (eg, *BRCA*-based selection for poly ADP-ribose polymerase inhibitor [PARPi]) has proven beneficial, leading to improved outcomes in patients with platinum-sensitive ovarian cancer, no specific biomarker has been successfully developed for PROC.[18,19] Effective treatment for patients with PROC continues to be elusive and is urgently needed.

Mirvetuximab soravtansine (MIRV) is an antibody-drug conjugate composed of an antifolate receptor α (FRα) monoclonal antibody, a cleavable linker, and the maytansinoid DM4 payload, a potent tubulin-targeting antimitotic agent.[20] FRα is a membrane protein that binds to and transports folate into cells. This receptor is commonly overexpressed in epithelial tumors, particularly in high-grade serous ovarian and serous endometrial cancers, in contrast to normal adult tissues that generally exhibit more restricted FRα expression.[21-27] A prior study demonstrated reasonable concordance of FRα expression in archival tissue obtained at diagnosis with data from fresh biopsies obtained at enrollment after multiple lines of therapy.[28] Moreover, there is growing evidence, including clinical findings from the phase III evaluation of MIRV in PROC,[16] that elevated FRα expression may be a negative prognostic marker for response to standard chemotherapy in ovarian cancer.[29,30] These attributes make FRα a promising candidate for targeted pharmacologic approaches in this disease. Other agents have been tested that target the FRα receptor such as the humanized anti-FRα monoclonal antibody farletuzumab and the small molecule drug conjugate vintafolide; these agents demonstrated limited single-agent activity, and phase III trials testing these agents combined with chemotherapy were negative.[31] MIRV has several potential advantages over these prior modalities, including increased antigen specificity, extended half-life, and bystander killing activity even in the absence of cellular FRα expression because of its cleavable linker.

The clinical experience to date in ovarian cancer with MIRV has shown encouraging antitumor activity and a tolerable safety profile, primarily consisting of low-grade and reversible gastrointestinal and ocular adverse events.[28,32] The phase III FORWARD I trial comparing MIRV to investigator's choice chemotherapy in patients with PROC did not meet its primary end point of progression-free survival (PFS). In the Protocol (online only)-specified subset of patients with high FRα expression, MIRV antitumor activity was observed across all efficacy end points; however, these results did not reach statistical significance because of the analysis plan.[16] This finding is in agreement with the association of FRα expression level with depth and DOR identified in prior phase I evaluation.[28] Moreover, the study clearly demonstrated a favorable benefit/risk safety profile compared with standard chemotherapy. Together, these observations guided the design of two subsequent studies conducted in patients with FRα-high PROC who appear most likely to benefit from MIRV—MIRASOL (NCT04209855) and SORAYA (NCT04296890). MIRASOL is a global randomized phase III trial comparing MIRV with standard single-agent chemotherapy.[33] Here, we report the findings from SORAYA, a single-arm phase II study evaluating the efficacy and safety of MIRV in patients with FRα-high, platinum-resistant, advanced high-grade serous ovarian cancer.

## METHODS

### Patients

Eligible patients were of female sex age ≥ 18 years with a confirmed diagnosis of high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer (herein collectively referred to as ovarian cancer). All patients were required to have platinum-resistant disease (see study protocol in the supplementary section for additional details) and high FRα tumor expression as assessed by the

Ventana FOLR1 assay,[28] with at least 75% of viable tumor cells exhibiting at least 2+ level membrane staining intensity by immunohistochemistry. Exploratory rescoring analyses of patient samples from FORWARD I suggested that this PS2+ scoring was a more reliable methodology than the alternative 10× scoring method to identify patients more likely to benefit from MIRV.[16] Per protocol, testing was performed on archival tissue from the initial debulking or interval cytoreductive surgery; if archival tissue was not available, tissue from a new biopsy was permitted. In addition, efficacy evaluable patients needed at least one measurable lesion (RECIST 1.1).[34] All patients had an Eastern Cooperative Oncology Group performance status score of 0 or 1 and had received one to three previous lines of systemic anticancer therapy (maintenance therapies were considered part of the prior line of treatment). Patients with more than three prior lines were ineligible on the basis of lower activity seen in more heavily pretreated patients as part of the expansion cohort of the initial phase I evaluation of MIRV.[32] Patients with primary platinum-refractory disease, defined as disease that did not respond to first-line platinum therapy or which progressed within 3 months of the last dose of first-line platinum therapy, were excluded.

The study was performed in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council on Harmonisation, and local regulatory requirements. The protocol was approved by the institutional review board or independent ethics committee at each investigative site. All patients or their legally authorized representatives provided written informed consent.

### Study Design and Treatment

SORAYA is a single-arm phase II study. A total of 72 sites in 11 countries screened patients with 39 sites in eight countries enrolling patients. Patients received single-agent MIRV at 6 mg/kg using adjusted ideal body weight, administered IV once every 3 weeks. Patients continued to receive MIRV until progressive disease, unacceptable toxicity, withdrawal of consent, or death. All patients had an ophthalmic examination performed at screening, and ocular symptoms were assessed before each dose. As a prophylactic measure for ocular symptoms, patients were mandated to use preservative-free lubricating artificial tears daily and corticosteroid eye drops[35] starting the day before their dose and continuing through day 8 of each cycle. Patients reporting ocular symptoms at any assessment point underwent ophthalmic examinations at the time of the event and every other cycle thereafter until toxicity resolution.

### Study End Points and Assessments

The primary end point was ORR by RECIST 1.1 criteria as assessed by the investigator. The key secondary end point was DOR, defined as the time from the initial complete or partial response (PR) until progressive disease, as assessed by the investigator. The data cutoff was April 29, 2022. Additional secondary end points included safety, PFS (defined as the time from first dose of MIRV to radiologic progressive disease or death), Gynecological Cancer InterGroup CA-125 response rate,[36] and overall survival (defined as the time from first dose until death).

Tumor assessments, including radiologic assessment by computed tomography or magnetic resonance imaging scan, were performed at screening, then every 6 weeks (± 1 week) from the first day of dosing for 36 weeks, and then every 12 weeks (± 3 weeks) until progressive disease, death, the start of new anticancer therapy, or the patient's withdrawal of consent, whichever occurred first. Computed tomography or magnetic resonance imaging scans were collected for sensitivity analysis by blinded independent central review (BICR).

Patients who discontinued MIRV for reasons other than progressive disease continued with scheduled tumor assessments until documentation of progressive disease or the start of a new anticancer therapy, whichever came first. All patients who discontinued MIRV were followed for survival every 3 months (± 1 month) until death, loss to follow-up, withdrawal of consent for survival follow-up, or the end of the study, whichever came first.

### Statistical Analysis

The safety population included all patients who received at least one dose of MIRV. The efficacy evaluable population included all patients in the safety population who had measurable disease at baseline (per RECIST 1.1). Two preplanned, protocol-defined subgroups were analyzed for objective response: the number of prior lines of treatment (one to two *v* three prior lines), and prior PARPi (yes *v* no). Additional non–protocol-specified exploratory analyses of tumor reduction and disease control rate were assessed.

The sample size of approximately 110 patients was calculated to result in 105 efficacy-evaluable patients, which would achieve 90% power to detect a difference in ORR of 12% (24% *v* 12%) using a one-sided binomial test and a one-sided $\alpha$ level of 0.025. A reference ORR of 12% was chosen for the statistical comparison on the basis of the ORR for single-agent chemotherapy reported in prior trials of PROC, which range from 4% to 13%.[4-12]

The null hypothesis would be rejected if the lower bound of the 95% (two-sided) CI for ORR was > 12%. DOR was estimated using the Kaplan-Meier method. Descriptive statistics are reported.

## RESULTS

### Patients

Between June 2020 and May 2021, 467 patients were screened, and 106 patients were enrolled into the study. Thirty-seven percent of enrolled patients received prior treatment in the platinum-resistant setting before the study. Of the patients with PROC screened with evaluable tissue samples, 36% had ≥ 75% of viable tumor cells exhibiting at

**TABLE 1.** Baseline Demographics and Clinical Characteristics

| Characteristic | N = 106 |
|---|---|
| Age, years | |
| Median | 62.0 |
| Range | 35-85 |
| Race, No. (%) | |
| White | 102 (96) |
| Asian | 2 (2) |
| Not reported | 2 (2) |
| Ethnicity, No. (%) | |
| Hispanic or Latino | 2 (2) |
| Not Hispanic or Latino | 99 (93) |
| Not reported | 4 (4) |
| Unknown | 1 (1) |
| Primary diagnosis, No. (%) | |
| Epithelial ovarian | 85 (80) |
| Fallopian tube[a] | 8 (8) |
| Primary peritoneal[a] | 12 (11) |
| Other[b] | 1 (1) |
| Histology, No. (%) | |
| High-grade serous | 106 (100) |
| Stage at initial diagnosis, No. (%) | |
| I | 2 (2) |
| II | 0 (0) |
| III | 63 (59) |
| IV | 40 (38) |
| Missing | 1 (1) |
| ECOG performance status, No. (%) | |
| 0 | 60 (57) |
| 1 | 46 (43) |
| *BRCA* mutations, No. (%)[c] | |
| Yes | 21 (20) |
| *BRCA1* | 15 (14) |
| *BRCA2* | 6 (6) |
| No/unknown | 85 (80) |
| Prior systemic therapy, No. (%)[d] | |
| 1 | 10 (9) |
| 2 | 41 (39) |
| 3 | 54 (51) |
| Prior exposure, No. (%) | |
| Platinum-containing regimen | 106 (100) |
| Bevacizumab | 106 (100) |
| Taxanes | 105 (99) |
| Liposomal doxorubicin | 75 (71) |
| PARP inhibitor | 51 (48) |
| Topotecan | 0 (0) |
| Primary platinum-free interval, No. (%)[e] | |
| 0-12 months | 63 (59) |
| > 12 months | 43 (41) |
| Platinum-free interval, No. (%)[f,g] | |
| 0-3 months | 39 (37) |
| 3-6 months | 64 (60) |

(continued in next column)

**TABLE 1.** Baseline Demographics and Clinical Characteristics (continued)

Abbreviations: *BRCA*, breast cancer gene; *BRCA1*, breast cancer susceptibility gene 1; *BRCA2*, breast cancer susceptibility gene 2; ECOG, Eastern Cooperative Oncology Group; PARP, poly ADP-ribose polymerase.

[a]The term epithelial ovarian cancer often includes fallopian tube carcinoma and primary peritoneal carcinoma, as they have the same prognosis and treatment.

[b]One patient with primary diagnosis categorized as other had histopathology consistent with the inclusion/exclusion criteria, intraepithelial tubo-ovarian carcinoma.

[c]The *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.

[d]One patient had received four prior lines of therapy.

[e]Time from last dose of the first-line platinum therapy to the date of disease progression and/or relapse following the first-line therapy.

[f]Time from last dose of the latest-line platinum therapy to the date of disease progression and/or relapse following that line of therapy.

[g]Three patients were enrolled with a platinum-free interval of > 6 months, of which two patients had a platinum-free interval of 6.01 months and one patient had a platinum-free interval of 18.07 months.

least 2+ level membrane staining intensity and were considered FRα-high. In addition to FRα expression, reasons for screen failure include tissue not available (n = 16), more than three lines of therapy (n = 16), and active ocular disorder (n = 15). The final safety and efficacy populations were 106 and 105 patients, respectively. Patient disposition is shown in Appendix Figure A1 (online only).

Baseline characteristics are summarized in Table 1. The median age of the study population was 62 years. All patients had high-grade serous histology, and 59% had stage III and 38% had stage IV disease at diagnosis. The platinum-free intervals were 0-3 months in 37% (after second- or third-line platinum-based chemotherapy) and 3-6 months in 60% of patients. All patients received prior bevacizumab, 51% had received three prior lines of systemic therapy, and 48% of patients had received a prior PARPi. At the time of data cutoff, the median follow-up time was 13.4 months, including five responders continuing to receive MIRV.

## Efficacy

The study met its primary end point, as evidenced by an investigator-assessed confirmed ORR of 32.4% (95% CI,

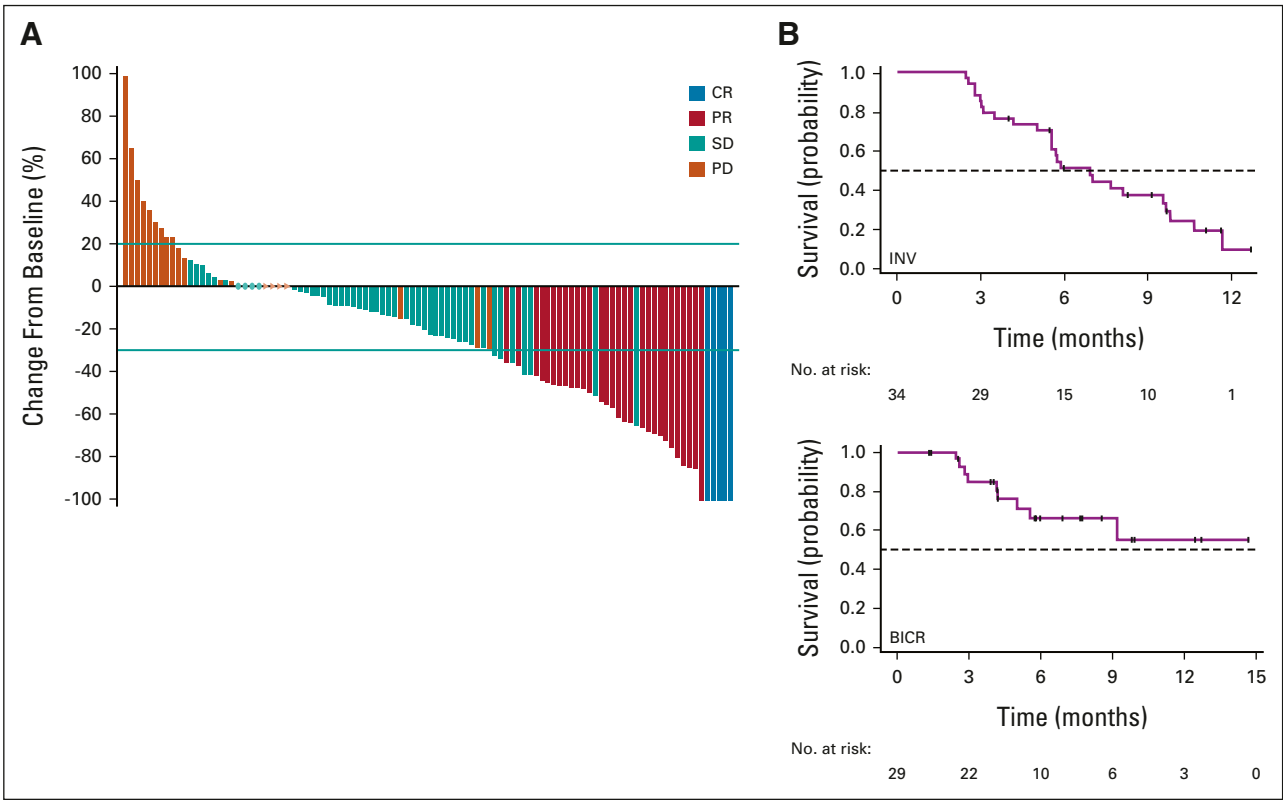


**FIG 1.** Antitumor activity of mirvetuximab soravtansine. (A) Maximum percentage change in target lesion size from baseline. Best response according to RECIST is indicated by color coding of bars. (B) Kaplan-Meier plot of DOR in patients with confirmed complete or partial response as assessed by INV (upper panel) and BICR (lower panel). Median DOR by INV was 6.9 months and NR by BICR. BICR, blinded independent central review; CR, complete response; DOR, duration of response; INV, investigator; NR, not reached; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

23.6 to 42.2; $P < .0001$), including five patients with a complete response (CR) and 29 achieving a PR. Tumor reductions occurred in 71.4% of patients (Fig 1A), which includes all patients who experienced at least transient tumor reduction on the basis of the sum of the longest diameters of target lesions per RECIST, regardless of whether or not they met RECIST criteria for a PR or CR. The disease control rate (CR, PR, or stable disease ≥ 12 weeks) was 51.4% (Table 2). In the BICR efficacy evaluable population (n = 96 patients), the ORR was 30.2% (95% CI, 21.3 to 40.4), with 6 and 23 patients having confirmed CR and PRs, respectively.

Kaplan-Meier estimates of DOR for patients with confirmed responses are shown in Figure 1B. The median DOR was 6.9 months (95% CI, 5.6 to 9.7) as assessed by investigator and not reached (NR) by BICR assessment (95% CI, 5.0 to NR; Table 3). The median time to response was 1.5 months (range, 1.0 to 5.6 months), coinciding with the first post-baseline scan, as assessed by investigator, and 1.4 months (range, 1.0 to 5.4 months) by BICR.

Of note, subgroup analyses revealed that MIRV was effective regardless of the number of prior lines of therapy or prior PARPi. The investigator-assessed ORRs were 35.3% (95% CI, 22.4 to 49.9) for patients with one to two prior lines of therapy and 30.2% (95% CI, 18.3 to 44.3) for those with three prior lines (Table 2). The corresponding median DORs (by investigator assessment) were 5.9 months (95% CI, 4.2 to 9.6) and 7.4 months (95% CI, 3.5 to 10.7) for the one to two or three prior line subsets, respectively (Table 3). With respect to prior PARPi exposure, the ORR was 38.0% (95% CI, 24.7 to 52.8) in patients who had received prior PARPi treatment and 27.5% (95% CI, 15.9 to 41.7) in those without prior PARPi use (Table 2). For those patients with PARPi therapy, the median DOR by investigator was 5.7 months (95% CI, 3.5 to 9.6) and was 6.4 months (95% CI, 3.0 to NR) for patients without prior PARPi use (Table 3).

The median PFS assessed by investigator was 4.3 months (95% CI, 3.7 to 5.2); median PFS in the BICR efficacy evaluable population was 5.5 months (95% CI, 3.8 to 6.9). Median overall survival was 13.8 months (95% CI, 12.0 to NR) with 46% of events reported.

## Safety

The safety population included 106 patients who received at least one dose of MIRV. Overall, no new safety signals were observed. Treatment-related adverse events (TRAEs) were experienced by 86% of patients, with 28% of patients experiencing at least 1 grade 3 event and 1% experiencing

**TABLE 2.** ORR and Subgroup Analysis in the Efficacy Evaluable Population

| ORR | Investigator-Assessed | BICR-Assessed |
|---|---|---|
| Efficacy evaluable patients, No. | n = 105 | n = 96 |
| ORR, No. (%) [95% CI][a] | 34 (32.4) [23.6 to 42.2] | 29 (30.2) [21.3 to 40.4] |
| Best overall response, No. (%) | | |
| CR | 5 (4.8) | 6 (6.3) |
| PR | 29 (27.6) | 23 (24.0) |
| SD | 48 (45.7) | 54 (56.3) |
| PD | 20 (19.0) | 9 (9.4) |
| NE | 3 (2.9) | 4 (4.2) |
| Tumor reduction, No. (%) | 75 (71.4) | ND |
| Disease control rate, No. (%) | 54 (51.4) | ND |
| CA-125 response[b] | n = 86 | |
| No. (%) [95% CI] | 40 (46.5) [35.7 to 57.6] | ND |
| ORR subgroup analysis | | |
| Prior lines of therapy, No. (%) [95% CI][a] | | |
| 1 or 2 | n = 51 | n = 46 |
| | 18 (35.3) [22.4 to 49.9] | 15 (32.6) [19.5 to 48.0] |
| 3 | n = 53 | n = 49 |
| | 16 (30.2) [18.3 to 44.3] | 14 (28.6) [16.6 to 43.3] |
| Prior exposure to PARPi, No. (%) [95% CI][a,c] | | |
| Yes | n = 50 | n = 47 |
| | 19 (38.0) [24.7 to 52.8] | 14 (29.8) [17.3 to 44.9] |
| No | n = 51 | n = 46 |
| | 14 (27.5) [15.9 to 41.7] | 15 (32.6) [19.5 to 48.0] |

NOTE. The denominator for the percentage is the number of patients in the investigator-assessed or BICR-assessed efficacy evaluable population. Patients without at least one postbaseline RECIST assessment were treated as not evaluable. Disease control rate is the proportion of patients who achieved a CR, PR, or SD for ≥ 12 weeks.

Abbreviations: BICR, blinded independent central review; CR, complete response; GCIG, Gynecological Cancer InterGroup; ND, not done; NE, not evaluable; ORR, objective response rate; PARPi, poly ADP-ribose polymerase inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

[a]95% exact CI is estimated by Clopper-Pearson method.

[b]In CA-125 response-evaluable patients per GCIG criteria.[36]

[c]Prior PARPi exposure was uncertain for four patients in the investigator-assessed population and three patients in the BICR-assessed population.

grade 4 (Table 4). The most common TRAEs included blurred vision (41% all grades; 6% grade 3, no grade 4), keratopathy (29% all grades; 8% grade 3, 1% grade 4), and nausea (29% all grades; no grade ≥ 3; Table 5). Regarding ocular adverse events, 55/106 patients (52%) experienced any-grade blurred vision or keratopathy (grouped term); median time to onset was 1.3 months (range, 0.0 to 9.9 months), and 1.5 months (range, 1.1 to 8.6 months), respectively. Twelve of these patients (11%) had an ocular event that resulted in a dose reduction. Only one patient required treatment discontinuation because of an ocular treatment-emergent adverse event (< 1%). At the time of data cutoff, 96% of grade 2 or greater ocular events (both blurred vision and keratopathy) had resolved to grade 1 or 0. The patients with unresolved ocular events were still on treatment either with keratopathy (n = 1) or blurred vision because of a cataract (n = 1). No corneal ulcers or corneal perforations were identified, and no patients had permanent ocular sequelae at data cutoff. The grading system for the observed ocular adverse events is shown in Appendix Table A1 (online only).

The most common hematologic TRAEs included neutropenia (13% all grades; 2% grade 3, no grade 4), thrombocytopenia (9% all grades; 2% grade 3, no grade 4), and anemia (8% all grades; 1% grade 3 and no grade 4). Peripheral neuropathy was observed in 19 (18%) patients, all were grades 1 (13%) or 2 (5%); no grade ≥ 3 events were reported. Ten (9%) patients reported grade 1 peripheral neuropathy at study entry.

Serious grade ≥ 3 TRAEs were reported in 9% of patients (Table 4), and no singular type was experienced by more than one patient. TRAEs led to dose delay in 33% of patients

**TABLE 3.** DOR and Subgroup Analysis in the Efficacy Evaluable Population

| DOR | Investigator-Assessed | BICR-Assessed |
|---|---|---|
| Kaplan-Meier estimates for DOR | n = 34 | n = 29 |
| Months, median [95% CI] | 6.9 [5.6 to 9.7] | NR [5.0 to NR] |
| Radiologic progression, No. (%) | 24 (70.6) | 9 (31.0) |
| Death without documented progression, No. (%) | 1 (2.9) | 0 (0) |
| DOR subgroup analysis | | |
| Prior lines of therapy, months, median [95% CI] | | |
| 1 or 2 | n = 18 | n = 5 |
| | 5.9 [4.2 to 9.6] | NR [3.0 to NR] |
| 3 | n = 16 | n = 14 |
| | 7.4 [3.5 to 10.7] | NR [5.0 to NR] |
| Prior exposure to PARPi, months, median [95% CI][a] | | |
| Yes | n = 19 | n = 14 |
| | 5.7 [3.5 to 9.6] | NR [5.0 to NR] |
| No | n = 14 | n = 15 |
| | 6.4 [3.0 to NR] | NR [4.2 to NR] |

Abbreviations: BICR, blinded independent central review; DOR, duration of response; NR, not reached; PARPi, poly ADP-ribose polymerase inhibitor.

[a]Prior PARPi exposure was uncertain for one patient in the investigator-assessed population.

and dose reduction in 20% of patients. Overall, 9% of patients discontinued treatment because of TRAEs (Table 4), including one because of grade 4 keratopathy (one eye with grade 4 best-corrected visual acuity change and grade 2 corneal findings that resolved to grade 0 in 15 days, including complete resolution to baseline best-corrected visual acuity) and others because of thrombocytopenia (grade 1 and grade 3), fatigue, infusion-related reaction, sensory neuropathy (all grade 3), and respiratory failure (grade 5). The respiratory failure death occurred in an 86-year-old patient and was originally considered possibly related to study drug. However, an autopsy confirmed advanced metastatic ovarian cancer, which included metastatic involvement of the lung that was complicated by diffuse alveolar damage in the background of idiopathic pulmonary fibrosis with recent bronchopneumonia; there was no evidence of drug reaction in this patient. Six other patients died while on study, four because of disease progression and two because of unrelated adverse events.

## DISCUSSION

SORAYA is a phase II study that evaluated the efficacy and safety of MIRV as a single-agent therapy in patients with FRα-high PROC who had received one to three prior therapies, including prior bevacizumab. Consistent with prior clinical experience, 36% of patients screened were found to have high tumor FRα expression, representing a significant proportion of patients with ovarian cancer who could potentially benefit from MIRV-based therapy. In addition, the expansion phase of the phase I evaluation of MIRV revealed that patients who had received three or fewer lines of prior treatments had better efficacy outcomes than those who developed resistant disease beyond the third line.[32] The confirmed ORR in the SORAYA study population as assessed by the investigator was 32.4%, with five complete responders, and a median DOR of 6.9 months; assessment is ongoing. Benefit from MIRV was observed in all prespecified subgroups, including patients who had received one to two or three prior lines of treatment and regardless of whether patients had received a prior PARPi.

**TABLE 4.** Treatment-Related Adverse Events in the Safety Population

| Event | Patients (N = 106), No. (%) |
|---|---|
| Any TRAE | 91 (86) |
| Grade ≥ 3 TRAE | 32 (30) |
| Any serious TRAE | 12 (11) |
| Grade ≥ 3 serious TRAE | 9 (9) |
| TRAE leading to dose reduction | 21 (20) |
| TRAE leading to dose delay | 35 (33) |
| TRAE leading to discontinuation of study drug | 10 (9) |
| TRAE leading to death | 1 (1) |

NOTE. Adverse events are evaluated on the basis of NCI-CTCAE (version 5.0). Related events include those with a drug relationship of possibly related, probably related, or definitely related. Patients with multiple events are counted once only at the worst severity.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event.

**TABLE 5.** Most Common (≥ 10%) TRAEs in the Safety Population

| TRAEs | All Grades, No. (%) | Grades 3-4, No. (%) |
|---|---|---|
| Patients with any event | 91 (86) | 31 (29) |
| Blurred vision | 43 (41) | 6 (6) |
| Keratopathy[a] | 31 (29) | 9 (9) |
| Nausea | 31 (29) | 0 (0) |
| Dry eye | 26 (25) | 2 (2) |
| Fatigue | 25 (24) | 1 (1) |
| Diarrhea | 23 (22) | 2 (2) |
| Asthenia | 16 (15) | 1 (1) |
| Photophobia | 14 (13) | 0 (0) |
| Peripheral neuropathy | 14 (13) | 0 (0) |
| Decreased appetite | 14 (13) | 1 (1) |
| Neutropenia | 14 (13) | 2 (2) |
| Vomiting | 12 (11) | 0 (0) |

NOTE. Safety population, N = 106. Adverse events are evaluated on the basis of NCI-CTCAE (version 5.0). Adverse events were linked to system organ class and preferred term (group and list terms included) using 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.

Abbreviations: NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a]The grouped preferred term keratopathy includes all TEAEs 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.

No biomarker-directed therapy is indicated specifically for patients with platinum-resistant disease. Clinical studies of immune checkpoint inhibitors have failed to make a substantial impact in high-grade serous ovarian cancer, with several negative phase III studies.[15,17,37] There remains an unmet need for patients with PROC. Current available therapies for patients with PROC include non–platinum-based chemotherapies, either administered alone or in combination with bevacizumab. Although many patients diagnosed with ovarian cancer may receive bevacizumab in earlier lines of therapy, most who relapse with PROC ultimately receive sequential single-agent chemotherapy, an approach that is associated with low response rates (4%-13%), brief durations of response, and significant toxicities.[12,14-17] Moreover, in the platinum-resistant disease setting, there is a consistent decline in efficacy seen with each subsequent line of therapy that is independent of platinum-free interval, and fewer patients are healthy enough to tolerate additional therapy. Specifically, both PFS and ORR have been shown to decrease with further therapy, with ORRs dropping from 16% for therapy given as first-line after platinum resistance to 3% in the third-line.[11,38,39] As such, treatment guidelines published by the National Comprehensive Cancer Network[2] recommend that patients with PROC participate in clinical studies in lieu of current therapeutic options.

These outcomes with available single-agent chemotherapies provide important context for the interpretation of the SORAYA results. At 32.4%, the confirmed ORR (five CRs and 29 PRs) in SORAYA was more than double the ORR of single-agent chemotherapies reported in prior trials of PROC. The responses were also durable with a median duration of response of 6.9 months [95% CI, 5.6 to 9.7]. This compelling anticancer activity was seen in a more heavily pretreated population in which all patients had received bevacizumab, 51% had received three lines of therapy, and 48% had received PARPi. The ORR and DOR were consistent regardless of the number of prior lines of therapy or prior PARPi.

The tolerability profile of MIRV consisted primarily of low-grade and reversible ocular and gastrointestinal adverse events. Overall, grade 3 or above TRAEs occurred in 30% of patients on MIRV, consistent with observed rates in prior MIRV trials,[16,28,32,40] and lower than that observed for chemotherapy in previous studies (44%-65%).[14-17] The ocular events observed in approximately 50% of patients were expected on the basis of prior clinical experience,[16,28,32,40] were primarily low-grade, generally resolved with supportive care or dose modifications (23%), and resulted in very few discontinuations (< 1%). MIRV administration did not result in any corneal ulcers or perforations, and no permanent sequelae were reported. Other common TRAEs, such as nausea and diarrhea, were effectively managed with antiemetics and antidiarrheals. Of note, the incidence of peripheral neuropathy, a common toxicity with tubulin-directed agents, was mostly grade 1. In addition, cytopenias associated with MIRV were infrequent and low-grade. Overall, treatment-related dose delays, reductions, and discontinuations observed in this study were comparable with those reported for MIRV monotherapy in the phase III FORWARD I trial.[16] Taken together, the safety findings are consistent with the differentiated profile observed for MIRV compared with chemotherapy seen in FORWARD I, which was also characterized by fewer treatment-related grade ≥ 3 adverse events, fewer discontinuations, less myelosuppression and neuropathy, and no new alopecia when compared with the chemotherapy control arm.[16] On the basis of this differentiated safety profile, MIRV is additionally being explored in other ongoing trials in platinum-sensitive ovarian cancer, both as monotherapy (PICCOLO; NCT05041257) and in combination with carboplatin (NCT05456685) and bevacizumab (GLORIOSA; NCT05445778). The ongoing phase III randomized trial (MIRASOL; NCT04209855) is

evaluating MIRV versus investigator's choice chemotherapy in high-FRα–expressing PROC.

In conclusion, the SORAYA trial demonstrated that MIRV monotherapy elicited high ORRs, durable responses, and a tolerable safety profile in patients with high-FRα PROC. Activity was observed irrespective of number of previous lines of therapy received or PARPi exposure in patients having received prior bevacizumab. Given the lack of effective therapies and poor prognosis for patients in this setting, the findings reported here underscore the potential for MIRV to become a biomarker-driven, standard-of-care option in this difficult-to-treat population.


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## SUPPORT

This study was designed and funded by ImmunoGen, Inc. The sponsor collected, analyzed, and interpreted the trial data in collaboration with the authors.

## CLINICAL TRIAL INFORMATION

NCT04296890 (SORAYA)


## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.01900.

## DATA SHARING STATEMENT

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. The research protocol and Statistical Analysis Plan will be provided following the execution and approval of a Data Sharing Agreement. Data requests can be submitted at any time via medicalaffairs@immunogen.com.

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## ACKNOWLEDGMENT

The authors thank the patients and their families, investigators, coinvestigators, and study teams at each of the participating centers, and Cadent Medical Communications, a Syneos Health company, for medical writing assistance, which was funded by ImmunoGen, Inc.


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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study**

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No other potential conflicts of interest were reported.

## APPENDIX

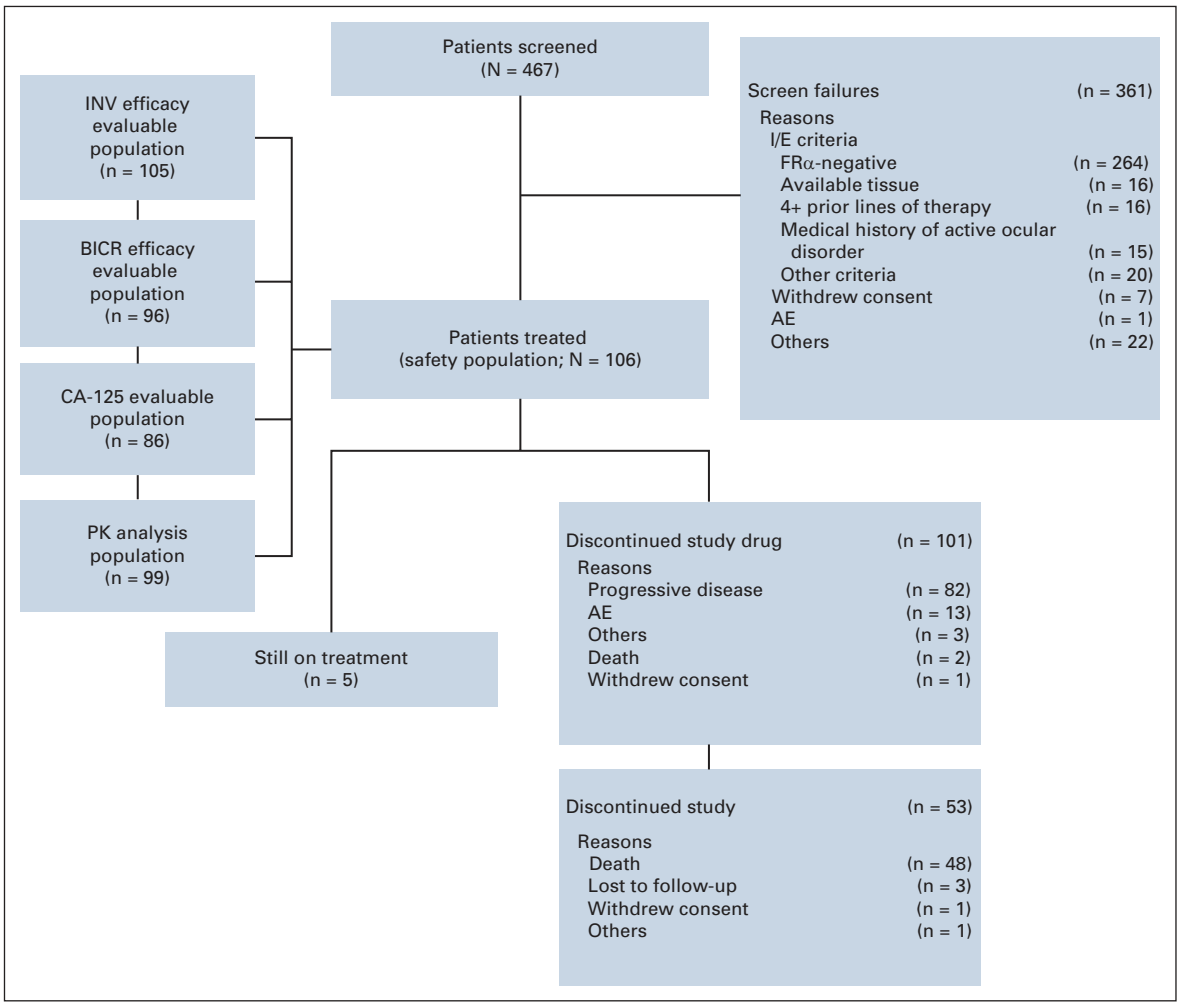


**FIG A1.** Patient disposition. AE, adverse event; BICR, blinded independent central review; CA-125, cancer antigen 125; FRα, folate receptor α; I/E, inclusion/exclusion; INV, investigator; PK, pharmacokinetic.

**TABLE A1.** Common Terminology Criteria for Ocular Adverse Events Observed in the SORAYA Study

| CTCAE Term | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Blurred vision[a] | Intervention not indicated | Symptomatic; moderate decrease in visual acuity (best-corrected visual acuity 20/40 and better, or three lines or less of decreased vision from known baseline); limiting instrumental ADL | Symptomatic, with marked decrease in visual acuity (best-corrected visual acuity worse than 20/40, or more than three lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL | Best-corrected visual acuity of 20/200 or worse in the affected eye |
| Keratitis[b] | Asymptomatic; clinical or diagnostic observations only; intervention not indicated | Symptomatic; moderate decrease in visual acuity (best-corrected visual acuity 20/40 and better, or three lines or less of decreased vision from known baseline) | Symptomatic, with marked decrease in visual acuity (best-corrected visual acuity worse than 20/40 or more than three lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self-care ADL | Perforation; best-corrected visual acuity of 20/200 or worse in the affected eye |
| Dry eye[c] | Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants | Symptomatic; moderate decrease in visual acuity (best-corrected visual acuity 20/40 and better, or three lines or less of decreased vision from known baseline) | Symptomatic, with marked decrease in visual acuity (best-corrected visual acuity worse than 20/40 or more than three lines of decreased vision from known baseline, up to 20/200); limiting self-care ADL | — |
| Photophobia[d] | Symptomatic but not limiting ADL | Limiting instrumental ADL | Limiting self-care ADL | — |

NOTE. NCI-CTCAE version 5.0, published November 27, 2017.

Abbreviations: ADL, activities of daily living; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

[a]Disorder characterized by visual perception of unclear or fuzzy images.

[b]Disorder characterized by inflammation to the cornea of the eye.

[c]Disorder characterized by dryness of the cornea and conjunctiva.

[d]Disorder characterized by fear and avoidance of light.