

Folate Receptor Alpha as a Therapeutic Target for Ovarian Cancer



With the introduction of agents such as bevacizumab and PARP inhibitors, the treatment spectrum for ovarian cancer has evolved from a broad utilization of cytotoxic agents into more tailored approaches.¹ Additional molecular targets are being investigated in an effort to improve the clinical outcomes of recurrent ovarian cancer. One such target is folate receptor α (FR α), which modulates folate uptake, thereby facilitating the activation of tumor growth signals and DNA synthesis.^{2,3} FR α expression may also enhance tumor cells' antiapoptotic ability, rendering them resistant to chemotherapy.^{3,4}

Several FR α -targeting agents that are in active development represent different drug classes and mechanisms of action. This article reviews investigational data associated with these agents, with an emphasis on the recent development and therapeutic potential of antibody–drug conjugates (ADCs) for the treatment of ovarian cancer.

Early FR α -Targeting Agents

Farletuzumab

One of earliest agents developed to target FR α is farletuzumab, a humanized monoclonal antibody with a high affinity for FR α .⁵ Farletuzumab binds to FR α and induces antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and cell death associated with autophagy.⁵

In a first-in-human phase I dose-escalation study, 25 heavily pretreated patients with platinum-resistant or platinum-refractory ovarian tumors were treated with farletuzumab. The drug was generally well tolerated, and dose-limiting toxicities were not reported up to the maximum dose administered (400 mg/m²).⁶ A subsequent phase I study investigating solid tumors in Japanese patients corroborated the safety data that were initially reported.⁷ Pharmacokinetic profiles were also comparable with those reported previously.⁷

An additional phase Ib study evaluated the safety of farletuzumab when used in combination with carboplatin and pegylated liposomal doxorubicin (PLD) in 15 patients with platinum-sensitive ovarian cancer.⁸ Enrolled patients had relapsed disease at least 6 months after first- or second-line platinum-based chemotherapy.⁸ All patients received 6 cycles of intravenous (IV) carboplatin (area under the curve [AUC] of 5-6) and PLD (30 mg/m²) every 4 weeks, in addition to weekly farletuzumab IV (2.5 mg/kg).⁸ After completion of therapy, patients received farletuzumab 7.5 mg/kg every 3 weeks as maintenance treatment until disease progression.⁸ The most common adverse events (AEs) during the combination treatment were fatigue (73.3%), nausea (46.7%), and neutropenia (40.0%).⁸ During farletuzumab maintenance, the most

frequently reported AE was urinary tract infection (25%).⁸ Serious AEs were reported in 4 patients, including small bowel obstructions (n = 2), febrile neutropenia (n = 1), and venous thrombosis (n = 1).⁸ Median progression-free survival (PFS) was 10.4 months.⁸ One patient had a complete response (CR), 10 had a partial response (PR), and 4 had stable disease.⁸

In an open-label phase II study, farletuzumab with or without chemotherapy (taxane and platinum) was evaluated in 54 platinum-sensitive patients with relapsed ovarian cancer.⁹ Patients with nonsymptomatic relapse received weekly farletuzumab monotherapy.⁹ Participants with symptomatic relapse or those whose disease progressed on farletuzumab monotherapy received farletuzumab in combination with carboplatin (AUC, 5-6) and a taxane (paclitaxel 175 mg/m² or docetaxel 75 mg/m²).⁹ Carboplatin and the taxane were administered every 21 days for 6 cycles.⁹ Farletuzumab was administered at 37.5 mg/m² doses in 4 patients, 62.5 mg/m² doses in 5 patients, and 100 mg/m² doses in 45 patients.⁹ The primary endpoints were the rate of normalized CA-125 concentration and overall response rate (ORR). The majority (n = 47; 87%) of patients received combination chemotherapy.⁹ No patients who received farletuzumab monotherapy achieved a normalized CA-125 concentration.⁹ CA-125 levels normalized after 6 cycles of combination therapy in 38 of 47 patients (81%).⁹ Of the 44 patients with evaluable radiographs, 3 patients (7%) had a CR, 30 (68%) had a PR, and 9 (21%) had stable disease.⁹ Of all patients who participated (N = 54), 59.3% experienced grade 3 or higher AEs, and 18.5% experienced grade 3 or 4 AEs related to farletuzumab; there were no treatment-related deaths.⁹

The data from phase II trials suggest that the safety profile of farletuzumab in combination with conventional chemotherapy is manageable, and the initial clinical activity in platinum-sensitive relapsed ovarian cancer supports the rationale for farletuzumab's phase III studies.⁹ Another phase II trial evaluating PFS in patients with platinum-resistant or refractory relapsed ovarian cancer who received farletuzumab in combination with weekly paclitaxel versus paclitaxel alone was terminated because it did not reach prespecified trial continuation compared with paclitaxel alone.¹⁰ At interim analysis, PFS was 3.5 months (95% CI, 3.3-3.9) in the group that received farletuzumab in combination with paclitaxel compared with 3.7 months (95% CI, 3.3-5.2) in patients who received paclitaxel alone (HR, 1.13; 95% CI, 0.88-1.46; *P* = .8360). The data suggest that the addition of farletuzumab was not more beneficial than paclitaxel alone in the population with platinum-resistant recurrent ovarian cancer.¹⁰

Phase III findings echoed the results of the aborted phase II study. The role of farletuzumab was evaluated in 1100 women with ovarian cancer in first platinum-sensitive relapse.¹¹ All patients received carboplatin in combination with docetaxel or paclitaxel for 6 cycles and were randomized to either 1.25 mg/kg doses of farletuzumab, 2.5 mg/kg doses of farletuzumab, or placebo. Farletuzumab dosing was continued weekly until disease progression. The primary endpoint was PFS. The duration of PFS was 9.7, 9.5, and 9.0 months for 2.5 mg/kg doses of farletuzumab, 1.25 mg/kg doses of farletuzumab, and placebo, respectively. Both farletuzumab groups were not significantly different from the placebo arm (HR, 0.99; 95% CI, 0.81-1.21 for the farletuzumab 1.25 mg/kg group; and HR 0.86; 95% CI, 0.70-1.06 for the farletuzumab 2.5 mg/kg group).

Baseline CA-125 levels less than 3 times the upper limit of normal were associated with improved PFS (HR, 0.49; $P = .0028$) and with overall survival (OS) (HR, 0.44; $P = .0108$) for the 2.5 mg/kg dosage arm compared with placebo. Patients with above-median farletuzumab exposure also had significantly better PFS versus placebo.¹¹

Despite these disappointing results, the suggestion that baseline CA-125 levels and farletuzumab exposure may be predictors of efficacy led to the design of another phase II, multicenter, randomized, double-blind, placebo-controlled study.¹² This study will evaluate the safety and efficacy of farletuzumab in platinum-sensitive patients with high-grade, serous ovarian cancer.¹² To be enrolled in the study, patients will be in their first relapse and must have low CA-125 levels (less than or equal to 3 times the upper limit of normal).¹² Weekly farletuzumab doses (5 mg/kg) will be compared with chemotherapy (carboplatin + paclitaxel or carboplatin + PLD, at the investigator's discretion).¹² The primary endpoint is PFS; secondary endpoints are OS, tumor response, and length of the second platinum-free interval versus the first.¹²

The lack of efficacy demonstrated in phase III data could be due to the lack of FR α expression as an inclusion criterion.⁵ Although additional phase II studies are ongoing, the current results highlight the importance of patient selection based on FR α expression status into the design of clinical trials targeting FR α .

Vintafolide

Another method of targeting FR α is through the direct conjugation of chemotherapeutic agents to folate, which results in small-molecule drug conjugates (SMDCs).¹³ Conjugates with folate have several advantages. Through its γ -carboxyl group, folate can be conjugated with other molecules without affecting its binding affinity to FR α . Because folate is a physiological compound, it lacks immunogenicity. Folate's low molecular weight also allows folate derivatives to be easily synthesized.¹³

Vintafolide is a SMDC consisting of a folate conjugate of the vinca alkaloid desacetylvinblastine monohydrazone (DAVLBH).¹³ DAVLBH is a potent microtubule-destabilizing agent.¹³ Vintafolide binds to both FR α and FR β with high affinity,² and upon endocytosis, it releases the active DAVLBH.¹³ Because FR expression in nonmalignant cells is typically restricted to the luminal membrane, which is not in contact with the circulation, vintafolide is preferentially taken up by tumor cells expressing FR.³ Targeted chemotherapy delivery with limited toxicity to off-target nonmalignant cells can be expected.

In a single-arm, multicenter, phase II study, patients with pretreated recurrent platinum-resistant ovarian cancer were evaluated for tumor FR status.¹⁴ ^{99m}Tc-etafolatide imaging is a key component of vintafolide trials and acted as a companion diagnostic to determine the percentage of FR-positive target lesions.¹⁴ Patients were grouped by the percentage of FR-positive target lesions: FR 0%, FR 10% to 90%, and FR 100%. Disease control (stable or response) was observed in 33%, 36%, and 57% of patients with FR 0%, FR 10% to 90%, and FR 100%, respectively.¹⁴ The median OS was 3.0, 9.6, and 14.6 months in the FR 0%, FR

10% to 90%, and FR 100% groups, respectively.¹⁴ Vintafolide led to lesion disease control (stable or response) in 56.4% of FR-positive lesions compared with 20.7% of FR-negative lesions ($P < .001$).¹⁴ The most common vintafolide-related AEs were constipation (45%), fatigue (37%), nausea (29%), anorexia (22%), and neuropathy (20%).¹⁴ The most common grade 3 AEs were constipation (6%) and fatigue (8%). There were no grade 4 AEs.¹⁴

A subsequent phase II trial (PRECEDENT) randomized vintafolide patients 2:1 to PLD (50 mg/m² IV every 28 days) alone or in combination with vintafolide (2.5 mg IV 3 times per week during weeks 1 and 3).¹⁵ The primary endpoint was PFS.¹⁵ Among the intention-to-treat population ($n = 149$), median PFS was 5.0 months in patients who received vintafolide and PLD compared with 2.7 months in those receiving PLD alone (HR, 0.63; 95% CI, 0.41-0.96; $P = .031$).¹⁵ In patients with FR 100% positive lesions, median PFS was 5.5 months in the combination group compared with 1.5 months in the PLD monotherapy arm (HR, 0.38; 95% CI, 0.17-0.85; $P = .013$).¹⁵ In patients with FR 10% to 90% positive lesions, the benefit in PFS was not significant (HR, 0.873; $P = .79$).¹⁵ Patients who did not have FR-positive disease did not derive any PFS benefit from the addition of vintafolide (HR, 1.806; $P = .468$).¹⁵ Most AEs were grade 1 to 2 in severity.¹⁵ There were more incidents of grade 3 and 4 leukopenia (9% vs 0%; $P = .031$) and neutropenia (23% vs 10%; $P = .052$) in the combination arm compared with the PLD-alone group.¹⁵ In summary, the vintafolide + PLD combination appeared to improve median PFS compared with PLD alone. Toxicity with the combination therapy was also manageable.¹⁵

Despite the early clinical activity signals, benefits of vintafolide were not replicated in a phase III trial (PROCEED). In this study, patients with platinum-resistant ovarian cancer were randomized to a 28-day cycle of PLD alone (50 mg/m² IV) or in combination with 2.5 mg vintafolide IV on days 1, 3, and 5 in week 1 and week 3.¹⁶ The primary endpoint was PFS in FR 100% patients. At the interim analysis, 230 FR 100% patients were randomized. PFS was not significantly different between treatment groups (HR, 0.976; 95% CI, 0.633-1.505; $P = 0.4617$). Response rates were also comparable between groups (23.1% in the combination group and 22.9% in the PLD-alone arm). There were more grade 3/4 treatment-related AEs (TRAEs) in the combination group as compared with the PLD-alone group, including stomatitis (9% vs 6%), sensory neuropathy (4% vs 0%), and neutropenia (27% vs 10%).¹⁶ These findings did not meet the interim futility analysis threshold, and the trial was terminated.¹⁶ Later studies suggest that high P-glycoprotein (P-gp) expression confers resistance to DAVLBH, and targeted delivery of DAVLBH via vintafolide could not overcome the P-gp-mediated DAVLBH efflux.¹⁷ The potential of P-gp-mediated drug resistance suggests that FR-targeted therapeutics may not benefit patients whose tumors express high levels of P-gp.¹⁷

Evolution in FR α -Targeted Therapy

Although past phase III study results have been negative for farletuzumab and vintafolide, these results do highlight opportunities, particularly with ADCs, to overcome the limitations of FR-targeting therapies in ovarian cancer. ADCs are engineered molecules composed of highly cytotoxic compounds conjugated to

antibodies directed toward tumor-associated antigens.¹⁸ ADCs appear to have favorable pharmacokinetic features and the specific tumor-targeting properties of an antibody, as well as the potent cancer-killing effect of the attached small molecule cytotoxic agent (also known as payload).¹⁸

Mirvetuximab soravtansine is a first-in-class anti-FR α ADC.¹⁹ It is a humanized anti-FR α antibody conjugated to the maytansinoid DM4, a potent antitubulin cytotoxic agent.^{18,20} The development of mirvetuximab soravtansine, including the selection of the antibody and linker components, was based on the optimization of the antitumor activity.¹⁸ In preclinical studies, the level of FR α expression on the tumor lesion was a major determinant of mirvetuximab soravtansine's antitumor activity. Importantly, mirvetuximab soravtansine exhibited potent anticancer activity in tumor models; FR α expression was representative of patients with ovarian cancer.¹⁸

The mechanism of action of mirvetuximab soravtansine is depicted in the [Figure](#).²¹ Mirvetuximab soravtansine exerts its antitumor activity by binding with high affinity to FR α that is expressed on the surface of tumor cells. The ADC-FR α receptor complex is then internalized through antigen-mediated endocytosis. Once inside the cell, active DM4 catabolites are released through lysosomal processing. DM4 inhibits tubulin polymerization, as well as microtubule assembly, resulting in cell-cycle arrest and apoptosis. In addition, active DM4 metabolites can diffuse into neighboring cells and exert their cytotoxic effects; this process is known as bystander killing.¹⁹

Mirvetuximab soravtansine has several therapeutic advantages over vintafolide and farletuzumab.¹ Unlike folate-based SMDCs, the use of an antibody to target FR α provides antigen specificity and also extends the half-life to confer adequate delivery of the cytotoxic payload to tumor lesions. In addition, the ability of FR α to internalize large molecules makes it well suited for ADC-based approaches. Mirvetuximab soravtansine's cleavable linker also allows active DM4 metabolites to diffuse from FR α -positive cancer cells into neighboring cancer cells and kill them through bystander cytotoxic activity.^{1,18} Bystander cytotoxic activity is especially advantageous in tumors in which FR α expression is heterogeneous.¹⁸

Mirvetuximab Soravtansine as Monotherapy

The clinical activity and safety of mirvetuximab soravtansine have been explored in numerous clinical trials; some are ongoing.

In a phase I dose-escalation trial, patients with advanced solid tumors refractory to conventional therapy received mirvetuximab soravtansine at doses escalating from 0.15 mg/kg to 7.0 mg/kg once every 3 weeks until dose-limiting toxicity or disease progression was reached.²² Among the 44 patients who received treatment, there were no meaningful drug accumulations with this dosing schedule.²² The majority of TRAEs were of grade 1 or 2 severity and included fatigue (25%), blurred vision (23%), diarrhea (21%), and peripheral neuropathy (21%).²² Six patients had a grade 3 AE and 1 patient had a grade 4 AE.²² Dose-limiting toxicities were reported in 4 patients (9%) and included grade 3 hypophosphatemia (at 5 mg/kg) and grade 3 punctate keratitis (at 7.0 mg/kg).²² Investigators implemented a phase II dose of 6 mg/kg once every

3 weeks, based in adjusted ideal body weight (AIBW), with the goal of decreasing the incidence of ocular toxicity and reduce total dose across a wide weight range of patients.²²

The grade 1/2 TRAEs, fatigue and diarrhea, suggest that the safety profile of mirvetuximab soravtansine is similar to that of farletuzumab without the frequent cases of infusion-related reactions and hypersensitivity.^{6,7,19} Peripheral neuropathy is typically associated with tubulin-targeting agents and is probably a consequence of the DM4 maytansinoid payload.¹⁹ Overall, the safety profile of mirvetuximab soravtansine compares favorably with that of conventional tubulin-targeting chemotherapy, such as paclitaxel.¹⁹

Blurred vision and corneal keratopathy were AEs of interest in the study.²² Ocular AEs have been reported for several ADCs using different cytotoxic payloads and targeting different antigens, and the mechanisms underlying ocular AEs remain to be elucidated. The grade 3 corneal opacity and punctate keratitis experienced in the phase I dose-escalation trial were seen in individuals who had received mirvetuximab soravtansine at doses of 5.0mg/kg and 7.0 mg/kg, respectively, based on initial total body weight-based dosing. After the change to AIBW dosing, corneal and visual abnormalities observed were mild (grade 1 or grade 2).²²

Vision- and corneal-related AEs were also observed in expansion phases of the trial at similar frequencies.¹⁹ As a result, proactive measures were mandated, which included daily lubricating eye drop use, wearing sunglasses during daylight exposure, avoidance of contact lenses, warm compress use, and regular cleaning. These proactive measures subsequently decreased both the grade and incidence of visual disturbances in patients who were treated with mirvetuximab soravtansine.

In an expansion cohort of the phase I study, primary prophylaxis of visual disturbances with corticosteroid eye drops was evaluated as a strategy to decrease ocular toxicities associated with mirvetuximab soravtansine.¹⁹ All 40 patients in the expansion cohort received phase II mirvetuximab soravtansine doses at 6 mg/kg every 3 weeks and prednisolone acetate 1% eye drops 4 to 6 times daily for the first 10 days during each treatment cycle.²³ Reversible blurred vision occurred in 16 patients (40%), and keratopathy occurred in 12 (30%) patients.²³ There were no grade 3 or 4 ocular AEs.²³ Compared with a pooled population of patients in phase I studies, corticosteroid eye drops resulted in fewer dose reductions compared with patients who did not receive corticosteroid eye drops prophylaxis (5% vs 15%). In addition, no patients discontinued mirvetuximab soravtansine use due to ocular AEs.²³ Prophylactic steroid eye drops were mandated in conjunction with lubricating eye drops in ongoing mirvetuximab soravtansine trials because of the results of this trial.²³

The trial experience from previous FR α -targeted agents suggest that the quantification of tumor FR α expression is an important step in patient selection.⁵ Patient selection for mirvetuximab soravtansine trials are based on immunohistochemical assessment of FR α expression in archival tumor tissue.²⁴ It has been reported that chemotherapy does not alter FR α expression in ovarian tumors,^{25,26} including those that are platinum-resistant.²⁷

FR α expression from fresh biopsy samples were compared with archival tumor tissues during the same phase I study, to confirm that the use of archival tissue for the quantification of FR α expression is a valid approach.²⁴ In this expansion cohort study, patients with relapsed ovarian cancer, fallopian tube cancer, or primary peritoneal cancer with tumors amenable to biopsy were enrolled.²⁴ Inclusion criteria included FR α positivity by immunohistochemistry (IHC) (defined as $\geq 25\%$ tumor at $\geq 2+$ minimum staining intensity) in archival specimens.²⁴ Patients enrolled were heavily pretreated, with a median of 4 prior systemic therapies (range 1-11), and all had prior exposure to platinum- and taxane-based therapy.²⁴ It was discovered that a considerable amount (22%) of patients' pretreatment biopsy samples did not have sufficient tumor cells for FR α quantification.²⁴ This was likely due to the small amount of samples provided by a core biopsy compared with the amount of ovarian tumor tissue surgically procured and archived.²⁴ Nonetheless, there was a high concordance (71%) of FR α expression among evaluable pretreatment biopsy samples and archival tumor samples.²⁴ The results suggest that tumor FR α expression stays constant between the original diagnosis and the disease recurrence, despite multiple lines of therapy. In addition, archival tumor samples can be reliably used to identify patients with FR α -expression tumors.²⁴

As part of the same phase I expansion cohort study, the recommended phase II dose of mirvetuximab soravtansine, 6.0 mg/kg (AIBW) IV, was administered once every 3 weeks until disease progression, investigator or patient decision, or intolerable toxicity or AEs.²⁴ Patients enrolled (N = 27) experienced AEs that included keratopathy (48%), fatigue (44%), diarrhea (37%), and blurred vision (37%). Most AEs were of grade 1 and 2 severity. There were 2 grade 3/4 AEs, including one case of grade 3 hypokalemia and one case of grade 4 organizing pneumonia, which resolved after study withdrawal. There were no fatalities related to study findings.²⁴ The ORR was 22%, with CR in 2 patients and PR in 4 patients.²⁴ FR α expression was scored as high ($\geq 50\%$), medium (25%-49%), and low ($< 25\%$).²⁴ High FR α expression was associated with improved ORR. In patients with high FR α expression, ORR was 31% (5 of 16 patients, which included the 2 patients with CR). In patients with medium FR α expression, ORR was 20% (1 of 5 patients). There was no objective response in patients with low FR α -expression tumors. The median PFS in all patients was 4.2 months (95% CI, 2.8-5.4). Median PFS was 5.4 months (95% CI, 2.8-not estimable) in patients with high FR α expression; 3.9 months (95% CI, 2.6-12.7) in patients with medium FR α expression; and 2.8 months (95% CI, 1.3-5.4 months) in patients with low FR α expression.²⁴

In summary, the phase I expansion cohort study demonstrated a favorable safety profile and promising clinical activity of mirvetuximab soravtansine in recurrent ovarian cancer. Importantly, the depth and duration of response were associated with the degree of FR α expression, underscoring the importance of patient selection based on FR α expression. Finally, the study demonstrated that use of archival tumor tissues for FR α quantification is a valid approach for patient selection.

Platinum-Resistant Ovarian Cancer

The clinical activity of mirvetuximab soravtansine was investigated in a platinum-resistant population in another expansion cohort of the same phase I study.²⁸ Similar to the previous phase I extension cohort study,

enrolled patients had to meet the minimum requirement of FR α positivity by IHC on tumor samples ($\geq 25\%$ tumor at $\geq 2+$ staining intensity).²⁸ Included patients had recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer.²⁸ Half of the patients (23 of 46) had 1 to 3 prior lines of systemic therapies, and the other half had 4 or more previous lines of systemic therapies.²⁸ All patients had prior exposure to platinum and taxane compounds.²⁸ Doses of 6 mg/kg mirvetuximab soravtansine (AIBW) were administered IV once every 3 weeks. The ORR was 26%, with 1 CR and 11 PRs.²⁸ The median PFS rate in all patients was 4.8 months (95% CI, 3.9-5.7).²⁸ The efficacy measures of mirvetuximab soravtansine in the study compared favorably with those of established chemotherapies for recurrent ovarian cancer in the second-line setting.¹⁹

When patients were stratified by number of previous therapies, median PFS was 6.7 months (95% CI, 3.9-8.7) in patients who had previously received 3 or fewer lines of therapy compared with 3.9 months (95% CI, 2.6-5.4) in those who had received 4 or more lines ($P = .002$).²⁸ Efficacy with mirvetuximab soravtansine as a monotherapy in patients who were less pretreated were comparable with those observed in the registration trial (AURELIA) for bevacizumab in platinum-resistant relapsed ovarian cancer (ORR, 27.3%; median PFS, 6.7 months).²⁹ Of note, the AURELIA trial excluded patients who had more than 2 prior lines of anticancer regimens or who had refractory disease during platinum-containing therapy.²⁹ Bevacizumab is approved for use in combination with chemotherapy in women with platinum-resistant ovarian cancer who have received no more than 2 prior lines of chemotherapy regimens.³⁰ A framework was provided for ongoing mirvetuximab soravtansine trials in less pretreated patients.

The safety profile observed was similar to that of previous studies. Most TRAEs were grade 1 or 2, including diarrhea (44%), blurred vision (41%), nausea (37%), fatigue (30%), neuropathy (28%), keratopathy (26%), increased aspartate aminotransferase (AST) (24%), and vomiting (22%). Grade 3 AEs occurred in 12 patients (26%); fatigue and hypotension were the most common. One patient had grade 4 febrile neutropenia and septic shock, which did not result in fatality after withdrawal from the study.²⁸

In summary, mirvetuximab soravtansine exhibits an acceptable tolerability profile and encouraging PFS and response rates.²⁸ In addition, the results further defined the target population for mirvetuximab soravtansine monotherapy. In 2018, the FDA granted mirvetuximab soravtansine fast-track designation for the treatment of patients with platinum-resistant recurrent ovarian cancer who express medium-to-high levels of FR α .³¹

FORWARD I

Data from phase I studies of mirvetuximab soravtansine helped define the study population for the randomized, open-label, phase III trial FORWARD I. The trial compared mirvetuximab soravtansine monotherapy with the investigators' choice of chemotherapy in patients with platinum-resistant, recurrent ovarian, fallopian tube, or primary peritoneal cancer.³² Based on phase I results, 3 main eligibility criteria were included: platinum-resistant disease, medium or high FR α expression (defined as $\geq 50\%$ of cells with moderate or higher staining intensity), and ≤ 3 prior lines of therapy.^{19,33} This enrollment strategy was supported by a pooled analysis of the 3 expansion cohorts of the phase I trial.³⁴ From the pooled population

of 113 patients, 37 patients met the inclusion criteria for FORWARD I. There was 1 CR and 16 PRs, with an ORR of 46% (95% CI, 29.5%-63.1%). Median PFS was 6.7 months (95% CI, 4.1-9.0). The safety profile was consistent with previous reports. The most common TRAEs were diarrhea, fatigue, blurred vision, and nausea.³⁴ These efficacy values are favorable to outcomes typically observed with conventional single-agent chemotherapy in platinum-resistant disease.¹⁹ The pooled phase I analysis supported the patient selection strategy selected for FORWARD I.

Investigators randomized 366 patients 2:1 to receive either mirvetuximab soravtansine 6 mg/kg (AIBW) every 3 weeks or the investigator's choice of chemotherapy (paclitaxel, PLD, or topotecan).^{32,33} The primary endpoint was PFS in all patients and in patients with high FR α expression. Secondary endpoints were ORR, OS, and quality of life.³² According to top-line results shared by manufacturer Immunogen in March 2019, there was no significant difference in PFS in the overall study population (HR, 0.98; $P = .897$).³⁵ Although the PFS was longer with mirvetuximab soravtansine in the prespecified high FR α -positive subgroup (HR, 0.69; $P = .049$), it did not reach statistical significance, per a prespecified statistical analysis plan.³⁵ Additional findings will be presented at an upcoming medical meeting, according to the company.

Mirvetuximab Soravtansine in Combination Regimens

A promising new strategy for the management of relapsed ovarian cancer involves adding targeted agents with different mechanisms of action and safety profiles to established chemotherapeutic agents.¹⁹ The approval of bevacizumab for use in combination with conventional chemotherapeutic agents exemplifies this new approach.¹⁹ In preclinical models, combinations with carboplatin, PLD, or bevacizumab led to synergistic antitumor activity,³⁶ supporting the rationale to evaluate mirvetuximab soravtansine in combination with other antitumor agents.

FORWARD II is an open-label, phase Ib/II study of mirvetuximab soravtansine in combination with either bevacizumab, carboplatin, PLD, pembrolizumab, or bevacizumab + carboplatin.^{37,38} The overall study has 2 phases: a dose-escalation phase that assesses safety and determines the maximum tolerated dose of mirvetuximab soravtansine in combination regimens with bevacizumab, carboplatin, PLD, and pembrolizumab; and a dose-expansion phase that assesses antitumor activity and safety of mirvetuximab soravtansine in combination regimens with bevacizumab, pembrolizumab, and bevacizumab + carboplatin.³⁷

Mirvetuximab Soravtansine and Bevacizumab

In FORWARD II, mirvetuximab soravtansine was administered once every 21 days in combination with bevacizumab or carboplatin.³⁸ For combinations with PLD, mirvetuximab soravtansine was administered every 28 days.³⁸ The mirvetuximab soravtansine starting dose was 5 mg/kg (AIBW), 1 level less than the recommended phase II single-agent dose (6 mg/kg [AIBW]).³⁸ In an initial report, 46 patients have been enrolled in bevacizumab, carboplatin, and PLD cohorts.³⁸ Mirvetuximab soravtansine dosing was escalated from 5 mg/kg to

6 mg/kg. Bevacizumab dosing remained unchanged at 15 mg/kg.³⁸ Patients (n = 14) who received the mirvetuximab soravtansine + bevacizumab combination were previously treated with a median of 6 (range,

2-8) lines of therapy.³⁸ Common AEs observed with the combination, most grade 1 or 2, included diarrhea (50%), nausea (43%), blurred vision (43%), fatigue (36%), and proteinuria (36%). Thrombocytopenia (29%) and grade 3 hypertension (21%) were also observed.³⁸ ORR was 29% and the median PFS was 9.5 months. Taken together, the AE profile for the combination was as expected based on the known tolerability profiles of the individual agents, and no new safety signals were identified. The clinical activity in this group of heavily pretreated patients was encouraging.³⁸

Updated safety and efficacy data from the same trial included 11 patients from the escalation phase, and 48 of 55 planned patients from the expansion cohort.³⁹ Patients had platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer (progression within 6 months of completing platinum-based therapy) and low FR α expression as assessed by IHC ($\geq 25\%$ tumor cells with $\geq 2+$ staining intensity). Mirvetuximab soravtansine doses of 6 mg/kg (AIBW) and bevacizumab doses of 15 mg/kg were administered once every 3 weeks.³⁹ Preplanned subset analyses included populations with various FR α expression by IHC, including low (25%-49% of tumor cells with $\geq 2+$ staining) versus medium/high ($\geq 50\%$); 1 to 3 versus ≥ 4 prior lines of therapy; FORWARD I-matched subset (medium/high FR α expression and 1-3 prior lines of therapy) corresponding to the target population in the pivotal phase III monotherapy study; and AURELIA-matched type subset (bevacizumab-naïve, 1-2 prior lines of therapy) with medium/high FR α expression.³⁹ In the overall population, enrolled patients had a median of 3 (range, 1-8) prior lines of therapy.³⁹ The most common AEs were nausea (49%), diarrhea (48%), blurred vision (46%), fatigue (41%), and peripheral neuropathy (34%); most AEs were grade 1 or 2.³⁹ Fifteen patients discontinued the combination due to AEs; the most common AE that led to discontinuation was thrombocytopenia. Intestinal perforation from bevacizumab use resulted in 1 death.³⁹ In the overall population, ORR was 43%, median survival was 7.8 months, and median duration of response (DOR) was 10.6 months. The efficacy measures were even more remarkable in the FORWARD I-matched and AURELIA-matched type subsets, in which ORR was 48% and 50%, median PFS was 9.9 months for both, and median duration of response was 10.6 and 12.0 months, respectively.³⁹ In summary, the AE profile of mirvetuximab soravtansine in combination with bevacizumab was manageable. AEs were predominantly grade 1 or 2 and were consistent with the known tolerability profiles of each agent.³⁹ The median PFS and DOR (9.9 and 10.6 months, respectively) seen with the combination in the FORWARD I-matched subset compared favorably with that observed with mirvetuximab soravtansine monotherapy (6.7 and 5.8 months, respectively). Efficacy measures observed for the AURELIA-matched type, medium/high FR α subset were also favorable when compared with bevacizumab + chemotherapy.³⁹

Mirvetuximab Soravtansine and Pembrolizumab

In the dose-escalation phase in FORWARD II, mirvetuximab soravtansine dosing was escalated from 5 mg/kg to 6 mg/kg, while pembrolizumab dosing remained unchanged during escalation at 200 mg.⁴⁰ In 14 patients who had been treated with a median of 5 previous lines of therapy (range, 2-7), the most commonly observed AEs with the mirvetuximab soravtansine + pembrolizumab combination were fatigue (93%), nausea (79%), and diarrhea (57%), typically grade 1 or grade 2.⁴⁰ There was 1 discontinuation due to grade 1 pneumonitis. Dry eye (50%), keratopathy (36%), and blurred vision (36%) were all grade 1 or 2 events.

Incidences of peripheral neuropathy (43%) were also grade 1 or grade 2 events.⁴⁰ In 8 patients with medium-to-high FR α expression ($\geq 50\%$ of cells with $\geq 2+$ staining intensity), the ORR was 63%, with a median PFS rate of 8.6 months. The duration of therapy was 36.1 weeks.⁴⁰ The mirvetuximab soravtansine and pembrolizumab combination exhibited a favorable tolerability profile at full dosing. In addition, preliminary efficacy signals in this heavily pretreated population were encouraging.⁴⁰

Preliminary data of 10 patients who received the mirvetuximab soravtansine + pembrolizumab combination at full dosing and of 46 patients from the expansion phase of the trial have been reported.⁴¹ The inclusion criteria were the established FORWARD I criteria: platinum-resistant ovarian cancer (progression within 6 months from completion of platinum-based therapy) and positive FR α expression by IHC ($\geq 25\%$ of tumor cells with $\geq 2+$ staining intensity).⁴¹ Included patients had been treated by a median of 3 (range, 2-7) prior lines of systemic therapies.⁴¹ All patients had been previously exposed to platinum compounds and taxanes, and about half of the patients had previous exposure to bevacizumab and PARP inhibitors.⁴¹ Most AEs were manageable and were reported as grade 1 or grade 2. Grade 3 events were reported in 21 (38%) patients and included diarrhea (n = 2), nausea (n = 2), blurred vision (n = 1), vomiting (n = 2), increased AST (n = 1), increased alanine aminotransferase (n = 2), constipation (n = 1), and decreased appetite (n = 1).⁴¹ Grade 4 events were reported in 4 (7%) patients. In 10 (18%) patients, pneumonitis was reported, and 8 were grade 1 or grade 2. Two patients (4%) discontinued treatment: 1 due to grade 3 pneumonitis/grade 4 acute kidney injury, and 1 due to grade 3 pleurisy/grade 1 pneumonitis.⁴¹ In the overall population, ORR was 30%, median PFS was 4.2 months, and median DOR was 6.9 months.⁴¹ In 39 patients with medium-to-high FR α expression (defined as $\geq 50\%$ tumor cells with $\geq 2+$ staining intensity by IHC), median ORR was 31%, median DOR was 8.1 months, and median PFS was 5.5 months.⁴¹ Overall, the tumor shrinkage of the target lesions was observed in 83% of patients.⁴¹ In summary, the safety profile of mirvetuximab soravtansine in combination with pembrolizumab is consistent with AEs expected of each individual agent.⁴¹ Pneumonitis may represent a potential overlapping toxicity.⁴¹ Clinical activity of the combination is encouraging, especially in heavily pretreated patients.⁴¹

Mirvetuximab Soravtansine and PLD

During the FORWARD II dose-escalation phase, mirvetuximab soravtansine dosing was escalated from 5 mg/kg to 6 mg/kg, and PLD dosing was escalated from 30 mg/m² to 40 mg/m².³⁸ The most common AEs in 16 patients were diarrhea (56%), constipation (50%), fatigue (44%), and nausea (44%).³⁸ Grade 3 or higher anemia (13%) and vomiting (13%) were also observed. In summary, the AE profiles were as expected from the known tolerability profiles of each agent, and no new safety signals were identified.³⁸

Mirvetuximab Soravtansine + Carboplatin in Patients With Platinum-Sensitive Ovarian Cancer

The mirvetuximab soravtansine + carboplatin arm in FORWARD II was conducted in platinum-sensitive patients.³⁸ During the escalation phase in FORWARD II, mirvetuximab soravtansine dosing was escalated from 5 mg/kg to 6 mg/kg. Carboplatin dosing was escalated from AUC4 to AUC5.³⁸ The patients who received the combination (n = 18) had a median of 2.5 (range, 1-6) lines of prior therapy.⁴² The most

common AEs were nausea (67%), diarrhea (61%), thrombocytopenia (61%), and blurred vision (61%). Most AEs were grade 1 or 2.⁴² Grade 1 or 2 keratopathy occurred in 4 patients (22%); all incidences were reversible.⁴² Occurrences of peripheral neuropathy (28%) were mostly reported as grade 1. Fatigue (56%) and neutropenia (56%) were also seen, with 1 patient experiencing grade 4 neutropenia.⁴² Confirmed ORR was 71%, and the median PFS was 15 months.⁴¹ This clinical activity compared favorably with benchmark values of 9.4 to 10.4 months for conventional carboplatin/paclitaxel therapy and 8.4 months observed with carboplatin/gemcitabine.⁴¹ Three CRs occurred, all in patients with high FR α , affirming the relationship between FR α expression and response.⁴²

Additional Exploratory Combinations

Additional regimens with mirvetuximab soravtansine in combination with established anticancer agents are underway. Mirvetuximab soravtansine in combination with gemcitabine is being evaluated in a dose-escalation phase I study in patients with FR α -positive recurrent ovarian, fallopian tube, primary peritoneal, endometrial, or triple-negative breast cancer.⁴³ The enrollment goal is 44 participants.⁴³ The primary objective is to determine the maximum tolerated dose and recommended phase II dose of the mirvetuximab soravtansine + gemcitabine combination in this patient population.⁴³

The combination of mirvetuximab soravtansine with rucaparib is also being explored in a dose-escalation and dose-expansion phase I study in patients with recurrent endometrial cancer and recurrent platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer.⁴⁴ Included patients must have FR α expression as assessed by IHC ($\geq 25\%$ of tumor cells with $\geq 2+$ staining intensity). The enrollment goal is 42 participants.⁴⁴ The primary objective is to determine the recommended phase II dose of the mirvetuximab soravtansine + rucaparib combination. See [Table](#) for a listing of current mirvetuximab soravtansine combination trials.^{37,42,43}

Conclusions

Relapsed ovarian cancer carries a dismal prognosis. Effective and tolerable agents used to treat this disease represent a significant unmet medical need. FR α is an attractive tumor-associated antigen and a candidate for the development of targeted therapies for this patient population. The results of trials with early FR α -targeted agents, such as farletuzumab and vintafolide, were met with disappointment due to the inability to demonstrate superiority over conventional chemotherapy. Mirvetuximab soravtansine is the first-in-class FR α -targeted ADC. Early clinical studies of mirvetuximab soravtansine monotherapy demonstrated a favorable tolerability profile and encouraging antitumor activity in patients with relapsed platinum-resistant ovarian cancer. These studies also provide data for optimal patient selection for mirvetuximab soravtansine. Notably, patients with tumors that express high levels of FR α and patients who have been less heavily pretreated (1-3 prior lines of therapy) seem to have the best PFS and ORR.

The full results from FORWARD I and the likely subsequent confirmatory trials may help to define the therapeutic role of targeting FR α . Moreover, the combination of mirvetuximab soravtansine and other established therapeutics are actively under investigation. Initial data have shown tolerability with mirvetuximab soravtansine combined with other antitumor agents at full doses. The robust efficacy signals

that have emerged thus far suggest that mirvetuximab soravtansine and FR α -targeting therapies hold promise for a patient population with limited treatment options.

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