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Phase 1 study of anti-CD47 monoclonal antibody CC-90002 in patients with relapsed/refractory acute myeloid leukemia and high-risk myelodysplastic syndrome

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Abstract

CC-90002 is an anti-CD47 antibody that inhibits CD47-SIRPα interaction and enables macrophage-mediated killing of tumor cells in hematological cancer cell lines. In this first clinical, phase 1, dose-escalation and -expansion study (CC-90002-AML-001; NCT02641002), we evaluated CC-90002 in patients with relapsed/refractory acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS). CC-90002 was administered in escalating doses of 0.1–4.0 mg/kg, using a modified 3+3 design. Primary endpoints included dose-limiting toxicities (DLTs), non-tolerated dose (NTD), maximum tolerated dose (MTD), and recommended phase 2 dose. Secondary endpoints included preliminary efficacy, pharmacokinetics, and presence/frequency of anti-drug antibodies (ADAs).

Between March 2016 and July 2018, 28 patients were enrolled (24 with AML and 4 with MDS) at 6 sites across the United States. As of July 18, 2018, all patients had discontinued, mainly due to death or progressive disease. The most common treatment-emergent adverse events were diarrhea (46.4%), thrombocytopenia (39.3%), febrile neutropenia (35.7%), and aspartate aminotransferase increase (35.7%). Four patients experienced DLTs (1 patient had grade 4

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Ethics approval: The protocol was reviewed and approved by each site's Institutional Review Board prior to initiation of the study.

Consent to participate: 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 guidance. All patients provided written informed consent.

disseminated intravascular coagulation and grade 5 cerebral hemorrhage, 1 had grade 3 purpura, 1 had grade 4 congestive cardiac failure and grade 5 acute respiratory failure, and another had grade 5 sepsis). The NTD and MTD were not reached. No objective responses occurred. CC-90002 serum exposure was dose-dependent. ADAs were present across all doses, and the proportion of ADA-positive patients in cycle 1 increased over time. Despite no unexpected safety findings, the CC-90002-AML-001 study was discontinued in dose escalation for lack of monotherapy activity and evidence of ADAs. However, as other anti-CD47 agents in clinical trials are showing promising early results for AML and MDS, understanding preclinical and clinical differences between individual agents in this class will be of high importance.

Keywords

Safety; SIRPα; IgG4PE; Macrophages; Hematological Cancer

Introduction

Acute myeloid leukemia (AML) is a biologically and clinically heterogeneous disease characterized by rapid disease progression [1]. Although progress has been made in understanding the biology of AML and advances in prognostic risk stratification have optimized established therapies, the overall long-term survival remains poor [1]. Myelodysplastic syndromes (MDS) comprise a group of clonal myeloid neoplasms characterized by cytopenias due to ineffective hematopoiesis and abnormal blood and marrow cell morphology [2]. High-risk MDS is generally progressive in nature with an inherent tendency for leukemic transformation [3]. Currently approved therapies for MDS have a limited effect on overall survival, and no treatment options have been approved post-hypomethylating agent failure [3]. Novel targeted therapies offer the promise of effective anti-leukemic activity with reduced toxicity from off-target effects.

CD47 is a widely expressed transmembrane protein involved in diverse cellular functions, including proliferation, adhesion, migration, apoptosis, self-recognition, and phagocytosis [4–9]. CD47 interaction with signal-regulatory protein-alpha (SIRPα), expressed on macrophages, delivers an antiphagocytic “don’t eat me” signal that promotes tumor cell escape of immune surveillance and destruction by phagocytes [10,11,6]. CD47 is overexpressed in various malignancies and is correlated with negative prognosis in AML [6]. Additionally, expression of CD47 is increased in patients with higher-risk MDS than those with lower-risk MDS [12].

CC-90002, a humanized IgG4-PE (immunoglobulin G4 with S228P and L235E mutation) anti-CD47 monoclonal antibody, blocks CD47-SIRPα interactions, thereby enabling macrophage-mediated killing of tumor cells [13,14]. CC-90002 contains a mutated heavy chain constant region, γ4, from IgG4, which reduces the production of the half-antibody and the interaction of the γ4 chain with the FcγR receptor, and was designed to reduce Fc-mediated effector function in order to minimize the risk of effector function-related complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity in CD47-expressing normal tissues [13–16]. In preclinical studies, CC-90002 enabled antibody-

mediated phagocytosis of a panel of hematological cancer cell lines in vitro, including acute lymphocytic leukemia, multiple myeloma, and AML, as well as 3 primary AML patient samples [14]. CC-90002 also demonstrated antitumor activity against several hematologic and solid tumor cell lines in xenograft models [14]. In multiple myeloma xenograft models, weekly dosing of CC-90002 led to macrophage-dependent tumor regression, with the majority of animals being tumor-free by the end of the study [17]. Furthermore, CC-90002 demonstrated robust antitumor activity and significantly prolonged survival in a patient-derived AML (HL-60) xenograft model in mice, providing the rationale for this phase 1 clinical trial. CC-90002 also showed acceptable pharmacokinetic properties and was well tolerated in cynomolgus monkeys [17]. Herein, we report key results from the AML xenograft model and from the dose-escalation portion of the subsequent phase 1 CC-90002-AML-001 study evaluating CC-90002 in patients with relapsed and/or primary refractory (R/R) AML and higher-risk MDS.

Materials and Methods

Patient-Derived AML Xenograft Mouse Model

Four-week-old, female, non-obese, diabetic, severe combined immunodeficiency (NOD-SCID) gamma (NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ; NSG) mice (The Jackson Laboratory, Sacramento, CA) were irradiated with a sublethal dose (≤150 RAD) of whole-body irradiation (WBI) prior to intravenous inoculation with human AML cells derived from a patient with an *FLT3*-ITD mutation who presented with circulating white blood cell counts of 293,000 cell/μL and died within 48 hours of hospital admission. After injection of viable human AML cells at 1.2×10^6 cells/mouse, the mice were randomized to one of the following 5 treatment groups 11 weeks after inoculation based on tumor burden in the blood (minimum of 10% human CD33+ [hCD33+] cells at baseline [day −8]; mean, 20% to 21% for all treatment groups): CC-90002 1 mg/kg, CC-90002 3 mg/kg, CC-90002 10 mg/kg, cytarabine (Ara-C) 60 mg/kg, and hIgG4 isotype control 10 mg/kg. Beginning at 12 weeks after inoculation (study day 0), treatment was administered intraperitoneally once weekly for 3 weeks (CC-90002 and hIgG4 isotype control) or once daily for 5 days (Ara-C). Tumor burden (percentages of hCD33+ cells) in the blood was assessed on study days 7, 14, and 21 by flow cytometry (Supplementary Figure 1). This study was conducted at the Jackson Laboratory, an Office of Laboratory Animal Welfare-assured and Association for Assessment and Accreditation of Laboratory Animal Care-accredited organization, according to an Institutional Animal Care and Use Committee-approved protocol and in compliance with the *Guide for the Care and Use of Laboratory Animals* [18].

Preclinical Pharmacokinetic Assessment in Cynomolgus Monkeys

A single-dose toxicity study was conducted using female, experimentally naïve, cynomolgus monkeys (*Macaca fascicularis*) from Charles River Laboratories (Reno, NV). Monkeys were administered 0 mg/kg (vehicle), 10 mg/kg, 30 mg/kg, or 100 mg/kg of CC-90002 via single intravenous (IV) injection (n = 3/group). A repeat-dose toxicity study was conducted using cynomolgus monkeys from Charles River Laboratories (Houston, TX); monkeys were administered 0 mg/kg (vehicle), 20 mg/kg, 60 mg/kg, or 150 mg/kg of CC-90002 via IV injection once weekly (Days 1, 8, 15, 22, and 29). Monkeys were

approximately 3 to 5 years of age and weighed 2.8 kg to 4.5 kg. Serum concentration of CC-90002 was determined using an enzyme-linked immunosorbent assay (ELISA) method. A CD47-mouse Fc fusion (CD47-mFc) protein was used as the coating and capture reagent, and CC-90002 was detected with a peroxidase-conjugated AffiniPure donkey anti-human IgG secondary antibody (Jackson ImmunoResearch; cat# 709–036-149). Subsequently, tetramethylbenzidine (TMB) was added to produce a colorimetric change. All experimental procedures were conducted in the accredited organizations and in compliance with the *Guide for the Care and Use of Laboratory Animals* at Huntington Life Sciences.

CC-90002-AML-001 Study Design

CC-90002-AML-001 was a phase 1 dose-escalation and -expansion study in patients with R/R AML or high-risk MDS (Supplementary Figure 2) [19]. The dose-escalation portion of the study explored escalating doses of CC-90002, using a modified 3+3 design [20]. 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 guidance. The protocol was reviewed and approved by each site's Institutional Review Board prior to initiation of the study. All patients provided written informed consent.

Primary objectives were to determine the safety and tolerability of CC-90002 and to determine the non-tolerated dose (NTD), maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D). Secondary objectives were to determine the preliminary efficacy of CC-90002, to characterize the pharmacokinetics (PK) of CC-90002, and to determine the presence and frequency of anti-drug antibodies (ADAs).

Exploratory objectives included the evaluation of pharmacodynamic (PD) markers of CC-90002 and leukemia response markers, exploration of the functional impacts of ADAs, the relationship between PD biomarkers and clinical activity, and the relationship between CC-90002 dose, exposure, and PD biomarkers.

Patients

Patients had R/R AML or MDS with subtype refractory anemia with excess blasts, defined as high- or very high-risk by the Revised International Prognostic Scoring System (IPSS-R) that is recurrent, refractory, or intolerant to established therapy. An Eastern Cooperative Oncology Group performance score of 0 to 2 was required. Key inclusion criteria were adequate hematologic (total white blood cell count $<25 \times 10^9$/L prior to first infusion), hepatic (aspartate aminotransferase and alanine aminotransferase $\leq 2.5 \times$ upper limit of normal [ULN], and serum bilirubin $\leq 1.5 \times$ ULN), and renal function (serum creatinine clearance ≥60 mL/min, uric acid ≤7.5 mg/dL), potassium within the normal limits or correctable with supplements, fibrinogen greater than the lower limit of normal, and partial thromboplastin time $<1.5 \times$ ULN.

Treatment

The starting dose of CC-90002 0.1 mg/kg was based on the preliminary clinical and laboratory data from the first-in-human phase 1 clinical study CC-90002-ST-001, the

efficacy and tolerability of CC-90002 observed in murine xenograft models, and findings from the nonclinical toxicology and PK studies [21]. In this study, CC-90002 was administered as an IV infusion in doses of 0.1, 0.3, 1.0, 2.0, and 4.0 mg/kg on days 1, 8, 15, and 22 of each 42-day cycle for cycles 1–4, followed by dosing on day 1 of each 28-day cycle for cycles 5–24 during the maintenance phase for patients with nonprogressive disease (Supplementary Figure 2). This schedule was based on the predicted half-life of CC-90002, following repeated dosing in cynomolgus monkeys in a previous preclinical study [17].

Study Assessments

Adverse events (AEs) were assessed according to the National Cancer Institute Common Terminology for Adverse Events, version 4.03. The dose-limiting toxicity (DLT) assessment window was cycle 1 (days 1 to 42). DLTs were defined as any grade ≥3 nonhematologic toxicity (excluding nausea or grade 3 tumor lysis syndrome [TLS], with medical management or grade 3 infusion-related reaction [IRR] with interruption of the infusion and medical management), hematologic toxicities (failure of recovery to an absolute neutrophil count $>0.5 \times 10^9$/L and/or platelet count $>25 \times 10^9$/L within 42 days after the first dose of CC-90002 or marrow without evidence of persistent leukemia/MDS, and grade 4 hemolysis), or any AE suspected to be drug-related and necessitating a dose-level reduction during cycle 1.

Blood samples for PK analysis were collected on days 1, 8, 15, and 22 of cycle 1, day 1 of cycles 2–4, and days 8 and 22 of cycle 2. Blood samples for the PD biomarker analyses for circulating AML blasts and peripheral blood mononuclear cells were collected on days 1, 2, and 16 of cycle 1. Serum-circulating tumor markers were assessed on days 1, 2, 4, 16, and 18 of cycle 1. Blood samples for ADA analysis were collected on days 1, 8, 15, and 22 of cycle 1, days 1 and 15 of cycles 2–4, and day 1 of each cycle thereafter.

Tumor assessments were performed in cycle 1 before the first dose of CC-90002, after infusion on day 15 of cycle 1, at the beginning of cycles 2–5, then every 3 cycles thereafter. Responses were assessed by the investigator per International Working Group criteria in AML and in MDS [22,23]. The objective response rate (ORR) for AML includes the rate of morphologic leukemia-free state (MLFS) + complete response (CR) + morphologic complete remission with incomplete blood count recovery (CRi) + cytogenic complete remission (CRc) + molecular complete remission (mCR) + partial response (PR). For MDS, the ORR includes the rate of CR + PR + marrow CR + hematologic improvement.

Statistical Analyses

All statistical analyses were performed by dose cohort as needed or applicable. Safety analyses were performed for all patients who received ≥1 dose of study treatment. The PK population comprised all patients who received ≥1 dose of study treatment and had ≥1 measured drug concentration assessment. For PK analysis, descriptive statistics were provided. The efficacy-evaluable population comprised all patients who completed ≥1 treatment cycle and had a baseline and ≥1 valid postbaseline efficacy assessment. A descriptive analysis of antitumor activity was provided based on clinical, laboratory, molecular, and cytogenetic assessments. The efficacy variables of focus were objective

response rate and complete remission rate. The PD biomarker-evaluable population comprised all patients who received ≥1 dose of study treatment and had a baseline and ≥1 postbaseline evaluation.

Data Sharing Statement

Bristol Myers Squibb company policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. Data requests may be submitted to Celgene, a Bristol Myers Squibb Company, at https://vivli.org/ourmember/Celgene/ and must include a description of the research proposal.

Results

Preclinical Antitumor Activity

NSG mice irradiated with sublethal WBI and inoculated with human AML cells were treated with CC-90002 (1, 3, and 10 mg/kg), Ara-C (60 mg/kg), or human IgG4 isotype control (10 mg/kg). On study day 2, 9 of 10 mice in the CC-90002 10 mg/kg treatment group and 2 of 10 mice in the 3 mg/kg treatment group died. The baseline percentage of hCD33+ cells for the one surviving animal from the CC-90002 10 mg/kg group was 15.2%. No tolerability issues were detected in the other groups. Dose-dependent deaths in the CC-90002–treated animals were attributed to rapid tumor reduction analogous to TLS. In surviving mice, tumor burden was assessed in the blood on study day 7. The results showed that CC-90002 decreased tumor burden from baseline by 85%, 85%, and 92% in the 1, 3, and 10 mg/kg treatment groups, respectively, compared with a 56% reduction in the Ara-C treatment group and no reduction in the isotype control group (Figure 1). The reduction of AML burden persisted at later time points in the CC-90002–treated mice, with no further deaths following repeated dosing. In summary, results from the preclinical study demonstrating potent tumor reduction in a primary AML xenograft model with toxicity similar to TLS in mice receiving higher doses of CC-90002 confirmed previous preclinical findings and provided the rationale for investigating CC-90002 monotherapy in patients with AML/MDS [17,14].

Preclinical Pharmacokinetic Assessment

Following a single IV dose of CC-90002 at 10, 30, and 100 mg/kg in cynomolgus monkeys, drug clearance was approximately 2.8-fold higher at 10 mg/kg (0.91 mL/h/kg) than at 30 mg/kg (0.32 mL/h/kg) or 100 mg/kg (0.32 mL/h/kg). The higher clearance at the 10 mg/kg dose of CC-90002 and the nonlinear kinetics were attributed to target-mediated drug disposition. In the repeat-dose toxicity study, the rate of clearance was higher at 20 mg/kg (0.74 mL/h/kg) than at 60 mg/kg (0.33 mL/h/kg) or 150 mg/kg (0.26 mL/h/kg), which was consistent with the higher rate of clearance observed for the 10 mg/kg dose in the single-dose study. Longer half-life was observed at ≥30 mg/kg dose of CC-90002 (4.5 to 5.5 days), as compared with doses of 10 mg/kg (0.6 days) and 20 mg/kg (2.4 days) (Supplementary Table 1).

Patients and Treatment

A total of 28 patients were enrolled and treated in the CC-90002-AML-001 study, including 24 with R/R AML and 4 with MDS at 6 sites across the United States (Supplementary Table 2). The overall median age was 70 years (range, 28–85), and 57.1% were male (Table 1). Patients had received a median of 3 (range, 1–10) prior systemic anticancer regimens, and 28.6% of patients had received a prior allogeneic stem cell transplant. The proportion of patients with cytogenetic abnormalities was the same among those with AML (n = 18/24 [75.0%]) and MDS (n = 3/4 [75.0%]). Among the 24 patients with AML, 4 (16.7%) had recurrent genetic abnormalities, 9 (37.5%) had AML with myelodysplasia-related changes, 9 (37.5%) had AML not otherwise specified, and 2 (8.3%) had therapy-related myeloid neoplasms. Patients with AML had a median of 40.6% (range, 10.0%–85.0%) bone marrow blasts, and patients with MDS had a median of 11.8% (range, 1.4%–14.0%) bone marrow blasts at study entry. The median peripheral blast count was 0.0×10^9 cells/L (range, 0–73 $\times 10^9$ cells/L) and median white blood cell count was 2.6×10^9 cells/L (range, 0.3–14.7 $\times 10^9$ cells/L) among all 28 patients. Most patients were red blood cell (82.1%) and platelet (71.4%) transfusion dependent. All 4 patients with MDS were classified as having refractory anemia with excess blasts-2. Three patients had high- or very high-risk disease per the IPSS-R.

As of the July 18, 2018, the data cutoff date, all 28 patients had discontinued the study. Reasons for discontinuation were death (n = 14; 50.0%), progressive disease (n = 7; 25.0%), treatment-emergent adverse events (TEAEs) (n = 3; 10.7%), withdrawal by patient (n = 2; 7.1%), lack of efficacy (n = 1; 3.6%), or an unspecified reason (n = 1; 3.6%). The overall median duration of CC-90002 treatment was 6.9 weeks (range, 2.0–44.1) (Supplementary Table 3). The median number of cycles administered in the induction phase was 1.5, and the median number of completed treatment cycles was 1.0. The single patient who proceeded to the maintenance phase completed 4.0 treatment cycles. The median relative dose intensity was 100% (range, 87.5%–104.8%). There were 6 PK-evaluable patients in each of the CC-90002 0.1 mg/kg, CC-90002 0.3 mg/kg, CC-90002 1.0 mg/kg, and CC-90002 4.0 mg/kg dose cohorts and 4 PK-evaluable patients in the CC-90002 2.0 mg/kg dose cohort.

Safety

TEAEs occurring in ≥15% of patients are reported in Table 2. All patients experienced ≥1 TEAE, and the incidence of events was comparable across all dose cohorts. The most common any-grade TEAEs overall were diarrhea (46.4%), thrombocytopenia (39.3%), febrile neutropenia (35.7%), aspartate aminotransferase increased (35.7%), and anemia, alanine aminotransferase increased, and cough (32.1% each). The most frequent grade 3/4 TEAEs were hematologic, with febrile neutropenia occurring in 10 patients (35.7%), thrombocytopenia in 9 patients (32.1%), anemia in 8 patients (28.6%), and neutropenia in 5 patients (17.9%). Overall, 19 patients (67.9%) had ≥1 TEAE suspected of being treatment-related (Supplementary Table 4). The most common treatment-related AEs (>10%) of any grade were aspartate aminotransferase increase (17.9%), alanine aminotransferase increase (14.3%), and diarrhea (10.7%). Among 8 patients (28.6%) who experienced grade 3/4 treatment-related AEs, only anemia and thrombocytopenia (7.1% each) occurred in >1 patient. Most patients (82.1%) had a serious AE, with febrile neutropenia (n = 10),

bacteremia (n = 4), pneumonia (n = 4), and general physical health deterioration (n = 3) occurring in >2 patients (Supplementary Table 5). No patients experienced adverse events of hemolysis, TLS, macrophage activation or cytokine release syndrome. Three patients (10.7%) had ≥1 IRR during the study, 1 in the 1.0-mg/kg dose cohort and 2 in the 4.0-mg/kg dose cohort.

No patients had a dose reduction. One patient (3.6%) in the 0.1-mg/kg dose cohort had a TEAE that led to dose interruption 7.1 weeks after treatment initiation, and 7 patients (25%) discontinued CC-90002 due to TEAEs. Sixteen patients died during the study with 11 deaths considered treatment-emergent, defined as death that occurred within 56 days of the last dose. Primary causes were death from an AE in 6 patients (37.5%) and malignant disease or complication due to malignant disease in 10 patients (35.7%).

Among the 26 DLT-evaluable patients, 4 experienced a DLT: 1 patient in the 0.1-mg/kg cohort had grade 4 disseminated intravascular coagulation and grade 5 cerebral hemorrhage in the setting of rapid AML progression, 1 patient in the 0.3-mg/kg cohort had grade 3 purpura, 1 patient in the 1.0-mg/kg cohort had grade 4 congestive cardiac failure and grade 5 acute respiratory failure, and 1 patient in the 4.0-mg/kg cohort had grade 5 sepsis. The NTD and MTD were not identified.

Efficacy

No objective responses were observed in either patients with AML or MDS in the study. Of the 15 efficacy-evaluable patients with AML, 14 (93.3%) were classified as having treatment failure and data for the remaining patients were not reported. Of the 3 efficacy-evaluable patients with MDS, 2 patients (1 in the 1.0-mg/kg cohort and 1 in the 2.0-mg/kg cohort) achieved a best overall response of stable disease; the remaining patient (in the 0.1-mg/kg cohort) was classified as having treatment failure. Furthermore, hematologic improvements in MDS were not observed for any patient through day 1 of cycle 5. At the end of treatment, 1 MDS patient in the 1.0-mg/kg cohort achieved an erythroid response and platelet response.

Pharmacokinetics and Immunogenicity

CC-90002 rapidly reached maximum serum concentration within 0.8 to 2.4 hours after infusion (Figure 2; Table 3). Steady-state PK parameters (cycle 1, day 15) are summarized in Table 3. Serum exposures appeared to increase with dose over the 0.3 to 4.0 mg/kg dose range. The terminal half-life ranged from 4.6 to 17 hours. In general, as assessed from the geometric coefficient of variation, moderate-to-high interpatient variability was noted for CC-90002. No significant accumulation of CC-90002 was observed when comparing day 15 exposure with day 1 exposure.

ADAs targeting CC-90002 were present across all dose levels tested, and the proportion of patients testing positive for ADAs in cycle 1 increased over time (Table 4). At baseline, 2 of 28 patients (7.1%) were positive for ADAs, with a median titer of 3.0 (range, 1–5). Moreover, 4 (14.3%), 6 (21.4%), and 8 (28.6%) patients were positive for ADAs on days 8, 15, and 22, respectively. A similar trend was observed within each dose group, with an increasing proportion of ADA-positive patients over time (Supplementary Table 6). No apparent dose-ADA relationship was observed, and ADAs continued to be present across

different doses with increases in median serum titers after cycle 1. Additionally, 5 patients (17.9%) tested positive for ADAs 2 weeks and 4 weeks after their last dose.

Discussion

Prompted by promising data demonstrating rapid and robust tumor burden reduction in a disseminated disease animal model using patient-derived AML cells, this phase 1 clinical study evaluated the safety and efficacy of CC-90002 monotherapy in patients with R/R AML or high-risk MDS. No unexpected safety findings were observed compared with other studies in this patient population characterized by high morbidity and mortality rates. Most patients were red blood cell or platelet transfusion dependent at baseline in this study; however, in contrast to reports of other anti-CD47 antibodies [24,25], no patients experienced hemolysis. The NTD of CC-90002 could not be determined; therefore, the MTD could not be derived for this study. No objective responses were observed. The proportion of ADA-positive patients increased across all doses, which may have affected the efficacy of CC-90002. Thus, the study was discontinued in dose escalation, not based on safety concerns that posed unacceptable risk in this patient population but based on a preliminary lack of CC-90002 monotherapy clinical activity and evidence of ADAs.

In a mouse xenograft model of disseminated AML, CC-90002 resulted in a rapid reduction of tumor burden of at least 85% by day 7 after the first dose, compared with a 56% reduction with Ara-C and no reduction with isotype control antibody. Consistent results were obtained at later time points, supporting a sustained tumor-reducing effect of CC-90002. The occurrence of mouse deaths in two of the CC-90002 groups after the initial dose was concluded to be due to the introduction of CC-90002 in the presence of high disseminated AML tumor burden (e.g., TLS), because no additional deaths occurred following repeated dosing after >80% reduction in tumor burden.

In the CC-90002-AML-001 study, the best overall response was stable disease, reported in 2 patients with MDS. It was not possible to determine whether the active dose level of CC-90002 in patients was in the range of that associated with anti-tumor activity in the mouse xenograft studies because of the lack of a CD47 tissue sink in the mouse model and functional differences in the interaction of NSG innate immune cells with the CC-90002 IgG4PE isotype. Immunogenicity analysis showed that many patients receiving CC-90002 monotherapy were positive for ADAs, which were present across different doses, throughout the treatment cycle, and even after the last dose. ADAs are thought to neutralize target binding or enhance drug clearance, resulting in suboptimal levels of active drug [26–28]. The presence of ADAs in patients after cycle 2, and the fact that the proportion of ADA-positive patients generally increasing with dosing, suggests that ADAs may have impacted CC-90002 PK and reduced exposure, thereby affecting clinical activity. However, a direct effect of ADAs on the PK of CC-90002 would require confirmation in future analyses.

Consistent with this, moderate-to-high interpatient variability of PK parameters was noted, and there was no significant accumulation of CC-90002 when comparing exposure on day 15 and day 1. There was no clear relationship between dose and ADAs; however, the small sample size in each dosing group limits interpretation of these results. In addition to ADAs,

an extensive CD47 tissue sink in humans may have impacted exposure. PK assessments of CC-90002 in cynomolgus monkeys following single and repeated weekly IV administration showed higher clearance and a shorter half-life of CC-90002 at 10 mg/kg and 20 mg/kg versus ≥30 mg/kg. This non-linear PK was similarly observed for magrolimab, another anti-CD47 monoclonal antibody, in patients with solid tumors [29]. These findings, together with the results of a cross-reactivity study of CC-90002 in human tissues showing extensive binding (data on file), indicate the presence of a large CD47 tissue sink in humans.

In this study, CC-90002 monotherapy did not produce an objective response in patients with R/R AML and MDS. Given the persistent presence of ADAs across all doses of 0.1 mg/kg to 4.0 mg/kg, a dose level of >4.0 mg/kg of CC-90002 monotherapy may not lead to improved efficacy. Results from this study in R/R AML and high-risk MDS did not offer a sufficiently encouraging profile for further dose escalation/expansion. However, a phase 1 dose-escalation and -expansion study evaluated CC-90002 plus rituximab in patients with CD20-positive non-Hodgkin lymphoma (NHL) and investigated whether this combination enhanced the efficacy of CD47 blockade or reduced the occurrence of ADAs as secondary endpoints (NCT02367196) [21].

Agents targeting the CD47-SIRPα pathway have nevertheless shown promising activity in hematologic malignancies. Magrolimab given in combination with rituximab, demonstrated a 50% objective response rate and 32% complete response rate in heavily pretreated and rituximab-refractory patients with R/R diffuse large B-cell lymphoma and follicular lymphoma [24]. In patients with AML or MDS, magrolimab monotherapy showed a 10% objective response rate and a favorable safety profile, but further development of magrolimab as a single agent has not been continued [30,31]. When magrolimab was given in combination with azacitidine, the objective response rate was 64% in patients with AML and 91% in patients with MDS [32]. The modest clinical activity of magrolimab monotherapy observed in patients with AML or MDS compared with the lack of activity with CC-90002 monotherapy may be due to isotype differences in magrolimab (IgG4) and CC-90002 (IgG4-PE) as well as increased magrolimab exposure with higher doses achievable without a significant impact of ADAs. Based on the improved efficacy of magrolimab in combination with other agents, it is possible that the antitumor activity of CC-90002 in AML or MDS could improve when given in combination with azacitidine or with measures to improve CC-90002 exposure (e.g., higher doses) and reduce ADAs (e.g., rituximab). Additionally, the combination of anti-CD47 with cytarabine has been shown to have synergistic effects in-vitro [33]. It is also important to note that intact T-cell function is required to harness the full therapeutic potential of anti-CD47 antibodies [8,34]. As R/R AML has been associated with T-cell exhaustion [35], additional studies to elucidate the immunologic landscape in patients treated with anti-CD47 antibodies are needed. This could provide further insights into the limited efficacy of CC-90002 in the R/R setting and may inform whether a combination of anti-CD47 antibodies with e.g., anti-PD1-directed therapies could have synergistic effects or whether responses in newly diagnosed AML or MDS differ from those in patients with R/R disease.

Potent CC-90002 preclinical activity in an AML xenograft model compared with the lack of objective responses in patients with R/R AML and MDS suggests murine models may

not accurately recapitulate the clinical experience with CD47-directed agents. There are several possible mechanisms for the disparate responses observed. CC-90002 does not bind murine CD47, which may have led to the lack of a tissue sink and increased concentration of CC-90002 in serum of xenograft models. Furthermore, the 10-fold enhanced affinity of the NSG SIRPα allele to human CD47 compared with syngeneic CD47-SIRPα interaction perhaps overrepresents the activity of CD47 blockade in mice engrafted with human tumors [36]. Finally, although human IgG4 is characterized as largely inert with respect to human effector cells, the IgG4-PE isotype of CC-90002 likely engages mouse FcγRs and provides an opsonization signal for mouse macrophages in xenograft models [37]. In light of these observations, achieving higher exposures (e.g., through increasing the dose or limiting ADA) and pairing CC-90002 with a tumor-specific, effector-competent monoclonal antibody (e.g., a tumor-specific IgG1) to provide an opsonization signal to macrophages may enhance the clinical activity of CD47 blockade with CC-90002.

Conclusion

The results presented here from the dose-escalation portion of this trial show that, despite promising preclinical antitumor effects, CC-90002 monotherapy did not show sufficient evidence of clinical activity in patients with R/R AML or high-risk MDS to warrant further clinical development of CC-90002 monotherapy for these indications. The presence of ADAs suggests reduced concentration of CC-90002 free to bind CD47 on tumors, potentially impacting the efficacy of single-agent CC-90002. Therefore, this study was discontinued due to the preliminary lack of CC-90002 single-agent activity and the evidence of ADAs and not for safety concerns in patients with R/R AML or high-risk MDS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest:

A.M.Z. received research funding from Celgene (a Bristol Myers Squibb Company), AbbVie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics; served as a consultant for and received honoraria from AbbVie, Otsuka, Pfizer, Celgene (a Bristol Myers Squibb Company), Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, BeyondSpring, Trovagene, Takeda, Ionis, Tyme, Amgen, Janssen, Gilead, Kura, Aprea, and Epizyme; and received travel support for meetings from Pfizer, Novartis, and Trovagene. D.J.D. received research funding from AbbVie, Glycomimetics, Novartis, and Blueprint Pharmaceuticals and served as a consultant for and received honoraria from Amgen, Autolus, Blueprint, Incyte, Jazz, Novartis, Pfizer, Servier, and Takeda. M.S.T. received research funding from AbbVie, Cellerant, Orsenix, ADC Therapeutics, and Biosight; served as a consultant for AbbVie, BiolineRx, Daiichi-Sankyo, Orsenix, KAHR, Rigel, Nohla, Delta Fly Pharma, Tetraphase, Oncolyze, and Jazz Pharma; and holds royalties with UpToDate. M.B. holds patents and royalties with Celgene (a Bristol Myers Squibb Company) and University of California and is an employee and equity owner with Bristol Myers Squibb. K.H. is an employee and equity owner with Bristol Myers Squibb and served

as a member of advisory board for Arcus Biosciences, Mersana Therapeutics, and Society for Immunotherapy of Cancer. W.S. received research funding from AbbVie, Amgen, Jazz, Pfizer, and Xencor; received honoraria from AbbVie, Amgen, and Pfizer; and served as a consultant for AbbVie, Amgen, Astella, GlaxoSmithKline, Kite, Jazz, Morphosys, and Pfizer. H. Raymon was an employee of and is an equity owner with Bristol Myers Squibb. X.W., P.S., and S.K. are employees of and equity owners with Bristol Myers Squibb. J.P., J.P.B. and C.S.S. declare no potential conflicts of interest.

Availability of data and material:

Bristol Myers Squibb company policy on data sharing may be found at https://www.bms.com/researchers-and-partners/independent-research/data-sharing-request-process.html. Data requests may be submitted to Celgene, a Bristol Myers Squibb Company, at https://vivli.org/ourmember/Celgene/ and must include a description of the research proposal.

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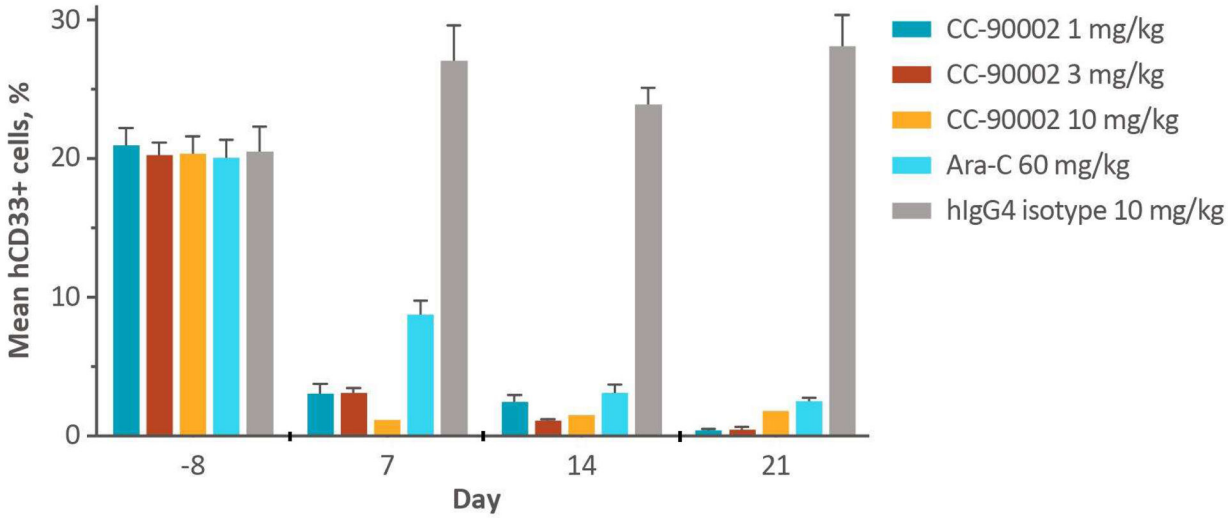

Figure 1. Tumor burden in blood from CC-90002–treated mice engrafted with human AML cells at 7-day intervals after the first weekly dose of CC-90002.

Error bars represent the standard error of the mean.

Abbreviations: Ara-C = cytarabine; hCD33+ cells = human CD33+ cells; hIgG4 = human immunoglobulin G subclass 4.

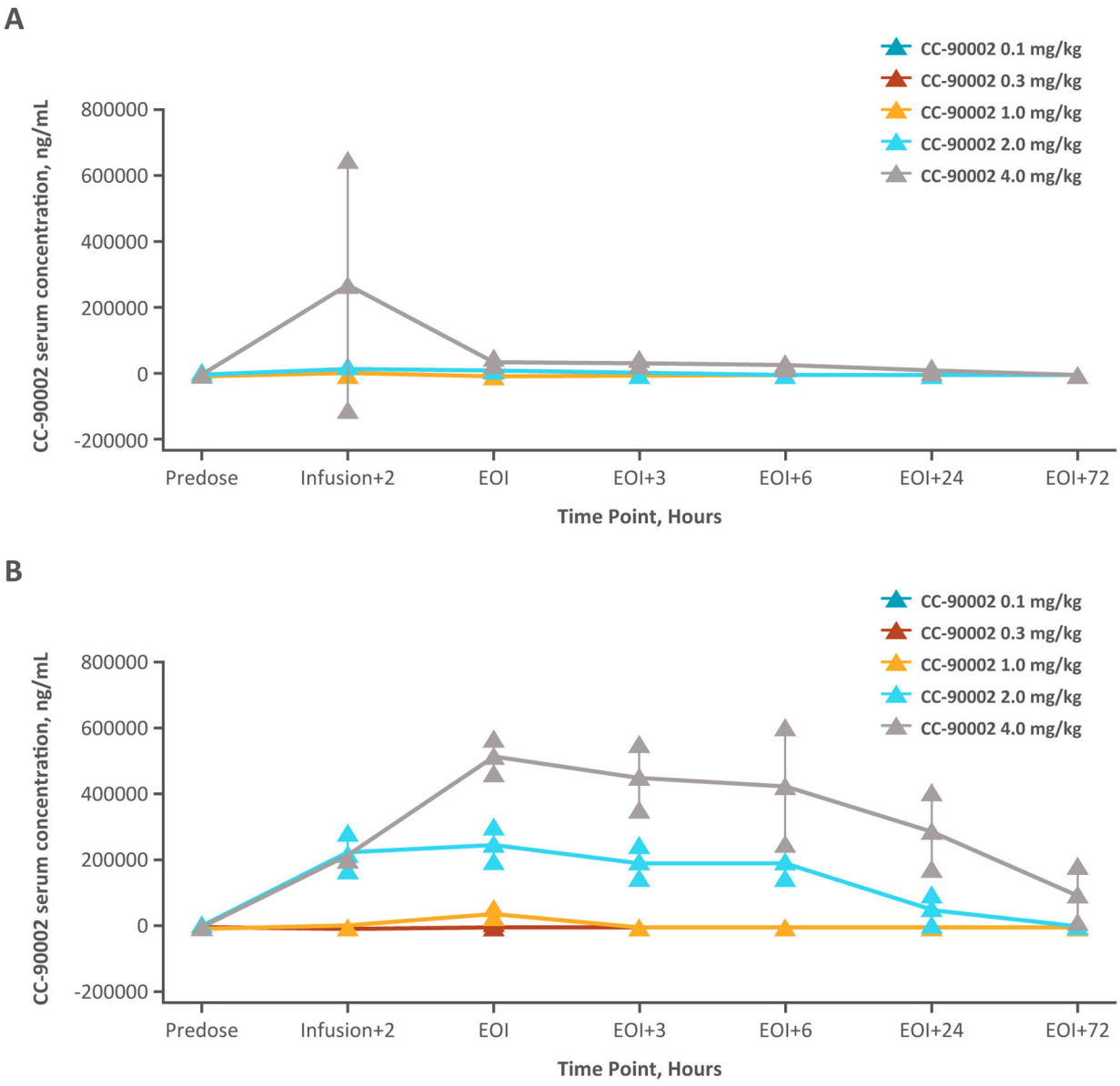

Figure 2. Mean serum concentration-time profiles of CC-90002 on cycle 1 day 1 (A) and cycle 1 day 15 (B).

Error bars represent standard deviation.

Abbreviation: EOI = end of infusion.

Table 1.

Patient Baseline Characteristics

Characteristic	Overall (n = 28)
Median age, y (range)	70 (28–85)
Age ≥65 y, n (%)	15 (53.6)
Male, n (%)	16 (57.1)
ECOG PS, n (%)	
0	6 (21.4)
1	18 (64.3)
2	2 (7.1)
Missing	2 (7.1)
Prior allogeneic SCT, n (%)	8 (28.6)
Median prior systemic anticancer regimens, n (range)	3 (1–10)
Median WBC, 10^9 cells/L[a] (range)	2.6 (0.3–14.7)
Median peripheral blast count, 10^9 cells/L (range)	0.0 (0.0–73.0)
AML disease diagnostics, n (%)	
With myelodysplasia-related changes	9 (37.5)
Not otherwise specified	9 (37.5)
With recurrent genetic abnormalities	4 (16.7)
Therapy-related myeloid neoplasms	2 (8.3)
AML cytogenetic abnormalities	
Complex (≥3 abnormalities)	4 (16.7)
inv(16)	1 (4.2)
5q-	1 (4.2)
Other	10 (41.7)
Missing	2 (8.3)
MDS disease diagnostics, n (%)	
High-risk MDS[b,c]	4 (100)
MDS cytogenetic abnormalities, n (%)	
Single/double independent clones[c]	1 (25.0)
Other	2 (50.0)
Median bone marrow blast for AML patients, % (range)[d]	40.6 (10.0–85.0)
Median bone marrow blast for MDS patients, % (range)[e]	11.8 (1.4–4.0)
RBC transfusion dependent, n (%)	23 (82.1)
Platelet transfusion dependent, n (%)	20 (71.4)
IPSS-R classification MDS, n (%)	
High	2 (50.0)
Very high	1 (25.0)
Missing	1 (25.0)

Abbreviations: AML = acute myeloid leukemia; ECOG PS = Eastern Cooperative Oncology Group performance status; IPSS-R = Revised International Prognostic Index Scoring System; MDS = myelodysplastic syndrome; RBC = red blood cell; SCT = stem cell transplantation; WBC = white blood cell.

[a] Collected in hematology laboratory tests.

[b] High-risk defined as refractory anemia with excess blasts-2.

[c] Denominator is number of patients with MDS.

[d] IPSS-R classification was not indicated in the clinical database; however, very high-risk disease in the patients was confirmed by IPSS-R classification indicated in eligibility forms.

[e] Collected in bone marrow aspirate.

Table 2.

Treatment-Emergent Adverse Events by Dose Cohort

	CC-90002 Dose Cohort, mg/kg										Overall (n = 28)	
	0.1 (n = 6)		0.3 (n = 6)		1.0 (n = 6)		2.0 (n = 4)		4.0 (n = 6)			
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
≥ 1 TEAE	6 (100)	6 (100)	6 (100)	5 (83.3)	6 (100)	5 (83.3)	4 (100)	4 (100)	6 (100)	5 (83.3)	28 (100)	25 (89.3)
Hematologic												
Thrombocytopenia	3 (50.0)	2 (33.3)	4 (66.7)	3 (50.0)	2 (33.3)	2 (33.3)	1 (25.0)	1 (25.0)	1 (16.7)	1 (16.7)	11 (39.3)	9 (32.1)
Febrile neutropenia	1 (16.7)	1 (16.7)	3 (50.0)	3 (50.0)	1 (16.7)	1 (16.7)	3 (75.0)	3 (75.0)	2 (33.3)	2 (33.3)	10 (35.7)	10 (35.7)
Anemia	2 (33.3)	2 (33.3)	3 (50.0)	2 (33.3)	2 (33.3)	2 (33.3)	0	0	2 (33.3)	2 (33.3)	9 (32.1)	8 (28.6)
Neutropenia	2 (33.3)	1 (16.7)	2 (33.3)	2 (33.3)	1 (16.7)	1 (16.7)	1 (25.0)	1 (25.0)	0	0	6 (21.4)	5 (17.9)
Gastrointestinal												
FDiarrhea	2 (33.3)	0	1 (16.7)	0	3 (50.0)	0	4 (100)	0	3 (50.0)	0	13 (46.4)	0
Abdominal Pain	1 (16.7)	0	2 (33.3)	0	1 (16.7)	0	1 (25.0)	0	1 (16.7)	0	6 (21.4)	0
Constipation	1 (16.7)	0	0	0	0	0	3 (75.0)	0	2 (33.3)	0	6 (21.4)	0
Nausea	1 (16.7)	0	0	0	2 (33.3)	0	1 (25.0)	0	1 (16.7)	0	5 (17.9)	0
Stomatitis	2 (33.3)	0	2 (33.3)	1 (16.7)	0	0	0	0	1 (16.7)	0	5 (17.9)	1 (3.6)
Other												
AST increased	1 (16.7)		1 (16.7)	0	3 (50.0)	0	2 (50.0)	0	3 (50.0)	0	10 (35.7)	0
ALT increased	1 (16.7)	0	1 (16.7)	1 (16.7)	3 (50.0)	0	2 (50.0)	0	2 (33.3)	1 (16.7)	9 (32.1)	2 (7.1)
Cough	4 (66.7)		2 (33.3)	0	0	0	0	0	3 (50.0)	0	9 (32.1)	0
Fatigue	2 (33.3)	0	1 (16.7)	1 (16.7)	2 (33.3)	0	3 (75.0)	1 (25.0)	0	0	8 (28.6)	2 (7.1)
Hypocalcemia	2 (33.3)	0	1 (16.7)	0	2 (33.3)	1 (16.7)	1 (25.0)	0	2 (33.3)	0	8 (28.6)	1 (3.6)
Hypokalemia	2 (33.3)	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	1 (16.7)	1 (25.0)	0	2 (33.3)	0	8 (28.6)	3 (10.7)
Blood alkaline phosphatase increased	2 (33.3)	0	1 (16.7)	0	2 (33.3)	0	0	0	2 (33.3)	0	7 (25.0)	0
Edema peripheral	2 (33.3)	0	3 (50.0)	0	0	0	1 (25.0)	0	1 (16.7)	0	7 (25.0)	0
Hypotension	1 (16.7)	0	2 (33.3)	0	1 (16.7)	0	1 (25.0)	0	2 (33.3)	0	7 (25.0)	0
Dyspnea	2 (33.3)	0	2 (33.3)	1 (16.7)	0	0	0	0	2 (33.3)	0	6 (21.4)	1 (3.6)
Hematuria	2 (33.3)	0	2 (33.3)	0	1 (16.7)	0	1 (25.0)	0	0	0	6 (21.4)	0
Hypomagnesemia	1 (16.7)	0	1 (16.7)	0	1 (16.7)	0	1 (25.0)	0	2 (33.3)	0	6 (21.4)	0

	CC-90002 Dose Cohort, mg/kg										Overall (n = 28)	
	0.1 (n = 6)		0.3 (n = 6)		1.0 (n = 6)		2.0 (n = 4)		4.0 (n = 6)			
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
White blood cell count decreased	2 (33.3)	1 (16.7)	0	0	3 (50.0)	0	0	0	0	0	5 (17.9)	3 (10.7)
Decreased appetite	0	0	1 (16.7)	0	0	0	2 (50.0)	1 (25.0)	2 (33.3)	0	5 (17.9)	1 (3.6)

Data presented as n (%). TEAEs occurring in ≥ 15% of patients are reported.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; TEAE = treatment emergent adverse event.

Table 3.

Summary of CC-90002 Serum Pharmacokinetic Parameters

CC-90002 PK Parameter	CC-90002 Dose Cohort, mg/kg					
	1.0		2.0		4.0	
	C1D1 (n = 2)	C1D15 (n = 4)	C1D1 (n = 3)	C1D15 (n = 3)	C1D1 (n = 6)	C1D15 (n = 4)
$AUC_{0-\infty}$, h · μg/mL	*NA*	9.7 (61.5)[b]	81.1 (144.6)	390.6 (43.2)	858.8 (57.1)[c]	1345.6 (2.9)[b]
AUC_{0-t}, h · μg/mL	2.7 (32.4)	10.5 (41.9)	77.1 (130.5)	386.6 (42.1)	747.2 (58.1)	1557.0 (41.7)
C_{max}, μg/mL	1.8 (15.3)	4.6 (29.6)	12.6 (51.3)	23.5 (27.7)	60.5 (156.8)	54.3 (15.8)
t_{max}, h[a]	1.2 (1.1–1.3)	0.8 (0.7–1.2)	1.6 (1.4–2.1)	1.2 (1.0–1.3)	2.4 (2.1–2.8)	2.3 (1.0–6.4)
$t_{1/2}$, h	*NA*	5.4 (37.1)[b]	4.6 (46.8)	8.6 (13.9)	8.9 (33.2)[c]	17.0 (84.1)[d]
CL, mL/h/kg	*NA*	102.9 (61.5)[b]	24.7 (144.6)	5.1 (43.2)	4.7 (57.1)[c]	3.0 (2.1)[b]
V_{ss}, mL/kg	*NA*	382.9 (83.9)[b]	*NA*	43.7 (65.2)	*NA*	66.1 (60.5)[b]
R_{ac}, λ	*NA*	1.0 (0.0)[b]	*NA*	1.0 (0.0)	*NA*	1.0 (0.9)[b]

Data are presented as geometric mean (GCV).

Abbreviations: AUC_{0-t} = area under the serum concentration time curve from time zero to last time with detectable levels; $AUC_{0-\infty}$ = area under the serum concentration time curve from time zero extrapolated to infinity; C = cycle; CL = total serum clearance; C_{max} = maximum observed serum concentration; D = day; GCV = geometric coefficient of variation; NA = not available; PK = pharmacokinetics; $R_{ac}(\lambda)$ = accumulation index; $t_{½}$ = terminal half-life; t_{max} = time to maximum serum concentration; V_{ss} = steady state volume of distribution.

[a]Median (min–max).

[b]n = 2.

[c]n = 5.

[d]n = 3.

Table 4.

Summary of ADA Test Results

ADA Statistic	Overall Population (n = 28)[a]						
	C1D1	C1D8	C1D15	C1D22	2 Weeks After End of Dose	4 Weeks After End of Dose	Follow-up (D56)
ADA-negative, n (%)	25 (89.3)	23 (82.1)	19 (67.9)	14 (50.0)	6 (21.4)	5 (17.9)	4 (14.3)
ADA-positive, n (%)	2 (7.1)	4 (14.3)	6 (21.4)	8 (28.6)	5 (17.9)	5 (17.9)	4 (14.3)
Serum ADA titer, median (range)	3.0 (1–5)	1.0 (1–5)	25.0 (5–125)	25.0 (1–3125)	7812.0 (1–78,125)	625.0 (25–39,062)	75.0 (1–625)

Abbreviations: ADA = anti-drug antibodies; C = cycle; D = day.

[a]The number of patients evaluable for ADA decreased over time due to study discontinuation (most commonly because of death, progressive disease, and adverse events).