HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2019 June 15.

Published in final edited form as:

Clin Cancer Res. 2018 June 15; 24(12): 2749–2757. doi:10.1158/1078-0432.CCR-17-1775.

Phase I Study of MEDI3617, a Selective Angiopoietin-2 Inhibitor Alone and Combined with Carboplatin/Paclitaxel, Paclitaxel, or Bevacizumab for Advanced Solid Tumors

David M. Hyman[1], **Naiyer Rizvi**[2], **Ronald Natale**[3], **Deborah K. Armstrong**[4], **Michael Birrer**[5], **Lawrence Recht**[6], **Efrat Dotan**[7], **Vicky Makker**[1], **Thomas Kaley**[1], **Denison Kuruvilla**[8], **Matthew Gribbin**[9], **Jennifer McDevitt**[9], **Dominic W. Lai**[9], and **Mohammed Dar**[9]

[1]Developmental Therapeutics, Memorial Sloan Kettering Cancer Center, New York, New York. [2]Division of Hematology/Oncology, Columbia University Medical Center, New York, New York. [3]Hematology/Oncology, Cedars-Sinai Medical Center, Los Angeles, California. [4]Oncology, Johns Hopkins University, Baltimore, Maryland. [5]Hematology/Oncology, Massachusetts General Hospital, Boston, Massachusetts. [6]Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, California. [7]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, Pennsylvania. [8]Clinical Pharmacology, Med Immune, Mountain View, California. [9]Clinical Development Oncology, MedImmune, Gaithersburg, Maryland.

Abstract

Purpose: This first-in-human study aimed to determine the MTD and safety of MEDI3617, a selective anti–angiopoietin-2 (Ang2) mAb, alone and combined with bevacizumab or cytotoxic chemotherapy.

Patients and Methods: This phase I/Ib, multicenter, open-label, dose-escalation and dose-expansion study evaluated patients with advanced solid tumors. Patients received intravenous MEDI3617 as monotherapy [5–1,500 mg every 3 weeks (Q3W)] or with bevacizumab every 2

Corresponding Author: David M. Hyman, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. Phone: 646-888-4544; Fax:646-888-4268; hymand@mskcc.org.
Current address for D.W. Lai: Abbvie, San Francisco, California.

Authors' Contributions

Conception and design: D.M. Hyman, V. Makker, M. Gribbin, J. McDevitt, M. Dar

Development of methodology: D. Kuruvilla, J. McDevitt

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D.M. Hyman, N. Rizvi, R. Natale, D.K. Armstrong, M. Birrer, L. Recht, E. Dotan, V. Makker, T. Kaley

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.M. Hyman, D.K. Armstrong, M. Birrer, V. Makker, T. Kaley, D. Kuruvilla, M. Gribbin, J. McDevitt, M. Dar

Writing, review, and/or revision of the manuscript: D.M. Hyman, N. Rizvi, R. Natale, D.K. Armstrong, M. Birrer, L. Recht, E. Dotan, V. Makker, T. Kaley, D. Kuruvilla, M. Gribbin, J. McDevitt, D.W. Lai, M. Dar

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M. Gribbin, J. McDevitt

Study supervision: D.M. Hyman, V. Makker, J. McDevitt, D.W. Lai, M. Dar

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed by the other authors.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

weeks (Q2W) or Q3W, weekly paclitaxel, or carboplatin plus paclitaxel Q3W. Dose expansions included a monotherapy cohort in platinum-resistant ovarian cancer and a bevacizumab combination cohort in bevacizumab-refractory malignant glioma. Safety/tolerability, pharmacokinetics, pharmacodynamics, and clinical activity were assessed.

Results: We enrolled 116 patients. No formal MTD was identified (monotherapy or combination therapy). MEDI3617 demonstrated linear pharmacokinetics and maximal accumulation of peripheral Ang2 binding at doses above 300mgQ3W. MEDI3617 monotherapy safety profile was acceptable, except in advanced ovarian cancer [prolonged grade 3 edema-associated adverse events (AE) occurred]. Otherwise, MEDI3617 combined with chemotherapy or bevacizumab was well tolerated. The AE profiles of MEDI3617 and bevacizumab were largely non-overlapping. Overall response rates in ovarian cancer and glioma monotherapy dose-expansion arms were 6% and 0%, respectively.

Conclusions: Recommended MEDI3617 monotherapy dosage is 1,500 mg Q3W or 1,000 mg Q2W, except in ovarian cancer. Although peripheral edema has occurred with other Ang2 inhibitors, the severity and duration seen here in ovarian cancer potentially identifies a new, clinically significant safety signal for this class of agents. On the basis of limited clinical activity, MEDI3617 development was discontinued.

Introduction

Angiopoietins and the tyrosine kinase with immunoglobulin like and EGF-like domains 2 (Tie2) receptor have important roles in the physiologic growth and maintenance of blood vessels, as well as in pathological angiogenesis in malignancy (1). Overexpression of angiopoietin-2 (Ang2) has been documented in several solid tumor malignancies, including breast cancer (2), colorectal cancer (3), non–small cell lung cancer (NSCLC; ref. 4), ovarian cancer (5), and glioblastoma (6). In breast cancer and NSCLC, Ang2 overexpression has been associated with aggressive disease and poor prognosis (2, 4), and in ovarian tumors, a low ratio of angiopoietin-1 (Ang1)/Ang2 expression has been correlated with increased microvessel density and poorer prognosis (7). Dysregulation of angiogenic signaling disrupts the local balance of proangiogenic cytokine factors, which increases the formation of tumoral vasculature and the supply of oxygen and nutrients available to growing tumors (8).

Because Ang2 has limited expression in normal tissues but broad expression in the remodeling vasculature of human tumors, it is an attractive target for antiangiogenic cancer therapy. High levels of both VEGF and Ang2 have been shown to correlate with a worse prognosis than elevation of either VEGF or Ang2 alone (4, 5). Thus, dual antiangiogenic therapy consisting of a VEGF inhibitor and an Ang2 inhibitor may provide additional benefit.

MEDI3617 is an investigational, fully humanized immunoglobulin G1 kappa (IgG1κ) mAb that binds to human Ang2 with approximately 20-fold greater affinity versus human Ang1 (9). This binding prevents the interaction of the Ang2 ligand with the Tie2 receptor, inhibiting angiogenesis and thereby tumor growth (9). In preclinical studies, MEDI3617 inhibited the number of tumor cell–induced blood vessels in a renal cell tumor model (10)

and inhibited tumor growth in xenograft models of colorectal cancer, renal cell cancer, ovarian cancer, and hepatocelluar carcinoma (9). A dose-dependent effect on tumor growth inhibition was observed with MEDI3617 between 1 and 10 mg/kg in mice bearing Colo205 tumors, with 56% inhibition observed at 1 mg/ kg and 86% inhibition at 10 mg/kg (9).

We report the final results of a first-in-human study of MEDI3617 that was carried out to determine the MTD or optimal biologic dose (OBD) and the safety profile of MEDI3617 administered as a single agent and in combination with the VEGF inhibitor bevacizumab, as well as in combination with paclitaxel, or carboplatin and paclitaxel in patients with advanced solid tumor malignancies refractory to standard therapy or for which no standard therapy exists. The inclusion of dose expansion arms evaluating MEDI3617 as monotherapy in platinum-resistant ovarian cancer and in combination with bevacizumab in bevacizumab-refractory recurrent malignant glioma allowed for preliminary evaluation of efficacy in defined populations of particular interest. This trial is registered at ClinicalTrials.gov (NCT01248949). The primary objective of the dose-escalation phase was to determine the MTD or OBD and the safety profile of MEDI3617 administered as a single agent and in combination with bevacizumab, paclitaxel, carboplatin, and paclitaxel in patients with advanced solid tumor malignancies refractory to standard therapy or for which no standard therapy exists. Secondary objectives included determination of the pharmacokinetics, pharmacodynamics, immunogenicity, and the antitumor activity of MEDI3617 as a single agent and in combination with bevacizumab or chemotherapy. Evaluation of predictive biomarkers for MEDI3617 treatment was an exploratory objective.

Patients and Methods

Patients

Eligible patients were at least 18 years of age, had advanced solid tumors refractory to standard therapy or for which no standard therapy exists (monotherapy arm), and lacked curative options for whom chemotherapy and/or bevacizumab was standard of care (combination arms). Patients were also required to have a Karnofsky performance status of at least 60 for patients with recurrent malignant glioma or at least 70 for patients with other malignancies and adequate organ and marrow function (hemoglobin ≥9 g/dL, absolute neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, aspartate aminotransferase [AST] and alanine aminotransferase [ALT] levels ≤2× upper limit of normal [ULN; no liver metastasis] or ≤5× ULN [patients with liver metastasis], bilirubin ≤1.5× ULN [except for patients with Gilbert's disease: ≤5× ULN], and creatinine clearance ≥50 mL/min as determined by the Cockcroft-Gault equation). Prior radiotherapy was allowed if exposure was not estimated to have exceeded an area of 25% of marrow space.

Patients in the MEDI3617 single-agent, dose-expansion arm in ovarian cancer were required to have recurrent or persistent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma, Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, and at least 1 prior line of treatment, including at least 1 prior platinum-based therapy. Patients in the expansion cohorts were required to have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (v1.1) or MacDonald criteria in the case of malignant gliomas. The protocol was approved by the institutional review board or

independent ethics committee at each site and complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki, and local laws. All patients provided written informed consent before any protocol-related procedures, including screening evaluations, were performed.

Study design

This was a first-in-human, phase I/Ib, 3+3 dose escalation, multicenter, open-label study of MEDI3617 in patients with advanced solid tumors. As shown in Fig. 1, the phase I portion consisted of a single-agent MEDI3617 dose-escalation phase, followed by a monotherapy dose-expansion phase in patients with advanced recurrent ovarian cancer. The primary and secondary end points were the same for both phases. Dose escalation followed a standard 3+3 design, with patients receiving MEDI3617 at doses of 5, 10, 20, 100, 300, 1,000, or 1,500 mg intravenously (IV) on day 1 of a 3-week cycle. In the phase I dose expansion arm, ovarian cancer patients initially received MEDI3617 at a dose of 1,500 mg IV on day 1 of a 3-week cycle. Following identification of edema-associated adverse events (AE), the dose was lowered to 1,000 mg on day 1 of a 3-week cycle for the remainder of enrolled patients.

The phase Ib portion consisted of multiple combination dose-escalation arms (two MEDI3617 plus bevacizumab arms and three MEDI3617 plus chemotherapy arms), as well as one disease-specific dose-expansion combination cohort comprising patients with bevacizumab-refractory recurrent malignant glioma who received MEDI3617 1,000 mg IV plus bevacizumab 10 mg/kg IV on days 1 and 15 of a 4-week cycle. Further details are provided in Fig. 1.

In all treatment arms, MEDI3617 was infused over 60 minutes at doses less than 1,000 mg and over 90 minutes at doses of at least 1,000 mg. The time from the first dose of MEDI3617 to 21 or 28 days, depending on treatment arm (MEDI3617 administration every 3 weeks [Q3W] versus every 2 weeks [Q2W]), was defined as the dose-limiting toxicity (DLT) period; DLTs were all AEs that were suspected of having a causal relationship to MEDI3617 and were at least grade 3. In the MEDI3617 plus carboplatin and paclitaxel arm, treatment was continued for up to 6 cycles or until progressive disease or unacceptable toxicity; in all other treatment arms, treatment was continued until progressive disease, unacceptable toxicity, initiation of other anticancer therapy, or other reason for discontinuation.

Study assessments

Safety assessments included collection of AEs, serious AEs (SAE), and abnormal clinical and laboratory evaluations from the signing of the informed consent form through 90 days after the last dose of MEDI3617. AEs were summarized for all patients who received at least one dose of any study drug. AEs and SAEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.0.

Pharmacokinetic assessments included maximum observed serum concentration (C_{max}), area under the plasma concentration–time curve (AUC), systemic clearance (CL), and terminal half-life ($t_{1/2}$). Blood samples for pharmacokinetic assessments were collected on days 1, 2,

4, 8, and 15 of cycle 1, day 1 of each subsequent cycle, at end of treatment, 30 days after the last dose of MEDI3617, and every 3 months thereafter. Pharmacodynamic assessments included profiles of total Ang2 (free and bound) following administration of MEDI3617 on days 1, 2, 4, 8, and 15 of cycle 1, day 1 of each subsequent cycle, at end of treatment, 30 days after the last MEDI3617 dose, and every 3 months thereafter. Immunogenicity was determined by a validated immunoassay examining the presence of anti-drug antibody (ADA) in blood samples collected prior to initial infusion of MEDI3617 on day 1 of each cycle, at end of treatment, and at 30 days, 3 months, and 6 months after the last dose of MEDI3617. Antitumor activity was evaluated on the basis of objective response rate (ORR) and progression-free survival (PFS). Tumor response was determined with RECIST v1.1 in patients with malignancies other than malignant glioma and with the MacDonald criteria in patients in the recurrent malignant glioma cohort. In malignancies other than malignant glioma, imaging was performed every 2 cycles up to cycle 13 (cycles 2, 4, 8, 10, and 12), then every 4 cycles thereafter. In patients with malignant glioma, imaging was performed every 6 weeks beginning with cycle 1, day 1 (±3 days).

Statistical analyses

Efficacy and safety analyses were based on the safety population, defined as all patients who received treatment with MEDI3617. Secondary analyses to evaluate efficacy activity endpoints were performed using the efficacy evaluable population, defined as all patients in the safety population who completed at least one post-baseline disease assessment.

In general, categorical data were summarized by the number and percentage of patients falling within each category, and continuous variables were summarized by descriptive statistics including mean, standard deviation, median, minimum, and maximum. PFS was estimated using the Kaplan–Meier method. Data analyses were conducted with SAS Version 9.3 or higher (SAS Institute Inc.), in a UNIX environment. All SAS programs used to generate analytical results were developed and validated according to MedImmune SAS programming standards and MedImmune SAS validation procedures.

Results

Patients

Across all treatment arms, 116 patients were enrolled in the study at 11 US sites between October 2010 and 2015. The phase I MEDI3617 monotherapy portion contained 25 patients in the dose-escalation arm and 17 patients in the dose-expansion arm ($n = 42$ total). In the phase Ib MEDI3617 combination portion, the dose-escalation phase contained 16 patients in the MEDI3617 plus bevacizumab 15 mg/kg Q3W arm, 27 patients in the MEDI3617 plus bevacizumab 10 mg/kg Q2W arm, 13 patients in the MEDI3617 plus paclitaxel arm, and 7 patients in the MEDI3617 plus carboplatin and paclitaxel arm, and the MEDI3617 plus bevacizumab Q2W dose expansion contained 11 patients with recurrent glioma. The median age of the total population was 60 years (range, 21–81 years), and 56% of the population was female. Patient demographic and baseline characteristics are summarized by cohort in Table 1.

A total of 116 patients were included in the safety population. All 116 patients have discontinued treatment with the last visit of the last patient taking place on October 22, 2015. Reasons for discontinuation included disease progression (56%), AEs (22.4%), investigator discretion (8.6%), other (7.8%), withdrawal of consent (4.3%), and death (0.9%). The study was closed due to lack of clinical activity reported with MEDI3617 as monotherapy and as combination therapy, and not due to any safety issues related to MEDI3617 treatment, with the exception of the ovarian cancer dose-expansion arm, which was closed due to multiple treatment-related edema-associated AEs. Clinical development of MEDI3617 was discontinued.

Safety and tolerability

During phase I MEDI3617 monotherapy dose escalation, 1 patient at the 20-mg Q3W dose level experienced a DLT of uncomplicated grade 4 neutropenia; however, the MTD of MEDI3617 was not reached after evaluating the highest protocol-specified dose of 1,500 mg Q3W. During the phase Ib MEDI3617 combination portion, 5 patients experienced DLTs across the various combination dose-escalation arms, including grade 3 hypertension (MEDI3617 1,500 mg/bevacizumab 15 mg Q3W), grade 3 female genital tract fistula (MEDI3617 60 mg/bevacizumab 10 mg/kg Q2W), grade 3 acute pancreatitis (MEDI3617 600 mg/bevacizumab 10 mg/kg Q2W), grade 3 increase in troponin with grade 4 decrease in ejection fraction, grade 3 nausea, and grade 3 vomiting (in 1 patient; MEDI3617 600 mg/ paclitaxel 80 mg/m^2 QW), and nephrotic syndrome (MEDI3617 1500 mg/carboplatin AUC 5/ paclitaxel 175 mg/m^2 Q3W). However, an MTD was not clearly reached for any of the dose-escalation arms. In the MEDI3617 plus bevacizumab Q3W dose-escalation arm, at the highest dose level tested (1,500 mg Q3W and 15 mg/kg Q3W, respectively), 5 of 6 patients were evaluable for DLTs and 1 DLT was observed (grade 3 hypertension). In the related cohort of the MEDI3617 plus bevacizumab Q2W dose-escalation arm, however, the MTD was not reached after evaluating the highest protocol-specified dose of MEDI3617 1,000 mg Q2W plus bevacizumab 10 mg/kg Q2W. DuringMEDI3617 plus paclitaxel dose escalation, the MTD was not reached, as no DLTs were observed at the highest dose level (MEDI3617 1,000 mg Q2W and paclitaxel 80 mg/m^2 QW, respectively) after enrolling a total of 5 evaluable patients. At the highest dose level of the MEDI3617 plus carboplatin and paclitaxel arm (MEDI3617 1,500 mg Q3W, carboplatin AUC 5, and paclitaxel 175 mg/m^2 Q3W, respectively), one DLT of grade 3 nephrotic syndrome was observed in 3 evaluable patients.

Treatment-emergent AEs of any grade with an incidence greater than 20% and all treatment-related grade 3 or higher AEs are listed by cohort in Table 2. Grade 3 or higher AEs, regardless of attribution, are shown in Supplementary Table S1. Treatment-related AEs of interest in the combined MEDI3617 monotherapy arms(n = 42) and the combined MEDI3617/bevacizumab arms (n = 54) included, respectively, hypertension (2.4% and 16.7%), proteinuria (2.4% and 7.4%), female genital tract fistula (0 and 1.9%), peripheral edema (16.7% and 9.3%), weight gain (16.7% and 1.9%), lymphedema (4.8% and 0), and pleural effusion (4.8% and 1.9%).

Treatment-related grade 3/4AEsareshown by cohort in Table 2. In the phase I dose-expansion cohort in ovarian cancer (n = 17), single-agent MEDI3617 at a dose of 1,500 mg Q3W was associated with grade 3 edema-related toxicities; 2 patients had persistent grade 3 peripheral edema and lymphedema, respectively, despite treatment discontinuation after 2 cycles. Therefore, a dose of MEDI3617 1,000 mg Q3W was selected for subsequent patients in this cohort (n = 15). However, multiple patients subsequently experienced treatment-related edema-associated AEs (peripheral edema: grade 1, n = 4; grade 2, n = 1; grade 3, n = 1; edema: grade 2, n = 1; grade 3, n = 1) with accompanying weight gain following their initial dose; therefore, enrollment in this cohort was terminated. In total, 10 patients with ovarian cancer received MEDI3617/bevacizumab, and a total of 5 patients with ovarian cancer received MEDI3617/chemotherapy. Edema related events of this severity were not observed in ovarian cancer patients in the dose-escalation phase (doses of 5 mg, 10 mg, and 20 mg) or in patients with other tumor types receiving MEDI3617 at either 1,000 mg or 1,500 mg Q3W or in combination with bevacizumab or chemotherapy. The MEDI3617 plus bevacizumab combinations were tolerable, including in patients with ovarian cancer, with a low incidence of grade 3/4 hypertension, proteinuria, and other AEs. No treatment-related grade 3/4 AEs occurred in the MEDI3617 plus bevacizumab dose-expansion cohort in patients with recurrent malignant glioma.

The overall rate of treatment discontinuation due to treatment related AEs was 9.5% in the combined MEDI3617 monotherapy arms and 13% in the MEDI3617/bevacizumab combination therapy arms. The most frequent treatment-related AE leading to discontinuation overall was peripheral edema (n = 3). Overall, 7 patients died due to AEs, including 3 patients in the MEDI3617 monotherapy arm (due to respiratory failure, small intestine obstruction, and pneumonia; n = 1 each), 3 patients in the MEDI3617/bevacizumab combination arm (all due to progressive disease), and 1 patient in the MEDI3617/paclitaxel combination arm (due to acute respiratory failure and cardiac arrest). None of the AEs that led to death was considered related to treatment.

Pharmacokinetics, pharmacodynamics, and immunogenicity

Pharmacokinetic parameters for MEDI3617 are summarized in Supplementary Table S2. Serum concentrations of MEDI3617 versus time are shown by cohort in Fig. 2A–F. MEDI3617 exhibited nonlinear pharmacokinetics over the dose range of 5 to 100 mg Q3W. The increase in MEDI3617 exposure (AUC and C_{max}) was more than dose proportional, and the systemic CL of MEDI3617 decreased with dose. The pharmacokinetics approached linearity at dose levels of at least 300 mg Q3W. The mean systemic CL and terminal $t_{1/2}$ of MEDI3617 following intravenous infusions in the dose range of 300 to 1,500 mg were 355 to 679 mL/d and 6 to 8 days, respectively. Steady state was generally reached after the third dose. There was no difference in MEDI3617 pharmacokinetics between single-agent and combination therapy with bevacizumab or chemotherapy, indicating no impact of these combinations on MEDI3617 pharmacokinetics.

Maximum accumulation of total Ang2 (≈100x baseline) was observed at MEDI3617 doses of 300 mg Q3W and above, and generally reached steady state after the third dose. The

recovery was dose dependent. Serum concentrations of Ang2 versus time are shown by cohort in Fig. 3A–F. None of the patients had a positive ADA response to MEDI3617.

Clinical response

The efficacy evaluation was based on the safety population (n = 116). Objective responses and PFS by cohort are shown in Supplementary Table S3. In all patients receiving MEDI3617 monotherapy (n = 42), the ORR was 2.4% (1/42). The highest ORRs were observed in the MEDI3617 plus bevacizumab Q2W and MEDI3617 plus paclitaxel cohorts (7% and 15%, respectively). In the dose expansion cohort in bevacizumab-refractory recurrent malignant glioma (n = 11) no objective responses were observed with the combination of MEDI3617 plus bevacizumab (based on MacDonald criteria), 2 patients (18%) had stable disease, and 6 patients (55%) had progressive disease (3 were not evaluable).

In the dose-expansion cohort of MEDI3617 monotherapy in platinum-resistant ovarian cancer (n = 17), the ORR was 6% (per RECIST criteria). One patient with ovarian cancer in the MEDI3617 plus bevacizumab Q3W dose escalation cohort and 2 patients (one with ovarian cancer) in the MEDI3617 plus paclitaxel cohort had responses lasting more than 68 weeks.

Discussion

In this first-in-human phase I/Ib trial of the Ang2 inhibitor MEDI3617 in patients with advanced solid tumors, no MTD for MEDI3617 was defined as monotherapy or in combination with bevacizumab or cytotoxic chemotherapy when the highest protocol-defined doses were evaluated. The pharmacodynamics data demonstrated that MEDI3617 achieved maximal anti-angiogenic inhibition at doses of 300 mg Q3W and above. The pharmacodynamics data, along with the observed linear pharmacokinetics profile in the same dose range, indicated that the OBD may be selected in the dose range of 300 mg to 1,500 mg Q3W. On the basis of the safety, pharmacokinetics, and pharmacodynamics observations, the recommended monotherapy dose for MEDI3617 (excluding patients with ovarian cancer) is 1,500 mg Q3W.

Patients with ovarian cancer appeared to be particularly sensitive to early-onset grade 2 or 3 edema-associated AEs with accompanying weight gain while receiving MEDI3617 as monotherapy at 1,000 and 1,500 mg Q3W; therefore, a recommended dose for patients with ovarian cancer was not defined during this study. Edema has been reported as a common AE across multiple investigational agents that include Ang2 inhibition (11, 12). Consistent with this clinical observation, Ang2-deficient mice demonstrate defective remodeling and maturation of lymphatic vasculature (13). Taken together, these observations suggest that Ang2 inhibitors promote edema via direct interaction with lymphatics but, to our knowledge, severe or prolonged edema and weight gain have not been reported in the clinical experience with other inhibitors of this target. In the impacted patients reported here, alternative etiologies of severe edema and weight gain, such as nephrotic syndrome, heart failure, thrombosis, or direct venous compression, were all ruled out. Moreover, the specific risk factors for the development of severe treatment-related edema and ovarian cancer were not

identified. The medical histories of ovarian cancer patients, both those who did and did not experience severe edema and/or weight gain, were examined, and no consistent risk factor, including prior lymph node dissection, was identified. Interestingly, severe edema-associated AEs were not observed in ovarian cancer patients treated with the bevacizumab combination at doses similar to the MEDI3617 monotherapy cohorts. Whether this is attributable to small sample size or possibly to some protective effective of bevacizumab on the development of MEDI3617-associated edema is unclear.

In a study of murine models of glioblastoma, dual antiangiogenic therapy with MEDI3617 and the pan-VEGF receptor tyrosine kinase inhibitor cediranib improved survival over that with either agent as monotherapy, delayed tumor growth, increased tumor necrosis, and improved vascular normalization (14). In the current study, antitumor activity was seen in 1 patient with recurrent glioma (bevacizumab naive) treated with dual antiangiogenic therapy with MEDI3617 plus bevacizumab during dose escalation (based on MacDonald criteria); however; when the combination was evaluated in a dose-expansion cohort of patients with bevacizumab-refractory recurrent glioma, most responses were SD or progressive disease. The observed toxicity profile of MEDI3617 monotherapy and the known bevacizumab safety profile (15) do not appear to overlap, and the combination had an acceptable safety and tolerability profile. In the bevacizumab-refractory recurrent malignant glioma dose-expansion cohort, MEDI3617 Q2W in combination with bevacizumab 10 mg Q2W was well tolerated, with a lack of treatment-related grade 3/4 AEs.

Some antitumor activity was observed with MEDI3617 as a single agent and in combination therapy in patients with ovarian cancer. The CA125 response in patients with ovarian cancer demonstrated the biochemical antitumor activity of MEDI3617, but evaluation in a larger patient population would be necessary to determine the significance of this finding and its relationship with clinical outcome. Furthermore, the advanced recurrent ovarian cancer monotherapy dose-expansion cohort was closed early due to the occurrence of treatment-related edema-associated AEs with MEDI3617 1,500 and 1,000 mg Q3W. In addition, a phase III study of an Ang 1,2-targeting biologic (trebananib) plus standard chemotherapy in ovarian cancer failed to demonstrate a statistically significant improvement in overall survival compared with standard chemotherapy, despite improving PFS (11, 16).

In conclusion, the recommended single-agent MEDI3617 dose is 1,500 mg Q3W (1,000 mg Q2W) for patients with advanced solid tumors, excluding advanced ovarian cancer where multiple cases of treatment-related edema-associated AEs were observed, resulting in treatment discontinuation. MEDI3617 was combined with bevacizumab (Q2W and Q3W) and chemotherapy (weekly paclitaxel, carboplatin plus paclitaxel) at its recommended monotherapy dose (1,000 mg Q2W or 1,500 mg Q3W) and was well tolerated overall, without exacerbation of the safety profile for either combination agent(s), including edema-associated AEs. A central hypothesis of this study was that the non-overlapping mechanisms of anti-angiogenic effects mediated by Ang2 and VEGF receptor 2 (VEGFR2) would permit the safe combination of inhibitors targeting these two pathways. In distinction, the combination of more than one VEGFR2 inhibitor has been generally intolerable (17). However, although the current study design did not permit definitive evidence of the activity of MED3617 either alone or in combination with bevacizumab, overall, limited activity was

observed and the decision was made not to pursue further development. The absence of reliable biomarkers to identify patients whose tumors are susceptible to inhibition of these anti-angiogenic pathways remains a substantial unmet medical need.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This study was sponsored by MedImmune, the global biologics R&D arm of AstraZeneca. Medical writing and editorial support were provided by Amy Zannikos, PharmD, and Stephanie Leinbach, PhD, of Peloton Advantage and were funded by MedImmune. The authors thank the patients and clinical personnel who participated in this study. The authors also thank Vanessa Yu, PhD, of MedImmune for her contributions to the editing and data verification of this article. D.M. Hyman acknowledges the NIH for providing a Memorial Sloan Kettering Cancer Center Support Grant/Core Grant (P30 CA008748).

D.M. Hyman reports receiving commercial research grants from Astra Zeneca, Loxo Oncology, and Puma Biotechnology, and is a consultant/ advisory board member for AstraZeneca, Atara Biotherapeutics, Boehringer Ingelheim, Chugai, CytomX, and Pfizer. R. Natale reports receiving commercial research grants from Amgen, AstraZeneca, MedImmune, and Pfizer, and is a consultant/advisory board member for AstraZeneca and Eli Lilly. V. Makker reports receiving speakers bureau honoraria from Eisai Pharmaceuticals.

References

1. Shim WS, Ho IA, Wong PE. Angiopoietin: a TIE(d) balance in tumor angiogenesis. Mol Cancer Res 2007;5:655–65. [PubMed: 17634421]
2. Sfiligoi C, de Luca A, Cascone I, Sorbello V, Fuso L, Ponzone R, et al. Angiopoietin-2 expression in breast cancer correlates with lymph node invasion and short survival. Int J Cancer 2003;103:466–74. [PubMed: 12478661]
3. Yoshida Y, Oshika Y, Fukushima Y, Tokunaga T, Hatanaka H, Kijima H,et al. Expression of angiostatic factors in colorectal cancer. Int J Oncol 1999;15:1221–5. [PubMed: 10568831]
4. Tanaka F, Ishikawa S, Yanagihara K, Miyahara R, Kawano Y, Li M, et al. Expression of angiopoietins and its clinical significance in non-small cell lung cancer. Cancer Res 2002;62:7124–9. [PubMed: 12460935]
5. Zhang L, Yang N, Park JW, Katsaros D, Fracchioli S, Cao G, et al. Tumor-derived vascular endothelial growth factor up-regulates angiopoietin-2 in host endothelium and destabilizes host vasculature, supporting angiogenesis in ovarian cancer. Cancer Res 2003;63: 3403–12. [PubMed: 12810677]
6. Audero E, Cascone I, Zanon I, Previtali SC, Piva R, Schiffer D, et al. Expression of angiopoietin-1 in human glioblastomas regulates tumor induced angiogenesis: *in vivo* and *in vitro* studies. Arterioscler Thromb Vasc Biol 2001;21:536–41. [PubMed: 11304469]
7. Hata K, Nakayama K, Fujiwaki R, Katabuchi H, Okamura H, Miyazaki K. Expression of the angopoietin-1, angopoietin-2, Tie2, and vascular endothelial growth factor gene in epithelial ovarian cancer. Gynecol Oncol 2004;93:215–22. [PubMed: 15047239]
8. Bergers G, Benjamin LE. Tumorigenesis and the angiogenic switch. Nat Rev Cancer 2003;3:401–10. [PubMed: 12778130]
9. Leow CC, Coffman K, Inigo I, Breen S, Czapiga M, Soukharev S, et al.MEDI3617, a human anti-Angiopoietin 2 monoclonal antibody, inhibits angiogenesis and tumor growth in human tumor xenograft models. Int J Oncol 2012;40:1321–30. [PubMed: 22327175]
10. Molnar N, Siemann DW. Inhibition of endothelial/smooth muscle cell contact loss by the investigational angiopoietin-2 antibody MEDI3617. Microvasc Res 2012;83:290–7. [PubMed: 22387475]

11. Monk BJ, Poveda A, Vergote I, Raspagliesi F, Fujiwara K, Bae DS, et al. Anti-angiopoietin therapy with trebananib for recurrent ovarian cancer (TRINOVA-1): a randomised, multicentre, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:799–808. [PubMed: 24950985]
12. Papadopoulos KP, Kelley RK, Tolcher AW, Razak AR, Van Loon K, Patnaik A, et al. A phase I first-in-human study of nesvacumab (REGN910), a fully humananti-Angiopoietin-2(Ang2) monoclonal antibody, in patients with advanced solid tumors. Clin Cancer Res 2016;22:1348–55. [PubMed: 26490310]
13. Dellinger M, Hunter R, Bernas M, Gale N, Yancopoulos G, Erickson R, et al. Defective remodeling and maturation of the lymphatic vasculature in Angiopoietin-2 deficient mice. Dev Biol 2008;319:309–20. [PubMed: 18514180]
14. Peterson TE, Kirkpatrick ND, Huang Y, Farrar CT, Marijt KA, Kloepper J, et al. Dual inhibition of Ang-2 and VEGF receptors normalizes tumor vasculature and prolongs survival in glioblastoma by altering macrophages. Proc Natl Acad Sci U S A 2016;113:4470–5. [PubMed: 27044097]
15. Avastin [package insert]. South San Francisco, CA: Genentech, Inc.; 2013.
16. Amgen announces top-line secondary endpoint results of phase 3 trebananib TRINOVA-1 trial in patients with recurrent ovarian cancer [press release]. Amgen; 2014 Available from: http://www.prnewswire.com/news-releases/amgen-announces-top-line-secondary-endpoint-results-ofphase-3-trebananib-trinova-1-trial-in-patients-with-recurrent-ovarian-cancer-281442761.html.
17. Castellano D, Capdevila J, Sastre J, Alonso V, Llanos M, Garcia-Carbonero R, et al. Sorafenib and bevacizumab combination targeted therapy in advanced neuroendocrine tumour: a phase II study of Spanish Neuroendocrine Tumour Group (GETNE0801). Eur J Cancer 2013;49: 3780–7. [PubMed: 24012098]

Translational Relevance

MEDI3617 is an investigational human immunoglobulin G1 kappa antibody that preferentially binds to angiopoietin-2 (Ang2). Ang2 overexpression is observed in several solid tumor malignancies, and binding of Ang2 to the Tie2 receptor mediates pathologic angiogenesis in malignancy. Selective Ang2 inhibition provided by MEDI3617 has the potential to provide antiangiogenic antitumor activity, and the combination of MEDI3617 with the VEGFR2 inhibitor bevacizumab may permit intensification of antiangiogenic activity without overlapping toxicities. We investigated the safety, tolerability, pharmacology, and clinical activity of MEDI3617 as monotherapy and combined with bevacizumab and with cytotoxic chemotherapy in a first-in-human trial of adult patients with solid tumors. Results showed that although MEDI3617 monotherapy and combination therapy were generally tolerable, the adverse event profile, specifically peripheral edema, may vary by disease type. An overall lack of clinical efficacy was observed, suggesting that preclinical models demonstrating efficacy may not accurately be phenocopying the biology of human cancers.

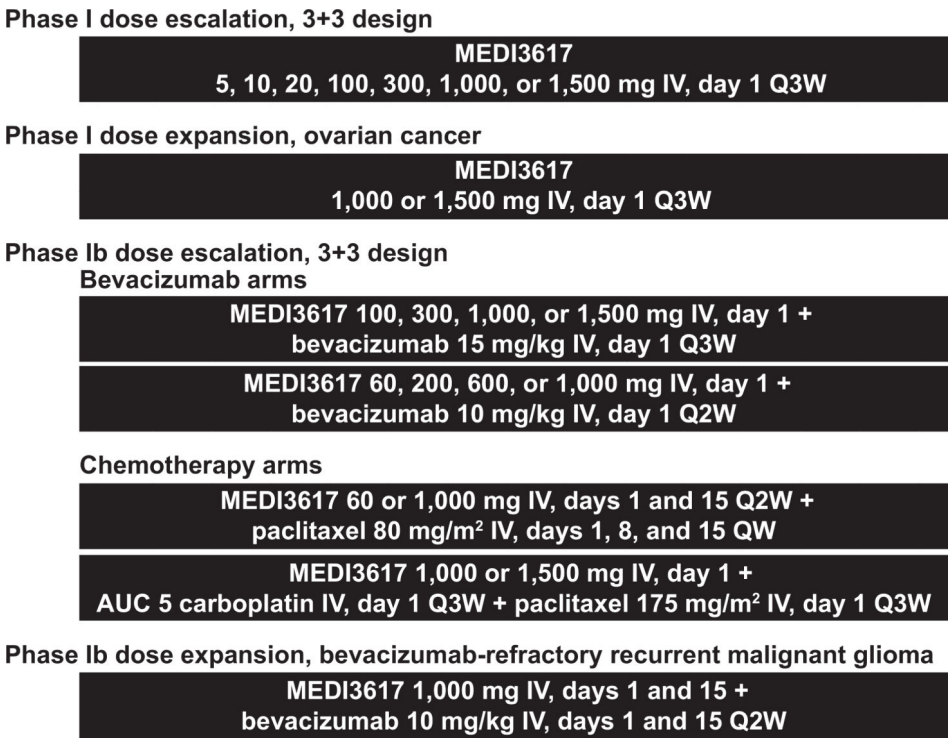

Figure 1.

Study schema. Except where indicated, all other cohorts enrolled patients with any advanced solid tumor malignancy. IV, intravenous; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks.

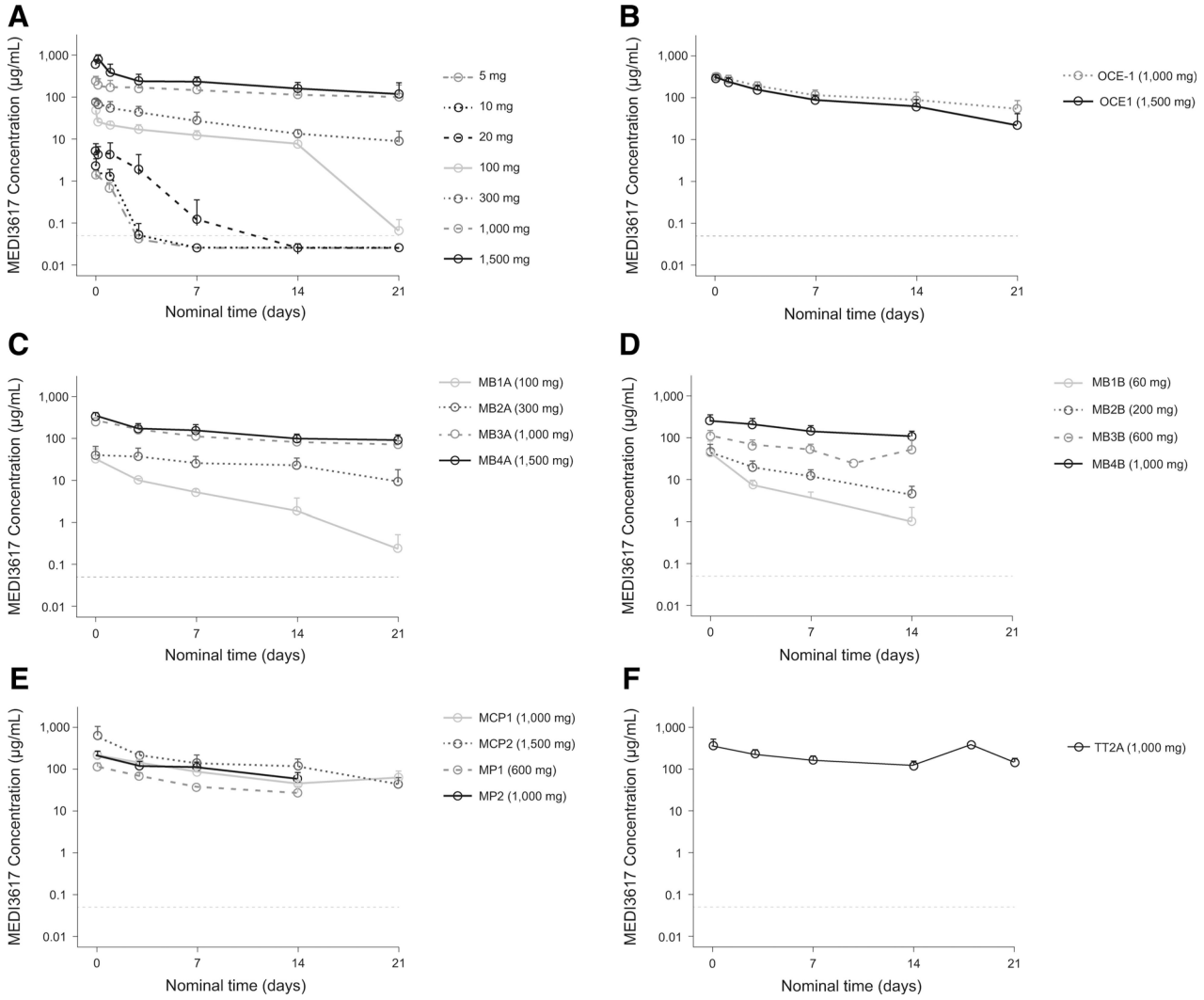

Figure 2.

Mean MEDI3617 serum concentration versus time profiles. **A**, Phase I dose escalation; **B**, phase I dose expansion in ovarian cancer; **C**, phase I dose escalation, bevacizumab Q3W; **D**, phase I dose escalation, bevacizumab Q2W; **E**, phase I dose escalation, chemotherapy regimens; and **F**, phase I dose expansion, bevacizumab- refractory recurrent malignant glioma. MB, MEDI3617 plus bevacizumab cohort; MCP, MEDI3617 plus carboplatin and paclitaxel cohort; MP, MEDI3617 plus paclitaxel cohort; OCE, ovarian cancer extension; TT, bevacizumab-refractory cohort; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks. The assay lower limit of quantification (LLOQ) was 51.2 ng/mL in undiluted serum (dashed line).

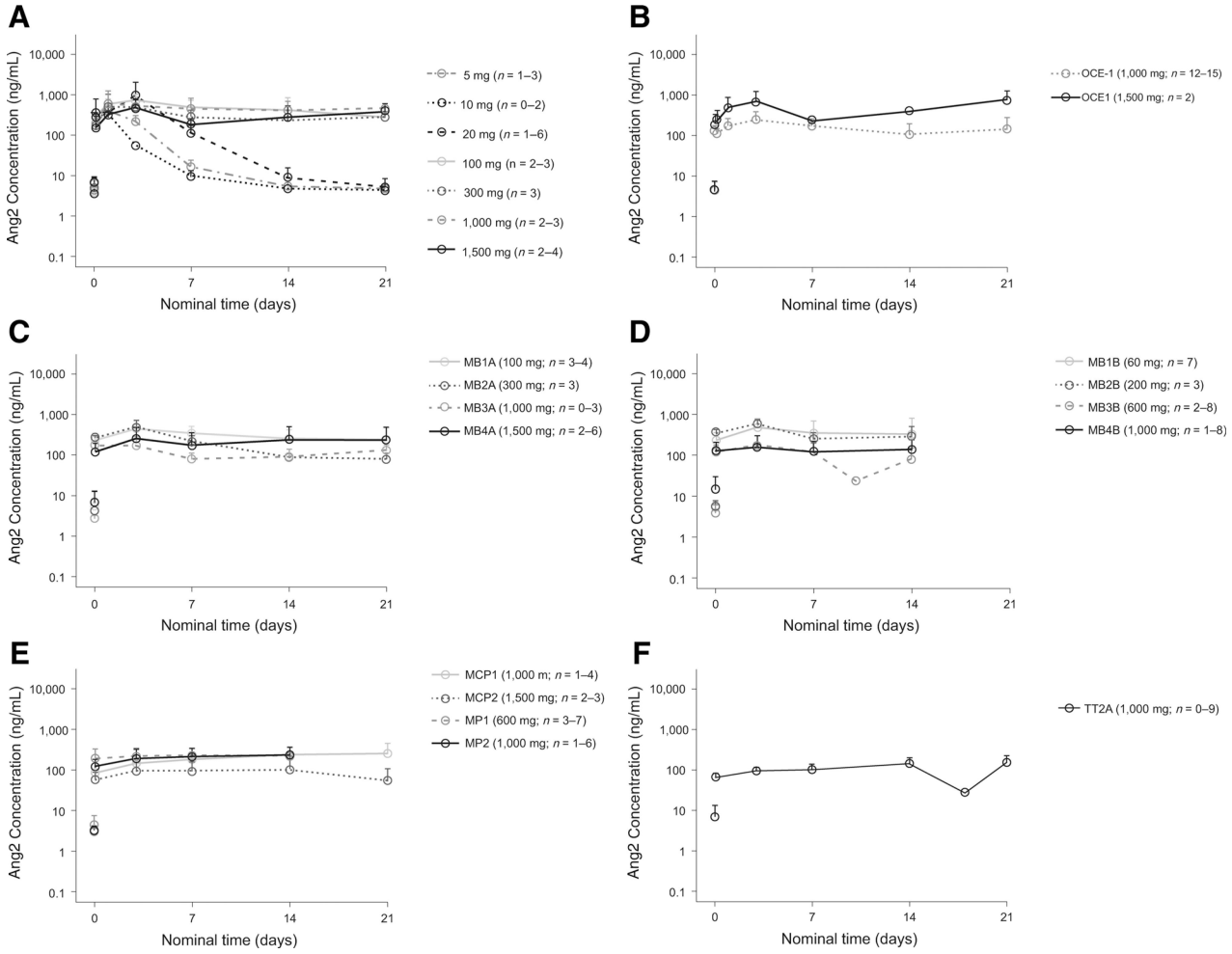

Figure 3.

Mean total circulating Ang2 concentration versus time profiles. **A**, Phase I dose escalation; **B**, phase I dose expansion in ovarian cancer; **C**, phase I dose escalation, bevacizumab Q3W; **D**, phase I dose escalation, bevacizumab Q2W; **E**, phase I dose escalation, chemotherapy regimens; **F**, phase I dose expansion, bevacizumab-refractory recurrent malignant glioma. Ang2 angiopoietin-2; MB, MEDI3617 plus bevacizumab cohort; MCP, MEDI3617 plus carboplatin and paclitaxel cohort; MP, MEDI3617 plus paclitaxel cohort; OCE, ovarian cancer extension; TT, bevacizumab-refractory cohort; QW, once weekly; Q2W, every 2 weeks; Q3W, every 3 weeks.

Table 1.

Patient demographics and baseline characteristics

	MEDI3617 monotherapy		MEDI3617 plus bevacizumab	MEDI3617 plus chemotherapy	
	Escalation	Expansion in ovarian cancer	All cohorts	Paclitaxel	Carboplatin plus paclitaxel
Variable	**(*n* = 25)**	**(*n* = 17)**	**(*n* = 54)**	**(*n* = 13)**	**(*n* = 7)**
Median age, y (range)	63 (21–81)	59 (27–79)	59 (25–80)	61 (31–79)	60 (38–75)
Female, *n* (%)	10 (40)	17 (100)	25 (46)	8 (62)	5 (71)
KPS, *n* (%)					
<70	0	0	4 (7)	0	0
70–80	9 (36)	5 (29)	27 (50)	7 (54)	5 (71)
90–100	16 (64)	12 (71)	23 (43)	6 (46)	2 (29)
Primary disease, *n* (%)					
Ovarian	3 (12)	17 (100)	10 (19)	3 (23)	2 (29)
NSCLC	11 (44)	0	1 (2)	3 (23)	0
Other	7 (28)	0	10 (19)	3 (23)	2 (29)
Colon/CRC	3 (12)	0	6 (11)	0	0
RCC	1 (4)	0	3 (6)	0	0
Esophageal/gastroesophageal	0	0	3 (6)	0	1 (14)
Endometrial	0	0	2 (4)	1 (8)	1 (14)
HCC	0	0	2 (4)	0	0
Glioblastoma	0	0	13 (24)	0	0
Prostate	0	0	1 (2)	0	0
Laryngeal	0	0	1 (2)	0	0
Pancreatic	0	0	1 (2)	0	0
Cervical	0	0	1 (2)	0	0
Thyroid	0	0	0	2 (15)	0
Melanoma	0	0	0	0	1 (14)
Median no. any prior treatments (range)	7 (1–21)	9 (5–18)	7 (2–21)	8 (3–15)	6 (2–15)

Abbreviations: CRC, colorectal cancer, HCC, hepatocellular carcinoma; KPS, Karnofsky performance status; NSCLC, non-small cell lung cancer; Q2W, every 2 weeks; Q3W, every 3 weeks; RCC, renal cell carcinoma.

Table 2.

Treatment-emergent AEs in at least 20% of patients in any cohort and all treatment-related grade 3/4 AEs

	MEDI3617 monotherapy		MEDI3617 plus bevacizumab	MEDI3617 plus chemotherapy	
	Escalation	Expansion in ovarian cancer	All cohorts	Paclitaxel	Carboplatin plus paclitaxel
Adverse event, *n* (%)	**(*n* = 25)**	**(*n* = 17)**	**(*n* = 54)**	**(*n* = 13)**	**(*n* = 7)**
Treatment-emergent AEs in ≥20% of patients					
Fatigue	9 (36)	9 (53)	22 (41)	5 (39)	3 (43)
Nausea	9 (36)	3 (18)	19 (35)	5 (39)	4 (57)
Hypertension	1 (4)	9 (53)	20 (37)	3 (23)	2 (29)
Constipation	8 (32)	8 (47)	13 (24)	4 (31)	1 (14)
Vomiting	7 (28)	5 (29)	9 (17)	3 (23)	2 (29)
Abdominal pain	1 (4)	7 (41)	6 (11)	1 (8)	1 (14)
Dizziness	7 (28)	6 (35)	9 (17)	2 (15)	1 (14)
Peripheral edema	5 (20)	6 (35)	9 (17)	4 (31)	0
Myalgia	3 (12)	5 (29)	6 (11)	1 (8)	1 (14)
Pleural effusion	3 (12)	4 (24)	3 (6)	3 (23)	1 (14)
Decreased appetite	6 (24)	3 (18)	10 (19)	1 (8)	2 (29)
Diarrhea	7 (28)	1 (6)	8 (15)	4 (31)	1 (14)
Dyspnea	6 (24)	4 (24)	8 (15)	3 (23)	0
Cough	6 (24)	3 (18)	6 (11)	2 (15)	0
Peripheral neuropathy	3 (12)	1 (6)	5 (9)	4 (31)	2 (29)
Anemia	5 (20)	0	2 (4)	3 (23)	2 (29)
Increased weight	3 (12)	6 (35)	2 (4)	1 (8)	0
Dysgeusia	4 (16)	0	1 (2)	1 (8)	2 (29)
Dehydration	1 (4)	1 (6)	2 (4)	1 (8)	2 (29)
Oropharyngeal pain	0	1 (6)	3 (6)	1 (8)	2 (29)
Hypomagnesemia	0	1 (6)	1 (2)	1 (8)	3 (43)
Hyponatremia	0	0	3 (6)	1 (8)	2 (29)
Alopecia	2 (8)	0	0	3 (23)	0
Neutropenia	1 (4)	0	0	0	3 (43)
Leukopenia	0	0	0	1 (8)	2 (29)

Adverse event, *n* (%)	MEDI3617 monotherapy		MEDI3617 plus bevacizumab	MEDI3617 plus chemotherapy	
	Escalation (*n* = 25)	Expansion in ovarian cancer (*n* = 17)	All cohorts (*n* = 54)	Paclitaxel (*n* = 13)	Carboplatin plus paclitaxel (*n* = 7)
Thrombocytopenia	0	0	0	0	2 (29)
Grade 3/4 treatment-related AEs					
Neutropenia	1 (4)	0	0	0	3 (43)
Leukopenia	0	0	0	0	1 (14)
Nausea	0	0	0	1 (8)	0
Vomiting	0	0	0	1 (8)	0
Dehydration	0	0	0	0	1 (14)
Acute pancreatitis	0	0	1 (2)	0	0
Fatigue	0	0	0	0	1 (14)
Ascites	0	1 (6)	0	0	0
Edema	0	1 (6)	0	0	0
Peripheral edema	0	1 (6)	1 (2)	0	0
Lymphedema	0	1 (6)	0	0	0
Pleural effusion	0	1 (6)	0	0	0
Increased alkaline phosphatase	0	1 (6)	0	0	0
Infusion-related reaction	0	0	0	0	1 (14)
Decreased ejection fraction	0	0	0	1 (8)	0
Increased troponin	0	0	0	1 (8)	0
Decreased appetite	0	0	0	0	1 (14)
Peripheral neuropathy	0	0	1 (2)	0	0
Nephrotic syndrome	0	0	0	0	1 (14)
Proteinuria	0	0	2 (4)	0	0
Female genital tract fistula	0	0	1 (2)	0	0
Scrotal edema	0	0	1 (2)	0	0
Hypertension	0	1 (6)	3 (6)	0	0