Phase I Open-Label Study Evaluating the Safety, Pharmacokinetics, and Preliminary Efficacy of Dilpacimab in Patients with Advanced Solid Tumors

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ABSTRACT

Dilpacimab (formerly ABT-165), a novel dual-variable domain immunoglobulin, targets both delta-like ligand 4 (DLL4) and VEGF pathways. Here, we present safety, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy data from a phase I study (trial registration ID: NCT01946074) of dilpacimab in patients with advanced solid tumors. Eligible patients (≥18 years) received dilpacimab intravenously on days 1 and 15 in 28-day cycles at escalating dose levels (range, 1.25–7.5 mg/kg) until progressive disease or unacceptable toxicity. As of August 2018, 55 patients with solid tumors were enrolled in the dilpacimab monotherapy dose-escalation and dose-expansion cohorts. The most common treatment-related adverse events (TRAE) included hypertension (60.0%), headache (30.9%), and fatigue (21.8%). A TRAE of special interest was gastrointestinal perforation, occurring in 2 patients (3.6%; 1 with ovarian and 1 with prostate cancer) and resulting in 1 death. The PK of dilpacimab showed a half-life ranging from 4.9 to 9.5 days, and biomarker analysis demonstrated that the drug bound to both VEGF and DLL4 targets. The recommended phase II dose for dilpacimab monotherapy was established as 3.75 mg/kg, primarily on the basis of tolerability through multiple cycles. A partial response was achieved in 10.9% of patients (including 4 of 16 patients with ovarian cancer). The remaining patients had either stable disease (52.7%), progressive disease (23.6%), or were deemed unevaluable (12.7%). These results demonstrate that dilpacimab monotherapy has an acceptable safety profile, with clinical activity observed in patients with advanced solid tumors.

Introduction

Tumor angiogenesis, a multifaceted process associated with increased aggressiveness of disease, is based on outcomes from the interaction between endothelial and tumor cells, and various cellular signaling pathways. Tumor angiogenesis has been highlighted as one of the integral hallmarks of cancer (1). Two of the most relevant pathways that have a central role in tumor angiogenesis are the VEGF–VEGF receptor and the delta-like ligand 4 (DLL4)–Notch signaling pathways (2–4).

Clinical benefits have been demonstrated with anti-VEGF therapies (5–8); however, intrinsic and acquired resistance to such therapies occurs and highlights the need for more effective treatments capable of targeting both VEGF-dependent and -independent pathways crucial for tumor growth.

DLL4 is a cell-surface ligand that activates the Notch-1 receptor pathway involved in cell proliferation and cell-fate determination (9, 10), and was discovered as another pivotal signaling node in regulating tumor angiogenesis (11, 12). Of note, both DLL4 and VEGF activity are critically required for proper vascular function (13, 14). Several studies reported that DLL4 is upregulated on tumor vasculature relative to the endothelium of adjacent normal tissues (15–17), and endothelial expression levels were found to be inversely correlated with survival of some patients with cancer treated with anti-VEGF therapy (18, 19). This indicates a critical role in tumor angiogenesis that is VEGF independent. Blockade of DLL4 was shown to inhibit tumor growth across multiple tumor types, including those tumors that are resistant to VEGF inhibition (11, 12). Collectively, these observations indicate that targeting both the DLL4 and the VEGF pathways may improve outcomes of current anticancer therapies.

Dilpacimab, formerly called ABT-165, is a novel immunoglobulin G (IgG)–like DLL4/VEGF bispecific molecule that uses a proprietary dual-variable domain-Ig platform (20). In preclinical studies, dilpacimab potently inhibited both DLL4 and VEGF pathways, resulting in significantly greater tumor growth inhibition relative to blocking either axis alone (21). Importantly, in combination with chemotherapy agents in preclinical xenograft models, dilpacimab induced greater antitumor response and outperformed anti-VEGF treatment (21).

The present study describes the safety/tolerability, pharmacokinetic (PK) profile, and preliminary efficacy results of dilpacimab in patients with advanced solid tumors. Pharmacodynamic (PD) and predictive biomarkers for association with safety and efficacy are also discussed.

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Patients and Methods

Patient eligibility

Patients (≥18 years of age) with advanced solid tumors not amenable to surgical resection or other approved therapeutic options with demonstrated clinical benefit were enrolled and treated. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status from 0 to 2; measurable disease per RECIST version 1.1 or evaluable disease by assessment of peripheral blood tumor antigen markers; adequate bone marrow function (absolute neutrophil count ≥1,000 cells/mm^3, platelets ≥100,000/mm^3, hemoglobin ≥9.0 g/dL), renal function [serum creatinine ≤1.5× upper limit of normal (ULN) or creatinine clearance ≥50 mL/min], hepatic function (bilirubin ≤1.5× ULN, and aspartate aminotransferase and alanine aminotransferase ≤2.5× ULN or ≤5× ULN for patients with liver metastases), and coagulation function (activated partial thromboplastin time ≤1.5× ULN within 7 days prior to cycle 1 day 1). Exclusion criteria included: prior anticancer therapy (eg, chemotherapy, immunotherapy, radiotherapy, biologic therapy, or any investigational therapy) within 21 days or anticancer herbal therapy within 7 days prior to study-drug administration; clinically significant condition(s) that might put the patient at higher risk for (or history of intolerability to prior) antiangiogenic therapy; uncontrolled metastases to the central nervous system; unresolved clinically significant toxicities from prior anticancer therapies; prior history of clinically-significant pulmonary hypertension and cardiovascular disease.

The trial was registered with ClinicalTrials.gov (trial registration ID: NCT01946074) and was approved by institutional review boards (IRB) prior to initiation. The study was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the 1964 Declaration of Helsinki, with written informed consent obtained from all patients before study enrollment.

Study design

This phase I open-label, multicenter, dose-escalation, and safety-expansion study evaluated dilpacimab dosed every 14 days in 28-day cycles (Supplementary Fig. S1). Arms that enrolled dilpacimab plus other agents (chemotherapy and immune checkpoint inhibitor) will be reported elsewhere after data analysis. The primary objectives of this study were to evaluate the safety/tolerability and PK profile of dilpacimab monotherapy and to determine the recommended phase II dose (RP2D). The secondary objective was to assess the preliminary antitumor activity of dilpacimab. An exploratory objective was to evaluate PD and predictive biomarkers for associations with efficacy.

Dilpacimab was administered via a 60-minute intravenous infusion on days 1 and 15 in 28-day cycles at escalating dose levels ranging between 1.25 and 7.5 mg/kg to determine the maximum tolerated dose (MTD). A minimum of 6 (up to 9) patients were enrolled at each dose level (Supplementary Fig. S1) and MTD was defined as the highest dose level at which fewer than 2 of 6 (<33%) patients experience a dose-limiting toxicity (DLT). Patients with clinical benefit[), or stable disease) could continue dilpacimab at investigator's discretion until progressive disease or unacceptable toxicity.

Dose escalation

The initial dose-escalation enrolled patients at 2.5 ($n = 9$; 1 patient with a DLT of headache), 5 ($n = 6$), and 7.5 ($n = 3$) mg/kg. Due to hypertension not easily controlled by antihypertensives that occurred outside the 28-day DLT window in patients treated at 5 and 7.5 mg/kg, a second dose-escalation enrolled at least 6 patients per cohort at dose levels of 1.25 ($n = 8$), 2.5 [$n = 9$; 1 patient with DLT hypertension, 1 patient with DLTs (grade 3 elevated aspartate amino transferase and alanine aminotransferase)], 3.75 ($n = 9$), and 5 mg/kg ($n = 2$) so that safety observations could be made outside of the DLT window on patients who were able to continue therapy.

Dose expansion

The dose expansion was intended to enroll up to 24 patients, with expansion at or below the MTD to be performed to evaluate the safety, tolerability, and PK of dilpacimab. The dose expansion was terminated after 9 patients were enrolled, due to sponsor's decision to terminate further monotherapy development.

Safety

Treatment-emergent adverse events (AE) were assessed in the safety population (included all patients who received any study drug) from the time of study drug administration until 60 days following discontinuation of study drug and graded per the NCI Common Terminology Criteria for Adverse Events version (CTCAE) 4.03. Treatment-related AEs (TRAE) were those considered by investigator or sponsor to be related to dilpacimab.

Blood pressure and cardiac monitoring

The initial dose escalation did not have strict guidance for dosing based on blood pressure and after several patients had blood pressure that was difficult to control, a second dose escalation was started with stricter blood pressure monitoring and dosing criteria. In the second dose escalation (and expansion) enrolled patients recorded daily at-home blood pressure readings starting after dosing on cycle 1, day 1 and lasting through the end of cycle 1. Enrolled patients could receive up to 4 antihypertensive medications at any one time, and reduced monitoring was allowed if hypertension was well controlled at the start of cycle 2. Additionally, blood pressure was measured in triplicate at every study visit. If either an in-clinic or at-home reading showed systolic ≥140, diastolic ≥90 mm Hg, or if a patient required the addition of a fifth antihypertensive agent, study drug was withheld. If systolic was ≥180 or diastolic ≥110 mm Hg, patient was discontinued from study drug. Cardiac evaluations [including electrocardiogram (ECG) and echocardiogram] were performed every 2 cycles prior to dosing of dilpacimab, or upon the occurrence of any cardiac symptoms (including B-type natriuretic peptide greater than twice the institutional normal range, measured at the start of each cycle). Additionally, triplicate ECGs were collected before and within 30 minutes after dosing on cycle 1, day 1 and cycle 2, day 15, as well as within 45 days of the final study visit.

Pharmacokinetics

The PK population included all patients who received at least one dose of dilpacimab and from whom adequate drug concentration measurements were obtainable during the study. Blood samples for dilpacimab PK analyses were collected on day 1 (preinfusion and 30 minutes postinfusion), day 3 or 4, day 8, and day 15 (preinfusion and 30 minutes postinfusion) in cycle 1. In addition, blood samples were collected preinfusion and 30 minutes postinfusion on days 1 and 15 in cycle 2 and day 1 of each cycle thereafter, and at final visit. Serum concentrations of dilpacimab were determined using a validated method. PK parameters, including area under the serum concentration-time curve, maximum observed serum concentration (C_{max}), time to C_{max} (T_{max}), and terminal phase elimination half-life ($T_{1/2}$), were estimated using noncompartmental analysis [Phoenix WinNonlin 8.0 (QC 17320)].

Efficacy and biomarker assessments

The efficacy population included all patients who received at least one dose of dilpacimab. All efficacy analyses were exploratory in nature, and their end-points included objective response rate (ORR; CR or PR) and progression-free survival (PFS). Baseline radiographic tumor assessment (CT or MRI) was performed within 28 days prior to day 1 of cycle 1 and repeated every 2 cycles (56 days; assessments could occur up to 7 days prior to end of cycle). ORR included confirmed CR and PR and was assessed by RECIST version 1.1. PFS was defined as the time from first dose date of dilpacimab to either disease progression or death, whichever occurred first. If a patient was still responding, the patient's data were censored at the date of the last tumor assessment. If a patient received a new line of anticancer therapy, data were censored at the date of the last tumor assessment prior to initiating the new therapy.

Plasma, whole blood, serum, and tumor tissue (archival or fresh biopsy) samples were collected and stored at −70° C or below until quantitative biomarker assessment. Serum and plasma biomarker samples were collected predose on days 1 and 15 of cycle 1; day 1 of cycles 2 and 3; and at the final visit. Plasma was also collected 2 hours postdose on day 1 of cycle 1. Tumor tissue had to be confirmed available prior to enrollment.

Biomarker analysis

Blood sample collections for plasma VEGF/DLL4 measurements

Venous blood was drawn in EDTA tubes at day 1 (baseline), and 2 hours and 3 or 4 days post-dilpacimab dosing in cycle 1. Additional samples were also collected immediately before dosing on cycle 1 day 15, and then at the start of each new cycle. Plasma was extracted within 30 minutes of blood draw, aliquoted, and kept frozen until the analysis.

Circulating soluble DLL4

An electrochemilluminescent assay by Meso Scale Discovery (MSD) technology (Meso Scale Discovery; catalog no. 1506- D4/CF) was used to determine the concentration of soluble DLL4 in human plasma. Two DLL4 antibodies (E9–2B and h38H12.11, produced by AbbVie) that do not compete with dilpacimab for DLL4 binding were ruthenylated and biotinylated, respectively, and mixed with study samples. The homogeneous solutions were then pipetted into streptavidin-coated MSD plates. Following an incubation and wash step, assay plates were read on an MSD instrument.

Circulating VEGF

VEGF plasma levels were measured by Quantikine (R&D Systems, catalog no. DVE00) assay. In an additional step, dilpacimab was removed from post–dilpacimab-dosed samples using Protein A Spin Columns (Thermo Scientific; catalog no. 89952 or 89948), to decrease interferences in detecting free VEGF. The intensity of color was measured at 450 and 570 nmol/L using SpectraMax by Molecular Devices (catalog no. ABS).

Statistical analyses

Data were summarized by dose level and for all patients pooled in the dose-escalation and -expansion phase. Categorical data were summarized by frequency counts and percentages, and continuous data were summarized by descriptive statistics. All safety summaries were descriptive, and no statistical inference was performed on the safety data. The two-sided 95% confidence intervals (CI) for the ORR, as well as complete response and PR rates, were provided using the Clopper–Pearson exact method. PFS was estimated using the Kaplan–Meier method; median time and associated two-sided 95% CIs, and the 25th and 75th percentiles of the time were provided.

Table 1. Baseline demographics and clinical characteristics.

Characteristics	Dilpacimab $N = 55$
Median age, years (range)	60 (40–75)
Sex, *n* (%)	
Male	15 (27.3)
Female	40 (72.7)
Median number of prior therapies (range)	4 (1–10)
Primary tumor, *n* (%)	
Ovarian	17 (30.9)
Breast	6 (10.9)
Colon	4 (7.3)
Renal	4 (7.3)
Esophageal	3 (5.5)
Other types[a]	21 (38.2)

[a]Tumor types with <5% were combined.

Results

Patient demographics and baseline characteristics

As of August 2, 2018, 55 patients with solid tumors were enrolled in 2 sequential dose-escalation cohorts (46 patients) and a dose-expansion cohort (9 patients). Key patient demographics and clinical characteristics are summarized in **Table 1**. The median age was 60 years (range, 40–75) and the most common primary tumor was ovarian ($n = 17$; 30.9%). The sponsor chose to enrich for ovarian tumors, since VEGF inhibitors have monotherapy activity in ovarian cancer. Prior systemic therapies received by patients with ovarian cancer are listed in Supplementary Tables S1 and S2.

Safety profile

In the initial dose-escalation using a 3 + 3 design, the first patient treated with 2.5 mg/kg dilpacimab had a DLT of grade 3 headache, and although no other DLTs were observed in that or subsequent cohorts, patients receiving multiple doses at 5 and 7.5 mg/kg showed evidence of hypertension that was not easily controlled with antihypertensive agents, beyond the 28-day DLT window. Therefore, the initial dose-escalation was suspended, and after evaluation of the safety data, dose escalation was resumed starting at 1.25 mg/kg with revised treatment criteria requiring systolic blood pressure less than 140 mm Hg and diastolic blood pressure less than 90 mm Hg prior to any treatment with dilpacimab. The RP2D for dilpacimab monotherapy was determined to be 3.75 mg/kg (a total of 15 patients were treated at this dose level: 9 in dose escalation and 6 in dose expansion), on the basis of the safety and lack of tolerability of higher doses due to hypertension that occurred outside the DLT window. Further details of the dose-escalations are provided in the Patients and Methods section.

Treatment-emergent AEs regardless of attribution were reported in all patients ($N = 55$; 100%). Any-grade and grade ≥3 treatment-emergent AEs are summarized in **Table 2**. The most common treatment-emergent AEs (>40%) of any grade reported with dilpacimab monotherapy were hypertension (63.6%), fatigue (49.1%), headache (43.6%), and nausea (41.8%). Any-grade TRAEs were reported in 48 (87.3%) patients (**Table 2**). Most common TRAEs (>20%) of any grade were hypertension ($n = 33$; 60.0%), headache ($n = 17$; 30.9%), and fatigue ($n = 12$; 21.8%). The most common grade ≥3 TRAE was hypertension ($n = 21$; 38.2%). Less frequent TRAEs of special interest

Table 2. Summary of treatment-emergent AEs occurring in ≥10% of patients or treatment-emergent AEs considered to be related to dilpacimab occurring in ≥5% of patients.

	Related or unrelated to dilpacimab		Related to dilpacimab	
Treatment-emergent AEs	**Any grade dilpacimab (*N* = 55)**	**Grade ≥3 dilpacimab (*N* = 55)**	**Any grade dilpacimab (*N* = 55)**	**Grade ≥3 dilpacimab (*N* = 55)**
Any AE	55 (100)	47 (85.5)	48 (87.3)	28 (50.9)
Hypertension	35 (63.6)	22 (40.0)	33 (60.0)	21 (38.2)
Fatigue	27 (49.1)	2 (3.6)	12 (21.8)	0
Headache	24 (43.6)	1 (1.8)	17 (30.9)	1 (1.8)
Nausea	23 (41.8)	2 (3.6)	7 (12.7)	1 (1.8)
Abdominal pain[a]	22 (40.0)	3 (5.5)	1 (1.8)	0
Diarrhea	20 (36.4)	2 (3.6)	10 (18.2)	0
Decreased appetite	19 (34.5)	2 (3.6)	6 (10.9)	1 (1.8)
Urinary tract infection	13 (23.6)	1 (1.8)	0	0
Anemia	12 (21.8)	3 (5.5)	6 (10.9)	0
Arthralgia	12 (21.8)	0	0	0
Cough	12 (21.8)	0	0	0
Dizziness	11 (20.0)	0	3 (5.5)	0
Anxiety	10 (18.2)	0	0	0
Constipation	10 (18.2)	0	3 (5.5)	0
Depression	10 (18.2)	0	0	0
Back pain	9 (16.4)	1 (1.8)	0	0
Dehydration	9 (16.4)	2 (3.6)	0	0
Dyspnea	9 (16.4)	0	3 (5.5)	0
Hypokalemia	9 (16.4)	6 (10.9)	0	0
Malignant neoplasm progression	9 (16.4)	9 (16.4)	0	0
Pulmonary hypertension	9 (16.4)	2 (3.6)	8 (14.5)	1 (1.8)
Vomiting	9 (16.4)	2 (3.6)	0	0
Insomnia	8 (14.5)	0	0	0
Myalgia	8 (14.5)	0	3 (5.5)	0
Decreased weight	8 (14.5)	0	0	0
Hypomagnesemia	7 (12.7)	0	0	0
Peripheral edema	7 (12.7)	0	3 (5.5)	0
Upper respiratory tract infection	7 (12.7)	1 (1.8)	0	0
Pain in extremity	6 (10.9)	0	0	0
Proteinuria	6 (10.9)	0	6 (10.9)	0
Muscular weakness	5 (9.1)	0	3 (5.5)	0
Stomatitis	5 (9.1)	0	3 (5.5)	0
Confusional state	4 (7.3)	1 (1.8)	3 (5.5)	1 (1.8)
Dry mouth	4 (7.3)	1 (1.8)	3 (5.5)	0
Epistaxis	4 (7.3)	0	3 (5.5)	0
Increased blood ALP	4 (7.3)	1 (1.8)	3 (5.5)	0
Aphasia	3 (5.5)	0	3 (5.5)	0

Abbreviation: ALP, alkaline phosphatase.
[a]Includes upper abdominal pain.

were gastrointestinal perforation (GIP; $n = 2$; 3.6%) and pulmonary hypertension (any grade) detected by echocardiogram ($n = 8$; 14.5%); 1 patient died as a result of GIP.

All patients discontinued study drug except 1 patient with pancreatic adenocarcinoma. Reasons for treatment discontinuation included AEs ($n = 9$), clinical PD ($n = 8$), radiographic PD ($n = 20$), sponsor discontinued dosing ($n = 2$), patient withdrew consent ($n = 2$), and other reasons ($n = 4$).

Pharmacokinetics

PK parameters for dilpacimab are presented in **Table 3**. The $T_{1/2}$ for dilpacimab ranged from 5.0 to 7.2 days in the dose range tested (1.25–7.5 mg/kg). The exposure (C_{max} and AUC) of dilpacimab appeared to be dose proportional between 1.25- and 5-mg/kg dose groups, and slightly greater than dose proportional at 7.5 mg/kg. Body weight did not appear to be a significant covariate for dilpacimab exposure.

Preliminary efficacy

The best percentage change from baseline in tumor size is shown in **Fig. 1A**. ORRs for all treated patients with available data are presented in **Table 4**. The ORR was 10.9% (6 of 55); 6 patients achieved PR; median PFS was 3.7 months (95% CI, 2.7–3.9). The remaining patients either had stable disease ($n = 29$), PD ($n = 13$), or were not evaluable ($n = 7$). As expected for an antiangiogenic agent, the antitumor activity was concentrated in patients with ovarian cancer, with 25.0% (4 of 16) achieving PR (**Table 4** and **Fig. 1B**). Change in tumor target lesions sum of longest diameter over time for patients with ovarian cancer treated with dilpacimab at all dose levels is shown in **Fig. 1C**. The median time on treatment for patients with

Table 3. Pharmacokinetic parameters of dilpacimab for $N = 55$ available samples.

Pharmacokinetic parameters (units)	1.25 mg/kg ($N = 9$)[a]	2.5 mg/kg ($N = 20$)[b]	3.75 mg/kg ($N = 15$)[c]	5 mg/kg ($N = 8$)[d]	7.5 mg/kg ($N = 3$)[e]
T_{max}, h[e,f] Median (min, max)	1.5 (1.5, 1.5)	1.5 (1.5, 1.5)	1.5 (1.5, 49)	1.5 (1.5, 49)	1.5 (1.5, 49)
C_{max}, μg/mL Geometric mean (%CV)	27.6 (34)	60.0 (20)	108 (34)	125 (32)	207 (19)
AUC_{336h}, μg/day/mL Geometric mean (%CV)	139 (47)	309 (29)	659 (24)	796 (28)	1,421 (23)
AUC_{inf}, μg/day/mL Geometric mean (%CV)	192 (40)	416 (38)	946 (26)	943 (30)	1,666 (1,567, 1,765)[e]
$T_{1/2}$, day Harmonic mean	5.0	5.2	7.4	5.4	7.2 (7.9, 6.4)[e]
CL (mL/h/kg)	0.27 (55) (6.5 mL/d/kg)	0.25 (52) (6.0 mL/d/kg)	0.17 (28) (4.0 mL/d/kg)	0.22 (28) (5.3 mL/d/kg)	0.19 (0.20, 0.18) (4.5 mL/d/kg)[e]

Abbreviations: AUC_{336h}, area under the serum concentration-time curve from time zero to 336 hours; AUC_{inf}, area under the serum concentration-time curve from time zero to infinity; CL, clearance.
[a]$N = 8$ for $T_{1/2}$, AUC_{inf}, and CL.
[b]$N = 16$ for $T_{1/2}$, AUC_{inf}, and CL.
[c]$N = 11$ for $T_{1/2}$, AUC_{inf}, and CL.
[d]$N = 5$ for $T_{1/2}$, AUC_{inf}, and CL.
[e]$N = 2$, presented as a mean (individual values).
[f]Time relative to start of the infusion, presented as median (min, max).

ovarian cancer was 10.1 weeks (range, 0.1–96.3); 2 patients with PR were on treatment for more than 50 weeks (55.1 and 96.3). One patient with pancreatic adenocarcinoma continues on study, with sustained PR for appproximately 5 years. The original dosing regimen was dilpacimab 3.75 mg/kg every 14 days; the patient is currently receiving dilpacimab 2.5 mg/kg every 28 days. Dose and schedule were modified due to treatment-emergent pulmonary hypertension which resolved.

Correlative biomarkers

To evaluate target binding, circulating levels of free VEGF and total serum (s)DLL4 levels were measured in the dose-escalation cohort. The baseline levels of VEGF ($N = 53$ available samples) varied from 15 to 867 pg/mL (**Fig. 2A**). Within 2 hours of dilpacimab dosing, a significant decrease was observed in free VEGF levels, suggesting saturation of VEGF by dilpacimab. The decrease in VEGF levels compared with predose was statistically significant for all dose levels and time points tested ($P < 0.001$) but was not dose dependent. A dose-dependent desaturation of VEGF binding by dilpacimab was also observed.

The baseline levels of sDLL4 ($N = 53$) varied from 106 to 671 pg/mL (**Fig. 2B**). The immunoassay measured the total (dilpacimab-bound and -free) sDLL4. The levels of total sDLL4 increased after 3 to 4 days of dosing for all dose cohorts ($P < 0.01$). The increase in sDLL4 levels compared with predose was statistically significant for all dose levels at all time points except 2 hours after first dose. A trend for increased fold-change in sDLL4 levels with dose was also observed.

Discussion

This study represents the first-in-human phase I clinical trial of dilpacimab, a novel IgG-like DLL4/VEGF bispecific molecule. The results demonstrate that dilpacimab is clinically active and has a manageable tolerability and safety profile. The most common TRAEs were hypertension, headache, and fatigue. As expected, dilpacimab displayed anti-VEGF–like toxicity including hypertension, which is one of the most frequently described on-target treatment-related side effects associated with several anti-VEGF–targeted therapies (22) as well as with anti-DLL4 therapy (23). The RP2D of dilpacimab monotherapy was established as 3.75 mg/kg.

Regarding safety, two of 55 (3.6%) patients treated with monotherapy had GIP considered related to dilpacimab. The GIP occurred at the site of a diverticulum (prostate cancer) or diverticulum involved with tumor (ovarian cancer). It is currently unclear if diverticuli or metastatic or primary tumor invading bowel represent increased risk for dilpacimab-associated GIP. Pulmonary hypertension, generally asymptomatic, was detected in dilpacimab-treated patients by echocardiogram, usually after multiple cycles of drug therapy, and managed by dose delays or discontinuation. Although follow-up was not long enough to ensure complete reversal, decrease in pulmonary hypertension after drug cessation was noted, suggesting that the finding was reversible. One patient had a hypertensive emergency after presenting with a minor stroke and retinal vein occlusion. Certain other potential side effects of anti-VEGF therapy such as myocardial infarction, ischemic limbs, nephrotic syndrome, or delayed wound healing were not observed, possibly due to the low number of patients treated.

This phase I study also explored the PK and PD effects of dilpacimab. The exposure of dilpacimab appeared to be dose proportional between the 1.25- and 5-mg/kg dose groups, and slightly greater than dose proportional at 7.5 mg/kg. As expected, dilpacimab treatment resulted in significant decrease in free VEGF within 2 hours of even the lowest dose, suggesting binding of dilpacimab to circulating VEGF. This finding is consistent with prior observations with bevacizumab. We observed a dose-dependent desaturation of VEGF binding by dilpacimab, and increase in VEGF levels was observed predose for the second infusion on cycle 1 day 15. At higher doses, free VEGF was constantly suppressed.

We also observed significant increase in total sDLL4 over time, suggestive of binding of dilpacimab to sDLL4 ligand with stabilization of the complex in circulation. The increase in total sDLL4 was also dose dependent. The pattern of modulation of two ligands, VEGF and sDLL4, after dilpacimab dosing was different. Decrease in free VEGF peaked 3 to 4 days after dosing, then plateaued. The total sDLL4 receptor levels, however, did not plateau, and continued to rise until the loss of exposure after dilpacimab therapy was discontinued.

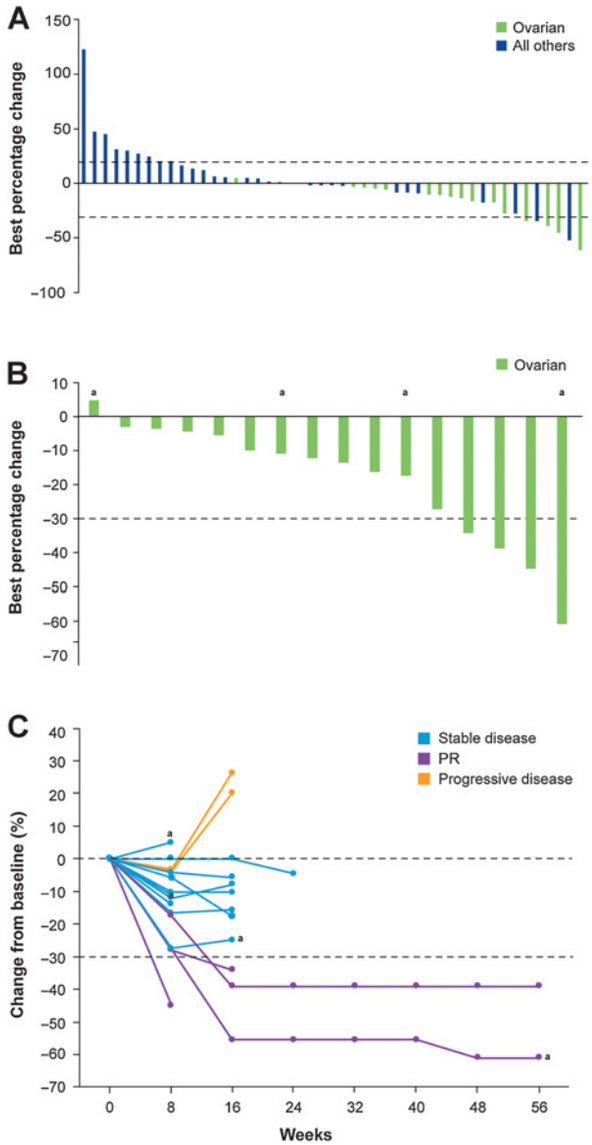

Figure 1.

A, Best percentage change in tumor lesion for dilpacimab at all dose levels ($n = 47$). **B,** Patients with ovarian cancer treated with dilpacimab at all dose levels ($n = 16$). **C,** Change in tumor lesion over time for patients with ovarian cancer treated with dilpacimab at all dose levels ($n = 16$). [a]Patients without prior bevacizumab treatment.

Dilpacimab has demonstrated robust preclinical efficacy in a wide range of tumor types (21). In our study, dilpacimab monotherapy showed promising clinical antitumor activity, particularly in patients with ovarian cancer, with 4 of 16 patients achieving a PR (25%). Three of the 4 (75%) patients with ovarian cancer with PR had previously received and progressed on bevacizumab in earlier lines of therapy. PRs were also noted in 2 other patients, each of whom had received two prior lines of systemic chemotherapy: 1 patient with cervical cancer and 1 with pancreatic cancer (the latter remaining on study with PR for >60 months).

Table 4. Best response for evaluable patient population.

Best response per investigator, *n* (%)	Dilpacimab (*N* = 55)[a]
PR	6 (10.9)
Ovarian ($n = 16$)	4 (25.0)
Stable disease[b]	29 (52.7)
Progressive disease	13 (23.6)

[a]7 patients were not evaluable for efficacy, including one patient with ovarian cancer.
[b]First scan performed within 7 days prior to the end of cycle 2.

In the first-in-human, phase I study of the anti-DLL4 mAb enoticumab (REGN421) in patients with advanced solid tumors, modest antitumor activity was demonstrated, with 2 of 44 (5%) evaluable patients achieving PR. One of the 2 patients who achieved PR had ovarian cancer, from a total of 7 evaluable patients with ovarian cancer. In the first-in-human phase Ia study of the bispecific anti-DLL4/anti-VEGF antibody navicixizumab (OMP-305B83) in patients with previously treated solid tumors, 4 of 66 (6.1%) patients achieved PR; 3 of the 4 patients with PR had ovarian cancer (out of 12 patients with ovarian cancer in total; 25%), comparable with our study. These results suggest the antitumor activity of dilpacimab seen in ovarian cancer may be, at least in part, attributed to the inhibition of DLL4, since some patients were previously treated with bevacizumab. However, no definitive conclusions can be drawn, due to the low number of patients and unknown response rate to bevacizumab rechallenge. Similarly, no conclusive correlation could be drawn between response and angiogenesis gene expression signatures in the ovarian cancer patients due to the small number of patients.

Further clinical studies are warranted to ascertain whether dilpacimab, through inhibition of both VEGF and DLL4, represents a potential improvement beyond VEGF inhibition alone. A phase II study evaluating the efficacy and tolerability of dilpacimab plus folinic acid, fluorouracil, irinotecan (FOLFIRI) compared with bevacizumab plus FOLFIRI in patients with previously-treated metastatic colorectal cancer (NCT03368859; ref. 24) was discontinued after interim analysis showed lack of improved efficacy beyond bevacizumab.

Disclaimers

AbbVie provided financial support for this study (NCT01946074) and participated in the study design, research, analysis, data collection, interpretation of data, and review and approval of the manuscript. All authors had access to relevant data and participated in the drafting, review, and approval of this manuscript. No honoraria or payments were made for authorship.

Data Sharing Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (e.g., protocols and Clinical Study Reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

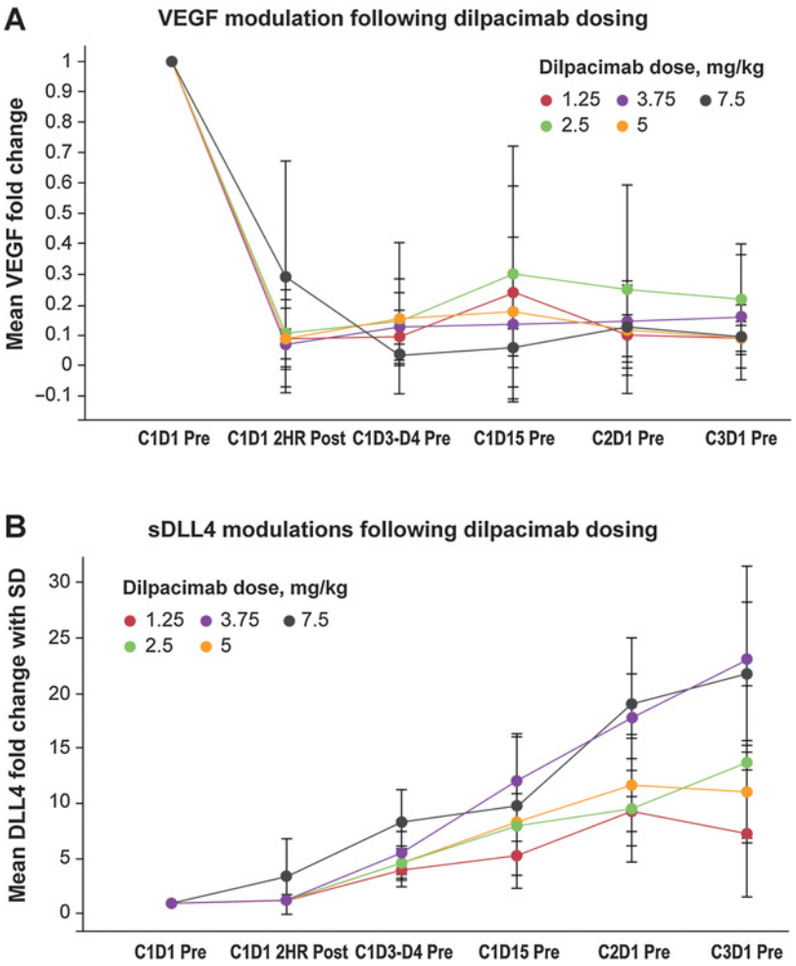

Figure 2.
Effect of dilpacimab administration on levels of free VEGF (**A**) and total sDLL4 (**B**). C, cycle. D, day.

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