ORIGINAL ARTICLE

Mirvetuximab Soravtansine in FRα-Positive, Platinum-Resistant Ovarian Cancer

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ABSTRACT

BACKGROUND

Mirvetuximab soravtansine-gynx (MIRV), a first-in-class antibody–drug conjugate targeting folate receptor α (FRα), is approved for the treatment of platinum-resistant ovarian cancer in the United States.

METHODS

We conducted a phase 3, global, confirmatory, open-label, randomized, controlled trial to compare the efficacy and safety of MIRV with the investigator's choice of chemotherapy in the treatment of platinum-resistant, high-grade serous ovarian cancer. Participants who had previously received one to three lines of therapy and had high FRα tumor expression (≥75% of cells with ≥2+ staining intensity) were randomly assigned in a 1:1 ratio to receive MIRV (6 mg per kilogram of adjusted ideal body weight every 3 weeks) or chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan). The primary end point was investigator-assessed progression-free survival; key secondary analytic end points included objective response, overall survival, and participant-reported outcomes.

RESULTS

A total of 453 participants underwent randomization; 227 were assigned to the MIRV group and 226 to the chemotherapy group. The median progression-free survival was 5.62 months (95% confidence interval [CI], 4.34 to 5.95) with MIRV and 3.98 months (95% CI, 2.86 to 4.47) with chemotherapy (P<0.001). An objective response occurred in 42.3% of the participants in the MIRV group and in 15.9% of those in the chemotherapy group (odds ratio, 3.81; 95% CI, 2.44 to 5.94; P<0.001). Overall survival was significantly longer with MIRV than with chemotherapy (median, 16.46 months vs. 12.75 months; hazard ratio for death, 0.67; 95% CI, 0.50 to 0.89; P=0.005). During the treatment period, fewer adverse events of grade 3 or higher occurred with MIRV than with chemotherapy (41.7% vs. 54.1%), as did serious adverse events of any grade (23.9% vs. 32.9%) and events leading to discontinuation (9.2% vs. 15.9%).

CONCLUSIONS

Among participants with platinum-resistant, FRα-positive ovarian cancer, treatment with MIRV showed a significant benefit over chemotherapy with respect to progression-free and overall survival and objective response. (Funded by ImmunoGen; MIRASOL ClinicalTrials.gov number, NCT04209855.)

Epithelial ovarian cancer, which includes fallopian tube and primary peritoneal cancer, is the deadliest gynecologic malignant neoplasm; an estimated 313,959 new cases of ovarian cancer and 207,252 ovarian cancer–related deaths occurred worldwide in 2020.[1-3] Despite the adoption of maintenance therapy for some patients with primary or recurrent ovarian cancer, the 5-year relative survival is approximately 50%, having increased only slightly in the past decade.[4]

Initial chemotherapy treatment for ovarian cancer typically yields high response; however, most tumors subsequently relapse and eventually become resistant to platinum-based regimens.[5-7] Current therapies in platinum-resistant ovarian cancer consist primarily of nonplatinum chemotherapy (e.g., weekly paclitaxel, pegylated liposomal doxorubicin, or topotecan), administered either as a single agent or in combination with bevacizumab.[8] In recent phase 3 trials, patients with platinum-resistant ovarian cancer receiving nonplatinum chemotherapy alone have had poor responses (with an objective response ranging from 4 to 13%).[9-11] In the Avastin Use in Platinum-Resistant Epithelial Ovarian Cancer (AURELIA) trial, the addition of bevacizumab to nonplatinum chemotherapy, as compared with chemotherapy alone, led to significant improvements in progression-free survival (median of 6.7 months vs. 3.4 months, P<0.001) and objective response (27.3% vs. 11.8%, P=0.001), but no benefit with respect to overall survival was observed (median of 16.6 months and 13.3 months, respectively; P<0.17).[12] In the AURELIA trial, at the time of disease progression, 40% of the participants in the chemotherapy group received bevacizumab, which may have contributed to the lack of a significant between-group difference in overall survival.[12] Additional challenges in the treatment of platinum-resistant ovarian cancer include the lack of meaningful, predictive biomarkers, as well as chemotherapy-associated hematologic and gastrointestinal toxic effects and cumulative neuropathy, which can impede the continuation of treatment.[12] Thus, platinum-resistant ovarian cancer has a poor prognosis with few effective therapeutic options, none of which have shown a substantial overall survival benefit.[13]

Mirvetuximab soravtansine-gynx (MIRV) is a first-in-class antibody–drug conjugate targeting folate receptor α (FRα), a biomarker that is commonly overexpressed on ovarian carcinomas and minimally expressed on normal tissues.[14-18] MIRV comprises an FRα-binding antibody, a cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent.[14,18] Clinical trials of single-agent MIRV have shown anticancer activity and a safety profile that primarily included low-grade gastrointestinal, neurosensory, and reversible ocular adverse events.[18-20] In the single-group SORAYA trial of MIRV in FRα-positive, bevacizumab-pretreated, platinum-resistant, high-grade serous ovarian cancer, the investigator-assessed objective response was 32.4% (95% confidence interval [CI], 23.6 to 42.2), with 5 complete and 29 partial responses, and the median duration of response was 6.9 months (95% CI, 5.6 to 9.7).[19] The median overall survival in the SORAYA trial was 15.0 months (95% CI, 11.5 to 18.7); an estimated 37% of patients were alive at year 2.[21] On November 14, 2022, on the basis of the positive results of the pivotal SORAYA trial, the Food and Drug Administration (FDA) granted accelerated approval to MIRV for adults with FRα-positive, platinum-resistant ovarian cancer (as assessed by an FDA-approved test) who had previously received one to three systemic treatments.[19,22,23]

In a previous phase 3, open-label, randomized, controlled trial (FORWARD I) that compared MIRV with chemotherapy in patients with platinum-resistant ovarian cancer with FRα expression, as determined according to the 10× scoring method (i.e., ≥50% of tumor cells with observable staining at 10× magnification), who had previously received one to three lines of therapy, MIRV did not result in a significant improvement in progression-free survival (the primary end point).[20] However, results for the secondary end points consistently favored MIRV, particularly in a prespecified population with high FRα tumor expression.[20] Furthermore, exploratory rescoring of FRα expression levels with an alternative scoring method referred to as PS2+ showed that the 10× scoring method used for screening diluted the treatment effect of MIRV by allowing enrollment of participants with lower-than-expected levels of FRα expression.[20,24] These findings supported the use of the PS2+ scoring method for determining FRα expression levels in subsequent clinical trials, thereby informing the trial designs for the reevaluation of MIRV in both the current trial and the SORAYA trial. Here, we report the results of a trial that investigated the efficacy and safety of

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Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Intention-to-Treat Population).*

Characteristic	MIRV (N = 227)	Chemotherapy (N = 226)
Age		
Median (range) — yr	64 (32–88)	62 (29–87)
≥65 yr — no. (%)	107 (47.1)	92 (40.7)
Race — no. (%)†		
White	156 (68.7)	145 (64.2)
Black	8 (3.5)	5 (2.2)
Asian	28 (12.3)	25 (11.1)
Not reported	32 (14.1)	49 (21.7)
Other	3 (1.3)	2 (0.9)
Ethnic group — no. (%)†		
Hispanic or Latino	12 (5.3)	15 (6.6)
Not Hispanic or Latino	177 (78.0)	163 (72.1)
Unknown	2 (0.9)	2 (0.9)
Not reported	35 (15.4)	45 (19.9)
Missing data	1 (0.4)	1 (0.4)
Primary cancer diagnosis — no. (%)		
Epithelial ovarian cancer	182 (80.2)	182 (80.5)
Fallopian tube cancer	27 (11.9)	23 (10.2)
Primary peritoneal cancer	16 (7.0)	20 (8.8)
Other	2 (0.9)	1 (0.4)
Stage at initial diagnosis — no. (%)‡		
IA or IIA	7 (3.1)	1 (0.4)
IIB or IIC	2 (0.9)	8 (3.5)
IIIA	14 (6.2)	16 (7.1)
IIIB	16 (7.0)	11 (4.9)
IIIC	107 (47.1)	120 (53.1)
IV	76 (33.5)	65 (28.8)
Missing data	5 (2.2)	5 (2.2)
ECOG performance-status score — no. (%)§		
0	130 (57.3)	120 (53.1)
1	97 (42.7)	101 (44.7)
2	0	3 (1.3)
Missing data	0	2 (0.9)
BRCA mutation — no. (%)		
BRCA1 positive	24 (10.6)	29 (12.8)
BRCA2 positive	9 (4.0)	7 (3.1)
Negative or unknown	198 (87.2)	190 (84.1)
Previous lines of systemic therapy		
1	29 (12.8)	34 (15.0)
2	90 (39.6)	88 (38.9)
3	108 (47.6)	104 (46.0)

Table 1. (Continued.)

Characteristic	MIRV (N=227)	Chemotherapy (N=226)
Previous exposure — no. (%)		
Bevacizumab	138 (60.8)	143 (63.3)
PARP inhibitor	124 (54.6)	127 (56.2)
Taxane	227 (100)	224 (99.1)
Doxorubicin or pegylated liposomal doxorubicin	130 (57.3)	133 (58.8)
Topotecan	1 (0.4)	2 (0.9)
Primary platinum-free interval — no. (%)¶		
≤12 mo	146 (64.3)	142 (62.8)
>12 mo	80 (35.2)	84 (37.2)
Missing data	1 (0.4)	0
Platinum-free interval — no. (%)‖		
≤3 mo	88 (38.8)	99 (43.8)
>3 to ≤6 mo	138 (60.8)	124 (54.9)
>6 mo	1 (0.4)	3 (1.3)

* Percentages may not total 100 because of rounding. MIRV denotes mirvetuximab soravtansine-gynx, and PARP poly(adenosine diphosphate–ribose) polymerase.
† Race and ethnic group were reported by the participants.
‡ Stage at diagnosis was assessed according to the ovarian cancer staging system used by the local institution.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale of 0 to 5, with higher scores indicating greater disability.
¶ Primary platinum-free interval was defined as the time from last dose of first-line platinum therapy to the date of disease progression or relapse after first-line therapy.
‖ Platinum-free interval was defined as the time from last dose of the latest line of platinum therapy to the date of disease progression or relapse after that line of therapy.

single-agent MIRV as compared with the investigator's choice of chemotherapy in participants with FRα-positive, platinum-resistant, high-grade serous ovarian cancer.

METHODS

TRIAL DESIGN AND RANDOMIZATION

The MIRASOL trial was a confirmatory, phase 3, randomized, controlled trial in which participants were enrolled at 253 sites in 21 countries. An open-label design was used because each trial drug has a unique dose and examination schedule and safety profile. The participants were assigned in a 1:1 ratio to receive single-agent MIRV or the investigator's choice of chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan; hereafter referred to as chemotherapy). Randomization was stratified according to the number of previous lines of therapy (one, two, or three) and chemotherapy agent (paclitaxel, pegylated liposomal doxorubicin, or topotecan). Participants continued to receive the trial drug until the occurrence of disease progression, an unacceptable toxic effect, withdrawal of consent, or death. A list of the investigators and additional details regarding the trial design and analysis are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial was funded by ImmunoGen.

The trial was conducted according to the principles of the Declaration of Helsinki, the 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, available at NEJM.org. All the participants (or their legally authorized representatives) provided written informed consent. The investigators designed the trial and interpreted the data. A sub-

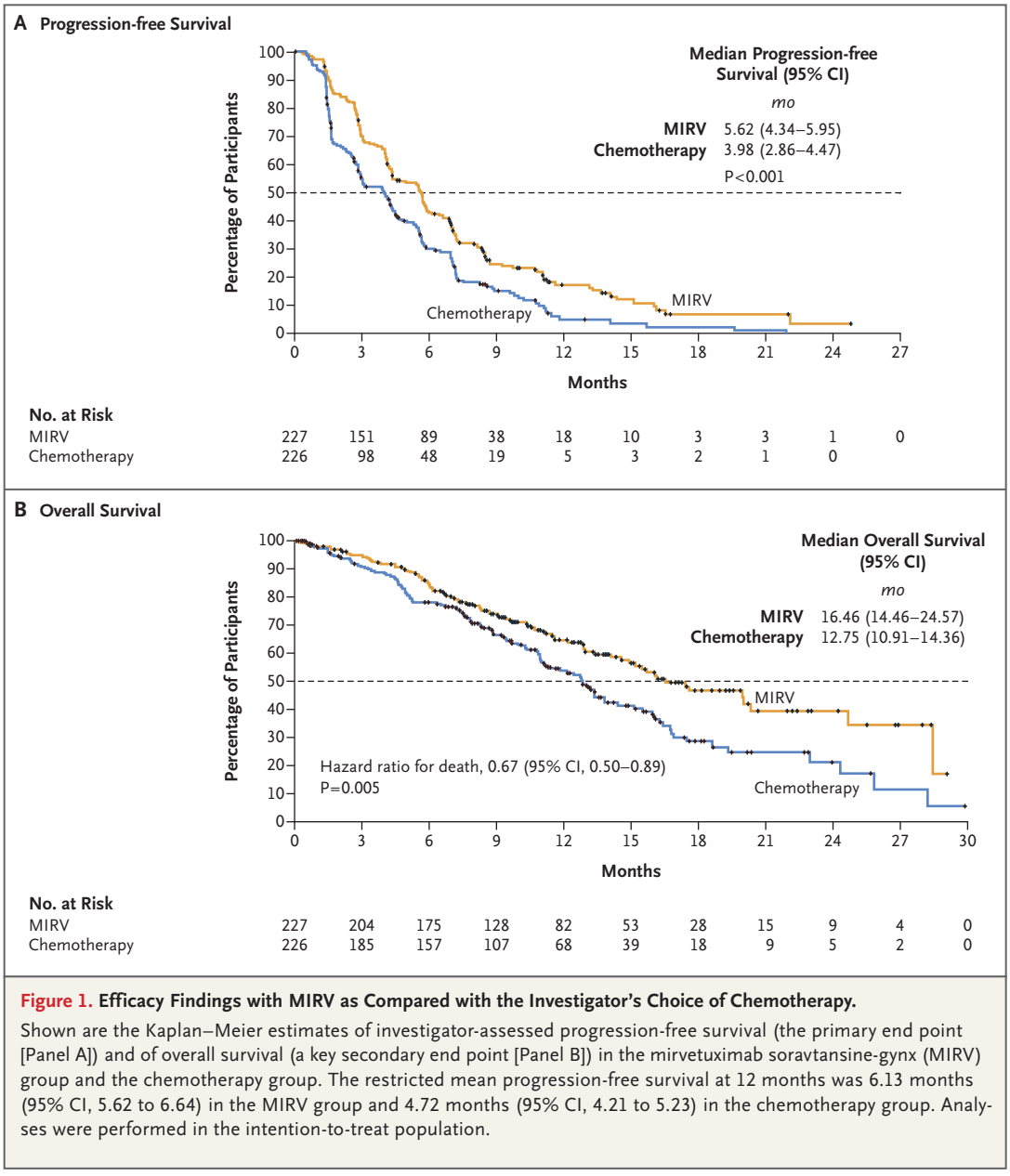

Figure 1. Efficacy Findings with MIRV as Compared with the Investigator's Choice of Chemotherapy.

Shown are the Kaplan–Meier estimates of investigator-assessed progression-free survival (the primary end point [Panel A]) and of overall survival (a key secondary end point [Panel B]) in the mirvetuximab soravtansine-gynx (MIRV) group and the chemotherapy group. The restricted mean progression-free survival at 12 months was 6.13 months (95% CI, 5.62 to 6.64) in the MIRV group and 4.72 months (95% CI, 4.21 to 5.23) in the chemotherapy group. Analyses were performed in the intention-to-treat population.

group of authors collected and analyzed the data. All the authors contributed to the development of the manuscript, approved the final version for submission, and vouch for the accuracy and completeness of the data and for the fidelity of the trial and protocol. Writing assistance was paid for by ImmunoGen.

PARTICIPANTS

Eligible participants were 18 years of age or older with a confirmed diagnosis of platinum-resistant, high-grade serous ovarian cancer. Participants must have received one to three previous lines of systemic anticancer therapy and had disease progression while receiving or immediately after receiving the previous therapy. Participants who had received one line of platinum-based therapy must have received at least four cycles of their initial platinum-containing regimen, had a response (complete or partial), and then had disease progression between 3 and 6 months after their last dose. Participants who had previ-

Table 2. Investigator-Assessed Objective Response and Other Secondary Efficacy End Points (Intention-to-Treat Population).

End Point	MIRV (N=227)	Chemotherapy (N=226)	Treatment Difference	Odds Ratio or Hazard Ratio*
			percentage points	
Key secondary end point				
Investigator-assessed objective response†				
Participants with response — no.	96	36		
% (95% CI)	42.3 (35.8–49.0)	15.9 (11.4–21.4)	26.4 (18.4–34.4)	3.81 (2.44–5.94)‡
Best overall response — no. (%)				
Complete response	12 (5.3)	0		
Partial response	84 (37.0)	36 (15.9)		
Stable disease§	86 (37.9)	91 (40.3)		
Progressive disease	31 (13.7)	62 (27.4)		
Not evaluable	14 (6.2)	37 (16.4)		
Other secondary end points				
Median duration of response (95% CI) — mo¶	6.77 (5.62–8.31)	4.47 (4.17–5.82)		0.62 (0.40–0.97)
CA-125 response‖				
Participants with response — no./total no. of evaluable participants	105/181	47/155		
% (95% CI)	58.0 (50.5–65.3)	30.3 (23.2–38.2)	27.7 (17.5–37.9)	

* An odds ratio is reported for investigator-assessed objective response (i.e., the chance of having a response during the treatment period), and a hazard ratio is reported for duration of response (i.e., the time from the date of first response until the occurrence of progressive disease or death from any cause).
† An objective response was defined as a complete response or a partial response.
‡ P<0.001.
§ Stable disease was defined as a tumor with neither sufficient shrinkage to qualify for partial response nor sufficient growth to qualify for progressive disease.
¶ The median duration of response was determined among the participants who had an investigator-confirmed objective response.
‖ Cancer antigen 125 (CA-125) response (i.e., a reduction in CA-125 levels of ≥50% from baseline, confirmed and maintained for at least 28 days) was determined according to Gynecologic Cancer InterGroup criteria. The participants who could be evaluated for this response included those who had undergone randomization and received at least one dose of MIRV or chemotherapy, whose pretreatment CA-125 was at least 2.0 times the upper limit of the normal range within the 2 weeks before randomization, and who had at least one postbaseline CA-125 evaluation.

ously received two or three lines of platinum-based therapy must have had disease progression while receiving the therapy or within 6 months after the last dose. Progression was calculated from the date of the last administered dose of platinum-based therapy to the date of radiographic imaging that showed evidence of progression.

All the participants were required to have "high" FRα tumor expression, as determined according to the PS2+ scoring method (i.e., ≥75% of viable tumor cells with moderate [2+] or strong [3+] staining intensity); immunohistochemical analysis of fresh biopsy or archival tissue was performed with the use of the VENTANA FOLR1 (FOLR1-2.1) RxDx assay, now approved by the FDA.[25] Participants must have had at least one lesion that met the definition of measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, and an Eastern Cooperative Oncology Group performance-status score of 0 or 1 (on a 5-point scale in which higher scores reflect greater disability). Patients were excluded if they had preexisting peripheral neuropathy with a grade higher than 1 (according to Common Terminology Criteria for Adverse Events, version 5.0), a chronic corneal disorder, a history of corneal transplantation, or an active ocular condition for which they were receiving ongoing treatment and monitoring. Full eligibility criteria are listed in the protocol.

Subgroup	No. of Participants	No. of Events	Hazard Ratio for Disease Progression or Death (95% CI)	No. of Events	Hazard Ratio for Death (95% CI)
All participants	453	342	NR	204	0.67 (0.50–0.89)
BRCA status					
Positive	65	50	0.33 (0.18–0.61)	36	0.36 (0.17–0.75)
Negative or unknown	388	292	0.72 (0.57–0.91)	168	0.72 (0.53–0.98)
Age					
18–64 yr	254	190	0.69 (0.52–0.92)	114	0.73 (0.50–1.05)
≥65 yr	199	152	0.62 (0.45–0.86)	90	0.57 (0.37–0.87)
18–69 yr	330	252	0.66 (0.51–0.84)	150	0.69 (0.50–0.96)
≥70 yr	123	90	0.65 (0.43–0.98)	54	0.58 (0.34–1.00)
ECOG performance-status score at baseline					
0	250	193	0.62 (0.46–0.82)	96	0.78 (0.52–1.16)
1	198	146	0.73 (0.52–1.01)	104	0.58 (0.39–0.86)
Previous exposure to bevacizumab					
Yes	281	220	0.64 (0.49–0.84)	142	0.74 (0.54–1.04)
No	172	122	0.66 (0.46–0.94)	62	0.51 (0.31–0.86)
Previous exposure to PARP inhibitor					
Yes	251	181	0.58 (0.43–0.78)	109	0.48 (0.33–0.71)
No	191	150	0.74 (0.54–1.03)	87	0.90 (0.59–1.38)
Uncertain	11	11	0.98 (0.27–3.53)	8	0.51 (0.10–2.59)
No. of previous lines of therapy					
1	63	48	0.44 (0.24–0.79)	28	0.51 (0.24–1.10)
2	182	138	0.68 (0.48–0.95)	77	0.76 (0.48–1.19)
3	208	156	0.71 (0.52–0.98)	99	0.65 (0.43–0.96)
1 or 2	245	186	0.61 (0.45–0.81)	105	0.66 (0.45–0.98)
Type of chemotherapy					
Pegylated liposomal doxorubicin	163	118	0.53 (0.37–0.77)	71	0.60 (0.37–0.96)
Paclitaxel	185	142	0.78 (0.56–1.08)	80	0.85 (0.55–1.32)
Topotecan	105	82	0.67 (0.43–1.04)	53	0.50 (0.29–0.87)
Primary platinum-free interval					
≤6 mo	147	118	0.71 (0.49–1.03)	73	1.02 (0.64–1.62)
>6 mo	305	224	0.63 (0.48–0.82)	131	0.50 (0.35–0.72)
Platinum-free interval					
≤3 mo	187	138	0.73 (0.52–1.03)	88	0.52 (0.33–0.80)
>3 mo	266	204	0.61 (0.46–0.81)	116	0.79 (0.55–1.14)
Stage at diagnosis					
I, II, or III	302	222	0.63 (0.48–0.82)	130	0.65 (0.46–0.93)
IV	141	112	0.71 (0.49–1.03)	70	0.70 (0.44–1.13)
Weight at baseline					
<60 kg	132	108	0.65 (0.45–0.95)	63	0.66 (0.40–1.09)
60–80 kg	195	153	0.67 (0.49–0.93)	90	0.65 (0.43–0.98)
>80 kg	84	67	0.58 (0.35–0.95)	38	0.74 (0.39–1.41)

Figure 2 (facing page). Exploratory Subgroup Analyses.
Shown are the results of exploratory subgroup analyses of progression-free survival and overall survival in the intention-to-treat population. The hazard ratio for death that is reported for all the participants was based on a Cox proportional-hazards model, stratified according to the randomization factors that were collected in the interactive response technology system. In each subgroup, the hazard ratio was estimated with the use of an unstratified Cox proportional-hazards model; under the assumption of proportional hazards, a hazard ratio of less than 1 indicates a reduction in the hazard in favor of the MIRV group. Restricted mean progression-free survival at 12 months was 6.13 months (95% CI, 5.62 to 6.64) in the MIRV group and 4.72 months (95% CI, 4.21 to 5.23) in the chemotherapy group. Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a scale of 0 to 5, with higher scores indicating greater disability. NR denotes not reported, and PARP poly(adenosine diphosphate–ribose) polymerase.

Interventions

MIRV was administered intravenously at a dose of 6 mg per kilogram of adjusted ideal body weight every 3 weeks. Participants in the chemotherapy group received paclitaxel (80 mg per square meter of body-surface area, administered intravenously on days 1, 8, 15, and 22 of a 4-week cycle), pegylated liposomal doxorubicin (40 mg per square meter, administered intravenously on day 1 of a 4-week cycle), or topotecan (4 mg per square meter, administered intravenously on days 1, 8, and 15 of a 4-week cycle, or 1.25 mg per square meter, administered intravenously on days 1 to 5 of a 3-week cycle).

Participants receiving chemotherapy were premedicated at the investigator's discretion. Participants receiving MIRV were premedicated with acetaminophen or paracetamol, dexamethasone, and diphenhydramine for infusion-related reactions. Prophylactic glucocorticoid eye drops were also administered (six times daily on days –1 [the day before each infusion of MIRV] to 4 and four times daily on days 5 to 8 of each cycle), and preservative-free lubricating artificial tears were recommended daily (additional details are provided in the Supplementary Methods section in the Supplementary Appendix). All the participants received ocular examinations at screening. Participants receiving MIRV underwent additional ocular examinations at the onset of ocular symptoms and at every other cycle thereafter.

Outcomes and Assessments

The primary end point was progression-free survival, defined as the time from the date of randomization until investigator-assessed progressive disease or death, whichever occurred first. Key secondary analytic end points included investigator-assessed objective response (i.e., a confirmed complete or partial response) according to RECIST, version 1.1; overall survival (the time from the date of randomization until the date of death); and participant-reported outcomes (a full description of participant-reported outcomes is provided in the Supplementary Appendix; results are not reported here). Additional secondary end points included the duration of response (the time from initial response until investigator-assessed progressive disease or death occurred for all participants who had a confirmed objective response), cancer antigen 125 (CA-125) response according to Gynecologic Cancer InterGroup criteria (i.e., a reduction in CA-125 levels of ≥50% from baseline, confirmed and maintained for at least 28 days), the time to occurrence of second disease progression or death, and safety. Exploratory subgroup analyses (e.g., previous exposure to bevacizumab or to poly[adenosine diphosphate–ribose] polymerase [PARP] inhibitors) were also conducted. Progression-free survival and objective response, as determined by blinded independent central review, were evaluated as sensitivity analyses. Adverse events were coded according to the *Medical Dictionary for Regulatory Activities*, version 24.0.

Statistical Analysis

We estimated that with approximately 430 participants randomly assigned in a 1:1 ratio to the MIRV group or the chemotherapy group, the trial would have 90% power to detect a hazard ratio for disease progression or death of 0.7 at a two-sided α level of 0.05, assuming a median progression-free survival of 5.0 months in the MIRV group and 3.5 months in the chemotherapy group. Efficacy was assessed in the intention-to-treat population, which included all the participants who underwent randomization, regardless of whether they received the assigned treatment. The safety population included all the participants who underwent randomization and received at least one dose of the assigned treatment.

The final analysis of investigator-assessed progression-free survival was conducted after at

Table 3. Adverse Events That Occurred during the Treatment Period in the Safety Population.*

Adverse Event	MIRV (N=218)		Chemotherapy (N=207)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of participants (percent)			
Any adverse event	210 (96.3)	91 (41.7)	194 (93.7)	112 (54.1)
Any treatment-related adverse event	188 (86.2)	53 (24.3)	167 (80.7)	77 (37.2)
Serious adverse event	52 (23.9)	44 (20.2)	68 (32.9)	59 (28.5)
Serious treatment-related adverse event	20 (9.2)	16 (7.3)	16 (7.7)	16 (7.7)
Adverse event leading to dose reduction	74 (33.9)	—	50 (24.2)	—
Adverse event leading to dose delay or hold	117 (53.7)	—	111 (53.6)	—
Adverse event leading to dose discontinuation	20 (9.2)	—	33 (15.9)	—
Adverse event leading to death	5 (2.3)	—	5 (2.4)	—
Treatment-related adverse event leading to death	1 (0.5)	—	1 (0.5)	—
Adverse events occurring in ≥20% of participants in a trial group				
Blurred vision	89 (40.8)	17 (7.8)	5 (2.4)	0
Keratopathy	70 (32.1)	20 (9.2)	0	0
Abdominal pain	66 (30.3)	6 (2.8)	31 (15.0)	3 (1.4)
Fatigue	66 (30.3)	5 (2.3)	52 (25.1)	11 (5.3)
Diarrhea	64 (29.4)	3 (1.4)	36 (17.4)	1 (0.5)
Dry eye	61 (28.0)	7 (3.2)	5 (2.4)	0
Constipation	59 (27.1)	0	40 (19.3)	2 (1.0)
Nausea	58 (26.6)	4 (1.8)	60 (29.0)	4 (1.9)
Peripheral neuropathy	47 (21.6)	3 (1.4)	30 (14.5)	4 (1.9)
Neutropenia	24 (11.0)	2 (0.9)	59 (28.5)	36 (17.4)
Anemia	21 (9.6)	2 (0.9)	71 (34.3)	21 (10.1)

* Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. The relatedness of adverse events to treatment was determined by the investigator.

least 330 disease progression events or deaths had occurred. Once the result with respect to the primary end point was determined to be significant, hierarchical testing was used to control the familywise type I error rate for the key secondary end points of objective response, overall survival, and participant-reported outcomes. The Kaplan–Meier method was used to estimate the curves for progression-free survival, overall survival, duration of response, and time to second disease progression or death in each trial group. The primary progression-free and overall survival hypotheses were tested with the use of the stratified log-rank test; hazard ratios and associated 95% confidence intervals were analyzed with the use of stratified Cox proportional-hazards models. The supremum test was used to assess nonproportionality for progression-free survival, overall survival, and time to second disease progression or death; analyses of piecewise hazard ratios for progression-free survival, when possible nonproportionality was observed, are described in the Supplementary Appendix. We also report the restricted mean survival time at 12 months for progression-free survival. The widths of the 95% confidence intervals were not adjusted for multiplicity and cannot be used to infer effects. Objective response and CA-125 response were compared between the trial groups with the use of stratified Cochran–Mantel–

Haenszel tests. The stratified analyses were conducted on the basis of the randomization stratification factors.

Results

Participants

Trial enrollment began on February 3, 2020; the data-cutoff date for the primary analysis was March 6, 2023. A total of 453 participants underwent randomization and were included in the intention-to-treat population; 227 were assigned to the MIRV group and 226 to the chemotherapy group (92 to receive paclitaxel, 81 to receive pegylated liposomal doxorubicin, and 53 to receive topotecan) (Fig. S1 in the Supplementary Appendix). A total of 425 participants received at least one dose of the assigned treatment (218 in the MIRV group and 207 in the chemotherapy group) and were included in the safety population.

The demographic and clinical characteristics of the participants at baseline are shown in Table 1. Most participants had high-grade serous (100%) epithelial ovarian cancer (80.4%), had received two or three previous lines of therapy (86.1%), and had previous exposure to taxane (99.6%), bevacizumab (62.0%), and PARP inhibitors (55.4%). In the safety population, the median duration of the assigned treatment was 4.98 months (range, 0.69 to 27.37; median cycles, 7 [range, 1 to 39]) in the MIRV group and 2.96 months (range, 0.46 to 18.10; median cycles, 3 [range, 1 to 19]) in the chemotherapy group. For individual chemotherapies, the median duration of the assigned treatment was 3.80 months (range, 0.46 to 8.41; median cycles, 4 [range, 1 to 9]) for paclitaxel, 2.76 months (range, 0.92 to 18.10; median cycles, 3 [range, 1 to 16]) for pegylated liposomal doxorubicin, and 2.3 months (range, 0.46 to 14.23; median cycles, 3 [range, 1 to 19]) for topotecan.

Efficacy

Investigator-assessed progression-free survival was significantly longer in the MIRV group (median, 5.62 months; 95% CI, 4.34 to 5.95) than in the chemotherapy group (median, 3.98 months; 95% CI, 2.86 to 4.47) (P<0.001) (Fig. 1A). The restricted mean progression-free survival at 12 months was 6.13 months (95% CI, 5.62 to 6.64) in the MIRV group and 4.72 months (95% CI, 4.21 to 5.23) in the chemotherapy group.

The percentage of participants with an investigator-assessed objective response (a key secondary end point) was significantly higher in the MIRV group (42.3%; 95% CI, 35.8 to 49.0) than in the chemotherapy group (15.9%; 95% CI, 11.4 to 21.4) (odds ratio, 3.81; 95% CI, 2.44 to 5.94; P<0.001) (Table 2). Among the participants in the MIRV group, 12 (5.3%) had a complete response and 84 (37.0%) had a partial response, as compared with 0 and 36 participants (15.9%), respectively, in the chemotherapy group. Best overall responses are shown in Table 2, and the results of exploratory analyses of best percent change in tumor burden from baseline are shown in Figures S2 and S3. The median overall survival was 16.46 months (95% CI, 14.46 to 24.57) in the MIRV group and 12.75 months (95% CI, 10.91 to 14.36) in the chemotherapy group; this difference was significant (hazard ratio for death, 0.67; 95% CI, 0.50 to 0.89; P=0.005) (Fig. 1B). The median duration of response was 6.77 months (95% CI, 5.62 to 8.31) among the 96 participants in the MIRV group who had a response, as compared with 4.47 months (95% CI, 4.17 to 5.82) among the 36 participants in the chemotherapy group who had a response (hazard ratio, 0.62; 95% CI, 0.40 to 0.97) (Table 2). The percentage of participants with a CA-125 response was higher in the MIRV group than in the chemotherapy group (58.0% vs. 30.3%; difference, 27.7 percentage points; 95% CI, 17.5 to 37.9) (Table 2). A Kaplan–Meier curve for the time to second disease progression or death is shown in Figure S4.

The results of subgroup analyses of investigator-assessed progression-free survival, objective response, and overall survival appeared to consistently favor MIRV over chemotherapy (Fig. 2 and Fig. S5). Sensitivity analyses of progression-free survival (hazard ratio, 0.72; 95% CI, 0.56 to 0.92) (Fig. S6) and objective response (odds ratio, 3.22; 95% CI, 2.04 to 5.09) (Table S1), as assessed by blinded independent central review, were concordant with the investigator-assessed results.

Safety

Adverse events that occurred during the treatment period are reported in Table 3. Such adverse events occurred in 210 participants (96.3%) in the MIRV group and in 194 participants (93.7%) in the chemotherapy group. The most

common adverse events among the participants in the MIRV group were blurred vision (in 89 [40.8%]), keratopathy (in 70 [32.1%]), abdominal pain (in 66 [30.3%]), and fatigue (in 66 [30.3%]). The most common adverse events among the participants in the chemotherapy group were anemia (in 71 [34.3%]), nausea (in 60 [29.0%]), neutropenia (in 59 [28.5%]), and fatigue (in 52 [25.1%]). Adverse events of interest (peripheral neuropathy, alopecia, and hematologic, gastrointestinal, and ocular events) that occurred with MIRV as compared with individual chemotherapies are summarized in Figure S7.

Adverse events of at least grade 3 occurred in 91 participants (41.7%) in the MIRV group and in 112 participants (54.1%) in the chemotherapy group. Serious adverse events occurred in 52 participants (23.9%) in the MIRV group and in 68 participants (32.9%) in the chemotherapy group. Dose reductions and delays or holds are reported in Table S2. A total of 20 participants (9.2%) discontinued MIRV owing to adverse events; the most common adverse events leading to discontinuation were blurred vision (in 3 participants) and pneumonitis (in 3). A total of 33 participants (15.9%) discontinued chemotherapy owing to adverse events, the most common being peripheral neuropathy (in 4), thrombocytopenia (in 3), and fatigue (in 3). Death due to a treatment-related adverse event occurred in 1 participant in the MIRV group (neutropenic sepsis) and in 1 participant who received topotecan in the chemotherapy group (septic shock).

In the MIRV group, ocular adverse events occurred in 122 participants (56.0%); grade 3 ocular adverse events of blurred vision occurred in 17 participants (7.8%), keratopathy in 20 (9.2%), and dry eye in 7 (3.2%) (Table S3). The median time to onset of ocular adverse events was 5.4 weeks (range, 0.1 to 68.6). Nearly all ocular adverse events resolved to grade 0 or 1. A total of 4 participants (1.8%) discontinued MIRV owing to ocular adverse events. No adverse events of blurred vision, keratopathy, or dry eye of grade 4 or higher occurred among the participants. No corneal ulcerations, perforations, or permanent ocular sequelae have been reported.

DISCUSSION

MIRV is an antibody–drug conjugate that has been approved by the FDA for FRα-expressing, platinum-resistant ovarian cancer.[22] We report the results of efficacy and safety assessments in the confirmatory, randomized, phase 3 MIRASOL trial. The results reinforce the clinical benefit of MIRV that was observed initially in the SORAYA trial involving bevacizumab-pretreated patients with platinum-resistant, high-grade serous ovarian cancer[19] and support the safety profile of MIRV as compared with chemotherapy that was observed during the FORWARD I trial.[20] The FORWARD I trial did not show a significant improvement in progression-free survival (the primary end point) with MIRV but used a suboptimal scoring method for measuring FRα expression that diluted the observed treatment effect of MIRV.[20] Thus, the positive results from the current trial comparing MIRV with chemotherapy, which enrolled a broader population of patients than SORAYA (i.e., previous bevacizumab treatment was not an inclusion criterion in the current trial), further reinforce the potential for MIRV to alter the treatment landscape for platinum-resistant ovarian cancer, a disease with historically poor prognosis.[13]

The MIRASOL trial showed a significant benefit of MIRV with respect to investigator-assessed progression-free survival (median, 5.62 months; 95% CI, 4.34 to 5.95) as compared with chemotherapy (median, 3.98 months; 95% CI, 2.86 to 4.47) ($P<0.001$). The restricted mean progression-free survival at 12 months was 6.13 months with MIRV and 4.72 months with chemotherapy. MIRV was associated with significant benefits with respect to investigator-assessed objective response (odds ratio, 3.81; 95% CI, 2.44 to 5.94; $P<0.001$) and overall survival (hazard ratio for death, 0.67; 95% CI, 0.50 to 0.89; $P=0.005$). Results for progression-free survival and objective response, as determined by blinded independent central review, were concordant with the investigator-assessed results. No new safety signals for MIRV were observed. It is notable that patients with platinum-resistant ovarian cancer have represented a difficult-to-treat population.[13]

The safety findings in the current trial reinforce the known safety profile of MIRV, which consists primarily of low-grade gastrointestinal, neurosensory, and reversible ocular adverse events. This trial further shows that ocular adverse events are common with MIRV; thus, recommended prophylactic and mitigative measures should be adhered to by patients and health care

professionals. To this end, Hendershot et al. have provided a detailed overview of recommended management and mitigation strategies for MIRV-associated ocular adverse events, such as eyedrop regimens and dose modifications that have been shown to be effective across multiple clinical trials.[26]

Our trial has several limitations. The eligibility criteria may have affected the generalizability of the trial population by restricting enrollment to participants who had previously received one to three lines of systemic therapy and excluding patients with primary refractory disease. Generalizability may also be limited by the lack of racial and ethnic diversity (Table S4).

In this phase 3, randomized trial involving patients with platinum-resistant, FRα-positive ovarian cancer, treatment with MIRV, as compared with chemotherapy, was associated with significant benefits with respect to progression-free survival, objective response, and overall survival. No new safety signals were observed. Platinum-resistant ovarian cancer is a lethal disease with few efficacious, targeted treatments. MIRV appears to be capable of inducing responses and improving survival in patients with this disease.

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Appendix

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