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Clinical Cancer Research

Phase I Study of the Investigational NEDD8-Activating Enzyme Inhibitor Pevonedistat (TAK-924/MLN4924) in Patients with Advanced Solid Tumors

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Abstract

Purpose: To determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of the investigational NEDD8-activating enzyme (NAE) inhibitor pevonedistat (TAK-924/MLN4924) and to investigate pevonedistat pharmacokinetics and pharmacodynamics in patients with advanced nonhematologic malignancies.

Experimental Design: Pevonedistat was administered via 60-minute intravenous infusion on days 1 to 5 (schedule A, $n = 12$), or days 1, 3, and 5 (schedules B, $n = 17$, and C, $n = 19$) of 21-day cycles. Schedule B included oral dexamethasone 8 mg before each pevonedistat dose. Dose escalation proceeded using a Bayesian continual reassessment method. Tumor response was assessed by RECIST 1.0.

Results: Schedule A MTD was 50 mg/m^2; based on the severity of observed hepatotoxicity, this schedule was discontinued. Schedules B and C MTDs were 50 and 67 mg/m^2, respectively. DLTs on both these schedules included hyperbilirubinemia and elevated aspartate aminotransferase. There were no grade ≥3 treatment-related serious adverse events reported on schedules B or C. Twenty-three (74%) evaluable patients on schedules B and C had stable disease. Intermittent dexamethasone use did not significantly influence pevonedistat pharmacokinetics. NAE inhibition by pevonedistat was demonstrated in multiple tumor types via IHC detection of pevonedistat-NEDD8 adduct and accumulation of Cullin-RING ligase substrates CDT1 and NRF2 in tumor biopsies.

Conclusion: Pevonedistat was generally well tolerated on a day 1, 3, 5 schedule every 3 weeks with an MTD between 50 mg/m^2 and 67 mg/m^2. DLTs were predominantly hepatic enzyme elevations. Pharmacodynamic studies demonstrated that pevonedistat inhibited NAE in tumors. Clinical trials are ongoing. *Clin Cancer Res; 1–11. ©2015 AACR.*

Introduction

The ubiquitin-proteasome system (UPS) is a key pathway for protein catabolism in mammalian cells and forms an integral part of a large number of cellular processes (1, 2). As the UPS is important in regulating mediators of cell growth, division, and apoptosis (3), UPS defects can be responsible for a number of diseases, including cancer (1, 2). Clinical activity with agents targeting the UPS has been demonstrated with proteasome inhibitors, such as bortezomib in malignancies such as multiple myeloma and mantle cell lymphoma (4). The UPS is an attractive target for anticancer agents (5).

Proteins are targeted for degradation within the UPS through the addition of ubiquitin chains by E3 ubiquitin ligases (2). The Cullin-RING E3 ubiquitin ligases (CRLs) are the largest family of E3 ligases (6, 7). Proteasomal degradation of CRL substrates requires conjugation of the ubiquitin-like protein NEDD8 (neural precursor cell-expressed, developmentally downregulated 8) to the cullin protein. NEDD8 is activated for conjugation by NEDD8-activating enzyme (NAE; refs. 8–11), making NAE activation of NEDD8 an essential step for CRL activity (8, 10, 11).

CRL substrates include proteins with roles in cell-cycle progression ($p27^{Kip1}$), DNA replication (CDT1), oxidative stress response (NRF2), and signal transduction (IκBα) (9–13). CRL substrates and CRL activity have been shown to be important in the development of multiple types of human cancer (14), providing rationale for developing an NAE inhibitor as an anticancer agent.

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Translational Relevance

The ubiquitin–proteasome system (UPS) plays a key role in intracellular protein degradation. Approximately 20% of UPS-degraded proteins are targeted for degradation by the Cullin-RING E3 ligases (CRLs). This includes several proteins important in the development of multiple types of human cancer, making the UPS an attractive target for anticancer agents. CRLs require activation through NEDD8 conjugation, which is regulated by NEDD8-activating enzyme (NAE). NAE activation of NEDD8 is therefore essential for CRL activity, providing rationale for an anticancer agent targeting NAE. This study investigated pevonedistat (TAK-924/MLN4924), an investigational first-in-class NAE inhibitor, in patients with advanced nonhematologic malignancies. Pharmacodynamic analyses showed effects consistent with NAE target inhibition in the clinical setting. Single-agent pevonedistat was generally well tolerated with an MTD between 50 mg/m^2 and 67 mg/m^2 and induced some disease stabilization. These findings indicate NAE inhibition may be an effective therapeutic strategy in patients with solid tumors.

Pevonedistat (TAK-924/MLN4924) is a first-in-class small-molecule NAE inhibitor (6). In the presence of enzymatically active NAE, pevonedistat covalently binds with NEDD8 forming a pevonedistat-NEDD8 adduct, which remains tightly bound to NAE. In this form, NAE is unable to process NEDD8 for CRL conjugation, preventing downstream cullin neddylation and CRL activity (15), resulting in CRL substrate accumulation (6). In various model systems, pevonedistat induces apoptotic cell death; the precise mechanism remains unclear (6). Preclinical studies have shown that pevonedistat is cytotoxic to a range of cell lines and primary human cancer cells derived from solid tumors and hematologic malignancies (6, 16–24). In multiple cell lines evaluated for pevonedistat's mechanism of action, accumulation of the CRL substrate CDT1 results in dysregulation of DNA synthesis, followed by a DNA-damage response and induction of cell death (6, 25, 26). Other CRL substrates implicated in pevonedistat-induced cell death include Wee1 (19, 24) and others in the p53, BRCA1/BRCA2, transcription-coupled DNA repair, and base excision repair pathways (27). Antitumor activity has been demonstrated in mouse xenograft models of solid tumors, including those derived from colon (6), lung (6), liver (18), pancreatic (24), and ovarian (22) cancers, melanoma (28, 29), and in xenograft models of hematologic malignancies (21, 23). These data provide the rationale for testing pevonedistat in various cancers.

This phase I study of three pevonedistat dosing schedules was undertaken in patients with advanced solid tumors to investigate its maximum tolerated dose (MTD), dose-limiting toxicity (DLT), safety, pharmacokinetics, pharmacodynamics, and antitumor activity.

Patients and Methods

Patients

Patients aged ≥18 years with nonhematologic malignancies for which standard, curative, or life-prolonging treatment did not exist or was no longer effective were eligible. Other eligibility criteria included Eastern Cooperative Oncology Group performance status of 0–2; life expectancy >6 weeks; radiographically or clinically evaluable tumor; adequate renal (calculated creatinine clearance >50 mL/minute), hepatic [total bilirubin ≤ the upper limit of normal (ULN), transaminases and alkaline phosphatase ≤2.5 × ULN], cardiac (B-type natriuretic peptide ≤1.5 × ULN; left ventricular ejection fraction ≥45%, pulmonary artery systolic pressure ≤1.5 × ULN), and hematologic (absolute neutrophil count ≥1,500/mm^3, platelets ≥100,000/mm^3) function; no systemic antineoplastic therapy or radiotherapy within 21 days before first pevonedistat dose, major surgery, serious infection, antibiotic treatment, or treatment with known cytochrome P450 (CYP) 3A inhibitors or inducers within 14 days of the first pevonedistat dose; prothrombin time or activated partial thromboplastin time ≤1.5 × ULN, and no history of coagulopathy or bleeding disorder.

Ethics review boards at all participating institutions approved the study, which was conducted in accordance with Good Clinical Practice guidelines. All patients provided written informed consent.

Study design

This open-label, phase I, dose-escalation study (NCT00677170) was conducted at seven sites in the United States and enrolled patients from April 2008 to March 2009 (schedule A), July 2009 to April 2010 (schedule B), and September 2009 to February 2011 (schedule C). Primary objectives were to determine the DLTs and MTD of pevonedistat and to describe its pharmacokinetics and pharmacodynamic effects in blood, skin, and tumor tissue. Secondary objectives included evaluation of disease response.

Pevonedistat was administered via 60-minute intravenous infusion on days 1 to 5 (schedule A), or days 1, 3, and 5 (schedules B and C) of 21-day cycles. These schedules were selected based on preclinical studies in tumor xenograft-bearing mice, in which daily dosing and various intermittent dosing schedules, including 5 consecutive days of treatment, were shown to result in antitumor activity (6). Schedule A preceded schedules B and C which occurred simultaneously. An acute elevation of liver enzymes and an associated rise in C-reactive protein were observed in some schedule A patients, indicating an acute phase reaction in response to pevonedistat. Other symptoms included postinfusion fever and musculoskeletal pain/myalgia. On the basis of these observations, schedule B and C patients received intermittent dosing, and in addition, schedule B patients received oral dexamethasone 8 mg the evening before the first pevonedistat dose, and before pevonedistat on days 1, 3, and 5, to determine whether addition of glucocorticoids would diminish the acute phase response and enable further dose escalation. Dose escalation (starting at 25 mg/m^2 for schedule A, which was the first-in-human dose based on results of nonclinical toxicology studies in dogs and rats, and at the schedule A MTD of 50 mg/m^2 for schedules B and C) and MTD determinations were based on an adaptive approach using a Bayesian continual reassessment method (CRM) using two-patient cohorts (30). Twelve patients were to be treated at the MTD (6 during dose escalation, and 6 in the MTD expansion to further evaluate the safety of that dose level).

DLT was defined as grade 4 neutropenia or thrombocytopenia for >7 days, grade 3 neutropenia with fever and/or infection, grade 3 thrombocytopenia with bleeding, or platelets <10,000/mm^3 at any time; grade ≥3 nonhematologic toxicity despite maximal

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Table 1. Demographics and baseline disease characteristics by treatment schedule

Characteristic	Schedule A *n* = 12	Schedule B *n* = 17	Schedule C *n* = 19	Total *n* = 48
Median age, y (range)	59 (35–71)	60 (35–84)	57 (34–69)	59 (34–84)
Male, *n* (%)	6 (50)	11 (65)	9 (47)	26 (54)
Ethnicity, *n* (%)				
Hispanic or Latino	0	1 (6)	5 (26)	6 (13)
Not Hispanic or Latino	11 (92)	15 (88)	14 (74)	40 (83)
Not reported	1 (8)	1 (6)	0	2 (4)
Race, *n* (%)				
White	11 (92)	14 (82)	15 (79)	40 (83)
Black or African American	0	2 (12)	3 (16)	5 (10)
Asian	0	0	1 (5)	1 (2)
Other	1 (8)	1 (6)	0	2 (4)
ECOG performance status, *n* (%)				
0	1 (8)	4 (24)	4 (21)	9 (19)
1	11 (92)	13 (76)	12 (63)	36 (75)
2	0	0	3 (16)	3 (6)
Primary diagnosis, *n* (%)				
Colorectal cancer	2 (17)	2 (12)	7 (37)	11 (23)
Melanoma	3 (25)	6 (35)	0	9 (19)
Breast cancer	3 (25)	0	5 (26)	8 (17)
Gastric cancer	0	2 (12)	3 (16)	5 (10)
Head and neck cancer	1 (8)	2 (12)	0	3 (6)
Small-cell lung cancer	1 (8)	1 (6)	1 (5)	3 (6)
Adrenal carcinoma	1 (8)	0	1 (5)	2 (4)
Ovarian cancer	0	1 (6)	1 (5)	2 (4)
Pancreatic cancer	0	2 (12)	0	2 (4)
Esophageal cancer	0	1 (6)	0	1 (2)
Non–small cell lung cancer	0	0	1 (5)	1 (2)
Prostate cancer	1 (8)	0	0	1 (2)
Prior therapy				
Prior chemotherapy	12 (100)	17 (100)	19 (100)	48 (100)
Prior radiation	6 (50)	8 (47)	10 (53)	24 (50)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

supportive therapy, except grade 3 arthralgia/myalgia, brief fatigue, or fever without neutropenia; grade ≥2 pevonedistat-related nonhematologic toxicity requiring dose reduction/discontinuation; or treatment delay of >1 week due to lack of recovery from pevonedistat-related toxicity. Dose reductions were required for ≥grade 3 myelosuppression and for grade 3 pevonedistat-related nonhematologic toxicities. Pevonedistat was discontinued for any grade 4 nonhematologic toxicity. Because of schedule A hepatotoxicity events, dosing only continued on schedules B and C if serum transaminase elevations were grade ≤1 and bilirubin elevation was ≤ULN on the treatment day.

Safety and efficacy assessments

Safety was assessed through 30 days after the last dose. Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for AEs, version 3.0 (31). Serious AEs (SAEs) were recorded from patient consent through 30 days after the last pevonedistat dose. Tumor response was assessed by CT/MRI scans using RECIST 1.0 (32) on cycle 1 day 21 and every two cycles thereafter.

Pharmacokinetic and pharmacodynamic analyses

Serial blood samples for pevonedistat pharmacokinetic analysis were collected in cycle 1 at prespecified time points pre- and postinfusion on days 1 and 5. Plasma concentrations were measured using a Good Laboratory Practice-validated liquid chromatography/mass spectrometry assay (dynamic range for the low- and high-range assay was 1–500 ng/mL and 75–7,500 ng/mL, respectively). Noncompartmental methods (WinNonlin ver. 6.2, Pharsight Corporation) were used to estimate pharmacokinetic parameters, as permitted by data. *In vitro* metabolism studies showed pevonedistat is metabolized via hydroxylation and oxidation, predominantly by CYP3A4. Therefore, the potential exists for drug–drug interactions between pevonedistat and known *in vivo* CYP3A inhibitors or inducers. Possible changes in plasma exposures to pevonedistat in the presence of dexamethasone, a weak inducer of CYP3A activity, were therefore assessed in this study.

Tumor biopsies for IHC assay of pevonedistat-NEDD8 adduct, CDT1, and NRF2 were obtained within 14 days before the first dose and 3 to 6 hours after the second dose in cycle 1 (detailed in the Supplementary Appendix). CRL substrate levels (CDT1 and NRF2) were quantified as percent area positive of the tumor region.

Statistical analysis

The safety population was defined as all enrolled patients who had received at least one dose of study medication. The DLT-evaluable population was defined as all patients who either experienced a DLT during cycle 1, or received all scheduled doses in cycle 1 without DLT. The response-evaluable population was defined as all patients who received at least one dose of study drug, had measurable disease at baseline, and had one postbaseline disease assessment. The pharmacokinetic-evaluable population was defined as all enrolled patients who had sufficient dosing in cycle 1 and pevonedistat concentration-time data to reliably estimate pharmacokinetic parameters by noncompartmental analysis methods and who had not received any excluded concomitant medications per the protocol.

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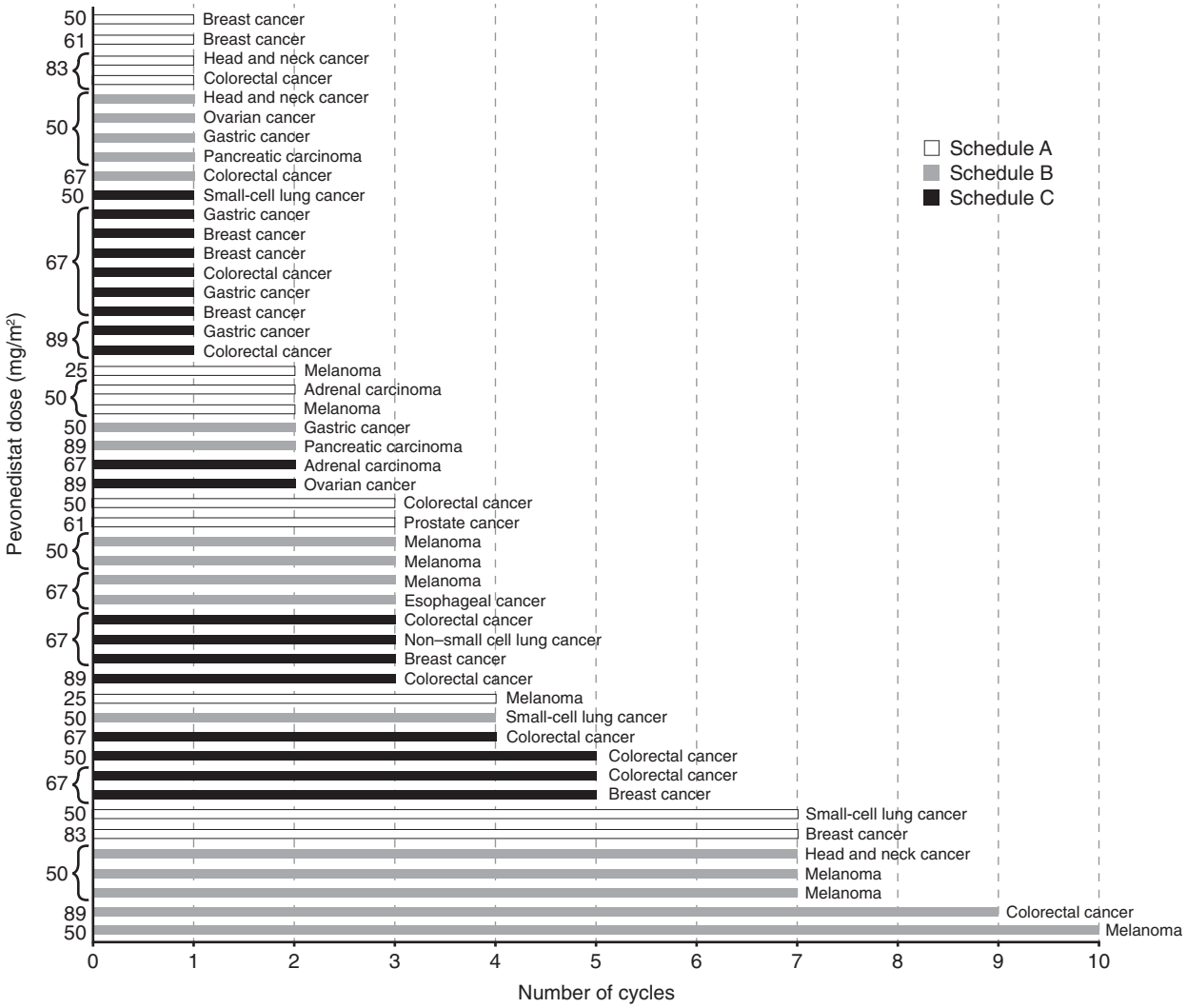

Figure 1.
Duration of pevonedistat treatment in individual patients on schedules A, B, and C.

The MTD was estimated, based on observed toxicities in all evaluable patients, using a modified form of the Bayesian CRM (30), as detailed in the Supplementary Appendix. This design was chosen over the traditional 3+3 method given improved accuracy of MTD estimation using the CRM, as previously reported (33, 34). MTD was defined as the dose closest to that predicted to have a 25% probability of DLT. Cohorts of no more than 2 patients were dosed at a given time. Dose levels were predefined. The decision to escalate, de-escalate, or expand a given dose was based on the model-predicted MTD. The dose level at which the total number of enrolled patients reached six was considered the observed MTD. All results were summarized descriptively. No formal hypothesis testing was conducted.

Results

Schedule A

Twelve patients (Table 1) were treated on schedule A at 25 ($n = 2$), 50 ($n = 5$), 61 ($n = 2$), and 83 ($n = 3$) mg/m^2. Ten patients were DLT- and response-evaluable. All 12 patients were evaluable for toxicity. Ten patients participated in the dose-escalation phase. Three patients experienced cycle 1 DLTs of grade 3 transaminase elevations (50, 61, and 83 mg/m^2 dose levels). Other hepatotoxicities (non-DLT) included grade ≥ 2 elevations in alkaline phosphatase ($n = 2$) and bilirubin ($n = 4$), which were generally, but not always, rapidly reversible upon cessation of pevonedistat. Two patients died on-study during cycle 1 due to treatment-related multiorgan failure (including liver failure) and disease progression (61 and 83 mg/m^2 dose levels, respectively). Because of the severity of the events at 61 and 83 mg/m^2, no additional patients were recruited to these cohorts, and 50 mg/m^2 was declared the MTD. Given the multiorgan failure and grade 3 DLTs, the continuous dosing schedule was deemed intolerable and discontinued before completion of MTD expansion. Additional schedule A results are presented in the Supplementary Appendix.

Schedules B and C

Seventeen and 19 patients were treated on schedules B and C, respectively (Table 1). Among these 36 patients, the median age was

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Table 2. AEs experienced by ≥10% of patients on any schedule, and grade ≥3 AEs reported in >1 patient overall

AE, *n* (%)	Schedule A[a] *n* = 12	Schedule B[b] *n* = 17	Schedule C[c] *n* = 19	Total *n* = 48
Any AE	12 (100)	17 (100)	19 (100)	48 (100)
Fatigue	6 (50)	10 (59)	9 (47)	25 (52)
Nausea	6 (50)	3 (18)	11 (58)	20 (42)
Anemia	5 (42)	2 (12)	9 (47)	16 (33)
Elevated alanine aminotransferase	4 (33)	4 (24)	3 (16)	11 (23)
Elevated aspartate aminotransferase	3 (25)	4 (24)	4 (21)	11 (23)
Hypoalbuminemia	4 (33)	0	7 (37)	11 (23)
Hypokalemia	3 (25)	4 (24)	4 (21)	11 (23)
Hypomagnesemia	4 (33)	1 (6)	6 (32)	11 (23)
Vomiting	2 (17)	2 (12)	7 (37)	11 (23)
Decreased appetite	1 (8)	4 (24)	5 (26)	10 (21)
Diarrhea	4 (33)	3 (18)	2 (11)	9 (19)
Cough	1 (8)	4 (24)	3 (16)	8 (17)
Dizziness	0	4 (24)	4 (21)	8 (17)
Headache	2 (17)	2 (12)	4 (21)	8 (17)
Hyperbilirubinemia	1 (8)	4 (24)	3 (16)	8 (17)
Increased blood alkaline phosphatase	2 (17)	2 (12)	4 (21)	8 (17)
Constipation	2 (17)	4 (24)	1 (5)	7 (15)
Dyspnea	1 (8)	3 (18)	3 (16)	7 (15)
Myalgia	1 (8)	1 (6)	5 (26)	7 (15)
Pyrexia	3 (25)	2 (12)	2 (11)	7 (15)
Peripheral edema	1 (8)	3 (18)	2 (11)	6 (13)
Hypocalcemia	0	0	6 (32)	6 (13)
Hyponatremia	2 (17)	0	4 (21)	6 (13)
Arthralgia	1 (8)	1 (6)	3 (16)	5 (10)
Back pain	1 (8)	1 (6)	3 (16)	5 (10)
Increased blood creatinine	0	2 (12)	3 (16)	5 (10)
Insomnia	1 (8)	2 (12)	1 (5)	4 (8)
Any grade ≥3 AE	7 (58)	9 (53)	10 (53)	26 (54)
Anemia	1 (8)	1 (6)	3 (16)	5 (10)
Elevated alanine aminotransferase	2 (17)	1 (6)	0	3 (6)
Congestive heart failure	0	1 (6)	1 (5)	2 (4)
Dyspnea	0	0	2 (11)	2 (4)
Elevated aspartate aminotransferase	2 (17)	0	0	2 (4)
Fatigue	0	2 (12)	0	2 (4)
Hyperbilirubinemia	1 (8)	0	1 (5)	2 (4)
Hypokalemia	1 (8)	0	1 (5)	2 (4)
Hyponatremia	0	0	2 (11)	2 (4)
Hypophosphatemia	1 (8)	1 (6)	0	2 (4)
Nausea	1 (8)	0	1 (5)	2 (4)
Vomiting	1 (8)	0	1 (5)	2 (4)

[a]In addition, the following grade ≥3 AEs were reported in one patient only on schedule A: back pain, hyperglycemia, multiorgan failure, neutropenia, sepsis, and increased transaminases.

[b]In addition, the following grade ≥3 AEs were reported in one patient only on schedule B: increased blood alkaline phosphatase, increased blood glucose, elevated γ-glutamyltransferase, gastric ulcer, localized edema, pulmonary embolism, and subclavian vein thrombosis.

[c]In addition, the following grade ≥3 AEs were reported in one patient only on schedule C: abdominal pain, ascites, gastrointestinal hemorrhage, hyperkalemia, hypoalbuminemia, hypovolemia, metastases to central nervous system, nausea, obstructive uropathy, pleural effusion, pneumonia, respiratory failure, small intestinal obstruction, and systemic inflammatory response syndrome.

58.5 years, and the most common primary diagnosis was colorectal cancer (25%). On schedule B, 12, 3, and 2 patients; and on schedule C, 2, 13, and 4 patients, were treated at 50, 67, and 89 mg/m^2, respectively. Fourteen and 16 patients on schedules B and C, respectively, were DLT-evaluable. All 36 patients were evaluable for toxicity. Fifteen and 16 patients on schedules B and C, respectively, were response-evaluable. Three schedule C patients died due to dyspnea, metastases, and disease progression, all considered unrelated to pevonedistat. No patients died on schedule B.

Dose escalation and MTD determination

Eleven and 12 patients on schedules B and C, respectively, participated in the dose-escalation phase. All patients were evaluable for MTD determination except one schedule C patient who was excluded due to not receiving all pevonedistat doses during cycle 1 due to grade 2 renal failure and grade 3 ascites, both considered unrelated to pevonedistat, and thus not a DLT. During dose escalation, 3 schedule B patients experienced a DLT: 1 patient experienced treatment-related grade 2 elevated AST and grade 3 elevated ALT (50 mg/m^2 dose level), and 2 patients experienced treatment-related grade 2 hyperbilirubinemia (67 and 89 mg/m^2 dose levels). Because of the hepatotoxicity events, no additional patients were recruited to the higher dose cohorts, and 50 mg/m^2 was declared the schedule B MTD. Two patients in the dose-escalation cohort on schedule C experienced DLTs of pevonedistat-related grade 2 hyperbilirubinemia and grade 2 AST elevation, respectively (both at 89 mg/m^2). Because of the hepatotoxicity events, there was no further dose escalation, and 67 mg/m^2 was declared the schedule C MTD. Although not strictly defined as DLTs per protocol, grade 2 hepatotoxicity

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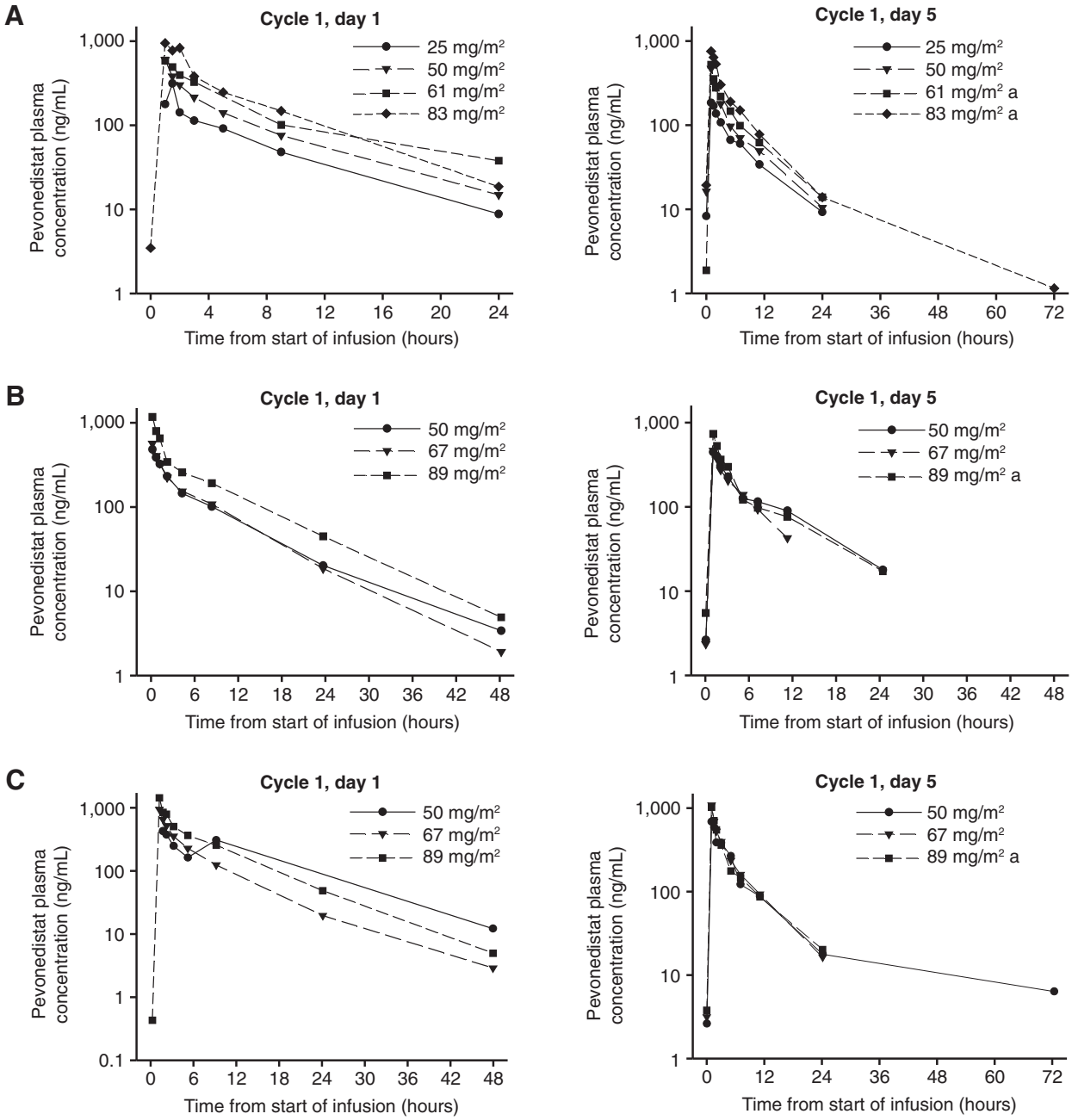

Figure 2.
Comparison of mean pevonedistat plasma concentration-time profiles on days 1 and 5, following daily (schedule A, panel A) and intermittent 1-hour intravenous infusion in patients with (schedule B, panel B) or without (schedule C, panel C) dexamethasone pretreatment. [a], $N = 1$.

requiring discontinuation or dose de-escalation ($n = 4$) was considered DLT per investigator decision, based on the intolerable hepatotoxicity observed in schedule A.

Safety and treatment duration

Patients on schedules B and C were treated for medians of three (range, 1–10) and two (range, 1–5) cycles, respectively (Fig. 1). All 36 patients were evaluable for toxicity. Nine (53%) and 10 (53%) patients on schedules B and C, respectively, experienced grade ≥3 AEs (Table 2). Only anemia ($n = 4$), congestive heart failure, dyspnea, fatigue, and hyponatremia (each $n = 2$) were reported at grade ≥3 in ≥1 patient overall. One schedule B patient discontinued due to AEs, specifically grade 2 hyperbilirubinemia. No schedule C patients discontinued due to AEs. The only treatment-related ≥ grade 2 SAE was reported in a schedule C patient with grade 2 nausea and vomiting. Treatment-related AEs are detailed in Supplementary Table S1. Hepatotoxicities reported with pevonedistat are summarized in Supplementary Table S2.

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Table 3. Pevonedistat pharmacokinetic parameters following daily (schedule A; days 1–5) and intermittent 1-hour intravenous infusion of pevonedistat in patients with (schedule B; days 1, 3, and 5) or without (schedule C; days 1, 3, and 5) dexamethasone pretreatment, at the established MTD dose

	Schedule A MTD = 50 mg/m^2		Schedule B, with dexamethasone MTD = 50 mg/m^2		Schedule C, without dexamethasone MTD = 67 mg/m^2	
Parameter (unit)	**Day 1**	**Day 5**	**Day 1**	**Day 5**	**Day 1**	**Day 5**
N	5	4	12	11	13	11
C_{max}, ng/mL	575 (31%)	500 (40%)	427 (34%)	398 (33%)	873 (29%)	883 (26%)
T_{max}, hr[a]	1.08 (1.0–1.1)	1.29 (1.1–1.5)	1.16 (1.0–2.1)	1.50 (1.1–2.1)	1.08 (1.0–1.2)	1.08 (0.5–1.5)
AUC_{0-24hr}, ng.hr/mL	2,180 (23%)	1,870 (10%)	2,244 (18%)	2,032 (24%)	3,383 (20%)	3,127(20%)
AUC_{0-48hr}, ng.hr/mL	—	—	2,417 (19%)[b]	2,560[c]	3,529 (21%)	3,250[c]
Rac[a]	—	0.92 (0.8–1.0)	—	1.05[c]	—	1.22[c]

NOTE: Blood samples were collected before and after the completion of the pevonedistat infusion on cycle 1, day 1 (up to 24 hours postdose), and day 5 (up to 120 hours postdose for schedule A, and up to 72 hours for schedules B and C). An additional blood sample was collected within 1 hour before dosing on cycle 1 day 4 for schedule A and cycle 1 day 3 for schedules B and C. Data are shown as geometric mean (coefficient of variation) unless specified otherwise.

Abbreviations: AUC_{0-24hr}, area under the plasma concentration-time curve from time zero to 24 hours postdose; AUC_{0-48hr}, area under the plasma concentration-time curve from time zero to 48 hours postdose; C_{max}, maximum observed concentration; Rac, observed accumulation ratio, defined as $AUC_{0-\tau}$ (day 5)/$AUC_{0-\tau}$ (day 1) where the dosing interval, τ, is equal to 24 hours for schedule A, and to 48 hours for schedules B and C; T_{max}, time at which C_{max} occurs.

[a]Data are shown as median (range [if available]).

[b]$N = 11$.

[c]$N = 1$.

Pharmacokinetics

All 12 schedule A patients were evaluable. Of these, 5 received the schedule A MTD of 50 mg/m^2. Thirty-six patients in schedule B and C were evaluable for assessing the relative effect on pevonedistat pharmacokinetics of dexamethasone pretreatment. Twelve and 13 patients received the schedule B and C MTD, respectively. For all three dosing schedules, mean plasma concentrations of pevonedistat exhibited a bi-exponential disposition phase (Fig. 2). Approximate dose-proportional increases in mean C_{max} and $AUC_{0-\tau}$ values were observed across the dose range studied. No marked differences in pevonedistat systemic exposures were noted between day 1 and day 5, suggesting little or no drug accumulation in plasma following daily or intermittent dosing. Parameter changes from day 1 to day 5 in schedule B were of similar magnitude to changes seen in schedule C patients who received no dexamethasone. In some patients, pevonedistat plasma exposure (AUC_{0-24hr} and C_{max}) was decreased on day 5 after dexamethasone pretreatment, while it was virtually unchanged in others (Table 3). Individual dose-normalized pevonedistat exposures for schedules B and C also show no marked effect of dexamethasone on pevonedistat exposure (Supplementary Fig. S1).

Pharmacodynamics

Pharmacodynamic assessment of pevonedistat-NEDD8 adduct, NRF2, and CDT1 levels was performed on 14 evaluable pairs of tumor biopsies obtained from schedule A, B, and C patients at screening and 3 to 6 hours after the second or third scheduled dose. IHC analysis of pevonedistat-NEDD8 adduct showed that drug was present in 13 of 14 postdose tumor biopsies. For one pair of biopsies, the drug adduct was detected in the sample labeled predose but not in the postdose sample, indicating a sample switch, and the pair was excluded from further analysis. Figures 3A and B show representative IHC assays of tumor tissue from schedule B patients with head and neck cancer and melanoma treated at 50 mg/m^2. Most patients (11/13) exhibited an increase of $\geq$20% in one or both of the CRL substrates CDT1 and NRF2 in the postdose tumor biopsy (Fig. 3C), suggesting a pharmacodynamic effect in solid tumors, including melanoma, gastric, ovarian, head and neck, adrenal, and breast cancer.

Antitumor activity

Twelve of 15 (80%) evaluable schedule B patients treated at 50, 67, and 89 mg/m^2 (n = 8, 2, and 2, respectively) and 11 of 16 (69%) evaluable schedule C patients (n = 1, 8, and 2, respectively) had a best response of stable disease (SD). The median duration of SD on schedules B and C was 2 (range, 0.5–7.4) and 2.1 (range, 0.6–3.6) months, respectively. No objective responses were observed on schedules B or C.

Discussion

This is the first study to investigate in the clinical setting the NAE inhibitor pevonedistat, which has a novel mechanism of action targeting the UPS. Unlike the proteasome inhibitors such as bortezomib and carfilzomib, which inhibit the degradation of most ubiquitinated proteins (35), pevonedistat disrupts only a proportion (approximately 20%; ref. 6) through inhibition of NAE and downstream inhibition of the CRLs. Thus, the clinical characteristics of pevonedistat were anticipated to differ from those of the proteasome inhibitors.

Our results show that day 1, 3, and 5 pevonedistat dosing was generally well tolerated with an MTD between 50 mg/m^2 and 67 mg/m^2. DLTs included grade 2/3 increased transaminases and grade 2 hyperbilirubinemia. Common AEs included fatigue, gastrointestinal toxicity, anemia, and hepatotoxicity. Pharmacodynamic studies of biologic correlates of NAE inhibition demonstrated target-specific activity of pevonedistat in tumor biopsies from patients treated with doses of 50 mg/m^2 and above. On the basis of a holistic review of all available data, the recommended phase II dose of pevonedistat is 50 mg/m^2 on days 1, 3, and 5 of a 21-day cycle with no dexamethasone pretreatment.

On schedule A, giving pevonedistat for 5 consecutive days on a 3-week schedule resulted in excessive hepatotoxicity that was generally but not always rapidly reversible upon cessation of dosing. Schedule A was discontinued with the MTD established as 50 mg/m^2. Transient transaminase elevations were also seen on the intermittent schedules B and C; however, hepatotoxicity was generally less than that seen on schedule A. Increased transaminases were among the common AEs in other phase I studies of pevonedistat in myeloma and lymphoma (36), and acute myeloid leukemia (AML; 23% of patients overall experienced AST/ALT

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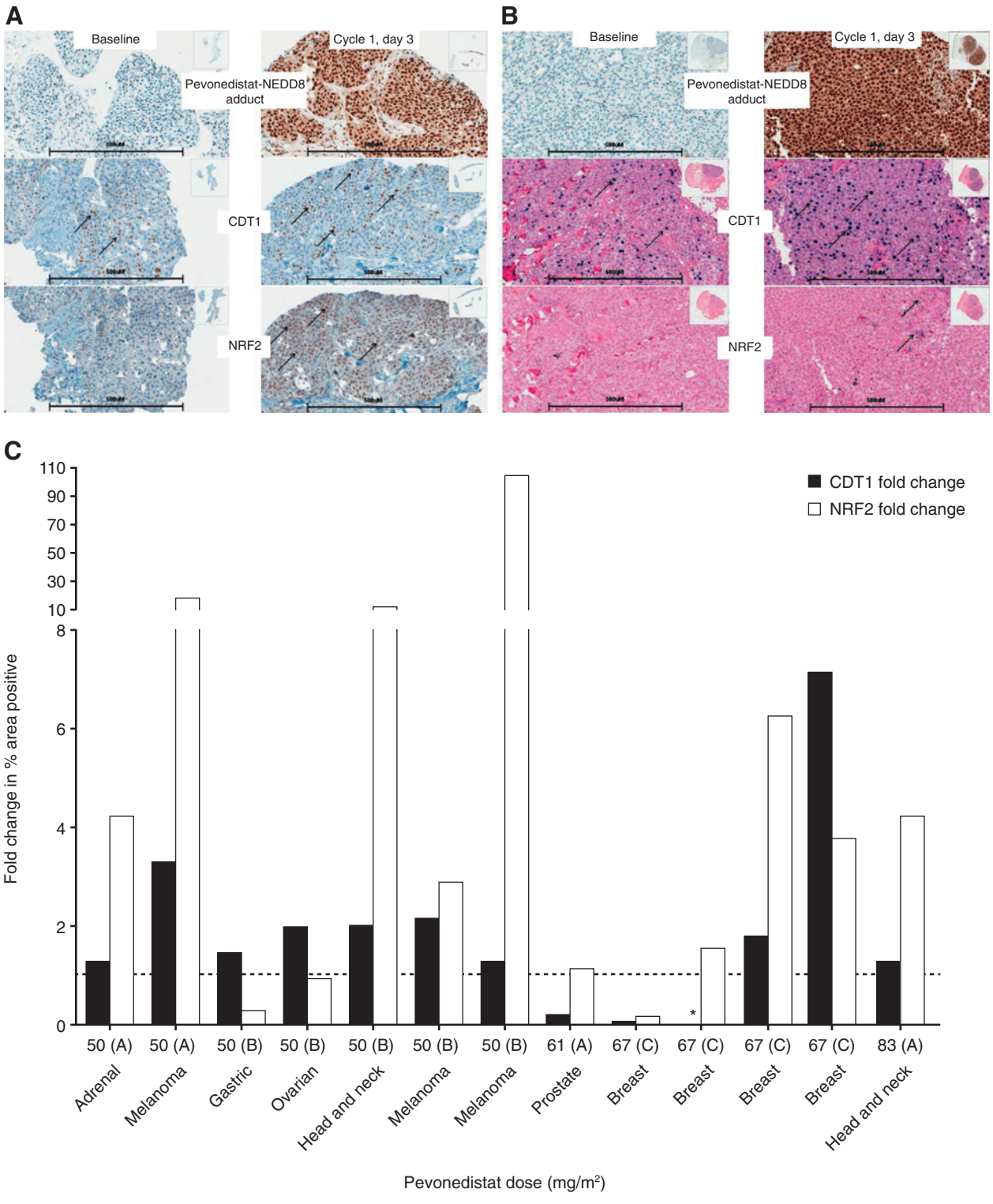

*10th patient has no reported result for CDT1 because of the zero baseline

Figure 3.
Representative images of formalin-fixed paraffin-embedded head and neck (A) and melanoma (B) tumor biopsies from patients treated on schedule B with pevonedistat 50 mg/m^2. Samples were collected at screening or postdose on cycle 1, day 3, and stained on serial sections for pevonedistat-NEDD8 (top), CDT1 (middle), or NRF2 (bottom). The arrows indicate examples of areas containing cells that are positive. Scale bar represents 500 μm. C, fold change in CDT1 and NRF2 from baseline to postdose on cycle 1, day 3 in 13 evaluable paired tumor biopsies from patients in schedules A, B, and C. Signal expression was calculated as the percent stained area of tumor and quantified using Metamorph imaging software.

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elevations; ref. 37). These studies and schedule B and C of this study all used day 1, 3, and 5 dosing schedules, which may have permitted recovery of effects on the liver between dosing, resulting in less hepatotoxicity and improved pevonedistat tolerability. Dexamethasone did not diminish the incidence of transaminitis or prevent any acute phase reaction as hypothesized. It did, however, decrease the frequency of nausea, vomiting, and myalgias. Because pevonedistat is a substrate of CYP3A4, we evaluated whether concurrent use of dexamethasone, a known, albeit weak, inducer of CYP3A activity via glucocorticoid receptor-mediated transcriptional upregulation (38), would increase pevonedistat systemic clearance, resulting in lower systemic exposure. On the basis of a limited sample size and after dose normalization (Supplementary Fig. S1), a short course of dexamethasone did not appear to notably alter pevonedistat pharmacokinetics; this was possibly due to the intermittent dexamethasone dosing schedule and the fact that it is only a weak CYP3A inducer.

Hepatotoxicity was considered dose-limiting on schedules B and C, with MTDs of 50 and 67 mg/m^2, respectively. Somewhat surprisingly, the intermittent dosing schedules did not permit substantial dose escalation beyond the MTD seen with 5-day continuous dosing. The schedule B MTD determined in this study is consistent with the results observed in a recent study of single-agent pevonedistat in advanced relapsed/refractory AML or myelodysplastic syndromes, in which the recommended dose was also 50 mg/m^2 on days 1, 3, and 5 of a 21-day cycle (39).

Pharmacodynamic analyses showed effects consistent with NAE target inhibition in tumor tissue following pevonedistat infusion. NAE inhibition was demonstrated in multiple tumor types via IHC assay of pevonedistat-NEDD8 adduct and accumulation of the CRL substrates CDT1 and NRF2. Detection of drug–protein adducts in patient specimens is challenging due to inherently low adduct levels and few have been characterized *in vivo*; detection of the pevonedistat-NEDD8 adduct is quite distinctive. Similar substrate elevations have been reported in preclinical studies with pevonedistat (6) and CDT1 elevations have been reported in tumor samples from the phase I study of pevonedistat in patients with AML (37).

In this study, pevonedistat caused some disease stabilization with patients remaining on therapy for $\geq$4 cycles. In particular, one patient with melanoma and one patient with colorectal cancer achieved SD for 6 and 7.4 months, respectively.

This study was part of a broader clinical program that included other phase I studies of single-agent pevonedistat in patients with solid tumors and hematologic malignancies, including metastatic melanoma (NCT01011530; ref. 40), AML (NCT00911066, NCT1814826; refs. 37, 41), and myeloma and lymphoma (NCT00722488; ref. 42). In additional preclinical studies, pevonedistat has demonstrated synergy in combination with azacitidine in AML cell lines and murine xenografts (43) and increased antitumor activity in certain solid tumor cell lines and xenograft models when combined with DNA-damaging agents including cisplatin, carboplatin, mitomycin C, and dacarbazine (17, 22, 28, 44, 45). Consequently, the focus of ongoing investigations is of pevonedistat in various combination regimens including with azacitidine in elderly AML patients (NCT01814826; ref. 41) and with docetaxel, gemcitabine, or carboplatin/paclitaxel in patients with solid tumors (NCT01862328).

Disclosure of Potential Conflicts of Interest

G.I. Shapiro and R.B. Cohen are consultants/advisory board members for Millennium Pharmaceuticals, Inc. G.J. Weiss reports receiving speakers bureau honoraria from Celgene, Medscape, Pfizer and Pharmatech, and is a consultant/advisory board member for Amgen and Blend Therapeutics. No potential conflicts of interest were disclosed by the other authors.

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Phase I Study of the Investigational NEDD8-Activating Enzyme Inhibitor Pevonedistat (TAK-924/MLN4924) in Patients with Advanced Solid Tumors

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