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Phase Ib Study of Navicixizumab Plus Paclitaxel in Patients With Platinum-Resistant Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

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abstract

PURPOSE This phase Ib study evaluated the safety and efficacy of paclitaxel plus navicixizumab, a bispecific antiangiogenic antibody to vascular endothelial growth factor and delta-like ligand 4, against platinum-resistant ovarian cancer.

PATIENTS AND METHODS This open-label, nonrandomized, dose-escalation and -expansion study included 44 patients with previously treated, recurrent, platinum-resistant grade 2/3 ovarian cancer. Treatment was intravenous navicixizumab (3 mg/kg or 4 mg/kg once every 2 weeks) plus paclitaxel (80 mg/m^2 intravenously on days 0, 7, and 14 of 28-day cycles). The primary and secondary objectives were to evaluate the safety and efficacy of navicixizumab plus paclitaxel. An RNA-based diagnostic panel was retrospectively used to test the hypothesis that tumors with high angiogenesis or immune-suppressed tumor microenvironment (TME) subtypes (biomarker-positive) are more likely to respond to navicixizumab than those with immune-active/-desert TME subtypes (biomarker-negative). RNA expression was analyzed in available pretreatment tumor tissue to classify 33 patients' TME subtypes, and TME panel findings were correlated with tumor response.

RESULTS The dose-escalation cohorts enrolled patients at navicixizumab doses of 3 mg/kg once every 2 weeks (n = 3) and 4 mg/kg once every 2 weeks (n = 2); 3 mg/kg was selected for expansion (n = 39). No dose-limiting toxicities occurred. The most common grade 3/4 treatment-related adverse events were hypertension (40.9%), neutropenia (6.8%), and thrombocytopenia (4.5%). Pulmonary hypertension occurred in 18.2% (grade 1-2). The overall objective response rate was 43.2% (95% CI, 28.3 to 59.0): 33.3% (95% CI, 17.3 to 52.8) in patients previously treated with bevacizumab, 64.3% (95% CI, 35.1 to 87.2) in bevacizumab-naive patients, and 62% (95% CI, 31.6 to 86.1) in biomarker-positive patients. The median duration of response was 6 months (95% CI, 5.4 months to not estimable).

CONCLUSION Navicixizumab plus paclitaxel demonstrated promising clinical activity in bevacizumab-treated and -naive patients with platinum-resistant ovarian cancer, with manageable toxicity.

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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

Platinum resistance portends a poor prognosis and occurs frequently following primary treatment of advanced epithelial ovarian cancer with cytoreductive surgery and platinum-based chemotherapy.[1-5] The AURELIA trial demonstrated improved outcomes when bevacizumab was added to chemotherapy in patients with platinum-resistant disease.[6] However, patients inevitably progress following this regimen.[7] Targeting other angiogenesis drivers may improve the response to vascular endothelial growth factor (VEGF) inhibition and may lead to more durable antiangiogenic efficacy and improved outcomes in patients with platinum-resistant ovarian cancer (PROC).

Notch signaling regulates angiogenesis via a different mechanism from VEGF that involves the interaction of delta-like ligand 4 (DLL4) with Notch receptors, making DLL4 a potential therapeutic target in overcoming anti-VEGF resistance.[8,9] DLL4 is overexpressed in ovarian cancer.[8,10] In preclinical studies, DLL4 blockade was active against tumors progressing on anti-VEGF therapy.[9,11] A DLL4 inhibitor, enoticumab, showed clinical activity against ovarian cancer.[12] Dual DLL4 and

CONTEXT

Key Objective

Delta-like ligand 4, a Notch ligand, has a critical role in angiogenesis and is associated with anti-vascular endothelial growth factor resistance. We evaluated the safety and efficacy of navicixizumab, a delta-like ligand 4 and vascular endothelial growth factor bispecific antibody, in combination with paclitaxel, in patients with heavily pretreated, platinum resistant ovarian cancer. A novel RNA expression–based biomarker retrospectively evaluated whether patients may preferentially benefit from therapy.

Knowledge Generated

Treatment with navicixizumab combination therapy resulted in 43% of patients achieving response. Patients benefited regardless of prior treatment including bevacizumab or poly (ADP-ribose) polymerase inhibitor. Response was enriched in patients with high angiogenesis score.

Relevance

This study demonstrates that navicixizumab in combination with paclitaxel has promising clinical activity and manageable safety in a treatment-resistant patient population. A randomized study is needed to compare the efficacy of navicixizumab monotherapy or combination to paclitaxel and determine whether the biomarker can be used predict patients more likely to benefit from navicixizumab.

VEGF blockade was additive and superior to inhibiting DLL4 or VEGF alone,[9,11] which, along with overcoming VEGF resistance, provided the clinical rationale for targeting both molecules simultaneously.

Navicixizumab is a first-in-class, bispecific, antiangiogenic antibody that inhibits both VEGF and DLL4. Since DLL4 is cell-bound, navicixizumab can localize to the tumor microenvironment (TME) to block DLL4 and sequester locally secreted VEGF.[13] In a phase Ia study in patients with refractory solid tumors, navicixizumab monotherapy modulated both Notch and angiogenesis signaling, and showed disease control in 64% of 11 patients with heavily pretreated PROC.[13] The toxicity profile was consistent with other VEGF and DLL4 inhibitors and the most common adverse event (AE), hypertension, could be managed using a standard treatment algorithm. This phase Ib study was conducted to determine the safety and efficacy of navicixizumab plus paclitaxel in patients with PROC progressing after two or more prior therapies, including bevacizumab.

Predictive biomarkers to enable personalized use of anti-VEGF therapy have not yet been developed. VEGF not only regulates blood vessel formation, but also modulates tumor-induced immunosuppression.[7] Understanding the dominant biology driving the TME state may help to determine the class of treatment that will be more likely to benefit the patient. For example, an antiangiogenic drug would likely be effective when the TME is aggressively promoting pathologic angiogenesis.

To this end, we used a novel RNA expression–based diagnostic panel involving approximately 100 genes expressed in the TME during angiogenic and immune biologic processes. The TME Panel had previously been developed using $>$ 1,000 patient samples and machine learning to train an algorithm to identify the dominant TME biology in an individual patient's tumor.[14] The assay classifies patient tumor samples into one of four subtypes on the basis of gene expression signatures of the angiogenic and immune processes that dominated their individual TME biology: angiogenic, immune-active, immune-desert, and immune-suppressed (Data Supplement).[14,15] We retrospectively tested the biomarker hypothesis that tumors positive for the angiogenic TME gene-expression signature, which include the angiogenic and immune-suppressed subtypes, are more likely to respond to anti-VEGF/anti-DLL4 treatment with navicixizumab than those that are negative for the angiogenic TME gene-expression signature, which include the immune-active and immune-desert phenotypes[14] in patients with ovarian cancer.

PATIENTS AND METHODS

Study Design and Treatment

This was a phase Ib open-label, nonrandomized, dose-escalation and -expansion study of the safety, tolerability, and efficacy of navicixizumab plus paclitaxel (ClinicalTrials.gov identifier: NCT03030287).

In the dose-escalation phase, three patients were to receive intravenous navicixizumab 3 mg/kg once every 2 weeks followed by paclitaxel on prespecified days (Protocol, online only). If no dose-limiting toxicities (DLTs; defined as grade 3 or 4 AEs) occurred within 28 days, three patients would be enrolled in the second dose level cohort and receive navicixizumab 4 mg/kg once every 2 weeks. Per protocol, three additional patients would then be treated at the dose chosen for

expansion and if ≤ 1 of the six patients had a DLT, then that dose level would be used in the expansion phase. Navicixizumab dose modifications within a dose cohort were not permitted.

Paclitaxel (80 mg/m^2) was administered intravenously on days 0, 7, and 14 of each 28-day cycle, preceded by dexamethasone, an antihistamine, and an H-2 blocker. Dose reductions were permitted according to standard modification criteria to manage toxicity. If paclitaxel was delayed or discontinued because of toxicity, navicixizumab could still be administered as scheduled, and vice versa.

Treatment was continued until confirmed complete response (CR), disease progression (PD), intolerance, or study withdrawal. A standard treatment algorithm was used for treating navicixizumab-induced hypertension (Data Supplement). Criteria for discontinuing navicixizumab and the protocol for treating pulmonary hypertension and other adverse events of special interest (AESIs) are described in the Data Supplement and the Protocol.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and relevant Institutional Review Board and Ethics Committee requirements. All patients provided written informed consent to participate.

Patient Eligibility

Eligible patients age ≥ 21 years had cytologically or histologically confirmed grade 2 or 3 PROC ≥ 1 cm, measurable by using computed tomography (CT) or magnetic resonance imaging. Platinum resistance was defined as PD within 6 months of completing platinum-based therapy without PD during the first-line treatment. Permitted histologies are described in the Protocol. Patients had to have received prior bevacizumab and/or ≥ 2 prior cancer treatment regimens (which could have included weekly paclitaxel), and an Eastern Cooperative Oncology Group performance status < 2.

Exclusion criteria included nonepithelial ovarian carcinoma; hypertension not controlled by ≤ 2 medications; a history of cardiac ischemia or heart failure with a peak tricuspid velocity > 3.0 m/s on Doppler ECG; clinically significant GI disease; and known bleeding disorders or coagulopathy (see Protocol for full list of eligibility criteria).

Outcomes

The primary end point was the maximum tolerated dose (MTD) of navicixizumab, defined as the highest dose level at which ≤ 1 patient experienced a DLT. Secondary end points were the safety profile of the treatment combination, the incidence of antinavicixizumab antibodies (ADAs), and efficacy. Efficacy end points included objective response rate (ORR), duration of response, and progression-free survival (PFS) per RECIST 1.1, and tumor response per Rustin Gynecologic Cancer Intergroup cancer antigen (CA)-125 criteria.[16] PFS was defined as the time from the first dose to PD or death on study because of any cause, whichever came first.

In an exploratory analysis, available pretreatment tumor tissue was retrospectively analyzed for RNA expression using a biomarker panel (Xerna TME Panel [OncXerna Therapeutics, Waltham, MA], Data Supplement) to determine the dominant angiogenic and immunogenic biology in the patient's TME, and the findings were correlated with tumor response.

Assessments

DLTs were assessed during the first 28 days. Safety was evaluated at every visit and for 30 days after treatment termination by assessment of treatment-emergent AEs per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03, laboratory tests including B-type natriuretic peptide (BNP) assessment, and cardiopulmonary monitoring (including Doppler ECG with left ventricular ejection fraction [LVEF] and peak tricuspid velocity at baseline, cycle 3, and then every 56 days). AESIs were defined by the sponsor as grade ≥ 2 hypertension, pulmonary hypertension, bleeding or GI/gallbladder perforation, and grade 4 thrombocytopenia. Patients monitored hypertension using home blood pressure cuffs and were assessed for hypertension at each study visit.

Tumor response per RECIST 1.1 was assessed by the investigators by CT every 8 weeks. CA-125 response (defined as a confirmed ≥ 50% reduction in CA-125 levels *v* pretreatment maintained for ≥ 28 days) was assessed centrally every 28 days using Gynecologic Cancer Intergroup criteria[16] in patients who had a pretreatment sample taken within 2 weeks of starting treatment that was at least twice the upper limit of normal.

Immunogenicity (ADAs) was assessed in blood samples at baseline, every 6 weeks during study treatment, at treatment termination, and then every 6 weeks for 12 weeks thereafter.

Biomarker Analysis

Available pretreatment formalin-fixed, paraffin-embedded tumor tissue samples were analyzed by total RNA-sequencing using the Roche Kapa Total RNA-seq kit and sequencing via Illumina HiSeq. Gene expression data were quantified to transcripts per million by standard bioinformatics processing, and these expression values were used as input for the TME Panel algorithm (Data Supplement).

Using the TME Panel (Data Supplement), patients with high angiogenesis (angiogenic or immune-suppressed) TME subtypes were classified as biomarker-positive and those with immune-active or immune-desert TMEs as biomarker-negative. Patients' TME profiles were retrospectively analyzed against their objective responses per RECIST 1.1.

Statistical Analysis

The study sample size was determined by a traditional dose-escalation study design (maximum six patients per dose level) followed by an expansion cohort, to achieve a total of 30-60 treated patients. All patients who received navicixizumab were included in the intent-to-treat (ITT) population analyzed for efficacy and ADA, and those with ≥ 1 postdosing safety evaluation were included in the safety population.

TABLE 1. Baseline Demographics, Disease Characteristics and Prior Treatment History

Characteristic	Overall ITT Population (N = 44)
Age, years, median (range)	63.0 (37-77)
Ethnicity, No. (%)	
White	39 (88.6)
Black	3 (6.8)
Asian	2 (4.5)
BMI, kg/m^2, median (range)	27.2 (19-54)
Cancer at diagnosis, No. (%)	
Ovarian	34 (77.3)
Primary peritoneal	3 (6.8)
Fallopian tube	7 (15.9)
Years from diagnosis, median (range)	3.21 (0.8-12.1)
Stage at diagnosis, No. (%)	
I	1 (2.3)
III	25 (56.8)
IV	17 (38.6)
Platinum-resistant, No. (%)	
Yes	43 (97.7)
No	1 (2.3)[a]
Platinum progression-free interval,[a] months, No. (%)	
< 3	25 (58.1)
≥ 3	18 (41.9)
Prior radiotherapy, No. (%)	2 (4.5)
Prior surgery, No. (%)	43 (97.7)
No. of prior treatment regimens, median (range)	4.0 (2-12)
Paclitaxel[b]	43 (97.7)
Bevacizumab	30 (68.2)
Immunotherapy	9 (20.5)
PARP inhibitor	20 (45.5)

Abbreviations: BMI, body mass index; ITT, intent-to-treat; PARP, poly (ADP-ribose) polymerase.

[a]Platinum progression-free interval calculated as the time from the penultimate platinum-based regimen until disease progression. One patient was not evaluable.

[b]One patient received protein-bound paclitaxel.

Efficacy was summarized for all patients in the ITT population, by navicixizumab dose cohort, and by prior bevacizumab treatment status. PFS was estimated using the Kaplan-Meier method. Post hoc subgroup analyses of efficacy by prior treatment and tumor characteristics were also conducted.

RESULTS

Patients and Treatment

Between February 7, 2017, and November 8, 2018, 44 patients were enrolled. Three patients were initially enrolled in the 3 mg/kg dose escalation cohort, followed by two patients at 4 mg/kg. Because emerging data from an ongoing phase Ia study[13] suggested that a dose equivalent to 3 mg/kg produced optimal efficacy and that higher doses were associated with greater toxicity, enrollment in the 4 mg/kg cohort was discontinued, and 39 patients were enrolled in the expansion cohort and treated with 3 mg/kg. The MTD for navicixizumab was not determined on the basis of protocol-defined criteria.

The reasons for study discontinuation were PD (27 patients [61.4%]), other (six patients [13.6%]), AEs (four patients [9.1%]), withdrawal of consent (four patients [9.1%]), investigator decision (two patients [4.5%]), and death (one patient [2.3%]). The patients' disease characteristics are summarized in Table 1 in the ITT and by cohort in the Data Supplement.

Safety

Patients received a median of 8 (range, 1-19) navicixizumab doses, and the median time from the first to last dose of navicixizumab was 113 (range, 1-337) days. No DLTs occurred in the study (Data Supplement).

All 44 patients (100%) had ≥ 1 any-cause AE and 79.5% had grade ≥ 3 AEs (Data Supplement). One patient (2.3%) had a grade 5 AE (sudden cardiac death) 119 days after starting treatment. The patient had increased abdominal pain related to ovarian cancer during the study and reported nausea on day 113. She was hospitalized with worsening dehydration and diarrhea related to paclitaxel and ovarian cancer. Sudden cardiac death 6 days later was assessed by the investigator as not related to study treatment, but to PROC. ECG findings 13 days before the patient's death were LVEF 51%, peak tricuspid velocity 3.2 m/s, and normal right ventricular function with mild to moderate aortic regurgitation.

Treatment-related AEs (TRAE) occurred in 90.9% of patients, with the most common being hypertension, fatigue, and headache (Table 2). Infusion-related reactions were reported in four patients, all nonserious, with treatment interruption in two patients who both tested positive for ADAs. The most common grade 3 or 4 TRAEs were hypertension (40.9%), neutropenia (6.8%), and thrombocytopenia (4.5%); all other grade 3 or 4 TRAEs occurred in

TABLE 2. Most Common TRAEs (safety set)

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4[a]	All Grades
Hypertension	2 (4.5)	10 (22.7)	18 (40.9)[b]	0	30 (68.2)
Fatigue	11 (25.0)	10 (22.7)	0	0	21 (47.7)
Headache	10 (22.7)	2 (4.5)	0	0	12 (27.3)
Dyspnea	6 (13.6)	3 (6.8)	0	0	9 (20.5)
Neutropenia	0	5 (11.4)	3 (6.8)	0	8 (18.2)
Diarrhea	7 (15.9)	1 (2.3)	0	0	8 (18.2)
Pulmonary hypertension	4 (9.1)	4 (9.1)	0	0	8 (18.2)
Edema peripheral	6 (13.6)	1 (2.3)	0	0	7 (15.9)
Nausea	3 (6.8)	2 (4.5)	1 (2.3)	0	6 (13.6)
Brain natriuretic peptide increased	5 (11.4)	0	0	0	5 (11.4)
Thrombocytopenia	0	0	1 (2.3)	1 (2.3)	2 (4.5)
Duodenal ulcer	0	0	0	1 (2.3)	1 (2.3)
Large intestine perforation	0	0	0	1 (2.3)	1 (2.3)

NOTE. Data are No. (%) of patients who had TRAEs occurring at > 10% in the overall population or at grade 4.
Abbreviation: TRAE, treatment-related adverse event.
[a]No grade 5 TRAEs occurred.
[b]One additional patient had grade 3 hypertension assessed as not related to treatment and is thus not included in this table.

one patient (2.3%) each. No grade 5 TRAEs occurred; seven patients (15.9%) had a treatment-related serious adverse event and three patients (6.8%) discontinued study treatment because of TRAEs (Data Supplement).

Regarding AESIs, 18 patients (40.9%) had grade 3 treatment-related hypertension: three (6.8%) were hospitalized (of whom one [2.3%] permanently discontinued navicixizumab); navicixizumab was interrupted in one (2.3%); and a dose was held in eight (18.2%). Hypertension was managed per standard treatment algorithm (Data Supplement) and no grade 4 hypertension occurred. Pulmonary hypertension occurred in eight patients (18.2%; seven of whom had a history of hypertension) and the highest severity was grade 2 (in 9.1%; Table 2). This AE occurred a median 148 days from the start of treatment (range, 32-196 days) and correlated with exposure (ie, duration of treatment). All events were nonserious, none led to treatment discontinuation, but seven patients interrupted navicixizumab treatment. Two patients required medication to manage pulmonary hypertension (one patient received sildenafil and one received riociguat). At study termination, pulmonary hypertension had resolved in two patients and was improving in the others.

One patient had a grade 4 duodenal ulcer and grade 3 small intestinal hemorrhage; both AESIs were related to treatment and led to treatment discontinuation. Secondary to these events, the patient experienced grade 4 sepsis and grade 3 hemorrhage. One patient had a grade 4 large intestine perforation related to navicixizumab, which required surgical repair, and did not receive further treatment. Two patients (4.5%) had treatment-related grade 3 or 4 thrombocytopenia, one of whom permanently discontinued navicixizumab.

Immunogenicity

Six of 40 evaluable patients (15%) developed treatment-emergent ADAs: one patient at day 42 (after two cycles), three at day 84 (after four cycles), and two after study termination. Three patients tested positive for ADA at baseline (ie, before receiving any study treatment). One patient who did not have a baseline sample tested positive for ADA at day 42.

Clinical Activity

The ORR and disease control rate (DCR) per RECIST 1.1 were 43.2% (95% CI, 28.3 to 59.0) and 77.3% (95% CI, 62.2 to 88.5), respectively (Table 3; Fig 1; Data Supplement). The ORR and DCR were higher in bevacizumab-naive patients than in patients who had progressed on prior bevacizumab-containing regimens (Table 3).

Although a repeat assessment to confirm CR or partial response (PR) 4 weeks after initial observation of response was not required per protocol, patients were evaluated every 8 weeks by CT scan. Among the 19 patients who had a tumor response, 16 (36.3%) had confirmation of response on subsequent scan.

Of the 19 patients who had a PR or CR to navicixizumab plus paclitaxel, 11 previously had PD as best response to immediate prior therapy (their third to twelfth treatment regimen), including three patients treated with the poly (ADP-ribose) polymerase (PARP) inhibitors rucaparib or niraparib (Data Supplement). Of 20 patients previously treated with a PARP inhibitor, nine (45%) had a PR.

TABLE 3. Tumor Response in the Intent-to-Treat Population

Response to Treatment	All (N = 44)	Bevacizumab-Treated (n = 30)	Bevacizumab-Naive (n = 14)
Best objective response[a] per RECIST 1.1			
ORR[b]	19 (43.2) [28.3 to 59.0]	10 (33.3) [17.3 to 52.8]	9 (64.3) [35.1 to 87.2]
CR	1 (2.3)	0	1 (7.1)
PR	18 (40.9)	10 (33.3)	8 (57.1)
SD	15 (34.1)	10 (33.3)	5 (35.7)
PD	7 (15.9)	7 (23.3)	0
Not evaluable[c]	3 (6.8)	3 (10.0)	0
DCR[d]	34 (77.3) [62.2 to 88.5]	20 (66.7) [47.2 to 82.7]	14 (100) [76.8 to 100.0]
DOR, months (95% CI)	6.0 (5.4 to NE)	6.3 (1.2 to NE)	5.6 (1.0 to NE)
GCIG CA-125 response			
CR[e]	8 (25.0)	3 (15.0)	5 (41.7)
PR	16 (50.0)	9 (45.0)	7 (58.3)
Total (CR plus PR)[f]	24 (75.0) [56.6 to 88.5]	12 (60.0) [36.1 to 80.9]	12 (100) [73.5 to 100]
No response	8 (25.0)	8 (40.0)	0
Not evaluable[g]	12 (27.3)	10 (33.3)	2 (14.3)

NOTE. Data are No. (%) [95% CI] unless indicated otherwise.

Abbreviations: CA, cancer antigen; CR, complete response; CT, computed tomography; DCR, disease control rate; DOR, duration of response; GCIG, Gynecological Cancer Intergroup; NE, not estimable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Best overall response was defined as the highest RECIST 1.1 response attained from the start of treatment until PD/death in the order of CR > PR > SD > PD > NE. Responses were not confirmed.

[b]The percentage of patients who achieved a best overall tumor response of either CR or PR using RECIST 1.1 guidelines before either PD or death occurred.

[c]Patients who had no evaluable tumor assessments or who had discontinued the study and did not have a CT scan done on day 49 or later unless an early CT was done that showed PD.

[d]The percentage of patients who achieved a CR, PR, or SD per RECIST 1.1 as their best overall response.

[e]The patients who had both a CA-125 response and whose CA-125 level fell to within the normal range were classified as CA-125 complete responders.

[f]Patients who achieved CA-125 response of either CR or PR.

[g]Defined as a patient without a baseline CA-125 value measured within 2 weeks of enrollment or without a baseline value that was at least twice the upper limit of normal. These patients were not included in the denominator for determining the response rate.

The median duration of response per RECIST 1.1 was 6.0 months (95% CI, 5.4 to not estimable [NE]) in the overall population, and was similar in the bevacizumab-treated and -naive subgroups (Table 3). Overall, 24 of the 32 evaluable patients (75.0% [95% CI, 56.6 to 88.5]) had a CA-125 response: 60.0% (95% CI, 36.1 to 80.9) of the bevacizumab-pretreated patients and 100% (95% CI, 73.5 to 100) of bevacizumab-naive patients (Data Supplement; Table 3).

The median PFS was 7.2 (95% CI, 3.9 to 8.9) months in the overall population, 5.4 (95% CI, 3.3 to 9.1) months in the bevacizumab-pretreated patients and 7.6 (95% CI, 5.3 to NE) months in the bevacizumab-naive patients (Data Supplement).

Biomarker Analysis

For this biomarker analysis, formalin-fixed, paraffin-embedded samples from 33 patients were available for RNA sequencing. As navicixizumab's mechanism of action is antiangiogenic, 13 samples (39.4%) classified using the TME Panel as having an angiogenic or immune-suppressed TME subtype were considered biomarker-positive (Data Supplement) and 20 (60.6%) samples classified as immune-active or immune-desert TMEs were considered biomarker-negative. Among biomarker-positive patients, the ORR was 62% and DCR was 100%, compared with 25% and 65%, respectively, in biomarker-negative patients (Table 4). PD as best response was observed only in biomarker-negative patients (Fig 2A). The biomarker-positive group had a median PFS gain of 5.3 months (9.2 *v* 3.9 months, hazard ratio 0.43 [95% CI, 0.188 to 0.999]) over the biomarker-negative group (Fig 2B). Biomarker analysis findings in bevacizumab-treated patients were consistent with those in the overall group.

DISCUSSION

Navicixizumab combined with paclitaxel showed promising, durable (median 6 months) responses in patients with heavily pretreated PROC. The ORR was 43%, the median PFS was 7.2 months, and 53% of patients who had a best response of SD also had durable disease control (PFS > 4 months). These patients had shown limited responses to

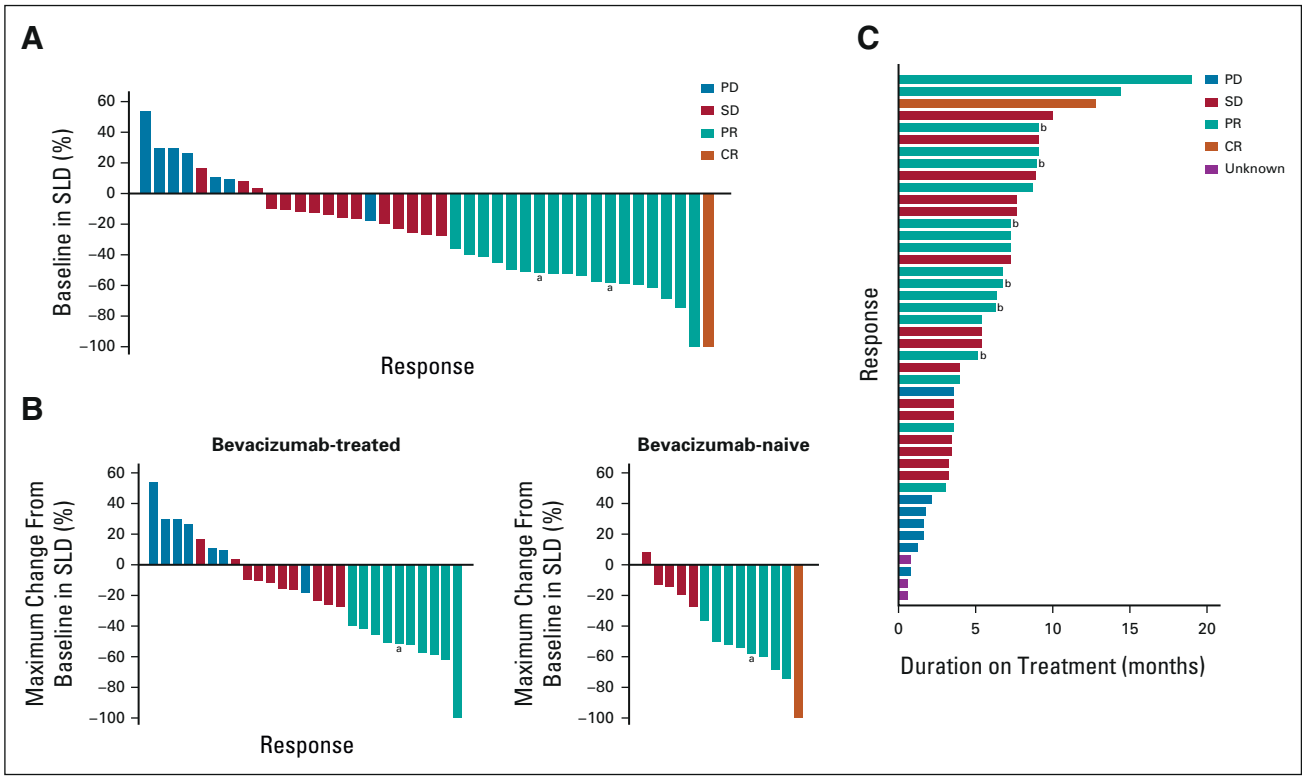

FIG 1. Tumor response per RECIST 1.1 and duration of treatment. Waterfall plots showing percentage change from baseline in sum of largest tumor diameter (A) overall and (B) according to prior bevacizumab treatment status. (C) Swimlane plot showing duration of treatment. [a]Patients in the 4 mg/kg dose escalation cohort; all other patients received 3 mg/kg in the dose escalation or expansion cohorts. [b]Ongoing response at the end of the study. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

TABLE 4. Tumor Response per RECIST 1.1 by Biomarker Status

Best Overall Response	Biomarker-Positive[a]	Biomarker-Negative[b]
All patients	n = 13	n = 20
ORR	8 (62) [31.6 to 86.1]	5 (25) [8.7 to 49.1]
DCR	13 (100) [75.3 to 100]	13 (65) [40.8 to 84.6]
CR	0	1 (5)
PR	8 (62)	4 (20)
SD	5 (38)	8 (40)
PD	0	6 (30)
NE/NA	0	1 (5)
Bevacizumab-treated patients	n = 9	n = 14
ORR	5 (56)	2 (14)
DCR	9 (100)	7 (50)
PR	5 (56)	2 (14)
SD	4 (44)	5 (36)
PD	0	6 (43)
NE/NA	0	1 (7)

NOTE. Data are No. (%) [95% CI] unless indicated otherwise.

Abbreviations: CR, complete response; DCR, disease control rate; NA, not applicable; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

[a]Angiogenic plus immune suppressed phenotype class (Data Supplement).

[b]Immune active plus immune desert phenotype class (Data Supplement).

their most recent previous treatments, with 58% of those who had PR/CR to navicixizumab plus paclitaxel having had PD as best response to their most recent prior treatment. They also obtained clinical benefit from navicixizumab regardless of prior treatment with bevacizumab and PARP inhibitors. The 45% ORR in PARP inhibitor–pretreated patients was consistent with that in the overall population.

The confirmed ORR of 36% with navicixizumab plus paclitaxel compares favorably to 27% observed with chemotherapy plus bevacizumab in the phase III AURELIA study in a less heavily pretreated patient population.[6] Other approaches targeting angiogenesis including tyrosine kinase inhibitors and VEGF-Trap, for example, have not demonstrated the level of efficacy required for regulatory approval.

The AE profile was monitorable and manageable, and no DLTs occurred at the doses studied. No evidence of overlapping toxicity between navicixizumab and paclitaxel, new safety signals, or unexpected safety findings were observed. Hypertension was the most common TRAE, and was manageable using a protocol-specified algorithm, with only one patient discontinuing treatment because of hypertension. Of the patients with grade 3 hypertension, all but one had a previous history of hypertension, and blood pressure was managed per standard treatment algorithms. At the end of

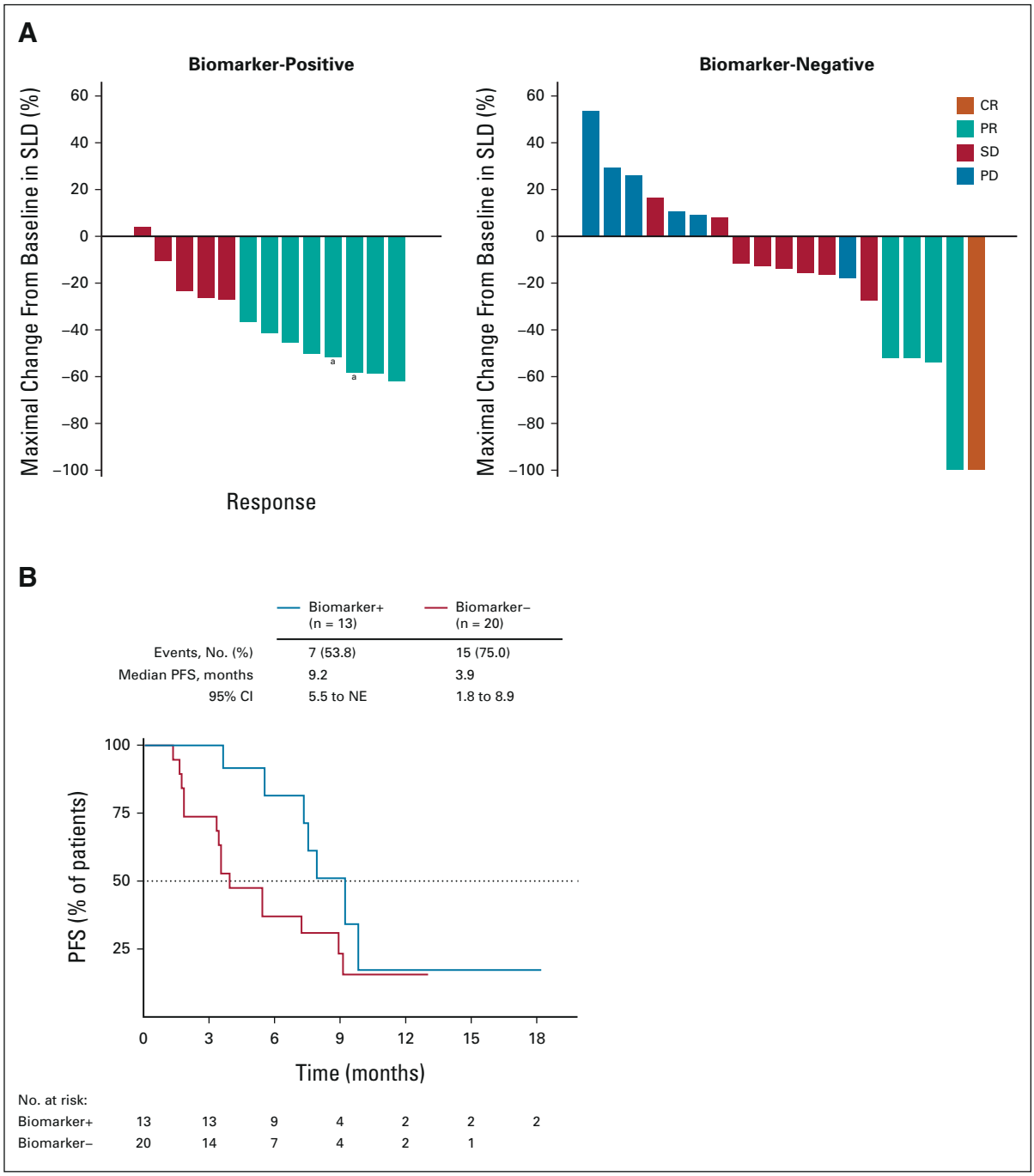

FIG 2. Efficacy according to biomarker status. (A) Tumor response per RECIST 1.1. (B) PFS. [a]Patients in the 4 mg/kg dose escalation cohort; all other patients received 3 mg/kg in the dose escalation or expansion cohorts. CR, complete response; NE, not estimable; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SLD, sum of longest diameters.

study, 16 had blood pressure < 140/90 mm Hg, whereas the other three patients had diastolic pressure < 90 mm Hg and systolic pressure < 160 mm Hg. Pulmonary hypertension occurred at grade ≤ 2, none of the events led to study discontinuation, and none of these patients had LVEF < 50%; one patient had grade 2 heart failure with preserved ejection fraction; none had treatment-related right-sided heart failure. At study termination, pulmonary hypertension had resolved or was resolving, with all patients having improved peak tricuspid velocity and BNP. At their last study assessment, three patients had grade 2 pulmonary hypertension with declining peak tricuspid valve values (≤ 3.2 m/s); all others were reported as resolved or grade 1. No grade 4 hypertension or grade 3 pulmonary hypertension occurred at the 3 mg/kg once every 2 weeks dose selected for further phase III study. Strategies to mitigate the risk of severe pulmonary

hypertension, including excluding patients with significant risk of cardiac toxicity, monitoring via BNP and ECGs, and management by withholding navicixizumab (and treatment with sildenafil or riociguat when required), were effective.

Navicixizumab ADA data are consistent with previous findings reported for other targeted anticancer agents and immunotherapies.[17,18]

Our retrospective analysis of archival tumor samples using the TME Panel showed enrichment of disease control in the biomarker-positive patients, and PD occurred only in biomarker-negative patients. To confirm whether the panel can improve the selection of patients with PROC who are more likely to respond to navicixizumab, it is being used to stratify patients enrolled in the planned phase III open-label, randomized study of navicixizumab plus paclitaxel versus paclitaxel or navicixizumab in patients with PROC (ClinicalTrials.gov identifier: NCT05043402).

We acknowledge several study limitations. *BRCA* mutation and homologous recombination deficiency status were not captured, but it is noteworthy that response rates to navicixizumab in the PARP-pretreated subgroup (likely to be representative of the *BRCA* homologous recombination deficiency population in which these treatments are approved in the United States) were consistent with those in the overall population. The single-arm design did not allow demonstration of whether the biomarker is predictive of treatment benefit. Nevertheless, angiogenesis is associated with poor prognosis and chemoresistance,[19] and our findings of improved responses to navicixizumab plus paclitaxel in patients identified as having highly angiogenic TMEs warrant further evaluation in a randomized study to determine whether the assay is predictive of treatment response. Another limitation is that biomarker status was based on archived and fresh samples of primary tumor and hence may not have reflected the TME status at the time of treatment. Additionally, the MTD for navicixizumab was not determined. The escalation dose was chosen on the basis of data emerging from a phase Ia study of navicixizumab monotherapy, which showed that doses of $\leq$ 3.5 mg/kg every 3 weeks led to clinical activity in ovarian cancer and were associated with a lower risk of pulmonary hypertension, whereas higher doses did not have improved activity but were associated with greater toxicity, including more severe hypertension and pulmonary hypertension.[13]

In conclusion, the efficacy observed with navicixizumab in patients with heavily pretreated PROC that had shown limited response to the most recent prior treatments is encouraging. Navicixizumab plus paclitaxel demonstrated durable clinical activity in both bevacizumab-naive and -pretreated patients, with monitorable, manageable toxicity. Taken together, the navicixizumab monotherapy[13] and combination data presented here suggest that navicixizumab may offer clinical benefits after other therapies for PROC, including bevacizumab, have been exhausted. Further phase III evaluation of navicixizumab is planned.

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DATA SHARING STATEMENT

Navicixizumab is an investigational agent; hence, the data collected for this study will not be made available to others.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase Ib Study of Navicixizumab Plus Paclitaxel in Patients With Platinum-Resistant Ovarian, Primary Peritoneal, or Fallopian Tube Cancer

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Patents, Royalties, Other Intellectual Property: Methods and monitoring of treatment with a WNT pathway inhibitor; Patent number: 9987357; Abstract: Methods for treating diseases such as cancer comprising administering a Wnt pathway inhibitor, either alone or in combination with other anti-cancer agents, and monitoring for skeletal-related side effects and/or toxicity. Type: Grant Filed: May 5, 2016; Date of Patent: June 5, 2018; Assignee: OncoMed Pharmaceuticals Inc. Inventors: Jakob Dupont, Robert J. Stagg, Therapeutic combination and methods of treatment with a DLL4 antagonist and an anti-hypertensive agent; Patent number: 10870693; Abstract: Methods for treating cancer comprising administering a DLL4 antagonist and one or more antihypertensive agents are described. Also described are pharmaceutical compositions comprising a DLL4 antagonist and one or more antihypertensive agents, and kits comprising the same. Type: Grant Filed: April 30, 2018; Date of Patent: December 22, 2020; Assignee: OncoMed Pharmaceuticals Inc. Inventors: Robert Joseph Stagg, Steven Eugene Benner, Methods and Compositions for Treatment of Cancer; Publication number: 20190023776; Abstract: The present invention relates to VEGF-binding agents, DLL4-binding agents, VEGF/DLL4 bispecific binding agents, and methods of using the agents for treating diseases such as cancer, particularly pancreatic, colorectal, and endometrial cancers. Also provided are methods, compositions, and kits for treatment of tumors or cancer using combinations that include a VEGF/DLL4 bispecific agent and one or more chemotherapeutic agents (eg, gemcitabine and ABRAXANEÂ; leucovorin, 5-fluorouracil, and irinotecan; and paclitaxel and carboplatin). The present invention further provides methods of using the agents or combinations of agents to inhibit growth of a pancreatic, colorectal, or endometrial tumor. Also described are methods of treating cancer, particularly pancreatic, colorectal, and endometrial cancer, comprising administering a therapeutically effect amount of an agent, antibody, or therapeutic combination of the present invention to a patient having a tumor or cancer. Type: Application Filed: September 23, 2016; Publication date: January 24, 2019; Inventors: Jakob Dupont, Hema Parmar, Robert Joseph Stagg, Methods and Monitoring of Treatment With A DLL4 Antagonist; Publication number: 20170299598; Abstract: Methods for treating diseases such as cancer comprising administering a DLL4 antagonist, either alone or in combination with other anti-cancer agents, and monitoring for cardiovascular side effects and/or toxicity. Type: Application Filed: February 1, 2017; Publication date: October 19, 2017. Inventors: Steven Eugene Benner, Robert Joseph Stagg, Jakob Dupont, Methods for Treating Cancer with DLL4 Antagonists; Publication number: 20160324961; Abstract: The present invention provides methods for treating cancer. More particularly, the invention provides methods for treating cancer comprising administrating doses of a DLL4 antagonist. Type: Application Filed: April 13, 2016; Publication date: November 10, 2016; Inventors: Robert Joseph Stagg, Steven Eugene Benner, John Lewicki, Timothy Charles Hoey, Methods of Treating Neuroendocrine Tumors Using Frizzled-Binding Agents; Publication number: 20160235844; Abstract: Novel methods of treating neuroendocrine tumors are provided. In one embodiment, the method comprises administering to a subject in need thereof a therapeutically effective dose of a Wnt antagonist. In one embodiment, the Wnt antagonist is an anti-FZD antibody. In another embodiment, the Wnt antagonist is a soluble FZD receptor polypeptide. In a further embodiment, the Wnt antagonist is an anti-Wnt antibody. Type: Application Filed: January 12, 2016; Publication date: August 18, 2016; Applicant: OncoMed Pharmaceuticals Inc. Inventors: Robert Joseph Stagg, Jakob Dupont, Methods of treatment with DLL4 antagonists and an anti-hypertensive agent; Patent number: 8883145; Abstract: Methods for treating cancer comprising administering a DLL4 antagonist and one or more antihypertensive agents are described. Also described are pharmaceutical compositions comprising a DLL4 antagonist and one or more antihypertensive agents, and kits comprising the same. Type: Grant Filed: October 18, 2010; Date of Patent: November 11, 2014; Assignee: Oncomed Pharmaceuticals Inc. Inventors: Robert Joseph Stagg, Steven Eugene Benner, Methods and Monitoring of Treatment with a DLL4 Antagonist; Publication number: 20140227252; Abstract: Methods for treating diseases such as cancer comprising administering a DLL4 antagonist, either alone or in combination with other anticancer agents, and monitoring for cardiovascular side effects and/or toxicity. Type: Application Filed: October 31, 2013; Publication date: August 14, 2014; Applicant: Oncomed Pharmaceuticals Inc. Inventors: Steven Eugene Benner, Robert Joseph Stagg, Jakob Dupont, Methods for Treating Cancer With DLL4 Antagonists; Publication number: 20130323265; Abstract: The present invention provides methods for treating cancer. More particularly, the invention provides methods for treating cancer comprising administrating doses of a DLL4 antagonist. Type: Application Filed: November 15, 2011; Publication date: December 5, 2013; Applicant: OncoMed Pharmaceuticals Inc. 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