Original Article

Clinical activity of CC-90011, an oral, potent, and reversible LSD1 inhibitor, in advanced malignancies

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BACKGROUND: CC-90011 is an oral, potent, selective, reversible inhibitor of lysine-specific demethylase 1 (LSD1) that was well tolerated, with encouraging activity in patients who had advanced solid tumors or relapsed/refractory marginal zone lymphoma. The authors present long-term safety and efficacy and novel pharmacodynamic and pharmacokinetic data from the first-in-human study of CC-90011. **METHODS:** CC-90011-ST-001 (ClincalTrials.gov identifier NCT02875223; Eudract number 2015–005243-13) is a phase 1, multicenter study in which patients received CC-90011 once per week in 28-day cycles. The objectives were to determine the safety, maximum tolerated dose, and/or recommended phase 2 dose (primary) and to evaluate preliminary efficacy and pharmacokinetics (secondary). **RESULTS:** Sixty-nine patients were enrolled, including 50 in the dose-escalation arm and 19 in the dose-expansion arm. Thrombocytopenia was the most common treatment-related adverse event and was successfully managed with dose modifications. Clinical activity with prolonged, durable responses were observed, particularly in patients who had neuroendocrine neoplasms. In the dose-escalation arm, one patient with relapsed/refractory marginal zone lymphoma achieved a complete response (ongoing in cycle 58). In the dose-expansion arm, three patients with neuroendocrine neoplasms had stable disease after nine or more cycles, including one patient who was in cycle 46 of ongoing treatment. CC-90011 decreased levels of secreted neuroendocrine peptides chromogranin A, progastrin-releasing peptide, and RNA expression of the blood pharmacodynamic marker *monocyte-to-macrophage differentiation–associated*. **CONCLUSIONS:** The safety profile of CC-90011 suggested that its reversible mechanism of action may provide an advantage over other irreversible LSD1 inhibitors. The favorable tolerability profile, clinical activity, durable responses, and once-per-week dosing support further exploration of CC-90011 as monotherapy and in combination with other treatments for patients with advanced solid tumors and other malignancies. ***Cancer* 2022;128:3185-3195**.

KEYWORDS: CC-90011, epigenetic repression, lysine-specific demethylase 1 (LSD1) inhibitor, neuroendocrine tumor, non-Hodgkin lymphoma, pulrodemstat besilate.

INTRODUCTION

Lysine-specific demethylase 1 (LSD1/KDM1A) is an epigenetic eraser that can modulate transcription through histone demethylation.[1–4] Histone demethylation by LSD1 plays an essential role in controlling wide-ranging biologic processes, including the regulation of genes involved in pluripotency and lineage commitment in stem cells and during embryonic development.[4–6] Overexpression of LSD1 may impede cell differentiation and contribute to metastasis and disease recurrence,[7–10] and its aberrant activity and/or expression plays a role in promoting cell proliferation, migration, and invasion in a variety of human cancers.[8,9,11,12] LSD1 dysregulation has been observed both in hematologic malignancies and in solid tumors,[7,9,13–15] including neuroendocrine neoplasms (NENs).[16,17] LSD1 is expressed in >25% of patients with mature B-cell non-Hodgkin lymphoma (NHL) and is in germinal centers.[18,19] Although aberrant expression is less common

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in low-grade disease, a greater proportion of patients with high-grade NHL express LSD1.[18] These findings highlight the therapeutic potential of LSD1 inhibitors for the treatment of oncologic malignancies.

CC-90011 is a potent, selective, and reversible oral LSD1 inhibitor[20] that has been shown to increase expression of tumor-suppressing genes and decrease expression of tumor-promoting genes, leading to decreased tumor cell growth.[21] CC-90011 has demonstrated antiproliferative activity in cancer cell lines and in patient-derived xenograft models.[20] CC-90011 has antiproliferative activity in various solid tumor cell lines in vitro, including small cell lung cancer (SCLC; a type of NEN), and in acute myeloid leukemia cell lines.[20]

CC-90011-ST-001 is a first-in-human dose-escalation and dose-expansion study. Primary results from this study demonstrated that CC-90011 is well tolerated, with the recommended phase 2 dose (RP2D) established as 60 mg once per week. The maximum tolerated dose and nontolerated dose were determined to be 80 and 120 mg once per week, respectively. Notably, in the dose-escalation arm of the study, a patient with relapsed/refractory (R/R) marginal zone lymphoma (MZL) achieved a durable complete response (CR) with CC-90011 monotherapy, a patient with a solitary fibrous tumor achieved a partial response (PR), and seven patients with NENs had stable disease (SD) for ≥6 months, including bronchial neuroendocrine tumors, kidney tumors, and paraganglioma.

Here, we report long-term results from the dose-escalation (with ≥60 months of follow-up) and dose-expansion arms of this study that included patients who had advanced NENs and R/R MZL. In addition, we provide further characterization of drug exposure through detailed pharmacokinetic and pharmacodynamic analyses.

MATERIALS AND METHODS

Study design and patients

CC-90011-ST-001 (ClincalTrials.gov identifier NCT02875223; Eudract number 2015–005243-13) is a phase 1, open-label, multicenter study of CC-90011 for the treatment of patients with advanced or unresectable solid tumors, including NENs and R/R NHL. This study consists of two parts: a dose-escalation arm, as reported previously,[22] and a dose-expansion arm (see Figure S1). Results for dose expansion and long-term follow-up of dose escalation are reported here. The study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki and in adherence to Good Clinical Practice as described in International Council for Harmonization Guideline E6. 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.

Eligible patients for dose escalation have been previously described.[22] Patients who were eligible for dose expansion were aged 18 years or older who had histologic or cytologic confirmation of NENs or R/R NHL. Patients with NENs had low-grade or intermediate-grade lung NEN (including typical carcinoid and atypical carcinoid) or neuroendocrine prostate carcinoma (according to the World Health Organization classification). Patients with R/R NHL, including MZL, were those who progressed during or after standard anticancer therapy or for whom no other approved conventional therapy exists or is acceptable. Patients with solid tumors had to have at least one site of measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Patients with R/R NHL had to have at least one site of measurable disease according to International Working Group criteria.[23] Additional inclusion criteria included an Eastern Cooperative Oncology Group performance status of 0 or 1 and adequate hematologic, hepatic, and renal function. Exclusion criteria for this study have been previously described.[22]

Treatment

In the dose-expansion arm, CC-90011 was administered orally once per week in each 28-day cycle at a dose of 60 mg (the RP2D). The RP2D was selected based on the safety and preliminary efficacy results from the dose-escalation arm of the study.[22] Dose reductions were permitted in any cycle, including cycle 1. Treatment could be interrupted up to 4 weeks until toxicity reached either grade ≤1 or baseline levels.

Study objectives

The primary objectives were to determine the safety and tolerability of CC-90011 and to define the maximum tolerated dose and the RP2D of CC-90011 (dose escalation). Secondary objectives were to determine preliminary efficacy and to characterize the pharmacokinetics of CC-90011. Exploratory objectives included evaluating the pharmacodynamic effects of CC-90011 on gene expression and secreted neuropeptides. Study end points included preliminary efficacy (the clinical benefit rate [CBR], defined as response and SD rates according to disease-appropriate response criteria; the overall response rate; the duration of response;

and progression-free survival [PFS]), overall survival (OS), pharmacokinetics (including the maximum observed plasma concentration, the area under the plasma concentration time-curve [AUC], and the terminal half-life), and pharmacodynamics (gene expression of monocyte-to-macrophage differentiation–associated [MMD] in peripheral blood and levels of the secreted neuropeptides progastrin-releasing peptide [pro-GRP] and chromogranin A [CgA]).

Efficacy and safety assessments

Efficacy evaluations were performed after every two cycles through cycle six, and every three cycles thereafter. Patients who discontinued treatment for reasons other than disease progression, start of new anticancer therapy, or withdrawal of consent were followed until progression and/or initiation of new anticancer therapies. Tumor responses were determined by the investigator according to RECIST 1.1 for solid tumors and according to International Working Group criteria for NHL.[24] For neuroendocrine prostate carcinoma, response assessment was based on the Prostate Cancer Working Group 3 criteria.[25] [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) or FDG PET/computed tomography imaging was required to confirm a CR in patients who had FDG-avid tumors. Adverse events (AEs) were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Pharmacokinetic and pharmacodynamic assessments

Serial blood samples for pharmacokinetic analysis were collected ≤30 minutes before the dose on days 1, 8, 15, and 22 (predose) and days 1, 2, 4, 6, 8, 11, 24, and 48; and 72 and 96 hours postdose on days 1 and 22. Pharmacodynamic biomarkers of CC-90011 (*MMD* gene expression and CgA and pro-GRP soluble protein levels) were assessed ≤3 hours predose on days 1, 3, 5, 8, and 24 of cycle 1. MMD is a biomarker of CC-90011 target engagement in the peripheral blood.[26] CgA and pro-GRP are widely accepted biomarkers for assessing NENs and were previously established as downstream biomarkers of LSD1 inhibition.[27,28] Relative dose intensity was calculated as the actual dose intensity divided by the planned dose intensity.

Statistical analyses

For dose expansion, sample sizes were not determined based on power calculation but, rather, on clinical, empirical, and practical considerations traditionally used for phase 1 studies. During dose expansion, at least 10–14 efficacy-evaluable patients for each tumor cohort were initially accrued. The tumor cohort was expanded to approximately 10–20 patients if a response or SD lasting ≥4 months was observed. The treated population consisted of all patients who received at least one dose of CC-90011. The efficacy-evaluable population included patients who completed at least one treatment cycle and had a baseline and at least one valid postbaseline tumor assessments. Two-sided 95% Clopper–Pearson exact confidence intervals (CIs) were determined for overall response rate and CBR estimates. All statistics were calculated based on observed values except for medians, which were calculated based on both observed and censored values using the Kaplan–Meier method. The pharmacokinetic-evaluable population included patients who received at least one dose of CC-90011 and had at least one measurement of CC-90011 in blood. Plasma pharmacokinetic parameters were calculated using the noncompartmental analysis method from the plasma concentration-time profiles of CC-90011. Biomarker-evaluable patients included those who received at least one dose of CC-90011 and had at least one biomarker assessment. *MMD* expression levels in peripheral blood were normalized to the housekeeping gene *PPIB* and plotted as a percentage of cycle 1 day 1 (pretreatment baseline). Protein levels of CgA and pro-GRP were assessed in serum. On-treatment nadir levels and last assessment levels were plotted as a percentage of the pretreatment baseline; individual patient's neuropeptide nadirs were also plotted in relation to days on study. Study data were summarized for disposition, demographic and baseline characteristics, exposure, efficacy, safety, pharmacokinetics, and pharmacodynamics. Categorical data were summarized by frequency distributions (number and percentage of patients), and continuous data were summarized by descriptive statistics (means, standard deviation, median, minimum, and maximum). All statistical analyses were conducted using SAS version 9.3 or higher.

RESULTS

Patients and treatment

As of the July 23, 2021, cutoff date, 69 patients who had solid tumors or R/R MZL were enrolled and treated, including 50 patients in the dose-escalation arm and 19 in the dose-expansion arm. In the dose-expansion arm, 14 patients had bronchial NENs, two had prostate neuroendocrine carcinomas, and three had R/R MZL. Patient demographics and baseline characteristics are provided in

TABLE 1. Patient Baseline Characteristics

Characteristic	No. (%)	
	Dose escalation, $n = 50$	Dose expansion, $n = 19$
Age: Median [range], years	61 [22–75]	64 [36–81]
Age ≥ 65 years	19 (38)	9 (47)
Men	26 (52)	11 (58)
ECOG PS		
0	19 (38)	11 (58)
1	31 (62)	8 (42)
Tumor type		
NHL, MZL	1 (2)	3 (16)
Solid tumor	49 (98)	16 (84)
NEN	27 (54)	16 (84)
Bronchial NET	4 (8)	14 (74)
Bronchial NEC	5 (10)	0 (0)
Prostate	5 (10)	2 (11)
SCLC	2 (4)	0 (0)
Other[a]	11 (22)	0 (0)
Solid tumor stage IV[b]	43 of 49 (88)	16 of 16 (100)
No. of prior systemic anticancer therapies: Median [range]	3 [1–9]	2 [1–6]
No. of prior systemic anticancer therapies		
1	2 (4)	6 (32)
2	17 (34)	4 (21)
≥3	29 (58)	8 (42)

Note: Data cutoff, July 23, 2021. Percentages may not total 100 because of rounding.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasm; NET, neuroendocrine tumor; NHL, non-Hodgkin lymphoma; SCLC, small-cell lung cancer.
[a]Tumor types listed as other included cervical, urinary bladder, medullary thyroid cancer, and Merkel cell carcinoma.
[b]Ann Arbor stage I in the one patient with MZL in the dose-escalation arm and stage IV in the three patients with MZL in the dose-expansion arm.

Table 1. In the dose-expansion arm, the median patient age was 64 years (range, 36–81 years), and the median number of prior systemic anticancer therapies was two (range, from one to six therapies); 42% had received at least three prior therapies. As of the cutoff date, 17 patients (89%) had discontinued treatment, and two (11%) were still receiving study treatment. The reasons for treatment discontinuation were disease progression ($n = 15$; 79%) and death from disease progression ($n = 2$; 11%; see Table S1).

Patients with NENs in the dose-expansion arm received a median of 4.5 treatment cycles (range, 1–36 treatment cycles). The median duration of study treatment was 17.6 weeks (range, 4–142 weeks), and the mean relative dose intensity was 85% (range, 44%–108%). Five patients (31%) had at least one dose reduction because of AEs, and 13 patients (81%) had at least one dose interruption, 10 (63%) of which were because of AEs. The duration of interruption was <3 days in seven patients (44%), 3–6 days in three patients (19%), and 7–14 days in three patients (19%; see Table S1). Among patients with R/R MZL, the median number of treatment cycles was one (range, from one to two cycles). The median duration of study treatment was 4.0 weeks (range, 3–5 weeks), and the mean relative dose intensity was 100%. None of the patients with R/R MZL had dose reductions. One patient in the MZL cohort had at least 1 dose interruption that was caused by AEs, with a duration less than 3 days.

Efficacy

In the dose-escalation arm, 1 patient with R/R MZL achieved a durable CR and was still ongoing treatment in cycle 58 as of April 2022 (Figure 1A). A patient with a solitary fibrous tumor achieved a PR in cycle 36 of treatment, with an approximately 55% reduction in target lesion size by cycle 36 (Figure 1B). That patient received 45 cycles of treatment before discontinuing treatment in March 2021. A reduction in target lesion size of up to approximately 30% was observed in six patients with a PFS >9 months in both arms of the study (Figure 1C). Among the 19 patients in the dose-expansion arm, the CBR was 37% (95% CI, 16.3%–61.6%) (Table 2). Ten patients (53%) had SD, and seven (37%) had SD of prolonged duration (≥4 months). Three patients with bronchial NENs had SD after nine or more cycles, with one patient still receiving treatment who had SD in cycle 46 as of April 2022. In the dose-escalation and dose-expansion arms, the median PFS was 3.4 months (95% CI, 1.7–3.7 months) and 1.8 months (95% CI, 1.1–5.4 months), respectively, and the median OS was 7.8 months (95% CI, 6.1–20.1 months) and 15.6 months (95% CI, 7.0, not estimable), respectively (Table 2). Seven patients in the dose-escalation arm who had grade ≥2 NENs and four who had NENs in the dose-expansion arm had prolonged SD lasting >6 months and PFS durations roughly twice as long as those achieved with their most recent prior therapy (see Figure S2).

Pharmacokinetics and pharmacodynamics

All patients with NENs in the dose-expansion arm ($n = 16$) were evaluable for pharmacokinetic assessments. Pharmacokinetic parameters are shown in Figure 2. Consistent with the dose-escalation arm of the study, the peak CC-90011 concentration was observed at an approximate median of 4 hours after treatment (Figure 2A). Negligible accumulation occurred with repeat dosing based on the AUC, and systemic exposures were similar between both arms of the study (Figure 2B).[22]

Similar to results observed in the dose-escalation arm at the 60-mg dose, a downregulation ≥50% in *MMD* gene expression in the peripheral blood was observed in

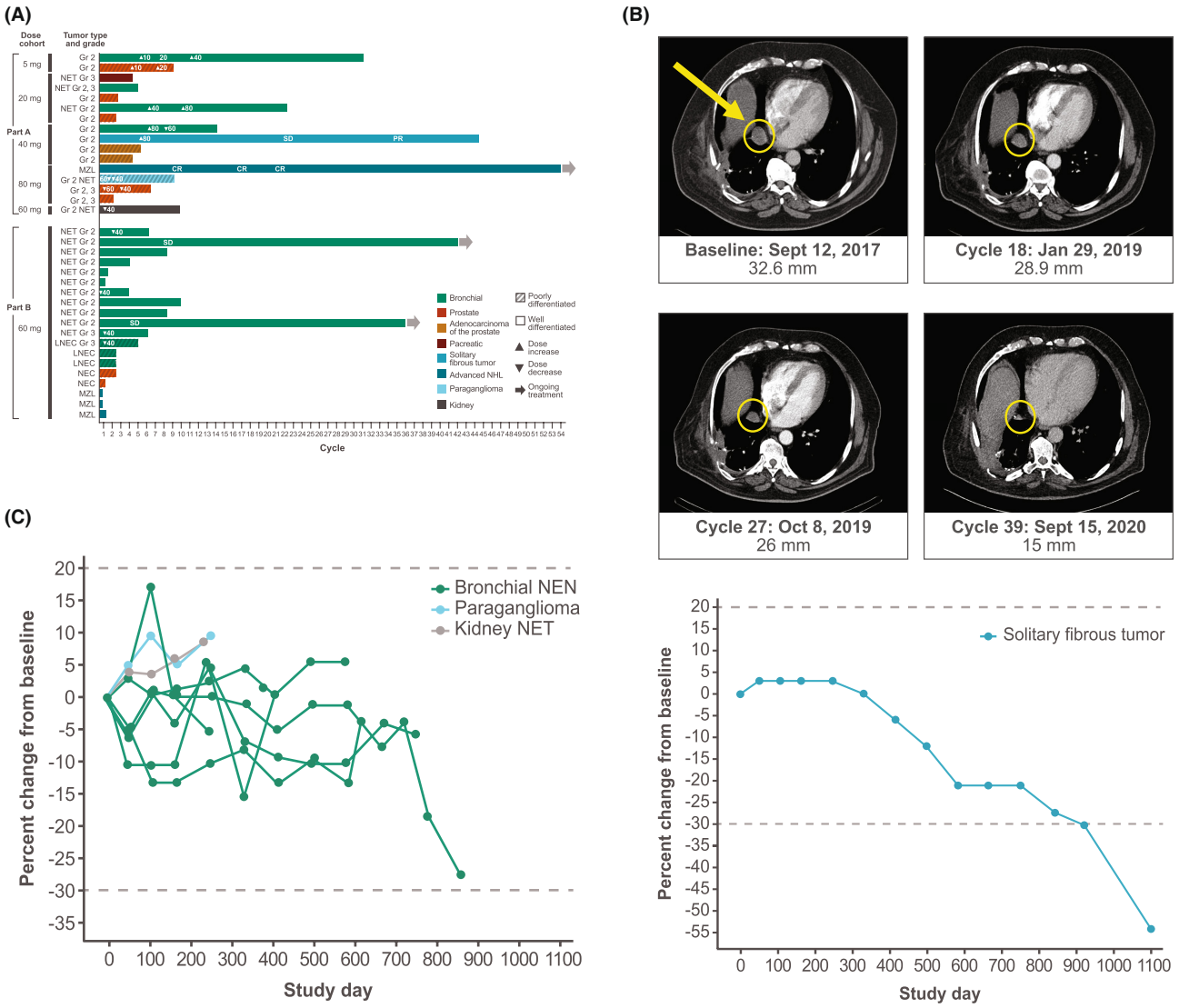
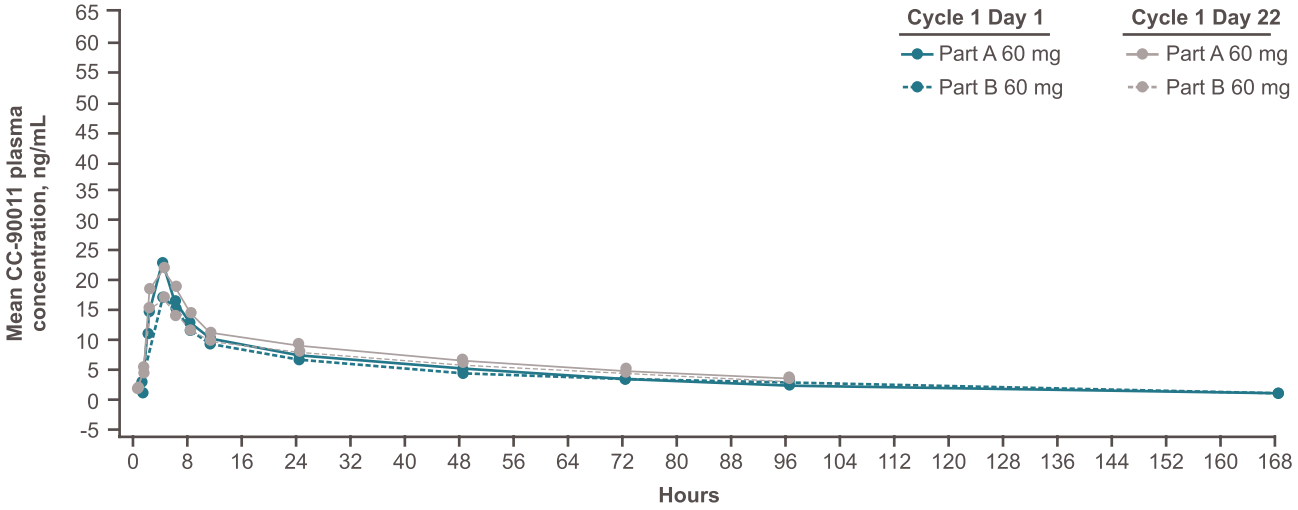


Figure 1. (A) Time on treatment for 16 evaluable patients in the dose-escalation arm and for all patients in the dose-expansion arm. (B) Changes in tumor burden in response to CC-90011 and the percentage change from baseline in tumor size over time are shown on computed tomography scans from a patient who had a solitary fibrous tumor. (C) Changes in patients with NENs/NETs and the percentage change from baseline in tumor size over time are shown in patients with NENs/NETs who had a progression-free survival >9 months, with each line representing an individual patient (data cutoff: January 6, 2022 for A; January 26, 2021, for B and C). CR indicates complete response; Gr, grade; LNEC, large cell neuroendocrine carcinoma; MZL, marginal zone lymphoma; NEC, neuroendocrine carcinoma; NENs, neuroendocrine neoplasms; NETs, neuroendocrine tumors; NHL, non-Hodgkin lymphoma; PR, partial response; SD, stable disease.

the dose-expansion arm (Figure 3A). Circulating tumor neuropeptide CgA levels decreased 0%–82% in the dose-expansion arm (Figure 3B). A CgA nadir at <50% of the baseline level was associated with longer time on treatment, with SD lasting >6 months, and pro-GRP levels decreased in 15 of 16 patients who had NENs in the dose-expansion arm (Figure 3C). Moreover, a decrease >30% was observed in 11 of 16 patients (65%). A higher pro-GRP nadir at >70% of the baseline level was associated with a shorter time on treatment (<6 months). Further analysis of pharmacodynamic markers for CC-90011 are ongoing.

Safety

Treatment-emergent AEs (TEAEs), which are listed in Table 3, primarily consisted of hematologic events, including thrombocytopenia, which is an on-target effect. Among patients with NENs, the most common any-grade



CC-90011 60 mg QW	n	C_{max}, ng/mL		AUC_{0-24}, n • h/mL		AUC_{0-t}, n • h/mL		t_{max}, h	
		Day 1	Day 22	Day 1	Day 22	Day 1	Day 22	Day 1	Day 22
Part B[a]	16	18 (69)	20 (73)	228 (66)	243 (73)	641 (56)	544 (89)	4 (2-6)	4 (1-6)

Figure 2. Mean CC-90011 concentration-time profiles and pharmacokinetic parameters on days 1 and 22 of cycle 1. [a]Data are the median (range) for t_{max} and the geometric mean (% coefficient of variation) for all other parameters. AUC_{0-24} indicates the area under the curve during 24 hours; AUC_{0-t}, area under the plasma drug concentration–time curve up to time *t*; C_{max}, maximum observed plasma concentration; QW, once per week; t_{max}, time of first occurrence of C_{max} (data cutoff: June 27, 2019).

TABLE 2. Efficacy

Variable	Dose escalation, *n* = 50	Dose expansion, *n* = 19
CBR [95% CI], %	20 [10.0–33.7]	37 [16.3–61.6]
ORR [95% CI], %	4 [0.5–13.7]	0 [0.0–17.6]
Best overall response, no. (%)		
CR	1 (2.0)	0 (0.0)
PR	1 (2.0)	0 (0.0)
SD	22 (44.0)	10 (53.0)
SD ≥4 months	8 (16.0)	7 (37.0)
PD	22 (44.0)	7 (37.0)
NE	4 (8.0)	2 (11.0)
mPFS [95% CI], months	3.4 [1.7–3.7]	1.8 [1.1–5.4]
mOS [95% CI], months	7.8 [6.1–20.1]	15.6 [7.0, NE]

Note: Data cutoff: July 23, 2021.
Abbreviations: CBR, clinical benefit rate defined as percentage of patients with confirmed tumor responses (as assessed by the investigators) of CR, PR, and durable SD (SD of ≥4 months' duration); CR, complete response; mPFS, median progression-free survival; mOS, median overall survival; NE, not estimable; NEN, neuroendocrine neoplasm; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

and grade 3 and 4 TEAE was thrombocytopenia (*n* = 11 [69%] and *n* = 6 [38%], respectively). For patients with R/R MZL, thrombocytopenia and fatigue/asthenia were the most common TEAEs (*n* = 2; 67%, each) and were grade 1 or 2. Other common grade 3 and 4 TEAEs were neutropenia (*n* = 3; two patients with NENs and one with R/R MZL) and fatigue/asthenia (*n* = 3 patients with NENs). These AEs were reversible, easily manageable, and mitigated by dose modifications. The most common any-grade treatment-related AE (TRAE) in the NEN cohort was thrombocytopenia (*n* = 11; 69%), followed by fatigue/asthenia (*n* = 6; 38%), and anemia (*n* = 4; 25%); in the R/R MZL cohort, thrombocytopenia was the most common any-grade TRAE (*n* = 2; 67%). The most common grade 3 and 4 TRAEs included thrombocytopenia (*n* = 6; all in the NEN cohort) and neutropenia (*n* = 3; two patients with NENs and one with R/R MZL; see Table S2).

In the dose-expansion cohort, six patients, all in the NEN cohort, experienced at least one serious TEAE (see Table S3). These serious AEs included thrombocytopenia, anemia, chest pain, fatigue, general physical health deterioration, hepatic hemorrhage, hepatic pain, biliary tract infection, upper respiratory tract infection, oxygen saturation decrease, pulmonary hemorrhage, and respiratory failure (*n* = 1 each). One patient in the dose-expansion arm had a TEAE (upper respiratory tract infection) with an outcome of death, which was caused by the progression of underlying disease and was not considered treatment-related.

Of the 19 patients in the dose-expansion arm, including both the NEN cohort and the MZL cohort, five (26%) had at least one TEAE leading to a dose reduction of CC-90011, all of which were for hematologic events.

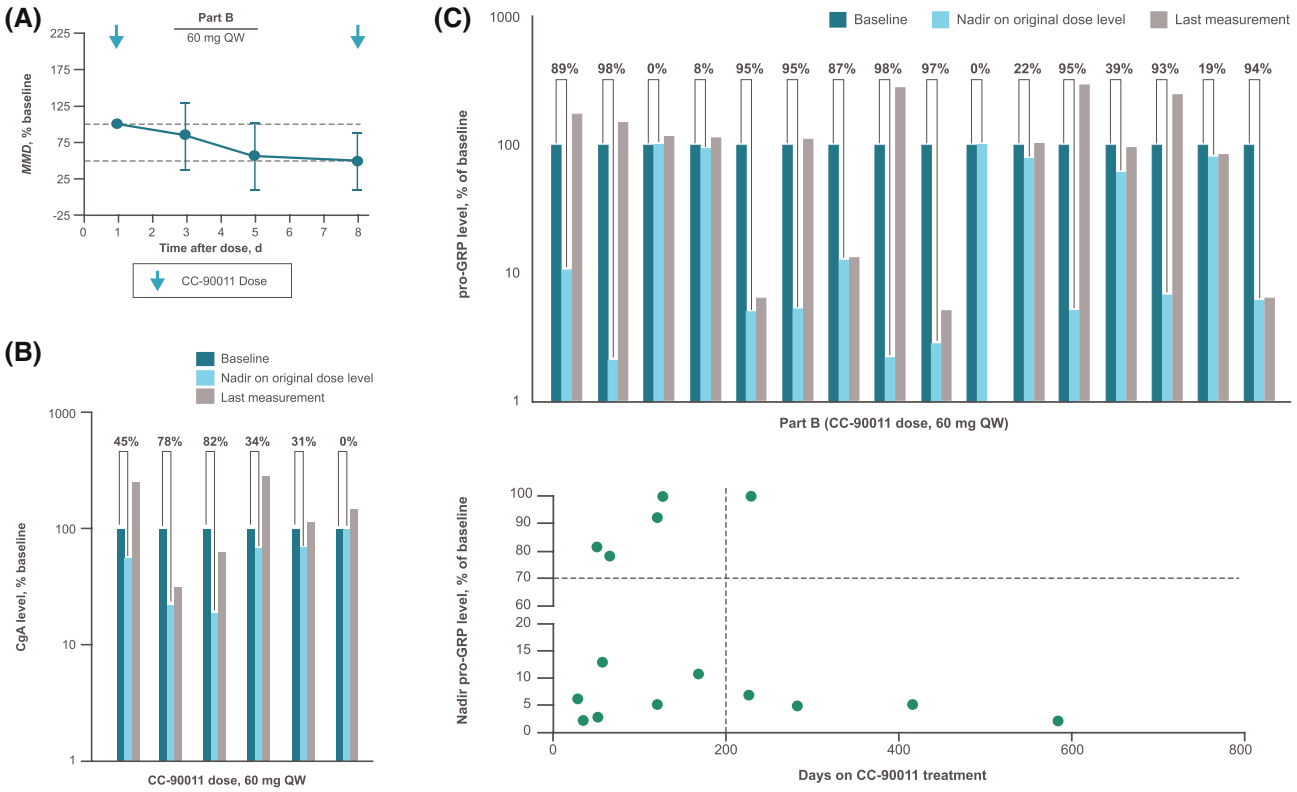


Figure 3. Changes in (A) peripheral blood pharmacodynamic marker *MMD* mRNA expression, (B) circulating tumor neuropeptide CgA, and (C) circulating tumor neuropeptide pro-GRP (C). (A) Mean levels of *MMD* mRNA relative to pretreatment baseline over time after the initial dose are shown in 16 patients with NENs. Error bars indicate standard deviations. (B,C) Baseline, nadir, and last measurements are shown, with each cluster of columns representing one patient. C also depicts pro-GRP nadir levels relative to baseline versus the time on study, with each dot representing one patient (data cutoff: June 27, 2019, for A and B; June 1, 2021, for C). CgA indicates chromogranin A; *MMD*, monocyte-to-macrophage differentiation–associated; mRNA, messenger RNA; NENs, neuroendocrine neoplasms; pro-GRP, prograstrin-releasing peptide; QW, once per week.

Five patients (26%) had thrombocytopenia, one (5%) had anemia, and one (5%) had neutropenia. Eleven patients (58%) had at least one TEAE leading to a dose interruption of CC-90011, and the majority ($n = 9$; 47%) had manageable hematologic events. No patients in the dose-expansion arm had a TEAE leading to treatment discontinuation.

DISCUSSION

Several LSD1 inhibitors are in clinical development for the treatment of cancer, most of which are irreversible and have safety signals in clinical trials.[29] In a first-in-human study, the irreversible LSD1 inhibitor iadademstat (ORY-1001) caused toxicities, including thrombocytopenia, anemia, and febrile neutropenia, as well as deaths possibly related to iadademstat.[30,31] In a phase 1 dose-escalation study of GSK2879552 in R/R SCLC,[32] favorable pharmacokinetic properties were demonstrated, but the rate of AEs, especially serious AEs, was high. Because that irreversible LSD1 inhibitor did not have a favorable risk–benefit profile, the study was subsequently terminated. CC-90011 is an oral, potent, selective, reversible inhibitor of LSD1 that was well tolerated in the dose-escalation arm of the CC-90011-ST-001 study.[22] Thrombocytopenia was the only dose-limiting toxicity reported, and all dose-limiting toxicities were reversible and easily manageable.[22] Safety results from the dose-expansion arm of the current study confirmed findings from the dose-escalation arm in that heavily pretreated patient population.[22] Most AEs with monotherapy were mild or moderate, reversible, and easily managed with dose modifications, supporting the exploration of CC-90011 in combinations. Importantly, none of the TEAEs in the dose-expansion arm led to discontinuation of treatment because of toxicity, and no febrile neutropenia was observed. The

TABLE 3. Treatment-Emergent Adverse Events[a]

Characteristic	Dose escalation		Dose expansion			
	Any grade, *n* = 50	Grade 3/4, *n* = 50	Any grade, *n* = 19		Grade 3/4, *n* = 19	
≥1 event	48 (96)	24 (48)	19 (100)		13 (68)	
Cohort			NEN, n = 16	R/R MZL. *n* = 3	NEN, *n* = 16	R/R MZL, *n* = 3
Fatigue/asthenia	24 (48)	1 (2)	9 (56)	2 (67)	3 (19)	0 (0)
Thrombocytopenia	23 (46)	12 (24)	11 (69)	2 (67)	6 (38)	0 (0)
Vomiting	14 (28)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)
Anemia	14 (28)	3 (6)	6 (38)	1 (33)	1 (6)	0 (0)
Nausea	11 (22)	0 (0)	5 (31)	1 (33)	0 (0)	0 (0)
Constipation	11 (22)	0 (0)	5 (31)	1 (33)	0 (0)	0 (0)
Pyrexia	10 (20)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Decreased appetite	10 (20)	1 (2)	3 (19)	0 (0)	0 (0)	0 (0)
Diarrhea	10 (20)	1 (2)	5 (31)	0 (0)	0 (0)	0 (0)
Arthralgia	9 (18)	0 (0)	6 (38)	0 (0)	0 (0)	0 (0)
Abdominal pain	7 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Back pain	7 (14)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Increased ALT	6 (12)	2 (4)	0 (0)	0 (0)	0 (0)	0 (0)
Increased AST	6 (12)	1 (2)	1 (6)	0 (0)	0 (0)	0 (0)
Neutropenia	6 (12)	4 (8)	3 (19)	1 (33)	2 (13)	1 (33)
Cough	6 (12)	0 (0)	3 (19)	1 (33)	0 (0)	0 (0)
Dyspnea	5 (10)	0 (0)	2 (13)	1 (33)	0 (0)	0 (0)
Hypokalemia	5 (10)	1 (2)	2 (13)	0 (0)	0 (0)	0 (0)
Headache	5 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Tumor pain	5 (10)	1 (2)	0 (0)	1 (33)	0 (0)	0 (0)
Dysgeusia	3 (6)	0 (0)	4 (25)	0 (0)	0 (0)	0 (0)
Pruritus	3 (6)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)
Dizziness	3 (6)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)
Bronchitis	2 (4)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)
Epistaxis	2 (4)	0 (0)	3 (19)	0 (0)	0 (0)	0 (0)
Lipase increased	2 (4)	2 (4)	2 (13)	0 (0)	0 (0)	0 (0)
Peripheral sensory neuropathy	2 (4)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)
Acute kidney injury	1 (2)	0 (0)	1 (6)	1 (33)	0 (0)	0 (0)
Bone pain	1 (2)	1 (2)	2 (13)	1 (33)	0 (0)	0 (0)
Hepatic pain	1 (2)	0 (0)	2 (13)	0 (0)	1 (6)	0 (0)
Musculoskeletal pain	1 (2)	0 (0)	1 (6)	0 (0)	0 (0)	0 (0)
Sciatica	1 (2)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)

Note: Data cutoff: July 23, 2021.
Abbreviations: NEN, neuroendocrine neoplasm; R/R MZL, relapsed/refractory marginal zone lymphoma.
[a]Treatment-emergent adverse events occurring in ≥10% of patients in either arm of the study are reported. Events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

most frequent toxicity was thrombocytopenia, which is an on-target effect of CC-90011, consistent with the role of LSD1 as a key regulator of platelet maturation.[33] The on-target thrombocytopenia reported was reversible and easily manageable with dose modifications.

Unlike chemotherapy that induces apoptosis, CC-90011 affects platelet maturation; therefore, the observed toxicity in response to CC-90011 treatment is readily reversible. Moreover, because overall toxicity is largely limited to manageable thrombocytopenia, CC-90011 is a promising agent for combination therapy. CC-90011 has been safely combined with cisplatin/etoposide and with carboplatin/etoposide in first-line extensive-stage SCLC,[21] with nivolumab in the second line for SCLC or squamous nonsmall cell lung cancer,[34] with abiraterone/prednisone in castration-resistant prostate cancer,[35] and with azacitidine in acute myeloid leukemia.[36]

CC-90011 pharmacokinetic parameters in the dose-expansion arm were consistent with results observed in the dose-escalation arm. The long terminal half-life of CC-90011 supports dosing once per week. These results also suggest the similarity of CC-90011 exposure parameters across different tumor types. Pharmacodynamic biomarker data demonstrated that CC-90011 decreased levels of the neuroendocrine peptides CgA and pro-GRP and decreased gene expression of a blood pharmacodynamic marker, *MMD*, by ≥50%. Our previous

findings demonstrated that downregulation of *MMD* RNA is a marker of target engagement by CC-90011.[37] Furthermore, CgA and pro-GRP are secreted by the tumors and are widely accepted biomarkers for assessing NENs,[27,28] and a CgA decrease may be predictive of response to therapy in these patients.[38] Of note, CgA nadir levels ≤50% of baseline were associated with a longer time on treatment, as previously shown.[39] Conversely, higher pro-GRP nadir levels ≥70% of baseline were associated with shorter on-treatment duration. These data suggest target engagement activity with CC-90011 and biologic responses of tumor cells to CC-90011.

In terms of efficacy, the longer follow-up of the dose-escalation arm revealed prolonged, durable responses in a patient with R/R MZL who achieved a CR after three or four previously failed treatments (currently ongoing in cycle 58 as of April 2022) and in a patient with solitary fibrous tumor who achieved a PR in cycle 36. The patient with the solitary fibrous tumor had previously received repeated treatment for recurring low-grade sarcoma. The deepening of the response to a PR after approximately 3 years on treatment with SD indicates that prolonged CC-90011 treatment could lead to a better response with minimal toxicity.

Efficacy results were consistent with the mechanism of action of CC-90011. LSD1 inhibitors have been shown to drive tumor differentiation rather than trigger tumor apoptosis, so single-agent activity in highly aggressive tumors was not expected. Rather, LSD1 inhibitors like CC-90011 are expected to have more pronounced effects on malignancies with a more indolent course, such as low-grade NENs, or a limited tumor burden, such as the patient with R/R MZL who was receiving ongoing treatment in cycle 58. The management of NENs, a heterogenous group of tumors that commonly originate in the lung, gastrointestinal tract, and pancreas, represents a clinical challenge because of the lack of a standard treatment strategy for this disease.[40–42] The number of new cases of NENs is rising, potentially because of increased detection.[42–44] Given the heterogeneity of NENs, their management and treatment is complex.[45] Recently developed treatments include somatostatin analogs, everolimus,[46] temozolomide plus capecitabine, sunitinib, and peptide receptor radionuclide therapy.[47] Despite an increase in treatment options for patients with NENs, an unmet medical need remains for additional novel therapies that provide optimal disease management.

Taken together, the efficacy results from the dose-escalation and dose-expansion arms of the current study suggest that CC-90011 has broad clinical activity across tumor types, including bronchial NENs and R/R MZL. In the dose-expansion arm, prolonged SD for >4 months was observed in 37% of patients, and three patients had SD lasting ≥9 months. Notably, one patient with bronchial NENs was still ongoing treatment in cycle 46 at the time of the writing of this article. In patients with bronchial NENs, the median PFS of 4.6 months was longer than the typical PFS observed in the prior therapies each of these patients received.

In conclusion, CC-90011 may have a significant advantage over other LSD1 inhibitors based on the reversible mechanism of action and the established, optimal dose/schedule that induced mostly mild and easily managed toxicity. No new safety concerns or late toxicities were identified with a longer follow-up of approximately 5 years and >4 years of treatment. The observed clinical activity was particularly evident in some patients who had more indolent diseases, such as low-grade bronchial NENs. or in malignancies with a limited tumor burden, such as MZL. The clinical activity of CC-90011, along with the prolonged, durable responses and convenient once-per-week dosing, provide support for further investigations of CC-90011 either as maintenance monotherapy or in combination with other cancer treatments.

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AUTHOR CONTRIBUTIONS

Antoine Hollebecque, **Zariana Nikolova**, and **Johann S. de Bono:** Conceptualization, supervision, and writing–original draft. **Marina Arias**, **Juan de Alvaro**, **Josep L. Parra-Palau**, **Tania Sánchez-Pérez**, **Ida Aronchik**, **Ellen H. Filvaroff**, **Manisha Lamba**, and **Zariana Nikolova:** Data curation, formal analysis, verification, methodology, and writing–original draft. All authors contributed to investigation, visualization, resources, and writing–review and editing.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Bristol Myers Squibb company policy on data sharing may be found online (https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html).

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