



# Phase I Study of Lysine-Specific Demethylase 1 Inhibitor, CC-90011, in Patients with Advanced Solid Tumors and Relapsed/Refractory Non-Hodgkin Lymphoma

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## ABSTRACT

**Purpose:** Lysine-specific demethylase 1 (LSD1) is implicated in multiple tumor types, and its expression in cancer stem cells is associated with chemoresistance. CC-90011 is a potent, selective, and reversible oral LSD1 inhibitor. We examined CC-90011 in advanced solid tumors and relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL).

**Patients and Methods:** CC-90011-ST-001 (NCT02875223; 2015-005243-13) is a phase I, multicenter, first-in-human dose-escalation study. Nine dose levels of CC-90011 (1.25–120 mg) given once per week were explored. Primary objectives were to determine safety, maximum tolerated dose (MTD), and/or recommended phase II dose (RP2D). Secondary objectives were to evaluate preliminary efficacy and pharmacokinetics.

**Results:** Fifty patients were enrolled, 49 with solid tumors (27 neuroendocrine tumors/carcinomas) and 1 with R/R NHL. Median

age was 61 years (range, 22–75). Patients received a median of three (range, 1–9) prior anticancer regimens. The RP2D was 60 mg once per week; the nontolerated dose (NTD) and MTD were 120 mg once per week and 80 mg once per week, respectively. Grade 3/4 treatment-related toxicities were thrombocytopenia (20%; an on-target effect unassociated with clinically significant bleeding), neutropenia (8%; in the context of thrombocytopenia at the highest doses), and fatigue (2%). The patient with R/R NHL had a complete response, currently ongoing in cycle 34, and 8 patients with neuroendocrine tumors/carcinomas had stable disease  $\geq 6$  months, including bronchial neuroendocrine tumors, kidney tumor, and paraganglioma.

**Conclusions:** CC-90011 is well tolerated, with the RP2D established as 60 mg once per week. The MTD and NTD were determined to be 80 mg once per week and 120 mg once per week, respectively. Further evaluation of CC-90011 is warranted.

## Introduction

Histone-modifying enzymes play a critical role in chromatin remodeling and are essential for influencing several genome processes, such as gene expression, and DNA repair and replication (1). Lysine-specific demethylase 1 (LSD1, KDM1A) acts on histone H3, as a transcriptional corepressor through demethylation of lysine 4 and as a transcriptional coactivator through demethylation of lysine

9 (2–5). Histone demethylation by LSD1 plays an essential role in the control of a wide range of biological processes, including regulation of genes involved in pluripotency and lineage commitment in stem cells and during embryonic development (6, 7). The importance of LSD1 in differentiation suggests that dysregulation of LSD1 activity may alter pathways associated with stem cell–like phenotypes (8). In support of this, overexpression of LSD1 has been shown to promote cell proliferation, migration, and invasion in a variety of human cancers (4, 8–14).

In addition to being implicated in the pathogenesis of multiple hematologic malignancies and solid tumors, aberrant expression of LSD1 may impede differentiation and contribute to metastasis and recurrence (3, 9, 14–18). Recent data from an ongoing study (NCT03136185) in patients with high- or intermediate-risk myelofibrosis resistant or intolerant to currently approved therapies showed that the LSD1 inhibitor, IMG-7289, was well tolerated and effective in reducing spleen volume in 6 of 9 (66.7%) evaluable patients, suggesting clinical utility for LSD1 inhibitors (19). These findings highlight the therapeutic potential of LSD1 inhibitors in cancer therapy.

CC-90011 is a potent, selective, oral, and reversible inhibitor of LSD1 that decreased growth of various solid tumor cell lines *in vitro*, including small cell lung cancer (SCLC), neuroendocrine tumors, neuroendocrine carcinomas, and Merkel cell carcinoma cell lines (20). CC-90011 also demonstrated potent antiproliferative activity in a cell line model of acute myeloid leukemia (AML; ref. 20) and antitumor activity in SCLC patient-derived xenografts (Supplementary Fig. S1). The selectivity of CC-90011 for LSD1 over other FAD-containing

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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

There is an unmet need for effective therapies for patients with advanced solid and hematologic malignancies. The histone demethylase lysine-specific demethylase 1 (LSD1) has been implicated in chemoresistance in patients with advanced cancer. In this first-in-human phase I study, we evaluated the safety profile, clinical activity, and pharmacokinetics/pharmacodynamics profile of CC-90011, an oral, potent, selective, and reversible inhibitor of LSD1, in patients with advanced solid tumors and relapsed/refractory non-Hodgkin lymphoma. CC-90011 monotherapy was well tolerated; most adverse events were mild or moderate, reversible, and easily managed with dose modifications. CC-90011 showed promising antitumor activity, particularly in patients with neuroendocrine neoplasms. The long terminal half-life of CC-90011 enabled less frequent dosing and the pharmacodynamics data showed significant target engagement of CC-90011 at doses below the MTD. These results support further exploration of CC-90011 as monotherapy or in combination with other therapeutic agents in patients with advanced malignancies.

enzymes (LSD2, MAO-A, and MAO-B) is greater than 60,000-fold, as demonstrated by the potent activity and low  $IC_{50}$  value observed with CC-90011 in AML cells versus normal human fibroblasts ( $IC_{50}$  of 0.0024 vs.  $>10 \mu\text{mol/L}$ ; Supplementary Fig. S2), further supporting LSD1 as a therapeutic target. We report herein, the safety and tolerability results from a first-in-human, phase I, dose-escalation study of CC-90011.

## Patients and Methods

### Study design and patients

CC-90011-ST-001 (NCT02875223; 2015-005243-13) is a phase I, open-label, multicenter study of CC-90011 for treatment of patients with advanced or unresectable solid tumors or relapsed and/or refractory (R/R) non-Hodgkin lymphoma (NHL). The two-part study consists of a dose-escalation phase (part A) reported here and a dose-expansion phase (part B), for which initial efficacy results are reported herein, and complete results will be reported separately. 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 the International Council for Harmonisation E6 guidelines. The protocol was reviewed and approved by each site's institutional review board or independent ethics committee before initiation of the study, and all patients provided written informed consent.

The primary objectives were to determine the safety and tolerability of CC-90011 per NCI Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, the maximum tolerated dose (MTD), the nontolerated dose (NTD), and/or the recommended phase II dose (RP2D). Secondary objectives were to evaluate the preliminary antitumor activity and characterize the pharmacokinetics and pharmacodynamics of CC-90011.

Eligible patients were aged  $\geq 18$  years with histologically or cytologically confirmed advanced or unresectable solid tumors (enriched for grade 2 or 3 neuroendocrine tumors/carcinomas, SCLC, and other neuroendocrine carcinoma) or R/R advanced NHL [diffuse large B-cell lymphoma, follicular lymphoma, and marginal zone lymphoma (MZL)], including those who have progressed on standard anticancer therapy or for whom no other approved conventional therapy exists.

Patients with solid tumors had to have  $\geq 1$  site of measurable disease per RECIST 1.1. Patients with NHL had to have  $\geq 1$  site of measurable disease per International Working Group (IWG) criteria (21).

Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, hepatic, and renal function. Exclusion criteria included grade 1 neuroendocrine tumors/carcinomas, including carcinoids ( $< 2$  per high-powered field or  $< 2$  per  $\text{mm}^2$  and/or  $\leq 2\%$  Ki67 index); prior autologous hematologic stem cell transplant within  $\leq 3$  months of receiving the first dose of study treatment; prior allogeneic stem cell transplant with either standard or reduced intensity conditioning; history of persistent diarrhea due to malabsorption syndrome of grade  $\geq 2$  that would interfere with the absorption, distribution, metabolism, or excretion of CC-90011; any grade  $> 2$  hemorrhage/bleeding event; a history of unstable central nervous system metastases (progressive neurologic symptoms regardless of whether the patient was untreated or received treatment); concurrent secondary cancers requiring ongoing systemic treatment; and impaired cardiac function or clinically significant cardiac diseases.

### Treatment

CC-90011 was administered orally once per week in each 4-week cycle. The study examined nine escalating dose levels of CC-90011: 1.25, 2.5, 5, 10, 20, 40, 60, 80, and 120 mg. Inpatient dose escalation was not allowed during the dose-limiting toxicity (DLT) assessment period; however, in cycles  $\geq 3$ , patients without evidence of disease progression who tolerated their assigned dose could escalate to the highest dose level shown to be adequately tolerated by  $\geq 1$  dose cohort of patients in this study. Dose interruptions were permitted if any treatment-related grade  $\geq 2$  toxicities were not resolved to grade  $\leq 1$  before the next scheduled dose. Toxicity leading to treatment discontinuation was assessed on a case-by-case basis by the treating physician. Patients who experienced drug-related toxicity that required two dose reductions or dose interruption lasting  $> 4$  weeks were discontinued.

During part A of the study, an adaptive Bayesian logistic regression model (BLRM) utilizing escalation with overdose control (EWOC) guided the CC-90011 dosing decisions (22, 23). *In vivo* CC-90011 toxicity studies were conducted in mice (dosed 5/7 days) and in dogs (dosed once per week for 4 weeks). Dogs were more sensitive to the toxicities associated with CC-90011 administration based on the doses and exposures at which the principal treatment-related adverse events (AE) occurred.

The starting human dose (1.25 mg CC-90011 on a once per week schedule) was proposed on the basis of the *in vivo* studies and was calculated using the approach described in the International Conference on Harmonisation Guidance on S9 Nonclinical Evaluation for Anticancer Pharmaceuticals (24). A minimum of 3 patients were enrolled at each dose level. After each cohort completed cycle 1 and the DLT data became available, the BLRM was updated and calculated the posterior probabilities of the true rate of DLT at each dose level in each of the following intervals: underdosing (0–0.16), targeted toxicity (0.16–0.33), and excessive toxicity (0.33–1.00). The parameters of the prior distributions of model parameters were selected on the basis of the method described previously (22). The recommended dose had the highest posterior probability of the DLT rate falling in the target interval. The decision to determine the next dose was based on the integration of the information from the adaptive Bayesian model and the clinical assessment of the toxicity profiles observed at the time of the analysis. The final decisions for the next dose were made by the safety review committee based on the dose recommendations from

BLRM and the review of the available safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy data.

Compared with traditional dose-escalation approaches, BLRM utilizes a flexible statistical model to describe the relationship between dose and dose toxicity. The simulation indicated that BLRM tended to treat patients at doses close to the MTD with more accurate estimation of MTD, whereas 3+3 design approach treated a higher proportion of patients at low, possibly ineffective doses.

### Study assessments

AEs and DLTs were assessed during cycle 1 (up to 28 days). AEs were graded according to NCI CTCAE, version 4.03. DLTs were defined as follows: febrile neutropenia of any grade or grade 4 neutropenia lasting >7 days; grade 4 thrombocytopenia lasting >7 days or grade  $\geq 3$  thrombocytopenia with clinically significant bleeding; any grade 4 nonhematologic toxicity and grade  $\geq 3$  nonhematologic toxicity, except for grade 3 gastric distress (diarrhea, nausea, or vomiting lasting  $\leq 3$  days), grade 3 rash (of the acneiform, pustular, or macropapular type), and fatigue that resolves to grade  $\leq 2$  within 7 days of dose interruption; and any AE that led to a dose level reduction. The MTD was defined as the highest dose at which less than 33% of the population treated with CC-90011 had a DLT in the first cycle, with  $\geq 6$  evaluable patients having been treated at this dose.

Serial blood samples for pharmacokinetics analysis were collected following dosing on day 1 (30 minutes prior to dose and 1, 2, 4, 6, 8, and 11 hours postdose), on days 2–4, and on day 22 of cycle 1. The relative dose intensity was the actual dose intensity divided by the planned dose intensity. The pharmacodynamics biomarkers of CC-90011 [monocyte to macrophage differentiation-associated (MMD) and chromogranin A (CgA)] were assessed on days 1 ( $\leq 3$  hours predose), 3, 5, 8 ( $\leq 3$  hours predose), and 24 of cycle 1. Tumor assessments (CT scans) were performed after every two cycles through cycle 6, and then after every three cycles until disease progression; neuroendocrine tumors and neuroendocrine carcinomas were assessed for neuroendocrine markers at baseline and on-study. Responses were assessed per RECIST 1.1 for solid tumors and per IWG criteria for NHL (25). PET/CT imaging interpretation was conducted according to Deauville criteria (20, 21, 26).

### Statistical analyses

An adaptive BLRM utilizing EWOC guided the CC-90011 dosing decisions and estimated the MTD. No formal statistical power calculations to determine sample size were performed for this study. The treated population consists of all patients who received  $\geq 1$  dose of CC-90011. Efficacy evaluable patients were those who had  $\geq 1$  tumor response assessment after completing  $\geq 1$  treatment cycle. DLT-evaluable patients were those who experienced a DLT after receiving  $\geq 1$  dose of CC-90011 or who received  $\geq 75\%$  of the total planned dose during cycle 1 without experiencing a DLT. The pharmacokinetics population includes patients who received  $\geq 1$  dose of CC-90011 and had evaluable concentration data to determine pharmacokinetics parameters. Plasma pharmacokinetic parameters, such as area under the concentration-time curve (AUC), time to maximum concentration ( $C_{max}$ ), terminal half-life ( $t_{1/2}$ ), apparent total body clearance, and apparent volume of distribution of CC-90011, were calculated by the noncompartmental analysis method from the plasma concentration-time profiles of CC-90011. Biomarker evaluable patients were those who received  $\geq 1$  dose of CC-90011 and had  $\geq 1$  biomarker assessment. Comparison of biomarker levels before and during treatment was performed by Wilcoxon signed-rank test. Study data were summarized for disposition, demographic and baseline characteristics, exposure,

efficacy, safety, pharmacokinetics, and pharmacodynamics. Categorical data were summarized by frequency distributions and continuous data were summarized by descriptive statistics. All statistical analyses were conducted using SAS version 9.3 or higher.

## Results

### Patients and treatment

Between August 2016 and July 2018, 50 patients were enrolled and treated in the dose-escalation phase of the study. On the basis of preclinical evidence suggesting anticancer activity in neuroendocrine tumors/carcinomas and the availability of the neuroendocrine biomarker, CgA, the study was enriched for patients with neuroendocrine tumors/carcinomas. One patient had R/R transformed MZL and 49 patients had advanced and/or unresectable solid tumors, including 27 (54%) with neuroendocrine tumors or neuroendocrine carcinomas. Of the 34 patients with neuroendocrine tumors/carcinomas enrolled in dose-escalation and dose-expansion phases, 29 were considered low grade (grade 1 or 2), 5 were considered high grade (grade 3), and 22 had a bronchial histology. All patients with neuroendocrine tumors/carcinomas were treated with various therapeutic options that are typically used for neuroendocrine neoplasms (NEN) and progressed on these previous therapies.

As of the May 3, 2019 data cutoff, 35 patients (70%) had discontinued the study and 46 patients (92%) had discontinued treatment; 15 patients (30%) were ongoing, including 4 still receiving study treatment. The most common reasons for treatment discontinuation were disease progression [ $n = 37$  (74%)] and AEs [ $n = 3$  (6%)]. Reasons for study discontinuation were disease progression [ $n = 31$  (62%)], withdrawal by patient [ $n = 3$  (6%)], and other [noncompliance;  $n = 1$  (2%)]. Patient demographics and baseline characteristics are shown in **Table 1**. The median age was 61 years (range, 22–75), and the median number of prior systemic anticancer therapies was 3 (range, 1–9); more than half of patients (58%) had received at least three prior therapies.

Patients received a median of 2 (range, 1–26) treatment cycles. The average number of cycles was 4.7, and 8 patients (16%) received >6 treatment cycles, including 1 who received 33 cycles (Supplementary Table S1). The median duration of study treatment for the overall population was 8.3 weeks (range, 1–110), and the mean relative dose intensity was 104.8% (standard deviation, 69%). Eleven patients (22%) had a CC-90011 dose reduction of the initially assigned dose, mainly due to the on-target thrombocytopenia; this result is consistent with the cellular function of LSD1 as a key regulator of platelet maturation (27, 28). Five patients (10%) had a dose escalation; 2 patients were escalated from 5 to 40 mg, 1 patient escalated from 20 to 80 mg, and 2 patients escalated from 40 to 80 mg. Eighteen patients (36%) had CC-90011 dose interruptions. These were typically of approximately 1 week in duration and mostly to manage reversible and on-target thrombocytopenia.

### Safety

Among all-causality treatment-emergent AEs, the most common events of any grade were thrombocytopenia (46%), vomiting (28%), anemia (26%), and fatigue (26%); the most common grade 3/4 AEs were thrombocytopenia (24%) and neutropenia (8%; in the context of clinically significant thrombocytopenia and at the higher dose levels; Supplementary Table S2). Thirty-four patients (68%) had a treatment-related AE. The most common treatment-related AEs and the only grade 3/4 treatment-related toxicities were thrombocytopenia (40%; grade 3/4, 20%), fatigue/asthenia (16%; grade 3/4, 2%), and

**Table 1.** Patient baseline characteristics.

Characteristic	Overall (N = 50)
Median (range) age, y	61 (22, 75)
Age ≥65 years, n (%)	19 (38.0)
Male, n (%)	26 (52.0)
ECOG PS, n (%)	
0	19 (38.0)
1	31 (62.0)
Tumor type, n (%)	
NHL	1 (2.0)
Solid tumor	49 (98.0)
NET/NEC	27 (54.0)
Bronchial NET	4 (8.0)
Bronchial NEC	5 (10.0)
Prostate	5 (10.0)
SCLC	2 (4.0)
Other <sup>a</sup>	11 (22.0)
Solid tumor stage IV, n/N (%)	43/49 (87.8)
Median (range) no. of prior systemic anticancer therapies	3 (1–9)
No. prior systemic anticancer therapies, n (%)	
1	2 (4.0)
2	17 (34.0)
≥3	29 (58.0)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor.

<sup>a</sup>Tumor types listed as other included cervical, urinary bladder, medullary thyroid cancer, and Merkel cell carcinoma.

neutropenia (12%; grade 3/4, 8%; **Table 2**). Neutropenia occurred only after clinically significant thrombocytopenia and at the highest dose levels of CC-90011. Incidence of thrombocytopenia, an on-target effect, correlated with dose level, with events occurring at higher doses only and usually around cycle day 15 (Supplementary Fig. S3). The median duration of thrombocytopenia was 7.5 days. Overall, 21 patients (42%) experienced a serious AE, and 4 patients (8%) had a serious AE considered to be treatment related (all 4 had serious AEs of thrombocytopenia; 1 patient also had neutropenia). Twenty-six patients died during the study, all because of progressive disease. Among the 47 DLT evaluable patients, 7 (15%) had a DLT. Throm-

**Table 2.** Treatment-related AEs occurring in >1 patient.

Characteristic	Any grade (N = 50)	Grade 3/4 (N = 50)
≥1 TRAE, n (%)	34 (68.0)	11 (22.0)
Thrombocytopenia	20 (40.0)	10 (20.0)
Fatigue/asthenia	8 (16.0)	1 (2.0)
Neutropenia <sup>a</sup>	6 (12.0)	4 (8.0)
Vomiting	3 (6.0)	0
Constipation	2 (4.0)	0
Nausea	2 (4.0)	0
Decreased appetite	2 (4.0)	0
Dysgeusia	2 (4.0)	0
Conjunctival hemorrhage	2 (4.0)	0
Pruritus	2 (4.0)	0
Rash maculopapular	2 (4.0)	0

Abbreviation: TRAE, treatment-related AE.

<sup>a</sup>Neutropenia only occurred after clinically significant thrombocytopenia and not as an isolated event.

bocytopenia was the only DLT reported, and all DLTs were reversible and easily manageable (**Table 3**). As of August 30, 2018, dose escalation was completed, and the primary objective of the study was met with an RP2D of 60 mg once per week established. The NTD and MTD were determined to be 120 mg once per week and 80 mg once per week, respectively.

### Efficacy

Of the 34 patients with neuroendocrine tumors/carcinomas enrolled in dose escalation and dose expansion, 8 (24%; 28% of patients with low-grade neuroendocrine tumors/carcinomas) had stable disease (SD) >6 months. Prolonged SD (≥4 months) was most frequently observed in low-grade tumors treated with CC-90011 >40 mg, particularly in those with bronchial neuroendocrine tumors (*n* = 6). Prolonged SD was also observed in 1 patient with renal neuroendocrine tumors and 1 patient with paraganglioma. A reduction in the target lesion size of up to approximately 30% was observed in a majority of neuroendocrine tumors/carcinomas treated with CC-90011 >40 mg (**Fig. 1**). Among the 5 ongoing patients with SD who received escalating doses of CC-90011, 2 remained in SD beyond 20 cycles of treatment, 1 of whom with bronchial neuroendocrine tumor is currently in cycle 33. Notably, a patient with R/R NHL achieved a durable complete response as early as the first assessment and is currently ongoing in cycle 27.

### Pharmacokinetics, pharmacodynamics, and biomarker analysis

All patients were evaluable for pharmacokinetics and pharmacodynamics. The  $C_{max}$  was observed 2–4 hours postdose across the dose groups (**Fig. 2A**); pharmacokinetic parameters are summarized in **Fig. 2B–E**. Drug accumulation was limited, with a mean accumulation ratio of 1.01 for the AUC (range across dose levels, 0.66–1.32) and 1.14 for  $C_{max}$  (range across dose levels, 1.1–1.57) upon repeated once per week dosing. At the RP2D of 60 mg once per week, the average  $t_{1/2}$  of CC-90011 in plasma was approximately 66 and 61 hours on days 1 and 22, respectively. Increases in CC-90011 plasma exposure for both  $C_{max}$  and AUC on days 1 and 22 were dose proportional across the approximately 100-fold dose range (Supplementary Fig. S4).

Preliminary findings suggest that downregulation MMD RNA is a marker of target engagement by CC-90011 (29). Overall decreases in MMD RNA of ≥50% were observed in patient blood samples at doses ≥60 mg once per week (**Fig. 3A**). In addition, blood pharmacodynamics analyses revealed a decrease in levels of the neuroendocrine peptide, CgA, in patients (*n* = 14) with neuroendocrine tumors and neuroendocrine carcinomas following treatment with CC-90011 at doses ≥2.5 mg once per week (**Fig. 3B**). CgA is currently used to help diagnose neuroendocrine tumors and neuroendocrine carcinomas, and decreased circulating CgA may be predictive of response to therapy in these patients (30). In support of this, a CgA nadir less than 50% of baseline was associated with longer time on treatment. Moreover, lower CgA nadir values were associated with SD >6 months in patients with neuroendocrine tumors and neuroendocrine carcinomas (**Fig. 3C and D**).

### Discussion

This first-in-human, phase I, dose-escalation study examined CC-90011 in heavily pretreated patients with advanced, unresectable solid tumors and R/R NHL. The primary objective of the study was met with an RP2D of 60 mg once per week; the MTD and NTD were determined to be 80 mg once per week and 120 mg once per week, respectively. The RP2D of 60 mg once per week enabled high patient

**Table 3.** DLTs.

CC-90011 dose	AE	Accompanying neutropenia	Platelet transfusion	Day of nadir on cycle 1
120 mg	Grade 3 thrombocytopenia	Grade 2	No	15
120 mg	Grade 3 thrombocytopenia	None	No	15
120 mg	Grade 4 thrombocytopenia	Grade 4	Yes	15
120 mg	Grade 4 thrombocytopenia	Grade 2	Yes	12 and 15
80 mg <sup>a</sup>	Grade 4 thrombocytopenia	Grade 4	Yes	25 (and C2D1)
80 mg <sup>a</sup>	Grade 3 thrombocytopenia	Grade 3	No	15
60 mg	Grade 4 thrombocytopenia	None	Yes	15

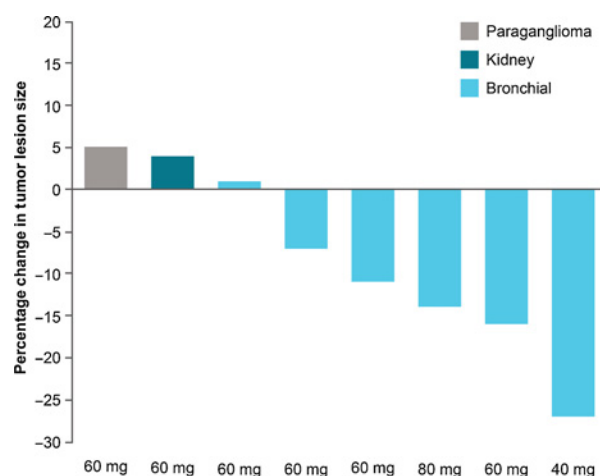
Abbreviations: C, cycle; D, day.

<sup>a</sup>Originally assigned to the 120-mg cohort at screening. Because of unacceptable toxicity (grade 3/4 thrombocytopenia) observed in 4 patients treated with 120 mg, the patients were reduced to 80 mg once per week.

compliance and this weekly oral dose is an ideal long-term treatment, as evidenced by the low frequency of dose reductions (occurring in 1 patient, 17%) and long treatment duration of ≥33 months in some patients.

CC-90011 was very well tolerated in this patient population. Most AEs were mild or moderate, reversible, and easily managed with dose modifications. The most frequent toxicity, and the only DLT reported, was thrombocytopenia. This is consistent with the cellular function of LSD1, as a key regulator of platelet maturation (27). Knockdown of LSD1 causes a block in the terminal platelet maturation step leading to thrombocytopenia with accumulation of megakaryocytes in the bone marrow in preclinical models (27). LSD1 inhibition affects the late-stage megakaryocyte maturation, namely the budding of platelets from the megakaryocytes (28).

Thrombocytopenia was also reported as a DLT with another LSD1 inhibitor, ORY-1001, along with lobar pneumonia and febrile neutropenia (31, 32). In our study, no febrile neutropenia was observed and the thrombocytopenia reported was reversible, manageable, and typically for ≤1 week in duration. The patient with prolonged treatment duration of 33 cycles reported very good tolerability with only occasional, mild episodes (grade ≤2) of thrombocytopenia.



**Figure 1.**

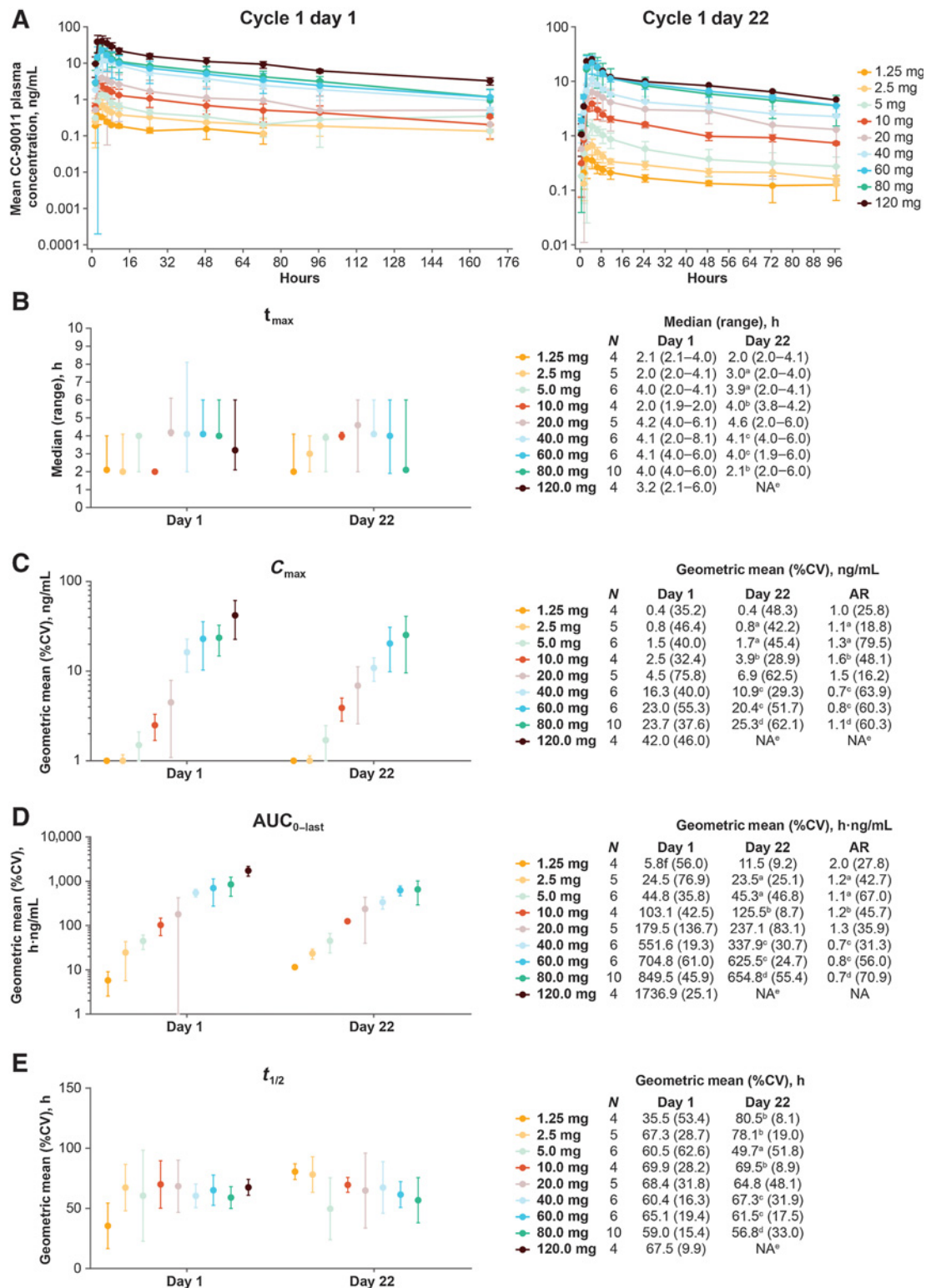
Best change in tumor burden in response to CC-90011. Changes in tumor lesion size are shown in reference to baseline in patients with neuroendocrine tumors/carcinomas with SD >6 months, enrolled in part A and B of the study. Each bar represents an individual patient. NEC, neuroendocrine carcinoma; NET, neuroendocrine tumors. Data cutoff: July 20, 2020.

The patients in this study were heavily pretreated with a median of 3 (range, 1–9) prior systemic regimens. On the basis of preclinical data and early efficacy signals, this study was enriched for patients with grade 2 or 3 bronchial neuroendocrine tumors and grade 3 prostate neuroendocrine carcinomas. For patients with bronchial neuroendocrine tumors, surgery remains the mainstay of treatment when feasible and there is no consensus regarding the recommended management approaches for unresectable advanced or metastatic disease owing to a lack of prospective clinical trials in this patient population (34). Systemic therapies for patients with advanced neuroendocrine tumors include somatostatin analogues (octreotide and lanreotide), targeted therapy (everolimus and sunitinib), IFN, and cytotoxic chemotherapy (34–36). Because the therapies in the R/R population usually produce response rates in <10% of patients, there is an unmet need for novel approaches to treat patients with advanced and progressive neuroendocrine tumors or neuroendocrine carcinomas (33). LSD1 overexpression has been reported in neuroendocrine tumors and neuroendocrine carcinomas; therefore, LSD1 inhibitors may be effective in these patients (9, 37). CC-90011 demonstrated preliminary efficacy in this difficult-to-treat population. Initial results from the dose-expansion portion of the study demonstrated that 8 patients with bronchial neuroendocrine tumors achieved SD lasting >6 months with good tolerance and clinical benefit.

R/R MZL represents a clinical challenge because it is a rare disease, no standard treatment strategy exists, and there is a paucity of clinical data; therefore, further clinical investigation is needed to optimize therapeutic approaches in MZL (38). Treatment across MZL subtypes range from autologous hematopoietic stem cell transplantation, ibrutinib monotherapy, and single-agent chemotherapy to combination therapies consisting of rituximab and chemotherapy-containing regimen (39–42). The patient with R/R NHL (transformed MZL) achieved a durable complete response, confirmed per IWG criteria, and is currently ongoing in cycle 34. This patient presented with a left inguinal node (detected with physical examination and confirmed by PET/CT scan) and had received six prior lines of therapy. After two cycles of CC-90011, the inguinal node was not detected by physical examination and a complete metabolic response was confirmed by PET/CT scan after four cycles. On the basis of the response observed, a cohort of patients with MZL is currently being recruited for part B of this study. These results are supported by previous reports of LSD1 overexpression in NHLs and the role of LSD1 in B-cell differentiation (43, 44).

In this study, CC-90011 pharmacokinetics parameters were dose proportional and time invariant. The long  $t_{1/2}$  of CC-90011 supports

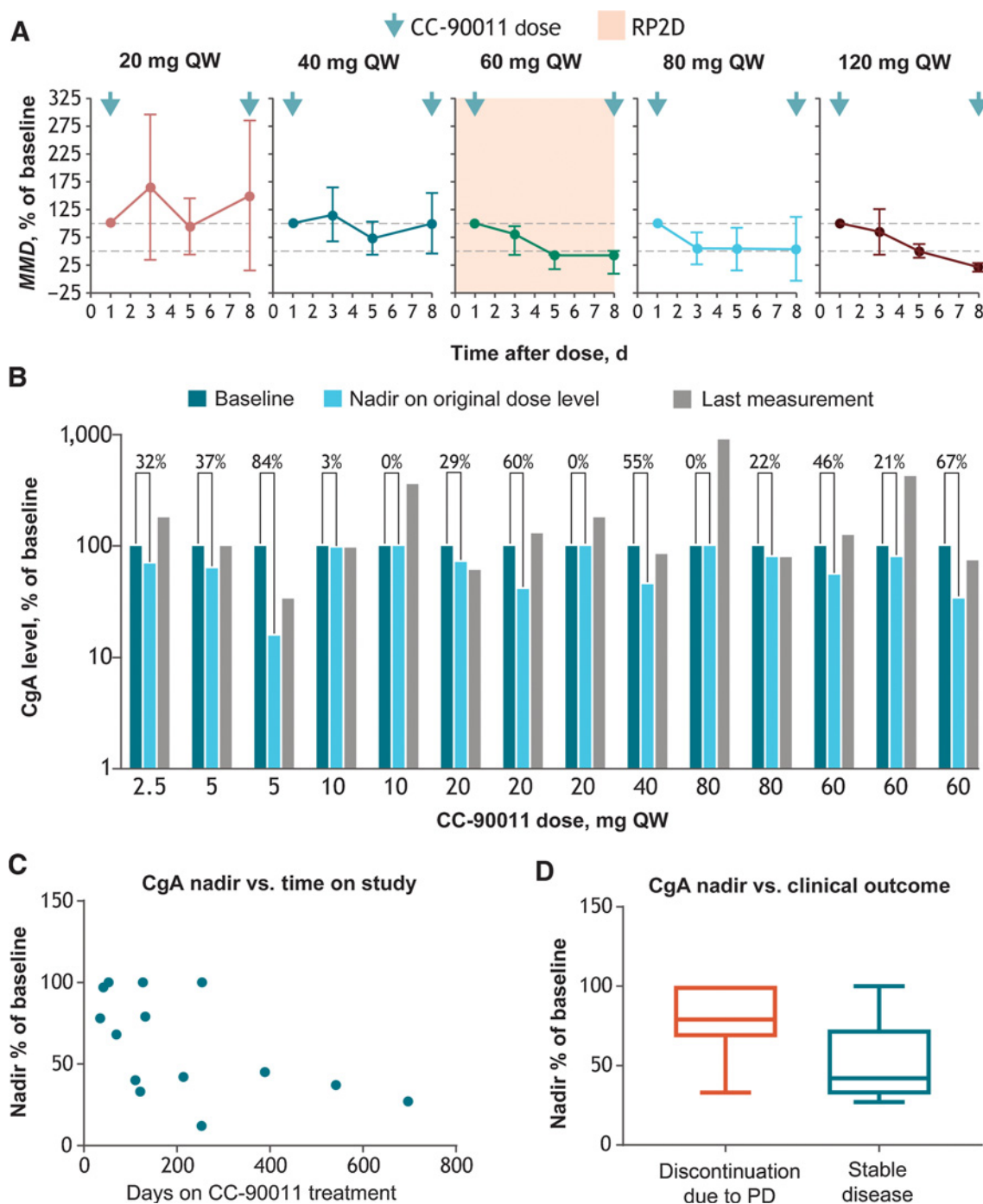
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**Figure 2.** Summary of CC-90011 pharmacokinetics parameters by dose level. Mean CC-90011 concentration-time profiles on a logarithmic scale (A) and pharmacokinetics parameters on days 1 and 22 of cycle 1 for  $T_{max}$  (B),  $C_{max}$  (C),  $AUC_{0-last}$  (D), and terminal  $t_{1/2}$  (E). Error bars in A represent standard deviation. AR, accumulation ratio (day 22/day 1);  $AUC_{0-last}$ , AUC from time zero to last measured time point; NA, not available;  $t_{max}$ , time to  $C_{max}$ . <sup>a</sup>N = 4. <sup>b</sup>N = 3. <sup>c</sup>N = 5. <sup>d</sup>N = 9. <sup>e</sup>Data for only 1 patient in the 120 mg cohort (who received a reduced dose of 100 mg) was obtained at day 22; therefore, no summary statistics are reported. <sup>f</sup> $AUC_{0-t}$  on day 1 represents AUC up to 24 hours postdose for the 1.25-mg dose level. CV, coefficient of variation.

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**Figure 3.** Peripheral blood pharmacodynamics markers of LSD1 inhibition. Percentage change from baseline in MMD in the biomarker-evaluable population (A) and CgA ( $n = 14$ , local laboratory measurements; B). The percentages represent the difference in CgA from baseline to nadir at the original dose level. CgA nadir in relation to time on study ( $n = 14$ ; C) and in association with clinical outcome at 6 months ( $n = 11$ ; D). MMD, monocyte to macrophage differentiation-associated; PD, progressive disease; QW, once weekly. Data cutoff: January 28, 2019.

once per week dosing. Early blood biomarker data demonstrated that CC-90011 decreased levels of the neuroendocrine peptide, CgA, at dose levels  $\geq 2.5$  mg once per week and decreased expression of a blood pharmacodynamics marker, MMD, by  $\geq 50\%$  at doses  $\geq 60$  mg once per week. These data suggest that target engagement

activity can be observed with CC-90011 at doses below the MTD of 80 mg once per week, further supporting the RP2D of 60 mg once per week.

In conclusion, CC-90011 was very well tolerated, and demonstrated favorable pharmacokinetics and sufficient target engagement in

peripheral blood and in neuroendocrine tumor markers. In addition, CC-90011 showed promising preliminary antitumor activity, particularly in patients with bronchial neuroendocrine tumors. Taken together, these results indicate that further investigation of CC-90011 is warranted. Enrollment for part B of this study is ongoing in several indications, including bronchial NEN and MZL; therefore, the completed results from dose expansion will be reported separately.

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