

# A First-in-Human Study of Novel Cereblon Modulator Avadomide (CC-122) in Advanced Malignancies



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## Abstract

**Purpose:** Avadomide is a novel, small-molecule therapeutic agent that modulates cereblon E3 ligase activity and exhibits potent antitumor and immunomodulatory activities. This first-in-human phase I study (NCT01421524) evaluated the safety and clinical activity of avadomide in patients with advanced solid tumors, non-Hodgkin lymphoma (NHL), and multiple myeloma.

**Patients and Methods:** Thirty-four patients were treated with avadomide in 7 dose-escalation cohorts using a 3 + 3 design (0.5–3.5 mg, 28-day continuous dosing cycles). The primary objectives were to determine the dose-limiting toxicity (DLT), nontolerated dose (NTD), maximum tolerated dose (MTD), recommended phase II dose, and pharmacokinetics of avadomide. The secondary objective was to determine preliminary avadomide efficacy. Exploratory objectives included evaluation of pharmacodynamic effects of avadomide.

**Results:** DLTs were reported in 2 patients, and grade  $\geq 3$  treatment-emergent adverse events (TEAEs) occurred in 14 patients (41%). The most common TEAEs ( $\geq 15\%$ ) were fatigue, neutropenia, and diarrhea. The NTD and MTD were 3.5 and 3.0 mg, respectively. Of 5 patients with NHL, 1 achieved a complete response, and 2 had partial responses. Although no objective responses were observed in patients with solid tumors, 5 of 6 patients with brain cancer experienced nonprogression of  $\geq 6$  months. A dose-dependent relationship between Aiolos degradation in peripheral B and T cells occurred within 5 hours of the first dose of avadomide administered, starting at 0.5 mg.

**Conclusions:** Avadomide monotherapy demonstrated acceptable safety and favorable pharmacokinetics in patients with solid tumors, NHL, and multiple myeloma. In addition, 3 objective responses were observed in NHL.

## Introduction

Avadomide (CC-122) is a novel cereblon-modulating agent with potent biological activities, including antilymphoma, antiangiogenic, and immunomodulatory properties (1, 2). Avadomide binds to and modulates cereblon to promote recruitment of the hematopoietic transcription factors Aiolos and Ikaros to the Cullin-4 RING E3 ubiquitin ligase complex. This binding results in the ubiquitination and rapid proteasomal degradation of Aiolos and Ikaros, leading to transcriptional changes in lymphoid cells (1, 3).

In general, Aiolos and Ikaros are transcriptional repressors known to play an important role in normal B- and T-cell function (4). In neoplastic B cells, such as diffuse large B-cell lymphoma (DLBCL), the degradation of Aiolos and Ikaros by avadomide results in derepression of IFN-stimulated genes, including *DDX58* and *IRF7*, leading to apoptosis of malignant cells in both activated B-cell (ABC) and germinal center B-cell (GCB) DLBCL cell lines (1, 5, 6). Avadomide has broader activity in comparison with lenalidomide, which is preferentially active in ABC DLBCL cell lines; this differential activity is hypothesized to be in part due to avadomide's faster kinetics and deeper levels of degradation of Aiolos and Ikaros (1, 7). Avadomide also induces apoptosis in multiple myeloma cells and shows antitumor activity in mouse xenograft models of DLBCL and multiple myeloma (6, 8, 9). In T cells, Aiolos degradation by avadomide leads to derepression of genes, including *IL2*, resulting in enhanced IL2 production, costimulation of T cells, and IL2-induced T-cell proliferation (1, 5, 10). In addition, avadomide has been shown to activate natural killer (NK) cells and exhibits potent antiangiogenic properties, as demonstrated in an *ex vivo* umbilical artery sprout outgrowth assay (9).

Current treatment options for patients with advanced solid and hematologic malignancies relapsed or refractory to standard therapies are limited. Avadomide's cell-autonomous effects, immune modulation, and antiangiogenic activity make it a potential therapeutic agent for hematologic and solid tumors

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

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### Translational Relevance

An unmet need exists for more effective therapeutic options for patients with advanced solid and hematologic malignancies. Avadomide is a novel, small-molecule modulator of the CUL4 E3 ligase substrate receptor cereblon and has been shown to exert multiple biological activities, including anti-proliferative activity, antiangiogenic activity, and immunomodulatory effects. In this first-in-human phase I study, we report pharmacokinetic and pharmacodynamic data, the safety profile, and clinical activity with avadomide monotherapy in patients with solid tumors, non-Hodgkin lymphoma, and multiple myeloma. Avadomide demonstrated acceptable safety and tolerability, along with favorable pharmacokinetics, in patients with advanced solid and hematologic malignancies and also showed signs of clinical activity in patients with non-Hodgkin lymphoma. These data demonstrate for the first time the utility of Aiolos as a pharmacodynamic biomarker for this class of molecules and provide the rationale for the ongoing phase Ib trials.

(1, 2, 10, 11). Herein, we report results from the first-in-human phase I dose-escalation study of avadomide in patients with advanced solid tumors, non-Hodgkin lymphoma (NHL), and multiple myeloma.

## Patients and Methods

### Study design

CC-122-ST-001 is a first-in-human study designed as a 2-part, multicenter, open-label, phase I clinical trial that included a dose-escalation part A reported here and a dose expansion part B to be reported separately (NCT01421524, EUDRACT number 2011-004603-20). Patients were enrolled at 2 study sites in the United States from September 12, 2011, to January 30, 2013. In part A, a standard 3 + 3 dose-escalation design was used by which patients received single and multiple ascending dose levels of avadomide taken orally (12). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in adherence to Good Clinical Practice as described in International Council for Harmonisation Guideline E6. The study protocol and informed consent form were approved by the Institutional Review Boards or independent ethics committees of participating institutions. All patients provided written informed consent before any study-related procedure was performed.

The primary objectives were to determine the safety and tolerability of oral avadomide; to define the nontolerated dose (NTD), the MTD, and the recommended phase II dose; and to determine the plasma pharmacokinetics and extent of urinary excretion of avadomide after treatment. The secondary objective was to make a preliminary assessment of the antitumor activity of avadomide. The primary efficacy endpoint was response rate for patients with NHL, multiple myeloma, and solid tumors (except brain cancer). For patients with brain cancer, progression-free survival (PFS) rate at 6 months was selected as the primary efficacy endpoint due to the difficulty of distinguishing between tumor changes and non-tumor-related treatment effects in recurrent high-grade gliomas, as described by the North American Brain Tumor Consortium

(13, 14). Exploratory objectives included evaluation of pharmacodynamic effects of avadomide on Aiolos expression in peripheral T and B cells; total T-, B-, and NK-cell counts; and *ex vivo* T-cell activation.

### Patients

Patients were  $\geq 18$  years of age and had histologically or cytologically confirmed advanced solid tumors, NHL (including B-cell malignancies), or multiple myeloma. Patients who had progressed on (or were not able to tolerate) standard anticancer therapy or for whom no standard anticancer therapy existed were included. Patients with primary central nervous system (CNS) malignancy were included provided that the neurological symptoms were stable. Stable neurological symptoms were defined as follows:  $\geq 12$  weeks after radiotherapy, no prior or scheduled Gliadel wafer implant was present, no prior interstitial brachytherapy or stereotactic radiosurgery had been received unless the area of assessment and planned resection was outside the previously treated region, no enzyme-inducing antiepileptic drugs were consumed  $\leq 28$  days before study day 1, and the patient was able to undergo repeated MRI scans. All patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS)  $\leq 2$ , except for hepatocellular carcinoma (HCC), which required an ECOG PS  $\leq 1$ . The required laboratory values included the following: absolute neutrophil count  $\geq 1.5 \times 10^9/L$ , hemoglobin  $\geq 9$  g/dL, platelets  $\geq 100 \times 10^9/L$ , hepatic function [serum bilirubin  $\leq 1.5 \times$  upper limit of normal (ULN), alanine aminotransferase, and aspartate aminotransferase  $\leq 3 \times$  ULN or  $\leq 5.0 \times$  ULN if liver tumor present], renal function (serum creatinine  $\leq$  ULN or 24-hour clearance  $\geq 50$  mL/min), and potassium within normal limits or correctable with supplements. Women of childbearing potential were required to have a negative serum pregnancy test, and both men and women were required to adhere to a pregnancy-prevention risk-management plan.

Key exclusion criteria included symptomatic CNS metastases, excluding glioblastoma multiforme (GBM; patients with previously treated brain metastases stable for 6 weeks were allowed); acute or chronic pancreatitis; peripheral neuropathy grade  $\geq 2$ ; persistent diarrhea or malabsorption grade  $\geq 2$ , despite medical management; impaired cardiac function or clinically significant cardiac diseases; other concurrent severe or uncontrolled concomitant medical conditions that might cause unacceptable safety risks or compromise compliance with the protocol; prior systemic anticancer treatments  $\leq 5$  half-lives or 4 weeks before the start of study drug, whichever was shorter; major surgery  $\leq 2$  weeks before the start of study drug or still recovering from the postoperative effects of surgery; pregnant or breast-feeding women; known human immunodeficiency virus infection; chronic hepatitis B or C virus infection (unless comorbidity in patients with HCC); solid organ transplant recipient;  $< 100$  days from autologous stem cell transplantation (SCT) or  $< 6$  months from allogeneic SCT; or otherwise not fully recovered from SCT-related toxicity. Luteinizing hormone-releasing hormone agonists were allowed for men with metastatic prostate cancer.

### Treatment

Treatment cohorts were used in a standard 3 + 3 dose-escalation design by which patients received avadomide taken orally (12). The MTD cohort was expanded to at least 6 evaluable patients. Avadomide was administered orally once daily (QD) on a 28/28-day schedule, with no rest period between cycles. The

first cohort of 3 patients received avadomide 0.5 mg. The maximum allowable dose escalation in subsequent cohorts proceeded according to a modified Fibonacci scheme at dose levels of 0.5 to 3.5 mg. After the first dose, patients were treated and observed for  $\geq 30$  days before another cohort received the next dose level. On day  $-1$  of the first cycle, patients received a single dose of avadomide followed by a 48-hour period of observation and pharmacokinetic sample collection, which was then followed on day 1 by daily dosing for 28 days (thus, the first cycle was 30 days). Treatment was administered until disease progression, unacceptable toxicity, or patient/physician decision to withdraw treatment.

### Safety, pharmacokinetics, and pharmacodynamics

The NTD was defined as the dose level at which  $\geq 2$  of 6 evaluable patients in a cohort experienced a drug-related dose-limiting toxicity (DLT) during cycle 1. The MTD was defined as the last dose level below the NTD at which  $\leq 1$  of 6 evaluable patients had a DLT during cycle 1. During cycle 1, any adverse event (AE) that led to dose reduction was considered a DLT. Patients could resume avadomide at a reduced dose only if they recovered to grade  $\leq 1$  within 14 days of dose interruption; 2 dose reductions were allowed before the patient was withdrawn from the study. After cycle 1, the dose level could be increased if the alternative dose level was well tolerated in a cohort of other patients. Other anticancer therapies were not allowed, except for focal palliative radiotherapy for cancer-related symptoms, at the investigator's discretion.

Intensive and sparse blood and urine samples for pharmacokinetic analysis were collected on cycle 1 predose days  $-1$  and 0, and dosing days 1, 2, 15, and 22 in all patients and in subsequent cycles on days 8, 15, and 22 in patients who had dose escalated. Samples for pharmacodynamic biomarker analysis were collected at screening (cycle 1 day  $-7$  to day  $-1$ ) and in cycle 1 on days 15 and 22 and in cycle 2 on days 15 and 22. Avadomide, CC-17339 (R-enantiomer), and CC-17342 (S-enantiomer) plasma and urine levels were measured using validated chiral liquid chromatography-mass spectrometry assays. Aiolos protein levels in peripheral blood B and T cells were determined by flow cytometry, essentially as described previously (15), using purified rabbit anti-Aiolos antibody (O-21, #sc-101982; Santa Cruz Biotechnology). Absolute counts of CD3<sup>+</sup>T and CD19<sup>+</sup>B lymphocytes and CD56<sup>+</sup>NK cells in patient whole blood samples were determined by flow cytometry, utilizing the BD TruCount platform (BD Biosciences) and BD Multitest antibody cocktails (CD3/CD8/CD45/CD4 and CD3/CD16<sup>+</sup>CD56/CD45/CD19) according to the manufacturer's protocols. *Ex vivo* cytokine production was evaluated from patient whole blood collected on cycle 1 day  $-1$  predose and 1.5 and 5 hours after dose, using the TruCulture system with anti-CD3 antibody stimulant (Myriad RBM), as previously described (16).

### Study assessments

AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 from the time of obtaining informed consent until 28 days after the last treatment. DLTs were defined as clinically relevant AEs related to avadomide that began  $\leq 30$  days within the first dose (cycle 1) and met one of the following criteria: a nonhematologic grade  $\geq 3$  AE (except for alopecia, grade 3 acneiform, or maculopapular rash  $\leq 4$  days duration, or grade 3 diarrhea or vomiting  $< 72$  hours), any febrile neutropenia, grade 4 neutropenia lasting

$> 7$  days, grade 4 thrombocytopenia lasting  $> 24$  hours, grade 3/4 thrombocytopenia with clinically significant bleeding, grade 4 liver function tests, or grade 3 alanine aminotransferase with grade  $\geq 2$  bilirubin, and any AE that necessitated a dose reduction during cycle 1 and was suspected of being related to avadomide. Individual investigators performed response assessments and determined DLTs. Patients were evaluable for DLT if, during the first 30 days after cycle 1 dosing, they had received  $\geq 24$  doses of the 29 planned avadomide doses at the cohort-specified dose, had sufficient data for safety evaluation, and had not experienced a drug-related DLT or if they had received  $\geq 1$  dose of avadomide and had experienced a drug-related DLT.

Tumor assessments were performed at screening and between days 15 and 28 of even-numbered cycles through cycle 6 and then every 3 cycles thereafter. Responses were assessed using the RECIST version 1.1 for patients with solid tumors, International Working Group Revised Response Criteria for NHL, International Uniform Response Criteria for multiple myeloma, and Response Assessment for Neuro-oncology (RANO) Working Group criteria for brain cancer (14, 17–19). Pharmacokinetic parameters were calculated using actual times relative to the most recent administration of avadomide.

### *In vitro* activity of avadomide in primary human T cells

Primary T cells were isolated from human leukocytes (Blood Center of New Jersey, East Orange, NJ), treated with dimethyl sulfoxide (DMSO) or avadomide, and stimulated with an anti-CD3 antibody (Ebioscience), as previously described (1). After 24 hours, the levels of Aiolos and  $\beta$ -actin were assessed by immunoblot analysis and quantification, as previously described (1). Supernatants of treated cells were collected after 48 hours for determination of IL2 protein levels using a human IL2 ELISA kit (#BMS221-2; Thermo Fisher Scientific), according to the manufacturer's protocol.

### Statistical analyses

Safety analyses were performed on all patients who took  $\geq 1$  dose of avadomide (used for safety analysis). The efficacy-evaluable population included all enrolled patients who met the eligibility criteria, completed  $\geq 1$  cycle of avadomide, and had baseline and  $\geq 1$  postbaseline efficacy assessment. Patients who took the study drug  $\geq 70\%$  of scheduled days during cycle 1 or who had cycle 2 dosing records were considered to have completed  $\geq 1$  treatment cycle. The pharmacokinetic population comprised all patients who took  $\geq 1$  dose of avadomide and had  $\geq 1$  measured avadomide concentration. Noncompartmental pharmacokinetic analysis was performed using a validated WinNonlin Enterprise version 5.2 Model 200 (extravascular, plasma) and Model 210 (extravascular, urine). The biomarker-evaluable population included all patients who took  $\geq 1$  dose of avadomide and had  $\geq 1$  nonmissing pharmacodynamic assessment. Table and figures were generated using SAS 9.2 and Microsoft Office Excel 2003/2007.

## Results

### Patient enrollment and disposition

Patients were enrolled at 2 study sites in the United States from September 12, 2011 to January 30, 2013. As of the August 1, 2015 data cutoff, 34 patients were enrolled in the dose-escalation phase across 7 dose levels, including 3 patients at

**Table 1.** Patient demographics

Characteristic	Patients (N = 34)
Median (range) age, y	57 (31-78)
Age distribution	
≤65 y	24 (71)
>65 y	10 (29)
Sex, n (%)	
Male	17 (50)
Female	17 (50)
ECOG PS	
0	13 (38)
1	21 (62)
Tumor type	
Brain cancer	6 (18)
HCC	2 (6)
MM	2 (6)
NHL	5 (15)
Other solid tumors	19 (56)
Prior systemic anticancer therapies	
0	1 (3)
1	6 (18)
2	2 (6)
3	8 (24)
4	5 (15)
5	3 (9)
6	6 (18)
7	2 (6)
9	1 (3)

NOTE: Values shown are n (%) unless otherwise indicated.  
Abbreviation: MM, multiple myeloma.

0.5 mg, 4 at 1.0 mg, 3 patients each at 1.5 and 2.0 mg, 6 at 2.5 mg, 8 at 3.0 mg, and 7 at 3.5 mg. Key patient demographics and baseline characteristics are listed in Table 1. The median age was 57 years (range, 31–78 years), most patients (71%) were ≤65 years of age, 50% were men, and 62% had an ECOG PS of 1. Histologies included 19 patients (56%) with solid tumors [the most common were endometrial carcinoma ( $n = 3$ ), pancreatic ( $n = 2$ ), and prostate cancer ( $n = 2$ )], 6 (18%) with brain cancer (including GBM, oligodendrogliomas, and anaplastic astrocytomas), 5 (15%) with NHL, and 2 (6%) each with HCC or multiple myeloma. The median number of prior systemic anticancer therapies was 3.5 (range, 0–9). Sixteen (47%) patients had received 1 to 3 prior systemic anticancer therapies, 17 (50%) patients had received ≥4 systemic therapies, and 1 patient (3%) with meningioma was only treated with surgery and radiotherapy prior to study entry; 2 patients had received a prior SCT, and 1 patient had 2 prior SCTs. As of data cutoff, 1 patient with brain cancer was ongoing at cycle 40 in the 3.5-mg cohort. Thirty-three patients discontinued treatment. Reasons for discontinuation were disease progression in 23 patients (68%), lack of clinical benefit in 3 patients (9%), release to hospice for 2 patients (6%), AEs in 2 patients (6%), withdrawal of consent in 2 patients (6%), and physician decision in 1 patient (3%).

#### Avadomide exposure and DLT

The median duration of avadomide treatment was 58 days (range, 4–1,119 days), with a median of 2 cycles (range, 1–40 cycles). The overall median cumulative actual dose of avadomide was 124.0 mg (range, 10.5–3,240 mg); the overall median actual dose intensity was 15.4 mg/wk (range, 3.4–23.4 mg/wk), and the median relative dose intensity was 96% (range, 46%–162%). One patient in the 1.0-mg cohort had a dose escalation to 2.0 mg,

resulting in a relative dose intensity of 162%. Eight patients had dose reductions, 2 in cohorts ≤2.0 mg and 6 in cohorts 3.0 or 3.5 mg; all but 1 (due to general noncompliance) were due to treatment-emergent AEs (TEAE). The overall median number of days to first dose reduction due to a TEAE was 62.5 days (range, 24–515 days). Sixteen patients had dose interruptions due to TEAEs. The median number of days to the first dose interruption due to a TEAE was 50.5 days (range, 3–246 days), and the median duration of the interruption was 14.5 days (range, 1–144 days). Two patients (6%) had ≥1 drug-related TEAE that led to discontinuation of avadomide (1 patient each in the 0.5-mg and 3.0-mg cohorts).

DLTs were reported in 2 patients in the 3.5-mg cohort; this dose was also identified as the NTD. One patient with endometrial carcinoma had a DLT of grade 3 pyrexia and fatigue that started on day 14 and resolved on days 21 and 24, respectively; the pyrexia resulted in treatment interruption and reduction, and the fatigue led to dose interruption. One patient with prostate cancer had a DLT of grade 3 muscular weakness requiring dose interruption that started on day 24 and resolved on day 30. The 3.0-mg dose level was the MTD. None of the 7 evaluable patients at the 3.0-mg dose levels had a DLT during cycle 1.

#### Safety

Most patients (85%) had ≥1 TEAE that was suspected by the investigators of being related to avadomide. Across all cohorts, the most common TEAEs (≥15%) were fatigue (44%), neutropenia (29%), and diarrhea (15%). Avadomide-related grade ≥3 TEAEs occurred in 14 patients (41%). The most common grade ≥3 TEAEs were neutropenia (2 patients in the 1.0-mg cohort; 1 patient each in the 1.5-, 2.0-, 2.5-, and 3.5-mg cohorts; and 3 patients in the 3.0-mg cohort) and pneumonia (2 patients in the 3.0-mg cohort). Table 2 summarizes the TEAEs in the treated

**Table 2.** TEAEs suspected to be avadomide-related

AEs, n (%)	Any grade (n = 34)	Grade 3/4 AE (n = 34)
≥1 TEAE	29 (85)	14 (41)
Fatigue	15 (44)	1 (3)
Neutropenia	10 (29)	9 (27)
Diarrhea	5 (15)	-
Alopecia	4 (12)	-
Pruritus	4 (12)	-
Maculopapular rash	4 (12)	-
Abdominal distension	3 (9)	-
Nausea	3 (9)	-
Vomiting	3 (9)	-
Asthenia	3 (9)	-
Decreased appetite	3 (9)	-
Hot flush	3 (9)	-
Anemia	2 (6)	-
Dry mouth	2 (6)	-
Pneumonia	2 (6)	2 (6)
Muscle spasms	2 (6)	-
Dysgeusia	2 (6)	-
Headache	2 (6)	-
Peripheral neuropathy	2 (6)	-
Thrombocytopenia	1 (3)	1 (3)
Cataract	1 (3)	1 (3)
Pyrexia	1 (3)	1 (3)
Pneumocystis jirovecii pneumonia	1 (3)	1 (3)
Muscular weakness	1 (3)	1 (3)
Angioedema	1 (3)	1 (3)

NOTE: Values shown are n (%). Avadomide-related TEAEs of any grade occurring in >1 patient and all grade 3/4 TEAEs are included.

**Table 3.** Best overall response to avadomide by investigator assessment per tumor type and cohort

Best response, n (%)	Avadomide (0.5 mg)	Avadomide (1.0 mg)	Avadomide (1.5 mg)	Avadomide (2.0 mg)	Avadomide (2.5 mg)	Avadomide (3.0 mg)	Avadomide (3.5 mg)	Overall
All patients	(n = 3)	(n = 4)	(n = 3)	(n = 3)	(n = 6)	(n = 8)	(n = 7)	(n = 34)
Other solid tumor	(n = 3)	(n = 2)	(n = 2)	(n = 2)	(n = 2)	(n = 4)	(n = 4)	(n = 19)
SD	2 (67)	0	0	1 (50)	1 (50)	0	1 (25)	5 (26)
PD	1 (33)	2 (100)	2 (100)	1 (50)	1 (50)	3 (75)	1 (25)	11 (58)
Not evaluable	0	0	0	0	0	1 (25)	2 (50)	3 (16)
HCC	-	-	(n = 1)	(n = 1)	-	-	-	(n = 2)
SD	-	-	1 (100)	1 (100)	-	-	-	2 (100)
Brain cancer	-	(n = 1)	-	-	(n = 2)	(n = 1)	(n = 2)	(n = 6)
Nonprogression	-	1 (100)	-	-	1 (50)	1 (100)	2 (100)	5 (83)
Progression	-	0	-	-	1 (50)	0	0	1 (17)
NHL	-	-	-	-	(n = 1)	(n = 3)	(n = 1)	(n = 5)
CR	-	-	-	-	0	1 (33)	0	1 (20)
PR	-	-	-	-	0	1 (33)	1 (100)	2 (40)
PD	-	-	-	-	0	1 (33)	0	1 (20)
Not evaluable	-	-	-	-	1 (100)	0	0	1 (20)
MM	-	(n = 1)	-	-	(n = 1)	-	-	(n = 2)
SD	-	1 (100)	-	-	0	-	-	1 (50)
PD	-	0	-	-	1 (100)	-	-	1 (50)

Abbreviations: MM, multiple myeloma; PD, progressive disease; SD, stable disease.

population. One death occurred within 28 days of the last dose of avadomide; 1 patient with pancreatic carcinoma in the 3.5-mg cohort died due to disease progression.

**Clinical activity**

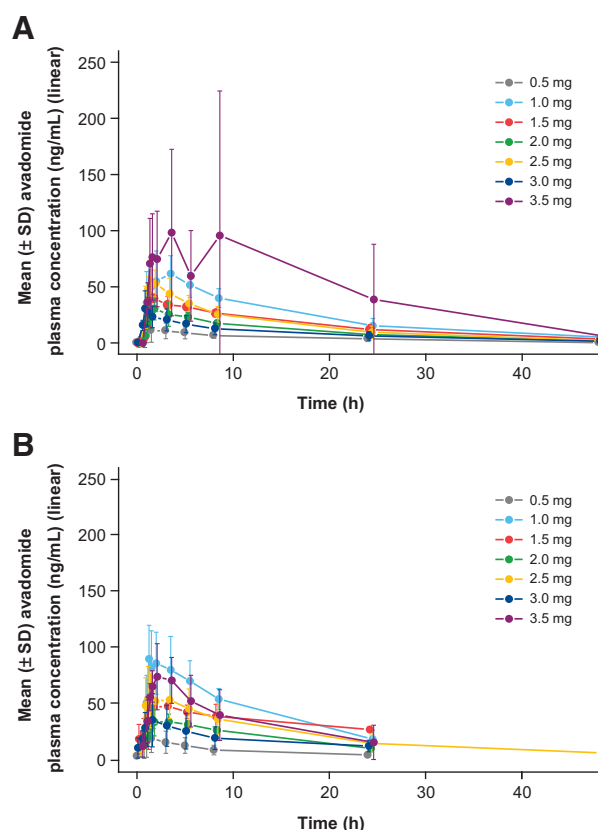
Objective responses [ $\geq$ partial response (PR)] were observed in 3 of 5 (60%) patients with NHL. Of these, 1 patient with follicular lymphoma in the 3.0-mg cohort had a complete response (CR), and 2 patients (1 with mantle cell lymphoma and 1 with follicular lymphoma) had a PR. No objective measures of clinical response were observed in patients with solid tumors or multiple myeloma. However, among patients with brain cancer, the overall PFS at 6 months was 83% (95% confidence interval, 27%–98%; Table 3), and the range of PFS duration was 58 to 1,079 days. Brain cancer patients with PFS greater than 6 months included 2 patients with oligodendroglioma and 1 patient each with meningioma and choroid plexus tumor with drop metastasis. In addition, 2 of 2 (100%) patients with HCC achieved stable disease that lasted 114 and 309 days, and 1 of 2 (50%) patients with multiple myeloma achieved stable disease that lasted 932 days.

**Pharmacokinetics, pharmacodynamics, and biomarkers**

At all dose levels, the avadomide plasma concentration versus time profiles were characterized by a rapid absorption phase and similar median time to maximum concentration (Fig. 1). After attainment of maximum observed concentration in plasma, avadomide appeared to decrease in a monophasic manner at all dose levels. By visual inspection of mean plasma concentrations versus time profiles, avadomide plasma exposures increased in a dose-dependent manner across the 0.5- to 3.5-mg dose range. All 7 dose levels showed mild-to-moderate accumulation of avadomide plasma exposure after multiple doses. Supplementary Table S1 summarizes avadomide plasma pharmacokinetic parameters by day and dose level. In general, as assessed from the geometric coefficient of variation percentage, interpatient variability was noted for both avadomide area under the concentration–time curve and maximum observed concentration in plasma. The mean total recovery of avadomide in urine within 24 hours ranged from 18% to 35% across the 0.5- to 3.5-mg dose range. The mean avadomide renal clearance ranged from 0.53 to

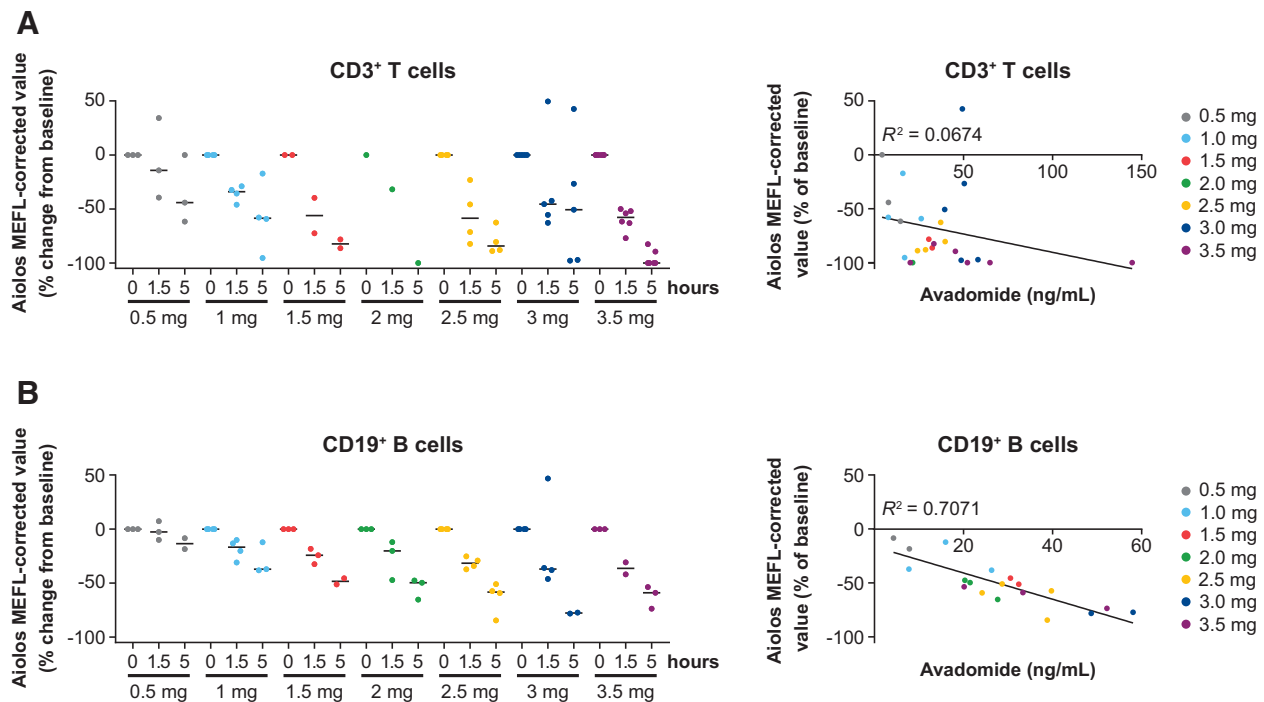
1.31 L/h across the 0.5- to 3.5-mg dose range. The  $t_{1/2}$  ranged from 7.68 to 27.91 hours.

Avadomide exposure-response analyses indicated an apparent exposure-related decrease in Aiolos protein levels in B cells ( $R^2 = 0.7071$ ). T cells appeared to be more sensitive than B cells to



**Figure 1.** Mean ( $\pm$ SD) plasma concentrations of avadomide time profiles for cycle 1, day –1 (A) and for cycle 1, day 15 (B). Abbreviation: SD, standard deviation.

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**Figure 2.**

Percentage change from baseline in Aiolos protein levels at 1.5 and 5 hours after a single dose of avadomide and exposure–response relationships at 5 hours in CD3<sup>+</sup> T cells (A) and CD19<sup>+</sup> B cells (B). Abbreviations: CD, cluster of differentiation; MEFL, molecules of equivalent fluorescence label.

avadomide-induced degradation of Aiolos (Fig. 2). A dose-dependent relationship between Aiolos degradation in B and T cells in peripheral blood occurred within 5 hours of the first dose of avadomide administration, starting at a dose of 0.5 mg (Fig. 2; Supplementary Fig. S1). Fifteen days after the start of avadomide administration (C1D15), peripheral blood B-cell counts were reduced compared with baseline counts (Fig. 3A); this decline demonstrated an exposure-dependent relationship ( $R^2 = 0.2115$ ). In contrast, no apparent differences existed in the median numbers of either T or NK cells at C1D15 compared with baseline, and no significant exposure-dependent relationships were observed (Fig. 3B and C). Cytokine production from *ex vivo*-stimulated peripheral blood collected predose and 1.5 hours after avadomide administration on C1D1 showed a trend toward increasing IL2 levels with increasing doses, although no significant exposure-dependent relationship was noted (Fig. 3D). In a preclinical study of avadomide activity in T cells from healthy donors, there was a strong correlation between Aiolos degradation in T cells and IL2 secretion, with an IL2 half maximal effective concentration ( $EC_{50}$ ) of 36 nmol/L avadomide (Supplementary Fig. S2). In contrast, we did not observe a correlation between the levels of Aiolos degradation and IL2 production in whole blood from patients in the study cohorts (data not shown). However, this result may be due in part to patient–patient variability, for example, in the activation/exhaustion status of the T cells and/or the ability to induce IL2 secretion.

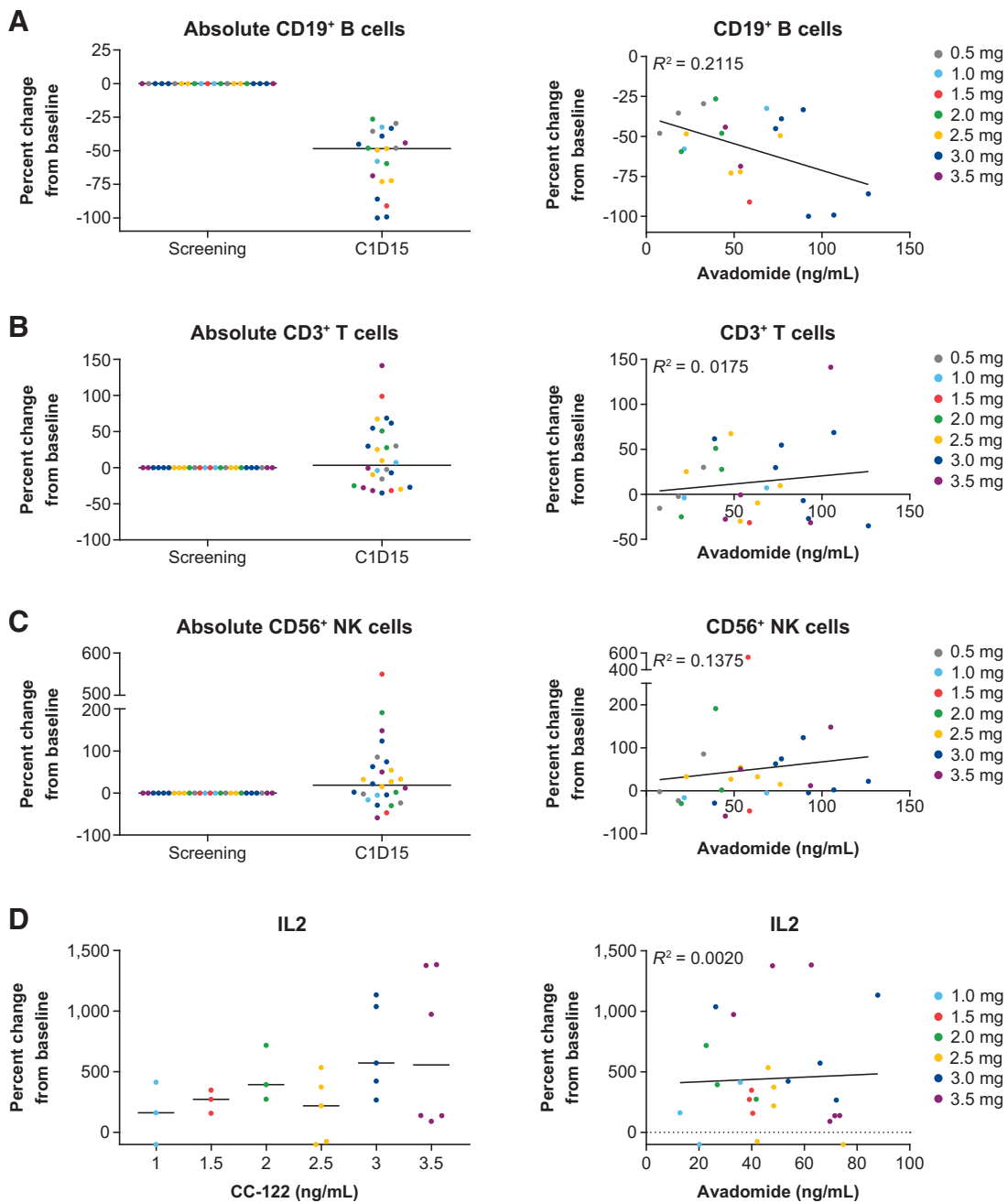
## Discussion

This phase I study is a first-in-human dose-escalation study of oral avadomide monotherapy in patients with advanced solid

tumors and hematologic malignancies. Avadomide was well tolerated with no unexpected safety concerns; the most common TEAEs were fatigue and neutropenia. The subsequent implementation of an intermittent dosing schedule in part B of the study mitigated the frequency and severity of neutropenia while maintaining the clinical activity (20).

One of the primary objectives of this study was to determine the MTD of avadomide in patients with solid tumors, NHL, and multiple myeloma. Of the 7 doses of avadomide evaluated in this study, 3.0 mg administered on a continuous, daily-dosing schedule was determined to be the MTD, and the NTD was 3.5 mg. Avadomide is a pharmacologically active drug starting at the 0.5-mg dose, with pharmacodynamic effects such as degradation of Aiolos in peripheral B and T cells and increased *ex vivo*-stimulated release of IL2, indicative of T-cell activation. Treatment with avadomide showed early signs of antitumor activity in NHL, where 3 of 5 (60%) patients had an objective response, including 1 CR and 2 PRs of greater than 234 days in duration.

Whereas cereblon-binding agents such as lenalidomide have been studied and in the clinic for years, a lack of knowledge about the molecular target precluded the possibility of monitoring for pharmacodynamic activity based on a precise mechanism of action. The discovery that Aiolos is directly targeted for degradation by cereblon bound to avadomide has allowed, for the first time in this class of drugs, the utilization of a mechanism-based pharmacodynamic measurement of pharmacological activity. A flow cytometric assay was developed for real-time detection of Aiolos protein levels in B and T cells of peripheral blood from patients administered avadomide at various doses. The degradation of Aiolos in peripheral T cells indicates that the 3-mg dose of avadomide is indeed pharmacologically active. The effect appears



**Figure 3.** Percentage change from baseline in absolute cell counts on cycle 1, day –1 and cycle 1, day 15 at 1.5 hours by cohort, and avadomide exposure–response relationships at cycle 1, day 15; for CD19<sup>+</sup> B cells (A), CD3<sup>+</sup> T cells (B), and CD56<sup>+</sup> NK cells (C) and *ex vivo* release of IL2 from peripheral blood mononuclear cells (D).

to be maximized at 3.5 mg, with up to 100% Aiolos degradation observed. An understanding of how T-cell activation is affected at various doses in patients can be valuable information for future use of avadomide in combination with other agents that modulate T-cell activity. The monitoring of specific immune cell populations, such as total T and NK cells, indicates that there is no significant impact on cell numbers, whereas the decrease in normal B cells is an on-target effect. Taken together, these data, along with analysis of T-cell subsets in future studies, may aid in

deciding which combination partner and avadomide dose are optimal for immune therapy combinations. In the present study, we did not observe any correlation between the extent of Aiolos degradation or IL2 production and clinical response, in part due to the diverse tumor types and differences in how avadomide works in hematologic versus solid tumor disease settings. In patients with B-cell malignancies, avadomide has a dual mechanism of action comprising both cell-autonomous activity and immunomodulation; whereas in solid tumor patients, the

mechanism is believed to be primarily through activation of immune cells, such as T and NK cells.

The preliminary signal of nonprogression in patients with brain cancers is intriguing and raises the question of which biological effects of avadomide may be driving the activity (e.g., antiangiogenesis or immune modulation). Avadomide has limited direct antiproliferative or cytotoxic activity *in vitro* in glioma models, and the cereblon substrates in this context are unknown (unpublished results). Based on their antiangiogenic and immune modulatory pharmacologic properties, other cereblon-binding agents, thalidomide and lenalidomide, have been studied in glioma patients (21–27). Modest activity was observed, with small numbers of patients having objective responses and/or prolonged periods of stable disease. Whether the antiangiogenic activity of thalidomide, lenalidomide, or avadomide contributes to their apparent activity in brain cancers is difficult to assess, because the molecular mechanism underlying this activity is not understood, and, thus, validated surrogate biomarkers are not available. Moreover, imaging studies are challenging to interpret, and on-treatment resections are difficult to obtain. None of the prior trials with thalidomide or lenalidomide in patients with brain tumors contained extensive immune monitoring to explore potential correlations between immune modulation and efficacy. In the current study, the immune effects of avadomide in glioma patients, as measured in peripheral blood, suggested that T-cell activation was similar to other indications. However, the relevance of immunomodulatory effects in peripheral blood to the CNS tumor microenvironment is not known. Future studies can assess the immunomodulatory effects of avadomide in glioma tumors and provide rationale for combination therapies, including the use of immuno-oncology agents.

In conclusion, results from part A of this multicenter phase I study demonstrated acceptable safety and tolerability profiles and favorable pharmacokinetics with avadomide monotherapy in patients with NHL, multiple myeloma, and solid tumors, including brain cancers. Preliminary signs of antitumor activity in NHL in the current study, coupled with preclinical activity of avadomide in DLBCL models that is cell of origin independent and differentiated from lenalidomide, support further evaluation in

NHL in dose expansion. The preliminary immune activation data in this study, as well as preclinical data showing antiangiogenic activity, provide the rationale for further evaluation of avadomide in patients with solid tumors, such as HCC and tumors of the CNS, including GBM and primary CNS lymphoma.

### Disclosure of Potential Conflicts of Interest

M. Pourdehnad, A.K. Gandhi, P.R. Hagner, R. Chopra, K. Hege, and J. DiMartino hold ownership interest (including patents) in Celgene Corporation. No potential conflicts of interest were disclosed by the other authors.

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