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Clinical Trials: Targeted Therapy

Clinical Cancer Research

Phase I Study of CC-486 Alone and in Combination with Carboplatin or nab-Paclitaxel in Patients with Relapsed or Refractory Solid Tumors

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Abstract

Purpose: This large two-part, three-arm phase I study examined the safety and tolerability of CC-486 (an oral formulation of azacitidine, a hypomethylating agent) alone or in combination with the cytotoxic agents, carboplatin or nab-paclitaxel, in patients with advanced unresectable solid tumors.

Patients and Methods: Part 1 ($n = 57$) was a dose escalation of CC-486 alone (arm C) or with carboplatin (arm A) or nab-paclitaxel (arm B). The primary endpoint was safety, MTD, and recommended part 2 dose (RP2D) of CC-486. In part 2 ($n = 112$), the primary endpoint was the safety and tolerability of CC-486 administered at the RP2D for each treatment arm, in tumor-specific expansion cohorts. Secondary endpoints included pharmacokinetics, pharmacodynamics, and antitumor activity of CC-486.

Results: At pharmacologically active doses CC-486 in combination with carboplatin or nab-paclitaxel had a tolerable safety profile and no drug–drug interactions. The CC-486 RP2D was determined as 300 mg (every day, days 1–14/21) in combination with carboplatin (arm A) or as monotherapy (arm C); and 200 mg in the same dosing regimen in combination with nab-paclitaxel (arm B). Albeit limited by the small sample size, CC-486 monotherapy resulted in partial responses (three/eight) and stable disease (four/eight) in patients with nasopharyngeal cancer. Three of the stable disease responses lasted more than 150 days.

Conclusions: CC-486 is well tolerated alone or in combination with carboplatin or nab-paclitaxel. Exploratory analyses suggest clinical activity of CC-486 monotherapy in nasopharyngeal cancer and provided the basis for an ongoing phase II clinical trial (ClinicalTrials.gov identifier: NCT02269943).
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(i) The AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 19–23, 2013, Boston, MA.

o LoRusso P, Rasco D, Bendell J, et al. A phase Ib study of CC-486 (oral azacitidine) as a priming agent for carboplatin or nab-paclitaxel in patients with relapsed or refractory solid tumors. *Mol Cancer Ther* 2013;12(11 Suppl):A120. Abstract A120 [Poster].

o Laille E, Nguyen AN, Chen G, et al. A phase Ib Study of CC-486 (oral azacitidine) to evaluate the pharmacokinetics and pharmacodynamics of azacitidine administered alone and in combination with carboplatin or ABI-007 (nab-Paclitaxel) in patients with solid tumors. *Mol Cancer Ther* 2013;12(11 Suppl):B217. Abstract B217 [Poster].

(ii) The 26th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, November 18–21, 2014, Barcelona, Spain.

o Von Hoff DD, Isambert N, Lopez-Martin J, et al. Phase 1B study of CC-486 (oral azacitidine) in tumors associated with a viral etiology. *Eur J Cancer* 2014;50 (6 Suppl):179. Abstract 551 [Poster].

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Translational Relevance

The hypomethylating agent 5-azacitidine (AZA) is approved for the treatment of MDS and AML but has shown limited activity in solid tumors as a single agent. The relatively limited dosing schedule for the parenteral formulation of this agent, 7/28 days, has been proposed as a possible explanation for this apparent lack of antitumor activity. Inhibition of DNMT1 by AZA requires DNA synthesis, and the cycling fraction of solid tumors is lower than that of hematologic malignancies. CC-486, an orally bioavailable form of AZA, provides an opportunity to achieve extended daily dosing. This trial was designed to determine whether CC-486 could be administered safely at pharmacologically active doses as a priming agent for cytotoxic chemotherapy or as a single agent on a continuous schedule. The results show that doses of AZA that consistently achieve global genomic hypomethylating effects are tolerated in combination with standard of care doses of nab-paclitaxel or carboplatin. Continuous daily administration of AZA, in contrast, leads to prolonged neutropenia in cycle 2 and beyond, confirming the need for a dosing holiday. Although responses to combination treatment were observed in heavily pre-treated subjects, randomized trials will be needed to determine whether AZA priming contributes to efficacy.

Introduction

Cytotoxic agents continue to be a mainstay of late-stage cancer treatment, but have limited ability to achieve durable responses (1). The limited efficacy is often attributable to epigenetic changes that silence genes involved in induction of cell death (1, 2). Cancer cell genomes typically have reduced global methylation, with focal areas of aberrant hypermethylation in the CpG islands of genes encoding known tumor suppressors such as *PTEN* and *BRCA1*, as well as genes encoding proteins required for apoptosis including caspase 8, death-associated protein kinase (DAPK), and apoptotic peptidase activating factor 1 (Apaf-1). Furthermore, a number of preclinical studies show that inhibition of DNA methylation can sensitize or resensitize cancer cells to cytotoxic therapy (3–5).

Methylation of DNA at promoter-associated CpG islands, which results in transcriptional repression (i.e., epigenetic silencing), is catalyzed by DNA methyltransferases (6). Azacitidine is a DNA methyltransferase inhibitor (also known as a hypomethylating agent), and the injectable form is approved in the United States and the European Union for certain hematologic malignancies (7, 8). Preclinical data suggest that the hypomethylating effects of azacitidine or decitabine (5-aza-2′deoxycitidine) take time, even in rapidly dividing cells in culture (5). This is consistent with the clinical observation that the optimal therapeutic effect of hypomethylating agents as monotherapy for myelodysplastic syndrome requires multiple treatment cycles (9). In a recent clinical study of decitabine administered once, 1 week before commencing carboplatin treatment, the effect of the hypomethylating agent did not persist throughout the treatment cycle (10). Thus, sustained exposure to a hypomethylating agent prior to the introduction of a cytotoxic agent may be required to observe sensitization. Co-administration of the hypomethylating agent with the cytotoxic agent starting on the first day of therapy would likely produce increased toxicity without added antitumor effects.

The oral formulation of azacitidine (CC-486) is currently being evaluated in clinical trials as a single agent or in combination with other drugs, for the treatment of solid tumors and hematologic malignancies. This two-part phase I study (ClinicalTrials.gov identifier: NCT01478685) evaluated CC-486 in combination with the cytotoxic agents carboplatin or nab-paclitaxel, or as monotherapy in patients with advanced solid tumors. Part 1 of the trial was a traditional dose finding study and included a PK assessment of carboplatin and nab-paclitaxel with and without CC-486 in order to assess the potential for epigenetic effects of the latter to alter metabolism of the former. Part 2 of the trial evaluated CC-486 alone or in combination in selected tumor types of interest. These were determined based on preclinical evidence suggesting reversal of resistance to conventional therapy (e.g., bladder and ovarian cancer; refs. 5, 11, 12), and phase I/II data suggesting improved response to subsequent chemotherapy in patients with non–small cell lung carcinoma (NSCLC) who received azacitidine in combination with entinostat (a histone deacetylase inhibitor; ref. 13). In addition, tumors with viral etiology (e.g., nasopharyngeal and cervical cancers) were assessed for response to CC-486 monotherapy based on evidence that DNA hypomethylating agents may demethylate viral DNA and thus enhance the immunogenicity of these tumors by upregulating the expression of viral antigens, thereby allowing recognition and elimination by the adaptive immune system and antigen presentation pathways (14–16).

Patients and Methods

Patient selection

Patients were ≥18 years old, with advanced unresectable solid tumors. Part 1 of this study was conducted at five investigative sites in the United States between December 6, 2011, and April 9, 2015. Part 2 was conducted at seven sites in the United States and six sites in European Union countries (France, Spain, and the Netherlands) between November 29, 2012, and November 17, 2015. All sites screened and enrolled patients. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice, Guidelines of the International Conference on Harmonization. Written informed consent was obtained from all patients before entering the study. Before the start of the study, the study protocol, informed consent document, and any other appropriate documents were reviewed and approved by the Institutional Review Board/Ethics Committee.

Part 1 patients included those who had progressed on or were not able to tolerate standard cancer therapy, or for whom no other known effective therapy existed. Part 2, arm A consisted of patients with relapsed or refractory urothelial carcinoma of the bladder, renal pelvis, ureter, or urethra (mixed histologies were permitted provided a component of urothelial carcinoma was present); or those with epithelial ovarian, fallopian tube, or primary peritoneal carcinoma. Arm B patients had either NSCLC or pancreatic ductal adenocarcinoma (PDAC). Arm C encompassed patients with tumor types known to be associated with Epstein–Barr virus (EBV), human papilloma virus (HPV), or Merkel cell (MC) polyomavirus, namely, nasopharyngeal carcinoma (NPC), cervical carcinoma, anal carcinoma, Merkel cell carcinoma of the skin, and head and neck squamous cell carcinoma (HNSCC).

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Study design and drug treatment

This phase I, open-label, three-arm, multicenter study (ClinicalTrials.gov identifier: NCT01478685) was conducted in two parts (Fig. 1). Part 1 was a dose-escalation study of CC-486 in combination with carboplatin (arm A) or nab-paclitaxel (arm B), or CC-486 as a single agent (arm C). Patients in arm A and arm B received CC-486 as a single agent for the first 7 days of the study before beginning combination treatment on cycle 1, day 8. In part 1 arm A, CC-486 was administered on days 1 to 7, 9 to 14, and 22 to 28 for cycle 1, and days 1 to 7 and 15 to 21 in subsequent cycles. Patients in arm A received carboplatin as an intravenous infusion over 1 hour on day 8 of cycle 1, and day 1 of each subsequent cycle. Carboplatin dosing in cycle 1 did not overlap with CC-486 so that single-agent PK of carboplatin could be compared with the combination PK in cycle 2. Carboplatin dose was based on the area under the plasma concentration–time curve of 4 (AUC 4). The CC-486 dosing for arm B was days 1 to 14 and 22 to 28 for cycle 1, and days 1 to 7 and 15 to 21 in subsequent cycles. Patients in arm B received nab-paclitaxel as an intravenous infusion 100 mg/m^2/dose on days 8 and 15 of cycle 1, and days 1 and 8 of each subsequent 21-day cycle. Cycle 1 was 28 days in duration whereas all subsequent cycles were 21 days. In arm C all cycles were 21 days. A key objective of arm C was to determine whether CC-486 could be safely administered for extended periods. Patients in arm C were treated with CC-486 alone on days 1 to 14 in all cycles. In all arms, CC-486 (100-mg tablets) was administered orally at 200- or 300-mg doses during dose escalation. In cycle 1, the dose of CC-486 was escalated independently in each arm based on tolerability to define the recommended part 2 dose (RP2D; Supplementary Tables S1, S2, and S3).

Part 2 was a Simon two-stage expansion study for CC-486 at the RP2D for each treatment arm. Patients were assigned to treatment arms according to tumor type (Fig. 1), and all treatment cycles were 21 days. Patients in arm A received carboplatin (AUC 4) on day 8 of each cycle. Patients in arm B received nab-paclitaxel (100 mg/m^2 i.v.) on days 8 and 15 of each cycle. Patients in arm C received CC-486 alone. In all treatment arms, CC-486 was administered on days 1 to 14 of each 21-day cycle; arms A and C patients received 300 mg, and arm B patients received 200 mg.

Objectives and endpoints

In part 1, the primary objective was to evaluate the safety and define the MTD or maximal administered dose (MAD) in patients with relapsed or refractory solid tumors. As 300 mg was already determined as a pharmacologically and clinically active single-agent dose in myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML; refs. 17, 18), this dose was defined as the MAD (without further escalation) if it could be delivered safely in combination with chemotherapy. In part 2, the primary objective was to assess the safety and tolerability of CC-486 administered at the RP2D in tumor-specific expansion cohorts. Secondary objectives included an evaluation of the pharmacokinetic, pharmacodynamic, and antitumor activities of CC-486 alone or in combination with carboplatin or nab-paclitaxel. Tumor response was assessed by the investigators based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (19).

Safety and tumor assessments

Dose-limiting toxicities (DLT) were assessed in cycle 1 of part 1 to determine the MTD; patients were assessable for DLT if they received a minimum relative dose intensity of 80% in cycle 1.

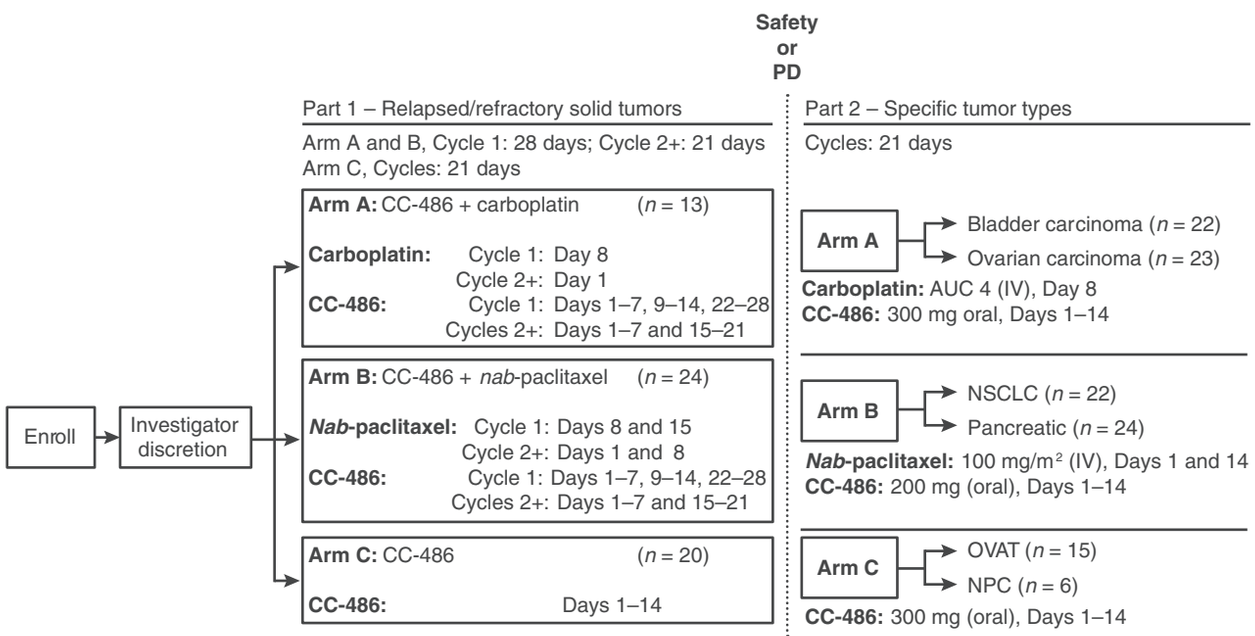

Figure 1.

Study design. The first part of the study consisted of three treatment arms, with CC-486 administered in combination with carboplatin (arm A), nab-paclitaxel (arm B), or as monotherapy (arm C). Patients were assigned to each arm based on investigator discretion. Patients continued treatment until either a DLT or progressive disease. In part 2, the treatment arms had the same drug combinations as in part 1, but patients were assigned to treatment arms based on tumor type. PD, pharmacodynamics.

Toxicities were assessed according to the Common Terminology Criteria for Adverse Events version 4.0. Any nonhematologic adverse event (AE) of grade ≥3 reported in cycle 1 that was believed to be related to CC-486 or to the combination treatments was considered a DLT, except for alopecia, emesis, or diarrhea that responded to clinical management within 72 hours, nonsymptomatic laboratory abnormalities that were not medically significant, and fatigue that recovered to baseline within 72 hours. Grade 4 neutropenia lasting >7 days or accompanied by fever, grade 3 thrombocytopenia with clinically significant bleeding, and failure to meet hematologic criteria for starting cycle 2 (neutrophil count [ANC] $\geq 1.5 \times 10^9$/L and platelets $\geq 75 \times 10^9$/L) were considered hematologic DLTs.

Tumor assessments were conducted at initial screening, at the end of cycles 2, 4, and 6, and at the end of every third cycle thereafter.

Pharmacokinetic assessments

CC-486 pharmacokinetic parameters are reported as its active moiety azacitidine. In part 1, blood samples for pharmacokinetic assessments were collected from patients in all arms predose and at specified intervals postdose (up to 8 hours for CC-486, up to 24 hours post-infusion for carboplatin, and up to 72 hours post-infusion for nab-paclitaxel). In arm A, blood samples were collected in cycles 1 and 2 on day 1 for CC-486 and cycle 1, days 8 and 9, cycle 2 days 1 and 2 for carboplatin. In arm B, blood samples were collected on cycle 1, days 1 and 8, for CC-486 and days 8 to 11 and 15 to 18 for nab-paclitaxel, and in cycle 1, day 1, for arm C. Validated proprietary, LC/MS-MS methods were used for quantitation of CC-486 (measured as azacitidine) and nab-paclitaxel levels in plasma. A validated proprietary, inductively coupled plasma mass spectrometric method (ICP-MS) was used for quantitation of CBDCA levels in plasma. CC-486 pharmacokinetic parameters assessed included time to maximum plasma concentration (T_{max}), AUC, peak plasma concentration (C_{max}), terminal half-life ($t_{1/2}$), apparent total clearance (CL/F), and apparent volume of distribution (Vz/F). Pharmacokinetic parameters were calculated using noncompartmental methods with Phoenix WinNonlin software (Pharsight Corp.).

Exploratory biomarker and pharmacodynamic assessments

The exploratory objective of the study was to determine whether there is any relationship among baseline tumor characteristics (genetic or epigenetic), pharmacodynamic activity, and antitumor activity. In part 1, whole blood (two 6-mL ACDC tubes at each time point) was collected for pharmacodynamic assessments prior to CC-486 dosing on days 1, 8, 15, and 22 of cycle 1, and on day 1 of cycles 2, 3, and 6, for a maximum of 14 samples collected per patient. Whole blood (peripheral blood mononuclear cells, PBMC) samples were assessed using the Infinium HumanMethylation27 and HumanMethylation450 assays (Illumina Inc.; refs. 20, 21). These assays measure the percent of hypermethylated CpG loci as the basis for determination of the Global DNA Methylation Score (GDMS), for each sample. GDMS data from 25 subjects in part 1 were evaluated to assess the relationship between systemic exposure to CC-486 (AUC) and changes from baseline in GDMS as measured at cycle 1, day 15. *P* value is based on Pearson product–moment correlation analysis.

Tumor biopsies (optional in Part 1, mandatory in Part 2) were collected before dosing on days 1 and 15 of cycle 1. Each tumor biopsy was divided into two parts, with one part snap frozen on dry ice and the second part formalin-fixed and embedded in paraffin (FFPE).

Statistical analyses

The primary safety population included patients who received at least 1 dose of any study drug. The DLT evaluable population (part 1) was defined as patients who experienced DLT in cycle 1, missed no more than four doses of CC-486 in cycle 1 and received the scheduled dose of carboplatin (arm A only) or, all scheduled doses of nab-paclitaxel in cycle 1 (arm B only). Patients who were not DLT evaluable were replaced so that dose escalation decisions could be based on a minimum of six DLT-evaluable patients. The efficacy-evaluable population included all patients who met eligibility criteria, completed at least two cycles of study treatment (i.e., received at least 70% of all assigned study treatment during the first two cycles), and had baseline and at least one post-baseline efficacy assessments. No formal statistical analyses were planned for safety, PK, or efficacy, and outcomes are summarized by study arms using descriptive statistics.

Results

Patient demographics

In part 1, 57 patients were treated, and 47 were evaluable for response; in part 2, 112 patients were treated, and 101 were evaluable for response (Table 1). Part 2 of the study included separate cohorts of patients with urothelial carcinoma (19.6% of the population), ovarian carcinoma (20.5%), NSCLC (19.6%), pancreatic carcinoma (21.4%), NPC (5.4%), and other virally associated tumors (OVAT; 13.4%).

Safety evaluation

All except one patient in part 2, arm B experienced at least one treatment emergent AE (TEAE).

Part 1. Generally, there were no unexpected safety signals, and we did not observe any evidence of drug–drug interactions related to toxicity. CC-486 MAD was 300 mg (every day, days 1–7, 9–14, and 22–28/28; with carboplatin AUC 4 on day 8/28) for arm A and arm C (every day, days 1–14/21). CC-486 MTD was 200 mg (every day, days 1–14 and 22–28/28; with nab-paclitaxel 100 mg/m^2 days 8 and 15/28) for arm B. The CC-486 RP2D was 300 mg every day for the first 14 days per 21-day cycle in combination with carboplatin (arm A) or as monotherapy (arm C); and 200 mg every day in the same dosing regimen in combination with nab-paclitaxel (arm B). The median percent relative dose intensity was 80.0% (range, 43%–100%) for arm A, 86.5% (range, 19%–119%) for arm B, and 77.0% (range, 39%–101%) for arm C.

In arm A, one patient had two DLTs (neutropenia and thrombocytopenia) at DL1 (CC-486: 200 mg, carboplatin: AUC 4). One patient in DL2 (CC-486: 300 mg, carboplatin: AUC 4) discontinued treatment because of an AE. The most common AE observed among patients in arm A was vomiting (10/13 patients), all grade 1/2; anemia, neutropenia, constipation, nausea, and fatigue were also commonly occurring AEs (7/13 patients for each; Table 2). In arm B, two patients experienced DLT (neutropenia) at DL1 (CC-486: 200 mg, nab-paclitaxel: 100 mg/m^2), most likely from weekly nab-paclitaxel dosing (100 mg/m^2, days 8, 15, and 22/28). Therefore, the study was amended and a DL1 rechallenge cohort was enrolled, wherein nab-paclitaxel was administered during 2 instead of 3 consecutive weeks in

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Table 1. Patient demographic and clinical characteristics

	Part 1			Part 2					
	Arm A (CC-486 + carboplatin) ($N = 13$) overall cohort	Arm B (CC-486 + nab-paclitaxel) overall cohort ($N = 24$)	Arm C (CC-486 monotherapy) ($N = 20$) overall cohort	Arm A (CC-486 + carboplatin) tumor cohort		Arm B (CC-486 + nab-paclitaxel) tumor cohort		Arm C (CC-486 monotherapy) tumor cohort	
				Bladder ($N = 22$)	Ovarian ($N = 23$)	NSCLC ($N = 22$)	Pancreatic ($N = 24$)	NPC ($N = 6$)	OVAT ($N = 15$)
Sex, *n* (%)									
Male	8 (61.5)	12 (50.0)	11 (55.0)	18 (81.8)	0	12 (54.5)	14 (58.3)	4 (66.7)	8 (53.3)
Female	5 (38.5)	12 (50.0)	9 (45.0)	4 (18.2)	23 (100)	10 (45.5)	10 (41.7)	2 (33.3)	7 (46.7)
Age, years[a]									
Mean (SD)	63.1 (11.38)	61.5 (9.06)	60.9 (9.72)	65.3 (7.88)	59.9 (9.04)	59.8 (7.42)	64.8 (7.59)	53.2 (7.31)	55.1 (13.77)
Median (min, max)	65.0 (36, 75)	61.0 (48, 86)	63.5 (42, 76)	64.0 (51, 82)	61.0 (46, 75)	60.5 (45, 72)	65.0 (48, 75)	53.5 (44, 63)	58.0 (24, 74)
Race, *n* (%)									
White	13 (100)	21 (87.5)	15 (75.0)	21 (95.5)	20 (87.0)	22 (100)	23 (95.8)	5 (83.3)	14 (93.3)
Ethnicity, *n* (%)									
Not Hispanic or Latino	13 (100)	19 (79.2)	17 (85.0)	22 (100)	20 (87.0)	20 (90.9)	23 (95.8)	5 (83.3)	14 (93.3)
Number of prior cancer regimens, *n* (%)[b]									
1–5	5 (38.5)	8 (33.3)	4 (20.0)	6 (27.3)	8 (34.8)	12 (54.5)	16 (66.7)	0	6 (40.0)
6–10	6 (46.2)	11 (45.8)	14 (70.0)	14 (63.6)	5 (21.7)	7 (31.8)	5 (20.8)	6 (100)	9 (60.0)
> 10	2 (15.4)	5 (20.8)	2 (10.0)	2 (9.1)	10 (43.5)	3 (13.6)	3 (12.5)	—	—
ECOG, *n* (%)									
0	2 (15.4)	6 (25.0)	6 (30.0)	9 (40.9)	13 (56.5)	5 (22.7)	12 (50.0)	4 (66.7)	3 (20.0)
1	9 (69.2)	16 (66.7)	9 (45.0)	13 (59.1)	10 (43.5)	16 (72.7)	12 (50.0)	2 (33.3)	12 (80.0)
2	2 (15.4)	2 (8.3)	5 (25.0)	—	—	1 (4.5)	0	—	—

Abbreviations: ECOG, Eastern Cooperative Oncology Group performance status; max, maximum; min, minimum.

[a]Age = (Date of Informed Consent − Date of Birth + 1)/365.25.

[b]On the basis of the treated population (same as enrolled population for part 1 arm C, part 2 arm A, arm B, arm C). Includes prior radiation, surgery, systemic chemo- and hormonal therapies, and other prior anticancer treatments. Percentage based on the treated population as denominator.

combination with DL1 CC-486 (200 mg every day on days 1–7/21 and 15–21/21). Two patients experienced DLT (neutropenia) at DL2. Four of 11 patients in the DL1 rechallenge cohort, and two in the DL2 cohort discontinued treatment due to an AE. Overall, the most common AE among arm B patients was fatigue (15/24 patients; Table 2). In arm C, three patients in DL2 developed prolonged grade 4 neutropenia in cycles 2 or 3 on the continuous (21/21 day) schedule. Later occurring (i.e., beyond cycle 1) severe myelosuppression was attributed to continuous exposure to CC-486 without a treatment break based on observations from earlier studies (unpublished data). As a consequence, a modified regimen consisting of CC-486 (300 mg every day) on days 1 to 14/21, which was well-tolerated in an earlier trial in subjects with hematologic malignancies, was examined (18). In this study, this modified dosing regimen was adequately tolerated. The most common AE observed in arm C patients was diarrhea (14/20), mostly grade 1/2 (Table 2). Details on frequencies of TEAEs are reported (Supplementary Table S4).

Part 2. Safety observations were consistent with part 1 (Table 3; Supplementary Table S5). The most frequent grade ≥3 AE was neutropenia, and the most frequent all-grade AE was nausea in each arm (Table 3). Discontinuation of CC-486 for TEAEs occurred in seven (15.6%) patients in arm A, four (8.7%) in arm B, and three (14.3%) in arm C, the most common reason being neutropenia ($n = 3$). No other individual TEAE resulted in CC-486 discontinuation in more than one patient in any treatment arm. Toxicity-related dose reductions/interruptions for

Table 2. TEAEs in part 1[a]

TEAEs preferred term, overall ≥ 20% incidence in ≥ 1 arm	TEAEs, *n* (%)					
	Arm A ($n = 13$)		Arm B ($n = 24$)		Arm C ($n = 20$)	
	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades
Anemia	2 (15.4)	7 (53.8)	2 (8.3)	5 (20.8)	1 (5.0)	4 (20.0)
Neutropenia	6 (46.2)	7(53.8)	10 (41.7)	11 (45.8)	9 (45.0)	11 (55.0)
Leukopenia	2 (15.4)	3 (23.1)	0	1 (4.2)	1 (5.0)	1 (5.0)
Thrombocytopenia	1 (7.7)	3 (23.1)	1 (4.2)	2 (8.3)	1 (5.0)	1 (5.0)
Vomiting	0	10 (76.9)	0	12 (50.0)	0	9 (45.0)
Constipation	0	7 (53.8)	0	7 (29.2)	0	6 (30.0)
Nausea	0	7 (53.8)	0	12 (50.0)	0	11 (55.0)
Diarrhea	0	6 (46.2)	0	11 (45.8)	2 (10.0)	14 (70.0)
Fatigue	1 (7.7)	7 (53.8)	1 (4.2)	15 (62.5)	1 (5.0)	5 (25.0)
Decreased appetite	0	5 (38.5)	0	6 (25.0)	0	3 (15.0)
Peripheral neuropathy and peripheral sensory neuropathy	0	3 (23.1)	0	7 (29.2)	0	0
Dysgeusia	0	1 (7.7)	0	5 (20.8)	0	1 (5.0)
Alopecia	0	0	0	14 (58.3)	0	0

[a]AEs were reported for all patients who received at least one dose of study treatment, and throughout the study until 28 days after the last dose of study drug.

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Table 3. TEAEs in part 2

TEAEs preferred term, overall ≥ 20% incidence in ≥ 1 arm	TEAEs, *n* (%)					
	Arm A (*N* = 45)		Arm B (*N* = 46)		Arm C (*N* = 21)	
	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades
Neutropenia	20 (44.4)	25 (55.6)	9 (19.6)	15 (32.6)	7 (33.3)	10 (47.6)
Anemia	7 (15.6)	19 (42.2)	5 (10.9)	12 (26.1)	4 (19.0)	7 (33.3)
Thrombocytopenia	6 (13.3)	14 (31.1)	0	1 (2.2)	1 (4.8)	3 (14.3)
Nausea	0	31 (68.9)	2 (4.3)	24 (52.2)	0	14 (66.7)
Vomiting	2 (4.4)	28 (62.2)	2 (4.3)	16 (34.8)	0	13 (61.9)
Diarrhea	2 (4.4)	22 (48.9)	0	13 (28.3)	0	9 (42.9)
Constipation	2 (4.4)	18 (40.0)	1 (2.2)	20 (43.5)	1 (4.8)	10 (47.6)
Abdominal pain	2 (4.4)	14 (31.1)	1 (2.2)	8 (17.4)	0	3 (14.3)
Fatigue[a]	NR	19 (42.2)	NR	16 (34.8)	NR	5 (23.8)
Asthenia[a]	NR	10 (22.2)	NR	10 (21.7)	NR	8 (38.1)
Decreased appetite[a]	NR	17 (37.8)	NR	11 (23.9)	NR	10 (47.6)
Back pain[a]	NR	12 (26.7)	NR	10 (21.7)	NR	1 (4.8)

Abbreviation: NR, not reported.
[a]Grade 3 or 4 TEAE incidence in 0 or 1 patients.

CC-486 occurred in 28/45 (62.2%) patients in arm A, 26/46 (56.5%) patients in arm B, and 9/21 (42.9%) patients in arm C. Neutropenia was the most common TEAE resulting in dose interruption/reduction (arm A, 44.4%; arm B, 28.3%; and arm C, 14.3%). Other common TEAEs leading to dose interruption/reduction in arm A were thrombocytopenia (22.2%) and vomiting, asthenia, and fatigue (6.7% each).

Pharmacokinetics

CC-486 was rapidly absorbed, and azacitidine T_{max} was attained within approximately 1.0 hours postdose (median) when administered alone or in combination with carboplatin or nab-paclitaxel (Fig. 2). Pharmacokinetic parameters (e.g., T_{max}, AUC, C_{max}, $t_{1/2}$, CL/F, and Vz/F) for the active moiety azacitidine were comparable following administration of CC-486 alone or in combination with carboplatin or nab-paclitaxel (Supplementary Table S6). Pharmacokinetics of carboplatin or nab-paclitaxel were not altered by concomitant CC-486 administration (Supplementary Figs. S1 and S2).

Pharmacodynamics

Global DNA methylation status was analyzed as a measure of CC-486 pharmacological activity. Results from part 1 ($n = 25$) reveal a weak correlation between CC-486 exposure (AUC) and the extent of reduction in CpG methylation (change in GDMS at cycle 1 day 15 vs. baseline; $r = -0.51639$, $P = 0.0069$; Supplementary Fig. S3). In part 2, correlations between GDMS changes versus baseline and clinical efficacy endpoints could not be assessed because of limited numbers of blood and tumor tissue samples for biomarker assessment collected for each treatment arm and tumor cohort. Paired biopsy samples were collected from six NPC patients; however, paired samples from only one patient were analyzed for DNA methylation because of insufficient tumor content in the other pairs of biopsies. For the analyzed NPC patient, the GDMS reduction seen in peripheral blood was concordant with reduction in tumor DNA methylation noted on day 15 (data not shown). Interestingly, this patient achieved prolonged disease control [stable disease (SD) for 330 days] on CC-486 monotherapy.

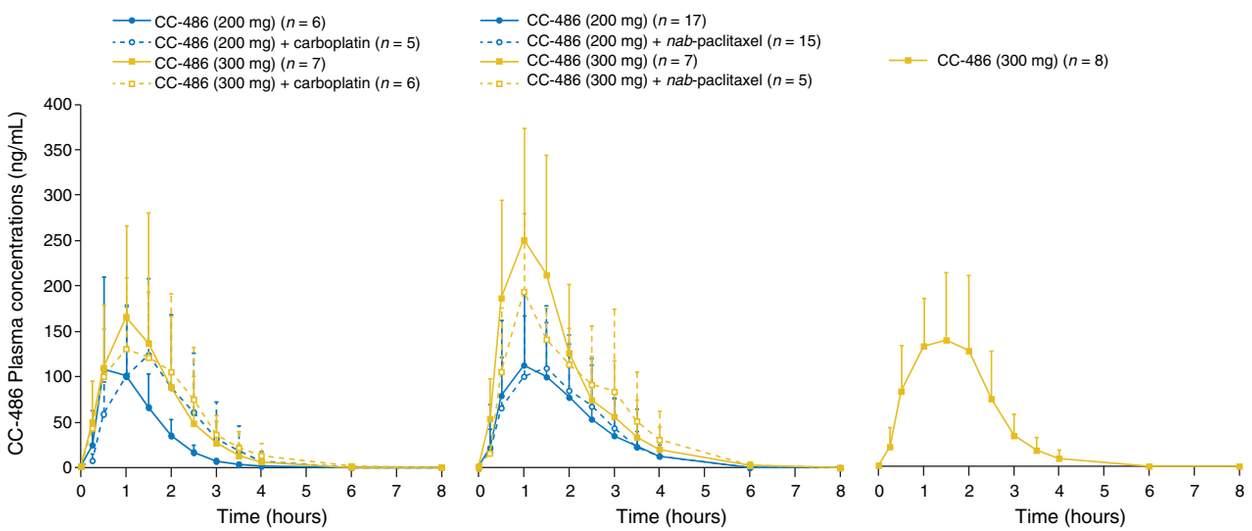

Figure 2.
Mean (±SD) CC-486 plasma concentration versus time profiles following CC-486 administration alone (arm C) or in combination with carboplatin (arm A) or *nab*-paclitaxel (arm B).

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Efficacy

In part 1, across all arms the objective response rate (ORR) was 10.5% (6/57), including one unconfirmed complete response (CR) and three confirmed partial responses (PR) in arm B, and two confirmed PRs in arm C (both in patients with NPC). The DCR (CR + PR + SD) ranged from 53.8% to 65.0%. Progression-free survival (PFS) ranged from 1+ to 1,149 days and overall survival (OS) ranged from 8+ to 1,185+ days.

In part 2, PRs were seen in 3/22 patients with bladder cancer (>94, 189, and 305 days), 2/23 patients (>100 and >225 days) with ovarian cancer (arm A), 2/22 patients (149 and 163 days) with NSCLC (arm B), one/six patients with NPC (370 days), and 1/15 patients (86 days) with OVAT (arm C; Supplementary Table S7). Disease control rates were 83.3% in the NPC cohort, 73.9% in ovarian cancer, 54.5% in NSCLC, 45.8% in pancreatic cancer, 40.0% in OVAT, and 36.4% in bladder cancer. Across all arms, PFS ranged from 1 to 568+ days and OS ranged from 9 to 624+ days.

The results of CC-486 monotherapy (arm C) in patients with NPC were unexpected, so we took a closer look at all patients with NPC across both parts of the study. These patients had failed a median 3.5 lines (range, 2–5) of prior treatment, which included at least one platinum-containing regimen in all cases. Of the eight NPC patients (two in part 1, and six in part 2), three achieved a confirmed PR (332, 370, 456 days), four had a best response of SD (three of which lasted >150 days), and one patient discontinued after two cycles of treatment (on study day 43) because of disease progression. Figure 3 displays the best overall responses and days on study (panel A) and a waterfall plot of percent change in the sum of longest diameters for target lesions (panel B). As of the data cutoff date, January 6, 2015, all eight NPC patients had progressed and none had died. Median PFS for the NPC cohort was 24.00 weeks (95% confidence interval, 5.86–47.43 weeks) and median time on study was 252 days (range, 43–456 days).

Discussion

In this study we investigated the tolerability, pharmacokinetics–pharmacodynamics, and potential antitumor activity of CC-486 alone or in combination with carboplatin or nab-paclitaxel in advanced solid tumors. There was no apparent evidence of a pharmacokinetic interaction between the active moiety azacitidine and either carboplatin or nab-paclitaxel. There were also no new, unique safety concerns or evidence of safety interaction between agents. The occurrence of severe neutropenia beyond cycle 1 in patients receiving CC-486 on an uninterrupted (21/21 day) schedule suggested that a 1-week dosing holiday would be

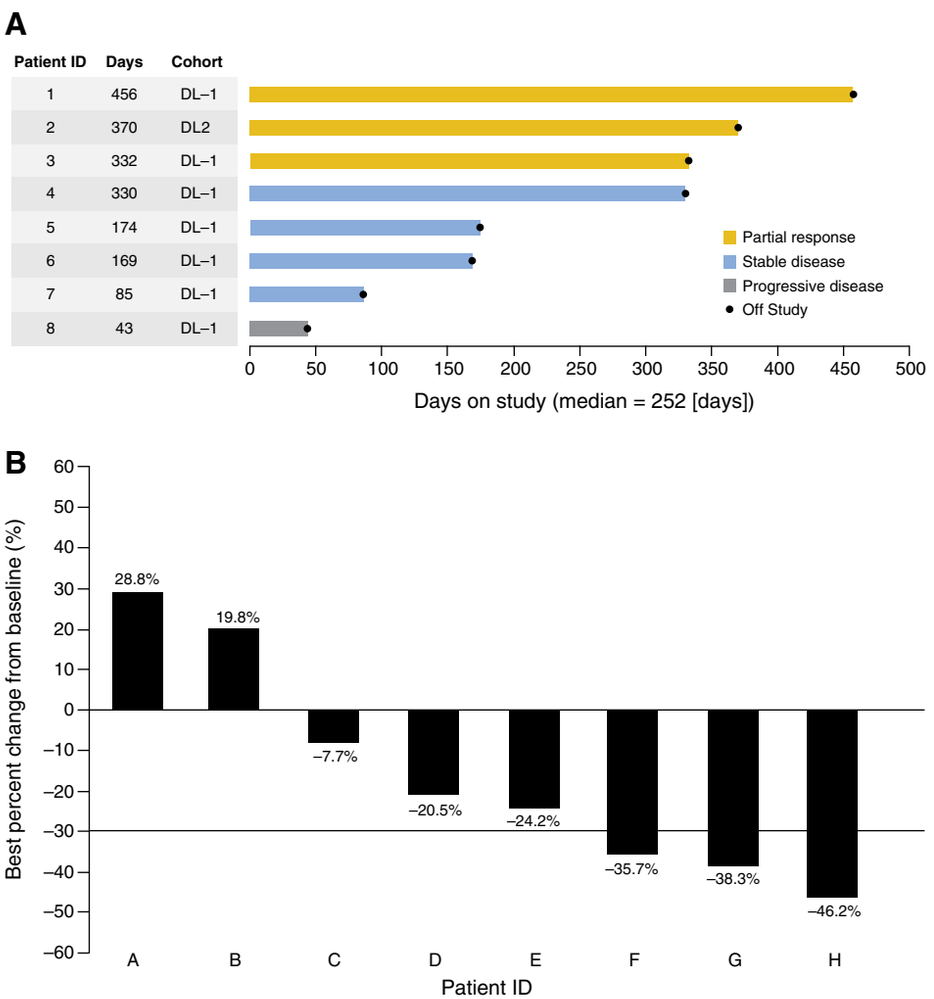

Figure 3.
Preliminary efficacy evaluation of CC-486 in eight patients with NPC. **A,** Investigator-assessed best overall response and days on study for patients with NPC in arm C of study parts 1 and 2. **B,** Waterfall plot of best target lesion response for patients with NPC in arm C of study parts 1 and 2. Percent changes from baseline in the sum of the longest diameter of target lesions are derived by the study sponsor. Only patients with nonmissing values are included in the graph. CC-486 doses were 200 mg every day on days 1 to 21 of each 21-day cycle (DL1), 300 mg daily on days 1 to 21 of each 21-day cycle (DL2), or 300 mg daily on days 1 to 14 of each 21-day cycle (DL–1; determined to be RP2D in part 1). DL, dose level.

necessary to avoid cumulative myelotoxicity, consistent with experience with CC-486 management of MDS/AML. The pharmacologic activity of CC-486 was confirmed in demethylation assays using peripheral blood mononuclear cells from patient whole blood samples and in one on-treatment tumor tissue sample from a patient with NPC.

CC-486 was initially investigated on a regimen consisting of 7 consecutive days/28 days in MDS, chronic myelomonocytic leukemia (CML), and AML (17). The MTD was 480 mg every day, with DLTs (grade 3/4 diarrhea) reported at 600 mg every day (17). Extended dosing of CC-486, out to 14 and 21 days per 28-day cycle at a dose of 300 mg every day was subsequently evaluated in a phase I study of patients with lower-risk MDS. The most frequent grade 3/4 hematologic AE was anemia on the 14-day regimen (14%) and neutropenia on the 21-day regimen (26%; ref. 18). Grade 3 to 4 neutropenia was observed at a rate of 7% on the 14-day regimen (18). CC-486 is currently under investigation in phase III trials at 300 mg every day 14/28 days as maintenance therapy for AML, and at 300 mg every day 21/28 days in lower-risk MDS (22, 23). The aforementioned study of CC-486 monotherapy in hematologic malignancies (ClinicalTrials.gov identifier: NCT00528983; ref. 17) demonstrated sustained demethylation with 14- and 21-day dosing of CC-486 out of a 28-day treatment cycle (24). In that study, patients with a clinical response in cycle 1 had significantly greater reductions in whole blood global DNA methylation than nonresponding patients, with similar trends noted in cycles 2 and 3 (24), suggesting that the extent of DNA demethylation is an important factor in determining the therapeutic response to CC-486. Unfortunately, this study did not provide sufficient patient samples to compare treatment efficacy with the extent of GDMS.

Combining CC-486 with cytotoxic chemotherapy did not appear to enhance response rates. However, the small number of patients per arm, nonrandom assignment of patients to each arm and dose cohort, multiplicity of tumor types, and uncontrolled nature of the study preclude definitive statements regarding the relative clinical benefit of the three treatment regimens tested. A novel preliminary finding was the potential treatment effect of single-agent CC-486 in presumed EBV-associated NPC. Our preliminary results are encouraging, as treatment outcomes for locoregionally advanced or metastatic, relapsed, and refractory NPC remain unsatisfactory. Response rates to conventional cytotoxic therapies for metastatic, recurrent NPC range from approximately 14% to 38% (25, 26). The median survival and PFS are approximately 8 to 14 months and 4 to 6 months, respectively, and the 5-year survival rate after retreatment is only 20%. The potential mechanism of action for CC-486 activity in EBV-associated NPC is its promotion of enhanced tumor immunogenicity by abrogation of viral genome epigenetic silencing (14). Based on these results, a phase II clinical trial of CC-486 in patients with advanced NPC that failed previous platinum chemotherapy (ClinicalTrials.gov identifier: NCT02269943) is currently ongoing.

There is evidence that the programmed death-1/programmed death ligand-1 (PD-1/PD-L1) immune checkpoint pathway is often active and associated with poorer survival in EBV-associated NPC (27). Furthermore, a phase Ib trial recently showed encouraging interim results of anti-PD-1 treatment in patients with relapsed and refractory EBV-associated NPC (ClinicalTrials.gov identifier: NCT02054806; ref. 28). Considering the potential clinical benefit with CC-486 as monotherapy in our study, the combination of CC-486 with immune checkpoint inhibitors could be a promising area of clinical investigation.

In summary, we have established tolerable doses and treatment regimens of CC-486 alone or in combination with carboplatin or nab-paclitaxel, with exploratory analyses supporting additional investigation of CC-486 in NPC.

Disclosure of Potential Conflicts of Interest

D.D. Von Hoff reports receiving commercial research grants from and is a consultant/advisory board member for Celgene. J.A. Lopez-Martin is a consultant/advisory board member for Celgene. M. Martin reports receiving commercial research grants from Novartis and Roche, and is a consultant/advisory board member for Novartis, Genentech, Lilly, and Pfizer. J. DiMartino holds ownership interest (including patents) in Celgene. E. Laille is an employee of and holds ownership interest (including patents) in Celgene. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

Phase I Study of CC-486 Alone and in Combination with Carboplatin or nab-Paclitaxel in Patients with Relapsed or Refractory Solid Tumors

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