


Phase 1 Dose-Escalation Study of Mirvetuximab Soravtansine (IMGN853), a Folate Receptor α -Targeting Antibody-Drug Conjugate, in Patients With Solid Tumors

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BACKGROUND: Mirvetuximab soravtansine (IMGN853) is an antibody-drug conjugate that selectively targets folate receptor α (FR α). In this phase 1 dose-escalation study, the authors investigated IMGN853 in patients with FR α -positive solid tumors. **METHODS:** Patients received IMGN853 on day 1 of a 21-day cycle (once every 3 weeks dosing), with cycles repeated until patients experienced dose-limiting toxicity or progression. Dose escalation commenced in single-patient cohorts for the first 4 planned dose levels and then followed a standard 3 + 3 scheme. The primary objectives were to determine the maximum tolerated dose and the recommended phase 2 dose. Secondary objectives were to determine safety and tolerability, to characterize the pharmacokinetic profile, and to describe preliminary clinical activity. **RESULTS:** In total, 44 patients received treatment at doses escalating from 0.15 to 7.0 mg/kg. No meaningful drug accumulation was observed with the dosing regimen of once every 3 weeks. The most common treatment-related adverse events were fatigue, blurred vision, and diarrhea, the majority of which were grade 1 or 2. The dose-limiting toxicities observed were grade 3 hypophosphatemia (5.0 mg/kg) and grade 3 punctate keratitis (7.0 mg/kg). Two patients, both of whom were individuals with epithelial ovarian cancer, achieved confirmed tumor responses according to Response Evaluation Criteria in Solid Tumors 1.1, and each was a partial response. **CONCLUSIONS:** IMGN853 demonstrated a manageable safety profile and encouraging preliminary clinical activity, particularly in patients with ovarian cancer. The results establish a recommended phase 2 dosing of 6.0 mg/kg (based on adjusted ideal body weight) once every 3 weeks. *Cancer* 2017;000:000-000. © 2017 American Cancer Society.

KEYWORDS: antibody-drug conjugate, clinical trial, folate receptor, phase 1, targeted therapy.

INTRODUCTION

The use of chemotherapeutic drugs has long provided a foundation for systemic cancer therapy; however, their effectiveness is commonly hampered because of dose-limiting toxicities (DLTs) that arise as a consequence of adverse effects on normal tissues. In addition, standard-of-care treatments for a large number of human malignancies involve multidrug combinations, and these typically require further dose reductions to maintain an acceptable tolerability profile for patients.¹ In an effort to overcome these limitations, various tumor-selective drug-delivery strategies have been developed that are designed to deliver cytotoxic amounts of therapeutic agents directly to tumors.²⁻⁴ In this regard, significant translational progress has been achieved in the field of antibody-drug conjugate (ADC) technology. ADCs provide targeted delivery of cytotoxic agents through linkage to monoclonal antibodies directed against tumor-associated antigens, thereby affording a means to minimize toxicities of highly potent drugs in normal tissues while maintaining or improving their antitumor efficacy.^{5,6}

Folate receptor α (FR α) is a member of a family of cell-surface glycoproteins that facilitate the transport and accumulation of folate, through endocytosis, into cells.⁷ In contrast to its highly restricted expression pattern in normal tissues,^{7,8} FR α is aberrantly expressed in a variety of epithelial tumors.⁹ Indeed, high receptor expression is characteristic of several common human malignancies, including ovarian cancer, endometrial cancer, and nonsmall cell lung cancer (NSCLC).¹⁰

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Additional supporting information may be found in the online version of this article.

DOI: 10.1002/cncr.30736, **Received:** November 3, 2016; **Revised:** February 2, 2017; **Accepted:** March 20, 2017, **Published online** Month 00, 2017 in Wiley Online Library (wileyonlinelibrary.com)

Therefore, FR α has emerged as an attractive candidate for molecularly targeted strategies designed to exploit this differential distribution pattern to maximize both antitumor efficacy and tolerability. Consequently, several experimental folate receptor-targeting agents are now under clinical evaluation.⁹⁻¹¹ The 2 primary approaches explored to date have involved either targeted cytotoxic drug delivery through small-molecule folate-cytotoxic agent conjugates, such as vintafolide,^{12,13} or the use of humanized anti-FR α monoclonal antibodies, exemplified by farletuzumab,¹⁴ intended to selectively induce tumor cell death. Unfortunately, neither approach has demonstrated meaningful efficacy in pivotal ovarian cancer trials to date.^{15,16} Of particular note, the ability of FR α to internalize large-molecule ligands underscores the potential utility of this receptor as a target for ADC-based therapeutic interventions, which couple the targeting and pharmacokinetic (PK) features of an antibody with the cancer-killing impact of a cytotoxic agent.

Mirvetuximab soravtansine (IMGN853) is an ADC comprised of a humanized anti-FR α monoclonal antibody (M9346A) linked to a cytotoxic effector molecule, the maytansinoid DM4.^{11,17} IMGN853 binds with high affinity and specificity to FR α , which upon antigen binding, promotes ADC internalization and intracellular release of DM4.¹⁸ Through its ability to inhibit tubulin polymerization and disrupt microtubule assembly, DM4 serves as a potent antimetabolic agent to induce cell cycle arrest and apoptosis.¹⁹ Preclinically, IMGN853 has exhibited robust antitumor activity against FR α -expressing tumors, including models of ovarian cancer and NSCLC.²⁰

Here, we present the dose-escalation phase of the first-in-human clinical evaluation of IMGN853 monotherapy in patients with advanced, FR α -positive solid tumors who were refractory to standard therapies. The primary objectives of this phase 1 study were to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RPD2) of IMGN853 administered intravenously once every 3 weeks. Secondary objectives included an evaluation of the safety, tolerability, and plasma pharmacokinetics of IMGN853 as well as any preliminary evidence of clinical activity.

MATERIALS AND METHODS

Patient Selection and Eligibility Criteria

Adults with pathologically confirmed, advanced solid tumors who were refractory to conventional therapy, or for whom standard treatments were either not available or

not an option, were eligible for inclusion. Enrollment without prior documentation of tumor FR α expression was limited to patients with the following tumor histologic subtypes, characterized by a high incidence of FR α -positivity: epithelial ovarian cancer (EOC) (serous or endometrioid), primary peritoneal cancer, fallopian tube cancer, serous or endometrioid endometrial cancer, NSCLC (adenocarcinoma or bronchoalveolar carcinoma), and renal cell cancer. Patients had measurable or nonmeasurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.²¹ Patients were also required to be age 18 years or older; to have an Eastern Cooperative Oncology Group performance status 0 or 1; and to have adequate hematologic, renal, and hepatic function. Key exclusion criteria included grade >1 neuropathy, known hypersensitivity to monoclonal antibody or maytansinoid therapy, any active or chronic corneal disorder, a history of other solid tumor malignancy with a disease-free interval <3 years (except for adequately treated basal cell or squamous cell skin cancer and in situ breast or prostate cancer), concomitant administration of folate-containing vitamins, or prior allogeneic or autologous bone marrow transplantation. All patients provided written informed consent in accordance with federal, local, and institutional guidelines.

Study Design and Treatment Administration

The primary objectives of this open-label, phase 1, dose-escalation study were to determine the MTD and the RPD2 of single-agent IMGN853 in patients with solid tumors. Secondary objectives were to evaluate safety and tolerability, characterize the PK profile, and describe any preliminary clinical activity. IMGN853 was administered intravenously once every 3 weeks (ie, on day 1 of a 21-day cycle). Escalated doses for this schedule were 0.15, 0.5, 1.0, 2.0, 3.3, 5.0, and 7.0 mg/kg, with 1 patient enrolled at each of the first 4 dose levels. Beyond this, a standard 3 + 3 design was used. Initially, administered doses were calculated on total body weight (TBW); however, early analyses revealed dose-dependent and exposure-dependent correlations with ocular adverse events (AEs). In an effort to minimize the total milligram dose administered across the wide weight range of patients (range, 48.2-135.8 kg) and to decrease the incidence of ocular toxicity, dosing was modified to use the adjusted ideal body weight (AIBW).

Study treatment continued until patients developed progressive disease, had unacceptable toxicity, withdrew consent, or died. Patients were followed for 28 days after the last dose of study drug or until they recovered from

any treatment-related toxicity, whichever came first. The trial was conducted in accordance with US Food and Drug Administration regulations, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. The study was compliant with all relevant Institutional Review Board and Independent Ethics Committee requirements and is registered at clinicaltrials.gov (NCT01609556).

Assessments

Baseline assessments included medical history and physical examination, Eastern Cooperative Oncology Group performance status, blood chemistry and hematology, serum pregnancy test, and electrocardiogram. During screening, radiologic imaging studies of the chest, abdomen, and pelvis for tumor evaluation were obtained. For patients who had measurable disease, overall tumor response was defined according RECIST 1.1 and was assessed using computerized tomography scans approximately every second cycle from the date of first dose to the 28-day follow-up visit. Patients with ovarian and endometrial cancers had concomitant cancer antigen 125 (CA 125) measurements taken approximately at the time of radiologic assessment. In accordance with Gynecologic Cancer Intergroup guidelines, a CA 125 response was defined as a reduction $\geq 50\%$ in the CA 125 level from pretreatment sampling that was confirmed and maintained for ≥ 28 days.

Toxicities were graded according to the National Cancer Institute *Common Terminology Criteria for Adverse Events*, version 4.0 and were monitored continuously throughout the study from the time of the first study dose until 28 days after treatment cessation. Serious AEs (SAEs) were defined as any AE that was fatal or life-threatening, required prolonged existing hospitalization, resulted in persistent or significant disability/incapacity, or required medical or surgical intervention. A DLT was defined as grade 4 neutropenia for ≥ 7 days; grade ≥ 3 neutropenia with fever; grade 3 thrombocytopenia accompanied by bleeding; grade 4 thrombocytopenia; or any grade ≥ 3 nonhematologic toxicity considered related to IMGN853 (other than nausea, vomiting, or diarrhea in the absence of appropriate prophylaxis; AEs related to underlying disease; or grade 3 fatigue).

Pharmacokinetics

Blood samples for PK analysis were collected after the first and third doses. Collection times were as follows: predose; end of infusion; and 2, 4, 24, 48, and 96 hours or 120, 168, 336, and 504 hours postdose. For the third dose on

day 15, an additional sample was also taken 336 hours postdose. Plasma samples were analyzed for concentrations of IMGN853 using a validated enzyme-linked immunosorbent assay method. The assay was validated in the range from 75 to 2500 ng/mL, with a lower limit of quantification of 75 ng/mL, using a 20- μ L sample volume. PK parameters were calculated by noncompartmental methods using Phoenix WinNonlin Version 6.4 (Certara, Princeton, NJ).

Statistical Analysis

The period of patient accrual spanned from July 2012 to March 2015, and the data analysis extended to April 2016. Descriptive statistics were used to summarize demographic and baseline characteristics, and additional analyses were performed using SAS statistical software (version 9.4; SAS Inc., Cary, NC). For the safety evaluations, baseline was defined as the last available assessment before day 1, cycle 1; and any AE with an onset date that was the same as the start of study treatment or later was reported as treatment-emergent. The safety population included all patients who received at least 1 dose of IMGN853. Tumor response was based on all patients who had received at least 1 dose of study drug and from whom at least 1 tumor assessment evaluation was attained.

RESULTS

Patient Characteristics

Forty-four patients were enrolled and received treatment using the once every 3 weeks dosing schedule. Patient demographics and baseline characteristics are summarized in Table 1. The median age was 58 years (range, 37-86 years), and the majority of patients were women (89%) who were diagnosed with either recurrent ovarian (52%) or endometrial (25%) cancer. Renal cell carcinoma and NSCLC (11% and 9%, respectively) accounted for non-gynecologic malignancies that were included in the trial. All individuals were heavily pretreated, having received a median of 5 prior systemic therapies (range, 1-14 prior systemic therapies), and greater than 84% had previous platinum and/or taxane exposure.

Dose Escalation, MTD, and RP2D

Dose escalation is summarized in Table 2. DLTs were assessed only during the first cycle of treatment. IMGN853 dosing was initially escalated from 0.15 to 7.0 mg/kg (based on TBW). The first 4 treatment groups (0.15, 0.5, 1.0, and 2.0 mg/kg) were single-patient cohorts, with the exception of the initial 0.15 mg/kg level

TABLE 1. Patient Demographics and Baseline Characteristics (N = 44)

Characteristic	No. of Patients (%)
Age: Median [range], y	58 [37-86]
Sex	
Men	5 (11.4)
Women	39 (88.6)
Race	
White	41 (93.2)
Black or African American	2 (4.5)
Asian	1 (2.3)
Tumor type	
Ovarian cancer	23 (52.3)
Endometrial	11 (25)
NSCLC adenocarcinoma	4 (9.1)
Renal cell cancer	5 (11.4)
Cervical cancer	1 (2.3)
ECOG PS	
0	22 (50)
1	22 (50)
Prior compound exposure	
Platinum	38 (86.4)
Taxane	37 (84.1)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status. NSCLC, nonsmall cell lung cancer.

(n = 2), in which the first patient enrolled progressed within cycle 1 and was replaced. No DLTs were observed at any of these dose levels. Similarly, no DLTs were observed in the first 3 patients who received with IMGN853 at either 3.3 or 5 mg/kg, and escalation proceeded to 7.0 mg/kg. At that dose level, 1 of 5 patients experienced a DLT of grade 3 punctate keratitis. Accordingly, the dose was reduced to 5.0 mg/kg, which was received by a total of 11 patients. In this cohort, dose-limiting grade 3 hypophosphatemia was observed, along with additional ocular AEs that arose during the second cycle. These factors contributed to a further reduction back to 3.3 mg/kg dosing. No further DLTs were observed in this treatment population (n = 6).

A modification in dosing based on AIBW instead of TBW was implemented to decrease the range of variance in interpatient drug exposures.²² This was designed to improve tolerability, particularly with respect to the incidence of visual disturbances (primarily blurred vision; see below) reported at the higher dose levels. Subsequently enrolled patients received IMGN853 at 5.0 and 6.0 mg/kg AIBW (n = 7 per group). No DLTs were observed, and the 6.0 mg/kg (AIBW) dose was declared to be the RP2D for the once every 3 weeks dosing regimen. No further escalation occurred beyond this level in an effort to decrease the likelihood of ocular AEs events; accordingly, the MTD was not reached on this schedule.

TABLE 2. Summary of IMGN853 Dose Escalation

IMGN853 Dose, mg/kg	No. of Patients	DLTs and Treatment-Related SAEs
0.15 ^a	2 ^b	None
0.5 ^a	1	None
1.0 ^a	1	None
2.0 ^a	1	None
3.3 ^a	9	None
5.0 ^a	11	DLT, grade 3 hypophosphatemia; SAE, grade 3 corneal opacity
7.0 ^a	5	DLT, grade 3 punctate keratitis
5.0	7	SAE, grade 3 pulmonary edema
6.0	7	None

Abbreviations: DLT, dose-limiting toxicity; IMGN853, mirvetuximab soravtansine; SAE, severe adverse event.

^aThese patients were dosed based on total body weight, and others were dosed according to adjusted ideal body weight.

^bThe original patient enrolled in this cohort progressed during cycle 1 and was replaced. Patients in this initial cohort were monitored for a safety assessment period of 28 days.

Safety

All 44 patients were included in the safety analyses. The most common treatment-emergent AEs (TEAEs) that occurred in $\geq 10\%$ of patients (all grades) are presented in Supporting Table 1 (see online supporting information). The most frequently reported TEAEs included diarrhea (34%), fatigue (32%), and nausea and blurred vision (25% each); the majority of these were generally mild (grade 1 or 2). In total, 33 patients (75%) had a TEAE that was deemed related to study drug. The majority of these were either grade 1 or 2. Treatment-related TEAEs that occurred in $>10\%$ of patients are listed in Table 3. The major adverse reactions observed across the study population were fatigue (25%), blurred vision (23%), and diarrhea and peripheral neuropathy (21% each). Six patients overall (14%) reported a grade 3 TEAE, and no individual event occurred in more than 1 patient. One patient experienced a grade 4 TEAE (decreased lymphocyte count), and no fatalities caused by related TEAEs were reported during the study.

Treatment-related SAEs were reported in 4 individuals (9%). These included DLTs of grade 3 hypophosphatemia and punctate keratitis and 1 episode each of grade 3 corneal opacity and pulmonary edema (Table 2). The corneal abnormalities, along with the blurred-vision TEAEs reported above, were reversible.

Pharmacokinetics

PK evaluations were based on all 44 patients who received treatment with IMGN853. The mean plasma concentration-time profiles of IMGN853 for cycles 1 and 3 are presented in Figure 1, and PK parameters are

TABLE 3. Treatment-Related, Treatment-Emergent Adverse Events Reported in $\geq 10\%$ of Patients

Adverse Event	Total, n = 44	IMGN853 Dose, mg/kg: No. of Patients (%)				
		0.15-2.0, n = 5 ^a	3.3, n = 9	5.0, n = 18 ^b	6.0, n = 7	7.0, n = 5
Fatigue	11 (25)	0 (0)	2 (22.2)	3 (16.7)	3 (42.9)	3 (60)
Vision blurred	10 (22.7)	0 (0)	0 (0)	3 (16.7)	2 (28.6)	5 (100)
Diarrhea	9 (20.5)	0 (0)	1 (11.1)	6 (33.3)	1 (14.3)	1 (20)
Peripheral neuropathy ^c	9 (20.5)	0 (0)	2 (22.2)	4 (22.2)	1 (14.3)	2 (40)
ALT increased	7 (15.9)	0 (0)	0 (0)	4 (22.2)	1 (14.3)	2 (40)
Keratopathy ^d	7 (15.9)	0 (0)	0 (0)	3 (16.7)	2 (28.6)	2 (40)
AST increased	6 (13.6)	0 (0)	1 (11.1)	3 (16.7)	0 (0)	2 (40)
Headache	5 (11.4)	0 (0)	1 (11.1)	3 (16.7)	0 (0)	1 (20)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; IMGN853, mirvetuximab soravtansine.

^aThe include patients who received IMGN853 at doses of 0.15, 0.5, 1.0, and 2.0 mg/kg.

^bThese include the initial 11 patients who were dosed based on total body weight and the additional 7 who were dosed according to adjusted ideal body weight.

^cThese events include neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, and hypoesthesia.

^dThese events include corneal epithelial microcysts, corneal opacity, corneal erosion, corneal pigmentation, and punctate keratitis.

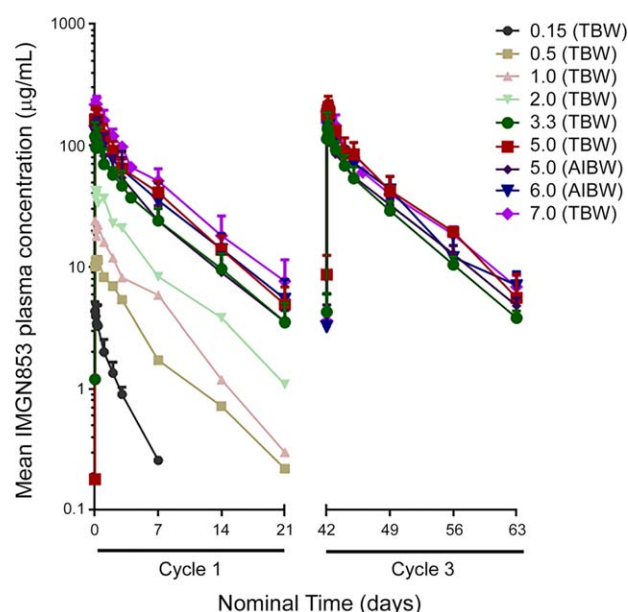


Figure 1. Mean concentration-time profiles are illustrated in cycles 1 and 3 after infusion of mirvetuximab soravtansine in dosing schedule of once every 3 weeks. All doses listed are in mg/kg and were calculated based on total body weight (TBW) or adjusted ideal body weight (AIBW), as indicated.

reported in Supporting Table 2 (see online supporting information). After the first administration of IMGN853, mean exposure (maximum plasma concentration [C_{max}] and area under the concentration-time curve from zero to infinity [$AUC_{0-\infty}$]) increased with dose in a generally proportional manner from 1.0 to 7.0 mg/kg. For cycle 1, the mean half-life ($t_{1/2}$) values for IMGN853 ranged from approximately 79 hours to 121 hours across doses, with no meaningful dose-dependence noted in total clearance (CL) or volume of distribution (V_{ss}) for cohorts that

received ≥ 1.0 mg/kg. In the 2 lowest dose cohorts examined (ie, 0.15 and 0.5 mg/kg), there appeared to be a trend toward higher CL; however, because of low patient numbers in these groups, definitive conclusions were not possible. After multiple doses, there appeared to be a trend toward time-dependent changes in CL (decreasing) and V_{ss} (decreasing), leading to a slight increase in $t_{1/2}$ by cycle 3. However, the exposure metrics at cycle 3 indicated that there was no meaningful accumulation after multiple doses of IMGN853.

Clinical Activity

Forty-three patients were evaluable for best response to therapy by RECIST and/or CA 125 response. Confirmed tumor responses were observed in 2 patients, both comprising partial responses (PRs), for an objective response rate (ORR) of 5%. Each of these involved patients with EOC, including 1 who remained on treatment for 33 weeks. Stable disease (SD) was observed in an additional 22 patients, including 4 who had SD that lasted ≥ 4 months. Five patients (4 with EOC and 1 with endometrial cancer) experienced a confirmed CA 125 response, resulting in an overall clinical benefit rate (ORR + SD ≥ 4 months + CA 125 response) of 23% (Table 4).

An example of a radiologic response is provided in Figure 2. This case involved a heavily pretreated woman aged 65 years who was diagnosed with platinum-resistant, transitional cell ovarian cancer in 2008 and who had received 3 previous lines of chemotherapy before receiving treatment with IMGN853 at 7.0 mg/kg (TBW). The patient achieved a PR after 2 cycles, which was subsequently confirmed at cycle 4.

DISCUSSION

Here, we report dose-escalation findings from the first-in-human phase 1 study of IMGN853, an FR α -targeting ADC, administered to heavily pretreated patients with advanced solid tumors. Systemic exposure to IMGN853, assessed by C_{\max} and $AUC_{0-\infty}$, increased in a generally dose-proportional manner across the 1.0 to 7.0 mg/kg range. It is noteworthy that the terminal half-life of IMGN853 determined at doses ≥ 1.0 mg/kg demonstrated no dose dependence with respect to clearance or volume of distribution parameters. In addition, no meaningful drug accumulation was observed with this dosing regimen.

IMGN853 was well tolerated, with escalation proceeding to doses of 5.0 and 7.0 mg/kg (TBW) before DLTs were observed. After the modification to AIBW-based calculations, patients received doses of 5.0 and 6.0

mg/kg. No DLTs or SAEs were reported in the 6.0-mg/kg AIBW cohort; and, based on a collective evaluation of safety, activity, and PK data, this dose was declared the RP2D. It is worth noting that, after the escalation stage of the current study, this RP2D has been used in several expansion cohorts, in which its tolerability has been confirmed.

The most frequent treatment-related AEs observed with IMGN853 included mild (primarily grade 1 or 2) fatigue and diarrhea, which were readily managed without requiring discontinuation of therapy. We note that this safety profile was similar to that reported during the phase 1 evaluation of farletuzumab, but without the high incidence of hypersensitivity and infusion-related reactions.^{23,24} Peripheral neuropathy, typically associated with cytotoxic chemotherapy, was experienced by 9 patients (21%), 5 of whom had a prior history of neuropathy after previous platinum/taxane therapy. All episodes were either grade 1 or 2 and were likely a consequence of the maytansinoid payload in IMGN853.²⁵

Ocular TEAEs, which primarily included reversible blurred vision and/or keratopathy, were considered AEs of interest in the current study. Although these have been reported for a diverse range of ADCs targeting different antigens and using different cytotoxic payloads, the molecular mechanisms underlying such events remain poorly defined.²⁶ Grade 3 punctate keratitis and corneal opacity were reported as a DLT and an SAE in individuals who received 7.0 and 5.0 mg/kg, respectively, once every 3 weeks. It is important to note that IMGN853 dosing in these particular patients was calculated based on TBW; PK analysis subsequently suggested an association between the AEs and initial exposure to higher plasma levels of IMGN853 when TBW dosing was used. In an effort to decrease variability in exposure levels, AIBW dosing

TABLE 4. Patients With Clinical Benefit

IMGN853 Dose, mg/kg	Diagnosis	Clinical Benefit ^a	Duration on Study, wk
3.3	EOC	CA 125 response	15
	EOC	PR	33
	NSCLC	SD ≥ 4 mo	21
5.0	EOC	CA 125 response	19
	EOC	SD ≥ 4 mo	29
	Endometrial	CA 125 response	16
	Endometrial	SD ≥ 4 mo	28
6.0	EOC	CA 125 response	9
7.0	EOC	PR	23
	EOC	CA 125 response, SD ≥ 4 mo	23

Abbreviations: CA 125, cancer antigen 125; EOC, epithelial ovarian cancer; IMGN853, mirvetuximab soravtansine; NSCLC, nonsmall cell lung cancer; PR, partial response; SD, stable disease.

^aClinical benefit was defined as a confirmed objective response (complete or partial response) according to Response Evaluation Criteria in Solid Tumors 1.1; a CA 125 response according to Gynecologic Cancer Inter-group criteria, or SD ≥ 4 months.

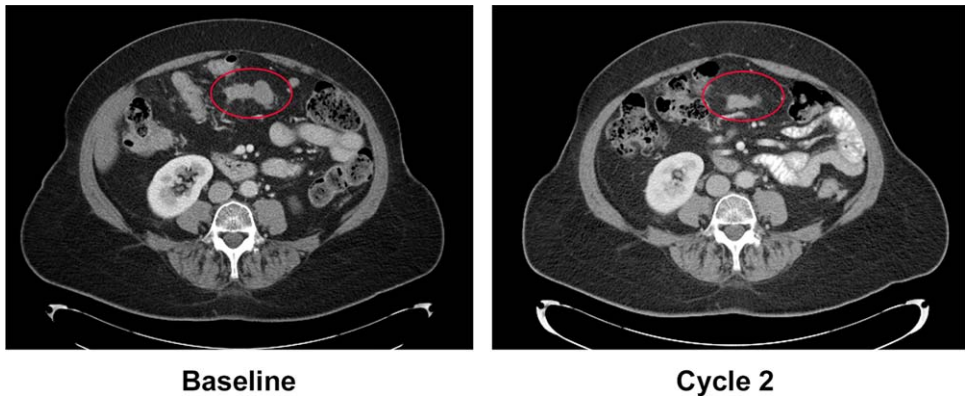


Figure 2. The activity of mirvetuximab soravtansine in a patient who had platinum-resistant ovarian cancer reveals a partial response.

was subsequently used for the duration of the study. After this change, the visual and corneal abnormalities observed were generally mild (grade ≤ 2) and were similar to those reported for other DM4-conjugated antibodies.²⁷ These effects appeared to be independent of the target antigen, consistent with the profile observed for other ADCs, because FR α does not exhibit significant expression in the eye. In addition to the inherent potential toxicity of the payload, it has been proposed that such events may also be a function of the linker used for drug attachment, because prolonged retention in the circulation conferred by stable linkers may be sufficient to enhance overall exposure in normal (including ocular) tissues.²⁸

Clinical benefit from IMGN853 monotherapy was observed across a range of solid tumor types, most notably within the subset of patients with EOC. Ovarian cancer represents an attractive indication for the application of folate receptor-targeting therapeutics,^{29,30} in part because of the high constitutive expression of FR α (approximately 80% of nonmucinous tumors) in this malignancy³¹—a feature that also has been proposed as a negative prognostic factor with respect to patient response to chemotherapeutics.³² RECIST-defined objective responses (PRs) were reported in 2 patients with EOC, with individuals remaining on study for periods ranging between 23 and 33 weeks. Clinical benefit was observed in additional patients with EOC, including 4 who had confirmed CA 125 responses and 2 with SD that lasted >4 months. On the basis of these findings, an expansion cohort evaluating the safety and efficacy of IMGN853 in a population of patients with FR α -positive, platinum-resistant ovarian cancer was opened as part of the current trial.³³

Overall, the results of this study support the continued exploration of IMGN853 as a novel, FR α -targeting therapeutic based on its favorable tolerability and encouraging signs of clinical efficacy, particularly in patients with ovarian cancer. The RP2D is 6 mg/kg AIBW administered once every 3 weeks. The trial is continuing, including an expansion cohort focused on the prophylactic use of corticosteroid eye drops for the management of ocular disorders. Moreover, additional trials of IMGN853 in advanced ovarian cancer have recently been initiated, including a pivotal phase 3 monotherapy trial in patients with platinum-resistant disease (FORWARD I; clinicaltrials.gov identifier NCT02631876) as well as a phase 1b study in which it is being evaluated in combination with both standard-of-care chemotherapeutics and targeted agents (FORWARD II; clinicaltrials.gov identifier NCT02606305).

FUNDING SUPPORT

This work was funded by ImmunoGen, Inc.

CONFLICT OF INTEREST DISCLOSURES

Kathleen N. Moore reports honoraria for advisory board service from AstraZeneca, Clovis, Immunogen, and Genentech/Roche; service on the Tesaro steering committee; and service on the Advaxis steering committee/advisory board outside the submitted work. Hossein Borghaei reports personal fees from and service on the advisory boards of Genentech, Lilly, Bristol-Myers-Squibb, Celgene, and Clovis; personal fees from AstraZeneca, Pfizer, Merck, EMD-Serono, and Trovogene; and clinical trial funding from Merck/Celgene and Millennium outside the submitted work. David M. O'Malley reports personal fees from Clovis, Janssen, AstraZeneca, Genentech/Roche, Amgen, and Eisai outside the submitted work. Shelly M. Seward reports service on the AstraZeneca Speakers' Bureau. Ursula A. Matulonis reports service on the advisory boards of AstraZeneca, Clovis, Eli Lilly, Genentech, and Immunogen outside the submitted work. Kelli L. Running reports employment at ImmunoGen. Xiaoyan Zhang reports employment at ImmunoGen. Jose F. Ponte reports employment at ImmunoGen and has a patent pending (US. Pub. no. 2015 of 0132323; International Pub. no. WO2015 of 054400). Rodrigo Ruiz-Soto reports employment at ImmunoGen. Woondong Jeong, Todd M. Bauer, Raymond P. Perez, and Michael J. Birrer made no disclosures.

AUTHOR CONTRIBUTIONS

Kathleen N. Moore: Conceptualization, methodology, formal analysis, investigation, data curation, writing—original draft, and writing—review and editing. **Hossein Borghaei, David M. O'Malley, Woondong Jeong, Shelly M. Seward, Todd M. Bauer, Raymond P. Perez, and Ursula A. Matulonis:** Investigation, formal analysis, data curation, and writing—review and editing. **Kelli L. Running, Xiaoyan Zhang, Jose F. Ponte, and Rodrigo Ruiz-Soto:** Conceptualization, methodology, formal analysis, data curation, writing—original draft, and writing—review and editing. **Michael J. Birrer:** Conceptualization, methodology, formal analysis, investigation, data curation, and writing—review and editing.

REFERENCES

- Frei E 3rd, Elias A, Wheeler C, Richardson P, Hryniuk W. The relationship between high-dose treatment and combination chemotherapy: the concept of summation dose intensity. *Clin Cancer Res*. 1998;4:2027-2037.
- Chari RV. Targeted cancer therapy: conferring specificity to cytotoxic drugs. *Acc Chem Res*. 2008;41:98-107.
- Yewale C, Baradia D, Vhora I, Misra A. Proteins: emerging carrier for delivery of cancer therapeutics. *Expert Opin Drug Deliv*. 2013;10:1429-1448.
- Mukherjee B, Karmakar SD, Hossain CM, Bhattacharya S. Peptides, proteins and peptide/protein-polymer conjugates as drug delivery system. *Protein Pept Lett*. 2014;21:1121-1128.
- Chari RV, Miller ML, Widdison WC. Antibody-drug conjugates: an emerging concept in cancer therapy. *Angewandte Chemie*. 2014;53:3796-3827.
- Chudasama V, Maruani A, Caddick S. Recent advances in the construction of antibody-drug conjugates. *Nat Chem*. 2016;8:114-119.
- Elnakat H, Ratnam M. Distribution, functionality and gene regulation of folate receptor isoforms: implications in targeted therapy. *Adv Drug Deliv Rev*. 2004;56:1067-1084.

8. Salazar MD, Ratnam M. The folate receptor: what does it promise in tissue-targeted therapeutics? *Cancer Metastasis Rev.* 2007;26:141-152.
9. Assaraf YG, Leamon CP, Reddy JA. The folate receptor as a rational therapeutic target for personalized cancer treatment. *Drug Resist Updat.* 2014;17:89-95.
10. Ledermann JA, Canevari S, Thigpen T. Targeting the folate receptor: diagnostic and therapeutic approaches to personalize cancer treatments. *Ann Oncol.* 2015;26:2034-2043.
11. Lutz RJ. Targeting the folate receptor for the treatment of ovarian cancer. *Transl Cancer Res.* 2015;4:118-126.
12. Dosio F, Milla P, Cattel L. EC-145, a folate-targeted Vinca alkaloid conjugate for the potential treatment of folate receptor-expressing cancers. *Curr Opin Investig Drugs.* 2010;11:1424-1433.
13. Ambrosio AJ, Suzin D, Palmer EL, Penson RT. Vintafolide (EC145) for the treatment of folate-receptor-alpha positive platinum-resistant ovarian cancer. *Expert Rev Clin Pharmacol.* 2014;7:443-450.
14. Spannuth WA, Sood AK, Coleman RL. Farletuzumab in epithelial ovarian carcinoma. *Expert Opin Biol Ther.* 2010;10:431-437.
15. Vergote I, Armstrong D, Scambia G, et al. A randomized, double-blind, placebo-controlled, phase III study to assess efficacy and safety of weekly farletuzumab in combination with carboplatin and taxane in patients with ovarian cancer in first platinum-sensitive relapse. *J Clin Oncol.* 2016;34:2271-2278.
16. Endocyte Inc. Merck and Endocyte Announce Independent DSMB Recommends Vintafolide PROCEED Phase 3 Trial Be Stopped for Futility Following Interim Analysis. Endocyte Inc. Available at: <http://investor.endocyte.com/releasedetail.cfm?ReleaseID=844838>. Accessed October 25, 2016.
17. Lambert JM. Drug-conjugated antibodies for the treatment of cancer. *Br J Clin Pharmacol.* 2013;76:248-262.
18. Erickson HK, Widdison WC, Mayo MF, et al. Tumor delivery and in vivo processing of disulfide-linked and thioether-linked antibody-maytansinoid conjugates. *Bioconjug Chem.* 2010;21:84-92.
19. Hong EE, Erickson H, Lutz RJ, et al. Design of coltuximab ravtansine, a CD19-targeting antibody-drug conjugate (ADC) for the treatment of B-Cell malignancies: structure-activity relationships and preclinical evaluation. *Mol Pharm.* 2015;12:1703-1716.
20. Ab O, Whiteman KR, Bartle LM, et al. IMGN853, a folate receptor-alpha (FRalpha)-targeting antibody-drug conjugate, exhibits potent targeted antitumor activity against FRalpha-expressing tumors. *Mol Cancer Ther.* 2015;14:1605-1613.
21. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45:228-247.
22. Moore KN, Ponte J, Lorusso PM, et al. Relationship of pharmacokinetics (PK), toxicity, and initial evidence of clinical activity with IMGN853, a folate receptor alpha (FRa) targeting antibody drug conjugate in patients (Pts) with epithelial ovarian cancer (EOC) and other FRa-positive solid tumors [abstract]. *J Clin Oncol.* 2014;32:15S. Abstract 5571.
23. Konner JA, Bell-McGuinn KM, Sabbatini P, et al. Farletuzumab, a humanized monoclonal antibody against folate receptor alpha, in epithelial ovarian cancer: a phase I study. *Clin Cancer Res.* 2010;16:5288-5295.
24. Sasaki Y, Miwa K, Yamashita K, et al. A phase I study of farletuzumab, a humanized anti-folate receptor alpha monoclonal antibody, in patients with solid tumors. *Invest New Drugs.* 2015;33:332-340.
25. Gomez-Roca CA, Boni V, Moreno V, et al. A phase I study of SAR566658, an anti CA6-antibody drug conjugate (ADC), in patients (Pts) with CA6-positive advanced solid tumors (STs) (NCT01156870) [abstract]. *J Clin Oncol.* 2016;34:15S Abstract 2511.
26. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. *J Ocul Pharmacol Ther.* 2015;31:589-604.
27. Parslow AC, Parakh S, Lee F, Gan HK, Scott AM. Antibody-drug conjugates for cancer therapy. *Biomedicines.* 2016;4:14.
28. Polakis P. Antibody drug conjugates for cancer therapy. *Pharmacol Rev.* 2016;68:3-19.
29. Marchetti C, Palaia I, Giorgini M, et al. Targeted drug delivery via folate receptors in recurrent ovarian cancer: a review. *Oncol Targets Ther.* 2014;7:1223-1236.
30. Vergote IB, Marth C, Coleman RL. Role of the folate receptor in ovarian cancer treatment: evidence, mechanism, and clinical implications. *Cancer Metastasis Rev.* 2015;34:41-52.
31. Kalli KR, Oberg AL, Keeney GL, et al. Folate receptor alpha as a tumor target in epithelial ovarian cancer. *Gynecol Oncol.* 2008;108:619-626.
32. Toffoli G, Russo A, Gallo A, et al. Expression of folate binding protein as a prognostic factor for response to platinum-containing chemotherapy and survival in human ovarian cancer. *Int J Cancer.* 1998;79:121-126.
33. Moore KN, Martin LP, O'Malley DM, et al. Safety and activity of mirvetuximab soravtansine (IMGN853), a folate receptor alpha-targeting antibody-drug conjugate, in platinum-resistant ovarian, fallopian tube, or primary peritoneal cancer: a phase I expansion study. *J Clin Oncol.* 2017;35:1112-1118.