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Safety and activity of anti-mesothelin antibody–drug conjugate anetumab ravtansine in combination with pegylated-liposomal doxorubicin in platinum-resistant ovarian cancer: multicenter, phase Ib dose escalation and expansion study

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ABSTRACT

Objectives Anetumab ravtansine is an antibody-drug conjugate consisting of a fully human anti-mesothelin monoclonal antibody conjugated to cytotoxic maytansinoid tubulin inhibitor DM4. Mesothelin is highly expressed in ovarian cancer. This phase Ib study determines the safety, pharmacokinetics, and anti-tumor activity of anetumab ravtansine and pegylated liposomal doxorubicin in mesothelin-expressing platinum-resistant ovarian cancer.

Methods Anetumab ravtansine (5.5 or 6.5 mg/kg) and pegylated liposomal doxorubicin (30 mg/m^2) were administered intravenously every 3 weeks to 65 patients with platinum-resistant epithelial ovarian cancer. Mesothelin expression was assessed by central immunohistochemistry. Adverse events, tumor response (RECIST 1.1), and progression-free survival were determined. Biomarker samples were assessed by ELISA and next-generation sequencing.

Results In dose escalation, nine patients received anetumab ravtansine across two doses (5.5 or 6.5 mg/kg). The maximum tolerated dose of anetumab ravtansine was 6.5 mg/kg every 3 weeks and no dose-limiting toxicities were observed. In dose expansion, 56 patients were treated at the maximum tolerated dose. The most common treatment-emergent adverse events of any grade were nausea (47.7%), decreased appetite (43.1%), fatigue (38.5%), diarrhea (32.3%), and corneal disorder (29.2%). In all treated patients the objective response rate was 27.7% (95% CI 17.3% to 40.2%), including one complete (1.5%) and 17 partial responses (26.2%), with median duration of response of 7.6 (95% CI 3.3 to 10.2) months and median progression-free survival of 5.0 (95% CI 3.2 to 6.0) months. In an exploratory analysis of a sub-set of patients (n=19) with high mesothelin expression who received ≤3 prior lines of systemic therapy, the objective response rate was 42.1% (95% CI 20.3% to 66.5%) with a median duration of response of 8.3 (95% CI 4.1 to 12.0) months and median progression-free survival of 8.5 (95% CI 4.0 to 11.4) months.

Conclusions Anetumab ravtansine and pegylated liposomal doxorubicin showed tolerability and promising clinical activity. These results established the dose schedule and the mesothelin-positive target population of this combination for a phase III study in platinum-resistant ovarian cancer.

Trial registration number NCT02751918.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A substantial proportion of patients with epithelial ovarian cancer are primarily resistant to platinum-based treatment or develop secondary resistance leading to disease progression and poor prognosis.

WHAT THIS STUDY ADDS

⇒ Our results showed that the combination of anetumab ravtansine and pegylated liposomal doxorubicin is safe and tolerated with promising clinical efficacy in platinum-resistant ovarian cancer.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Based on our study findings, a recommended dose schedule of anetumab ravtansine with pegylated liposomal doxorubicin was determined. In addition, a mesothelin-positive target population for a phase III study in platinum-resistant ovarian cancer was established.

INTRODUCTION

The standard of care treatment for ovarian cancer is cytoreductive surgery and chemotherapy using a platinum-based combination regimen with or without bevacizumab and in maintenance treatment.[1] Recently approved inhibitors of poly (ADPR-ribose) polymerase alone or in combination as a maintenance treatment have significantly impacted the management of first-line disease and platinum-sensitive recurrence, particularly in patients with homologous

recombination pathway deficiencies.[2 3] However, a substantial proportion of patients with epithelial ovarian cancer are primarily resistant to platinum-based treatment or develop secondary resistance leading to disease progression and poor prognosis.[4] Pegylated liposomal doxorubicin is approved as a single agent for the treatment of ovarian cancer that has progressed or recurred after platinum-based chemotherapy.[5] In the AURELIA phase III study, bevacizumab plus chemotherapy (pegylated liposomal doxorubicin, paclitaxel, or topotecan) showed an overall response rate of 27.3% and a median progression-free survival of 6.7 months in patients with platinum-resistant ovarian cancer who received ≤2 prior lines of systemic regimens and with no history of bowel obstruction. In the sub-group analysis, the pegylated liposomal doxorubicin cohort showed an overall response rate of 7.8% with a median progression-free survival of 3.5 months.[6] Thus, more effective treatment options for platinum-resistant ovarian cancer remain a high unmet need.

Mesothelin is a 70 kDa cell surface glycoprotein that is highly expressed in 60–65% of epithelial ovarian cancers with limited expression in normal tissues.[7 8] Anetumab ravtansine is an antibody-drug conjugate consisting of a fully human immunoglobulin G1 anti-mesothelin monoclonal antibody conjugated to the maytansinoid DM4.[9 10] Pre-clinical studies have shown that the combination of anetumab ravtansine with pegylated liposomal doxorubicin has additive anti-proliferative activity and improves the anti-tumor activity in ovarian cancer cell line- and patient-derived xenograft models.[10] Anetumab ravtansine has also shown anti-tumor activity in patients with recurrent ovarian cancer and malignant mesothelioma.[11] In the first in human phase I study, disease control rates were 57%, 42%, and 67% for 6.5 mg/kg once every 3 weeks, 1.8 mg/kg, and 2.2 mg/kg once a week dosing of anetumab ravtansine, respectively, in ovarian cancer cohorts,[11] suggesting its addition to pegylated liposomal doxorubicin could provide a greater clinical benefit through the delivery of a potent targeted cytotoxic DM4 agent leading to enhanced cell cycle arrest, apoptosis, and bystander killing of tumor cells. This phase Ib study (NCT02751918) was designed to determine the maximum tolerated dose of anetumab ravtansine in combination with pegylated liposomal doxorubicin and to characterize its safety, tolerability, pharmacokinetics, and antitumor activity in patients with mesothelin-expressing platinum-resistant epithelial ovarian cancer. The study also aimed to identify the potential molecular determinants of response or resistance to anetumab ravtansine and pegylated liposomal doxorubicin treatment in platinum-resistant ovarian cancer.

METHODS

Study Design

This was a multi-center, open-label, phase Ib dose escalation and dose expansion study conducted at nine sites in Spain, the USA, Belgium, and the Republic of Moldova.

The primary objectives were to evaluate the safety, tolerability, and maximum tolerated dose of anetumab ravtansine plus pegylated liposomal doxorubicin. The secondary objectives were to assess the pharmacokinetics, anti-tumor activity, and immunogenicity. In addition, the correlation between mesothelin expression and tumor response was assessed in an exploratory analysis, along with the evaluation of additional biomarkers in tumor tissues.

The study consisted of a dose escalation cohort to identify the maximum tolerated dose of anetumab ravtansine administered with a fixed dose of pegylated-liposomal doxorubicin (30 mg/m^2 every 3 weeks), followed by two dose expansion cohorts at the maximum tolerated dose of anetumab ravtansine (Figure 1). Pegylated-liposomal doxorubicin dosing has been previously used in a phase III study of trabectedin plus pegylated liposomal doxorubicin in recurrent ovarian cancer.[12] Anetumab ravtansine was administered as an intravenous infusion over 1 hour every 3 weeks in 21-day cycles. The starting dose was 5.5 mg/kg and the maximum dose was 6.5 mg/kg. Patients continued to receive the drug until disease progression, drug-related toxicity, consent withdrawal, death, or until another criterion for study withdrawal was met.

The study was conducted according to the traditional 3+3 model with a modified Fibonacci schema. Dose escalation was conducted in sequential dose cohorts and escalation or de-escalation decisions were based on the incidence of treatment-emergent adverse events that fulfilled criteria for a dose-limiting toxicity. Ocular adverse events (commonly reported as corneal epitheliopathies) were assessed before and during the treatment (at the discretion of the treating physician) using an internally developed Bayer Severity Grading System.[11 13]

The study protocol was approved by the institutional review boards of the participating institutions and complied with the Declaration of Helsinki, current Good Clinical Practice guidelines, and local laws and regulations. Written informed consent was obtained from all participants. The study was sponsored by Bayer AG.

Patients

Patients aged ≥18 years with histologically-confirmed predominantly epithelial (>50% of tumor component) platinum-resistant recurrent ovarian, fallopian tube, or primary peritoneal cancer were eligible. Low-grade serous, mucinous, clear-cell, and neuroendocrine tumors were excluded due to low or unknown mesothelin expression. Patients were required to have platinum-resistant cancer (relapsed >0 months and ≤6 months after the completion of previous platinum-based chemotherapy), measurable or evaluable tumor lesion according to RECIST 1.1, and Eastern Cooperative Oncology Group performance status of 0 or 1. Tumor tissue collection for mesothelin expression and biomarker assessments was mandatory in part 3 dose expansion and was not highly encouraged in the part 1 dose escalation and part 2 dose expansion cohorts.

Assessments

Safety

Common Terminology Criteria for Adverse Events v4.03 was used to grade toxicities and treatment-emergent adverse events, except for corneal epitheliopathy where the Bayer Severity Grading system was used. Multigated acquisition or echocardiography for assessment of left ventricular ejection fraction and New York Heart Association classification for the overall assessment of cardiovascular status was performed.

Anti-tumor Activity

Tumor response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) performed at screening (baseline), within 7 days pre-dose on C3D1, C5D1, C7D1, C9D1, and then within 7 days pre-dose every fourth cycle thereafter, and at the

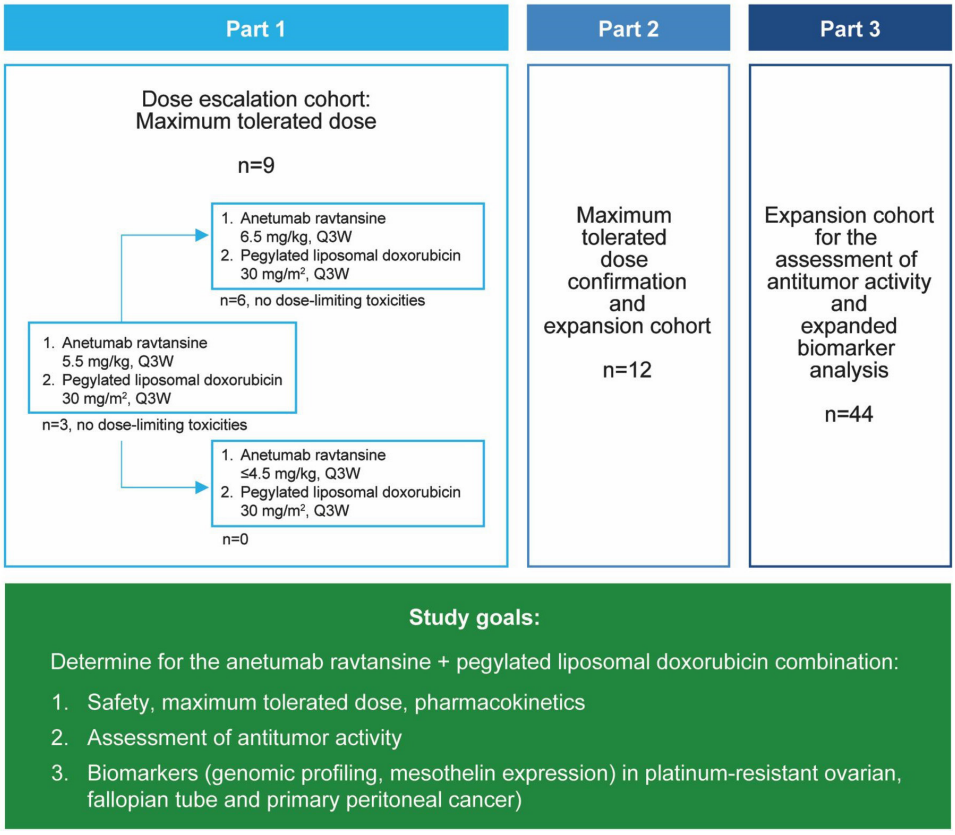

Figure 1 Study design.

end-of-treatment visit. The objective response rate (according to RECIST 1.1), duration of response, and progression-free survival were determined. For best overall response analysis, investigator-assessed overall response was used. The Kaplan–Meier method was used to estimate median progression-free survival and duration of response with two-sided 95% confidence intervals with censoring at the last evaluable tumor assessment. All statistical analyses were carried out using SAS version 9.4.

Pharmacokinetics

For pharmacokinetic assessments, anetumab ravtansine analytes (antibody-drug conjugate, total antibody, DM4 toxophore, and S-methyl metabolite of DM4) and pegylated liposomal doxorubicin were quantified in blood samples collected at scheduled time points. Evaluation of plasma pharmacokinetic parameters was performed by non-compartmental analysis.

Biomarker Assessment

Mesothelin expression was determined in 62 patients (archival or fresh tumor tissue samples) using the Ventana MSLN (SP74) immunohistochemistry assay as described previously.[11] The expression was classified by post-hoc subgroup analysis as high or low if mesothelin was detected at a 2+ or 3+ membrane intensity on ≥70% (median) or <70% of tumor cells, respectively.

Baseline (pre-treatment) levels of soluble mesothelin-related protein (SMRP) in plasma were determined in 22 patients by MESOMARK enzyme-linked immunosorbent assay (Fujirebio Diagnostics).

To identify potential additional biomarkers which may be predictive of response or resistance to anetumab ravtansine and pegylated doxorubicin treatment, archival tumor tissue samples from 30 patients were processed by next generation sequencing using a FoundationOne targeted gene panel to evaluate base substitutions, insertions-deletions, copy number changes, and rearrangements (Foundation Medicine; see Online supplemental table S1). Gene mutation frequencies were calculated by post-hoc analysis for the overall dataset and each group of patients with the best overall response (responders: partial response or complete response; non-responders: stable disease, progressive disease). Mutations in individual genes were investigated for associations with best overall response. The Clopper–Pearson method was used to calculate 95% confidence intervals for mutation frequencies.

RESULTS

Patient Enrollment, Baseline Characteristics, and Treatment

Ninety-seven patients were enrolled and 32 failed screening (study protocol criteria and tumor tissue requirement), leaving a total of 65 patients who were treated with anetumab ravtansine plus pegylated liposomal doxorubicin (Figure 1). In dose escalation, nine patients were treated across two anetumab ravtansine dose cohorts of 5.5 mg/kg (n=3 patients) or 6.5 mg/kg (n=6 patients) every 3 weeks. During dose expansion, an additional 56 patients received anetumab ravtansine at 6.5 mg/kg every 3 weeks. All patients received pegylated liposomal doxorubicin at 30 mg/m^2 (body surface area) every 3 weeks.

Baseline demographics and disease characteristics are shown in Table 1. Thirty-six (58%) of 62 patients had high mesothelin expression. The median age was 63 years (range 42–80) and the primary tumor type was epithelial ovarian carcinoma. The most common

Table 1 Patient demographics and baseline characteristics

	Cohort*		
	Anetumab ravtansine 5.5 mg/kg plus pegylated liposomal doxorubicin 30 mg/m^2 (n=3)	Anetumab ravtansine 6.5 mg/kg plus pegylated liposomal doxorubicin 30 mg/m^2 (n=62)	Total (n=65)
Age			
Median, years (range)	55 (51–65)	63 (42–80)	63 (42–80)
Ethnicity, n (%)			
Hispanic or Latino	0	3 (4.8)	3 (4.6)
Non-Hispanic or non-Latino	3 (100)	59 (95.2)	62 (95.4)
Eastern Cooperative Oncology Group performance status at baseline, n (%)			
0	2 (66.7)	35 (56.5)	37 (56.9)
1	1 (33.3)	27 (43.5)	28 (43.1)
Time since diagnosis			
Median (range), days	806.0 (261–1875)	1066.0 (181–5561)	1064.0 (181–5561)
Time since most recent progression			
Median (range), days	34.0 (30–89)	32.5 (8–247)	33.0 (8–247)
Primary location of cancer at initial diagnosis, n (%)			
Fallopian tube	0	5 (8.1)	5 (7.7)
Ovary	3 (100)	54 (87.1)	57 (87.7)
Peritoneum	0	3 (4.8)	3 (4.6)
FIGO stage, n (%)			
IC	0	1 (1.6)	1 (1.5)
IIB	0	3 (4.8)	3 (4.6)
IIIB	0	2 (3.2)	2 (3.1)
IIIC	3 (100)	31 (50.0)	34 (52.3)
IV	0	25 (40.3)	25 (38.5)
Prior systemic therapies, median (IQR and range), n (%)	3 (1–5 and 1–5)	4 (2–5 and 1–10)	4 (2–5 and 1–10)
1–≤3	2 (66.6)	29 (46.8)	31 (47.7)
4–≤6	1 (33.3)	24 (38.7)	25 (38.4)
>6	0	9 (14.5)	9 (13.8)
Most common prior systemic therapies, n (%)			
Platinum compounds			65 (100)
Taxanes			57 (87.7)
Doxorubicin compounds			41 (63.1)
Bevacizumab			33 (50.8)
PARP inhibitor			14 (21.5)
Antibody drug conjugates with DM4 payload			7 (10.8)
Immune checkpoint inhibitors			6 (9.2)

*All cohorts received anetumab ravtansine every 3 weeks in combination with pegylated liposomal doxorubicin.

histological type was serous (62 patients; 95.4%). Patients were heavily pre-treated, with a median number of prior lines of systemic treatment of 4 (IQR 2–5, range 1–10). Fifty-two percent (n=34) of patients received ≥4 prior lines of systemic therapies.

Safety

The maximum tolerated dose of anetumab ravtansine in combination was 6.5 mg/kg administered every 3 weeks.[11] No patient experienced a dose-limiting toxicity at either dose in the dose escalation

Table 2 Treatment-emergent adverse events including laboratory assessments occurring in ≥10% of all treated patients with anetumab ravtansine 5.5 or 6.5 mg/kg plus pegylated liposomal doxorubicin 30 mg/m^2 every 3 weeks (n=65)

Treatment-emergent adverse event *	Grade 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Nausea †	29 (44.6)	1 (1.5)	0	0	31 (47.7)
Decreased appetite	25 (38.5)	3 (4.6)	0	0	28 (43.1)
Fatigue	17 (26.2)	8 (12.3)	0	0	25 (38.5)
Diarrhea	18 (27.7)	3 (4.6)	0	0	21 (32.3)
Weight decreased	18 (27.7)	2 (3.1)	0	0	20 (30.8)
Corneal disorder	19 (29.2)	0	0	0	19 (29.2)
Aspartate aminotransferase increased	18 (27.7)	0	0	0	18 (27.7)
Abdominal pain †	11 (16.9)	2 (3.1)	0	0	14 (21.5)
Alanine aminotransferase increased	12 (18.5)	1 (1.5)	0	0	13 (20.0)
Asthenia	9 (13.8)	4 (6.2)	0	0	13 (20.0)
Blood bilirubin increased	12 (18.5)	1 (1.5)	0	0	13 (20.0)
Constipation ‡	11 (16.9)	0	0	0	13 (20.0)
Vomiting	11 (16.9)	2 (3.1)	0	0	13 (20.0)
Neutrophil count decreased	5 (7.7)	7 (10.8)	0	0	12 (18.5)
Dry eye	11 (16.9)	0	0	0	11 (16.9)
Neutropenia	4 (6.2)	6 (9.2)	1 (1.5)	0	11 (16.9)
Anemia	4 (6.2)	5 (7.7)	1 (1.5)	0	10 (15.4)
Rash	9 (13.8)	1 (1.5)	0	0	10 (15.4)
White blood cell count decreased	9 (13.8)	0	1 (1.5)	0	10 (15.4)
Dyspnea	7 (10.8)	1 (1.5)	0	1 (1.5)	9 (13.8)
Neuropathy, peripheral	9 (13.8)	0	0	0	9 (13.8)
Platelet count decreased	7 (10.8)	1 (1.5)	1 (1.5)	0	9 (13.8)
Fever	9 (13.8)	0	0	0	9 (13.8)
Vision blurred	7 (10.8)	2 (3.1)	0	0	9 (13.8)
Abdominal distension	7 (10.8)	1 (1.5)	0	0	8 (12.3)
Abdominal pain upper	8 (12.3)	0	0	0	8 (12.3)
Palmar-plantar erythrodysaesthesia syndrome	8 (12.3)	0	0	0	8 (12.3)
Hypokalemia	5 (7.7)	2 (3.1)	0	0	7 (10.8)
Myalgia	7 (10.8)	0	0	0	7 (10.8)
Peripheral sensory neuropathy	6 (9.2)	1 (1.5)	0	0	7 (10.8)
Urinary tract infection	7 (10.8)	0	0	0	7 (10.8)

*According to MedDRA v22.0.
†Data missing from one patient is not reported.
‡Data missing from two patients are not reported.

cohort. The most frequent treatment-emergent adverse events of any grade occurring in more than 25% of patients included nausea (47.7%), decreased appetite (43.1%), fatigue (38.5%), diarrhea (32.3%), and corneal disorder (29.2%) (Table 2). Adverse events were generally mild with grade ≤2. There were no deaths due to anetumab ravtansine-related adverse events and one death due to a pegylated liposomal doxorubicin-related adverse event (neutropenic sepsis). Thirty-one subjects (47.7%) had at least one treatment-emergent adverse event of corneal epitheliopathy which was either grade 1 or 2 in severity. Corneal epitheliopathy changes were corneal disorder (29.2%); corneal epithelial microcysts and keratitis (each at 6.2%); punctate keratitis and reduced visual acuity (each at 4.6%); vision blurred, dry eye, and keratopathy (each at 1.5%). Corneal epitheliopathy was reversible and managed with lubricating or corticosteroid eye drops. Ten patients (15.4%) were reported with at least one treatment-emergent adverse event leading to dose reduction or discontinuation.

Clinical Activity

In all treated patients (n=65), 17 patients (26.2%) achieved a partial response and one patient (1.5%) had a complete response. The objective response rate was 27.7% (95% CI 17.3% to 40.2%) with

Table 3 Best overall response with anetumab ravtansine plus pegylated liposomal doxorubicin in all treated patients and patients categorized by mesothelin expression and prior lines of systemic therapy

	All treated patients (n=65)	High mesothelin expression and ≤3 prior lines of systemic therapy (n=19)	High mesothelin expression and >3 prior lines of systemic therapy (n=13)
Best overall response, n (%)			
Complete response	1 (1.5)*	0	0
Partial response	17 (26.2)	8 (42.1)	2 (15.4)
Stable disease ≥4 months	12 (18.5)	5 (26.3)	4 (30.8)
Stable disease <4 months	16 (24.6)	5 (26.3)	5 (38.5)
Progressive disease	11 (16.9)	1 (5.3)	2 (15.4)
Not evaluable†	8 (12.3)	0	0
Objective response rate, % (95% CI)‡	27.7 (17.3 to 40.2)	42.1 (20.3 to 66.5)	15.4 (1.9 to 45.5)
Disease control rate, % (95% CI)§	70.8 (58.2 to 81.4)	94.3 (74.0 to 99.9)	84.6 (54.6 to 98.1)

*One patient with complete response had non-measurable disease with completely resolved lesions.
†Patients had no measurable lesions or follow-up assessments.
‡Proportion of patients with a complete response or partial response.
§Proportion of patients with a complete response, partial response, or stable disease.

a median duration of response of 7.6 (95% CI 3.3 to 10.2) months. The disease control rate was 70.8% (95% CI 58.2% to 81.4%) with a median progression-free survival of 5.0 (95% CI 3.2 to 6.0) months (Table 3 and Figure 2A–2C). We observed clinically relevant stable disease with ≥4 months by RECIST (1.1) in 12 patients (18.5%). As part of the post-hoc efficacy analysis, patients were grouped based on mesothelin expression and prior lines of systemic therapies. Overall, 58.0% (n=36) of patients showed high mesothelin expression. Among these patients, 30.6% (n=19) received ≤3 lines of prior systemic therapy. As shown in Table 3 and Figure 2A, in these patients the objective response and disease control rates were 42.1% (95% CI 20.3% to 66.5%) and 94.3% (95% CI 74.0% to 99.9%), respectively. Eight patients (42.1%) achieved a partial response with a median duration of response of 8.3 (95% CI 4.1 to 12.0) months and median progression-free survival of 8.5 (95% CI 4.0 to 11.4) months (Table 3 and Figure 2B,D). Median progression-free survival was 6.0 (95% CI 4.0 to 8.9) months in patients who received ≤3 lines of prior therapy (Figure 2E). Furthermore, in patients with high and low mesothelin expression, the median progression-free survivals were 5.7 (95% CI 4.0 to 10.9) months and 3.2 (95% CI 1.3 to 5.5) months, respectively (Online supplemental figure S1).

Pharmacokinetics

Following the single or multiple intravenous infusions of anetumab ravtansine, maximum antibody-drug conjugate and total antibody plasma concentrations were observed approximately 30–60 min after the end of 1 hour infusion and could be determined throughout the dosing interval of 3 weeks in all treatment cohorts (see Online supplemental figure S2). Consistent with previously reported results, the pharmacokinetics of anetumab ravtansine were dose proportional and anetumab ravtansine exposures were comparable between cycles.[11]

Biomarkers

The median baseline plasma level of soluble mesothelin-related protein was 3 (IQR 1.2–4.1) nmol/L (n=22), which is higher than the common diagnostic threshold of soluble mesothelin-related protein established in mesothelioma (2.0 nmol/L).[14] No correlation was observed between the plasma levels of soluble mesothelin-related protein and the mesothelin tumor expression on tumor tissue samples (Spearman rho 0.18, 95% CI −0.29 to 0.58).

To identify potential additional biomarkers which may be predictive of response or resistance to anetumab ravtansine and pegylated-liposomal doxorubicin treatment, tumor tissue samples from 30 patients were processed for next generation sequencing using a FoundationOne targeted gene panel (Online supplemental table S1). Post-hoc analysis of the somatic mutation frequencies between the responder and non-responder patient sub-groups did not show any significant difference between the two sub-groups (Online supplemental figure S3). To understand the nature of the observed somatic mutations, we analyzed the sequencing data of patients with an overall response. Different genomic alterations were detected, although no significant correlation could be established between the anti-tumor activity and these genomic alterations (Online supplemental figure S4).

Furthermore, since the alterations in homologous recombination pathway genes could sensitize cancer cells to pegylated liposomal doxorubicin, we investigated mutations or copy number changes in *ATM*, *BRCA1*, *BRCA2*, *CDK12*, *CHEK2*, *RAD51*, and *PALB2* genes.[15] The numbers of mutated DNA damage response genes per sample were not statistically different between responder and non-responder patients (two-sided Wilcoxon rank sum test, p=0.24; Online supplemental figure S4).

DISCUSSION

Summary of Main Results

In this phase Ib study, anetumab ravtansine plus pegylated-liposomal doxorubicin was safe, tolerated, and showed promising clinical activity in patients with platinum-resistant ovarian cancer. The objective response rate was 42.1%, with a median duration of response of 8.3 months and median progression-free survival

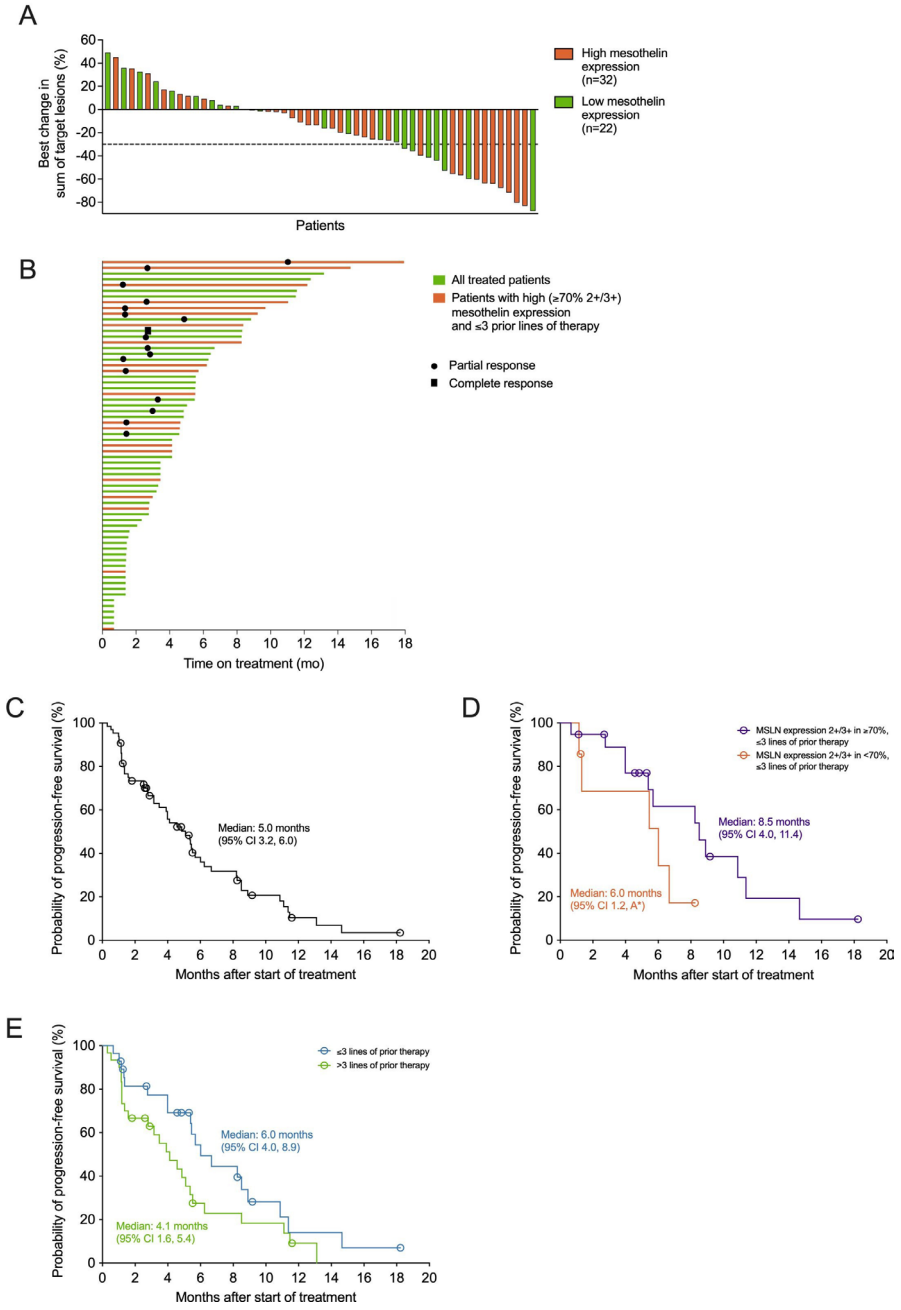

Figure 2 Anti-tumor activity of anetumab ravtansine plus pegylated liposomal doxorubicin. (A) Best change in tumor size in target lesions from baseline and level of mesothelin expression in patients with ovarian cancer. High and low mesothelin expression were defined as either ≥70% or <70%, respectively, of tumor cells membrane staining for mesothelin at the intensity level of 2+/3+. The solid line indicates the cut-off for a partial response (–30%). Data from eight patients were not included as they were not evaluable. Responses were categorized according to RECIST (1.1). (B) Duration of treatment in all treated patients including in patients with high mesothelin expression and ≤3 prior lines of therapy. Each bar represents one patient (n=65). (C) Kaplan–Meier estimates of progression-free survival in all treated patients (n=65). Censored patients are indicated by an open circle. (D) Kaplan–Meier estimates of progression-free survival in patients who received ≤3 prior lines of therapy and with high or low mesothelin (MSLN) expression (n=28). Censored patients are indicated by an open circle. *Value cannot be estimated. (E) Kaplan–Meier estimates of progression-free survival in patients who received ≤3 or >3 prior lines of therapy (n=58). Censored patients are indicated by an open circle.

of 8.5 months in patients with high mesothelin expression and ≤3 prior lines of systemic therapies.

Results in the Context of Published Literature

In the sub-group analysis of the AURELIA phase III study with ≤2 prior lines of treatment, the bevacizumab plus pegylated liposomal doxorubicin cohort showed an improved overall response rate and median progression-free survival compared with the pegylated liposomal doxorubicin cohort (13.7% vs 7.8% and 5.4 months vs 3.5 months, respectively).[16] There are additional phase III studies in patients with platinum-resistant

ovarian cancer who received ≤2 (PENELOPE) or ≤3 (FORWARD I and CORAIL) prior lines of treatments. In the phase III FORWARD I study, overall response rates were 24% and 10% with median progression-free survival of 4.8 and 3.3 months in the mirvetuximab soravtansine (high FRα) and chemotherapy arms (paclitaxel, pegylated liposomal doxorubicin, or topotecan), respectively.[17] In the PENELOPE phase III study, the chemotherapy arm (topotecan, paclitaxel, or gemcitabine) showed an 8.7% overall response rate with a median progression-free survival of 2.6 months while the pertuzumab plus chemotherapy arm had 13.1% and 4.3 months, respectively.[18] In the phase III CORAIL study, the overall response rate was 14.5% in the lurbinectedin arm and 12.7% in the chemotherapy arm (pegylated liposomal doxorubicin or topotecan) with median progression-free survival of 3.5 and 3.6 months, respectively.[19] There is an ongoing randomized phase II study (n=57) of bevacizumab and weekly anetumab ravtansine or weekly paclitaxel in platinum-resistant or refractory ovarian cancer.[20] Preliminary results show median progression-free survival of 5.3 months (95% CI 3.7 to 7.4) for anetumab ravtansine/bevacizumab and 9.6 months (95% CI 7.4 to 17.4) for bevacizumab/paclitaxel combination (HR 1.7 (95% CI 0.9 to 3.4)).

In this study, anetumab ravtansine plus pegylated liposomal doxorubicin showed an overall response rate of 27.7% with a median progression-free survival of 5.1 months in all treated patients, indicating that the combination treatment may provide an additional clinical benefit compared with single agent pegylated liposomal doxorubicin. In the first in human phase I study of anetumab ravtansine, a positive trend was observed between mesothelin expression and anti-tumor activity in the ovarian cancer cohort.[11] In this phase Ib study, in patients with high mesothelin expression and ≤3 prior lines of systemic therapies, anetumab ravtansine plus pegylated-liposomal doxorubicin showed an overall response rate of 42.1% with a median progression-free survival of 8.5 months, suggesting the significance of identifying a target patient population in platinum-resistant ovarian cancer. Furthermore, similar to previously reported studies, observed corneal adverse events were grade 1–2 in severity and managed with lubricating or corticosteroid eye drops.[11 13] Ocular adverse event is considered a class effect of antibody-drug conjugates with monomethyl auristatin-E, maytansinoid, and non-maytansinoid toxophores.[21]

Strengths and Weaknesses

The strengths of this study were the inclusion of an expanded cohort to further evaluate safety, anti-tumor activity, and the identification of mesothelin expression in the tumor tissue as a predictive biomarker. The latter finding could be explained based on the proposed mechanism of action of anetumab ravtansine targeting the toxophore DM4 to tumor cells via its anti-mesothelin antibody. Limitations of this study are that the data were obtained from a single-arm phase Ib study with overall response assessed by the investigators. Furthermore, although the molecular analyses of patient tumor samples were performed, additional genomic markers were not identified as the modulators of response or resistance to this combination treatment. Thus, a more detailed biomarker analysis may be required.

Implications for Practice and Future Research

Effective treatment options for platinum-resistant ovarian cancer remain an unmet medical need. The observed preliminary efficacy results in patients with mesothelin-positive ovarian cancer warrant further clinical development of anetumab ravtansine plus pegylated liposomal doxorubicin. This combination may provide an option for patients with platinum-resistant ovarian cancer.

CONCLUSIONS

Promising anti-tumor activity, a tolerable safety profile, and a mesothelin-positive target population for a phase III study have been determined for the combination of anetumab ravtansine 6.5 mg/kg plus pegylated liposomal doxorubicin 30 mg/m^2 every 3 weeks in patients with platinum-resistant ovarian cancer.

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Correction notice This article has been corrected since it was first published. The open access licence has been updated to CC BY.

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Ethics approval The study protocol was approved by the institutional review boards of participating institutions and complied with the Declaration of Helsinki, current Good Clinical Practice guidelines, and local laws and regulations. Written informed consent was obtained from all participants. Participants gave informed consent to participate in the study before taking part.

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Supplementary information for:

Safety and activity of anti-mesothelin antibody–drug conjugate anetumab ravtansine in combination with pegylated-liposomal doxorubicin in platinum-resistant ovarian cancer: Multicenter, phase Ib dose escalation and expansion study

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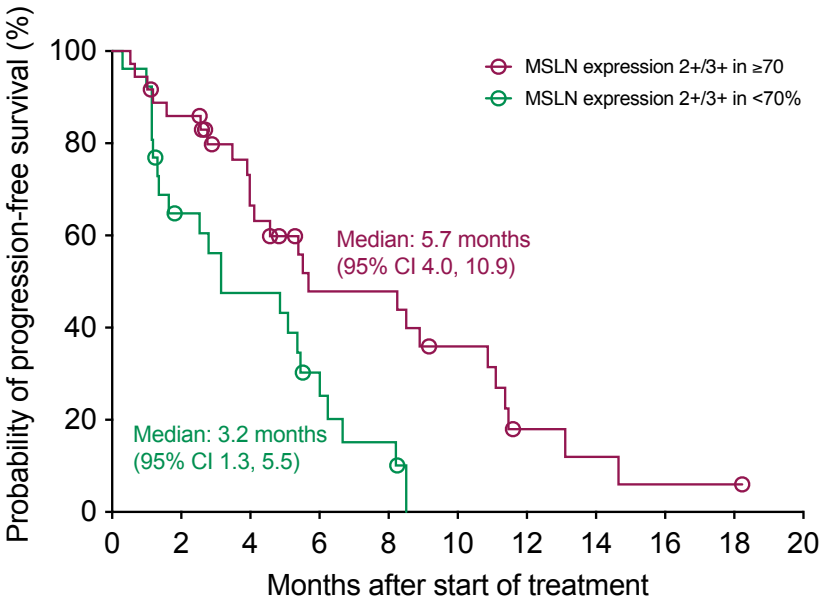
SUPPLEMENTARY TABLES

Supplementary Table S1. FoundationOne (Foundation Medicine) targeted gene panel used in next-generation sequencing of tumor tissue samples.

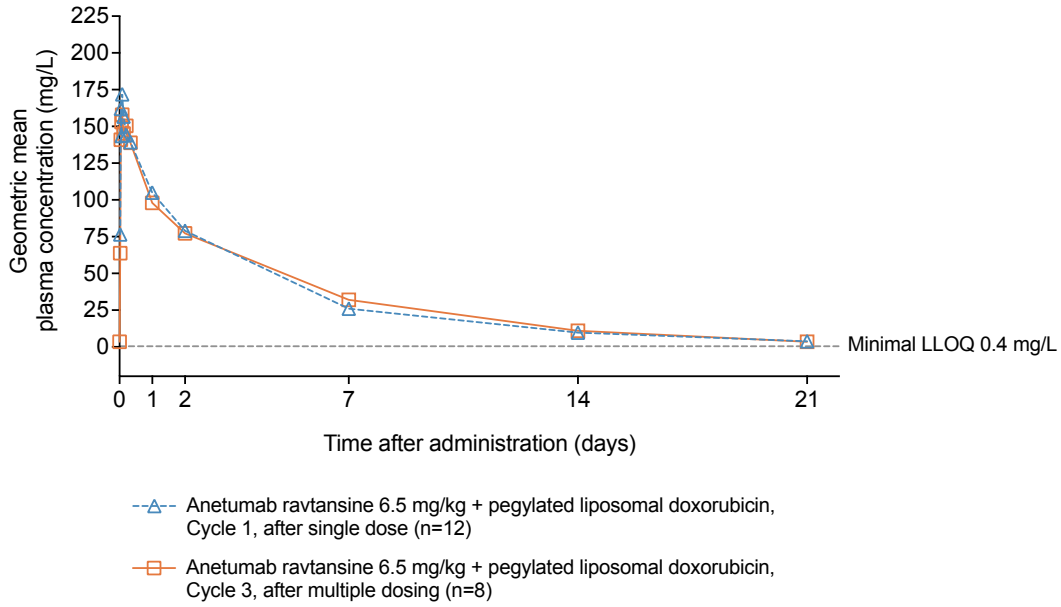
Genes included in the panel							
ABL1	*CASP8*	*DIS3*	*FGFR4*	*KEAP1*	*MYC*	*PIM1*	*SLC34A2*
ACVR1B	*CBFB*	*DNMT3A*	*FH*	*KEL*	*MYCL*	*PMS2*	*SMAD2*
AKT1	*CBL*	*DOT1L*	*FLCN*	*KIT*	*MYCL1*	*POLD1*	*SMAD4*
AKT2	*CCND1*	*EED*	*FLT1*	*KLHL6*	*MYCN*	*POLE*	*SMARCA4*
AKT3	*CCND2*	*EGFR*	*FLT3*	*KMT2A*	*MYD88*	*PPARG*	*SMARCB1*
ALK	*CCND3*	*EMSY*	*FOXL2*	*KMT2D*	*NBN*	*PPP2R1A*	*SMO*
ALOX12B	*CCNE1*	*EP300*	*FUBP1*	*KRAS*	*NF1*	*PPP2R2A*	*SNCAIP*
AMER1	*CD22*	*EPHA3*	*GABRA6*	*LTK*	*NF2*	*PRDM1*	*SOCS1*
APC	*CD274*	*EPHB1*	*GATA3*	*LYN*	*NFE2L2*	*PRKAR1A*	*SOX2*
AR	*CD70*	*EPHB4*	*GATA4*	*MAF*	*NFKBIA*	*PRKCI*	*SOX9*
ARAF	*CD74*	*ERBB2*	*GATA6*	*MAP2K1*	*NKX2-1*	*PTCH1*	*SPEN*
ARFRP1	*CD79A*	*ERBB3*	*GID4*	*MAP2K2*	*NOTCH1*	*PTEN*	*SPOP*
ARID1A	*CD79B*	*ERBB4*	*GNA11*	*MAP2K4*	*NOTCH2*	*PTPN11*	*SRC*
ASXL1	*CDC73*	*ERCC4*	*GNA13*	*MAP3K1*	*NOTCH3*	*PTPRO*	*STAG2*
ATM	*CDH1*	*ERG*	*GNAQ*	*MAP3K13*	*NPM1*	*QKI*	*STAT3*
ATR	*CDK12*	*ERRFI1*	*GNAS*	*MAPK1*	*NRAS*	*RAC1*	*STK11*
ATRX	*CDK4*	*ESR1*	*GRM3*	*MCL1*	*NT5C2*	*RAD21*	*SUFU*
AURKA	*CDK6*	*ETV4*	*GSK3B*	*MDM2*	*NTRK1*	*RAD51*	*SYK*
AURKB	*CDK8*	*ETV5*	*H3F3A*	*MDM4*	*NTRK2*	*RAD51B*	*TBX3*
AXIN1	*CDKN1A*	*ETV6*	*HDAC1*	*MED12*	*NTRK3*	*RAD51C*	*TEK*
AXL	*CDKN1B*	*EWSR1*	*HGF*	*MEF2B*	*NUTM1*	*RAD51D*	*TERC*
BAP1	*CDKN2A*	*EZH2*	*HNF1A*	*MEK1*	*P2RY8*	*RAD52*	*TERT*
BARD1	*CDKN2B*	*EZR*	*HRAS*	*MEK2*	*PALB2*	*RAD54L*	*TET2*
BCL2	*CDKN2C*	*FAM123B*	*HSD3B1*	*MEN1*	*PARK2*	*RAF1*	*TGFBR2*
BCL2L1	*CEBPA*	*FAM46C*	*ID3*	*MERTK*	*PARP1*	*RARA*	*TIPARP*
BCL2L2	*CHEK1*	*FANCA*	*IDH1*	*MET*	*PARP2*	*RB1*	*TMPRSS2*
BCL6	*CHEK2*	*FANCC*	*IDH2*	*MITF*	*PARP3*	*RBM10*	*TNFAIP3*
BCOR	*CIC*	*FANCG*	*IGF1R*	*MKNK1*	*PAX5*	*REL*	*TNFRSF14*
BCORL1	*CREBBP*	*FANCL*	*IKBKE*	*MLH1*	*PBRM1*	*RET*	*TP53*
BCR	*CRKL*	*FAS*	*IKZF1*	*MLL*	*PD1*	*RICTOR*	*TSC1*
BRAF	*CSF1R*	*FBXW7*	*INPP4B*	*MLL2*	*PDCD1*	*RNF43*	*TSC2*
BRCA1	*CSF3R*	*FGF10*	*IRF2*	*MMSET*	*PDCD1LG2*	*ROS1*	*TYRO3*
BRCA2	*CTCF*	*FGF12*	*IRF4*	*MPL*	*PDGFRA*	*RPTOR*	*U2AF1*
BRD4	*CTNNA1*	*FGF14*	*IRS2*	*MRE11A*	*PDGFRB*	*RSPO2*	*VEGFA*
BRIP1	*CTNNB1*	*FGF19*	*JAK1*	*MSH2*	*PDK1*	*SDC4*	*VHL*
BTG1	*CUL3*	*FGF23*	*JAK2*	*MSH3*	*PDL1*	*SDHA*	*WHSC1*
BTG2	*CUL4A*	*FGF3*	*JAK3*	*MSH6*	*PDL2*	*SDHB*	*WHSC1L1*
BTK	*CXCR4*	*FGF4*	*JUN*	*MST1R*	*PIK3C2B*	*SDHC*	*WT1*
C11orf30	*CYP17A1*	*FGF6*	*KDM5A*	*MTAP*	*PIK3C2G*	*SDHD*	*XPO1*
C17orf39	*DAXX*	*FGFR1*	*KDM5C*	*MTOR*	*PIK3CA*	*SETD2*	*XRCC2*
CALR	*DDR1*	*FGFR2*	*KDM6A*	*MUTYH*	*PIK3CB*	*SF3B1*	*ZNF217*
CARD11	*DDR2*	*FGFR3*	*KDR*	*MYB*	*PIK3R1*	*SGK1*	*ZNF703*

SUPPLEMENTARY FIGURES

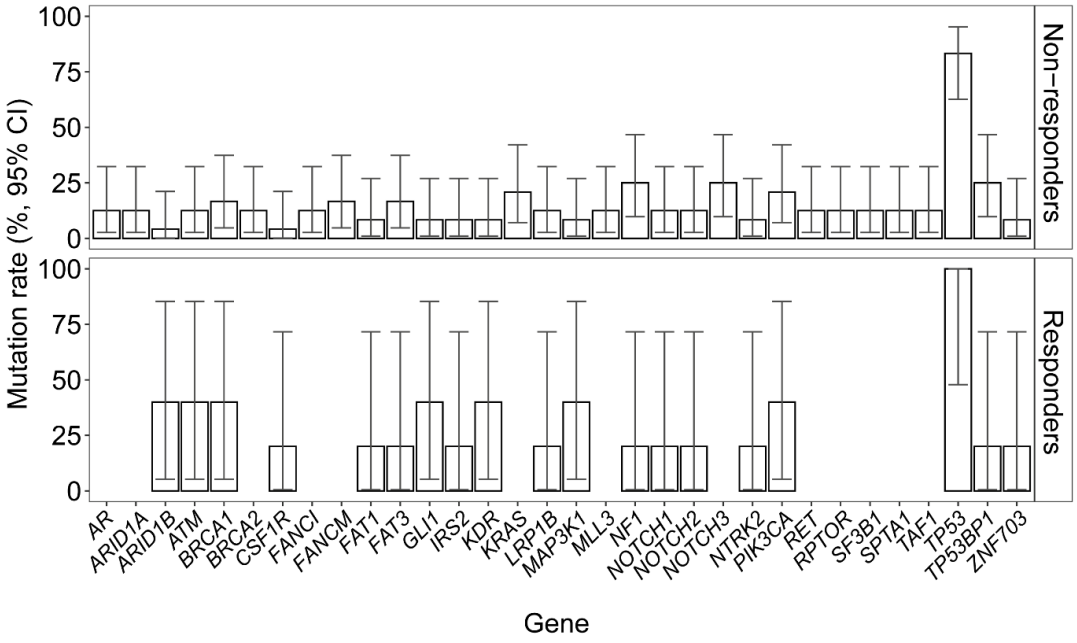
Supplementary Figure S1. Kaplan-Meier estimates of progression-free survival in patients with high (≥ median) or low (<median) mesothelin expression (n=62). The median value of mesothelin expression is 70% of tumor cells staining positive for mesothelin at the intensity level of 2+/3+.



Supplementary Figure S2. Geometric mean plasma concentration-time profiles of anetumab ravtansine antibody-drug conjugate after administration of 6.5 mg/kg anetumab ravtansine plus 30 mg/m² pegylated liposomal doxorubicin every three weeks. Minimal lower limit of quantification (LLOQ) was 0.4 mg/L. Samples in parts 1, 2 and 3 of study were collected at 0.5, 1, 1.5, 2, 3, 5, 8, 24, 48, 168 and 336 hours after the start of infusion on cycle 1; in less frequency on cycles 2 and 3; and every third cycle after cycle 4.



Supplementary Figure S3. The mutation rate of genes in ovarian cancer patients with response or non-response to anetumab ravtansine plus pegylated liposomal doxorubicin. Responders are patients with partial response or complete response and non-responders are patients with stable disease, or progressive disease. Error bars represent 95% Clopper-Pearson confidence intervals.



Supplementary Figure S4. Somatic mutations detected in the tumor tissue samples of ovarian cancer patients with best overall response. Patient samples are shown in columns. Genes and their overall mutation frequencies are represented in rows (only the genes with mutation frequencies greater than 11% are shown). Matrix cells are colored according to genomic functional consequence. Best overall response status is shown as a heatmap bar at the bottom of the figure.