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First-in-Human, Multicenter, Phase I Dose-Escalation and Expansion Study of Anti-Mesothelin Antibody–Drug Conjugate Anetumab Ravtansine in Advanced or Metastatic Solid Tumors

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abstract

PURPOSE This phase I study, which to our knowledge is the first-in-human study of this kind, investigates the safety, tolerability, pharmacokinetics, and clinical activity of anetumab ravtansine, an antibody–drug conjugate of anti-mesothelin antibody linked to maytansinoid DM4, in patients with advanced, metastatic, or recurrent solid tumors known to express the tumor-differentiation antigen mesothelin.

PATIENTS AND METHODS This phase I, open-label, multicenter, dose-escalation and dose-expansion study of anetumab ravtansine enrolled 148 adult patients with multiple solid tumor types. Ten dose-escalation cohorts of patients with advanced or metastatic solid tumors (0.15-7.5 mg/kg) received anetumab ravtansine once every 3 weeks, and 6 expansion cohorts of patients with advanced, recurrent ovarian cancer or malignant mesothelioma received anetumab ravtansine at the maximum tolerated dose once every 3 weeks, 1.8 mg/kg once per week, and 2.2 mg/kg once per week.

RESULTS Forty-five patients were enrolled across the 10 dose-escalation cohorts. The maximum tolerated dose of anetumab ravtansine was 6.5 mg/kg once every 3 weeks or 2.2 mg/kg once per week. Thirty-two patients were enrolled in the 6.5 mg/kg once-every-3-weeks, 35 in the 1.8 mg/kg once-per-week, and 36 in the 2.2 mg/kg once-per-week expansion cohorts. The most common drug-related adverse events were fatigue, nausea, diarrhea, anorexia, vomiting, peripheral sensory neuropathy, and keratitis/keratopathy. There were no drug-related deaths. Anetumab ravtansine pharmacokinetics were dose proportional; the average half-life was 5.5 days. Among 148 patients with mesothelioma or ovarian, pancreatic, non–small-cell lung, and breast cancers, 1 had a complete response, 11 had partial responses, and 66 had stable disease. High levels of tumor mesothelin expression were detected in patients with clinical activity.

CONCLUSION Anetumab ravtansine exhibited a manageable safety and favorable pharmacokinetic profile with encouraging preliminary antitumor activity in heavily pretreated patients with mesothelin-expressing solid tumors. The results allowed for the determination of recommended doses, schedules, and patient populations for anetumab ravtansine in phase II studies.

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ASSOCIATED CONTENT

Data Supplement

Protocol

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

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INTRODUCTION

Mesothelin is a transmembrane tumor differentiation antigen that is highly expressed in many solid tumors, including mesothelioma (85%-90%) and pancreatic (80%-85%), ovarian (60%-65%), non–small-cell lung (57%-64%), stomach (50%-55%), and breast (25%-30%) cancers as assessed by immunohistochemistry (IHC).[1-8] The normal biologic function of mesothelin is not well characterized, but it may play an important role in tumor implantation and metastasis.[9,10] Mesothelin expression in normal tissues is limited, making it a suitable target for tumor-specific therapy. Previous studies using anti-mesothelin antibodies or immunotoxins have demonstrated the safety of targeting mesothelin.[11-13]

Anetumab ravtansine (BAY 94-9343) is an antibody–drug conjugate (ADC) comprising a fully human immunoglobulin G1 anti-mesothelin monoclonal antibody

CONTEXT

Key Objectives:

This dose-escalation, dose-expansion study, to our knowledge the first in humans, investigated the safety, tolerability, pharmacokinetics, activity, and immunogenicity of once every 3 weeks and once-weekly anetumab ravtansine, an antibody–drug conjugate of antimesothelin antibody linked to maytansinoid DM4, in patients with advanced mesothelin-expressing solid tumors (eg malignant mesothelioma and ovarian cancer).

Knowledge Generated:

Anetumab ravtansine was well tolerated, with manageable adverse effects and favorable pharmacokinetics in patients with advanced solid tumors. While this study was not designed or statistically powered to assess clinical efficacy, preliminary antitumor activity was observed in patients with mesothelioma and ovarian cancer.

Relevance:

Anetumab ravtansine is being investigated as a potental treatment option for patients with mesothelin-expressing solid tumors, who currently have very limited treatment options. This phase I study showed that anetumab ravtansine was well tolerated in these patients, leading to the initiation of several phase II studies across multiple tumor types including mesothelioma, non–small-cell lung cancer, cholangiocarcinoma, and pancreatic adenocarcinoma.

conjugated to the maytansine derivative tubulin inhibitor DM4 through a reducible disulfide linker.[14] The drug–antibody ratio of anetumab ravtansine is 3.2. After binding to mesothelin on tumor cells, anetumab ravtansine is internalized and the disulfide linker is cleaved, releasing DM4. DM4 subsequently binds to tubulin; this disrupts microtubule polymerization, resulting in cell cycle arrest and apoptosis.[15,16] The release of DM4 into the tumor microenvironment leads to bystander killing of neighboring dividing cells.[14] Preclinical studies have shown that anetumab ravtansine was highly cytotoxic to mesothelin-expressing mesothelioma and pancreatic, non–small-cell lung, and ovarian cancer cell lines.[14] In vivo, anetumab ravtansine had robust antitumor activity in mesothelioma, pancreatic, and ovarian xenografts with mesothelin expression derived from patients with cancer[14]

On the basis of these preclinical results of anetumab ravtansine, we initiated a comprehensive, to our knowledge first-in-human, dose-escalation and dose-expansion study to investigate the safety, tolerability, pharmacokinetics, activity, and immunogenicity of once every 3 weeks and once per week anetumab ravtansine administration in patients with advanced mesothelin-expressing solid tumors.

PATIENTS AND METHODS

Study Design and Patients

This was a phase I, open-label, nonrandomized, dose-escalation and dose-expansion study. The sample size of the dose-escalation phase was 45 patients, and it was conducted according to the traditional 3+3 model with modified Fibonacci schema (Data Supplement, online only). The anetumab ravtansine dose was escalated in 10 cohorts: 0.15, 0.3, 0.6, 1.2, 2.4, 3.6, 4.5, 5.5, 6.5, and 7.5 mg/kg once every 3 weeks. The dose, schedule (maximum tolerated dose [MTD] once every 3 weeks, 1.8 mg/kg once per week, or 2.2 mg/kg once per week), and antitumor activity were evaluated in 6 expansion cohorts (n = 103) of patients with mesothelioma (pleural and peritoneal) or ovarian, fallopian tube, or primary peritoneal cancer (platinum-resistant or platinum-sensitive). Relapsed disease after $\leq$ 6 months and relapsed disease after $>$ 6 months after initial platinum-based chemotherapy were termed platinum resistant and platinum sensitive, respectively. The once-per-week dosing schedules were added after the establishment of the MTD for the once-every-3-weeks dosing schedule.

Patients

Eligible patients had advanced, metastatic, or recurrent solid tumors refractory to standard therapy. The study population was enriched with tumor types known to overexpress mesothelin. Additional inclusion criteria included age $\geq$ 18 years, Eastern Cooperative Oncology Group performance status of 0-1, evaluable or measurable disease, and written informed consent. The once-every-3-weeks MTD expansion cohort enrolled patients with advanced epithelial ovarian cancer or mesothelioma only. For the once-per-week expansion cohorts, eligibility was restricted to patients with advanced epithelial ovarian cancer or epithelioid pleural or peritoneal mesothelioma. All patients in the once-per-week cohorts had confirmed mesothelin expression with a membrane intensity score of 2+ or 3+ on $\geq$ 30% of tumor cells on evaluation of fresh or archival tumor tissue by IHC. In the once-every-3-weeks cohorts, mesothelin expression was determined retrospectively in a similar manner. Full selection criteria are provided in the Data Supplement. The trial adhered to the Declaration of Helsinki and Good Clinical Practice, and all patients provided written informed consent.

Procedures

Anetumab ravtansine was administered as a 1-hour intravenous infusion on day 1 (once every 3 weeks) or days 1, 8, and 15 (once per week) of each 21-day cycle. Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal of patient consent or from the study at the investigator's discretion. Anetumab ravtansine dose-modification criteria are provided in the Data Supplement.

Adverse events (AEs) were reported using the National Cancer Institute Common Terminology Criteria for AEs version 4.0.[17] Tumor response was evaluated every 6 weeks until cycle 8, and every 12 weeks thereafter, on the basis of modified Response Evaluation Criteria in Solid Tumors (mRECIST) in mesothelioma[18] and RECIST version 1.1 in all other solid tumors.[19]

In those patients in the once-every-3-weeks cohort who had archival or fresh tumor tissue samples available, mesothelin expression was evaluated retrospectively using the VENTANA MSLN (SP74) IHC assay. Tumors expressing mesothelin at any intensity were considered mesothelin positive. Tumors were considered to have high expression if mesothelin was detected at a 2+ or 3+ membrane intensity (0-3 scale) on ≥ 30% of viable tumor cells. Mesothelin expression on tumor cells was determined prospectively in the once-per-week expansion cohorts using IHC, and only those patients with high mesothelin expression were included. Plasma levels of soluble mesothelin-related peptide (SMRP) at baseline (pretreatment) were determined by the MesoMark enzyme-linked immunosorbent assay. Anetumab ravtansine recognizes an epitope present on SMRP; therefore, serial changes in SMRP levels over time during treatment were not measured.

Antidrug antibody (ADA) titers and neutralizing antibody-positive status were determined on cycle 1 day 1 (predose) and day 8, then on day 1 of every even cycle, and at end-of-treatment and follow-up visits. Serial plasma samples for pharmacokinetic characterization were collected during cycles 1, 3, and 6, and every third cycle thereafter, for analysis of ADC, total antibody (ADC and cleaved free antibody), DM4 (toxophore), and DM4-Me (S-methyl metabolite of DM4) concentrations. Evaluation of plasma pharmacokinetic parameters was performed by noncompartmental analysis.

Outcomes

The primary objectives were to determine the safety, tolerability, MTD, and pharmacokinetics of anetumab ravtansine. Secondary objectives included the assessment of tumor response, including the objective response rate (ORR; defined as a best response of complete response [CR] or partial response [PR]) and disease control rate (DCR; defined as a best response of CR, PR, or stable disease [SD]), median progression-free survival (PFS), evaluation of mesothelin expression, plasma SMRP, and immunogenicity of anetumab ravtansine.

Statistical Analysis

Baseline characteristics and safety data were assessed using summary statistics, with frequency tables generated for qualitative data. Antitumor activity was assessed using descriptive analyses of response assessments. For best overall response analysis, investigator-assessed overall response was determined. The Kaplan-Meier method was used to estimate median PFS and duration of response with 2-sided 95% CIs. All statistical analyses were performed with SAS version 9.4.

RESULTS

Between September 2011 and June 2015, 148 patients were enrolled at 8 centers. In total, 45 patients were enrolled in 10 dose-escalation cohorts (0.15 7.5 mg/kg once every 3 weeks), and 32, 35, and 36 patients in the 6.5 mg/kg once-every-3-weeks, 1.8 mg/kg once-per-week, and 2.2 mg/kg once-per-week expansion cohorts, respectively. The study profile is presented in Fig 1. Patient characteristics are summarized in Table 1.

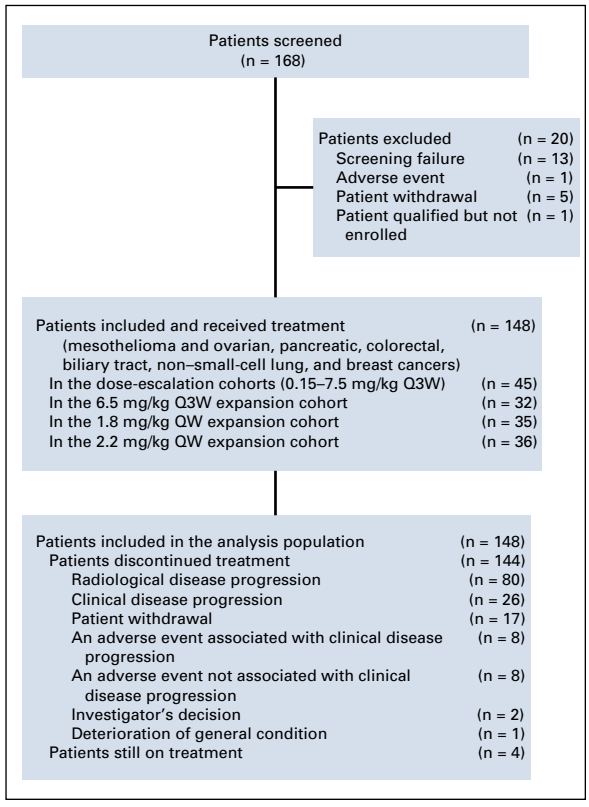

FIG 1. Trial profile for the anetumab ravtansine dose-escalation and dose-expansion cohorts. Q3W, every 3 weeks; QW, once per week.

TABLE 1. Patient Demographics and Baseline Characteristics

		Anetumab Ravtansine					
		6.5 mg/kg Dose (n = 38)[b]		1.8 mg/kg Dose (n = 35)		2.2 mg/kg Dose (n = 36)	
Demographic or Characteristic	Total Population (N = 148)[a]	Mesothelioma (n = 16)	Ovarian Cancer (n = 21)	Mesothelioma (n = 16)	Ovarian Cancer (n = 19)	Mesothelioma (n = 15)	Ovarian Cancer (n = 21)
Mean age, years ± SD	60.4 ± 12.6	64.7 ± 15.0	59.0 ± 10.9	59.5 ± 12.9	59.4 ± 9.9	63.3 ± 12.4	56.6 ± 14.3
Male	53 (36)	10 (63)	0	12 (75)	0	9 (60)	0
Female	95 (64)	6 (38)	21 (100)	4 (25)	19 (100)	6 (40)	21 (100)
ECOG performance status							
0	44 (30)	5 (31)	5 (24)	4 (25)	9 (47)	3 (20)	11 (52)
1	99 (67)	10 (63)	14 (67)	12 (75)	10 (53)	12 (80)	10 (48)
Missing	5 (3.4)	1 (6.3)	2 (9.5)	0	0	0	0
Body mass index, kg/m^2, mean ± SD	26.6 ± 6.5	24.9 ± 3.0	26.3 ± 6.6	25.5 ± 5.5	31.0 ± 8.7	25.6 ± 6.0	28.1 ± 7.6
Tumor type							
Breast cancer	5 (3.4)	0	0	0	0	0	0
NSCLC	2 (0.7)	0	0	0	0	0	0
Mesothelioma (peritoneal)	13 (8.8)	3 (19)	0	5 (31)	0	3 (20)	0
Histology subtypes							
Epithelioid	11 (7.4)	2 (13)	NA	4 (25)	NA	3 (20)	NA
Biphasic	0	0	NA	0	NA	0	NA
Not determined	2 (1.4)	1 (6.3)	NA	1 (6.3)	NA	0	NA
Mesothelioma (pleural)	51 (34)	13 (81)	0	11 (69)	0	12 (80)	0
Histology subtypes							
Epithelioid	42 (28)	10 (63)	NA	10 (63)	NA	8 (53)	NA
Biphasic	5 (3.4)	2 (12.5)	NA	0	NA	3 (20)	NA
Not determined	4 (2.7)	1 (6.3)	NA	1 (6.3)	NA	1 (6.7)	NA
Ovarian cancer	64 (43)	0	21 (100)	0	19 (100)	0	21 (100)
Histology subtypes							
Epithelial (serous)	49 (33)	NA	15 (71)	NA	17 (89)	NA	16 (76)
Epithelial (clear cell)	3 (2.0)	NA	0	NA	0	NA	3 (14.3)
Epithelial (undifferentiated)	3 (2.0)	NA	1 (4.8)	NA	2 (10.5)	NA	0
Epithelial (mucinous)	1 (0.7)	NA	0	NA	0	NA	1(4.8)
Carcinosarcoma (malignant Mullerian mixed tumor)	1 (0.7)	NA	1 (4.8)	NA	0	NA	0
Not determined	7 (4.7)	NA	4 (19)	NA	0	NA	1 (4.8)
Pancreatic cancer	9 (6.1)	0	0	0	0	0	0
Other	4 (2.7)	0	0	0	0	0	0
Time since diagnosis, months, mean ± SD	40.2 ± 35.2	23.5 ± 27.8	54.8 ± 37.7	45.5 ± 36.4	49.8 ± 37.1	23.3 ± 17.4	50.4 ± 35.0
Previous systemic anticancer treatment regimens							
Mean ± SD	3.5 ± 2.0	2.1 ± 2.0	5.2 ± 2.2	2.6 ± 1.5	4.6 ± 1.6	2.1 ± 1.5	4.0 ± 1.4
1	25 (17)	10 (63)	1 (5)	2 (13)	0	6 (40)	1 (5)
2	34 (23)	2 (13)	2 (10)	9 (56)	3 (16)	6 (40)	3 (14)
≥ 3	89 (60)	4 (25)	18 (86)	5 (31)	16 (84)	3 (20)	17 (81)

NOTE. Data are presented as No. (%) unless indicated otherwise.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NA, not applicable; NSCLC, non–small-cell lung cancer; SD, standard deviation.

[a]The total population includes all patients enrolled in the dose-escalation and maximum tolerated dose expansion cohorts.

[b]The 6.5 mg/kg once-every-3-weeks dose group comprises 6 patients enrolled in the dose-escalation cohort and 32 in the expansion cohort. One patient in the 6.5 mg/kg dose-escalation cohort had a diagnosis of breast cancer.

Safety

The MTD of anetumab ravtansine was 6.5 mg/kg once every 3 weeks, with 1 of 6 patients in the escalation cohort experiencing a dose-limiting toxicity (DLT, asymptomatic grade 3 increase in aspartate aminotransferase). One of the 6 patients in the 5.5 mg/kg once-every-3-weeks dose-escalation cohort experienced 2 DLTs (grade 3 hypertension and hyponatremia). There were no DLTs at doses of 4.5 mg/kg once every 3 weeks or lower. The 7.5 mg/kg once-every-3-weeks dose was not tolerated, with DLTs occurring in 2 of 4 patients: 1 patient with grade 3 peripheral neuropathy and another patient with grade 4 keratitis/keratopathy, and grade 4 increases in serum lipase and amylase.

Of 38 patients treated at 6.5 mg/kg once every 3 weeks (6 patients from the dose-escalation phase and 32 patients from the dose-expansion cohort), 1 (3%) died as the result of a treatment-emergent AE (TEAE) of sepsis, assessed as not related to the study drug, 3 (8%) discontinued treatment because of a TEAE (1 each with paroxysmal atrial tachycardia, sinus tachycardia, and dyspnea), and 18 (47%) and 17 (45%) had TEAEs leading to dose

TABLE 2. Summary of All-Cause and Drug-Related TEAEs, and TEAEs Occurring in ≥ 20% of Patients Receiving Anetumab Ravtansine 6.5 mg/kg Once-Every-3-Weeks, 1.8 mg/kg Once-per-Week, or 2.2 mg/kg Once-per-Week Expansion Cohorts

	Anetumab Ravtansine					
	6.5 mg/kg Q3W[a] (n = 38)		1.8 mg/kg QW (n = 35)		2.2 mg/kg QW (n = 36)	
TEAE	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TEAE	37 (97)	21 (55)	35 (100)	20 (57)	36 (100)	22 (61)
Any drug-related TEAE	35 (92)	11 (29)	28 (80)	8 (23)	25 (69)	7 (19)
Any serious TEAE	16 (42)	15 (39)	12 (34)	11 (31)	16 (44)	15 (42)
Any drug-related serious TEAE	5 (13)	4 (11)	4 (11)	3 (9)	1 (3)	1 (3)
TEAEs occurring in at least 20% of patients in the total of each group[b]						
Fatigue	24 (63)	6 (16)	19 (54)	0 (0)	20 (56)	0 (0)
Nausea	22 (58)	3 (8)	16 (46)	1 (3)	17 (47)	1 (3)
Diarrhea	20 (53)	1 (3)	13 (37)	1 (3)	12 (33)	0 (0)
Anorexia	19 (50)	1 (3)	9 (26)	0 (0)	9 (25)	0 (0)
Vomiting	15 (39)	1 (3)	5 (14)	1 (3)	10 (28)	0 (0)
Peripheral sensory neuropathy	14 (37)	1 (3)	7 (20)	0 (0)	7 (19)	0 (0)
AST increased	11 (29)	2 (5)	7 (20)	1 (3)	14 (39)	1 (3)
Blurred vision	11 (29)	1 (3)	5 (14)	0 (0)	8 (22)	1 (3)
Keratitis	11 (29)	2 (5)	4 (11)	1 (3)	6 (17)	3 (8)
Constipation	10 (26)	1 (3)	4 (11)	0 (0)	7 (19)	0 (0)
Abdominal pain	9 (24)	1 (3)	10 (29)	2 (6)	9 (25)	1 (3)
Hypoalbuminemia	9 (24)	1 (3)	7 (20)	0 (0)	6 (17)	2 (6)
ALP increased	9 (24)	1 (3)	3 (9)	0 (0)	6 (17)	0 (0)
Hyperglycemia	8 (21)	0 (0)	7 (20)	0 (0)	5 (14)	2 (6)
Dry eye	8 (21)	0 (0)	3 (9)	0 (0)	5 (14)	0 (0)
Platelet count decreased	8 (21)	0 (0)	3 (9)	0 (0)	5 (14)	0 (0)
Headache	8 (21)	0 (0)	2 (6)	0 (0)	2 (6)	0 (0)
Dyspnea	7 (18)	2 (5)	9 (26)	1 (3)	8 (22)	4 (11)
ALT increased	7 (18)	0 (0)	4 (11)	0 (0)	9 (25)	1 (3)
Anemia	6 (16)	1 (3)	7 (20)	0 (0)	9 (25)	2 (6)

NOTE. Data are presented as No. (%).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Q3W, every 3 weeks; QW, once weekly; TEAE, treatment-emergent adverse event.

[a]The 6.5 mg/kg Q3W dose group comprises 6 patients enrolled in the 6.5 mg/kg Q3W dose-escalation cohort and 32 in the 6.5 mg/kg Q3W expansion cohort. One patient in the 6.5 mg/kg Q3W dose-escalation cohort had a diagnosis of breast cancer.

[b]Data are sorted by the incidence of TEAEs in the total 6.5 mg/kg Q3W dose group, then the 1.8 mg/kg QW group, then the 2.2 mg/kg QW group.

reduction and treatment interruption, respectively. TEAEs leading to dose reduction and treatment discontinuation at 6.5 mg/kg once every 3 weeks and in the once-per-week expansion cohorts are presented in the Data Supplement.

TEAEs occurring in ≥ 20% of patients treated at 6.5 mg/kg once every 3 weeks or in the once-per-week expansion cohorts are listed in Table 2. The most frequent drug-related TEAEs of any grade were fatigue, nausea, diarrhea, anorexia, vomiting, and peripheral sensory neuropathy; these TEAEs were mild in severity. The most frequent grade 3 or higher drug-related TEAEs were fatigue, keratitis/keratopathy, and nausea.

Infusion-related reactions (IRRs) considered to be drug related were reported in 4 patients (11%) treated at 6.5 mg/kg once every 3 weeks and in 2 patients (6%) treated at 2.2 mg/kg once per week. Two IRRs (hypoxia and hypotension in combination with sinus tachycardia) in the 6.5 mg/kg once-every-3-weeks cohort were grade 3 in severity. All drug-related TEAEs either were reversible and resolved within 2-4 weeks of study drug cessation or showed a clear trend toward recovery at the last follow-up assessment. Drug-related TEAEs occurring in ≥ 5% of patients are presented in the Data Supplement. Eighteen deaths were reported in total, all of which were a result of disease progression and not considered drug related.

On the basis of DLTs and AEs observed in the dose escalation and expansion cohorts (Table 2 and Data Supplement), the recommended phase II dose and schedule of anetumab ravtansine was determined as 6.5 mg/kg once every 3 weeks or 2.2 mg/kg once per week.

Pharmacokinetics and Immunogenicity

Plasma concentration–time profiles for anetumab ravtansine and total plasma antibody were comparable with 6.5 mg/kg once-every-3-weeks dosing (Fig 2). The peak concentrations of both occurred at 1.5 hours; peak plasma concentrations of DM4 and DM4-Me were generally observed around 5 hours and 8 hours after the start of the anetumab ravtansine infusion, respectively. The average half-lives of anetumab ravtansine, DM4-Me, and DM4 were 5.5, 5.6, and 2.9 days, respectively, and no analytes accumulated after once-every-3-weeks dosing.

The pharmacokinetics of anetumab ravtansine were dose proportional, and anetumab ravtansine, DM4, and DM4-Me exposures were comparable between cycles 1 and 3 when anetumab ravtansine was administered once every 3 weeks (Data Supplement). In addition, plasma concentration–time profiles of anetumab ravtansine did not significantly differ in patients treated with once-every-3-weeks or once-per-week dosing (Data Supplement). These results suggest that plasma drug levels of anetumab ravtansine are by themselves unlikely to account for the somewhat lower antitumor activity in patients with mesothelioma treated with once-per-week dosing.

Of the 32 patients in the 6.5 mg/kg expansion cohort, 10 patients were ADA positive at baseline. Treatment-induced ADAs were detected in 8 of 22 patients who were ADA negative at baseline. Samples that tested ADA positive were also neutralizing antibody positive (Data Supplement). A comparable proportion of patients in the once-per-week expansion cohorts (54%) had no ADAs during treatment. No differences were observed in tumor response or in the type, incidence, or severity of TEAEs between patients with and without ADAs at any anetumab ravtansine dose level.

Clinical Activity

Tumor response was evaluated in 138 of the 148 patients enrolled in the study; 10 patients were not evaluable because of either premature withdrawal or nonevaluable lesions. Overall, 66 patients had SD, 11 patients had a PR,

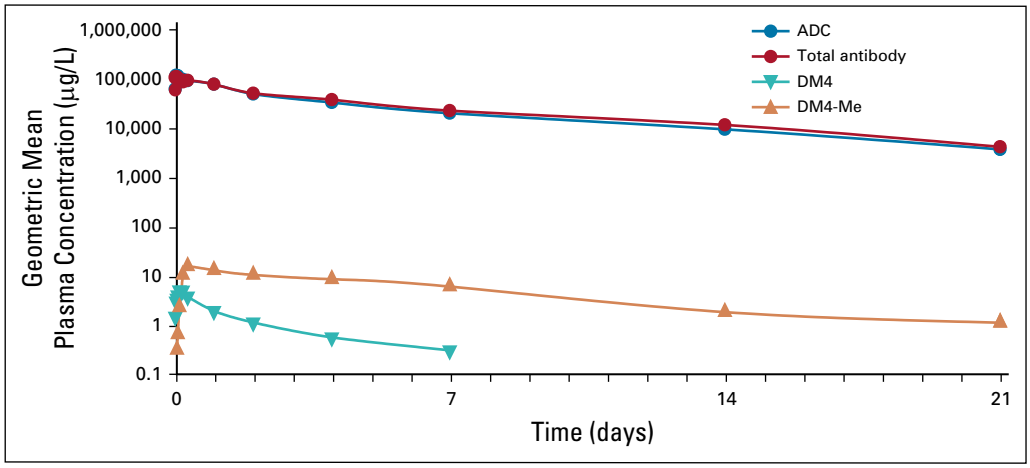

FIG 2. Plasma concentration–time profiles of anetumab ravtansine antibody–drug conjugate (ADC), total antibody, DM4, and DM4-Me after administration of 6.5 mg/kg anetumab ravtansine every 3 weeks.

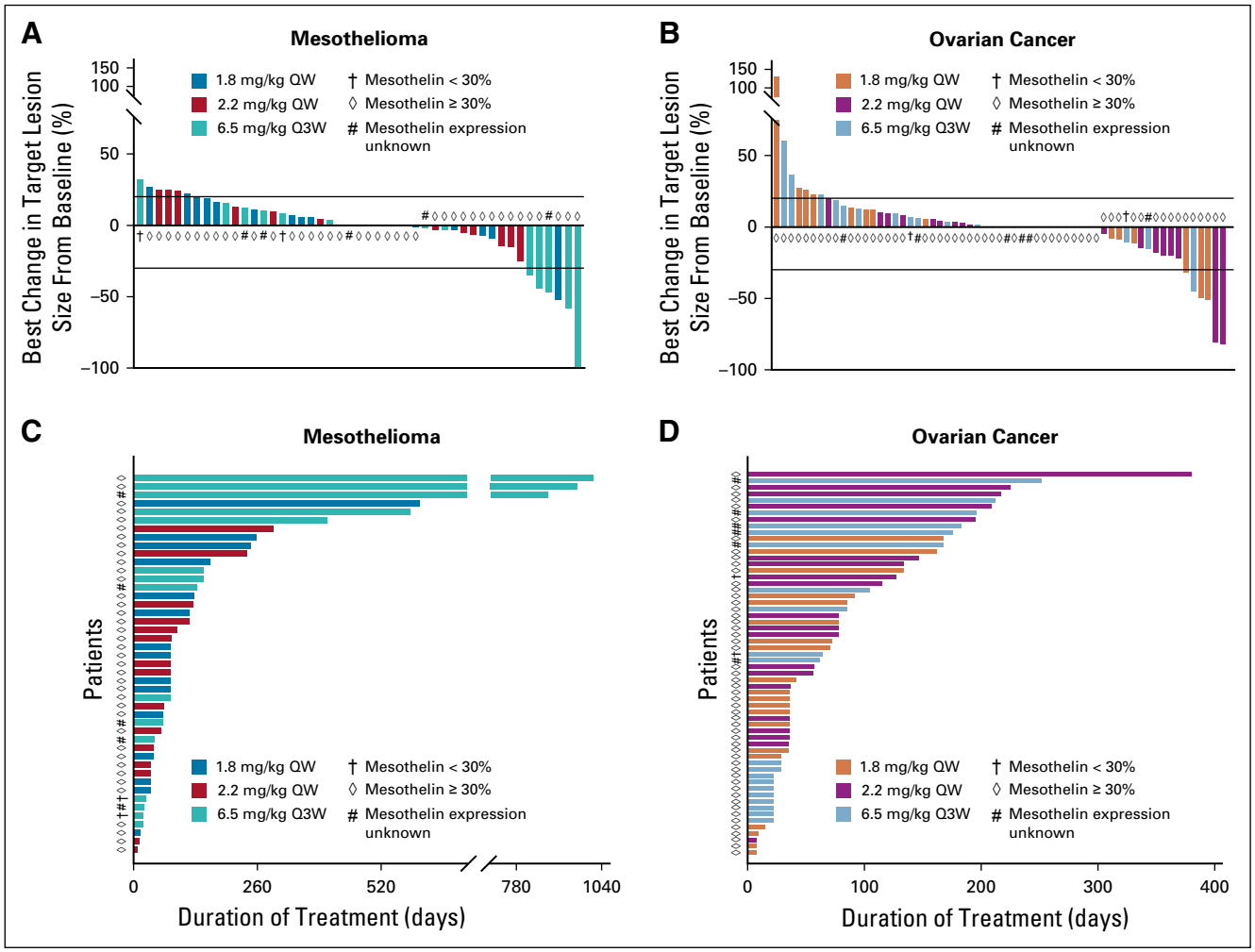

FIG 3. Antitumor activity of anetumab ravtansine. Best change in tumor size in target lesions from baseline and duration of treatments in (A and C) patients with mesothelioma (n = 47) and (B and D) patients with ovarian cancer (n = 61) receiving anetumab ravtansine 6.5 mg/kg every 3 weeks (Q3W), 2.2 mg/kg once per week (QW), or 1.8 mg/kg QW. Data are presented for all patients with at least 1 postbaseline tumor measurement. Symbols denote the proportion of tumors expressing mesothelin in tumor cells with membrane intensities of 2+ or 3+ as determined by immunohistochemistry analysis. Solid lines indicate cutoff for partial response (−30%) and progressive disease (+20%). Kaplan-Meier estimates of progression-free survival (PFS) in (E) all patients with mesothelioma and ovarian cancer, (F) patients with mesothelioma and (G) patients with ovarian cancer in the 6.5 mg/kg Q3W, 2.2 mg/kg QW, and 1.8 mg/kg QW cohorts. Plasma soluble mesothelin-related protein (SMRP) baseline levels as determined by enzyme-linked immunosorbent assay in patients with mesothelioma and patients with ovarian cancer in the (H) Q3W and (I) QW cohorts. Scatter plots represent individual patient results in the mesothelioma and ovarian cancer expansion cohorts. Box plots represent grouped data for all patients in each cohort (solid bar, median; gray box, 25th and 75th percentiles; whiskers, 1.5 × the interquartile range; orange cross, geometric mean).

and 1 patient achieved a CR with respect to best change in tumor size (Figs 3A and 3B). No objective responses were observed in the 0.15 4.5 mg/kg once-every-3-weeks dose-escalation cohorts, whereas 1 patient with mesothelioma in the 5.5 mg/kg once-every-3-weeks cohort had a PR (Data Supplement). SD was also observed in 1 patient with triple-negative breast cancer, 1 with non–small-cell lung cancer, 1 with ovarian cancer, and 3 with pancreatic cancer. The best ORR in the 6.5 mg/kg once-every-3-weeks, 1.8 mg/kg once-per-week, and 2.2 mg/kg once-per-week cohorts (mesothelioma and ovarian cancer) are listed in Table 3. Changes from baseline in target lesion size and PFS are presented in Fig 3. In the 6.5 mg/kg once-every-3-weeks, 1.8 mg/kg once-per-week, and 2.2 mg/kg once-per-week cohorts, the ORR was 16%, 9%, and 6%, and the DCR was 65%, 54%, and 64%, respectively. There was 1 CR in the 2.2 mg/kg once-per-week ovarian cancer cohort. The highest ORR and DCR were 31% and 75%, respectively, occurring in the 6.5 mg/kg once-every-3-weeks mesothelioma subgroup. ORRs in subgroups with pleural or peritoneal mesothelioma are presented in the Data Supplement.

The median durations of treatment in mesothelioma subgroups of the 6.5 mg/kg once-every-3-weeks,

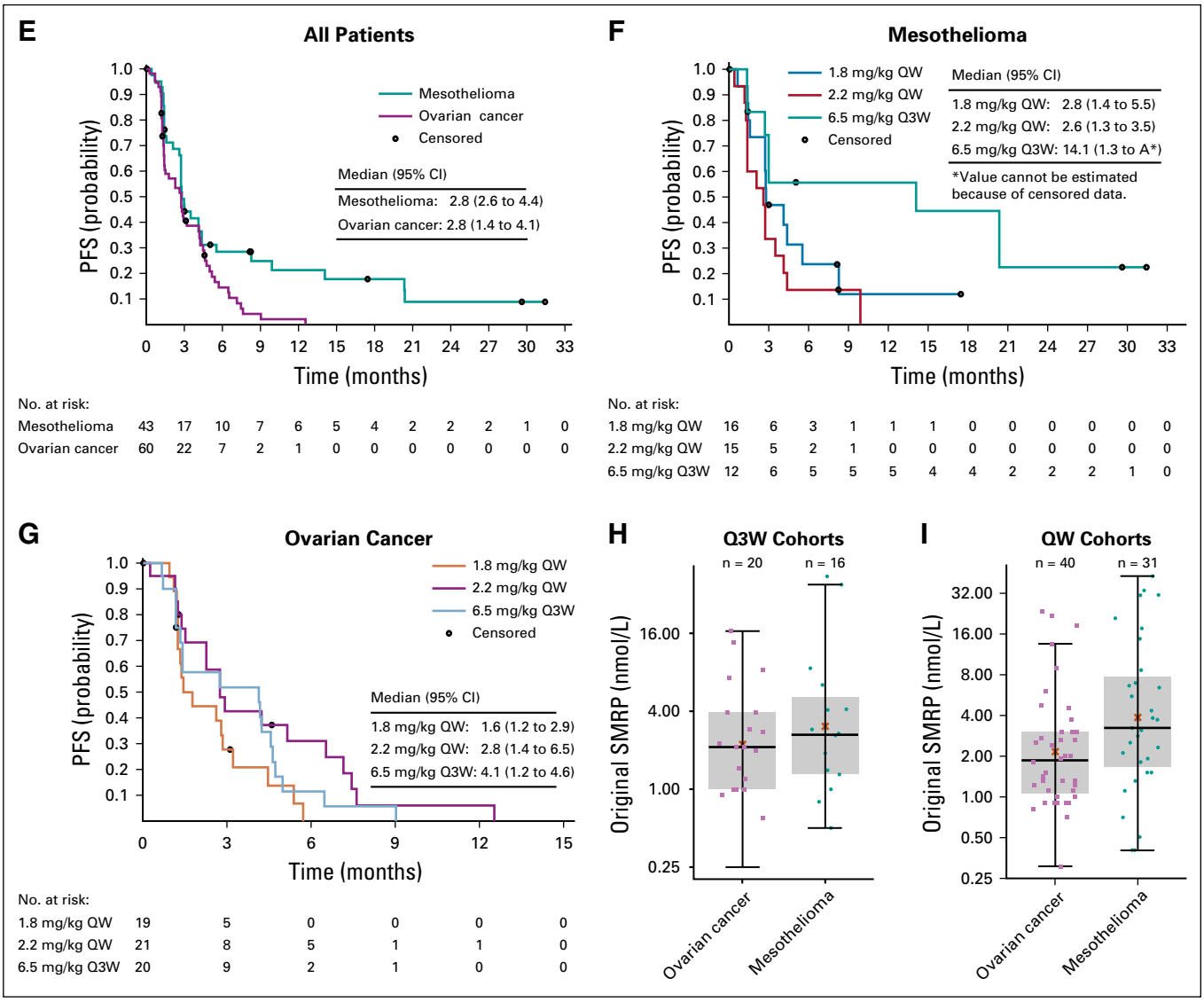

FIG 3. (Continued).

1.8 mg/kg once-per-week, and 2.2 mg/kg once-per-week cohorts were 105 days (range, 21-1,015 days), 78 days (range, 1-602 days), and 77 days (range, 8-294 days), respectively, and in the ovarian cancer subgroups were 62 days (range, 21-252 days), 36 days (range, 8-168 days), and 77 days (range, 1-380 days), respectively (Figs 3C and 3D). Median PFS was 2.8 months in each cohort (Fig 3E). PFS was longer in patients with once-every-3-weeks dosing than in those with once-per-week dosing in both the mesothelioma and the ovarian cancer subgroups (Figs 3F and 3G).

Five (31%) of the 16 patients with mesothelioma treated at 6.5 mg/kg once every 3 weeks had a PR; this lasted for 174 days in 1 patient, and for at least 600 days in the other 4 patients. As of February 2019, 2 patients with malignant peritoneal mesothelioma were still receiving treatment with a PR ongoing for longer than 1,700 days. In both patients, tumor mesothelin expression was high (90% and 100% of tumor cells with 2+/3+ membrane intensity).

Mesothelin Expression and SMRP

Tumor mesothelin expression was determined by IHC analysis of archival or fresh tissue samples in 97 of 108 patients enrolled in the mesothelioma and ovarian cancer expansion cohorts. Mesothelin expression was retrospectively analyzed in 68% of patients treated at 6.5 mg/kg once every 3 weeks and prospectively in all patients with once-per-week dosing. Mesothelin expression exceeding 30% (2+/3+ membrane intensity) was observed in 85% to 87% of patients in the mesothelioma and ovarian cancer expansion cohorts (Figs 3A and 3B and Table 4). In both cohorts, patients with objective responses had at least 60% tumor

TABLE 3. Best Overall Response in Patients with Mesothelioma or Ovarian Cancer Who Received Anetumab Ravtansine

	Anetumab Ravtansine					
	6.5 mg/kg Q3W (n = 37)[a]		1.8 mg/kg QW (n = 35)		2.2 mg/kg QW (n = 36)	
Overall Response	Mesothelioma (n = 16)	Ovarian Cancer (n = 21)	Mesothelioma (n = 16)	Ovarian Cancer (n = 19)	Mesothelioma (n = 15)	Ovarian Cancer (n = 21)
Complete response	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)
Partial response	5 (31)	1 (5)	1 (6)	2 (11)	0 (0)	1 (5)
Stable disease	7 (44)	11 (52)	10 (63)	6 (32)	9 (60)	12 (57)
Noncomplete response/nonprogressive disease	1 (6)	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
Progressive disease	3 (19)	7 (33)	4 (25)	9 (47)	5 (33)	6 (29)
Not evaluable	0 (0)	1 (5)	1 (6)	2 (11)	1 (7)	1 (5)
Objective response rate[b]	5 (31)	1 (5)	1 (6)	2 (11)	0 (0)	2 (10)
Disease control rate[c]	12 (75)	12 (57)	11 (69)	8 (42)	9 (60)	14 (67)

NOTE. Data are presented as No. (%).

[a]The 6.5 mg/kg once-every-3-weeks dose (Q3W) group comprises 6 patients enrolled in the 6.5 mg/kg once-every-3-weeks (QW) dose-escalation cohort and 32 in the 6.5 mg/kg Q3W expansion cohort. One patient in the 6.5 mg/kg Q3W dose-escalation cohort had a diagnosis of breast cancer; data for this patient are not presented.

[b]Objective response rate = complete response + partial response.

[c]Disease control rate = complete response + partial response + stable disease.

mesothelin expression (2+/3+ membrane intensity) and a trend for > 66% tumor mesothelin expression (Table 4).

Nine patients with mesothelioma with high mesothelin expression received treatment of > 200 days (4 received 6.5 mg/kg once every 3 weeks, 3 received 1.8 mg/kg once per week, and 2 received 2.2 mg/kg once per week; Fig 3C). Similarly, 5 patients with ovarian cancer with high mesothelin expression received treatment of > 200 days (1 received 6.5 mg/kg once every 3 weeks, and 4 received 2.2 mg/kg once per week; Fig 3D).

SMRP has a common diagnostic threshold of 2.0 nmol/L in malignant pleural mesothelioma.[20] Baseline plasma SMRP levels were determined in 107 of 108 patients in the mesothelioma and ovarian cancer expansion cohorts (Figs 3H and 3I). Median baseline plasma SMRP levels were 2.7 nmol/L (range, 0.5-44 nmol/L) and 3.2 nmol/L (range, 0.4-43 nmol/L) in the mesothelioma once-every-3-weeks and once-per-week

TABLE 4. Best Overall Response in Patients With Mesothelioma and Ovarian Cancer on the Basis of Mesothelin Expression Scores at Baseline in Tumor Tissue (6.5 mg/kg once-every-3-weeks, 1.8 mg/kg once-per-week, and 2.2 mg/kg once-per-week dosing)

Overall Response	Mesothelioma (n = 42)			Ovarian Cancer (n = 55)		
Mesothelin expression score, %[a]	< 33	≥ 33 to ≤ 66	> 66	< 33	≥ 33 to ≤ 66	> 66
Total	4	8	30	4	12	39
Complete response	0	0	0	0	0	1
Partial response[b]	0	1	4	0	0	4
Stable disease	1	5	16	4	7	13
Noncomplete response/nonprogressive disease	1	0	0	0	0	0
Progressive disease	2	2	8	0	3	19
Not evaluable	0	0	2	0	2	2
Objective response rate, %	0.0	12.5	13.3	0.0	0.0	12.8

NOTE. Data are presented as No. unless indicated otherwise.

[a]Mesothelin expression scores denote the proportion of viable tumor cells expressing mesothelin with membrane staining intensities of 2+ or 3+ as determined by immunohistochemistry analysis.

[b]One patient with mesothelioma not evaluated for mesothelin expression was excluded.

dosing cohorts, respectively. Median baseline plasma SMRP levels were 2.1 (range, 0.25-17 nmol/L) and 1.8 nmol/L (range, 0.3-23 nmol/L) in the ovarian cancer once-every-3-weeks and once-per-week cohorts, respectively.

DISCUSSION

In this phase I study, anetumab ravtansine, a mesothelin-targeting ADC, was well tolerated, with manageable AEs and favorable pharmacokinetics, and had encouraging preliminary clinical activity in heavily pretreated patients with advanced or metastatic solid tumors, including mesothelioma and ovarian cancer. The MTD and recommended dose for phase II trials of anetumab ravtansine as a single agent were determined to be 6.5 mg/kg once every 3 weeks or 2.2 mg/kg once per week.

The most common drug-related AEs in patients treated with 6.5 mg/kg once every 3 weeks or in the once-per-week expansion cohorts were fatigue, nausea, diarrhea, anorexia, vomiting, and peripheral sensory neuropathy. Ocular AEs (most commonly reported as keratitis, keratopathy, blurred vision, and dry eye) were manageable with mitigation strategies such as dose reductions, treatment delays, and the use of ocular lubricants or topical steroids. Similar strategies have been used to manage ocular AEs associated with other ADCs.[21] The visual impairment and corneal morphology changes found on the ophthalmologic examination either fully recovered within 2-9 weeks or showed a trend toward resolution at the last follow-up assessment. Ocular toxicity, keratitis/keratopathy in particular, seems to be a class effect of certain ADCs and has been observed with other ADCs using both maytansinoid and nonmaytansinoid toxophores (Data Supplement).[21-24]

Drug-related peripheral sensory neuropathy was seen in 32% of patients treated at 6.5 mg/kg once every 3 weeks, but only 1 case was grade 3 in severity. IRRs were also uncommon, occurring in only 4 patients (11%) at 6.5 mg/kg once every 3 weeks, 1 patient (3%) at 1.8 mg/kg once per week, and 2 patients (6%) at 2.2 mg/kg once per week. Peripheral sensory neuropathy, hematologic AEs, and IRRs have also been reported previously with other ADCs and microtubule inhibitor compounds.[21,25]

In this study, the baseline plasma SMRP levels of patients were higher than the common diagnostic threshold for patients with pleural mesothelioma.[26] Furthermore, while all patients who responded to treatment had high mesothelin expression, some patients with high mesothelin expression did not respond to treatment. All patients with PR and CR had at least 60% tumor mesothelin expression by IHC. These findings suggest that, although there is a positive trend in the correlation between mesothelin expression and antitumor activity, significance cannot be established on the basis of the preliminary data from this study. Currently, the phase Ib multi-indication basket study of anetumab ravtansine (ClinicalTrials.gov identifier: NCT03102320) is enrolling patients with different tumor types (triple-negative breast, pancreatic, thymic, lung, and gastric cancers) to evaluate antitumor activity in the context of tumor mesothelin expression.

In summary, anetumab ravtansine is a novel anti-mesothelin ADC that was well tolerated in patients with advanced solid tumors. Common AEs were manageable with treatment interruptions or dose reductions. While this phase I study was not designed or statistically powered to assess clinical efficacy, preliminary antitumor activity was observed in patients with metastatic and refractory mesothelioma and ovarian cancer. As this phase I study was ongoing, topline results from a randomized phase II study in patients with pleural mesothelioma were presented and indicated that anetumab ravtansine was not superior to vinorelbine.[27] Additional subgroup analysis of this phase II study is in progress, including correlation of PFS and OS with tumor mesothelin expression and baseline SMRP levels. On the basis of all the findings from the phase I study of anetumab ravtansine, several additional clinical trials are underway (ClinicalTrials.gov identifiers: NCT02751918, NCT03455556, NCT03126630, and NCT03102320) to evaluate the safety, tolerability, and activity of anetumab ravtansine as monotherapy or in combination with standard of care in a variety of mesothelin-expressing solid tumors. Anetumab ravtansine may also warrant future investigation in pediatric acute myeloid leukemia because a subset of these tumors has high mesothelin expression.[28,29]

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First-in-Human, Multicenter, Phase I Dose-Escalation and Expansion Study of Anti-Mesothelin Antibody–Drug Conjugate Anetumab Ravtansine in Advanced or Metastatic Solid Tumors

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No other potential conflicts of interest were reported.