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ORIGINAL ARTICLE

Phase III, randomized trial of mirvetuximab soravtansine versus chemotherapy in patients with platinum-resistant ovarian cancer: primary analysis of FORWARD I

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Background: Mirvetuximab soravtansine (MIRV) is an antibody-drug conjugate comprising a folate receptor alpha (FRα)-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. The randomized, open-label, phase III study FORWARD I compared MIRV and investigator's choice chemotherapy in patients with platinum-resistant epithelial ovarian cancer (EOC).

Patients and methods: Eligible patients with 1-3 prior lines of therapy and whose tumors were positive for FRα expression were randomly assigned, in a 2 : 1 ratio, to receive MIRV (6 mg/kg, adjusted ideal body weight) or chemotherapy (paclitaxel, pegylated liposomal doxorubicin, or topotecan). The primary endpoint was progression-free survival [PFS, Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, blinded independent central review] in the intention-to-treat (ITT) population and in the prespecified FRα high population.

Results: A total of 366 patients were randomized; 243 received MIRV and 109 received chemotherapy. The primary endpoint, PFS, did not reach statistical significance in either the ITT [hazard ratio (HR), 0.98, $P = 0.897$] or the FRα high population (HR, 0.69, $P = 0.049$). Superior outcomes for MIRV over chemotherapy were observed in all secondary endpoints in the FRα high population including improved objective response rate (24% versus 10%), CA-125 responses (53% versus 25%), and patient-reported outcomes (27% versus 13%). Fewer treatment-related grade 3 or higher adverse events (25.1% versus 44.0%), and fewer events leading to dose reduction (19.8% versus 30.3%) and treatment discontinuation (4.5% versus 8.3%) were seen with MIRV compared with chemotherapy.

Conclusions: In patients with platinum-resistant EOC, MIRV did not result in a significant improvement in PFS compared with chemotherapy. Secondary endpoints consistently favored MIRV, particularly in patients with high FRα expression. MIRV showed a differentiated and more manageable safety profile than chemotherapy.

Key words: ovarian cancer, antibody-drug conjugate, folate receptor alpha, mirvetuximab soravtansine, chemotherapy

INTRODUCTION

Epithelial ovarian carcinoma (EOC), including epithelial ovarian, fallopian tube, or primary peritoneal cancer, remains a highly lethal disease, although therapeutic progress has recently been made following the incorporation of molecularly-targeted agents into treatment paradigms.[1] Indeed, the integration of PARP (poly ADP-ribose

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polymerase) inhibitors into the front-line maintenance and recurrent, platinum-sensitive settings,[2-10] as well as bevacizumab in all lines of therapy,[11-13] have improved patient outcomes and resulted in an increased prevalence of women living with EOC, despite no real change in incidence or death.[14] Unfortunately, since the vast majority of these patients are not cured with initial therapy, most eventually relapse with disease that is resistant to currently available chemotherapies.[15] Outcomes for patients with platinum-resistant EOC remain particularly poor, with low response rates to further chemotherapy (e.g. 12% in the AURELIA trial),[13] median progression-free survival (PFS) of 3-4 months,[16] and median overall survival <1 year.[15] Further, subsequent lines of systemic therapy are often associated with cumulative toxicities and limited tolerability for patients. For these reasons, the development of novel therapies for use in the platinum-resistant setting is critical.

One actively pursued molecular target is the cell surface protein, folate receptor alpha (FRα).[17] In contrast to its highly restricted expression in normal tissues, heterogeneous overexpression of FRα is seen in EOC.[18] Its differential distribution pattern, as well as an inherent capacity to internalize large molecules, makes FRα ideally suited for antibody-drug conjugate (ADC)-based therapeutic approaches. ADCs consist of a monoclonal antibody, directed towards tumor-associated antigens, to which a potent cytotoxic agent ('payload') is conjugated via chemical linkage.[19] Moreover, ADCs are a clinically validated class of antineoplastic agents, with nine ADCs currently approved for cancer therapy and >60 others under evaluation in a variety of hematological and solid tumor indications.[20]

Mirvetuximab soravtansine (MIRV) is an ADC comprising an FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent.[21] Upon antigen binding, the FRα-ADC complex is rapidly internalized, and DM4 is released. DM4 subsequently elicits potent antimitotic activity through its ability to suppress microtubule dynamics,[22] resulting in cell cycle arrest and apoptosis. Further, the cleavable linker design of MIRV allows active DM4 metabolites to diffuse from antigen-positive tumor cells into neighboring cells and kill them in an antigen-independent manner, an effect known as 'bystander' killing.[23] The phase I clinical experience in patients with platinum-resistant EOC identified the dose, schedule, and target population for a pivotal evaluation of MIRV in this disease setting.[24] Here we present results of the phase III FORWARD I trial, designed to assess the safety and clinical activity of MIRV as compared with investigator's choice (IC) chemotherapy in patients with FRα-positive, platinum-resistant EOC.

PATIENTS AND METHODS

Study design and patients

FORWARD I was an open-label, randomized, phase III trial conducted in 12 countries (Trial registration: ClinicalTrials.gov: NCT02631876). The trial was conducted in accordance with the US Food and Drug Administration regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The trial was designed by a subset of academic co-authors in collaboration with the sponsor and the Gynecologic Oncology Group Partners (GOG-P), and the protocol was approved by the ethics committee at each participating center.

Eligible patients were 18 years of age or older with histologically confirmed EOC, primary peritoneal cancer, or fallopian tube cancer that was platinum-resistant (defined as progression within 6 months of completion of platinum-containing therapy). Patients were required to have at least one lesion that met the definition of measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1[25]; have received at least one, but not more than three, prior systemic lines of anticancer therapy. Confirmation of threshold FRα positivity by immunohistochemistry ($\geq$50% of tumor cells with any FRα membrane staining visible at $\leq\times$10 microscope objective; 50%-74% and $\geq$75% representing medium and high expression, respectively) was determined by central testing using the anti-FOLR1 2.1 antibody at Ventana Medical Systems. Cut-off thresholds for FRα expression level were selected based on the phase I clinical experience with MIRV.[24] All patients were required to provide tumor tissue for FRα analysis before enrollment; if archival material was not available, fresh biopsies were allowed using a non-significant risk procedure. Eligible patients also had an Eastern Cooperative Oncology Group performance status score of 0 or 1, and adequate hematologic, renal, and hepatic function. All patients provided written informed consent.

Treatment

Randomization was carried out by means of an interactive online response system with a block design, and stratified according to number of prior therapies, FRα expression, and IC chemotherapy regimen. Patients were randomly assigned, in a 2 : 1 ratio, to receive intravenous infusions of MIRV at a dose of 6 mg/kg (based on adjusted ideal body weight) once every 21 days or IC chemotherapy. All patients treated with MIRV received acetaminophen/paracetamol, dexamethasone, or diphenhydramine 30 min before infusion to prevent infusion-related reactions. Patients were also instructed to self-administer corticosteroid eye drops (1% prednisolone) six times daily on days 1-4 and four times daily on days 5-8 of each cycle during the study and mandated to use preservative-free, lubricating artificial tears on a daily basis (as directed by the product label or treating physician). The chemotherapy regimen selected—paclitaxel, pegylated liposomal doxorubicin (PLD), or topotecan—was stipulated before randomization. Permitted options in the chemotherapy arm were paclitaxel 80 mg/m^2 on days 1, 8, and 15 of a 4-week treatment cycle, PLD 40 mg/m^2 on day 1 of a 4-week treatment cycle, or topotecan 4 mg/m^2 on days 1, 8, and 15 of a 4-week cycle. Alternatively, topotecan could have been administered at 1.25 mg/m^2 on days 1-5 of a 3-week treatment cycle. The trial

intervention was continued until disease progression on imaging [per RECIST version 1.1, as assessed by blinded independent central review (BICR)], development of unacceptable toxicity, or withdrawal of consent. Crossover was not allowed.

Endpoints and assessments

The primary endpoint was PFS, assessed by BICR, in both the intention-to-treat population (ITT) (all patients who underwent randomization, regardless of the intervention actually received) and in the high FRα subgroup (≥75% of tumor cells with any FRα membrane staining visible at ≤×10 microscope objective). PFS was defined as the time from randomization to disease progression or time of death from any cause. Tumor response was also assessed by the investigators according to RECIST version 1.1. Computed tomography or magnetic resonance imaging was carried out at baseline and every 6 weeks for the first 36 weeks of study and then every 12 weeks thereafter, until disease progression, discontinuation of study treatment, or death. Secondary endpoints included objective response rate (ORR) by BICR, overall survival (OS), and a patient-reported outcome (PRO) endpoint [defined as number of patients achieving at least a 15% improvement on the QLQ-OV28 abdominal/gastrointestinal symptom subscale (Items 31-36) at week 8/9 assessment]. A hierarchical testing procedure in the order above was used in these key secondary endpoints to control the study-wise type I error. Investigator-assessed PFS and ORR were used as sensitivity analyses to BICR-assessed PFS and ORR. Other secondary endpoints were PFS 2 (PFS2) (defined as the time from randomization to second disease progression or death), duration of response (DOR), and cancer antigen-125 (CA-125) response rate per Gynecologic Cancer Intergroup (GCIG) criteria.[26]

Adverse events were graded with the use of National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 and monitored continuously throughout the study from the time of the first dose until 30 days after treatment cessation. Serious adverse events were defined as those that were fatal or life-threatening, required prolonged existing hospitalization, resulted in significant disability or incapacity, or required medical or surgical intervention. Safety data were reviewed by an independent data monitoring committee (IDMC) on a regular basis (approximately every 6 months) both before and after the interim analysis. Ongoing safety data review was carried out by the sponsor and trial investigators.

Statistics

Sample size calculations were based on efficacy assumptions. An interim futility analysis was conducted when 92 PFS events, as assessed by the BIRC, had occurred and was reviewed by the IDMC. The observed hazard ratio (HR) was <1 in all randomized patients as well as in the FRα high expression subgroup, and the study continued as planned. The final analysis was conducted when 244 PFS events were observed. The Hochberg procedure[27] was used to control the study-wise type I error (if the larger of the two *P* values is <0.05 then both null hypotheses will be rejected; otherwise, the smaller of the two *P* values will have to be <0.025 for the corresponding null hypothesis to be rejected). Assuming a FRα high : medium expression patient ratio of 2 : 1, the study had a power of 85% to 91% to detect a HR of 0.583 in the high FRα subgroup, with the corresponding power for all randomized patients ranging from 75% to 96%. A final OS analysis was conducted 1 year after the final analysis of the primary PFS endpoint. Demographics and baseline characteristics were summarized using descriptive statistics (*N*, mean, standard deviation, median, and range) for continuous variables and *N* (%) for discrete variables.

RESULTS

Patients

Between 24 January 2017 and 23 April 2018, 366 patients were randomly assigned to receive MIRV (248) or IC chemotherapy (118). After randomization, 352 patients received at least one dose of their assigned regimen (243 and 109 in the MIRV and IC chemotherapy groups, respectively) and were included in the safety population. The remaining 14 patients did not receive assigned therapy as part of the trial but were included in the ITT population (Figure 1). Baseline characteristics were well balanced between the two treatment groups (Table 1). Most patients had EOC with high-grade serous histology and one or two prior lines of systemic therapy. In total, 218 patients (59.6%) constituted the predefined subset of high FRα expression patients; 147 were assigned to receive MIRV and 71 to receive IC chemotherapy. The median duration of follow-up in the ITT population was 12.5 months for both the MIRV (range, 0.03 to 22.0) and IC chemotherapy groups (range, 0.03 to 20.4). At the time of data cut-off for primary analysis, 27 patients were continuing to receive MIRV (19 of whom were high FRα) and two were still receiving IC chemotherapy (Figure 1).

Efficacy

Analysis of the primary endpoint (PFS, assessed by BICR) was carried out when 244 randomized patients had disease progression or died (Figure 2). For the ITT population, Kaplan–Meier estimates showed no significant difference in PFS between groups [HR, 0.98; 95% confidence interval (CI), 0.73 to 1.31; $P = 0.897$] (Figure 2A); median PFS was 4.1 and 4.4 months for MIRV and IC chemotherapy, respectively. In the prespecified high FRα subgroup (Figure 2B), PFS was longer in patients in the MIRV group compared with IC chemotherapy (median, 4.8 months versus 3.3 months; HR, 0.69, 95% CI, 0.48 to 1.00; $P = 0.049$). However, based on the Hochberg procedure used in the statistical analysis plan for the study, this *P* value did not meet statistical significance; since the *P* value for the ITT was >0.05, this value was required to be <0.025 to be significant. Therefore, all *P* values for primary and secondary

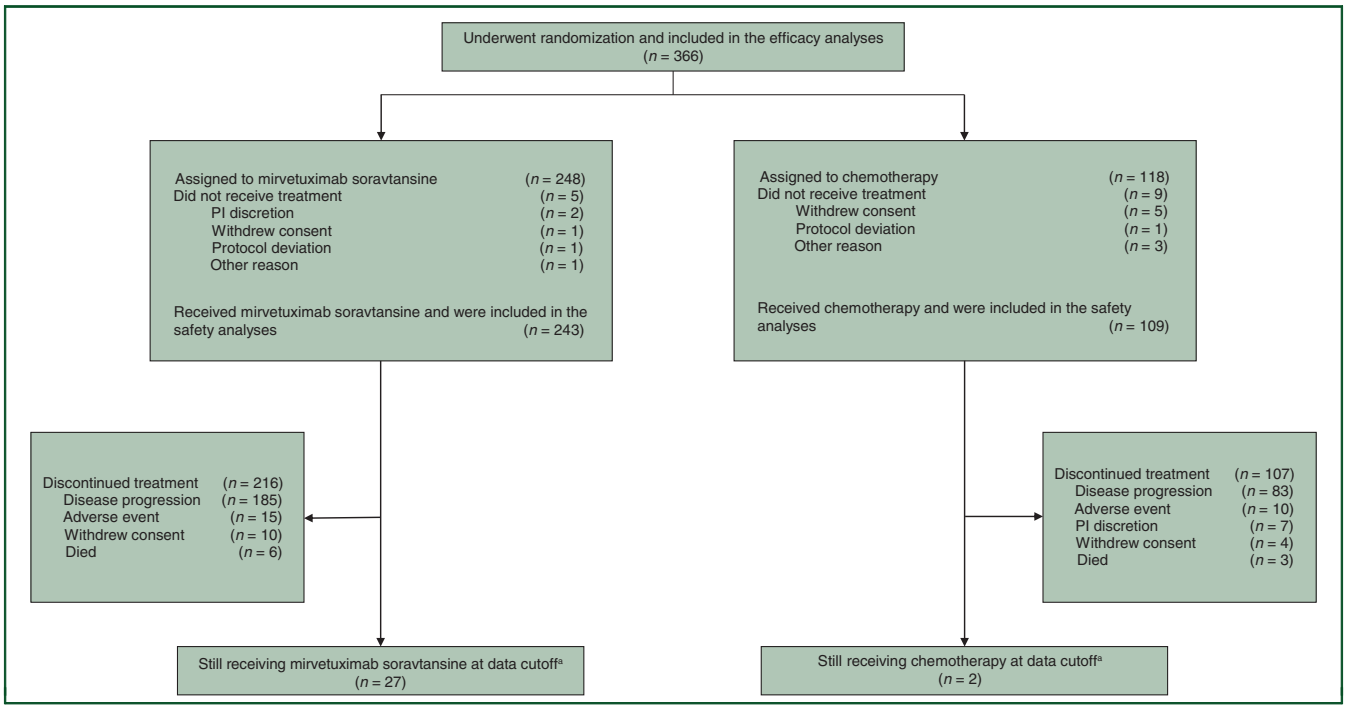

Figure 1. CONSORT diagram.
[a] As of 19 February 2019.
PI, principle investigator.

Table 1. Baseline characteristics in the intention-to-treat population

Characteristic	Mirvetuximab soravtansine (*n* = 248)	IC chemotherapy (*n* = 118)
Age, years		
Median	64	64
Range	34-89	31-86
Primary cancer diagnosis		
Epithelial ovarian cancer	207 (83.5)	105 (89.0)
Fallopian tube cancer	14 (5.6)	5 (4.2)
Primary peritoneal cancer	27 (10.9)	8 (6.8)
EOC Histology		
High-grade serous	245 (98.8)	114 (96.6)
Endometrioid	0	1 (0.8)
Serous adenocarcinoma	2 (0.8)	3 (2.5)
Mixed serous and carcinoma	1 (0.4)	0
ECOG PS[a]		
0	141 (56.9)	60 (50.8)
1	106 (42.7)	57 (48.3)
No. of prior systemic therapies[b]		
1 or 2	159 (64.1)	74 (62.7)
3	86 (34.7)	43 (36.4)
FRα expression[c]		
High	147 (59.3)	71 (60.2)
Medium	101 (40.7)	46 (39.0)
Prior exposure		
Paclitaxel	238 (96.0)	113 (95.8)
Bevacizumab	121 (48.8)	55 (46.6)
PARP inhibitor	44 (17.7)	19 (16.1)

Data are number of patients (%) unless indicated otherwise.
ECOG PS, Eastern Cooperative Oncology Group performance status; EOC, epithelial ovarian cancer, IC, investigators choice; PARP, poly ADP-ribose polymerase.
[a] Performance status data not available for one patient in each arm.
[b] Four patients enrolled were ineligible due to >3 prior lines of therapy.
[c] Medium, 50%-74%; High ≥75% of tumor cells with any FRα membrane staining visible at ≤×10 microscope objective; one patient randomized to the chemotherapy arm was subsequently determined to have a FRα expression level <50%.

endpoints presented hereafter are nominal and no results should be considered as statistically significant.

Secondary endpoint analyses for the ITT (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.02.017) showed the confirmed ORR was higher for MIRV than for IC chemotherapy (22% versus 12%, $P = 0.015$), CA-125 responses were better (51% versus 27%, $P < 0.001$), a longer PFS2 duration was observed (median 10.0 versus 8.4 months; HR, 0.64; 95% CI, 0.49 to 0.84; $P < 0.001$), and there was an improvement in PRO in the EORTC QLQ-OV28 Abdominal/GI Symptom Subscale (32% versus 14%, $P = 0.016$).

Subgroup analyses for survival outcomes are shown in Figure 3. No differences between arms were seen for either PFS or OS in the ITT population (Figures 3A and B); however, the HRs consistently favored MIRV over IC chemotherapy for both these efficacy measures within the high FRα subset (Figures 3C and D). Additional support for superior outcomes for MIRV compared with chemotherapy in this subset of biomarker-defined patients was provided by the secondary endpoint analyses (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2021.02.017). The confirmed ORR (24% versus 10%, $P = 0.014$), CA-125 response (53% versus 25%, $P = 0.001$), PFS2 (median 10.1 versus 8.4 months; HR, 0.56; 95% CI, 0.39 to 0.79; $P < 0.001$), and PRO improvement (27% versus 13%, $P = 0.143$) were all higher in MIRV-treated group.

No significant difference in OS was seen in the ITT population (Figures 4A and B). In the high FRα subgroup OS was longer with MIRV compared with IC chemotherapy, both at the first cut-off (median, not reached versus 11.8 months;

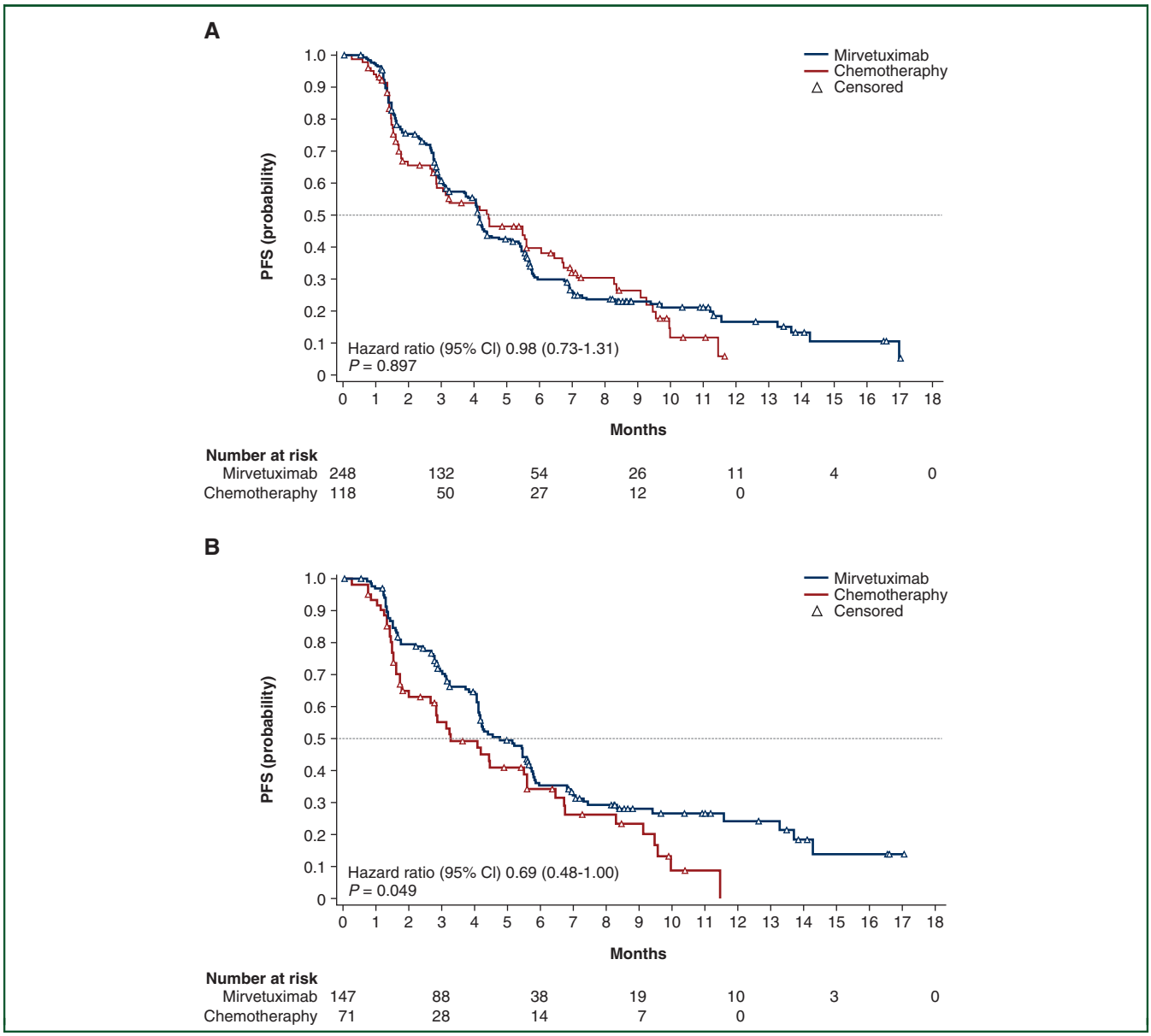

Figure 2. Kaplan–Meier analysis of progression-free survival (PFS) for the mirvetuximab soravtansine and chemotherapy groups in (A) the intention-to-treat population and (B) in the predefined subset of high FRα patients.
CI, confidence interval.

HR, 0.62; 95% CI, 0.40 to 0.97; $P = 0.033$; Figure 4C) and final analysis (17.3 versus 12.0 months; HR, 0.71; 95% CI, 0.49 to 1.02; $P = 0.063$; Figure 4D), but the differences were not considered statistically significant.

Safety

MIRV was well tolerated, with fewer patients experiencing ≥grade 3 drug-related adverse events (25.1% versus 44.0%), dose reductions (19.8% versus 30.3%), and discontinuations (4.5% versus 8.3%) compared with IC chemotherapy (Table 2). The most common adverse events related to MIRV exposure included nausea (all grades, in 45.7% of patients; grade ≥3 in 1%), diarrhea (all grades, in 31.3%; grade ≥3 in 2.1%), and fatigue (all grades, in 28.8%; grade ≥3 in 1.2%) (Table 2)—with the former two toxicities readily managed by appropriate supportive measures. Ocular disorders, primarily manifesting as blurred vision (all grades, in 42.0%; grade ≥3 in 2.5%) or keratopathy (all grades, 32.5%; grade ≥3 in 1.2%), were the most frequent adverse events leading to dose delays and/or reductions (19.8% of patients, Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2021.02.017). In addition to dose modification, these effects were managed by proactive mitigation strategies, and no long-term sequelae were reported. Peripheral neuropathy occurred in 26.7% of patients, with 11.9% of cases being ≥grade 2. The comparative frequency of peripheral neuropathy in the overall chemotherapy population was 18.3%; this was primarily driven by the incidence seen in patients treated with paclitaxel ($n = 32$; all grades, 43.8%, grade ≥2, 28.1%). Alopecia was another adverse event that occurred at a high frequency in

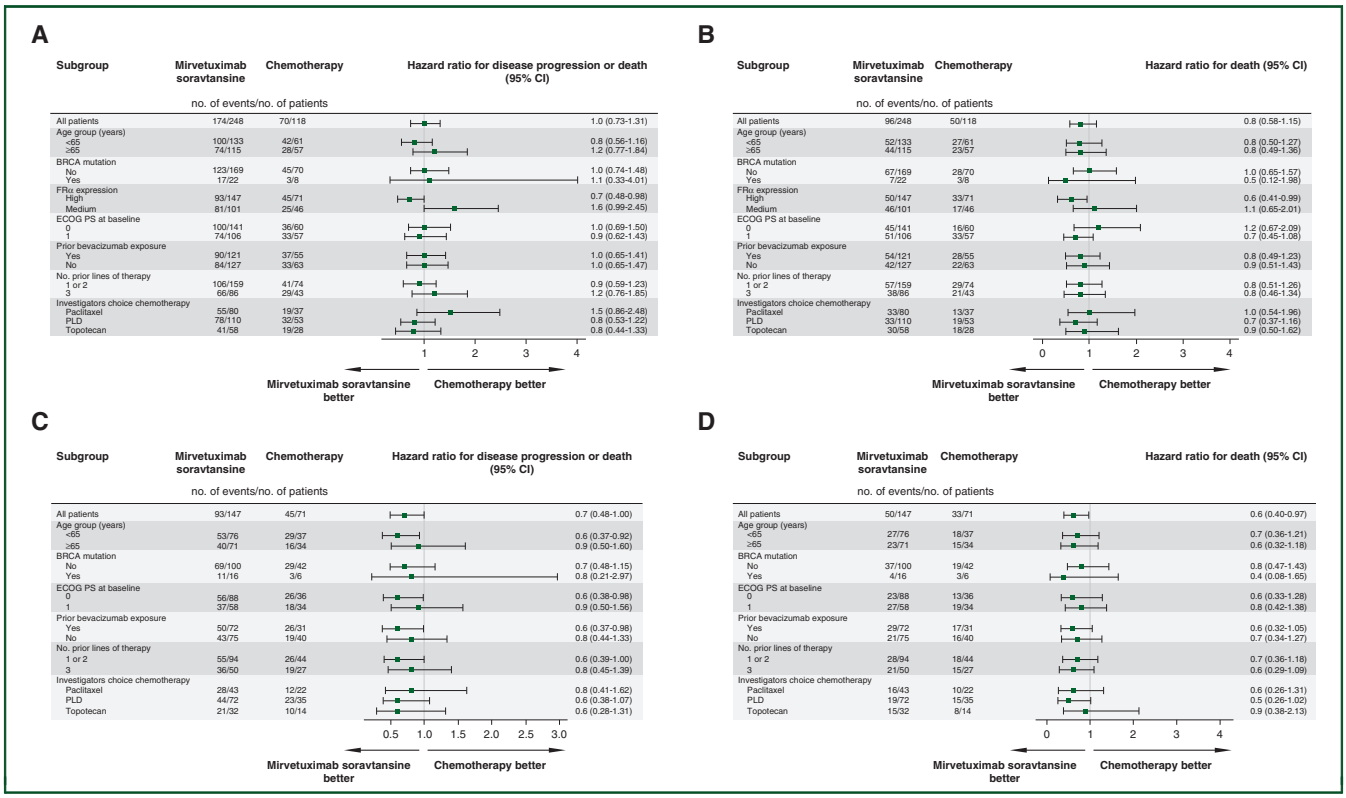

Figure 3. Subgroup analyses.

Progression-free survival (A) and overall survival (B) carried out in the ITT population according to stratification factors and exploratory endpoints at baseline. Progression-free survival (C) and overall survival (D) carried out in predefined subsets of high FRα expression patients according to stratification factors and exploratory endpoints at baseline.

BRCA, breast cancer gene (Foundation Medicine CDx testing); CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; ITT, intention-to-treat; PLD, pegylated liposomal doxorubicin.

paclitaxel-treated patients (21.9%) yet was seen in <1% of patients receiving MIRV. Hematological toxicities observed with MIRV involved cytopenias (all grades, 3.3%-10.7%) that were both lower in prevalence (anemia, 10.7% versus 28.4%; neutropenia, 6.6% versus 39.4%; leukopenia, 3.3% versus 14.7%) as well as severity compared with patients receiving chemotherapy (Table 2).

The percentages of patients experiencing serious adverse events were similar in the MIRV and IC chemotherapy groups (6.6% versus 6.4%; Table 2). Pneumonitis, an adverse event of special interest, occurred in 2.9% of patients (grades 1-3). Two treatment-related deaths due to sepsis occurred in the IC chemotherapy group, one each in patients who received PLD or topotecan. In contrast, no adverse events that emerged during trial intervention, or up to 30 days after the last dose, related to MIRV resulted in death (Table 2).

DISCUSSION

FORWARD I was a randomized, open-label, phase III study comparing MIRV versus IC chemotherapy in patients with platinum-resistant EOC. Baseline characteristics were well balanced between the treatment arms. The study did not meet its primary endpoint of superior PFS in the MIRV arm in the ITT population, nor in the predefined subgroup of FRα high patients.

Based on outcomes observed in corresponding patient populations during the earlier clinical evaluation of MIRV,[28,29] the negative result was unexpected. In-depth review of the study data revealed that the use of observable membranous staining at ×10 microscope objective (×10 scoring) as the method of determining FRα positivity for patient enrollment may not have been a reliable method for determining FRα status. In the phase I program for MIRV, the scoring used for eligibility considered not only the proportion score but the intensity of membranous FRα staining as well[30] and only samples with sufficient 2+ and 3+ intensity staining (PS2+ scoring) were deemed positive. Further, we have previously reported results from a cohort study evaluating fresh biopsy material that showed FRα expression levels did not significantly shift over time from matched archival samples,[30] thus validating the use of archival tissue for determination of eligibility. Exploratory rescoring analyses using PS2+ methodology suggested that use of ≤×10 scoring allowed enrollment of patients with lower than expected levels of FRα expression, thus diluting the treatment effect of MIRV, in both the ITT and high FRα populations.[31]

Despite this dilution, consistent treatment effects were observed in key secondary endpoints for patients in the protocol-defined high FRα subgroup. In these patients, the confirmed ORR, CA-125 response, PFS2 interval, and PRO improvement all favored MIRV over chemotherapy with

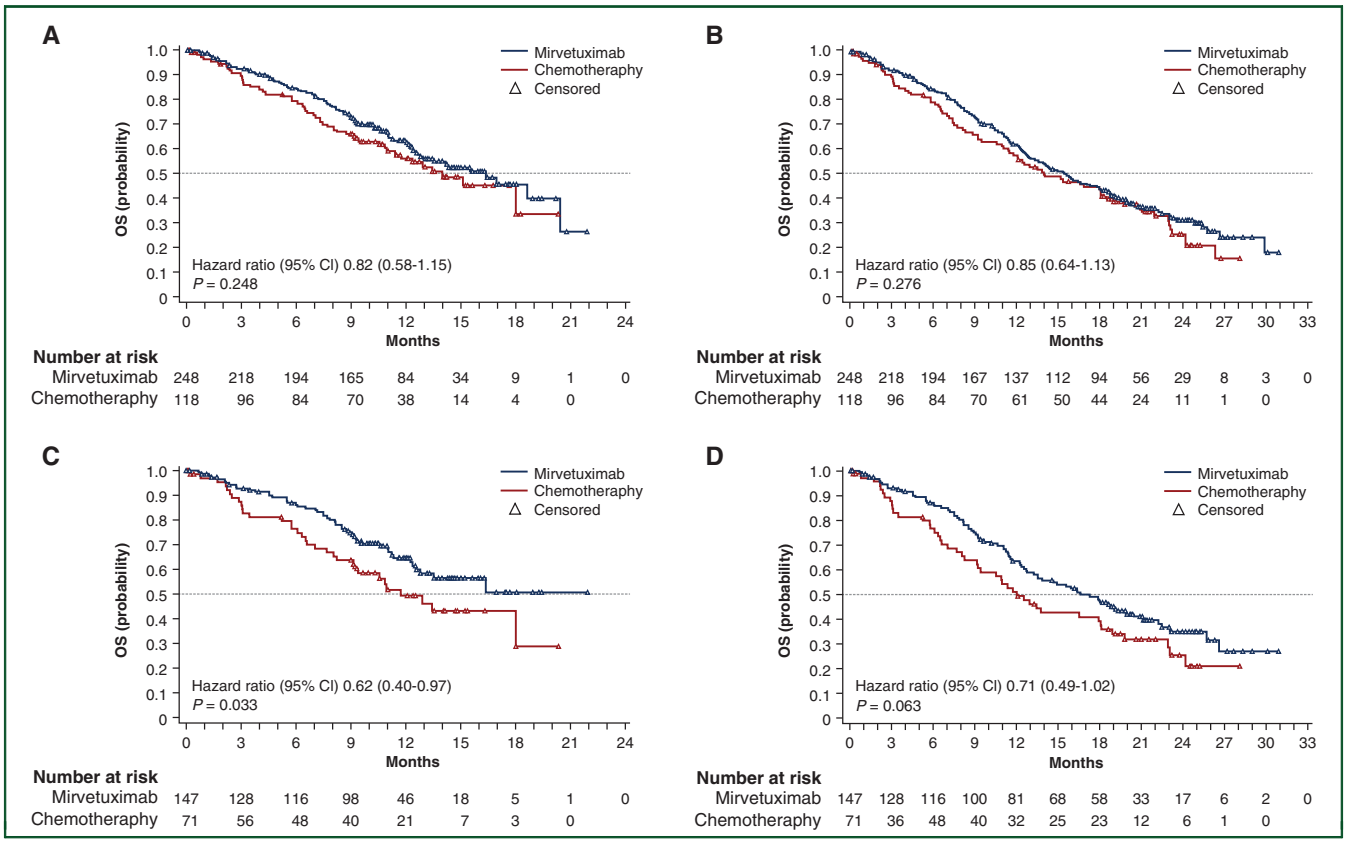

Figure 4. Kaplan–Meier plots of overall survival (OS) in the intention-to-treat population at (A) the time of first data cut-off and (B) final analysis, 1 year after the primary endpoint was reached.

OS estimates for the predefined subset of high FRα patients at first (C) and final analysis (D) are also shown. Hazard ratios (95% CI) are for death and estimated by Cox proportional-hazard regression analysis.

CI, confidence interval.

P values below 0.05, with the caveat that these values were not deemed significant due to the statistical analysis plan. Moreover, while FORWARD I was not powered to show a difference in OS, comparatively better OS outcomes were also seen in this subset of patients. Although this was not an unselected population of ovarian cancer patients, the findings additionally add to the body of evidence that elevated FRα expression may be a negative prognostic marker for chemotherapeutic response in EOC.[32] FRα high patients responded with limited efficacy to standard chemotherapy (ORR, 10%; median PFS, 3.3 months), further underscoring the critical need for active and tolerable therapies in this biomarker-defined population.

No unexpected toxicities were observed in FORWARD I, and the tolerability profiles of MIRV and chemotherapy were consistent with those from previous studies. MIRV displayed a differentiated safety profile relative to IC chemotherapy, with primarily low-grade nausea, diarrhea, and blurred vision as common adverse events that were readily mitigated with anti-emetics, anti-diarrheals, and lubricating and steroid eye drops. MIRV exposure was associated with significantly less myelosuppression than IC chemotherapy, as evidenced by lower rates of anemia, neutropenia, and thrombocytopenia overall, and no grade 3 or greater neutropenia or thrombocytopenia. Despite its tubulin-directed payload, MIRV was also associated with less peripheral neuropathy than paclitaxel (12% versus 28% grade $\geq$2) and virtually no alopecia. Patients receiving MIRV required fewer dose reductions or discontinuations due to drug-related adverse events than those on chemotherapy.

Prior efforts to therapeutically target FRα in EOC were hampered by limited single-agent activity, ultimately resulting in negative phase III trials in combinations. Despite negligible activity as monotherapy,[33] the humanized anti-FRα monoclonal antibody farletuzumab showed early promise when administered in combination with chemotherapy, but failed to meet its primary endpoints in randomized phase II or III combination trials in platinum-sensitive EOC[34,35] and a phase III trial in the platinum-resistant setting was terminated early due to futility.[36] A lack of a priori patient selection based on FRα expression level has been suggested to be a contributing factor to the failure of those studies.[17] Vintafolide, a small molecule drug conjugate consisting of a vinca alkaloid linked directly to folate with a short half-life of 20-25 min,[37] also displayed limited single-agent activity during its initial clinical evaluation.[37] However, this was the first FRα-targeted agent to show a statistically significant improvement, when used in combination, over standard therapy in the randomized phase II PRECEDENT study. This trial evaluated vintafolide in combination with PLD versus PLD alone in women with platinum-resistant ovarian cancer using a companion

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Table 2. Summary of treatment-related adverse events in the safety population

Event	Mirvetuximab soravtansine (n = 243)	IC chemotherapy (n = 109)
Any TRAE	230 (94.7)	98 (89.9)
Grade ≥3 TRAE	61 (25.1)	48 (44.0)
Serious TRAE	16 (6.6)	7 (6.4)
TRAE leading to dose reduction	48 (19.8)	33 (30.3)
TRAE leading to dose delay	71 (29.2)	31 (28.4)
TRAE leading to d iscontinuation of trial drug	11 (4.5)	9 (8.3)
TRAE leading to death[a]	0	2 (1.8)

TRAEs (≥15%)	Any grade	Grades 3-4	Any grade	Grades 3-4
Any	230 (94.7)	61 (25.1)	98 (89.9)	48 (44.0)
Nausea	111 (45.7)	3 (1.2)	38 (34.9)	0
Vision blurred	102 (42.0)	6 (2.5)	3 (2.8)	0
Keratopathy[b]	79 (32.5)	3 (1.2)	0	0
Diarrhea	76 (31.3)	5 (2.1)	11 (10.1)	0
Fatigue	70 (28.8)	3 (1.2)	34 (31.2)	4 (3.7)
Peripheral neuropathy[c]	65 (26.7)	6 (2.5)	20 (18.3)	3 (2.8)
Dry eye	63 (25.9)	3 (1.2)	2 (1.8)	0
Visual acuity decreased	47 (19.3)	0	1 (0.9)	0
Asthenia	44 (18.1)	2 (0.8)	20 (18.3)	8 (7.3)
Decreased appetite	41 (16.9)	2 (0.8)	9 (8.3)	2 (1.8)
Aspartate aminotransferase increased	40 (16.5)	3 (1.2)	3 (2.8)	1 (0.9)
Vomiting	39 (16.0)	3 (1.2)	16 (14.7)	1 (0.9)
Anemia	26 (10.7)	2 (0.8)	31 (28.4)	12 (11.0)
Constipation	23 (9.5)	0	20 (18.3)	0
Thrombocytopenia	23 (9.5)	0	17 (15.6)	4 (3.7)
Neutropenia	16 (6.6)	0	43 (39.4)	23 (21.1)
Stomatitis	10 (4.1)	0	23 (21.1)	1 (0.9)
Leukopenia	8 (3.3)	0	16 (14.7)	7 (6.4)

Data are number of patients (%).
IC, investigator's choice; PLD, pegylated liposomal doxorubicin; TRAE, treatment-related adverse event.
[a] Two deaths observed in the chemotherapy arm involved two cases of grade 5 sepsis seen in patients receiving either PLD or topotecan.
[b] Includes preferred terms of keratopathy, keratitis, punctate keratitis, corneal epithelial microcysts, corneal cyst, corneal deposits, limbal stem cell deficiency, corneal disorder, corneal opacity, corneal erosion, corneal pigmentation, keratitis interstitial, and corneal epithelium defect.
[c] Includes preferred terms of neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, and hypoesthesia.

diagnostic agent known as etarfolatide,[38] with the greatest benefit seen in patients whose tumors were 100% positive for FRα expression.[39] However, a confirmatory phase III study of the same design was also stopped at interim analysis due to futility. Importantly, MIRV has several potential advantages over these prior modalities, including robust single-agent activity, increased antigen specificity, an extended half-life, and the presence of a cleavable linker which allows for bystander cell killing even in the absence of FRα.[17]

The lessons learned from FORWARD I have guided the design of two subsequent studies of MIRV in patients with platinum-resistant, FRα high (by PS2+ scoring) EOC. The single-arm study SORAYA (NCT04296890; prior bevacizumab required) is designed to support accelerated approval, with ORR as the primary endpoint. The randomized MIRASOL trial comparing MIRV monotherapy with IC chemotherapy (NCT04209855) is designed as a confirmatory study, with PFS as the primary endpoint. MIRASOL incorporates a more efficient and conservative statistical design with 1 : 1 randomization without splitting the alpha and targeting a HR of 0.7.

In conclusion, PFS was not significantly improved with MIRV compared with chemotherapy in FORWARD I. MIRV exhibited a favorable tolerability profile and no new safety signals were observed. The encouraging efficacy outcomes seen in patients with high tumor FRα expression support further work to select patients most likely to benefit from MIRV, as is being done in ongoing clinical trials.

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