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ORIGINAL ARTICLE

Phase I study of CC-90010, a reversible, oral BET inhibitor in patients with advanced solid tumors and relapsed/refractory non-Hodgkin's lymphoma

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Background: Bromodomain and extra-terminal (BET) proteins are epigenetic readers that regulate expression of genes involved in oncogenesis. CC-90010 is a novel, oral, reversible, small-molecule BET inhibitor.

Patients and methods: CC-90010-ST-001 (NCT03220347; 2015-004371-79) is a phase I dose-escalation and expansion study of CC-90010 in patients with advanced or unresectable solid tumors and relapsed/refractory (R/R) non-Hodgkin's lymphoma (NHL). We report results from the dose escalation phase, which explored 11 dose levels and four dosing schedules, two weekly (2 days on/5 days off; 3 days on/4 days off), one biweekly (3 days on/11 days off), and one monthly (4 days on/24 days off). The primary objectives were to determine the safety, maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D) and schedule. Secondary objectives were to evaluate signals of early antitumor activity, pharmacokinetics, and pharmacodynamics.

Results: This study enrolled 69 patients, 67 with solid tumors and two with diffuse large B-cell lymphoma (DLBCL). The median age was 57 years (range, 21—80) and the median number of prior regimens was four (range, 1—9). Treatment-related adverse events (TRAEs) were mostly mild and manageable; grade 3/4 TRAEs reported in more than two patients were thrombocytopenia (13%), anemia, and fatigue (4% each). Six patients had dose-limiting toxicities. MTDs were 15 mg (2 days on/5 days off), 30 mg (3 days on/11 days off), and 45 mg (4 days on/24 days off). The RP2D and schedule selected for expansion was 45 mg (4 days on/24 days off). As of 8 October 2019, one patient with grade 2 astrocytoma achieved a complete response, one patient with endometrial carcinoma had a partial response, and six patients had prolonged stable disease $\geq$11 months.

Conclusions: CC-90010 is well tolerated, with single-agent activity in patients with heavily pretreated, advanced solid tumors.

Key words: BET inhibitor, CC-90010, non-Hodgkin's lymphoma, solid tumors

INTRODUCTION

The bromodomain and extra-terminal domain (BET) proteins are epigenetic readers that recognize and bind acetylated lysine residues.[1] The BET protein family comprises the ubiquitously expressed bromodomain (BRD) proteins BRD2, BRD3, and BRD4, as well as testis-restricted BRDT, which recognize acetylated lysines of histones 3 and 4 and on some transcription factors.[2,3] BET proteins play a pivotal role in cancer, mainly as part of regulatory complexes involved in the control of transcription elongation, proliferation, metabolism, cancer stem cells, and metastasis.[4—6]

The most extensively studied member of BET proteins is BRD4, which plays a key role in super-enhancer organization and in regulating the expression of *c-myc*, an essential oncogene in many tumor types.[7,8] Aberrant BRD4 activity or expression has been implicated in hematologic malignancies and solid tumors, and high expression of BRD2 and BRD4 is predictive of a worse prognosis.[9—12]

Preclinical studies suggesting a role of BET proteins in cancer provided the rationale for developing and using BET inhibitors as anticancer drugs.[9,10,13—15] BET inhibitors are small molecules that specifically bind bromodomains, preventing BET proteins from binding to chromatin, thereby inhibiting gene transcription.[6] BET inhibitors have broad anticancer activity in preclinical models; however, first generation inhibitors have generally shown modest clinical benefit, possibly due to a relatively narrow therapeutic index which precludes optimal target engagement.[12,16—23]

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CC-90010 is a novel, oral, reversible, small-molecule inhibitor of BET proteins. Preclinical studies have shown that CC-90010 has significant antiproliferative activity in glioblastoma cells and patient-derived xenograft models as monotherapy and in combination with temozolomide (TMZ). Based on the physicochemical properties of CC-90010 and results from a preclinical study using NSG^{TM} mice with an intact blood-brain barrier (BBB), CC-90010 seems to penetrate the BBB (unpublished data). Structurally differentiated next-generation BET inhibitors, such as CC-90010, have the potential to achieve robust target engagement and thus significant antitumor activity by leveraging different dosing schedules. Here we report results from the first-in-human phase I study of CC-90010 in patients with advanced or unresectable solid tumors or relapsed/refractory (R/R) advanced non-Hodgkin's lymphoma (NHL).

PATIENTS AND METHODS

Study design

CC-90010-ST-001 (NCT03220347; 2015-004371-79) is a phase I, open-label, dose-escalation and expansion study of CC-90010 in patients with advanced or unresectable solid tumors and R/R advanced NHL. We report here key results from the dose-escalation portion (part A) of the study. 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-90010 per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, the maximum tolerated dose (MTD), and/or recommended phase II doses (RP2Ds). The secondary objectives were to evaluate preliminary efficacy and CC-90010 pharmacokinetics (PK) and pharmacodynamics (PD).

Patients

Eligible patients were men and women aged $\geq$18 years with histologically or cytologically confirmed advanced or unresectable solid tumors or R/R advanced NHL [i.e. diffuse large B-cell lymphoma (DLBCL), follicular lymphoma, and marginal zone lymphoma], including those who have progressed on standard anticancer therapy or for whom no other approved conventional therapy exists. Patients also had measurable disease, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and adequate hematologic, hepatic, and renal function. Additional eligibility criteria are reported in the supplementary Methods, available at *Annals of Oncology* online.

Treatment

CC-90010 was administered orally once daily in 28-day cycles with the following dosing schedules: weekly dosing of 2 days on followed by 5 days off or 3 days on followed by 4 days off, biweekly dosing of 3 days on followed by 11 days off, and monthly dosing of 4 days on followed by 24 days off. Escalating doses of CC-90010 were examined; dose levels are shown in supplementary Figure S1, available at *Annals of Oncology* online. A Bayesian logistic regression model utilizing escalation with overdose control guided CC-90010 dosing decisions.

Study assessments

Adverse events (AEs) were assessed according to the NCI CTCAE, version 4.03. Response assessments were carried out after every two cycles through cycle 6 and then every three cycles until disease progression. Solid tumors were assessed per RECIST version 1.1.[24] NHL assessments were assessed per the International Working Group response criteria; scan interpretation was conducted according to the Deauville Criteria.[25–27] Patients with gliomas were assessed based on the Response Assessment in Neuro-Oncology criteria.[28] PK and PD analyses are described in supplementary Methods, available at *Annals of Oncology* online; sampling times are noted in supplementary Tables S1 and S2, available at *Annals of Oncology* online.

Statistical analyses

The treated population consisted of all patients who received one or more doses of CC-90010. Dose-limiting toxicities (DLTs) are defined in the supplementary Methods, available at *Annals of Oncology* online, and consisted of specified AEs occurring during the DLT assessment period (cycle 1). Patients were considered DLT-assessable if they experienced a DLT after receiving one or more doses of study treatment or received $\geq$80% of the total planned dose amount of CC-90010 without experiencing a DLT. The efficacy-evaluable population comprised all patients who complete one or more cycles of CC-90010 and had a baseline and one or more valid post-baseline tumor response assessments. The PK population included patients who received one or more doses of CC-90010 and had evaluable concentration data to determine the PK parameters. The PD marker-evaluable population included all enrolled patients who received one or more doses of CC-90010 and had at one or more biomarker assessments, excluding disqualified assessments.

RESULTS

Patients and treatment

As of the 9 April 2019 data cut-off, 69 patients were enrolled and treated in the dose-escalation phase of the study. Sixty-seven patients had advanced solid tumors, including 10 with high-grade gliomas (eight glioblastoma and two anaplastic astrocytomas); two patients had R/R DLBCL (Table 1). Eight patients (11.6%) were ongoing and 61 (88.4%) had discontinued treatment, all owing to progressive disease; there were no permanent discontinuations or deaths due to toxicity.

Table 1. Patient baseline characteristics

Characteristic	Overall (*N* = 69)
Median age (range), years	57 (21–80)
Age ≥65 years	21 (30.4)
Male	38 (55.1)
ECOG PS	
0	33 (47.8)
1	36 (52.2)
Tumor type	
Solid tumor	67 (97.1)
Glioma	10 (14.5)
NHL	2 (2.9)
No. of prior systemic anticancer therapies[a]	
Median (range)	4 (1–9)
1	7 (10.6)
2	17 (25.8)
3	8 (12.1)
≥4	34 (51.5)

Data are reported as *n* (%) unless otherwise noted.
ECOG PS, Eastern Cooperative Oncology Group performance status; GBM, glioblastoma; NHL, non-Hodgkin's lymphoma.
[a] Denominator is the number of patients with prior systemic anticancer therapies (*n* = 66).

Table 2. Treatment-related adverse events occurring in ≥5% of patients

TRAE	Any grade (*N* = 69)	Grades 3/4 (*N* = 69)
≥1 TRAE, *n* (%)	60 (87.0)	23 (33.3)
Hematologic		
Thrombocytopenia	32 (46.4)	9 (13.0)
Anemia	8 (11.6)	3 (4.3)
Neutropenia	5 (7.2)	1 (1.4)
Gastrointestinal		
Nausea/vomiting	39 (56.5)	0
Diarrhea	27 (39.1)	1 (1.4)
Stomatitis	16 (23.2)	0
Other		
Fatigue/asthenia	37 (53.6)	3 (4.3)
Dysgeusia	18 (26.1)	0
Decreased appetite	11 (15.9)	0
Dermatitis, acneiform	8 (11.6)	0
Hyperglycemia	8 (11.6)	1 (1.4)
Alanine aminotransferase increased	6 (8.7)	2 (2.9)
Rash, maculopapular	5 (7.2)	0

TRAE, treatment-related adverse event.

The median number of treatment cycles was two (range, 1–16). Ten patients (14.5%) received more than six treatment cycles. The median duration of study treatment for the overall population was 8 weeks (range, 1–64) (supplementary Table S3, available at *Annals of Oncology* online). Nine patients (13.0%) had one or more CC-90010 dose reductions at a median of 5 weeks (range, 4–30) from initiation of treatment. The monthly dose intensity ranged from 150 mg to 240 mg.

Safety

Seven patients were treated at the first dose level of 15 mg on a weekly dosing schedule (3 days on/4 days off). The on-target toxicity observed is typical for this class of compounds. One patient had a DLT (grade 4 thrombocytopenia associated with grade 3 skin hemorrhage) and grades ≤3 thrombocytopenia, hyperglycemia, and asthenia; therefore, the dose intensity was reduced to 15 mg (3 days on/11 days off). No DLTs, hyperglycemia, or thrombocytopenia leading to dose delay were observed with the reduced dose intensity; therefore, three alternative dosing schedules were escalated in parallel: a weekly schedule (2 days on/5 days off), a biweekly schedule (3 days on/11 days off), and a monthly schedule (4 days on/24 days off).

Among the 69 enrolled patients, 13 were not assessable for DLTs having received <80% of their total planned dose of CC-90010 during cycle 1 without experiencing a DLT. Of the 56 DLT-assessable patients, six (10.7%) had DLTs occurring in all three dosing schedules. One patient had fatigue, one patient had thrombocytopenia, and two patients had increased alanine aminotransferase. Two patients had multiple DLTs, including one who had thrombocytopenia, increased blood creatine phosphokinase, diabetes, diarrhea, and oral candidiasis, and another who had thrombocytopenia and skin hemorrhage. Descriptions of the DLT period and criteria are reported in the supplementary Methods, available at *Annals of Oncology* online. The MTDs were established as 15 mg given 2 days on/5 days off (weekly), 30 mg given 3 days on/11 days off (biweekly), and 45 mg given 4 days on/24 days off (monthly).

The most common treatment-emergent AEs were nausea/vomiting (65.2%), fatigue/asthenia (63.8%), and thrombocytopenia (50.7%) (supplementary Table S4, available at *Annals of Oncology* online). Most patients (87.0%) had one or more AEs suspected of being related to CC-90010 (Table 2). The most common treatment-related AEs were nausea/vomiting (56.5%), fatigue/asthenia (53.6%), thrombocytopenia (46.4%), and diarrhea (39.1%). Monthly dosing allowed for better recovery of platelet counts and delivery of a higher dose intensity compared with the weekly and biweekly dosing schedules (supplementary Figure S2, available at *Annals of Oncology* online). Overall, 31 patients (44.9%) had one or more serious AEs. Eight patients (11.6%) had SAEs that were considered treatment-related; inappropriate antidiuretic hormone section, hyponatremia, and diarrhea were reported in one patient each and fatigue was reported in two patients. Three patients had more than one serious AEs; one had thrombocytopenia and anemia, one had anemia, thrombocytopenia, and skin hemorrhage, and one had diarrhea, diabetes, and thrombocytopenia. Thirty-eight patients (55.1%) died during the study or within 28 days of the last dose due to progressive disease (*n* = 34), AE (*n* = 3), or unknown cause (*n* = 1).

Efficacy

All 69 patients were assessable for efficacy. Two patients achieved objective responses for an overall response rate of 2.9% (95% confidence interval 0.4–10.1) (Table 3). One patient [with isocitrate dehydrogenase (*IDH*)-mutant grade 2 diffuse astrocytoma with methylated O^6-methylguanine-DNA-methyltransferase (*MGMT*)] treated with

Table 3. Summary of best overall response for assessable patients

	Overall (N = 69)
CBR, % (95% CI)[a]	17.4 (9.3—28.4)
ORR, % (95% CI)	2.9 (0.4—10.1)
Best overall response	
CR, n (%)	1 (1.4)
PR, n (%)	1 (1.4)
SD, n (%)	23 (33.3)
≥11 mo[b]	6 (8.7)
≥4 mo	10 (14.5)
PD, n (%)	32 (46.4)
NE	12 (17.4)
mPFS, mo (95% CI)	1.9 (1.7—2.7)
mOS, mo (95% CI)	5.9 (5.3—8.4)

CBR, clinical benefit rate; CR, complete response; mOS, median overall survival; mPFS, median progression-free survival; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a] CBR is defined as CR, PR, or SD≥4 months.
[b] Data as of 8 October 2019. All other data are based on a cutoff of 9 April 2019.

CC-90010 30 mg for 4 days on/24 days off achieved a complete response (CR) and remains on treatment in cycle 11 (Figure 1). T2-weighted magnetic resonance imaging in this patient demonstrated the presence of an enhancing area surrounded by a non-enhancing infiltrative area at baseline. The radiological response was observed in this patient as evidenced by the disappearance of the enhancing and non-enhancing areas after six cycles of CC-90010 (Figure 2A). Another patient with endometrial carcinoma harboring amplifications of estrogen receptor-alpha (ERα), an *ESR1-AKAP12* gene fusion, and mutations in *PIK3CA* and *FGFR2* who received CC-90010 40 mg for 3 days on/11 days off achieved a partial response (PR); this patient remained on treatment for eight cycles (Figure 2B). Additionally, a patient with metastatic malignant thymoma on treatment for >1 year had tumor reduction of 17% in target lesions (Figure 2C). As of 8 October 2019, six patients (8.7%) had prolonged stable disease (SD) ≥11 months, four with salivary gland carcinoma, one with epithelial thymic carcinoma, and one with nasopharyngeal carcinoma. At the time of the analysis, eight patients were still on treatment with a median SD follow-up duration of 5.3 months. Twelve patients remained on treatment beyond 6 months with clinical benefit (CR, PR, or SD ≥4 months). The median duration of progression-free survival was 1.9 months (1.7—2.7).

Pharmacokinetics

Overall, there was a dose-proportional increase in CC-90010 plasma exposure in each dosing schedule**.** The median time to achieve peak plasma concentrations across all dose levels was approximately 1—2 h post-dose. The geometric mean terminal half-life of CC-90010 at the RP2D and schedule (45 mg 4 days on/24 days off) was approximately 60 h [±15% coefficient of variation (CV)] (Figure 3A and B).

There was a quantifiable pre-dose CC-90010 concentration in the cerebrospinal fluid (CSF) sample collected on cycle 1 day 23 from a patient with medulloblastoma treated with CC-90010 35 mg for 2 days on/5 days off each week (supplementary Table S5, available at *Annals of Oncology* online). The CSF/plasma concentration ratio of CC-90010 was 6.6%. CC-90010 in CSF samples continued to increase up to 2 h after the administration of the last dose on day 23, reaching the threshold for preclinical activity (supplementary Figure S3, available at *Annals of Oncology* online).

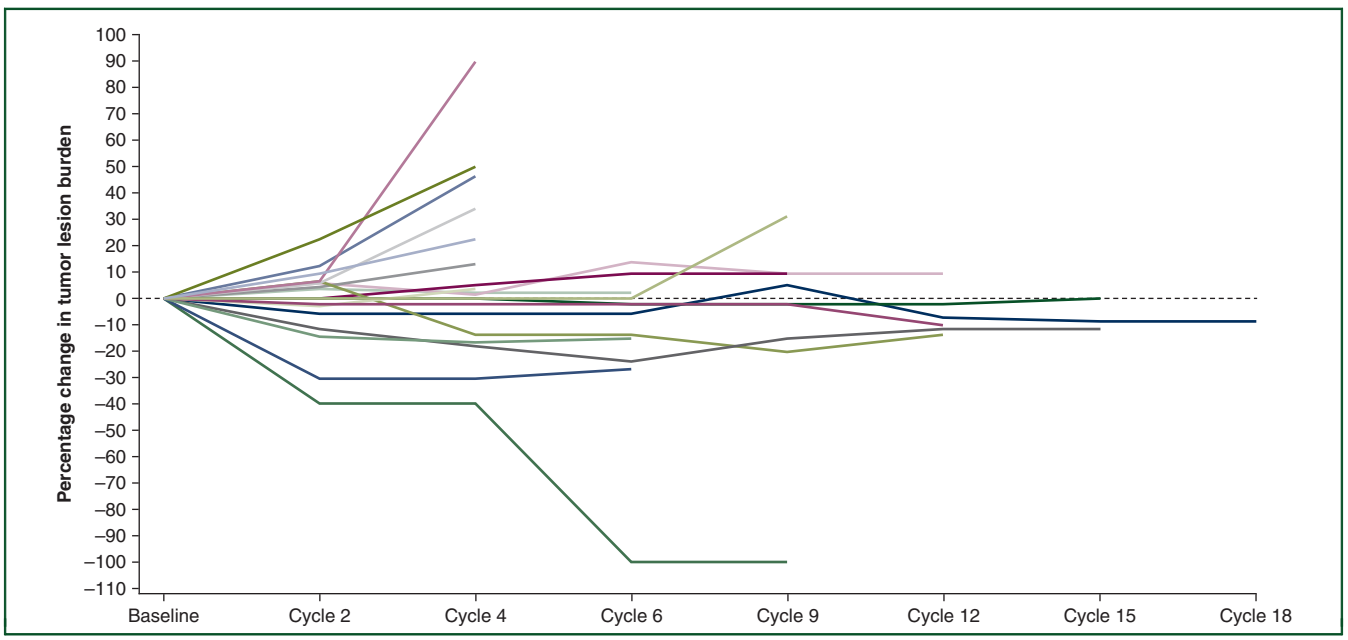


Figure 1. Change in tumor burden in response to CC-90010.
Spider plot tumor burden changes during CC-90010 therapy. Longitudinal changes of tumor burden therapy are shown in reference to baseline.

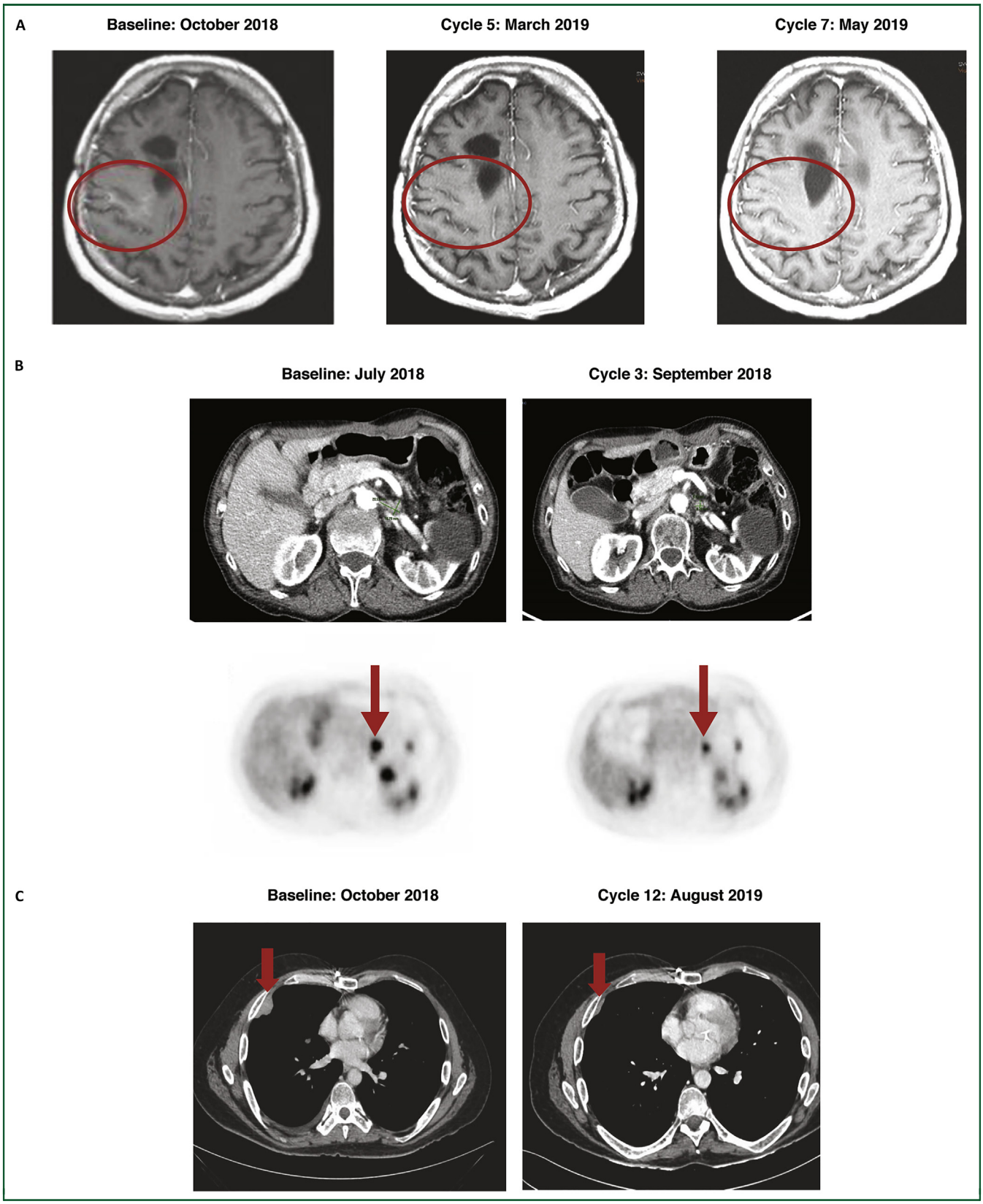
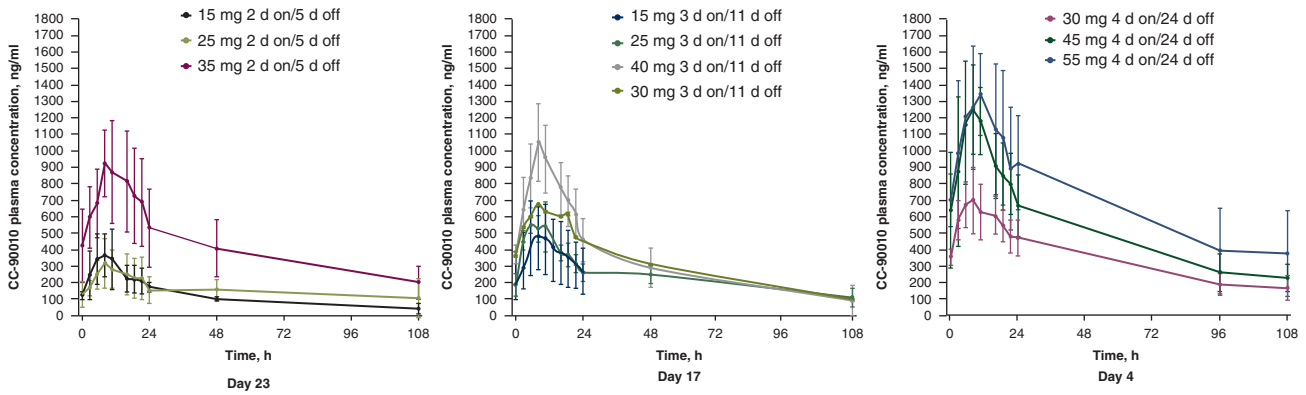


Figure 2. MRI and PET/CT scans of patients treated with CC-90010.
(A) T2-weighted MRI scans confirm the complete response in a patient with grade 2 astrocytoma demonstrated by the disappearance of both enhancing and non-enhancing areas compared with baseline (indicated with red circles). (B) PET/CT confirm the partial response after two cycles of CC-90010 in a patient with endometrial carcinoma. (C) CT scans demonstrate the reduction in tumor size in a patient with metastatic malignant thymoma.
CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

A



B

CC-90010 exposure		Weekly (2 days on/5 days off)			Biweekly (3 days on/11 days off)				Monthly (4 days on/24 days off)		
		15 mg (*n* = 6)	25 mg (*n* = 7)	35 mg (*n* = 6)	15 mg (*n* = 7)	25 mg (*n* = 4)	35 mg (*n* = 6)	40 mg (*n* = 6)	30 mg (*n* = 6)	45 mg (*n* = 7)	55 mg (*n* = 6)
$AUC_{0\text{-last}}$, ng·h/ml	LD	13121 (4)	12933 (95)	40563 (77)	6933 (62)	26364 (17)	35265 (15)	31794 (26)	38837 (26)	46216 (55)	58720 (73)
C_{max}, ng/ml	D1	216 (39)	309 (92)	451 (48)	239 (29)	371 (39)	486 (47)	550 (22)	383 (32)	631 (54)	707 (52)
	LD	362 (38)	302 (58)	979 (27)	485 (56)	609 (15)	792 (25)	1042 (22)	776 (16)	1303 (25)	1395 (23)
Median $T_{max, h}$	D1	2.0	1.6	1.8	1.5	1.7	1.5	1.6	1.5	1.1	1.6
	LD	1.6	1.5	2.1	1.4	1.0	1.5	1.5	1.8	1.5	1.7

Figure 3. Mean plasma concentration time profiles after last dose of CC-90010.
(A) Profiles following last dose of CC-90010 in cycle 1 by dose schedule. (B) Summary of CC-90010 plasma parameters by dose level and treatment. Data are the geometric mean (percent geometric coefficient of variation) for AUC and C_{max} parameters and median (range) for T_{max}. AUC_{0-last} values for dose levels 1 and 2 are identical to AUC values since pharmacokinetic sample collections were only collected up to 24 h post-dose. Cycle 1, last dose was on day 17 for dose levels 1, 2, 3A, 4A, and 5A; day 4 for dose levels 3B, 4B, and 5B; and day 23 for dose levels 3C, 4C, and 5C. The patients enrolled in dose level 1 ($n = 7$) are not reported.
AUC_{0-24}, area under the plasma concentration-time curve calculated from time 0 to 24 h; AUC_{0-last}, area under the plasma concentration-time curve calculated from time 0 to the last measurable sample; C_{max}, maximum plasma concentration; D1, day 1; LD, cycle 1 last dose; T_{max}, time to peak plasma concentration.

Pharmacodynamics

Modulation of the BRD2 and BRD4 target gene, C-C motif chemokine receptor 1 (CCR1), by BET inhibition has been demonstrated in a number of human hematologic and solid tumor cell lines, xenograft models, and *ex vivo* treated human peripheral blood mononuclear cells.[29,30] Additionally, CCR1 has been used as a PD marker of BET inhibition in clinical trials, where 50% suppression of this marker compared with pre-dose baseline was associated with clinical response in patients with R/R lymphoma.[31] Four hours after the first dose of CC-90010, CCR1 mRNA levels decreased by ≤36% (±5% CV) of baseline in patients who received 15 mg (2 days on/5 days off) and by 60% in patients who received the monthly schedule (55 mg 4 days on/24 days off) (supplementary Figure S4A, available at *Annals of Oncology* online). Maximal CCR1 decrease was observed after repeat dosing, with ≥50% (±5% CV) down-regulation at doses ≥25 mg 4 h after the last dose. Notably, among the MTDs established for each dosing schedule, the monthly dosing schedule demonstrated the most profound CCR1 suppression 4 h after the first dose and 4 h after the last dose of CC-90010 (supplementary Figure S4A, available at *Annals of Oncology* online). All MTDs maintained CCR1 levels below the baseline within the first 72 h after the first dose, with the monthly schedule (45 mg 4 days on/24 days off) achieving ≥50% suppression of CCR1 at 48 and 72 h (supplementary Figure S4B, available at *Annals of Oncology* online). CCR1 levels returned to at least 100% of pre-dose baseline in each of the three established MTDs at 168 h, coinciding with ≤50% CC-90010 concentration present in the blood. Although the levels of CCR1 return to baseline at 168 h after the first dose, correlating with a diminishing plasma concentration of CC-90010, ≥50% suppression of CCR1 was observed ≥96 h after the first dose (24 h after the last CC-90010 dose) at the selected RP2D (45 mg 4 days on/24 days off). This relatively long and deep post-dose suppression of CCR1 was the most sustained target engagement of all MTDs established in the study. Additionally, other markers, such as CCR2, demonstrated ≥50% suppression up to 192 h after the first dose at the higher dose levels tested (data not shown).

DISCUSSION

Multiple BET inhibitors are currently in phase Ib/II trials in solid and hematologic malignancies.[19,20,22,23] This phase I study investigated the tolerability, PK, and preliminary antitumor activity of CC-90010, a second-generation, oral, reversible BET inhibitor, in patients with advanced or unresectable solid tumors and R/R advanced NHL. CC-90010 was well tolerated in these heavily pretreated patients; treatment-related AEs were mostly mild and manageable, with short dose interruptions/reductions. The monthly and biweekly dosing schedules have a similar safety profile that is more tolerable than the weekly dosing schedules. Moreover, objective responses were seen with both the monthly (4 days on/24 days off) and biweekly dosing (3 days on/11 days off) schedules, suggesting that intermittent BRD4 inhibition is sufficient to drive antitumor effects.

CCR1 has been previously used as a blood PD marker of BET inhibition in clinical trials.[29–31] Biomarker analysis indicated target engagement and dose/schedule dependency, with the MTD on the monthly schedule (4 days on/24 days off) achieving the deepest CCR1 suppression ($\geq$50%) at least 96 h after the first dose of CC-90010 in cycle 1. Another BET inhibitor, CPI-0610, demonstrated $\geq$50% suppression of CCR1 at 6 h post-dose, which correlated with the clinical response in patients with R/R lymphoma.[31] Pharmacokinetic parameters were dose-proportional for the evaluated doses. Importantly, CC-90010 has a longer terminal half-life [$\sim$60 h ($\pm$15% CV)] for the RP2D than other BET inhibitors, which enables less frequent dosing. Birabresib, dosed once daily continuously, showed a terminal half-life of 3.6—5.3 h.[22] The terminal half-life of another BET inhibitor in development (OTX-015), was approximately 5.7 h at doses given once daily and 6.2 h at a dose given twice daily.[32] In contrast to other BET inhibitors, CC-90010 may be a suitable treatment option for CNS tumors, as evidenced by its detection in the CSF sample of a medulloblastoma patient on cycle 1 day 23 and the CR observed in a patient with diffuse astrocytoma. Additionally, the quantifiable pre-dose concentration of CC-90010 on cycle 1 day 23 suggests some accumulation of CC-90010 in the CSF, with CC-90010 concentrations increasing up to 2 h post-dose.

CC-90010 showed promising preliminary antitumor activity in patients with advanced malignancies, who have limited treatment options. The best clinical outcomes in the study were a durable CR in a patient with progressive grade 2 diffuse astrocytoma and a PR in a patient with advanced endometrial carcinoma. Molecular analysis revealed that the patient with endometrial carcinoma harbored an *ESR1* gene amplification. *ESR1* amplifications truncate the hormone-binding domain region of *ESR1*, contributing to resistance to anti-estrogen therapy in endometrial carcinomas.[33–35] This finding and the observed response warrant further investigation of the potential therapeutic role of BET inhibitors in endometrial carcinomas with hormone-binding alterations of ERα. The patient with progressive grade 2 astrocytoma had methylated *MGMT*. Methylation of the *MGMT* promoter is observed in approximately 50% of glioblastoma patients and is considered a strong prognostic factor; patients treated with radiotherapy and TMZ with methylated *MGMT* have a longer median survival time compared with those with unmethylated *MGMT*.[36,37] In preclinical studies, CC-90010 alone or in combination with TMZ down-regulated *MGMT* gene expression in glioblastoma patient-derived xenografts in a dose-dependent manner and sensitized glioblastoma cells to TMZ (unpublished data). Moreover, the decrease in MGMT protein in response to CC-90010 combined with TMZ in glioblastoma xenografts was maintained up to 48 h post-treatment (unpublished data).

Further clinical investigation of CC-90010 in combination with different therapeutic agents is warranted. The dose-escalation portion of the study is completed. The established MTDs were 15 mg (2 days on/5 days off), 30 mg (3 days on/11 days off) and 45 mg (4 days on/24 days off schedule). The RP2Ds were 30 mg (3 days on/11 days off) and 45 mg (4 days on/24 days off). CC-90010 at 45 mg using the monthly dosing schedule (4 days on/24 days off) was selected for further development because of fewer dose modifications and interruptions, higher cumulative exposures, and more extensive and prolonged target engagement (based on CCR1 decrease). Moreover, 4 days of dosing enabled high drug loading and provided an extended period for bone marrow recovery before the next dosing cycle. In part B of this study, the monthly dosing schedule is being evaluated in three cohorts: R/R DLBCL, advanced basal cell carcinoma, and other advanced solid tumors to evaluate food effect and preliminary efficacy signals.

In summary, the results from this dose-escalation study demonstrated a good safety profile, favorable PK and PD, with encouraging preliminary signs of antitumor activity of CC-90010 in heavily pretreated patients with advanced solid tumors and R/R NHL. BET inhibition may be effectively combined with various other treatments.[14,15,38,39] The results reported here support further exploration of CC-90010 as monotherapy or in combination with other therapeutic agents.

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DISCLOSURE

VM served as a consultant for Merck, Bristol-Myers Squibb, and Janssen, participated in a speaker's bureau for

Nanobiotix and Bristol-Myers Squibb, and received an educational grant from Medscape/Bayer. JMS served as a consultant for AbbVie, Celgene, GW Pharma, and Mabxience, received research grants from Pfizer and Catalysis, travel funding from Ibsen and AbbVie, and participated in the speaker's bureau for Astellas. MV received travel funding from Roche. T.H-G and B.G. have no conflicts of interest to declare. OS received travel funding from Mundipharma, Teva Pharmaceutical, Merck Sharp & Dohme, Grünenthal, Kyowa Kirin, and Boehringer-Ingelheim. OF has no conflicts of interest to declare. RS is an employee of and has received travel funding from Celgene Institute for Translational Research Europe, a Bristol-Myers Squibb Company, and has equity ownership with Bristol-Myers Squibb. MA has no conflicts of interest to declare. JdA is an employee of Celgene Institute for Translational Research Europe, a Bristol-Myers Squibb Company. JD is a former employee of Bristol-Myers Squibb. MZ is an employee of and has equity ownership with Bristol-Myers Squibb. TSP is an employee of and has received travel funding from Celgene Institute for Translational Research Europe, a Bristol-Myers Squibb Company. IA is an employee of and has equity ownership with Bristol-Myers Squibb. EF is an employee of and has received travel funding from Bristol-Myers Squibb, and has equity ownership with Bristol-Myers Squibb, Amgen, Gilead, Genentech/Roche. ML is an employee of Bristol-Myers Squibb and has equity ownership with Bristol-Myers Squibb, Pfizer. BH is an employee of, has equity ownership, and received research funding from Bristol-Myers Squibb. ZN is an employee of and has received travel funding from Celgene Institute for Translational Research Europe, a Bristol-Myers Squibb Company, and has equity ownership with Bristol-Myers Squibb. IB received research funding from Celgene, AstraZeneca, Bristol-Myers Squibb, Gliknik, GlaxoSmithKline, Janssen, Kura Oncology, Merck Sharp & Dohme, Novartis, Orion Pharma, and Pfizer, served as a consultant for Orion Pharma, participated in the speaker's bureau for Bristol-Myers Squibb, AstraZeneca, and Merck Serono, and received travel funding from AstraZeneca and Merck Serono.

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