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ORIGINAL ARTICLE

Cusatuzumab plus azacitidine in Japanese patients with newly diagnosed acute myeloid leukemia ineligible for intensive treatment

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Abstract

We present the results of a phase 1 study that evaluated the safety, pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary disease response to cusatuzumab, a novel anti-CD70 monoclonal antibody, in combination with azacitidine, in newly diagnosed acute myeloid leukemia Japanese participants who were not candidates for intensive treatment. In this multicenter, single-arm study, six participants were enrolled and treated. Only in cycle 1, participants received cusatuzumab monotherapy on day 14. Subsequently, cusatuzumab was administered intravenously on days 3 and 17 at 20 mg/kg in combination with azacitidine (75 mg/m^2) on days 1-7 of each 28-day cycle. All six participants had at least one treatment-emergent adverse event, and the most common treatment-emergent adverse events (all grades) were leukopenia (four participants [66.7%]) and constipation (three participants [50.0%]). No dose-limiting toxicity was observed during the study period. The combination of cusatuzumab and azacitidine is generally well tolerated in Japanese participants, and further exploration of this combination is warranted.

KEYWORDS
acute myeloid leukemia, azacitidine, cusatuzumab, human anti-CD70 monoclonal antibody, Japanese patients

1 | INTRODUCTION

Acute myeloid leukemia (AML) is a heterogeneous disease characterized by uncontrolled clonal expansion of hematopoietic progenitor cells. According to a survey conducted by the Ministry of Health, Labour and Welfare in 2017, AML is the most common acute leukemia and the number of patients in Japan with AML is approximately 7000.[1] Intensive treatment including allogenic stem cell transplantation is recommended for fit patients (young and no severe comorbidities) with AML. Less intensive treatment or clinical trials are recommended in front-line setting for elderly and unfit patients by the JSH guideline.[2]

Venetoclax was approved in Japan for the treatment of AML in combination with azacitidine or low-dose cytarabine in 2021 during

Abbreviations: AE, adverse event; AML, acute myeloid leukemia; CRh, complete remission with partial hematological recovery; ECOG, Eastern Cooperative Oncology Group; ELN, European Leukemia Networking; DLT, dose-limiting toxicity; IRR, infusion-related reaction; JSH, japanese society of hematology; LSC, leukemic stem cell; MDS, myelodysplastic syndromes; PK, pharmacokinetics; Q2W, every 2 weeks; RP2D, recommended phase 2 dose; SD, stable disease; SET, study evaluation team; TEAE, treatment-emergent adverse event.

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the conduct of this study. In this study, about half of the participants who received azacitidine/venetoclax treatment had disease progression or relapse after a median duration of about 18 months.[3] Drug resistance in AML treatment continues to be an important clinical problem.[4] Therefore, new regimens are needed for newly diagnosed unfit AML patients. Cusatuzumab was being codeveloped by Janssen Research and Development and argenx BV as a germline monoclonal antibody of camelid origin, binding with high affinity to human CD70 and with enhanced antibody-dependent cell-mediated cytotoxicity (ADCC).[5,6]

CD70, a cell surface antigen belonging to the tumor necrosis factor family, is transiently expressed in mature dendritic cells and a small subset of activated B and T lymphocytes and is involved in lymphocyte differentiation and proliferation.[7,8] Leukemic blasts and leukemic stem cells (LSCs) express both CD70 and its receptor, CD27.[9] When CD70 binds to CD27 (CD70-CD27), the nuclear factor kappa light chain enhancer of activated B cells pathway is activated, resulting in proliferation and survival of malignant cells and in the proteolytic shedding of the ectodomain of CD27 and secretion of soluble CD27 (sCD27). The CD70-CD27 signaling pathway also promotes regulatory T cell recruitment or survival, thereby potentially impeding immune surveillance in the tumor microenvironment.[10] Cusatuzumab restores immune surveillance by blocking CD70-CD27 interaction and kills CD70-expressing cells by Fc-mediated effector functions such as enhanced ADCC (using POTELLIGENT® technology), antibody-dependent cellular phagocytosis, and complement-dependent cytotoxicity.[5,6]

Cusatuzumab activity in AML results in a reduction in leukemic blast cells, inhibition of myeloid blast proliferation, and restoration of normal differentiation of LSCs.[11] Hypomethylating agents have been shown to upregulate CD70 expression on LSCs.[9] Preclinical data demonstrate that the combination of cusatuzumab and azacitidine will result in a synergistic effect on LSCs. Additionally, due to different mechanisms of action, the combination is expected to be tolerable. Based on early data from a phase 1 trial of cusatuzumab at 20 mg/kg plus azacitidine, two out of three subjects achieved complete remission (CR) and the other one subject achieved PR.[9] The rationale underlying this study is the fact that cusatuzumab in combination with azacitidine could be a new treatment option for unfit AML patients in the future. No data in Japanese participants using cusatuzumab monotherapy and cusatuzumab in combination with azacitidine have been available; therefore, tolerability, safety, pharmacokinetics (PK), and preliminary disease response to the regimen were evaluated in this study.

2 | MATERIALS AND METHODS

2.1 | Study design

This was an open-label phase 1 study conducted at six sites in Japan. The investigational review board at each study site approved the protocol. The study was conducted in accordance with the principles defined in the Declaration of Helsinki, International Conference on Harmonization guidelines (Good Clinical Practices), and the local regulatory guidelines. Informed consent was obtained from all participants prior to the enrollment.

The study included a screening phase, a treatment phase, and a follow-up phase. The screening phase was planned up to 28 days prior to the initiation of study intervention administration. Participants were treated with their assigned dose regimen until disease progression, relapse, unacceptable toxicity, death, withdrawal due to the investigator's discretion, or withdrawal of consent, whichever occurred first. The follow-up phase began once a participant discontinued the study intervention and was continued until death, lost to follow-up, consent withdrawal for study participation, or study end, whichever occurred first.

The treatment regimen included azacitidine 75 mg/m^2 s.c. or i.v. on day 1 through day 7, cusatuzumab at 20 mg/kg i.v. on day 3 and day 17 of each 28-day cycle. Participants received a single dose of cusatuzumab i.v. monotherapy on day -14 (Figure 1).

2.2 | Study population

The target population consisted of adult Japanese men or women of ≥20 years of age with treatment-naive AML who were not candidates for intensive treatment and had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.

Participants were excluded from the study if they had acute promyelocytic leukemia with t (15;17), or its molecular equivalent (PML-RARα); leukemic involvement or clinical symptoms of leukemic involvement of the central nervous system; or New York Heart Association class III and IV heart failure or ongoing unstable angina. Participants who had a diagnosis of other malignancy that required concurrent nonsurgical treatment or received prior treatment with a hypomethylating agent for treatment of AML or MDS were also excluded. Mutational status was provided that it includes testing for all mutations outlined of European Leukemia Networking (ELN) risk by genetics (2017) for AML following risk stratification.[12]

2.3 | Safety evaluations

Safety assessments were performed during the entire study period. These assessments included evaluation of adverse events (AEs), physical examination, electrocardiogram, spirometry test, vital signs (including systolic and diastolic blood pressure, pulse rate, and temperature), body weight, and clinical laboratory tests at predefined time points and, if clinically necessary, at additional timepoints. Severity of AEs were graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) Version 5.0. Dose-limiting toxicity (DLT) was defined as any of the following events related to cusatuzumab.

- Any grade 3 or higher drug-related nonhematological toxicity with a duration of more than 14 days
- Grade 3 or higher infusion-related reactions (IRRs) occurring during or within 24 hours after completion of the infusion

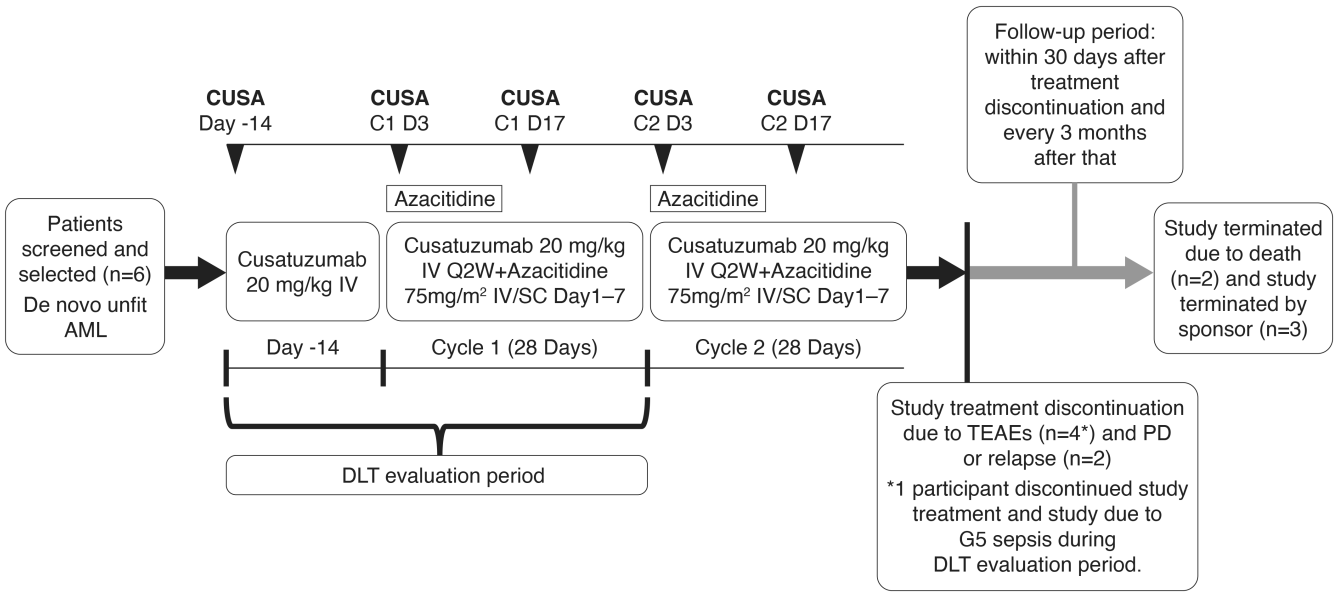


FIGURE 1 Schematic presentation of the study design. AML, acute myeloid leukemia; DLT, dose-limiting toxicity; IV, intravenous; PD, progressive disease; Q2W, every 2 wk; SC, subcutaneous; TEAE, treatment-emergent adverse event

- Inability to administer the next dose due to a drug-related AE or a delay of the administration of the next dose due to toxicities for more than 14 days despite adequate medication
- Drug-related grade 4 febrile neutropenia
- Drug-related grade 4 anemia which cannot be adequately treated by blood transfusions

Dose-limiting toxicity evaluation period was defined as from the first dose of study intervention (D-14) to the start of cycle 2. Participant safety and study conduct were monitored by the study evaluation team (SET) established by the sponsor. The SET consisted of the principal investigator(s), the internal physician responsible for the study, and internal clinical development members. In addition to dose escalation/de-escalation decisions, the team reviewed treatment-emergent data at any time during the study at the request of either the sponsor or the investigators to assess emerging safety signals and ensure the continued safety of participants enrolled in this study.

The recommended phase 2 dose (RP2D) was selected based on a cumulative review of safety and clinical activity observed in the study. A minimum of three participants had to be treated at a given dose level to determine the RP2D.

2.4 | Clinical preliminary disease response evaluations

Overall survival was defined as the time from initial study intervention administration to death from any cause. Participants were assessed for disease status per investigator assessment based on the ELN 2017 Response Criteria in AML.[12]

2.5 | Pharmacokinetic evaluations

Serum and bone marrow concentrations of cusatuzumab were analyzed using a validated, specific, and sensitive immunoassay method. The lower limit of quantification for the serum and bone marrow concentrations of cusatuzumab were 0.495 and 0.500 μg/ml, respectively. Noncompartmental analysis was applied for the serum PK parameter analysis.

Calculated PK parameters were maximum concentration, concentration immediately prior to the next drug administration, area under the concentration-time curve during the dose interval, and elimination half-life.

2.6 | Immunogenicity evaluation

Serum samples were analyzed to determine the generation of anti-cusatuzumab antibodies using validated immunoassay methods. Serum samples were screened for antibodies binding to cusatuzumab, and the titer of confirmed positive samples were reported. The positive samples of anti-cusatuzumab antibodies were further assayed for neutralizing antibodies to characterize the immunogenicity of cusatuzumab.

2.7 | Biomarker evaluation

Serum sCD27 was analyzed using validated electrochemiluminescence assay. In addition, flow cytometric immunophenotyping was performed on fresh bone marrow aspirates.

2.8 | Statistical methods

2.8.1 | Sample size determination

The sample size was not determined based on statistical hypothesis testing; the total number of participants enrolled in the study was dependent on the number of dose levels. In this study, the target number of participants was planned in a range of 3 to 12.

2.8.2 | Analysis sets

The following population sets were evaluated in the study:

- All-treated analysis set: This set consisted of participants who received at least one dose of study intervention
- PK-evaluable set: Participants who received at least one dose of study intervention and had at least one post-dose PK sample obtained

2.8.3 | Statistical analyses

All reported treatment-emergent AEs (TEAEs) were included in the analysis. For each AE, the number and percentage of participants who experienced at least one occurrence of the given event were summarized by group. The TEAEs were summarized by the Medical Dictionary for Regulatory Activities (version 24.0) system organ class and preferred term, by toxicity grade, and by relationship to study treatment administration.

3 | RESULTS

3.1 | Study population

Six participants were enrolled in the cohort of 20 mg/kg. Overall, the median age was 79.5 years (range: 72-84 years); five participants (83.3%) were male (Table 1). The median time from initial diagnosis to first dosing date was 13.5 days (range: 6-47). The ECOG performance status score was 0 or 1 (three participants [50.0%] in each score) (Table 1). A total of five participants had de novo (primary) AML while one participant had a secondary AML (prior radiation therapy for prostate cancer). Baseline median bone marrow blast (%) by aspiration (n = 5) was 39.6 (range: 22.4-58.0). Intermediate cytogenetic risk per 2017 ELN[12] was reported in three participants (genetic abnormality: three participants with cytogenetic abnormalities not classified as favorable or adverse), and adverse risk was reported in three participants (genetic abnormality: two participants with complex karyotype and monosomal karyotype; one participant with complex karyotype, monosomal karyotype, and -5 or del[5q]; -7; -17/abn[17p]).

TABLE 1 Patient demographics and baseline disease characteristics (all treated analysis set)

Factors	*n* (%)
Gender	
Male	5 (83.3%)
Female	1 (16.7%)
Age (years)	
≥65-<75	1 (16.7%)
≥75	5 (83.3%)
AML type	
Primary	5 (83.3%)
Secondary	1 (16.7%)
Previous leukemogenic exposure	1 (16.7%)
ECOG performance status (N%)	
0	3 (50.0%)
1	3 (50.0%)
2	0
Bone marrow blast[a] (%) aspiration	
Median	39.60
Range	(22.4; 58.0)
[0%, 20%]	0
[20%, 40%]	3 (60.0%)
[40%, 60%]	2 (40.0%)
[60%, 80%]	0
>80%	0
Risk category	
N	6
Adverse	3 (50.0%)
Intermediate	3 (50.0%)

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; N, total number; n, number of subjects.
[a]The bone marrow blasts (%) were based on the investigator's judgement with each hospital laboratory data. The bone marrow blast by biopsy in one subject was 51.20%.

3.2 | Exposure

The median treatment duration of cusatuzumab was 2.63 months (range: 0.7-8.4 months), and the median number of cycles was 2 (range: 1-9). The median treatment duration of azacitidine was 1.66 months (range: 0.2-7.6 months), and the median number of cycles was 2 (range: 1-9).

Four participants completed the DLT evaluation period (cycle 1), and 2 participants discontinued the study drugs due to TEAEs (not related to cusatuzumab) before completion of the DLT evaluation period.

3.3 | Safety

For this study, the key evaluation point to determine the RP2D was DLT. No DLTs were reported for any participants in this study

(Table 2). All six participants had at least one TEAE, and the TEAEs experienced by more than two participants were leukopenia (four participants [66.7%]) and constipation (three participants [50.0%]). Of these, four participants reported grade ≥3 leukopenia and three participants reported grade 1 or grade 2 constipation. A total of two participants (33.3%) had a TEAE related to cusatuzumab consisting of alanine aminotransferase increased (one episode each of grade 1 and 2), aspartate aminotransferase increased (grade 1), and erythema (grade 1) (one participant [16.7%] in each TEAE). The erythema was reported as IRR, and there were no other IRRs in this study. Three out of six participants, one participant each (16.7%), died due to the event of sepsis, disease progression, and deterioration of general condition due to AML after discontinuation of study treatments, respectively. The sepsis was not related to cusatuzumab. Five (83.3%) out of six participants reported serious TEAEs. Two participants each reported serious TEAEs of pneumonia, sepsis, and febrile neutropenia. All serious TEAEs were not related to cusatuzumab. Four participants (66.7%) reported TEAEs leading to treatment discontinuation of cusatuzumab and azacitidine. The grade ≥3 TEAEs of neutropenia, gastrointestinal hemorrhage, pneumonia, and delirium led to treatment discontinuation. None of the TEAEs leading to treatment discontinuation of cusatuzumab were related to cusatuzumab.

3.4 | Preliminary disease response

Out of six participants, one participant with intermediate risk per 2017 ELN[12] attained CR with partial hematological recovery (CRh), and the duration of response was 4.14 weeks (Table 3). Baseline bone marrow blast of the participant was 22.4%, and the time from diagnosis to treatment was 13 days. The participant achieved CRh on study day 126 (bone marrow blast was 1.0 % based on the investigator's evaluation) and developed progressive disease (PD) on study day 154 and went off trial. The other three participants had stable disease (SD) (two out of the three participants having SD duration less than 90 days, i.e., "unconfirmed"), one participant had disease progression, and one participant did not have an evaluable response due to study discontinuation without disease evaluation.

TABLE 2 Overall safety analysis (all treated analysis set)

Factors	*n* (%)
Analysis set: all-treated	6
TEAEs	6 (100.0%)
Cusatuzumab-related	2 (33.3%)
TEAEs leading to death[a]	1 (16.7%)
Serious TEAEs	5 (83.3%)
Cusatuzumab-related	0
TEAEs leading to treatment discontinuation of cusatuzumab	4 (66.7%)
Grade≥3 TEAEs	6 (100.0%)
DLT	0
TEAEs occurring in at least two subjects (all grades)	
Constipation	3 (50.0%)
Diarrhea	2 (33.3%)
Stomatitis	2 (33.3%)
Leukopenia	4 (66.7%)
Febrile neutropenia	2 (33.3%)
Thrombocytopenia	2 (33.3%)
Pneumonia	2 (33.3%)
Sepsis	2 (33.3%)
Weight decreased	2 (33.3%)
Renal impairment	2 (33.3%)
Urinary incontinence	2 (33.3%)
Dry skin	2 (33.3%)
Fall	2 (33.3%)
Delirium	2 (33.3%)
Epistaxis	2 (33.3%)
Productive cough	2 (33.3%)

Abbreviations: DLT, dose-limiting toxicity; TEAE, treatment-emergent adverse event.

[a]TEAEs leading to death are based on adverse events (AEs) with fatal outcome or AEs with toxicity grade 5.

TABLE 3 Preliminary disease response summary; all treated analysis set

Participant #	Best response	Time to first response (wk)	Duration of response (wk)	Time to death or censored[b] (mo)
1	SD	–	–	15.44+
2	SD[a]	–	–	4.11
3	PD	–	–	3.94
4	CRh	18.00	4.14	8.15+
5	NE	–	–	1.35
6	SD[a]	–	–	14.29+

Note: Response was evaluated based on ELN 2017 Response Criteria. It was based on the investigator's judgement of the hospital laboratory data. Best response is assigned in hierarchical order: complete remission (CR) > CR with partial hematological recovery (CRh) > CR with incomplete recovery (CRi) > morphologic leukemia–free state (MLFS) > NE Not Evaluable > partial remission (PR) > stable disease (SD) > progressive disease (PD).

[a]The two subjects having SD duration less than 90 days (i.e., "unconfirmed").

[b]+ means the participant was censored.

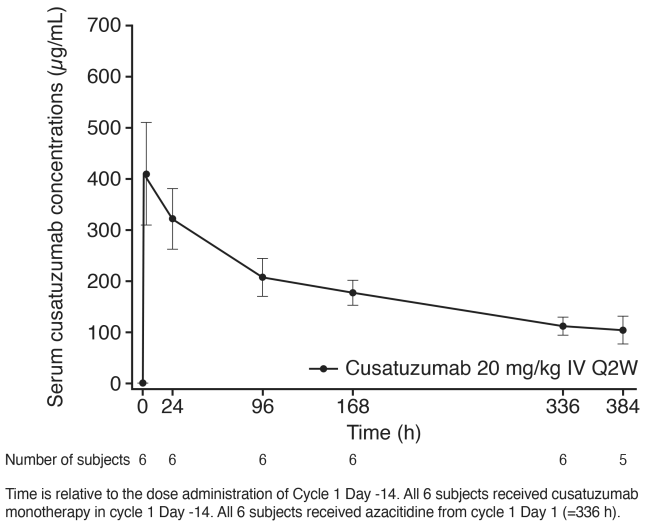


FIGURE 2 Mean (SD) serum concentration-time profile of cusatuzumab from cycle 1 day -14 to cycle 1 day 3; linear scale; pharmacokinetics-evaluable analysis set. IV, intravenous; Q2W, every 2 wk; SD, standard deviation.

One participant was withdrawn from the study on day 120 due to death secondary to PD. Baseline bone marrow blast of this participant was 53%, and the time from diagnosis to treatment was 6 days. The participant had intermediate cytogenetic risk.[12] Confirmed SD was reported in one (with an intermediate ELN genetic risk) of the six participants. The SD was maintained until discontinuation of cusatuzumab due to pneumonia (on study day 295). Out of six participants, three participants died at 4.11, 3.94, and 1.35 months after study start (cycle 1 day 14) respectively (Table 3).

The duration of single-agent cusatuzumab treatment was between day -14 and cycle 1 day 1. During the period, bone marrow samples were not collected, but peripheral blood samples were collected. The median changes (range) in peripheral blood blast ($10^{\wedge 9}$/L), neutrophils ($10^{\wedge 9}$/L), and platelet count ($10^{\wedge 9}$/L) from baseline to cycle 1 day 1 were 0.059 (−0.007; 0.714), 0.393 (0.080; 19.234), and 1.0 (−24; 29), respectively ($n = 6$).

3.5 | Pharmacokinetic findings

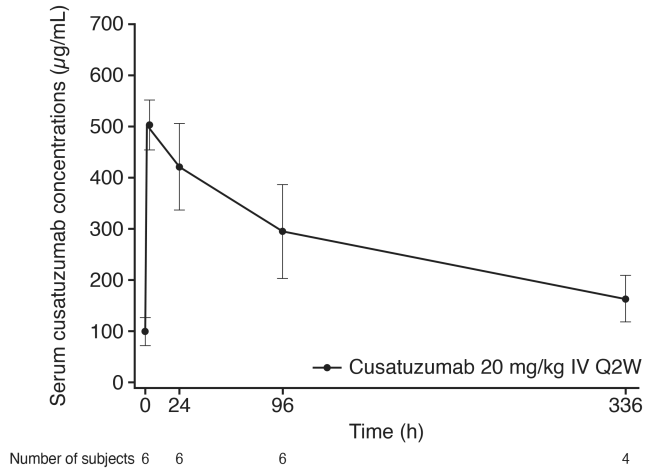
All the six participants who received cusatuzumab were included in the PK analysis set. After i.v. administration of a cusatuzumab dose, the maximum mean serum concentration was observed at the end of infusion for each schedule, which corresponded to the first sample taken after the end of infusion (Figures 2 and 3). A summary list of key serum PK parameters of cusatuzumab for cycle 1 day 14 (cusatuzumab monotherapy) and cycle 1 day 3 (cusatuzumab in combination with azacitidine) is presented in Table 4. Bone marrow concentrations of cusatuzumab were available in two participants. In one participant whose best response was confirmed SD, the bone marrow concentration of cusatuzumab was 164 μg/ml on day 99 and 126 μg/ml on day 155. It was 295 μg/ml on day 98 and 293 μg/ml on day 154 in the other participant whose best response was CRh.

3.6 | Immunogenicity findings

Of all the six participants who received cusatuzumab, one participant was considered positive for antibodies to cusatuzumab post dose. The participant had SD during the treatment period. None of the participants reported positive for neutralizing antibodies.

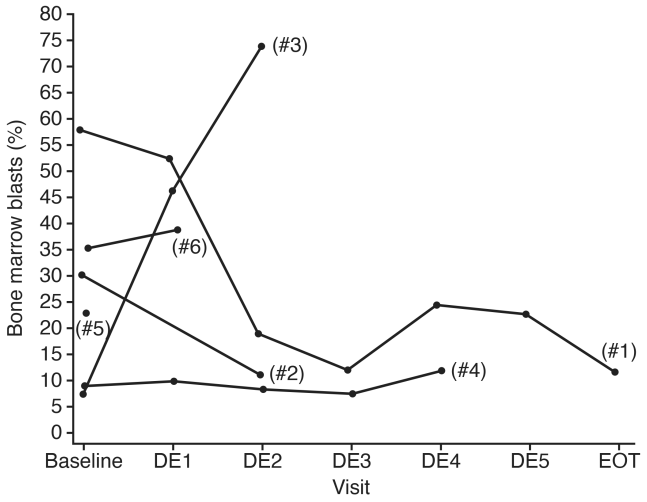
3.7 | Biomarker analysis

Of the five participants with measurable bone marrow blasts at disease evaluation, two participants showed a trend of decreasing bone marrow blasts. The participant with an increase in bone marrow blasts was discontinued due to disease progression (Figure 4). The sCD27 concentrations over time in one participant who achieved CRh decreased (4,994 ng/L) at the time of achievement of CRh compared with that at the time of screening (7,102 ng/L) and returned close to the baseline level at the time of progression (6,980 ng/L).



Time is relative to the dose administration of Cycle 1 Day 3. All 6 subjects received combination therapy with cusatuzumab and azacitidine on Cycle 1 Day 3.

FIGURE 3 Mean (SD) serum concentration-time profile of cusatuzumab from cycle 1 day 3 to cycle 1 day 17; linear scale; pharmacokinetics-evaluable analysis set (study 74494550AML1002). IV, intravenous; Q2W, every 2 wk; SD, standard deviation.



DE = Disease Evaluation, EOT = End of Treatment, (#) = Participant #

FIGURE 4 Individual bone marrow blasts over time; all treated analysis set. The BM blast data were from central laboratory. DE, disease evaluation; EOT, end of treatment; (#), participant number

TABLE 4 Overall pharmacokinetic analysis (pharmacokinetics-evaluable analysis set)

	20 mg/kg	
	Cycle 1 day -14	**Cycle 1 day 3**
Analysis set: pharmacokinetics-evaluable	6	6
C_{max} (μg/ml)		
N	6	6
Mean (SD)	410 (100)	504 (48.3)
C_{trough} (μg/ml)		
N	5	4
Mean (SD)	104 (26.8)	163 (45.9)
AUC_{tau} (μg × h/ml)		
N	5	4
Mean (SD)	68827 (9740)	101649 (13897)
T1/2 (h)		
N	5	2
Median (range)	223 (193; 341)	NC (NC)

Abbreviations: AUC, area under the curve; C, concentration; CL, clearance; N, total number; NC, not calculated; SD, standard deviation; T, time; $T_{1/2}$, half life; V, volume.

4 | DISCUSSION

In this phase 1 study, cusatuzumab at a dose of 20 mg/kg every 2 weeks (Q2W) in combination with azacitidine was generally well tolerated in Japanese participants with newly diagnosed AML. Cusatuzumab-related death, serious AEs, and TEAEs leading to study drug discontinuation were not reported. No DLT was reported in this study. The safety profile of cusatuzumab in combination with azacitidine was noted to be generally consistent with that reported of azacitidine alone as well as characteristics of the underlying disease and study population, with the addition of IRRs related to cusatuzumab.[13] One IRR of grade 1 was reported in one participant. The IRR resolved without medical treatment, and the participant was able to complete the dose of cusatuzumab. Premedications consisting of acetaminophen, antihistamine, and corticosteroid were administered to all participants prior to each dose. During study conduct, venetoclax was approved in Japan for the treatment of AML. In the VIALE-A data, 20% of participants in venetoclax/azacitidine arm had venetoclax dose interruptions and reductions because of neutropenia or febrile neutropenia.[3] In real world data of venetoclax treatment, one of the important adverse effects is prolonged cytopenias.[14] In this phase 1 study, neutropenia or febrile neutropenia related to cusatuzumab was not reported. Although more subjects should be evaluated, these results suggest that cusatuzumab may offer a new therapeutic option for patients intolerant to venetoclax.

In this study, one participant with an intermediate ELN genetic risk[12] achieved CRh at study day 126. The CR rate for our study was lower than anticipated based on earlier data from a phase 1 trial of cusatuzumab/azacitidine[9] and from a phase 2 trial of cusatuzumab 20 mg/kg/azacitidine (Pabst et al., in preparation). The preliminary disease response results of this study may be affected by the limited number of subjects evaluated (six subjects). However, this may be due to the high proportion of participants with adverse cytogenetic risk (50.0%) in our phase 1 study and no participant with favorable cytogenetic risk. Some participants may have discontinued prematurely due to PD or TEAEs prior to first response. In a global phase 1 study, median time to first response was 3.3 months.[9] In a global phase 2 study, median time to first response to cusatuzumab 20 mg/kg was 3.0 months (Pabst et al, in preparation). The time to response in one participant who achieved CRh in our study was 4 months. These data, together with the fact that the median exposure of cusatuzumab was 2.6 months in our study, suggest that the duration of exposure to cusatuzumab was not sufficient to determine the

response to this drug. The PK profile of cusatuzumab obtained from this study was not markedly different from the PK profile previously reported in non-Japanese participants.[15] Our study measured serum sCD27 levels as a potential biomarker in an exploratory manner. The sCD27 concentration was lower during the treatment period than at screening in one participant who achieved CRh. The mechanism of action of cusatuzumab suggests that serum sCD27 concentration may be a biomarker for response, although interpretation of results is limited because only one participant achieved CRh.

In conclusion, cusatuzumab at a dose of 20 mg/kg Q2W in combination with azacitidine was generally well tolerated in Japanese patients with newly diagnosed AML, and no DLT was observed in this study. While responses were limited, results should be interpreted with caution due to the small sample size. Further exploration of this combination is warranted.

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CONFLICT OF INTEREST

Takayuki Ikezoe has received research grants from Asahi Kasei, Astellas, AbbVie, Otsuka, Takeda, Nippon Shinyaku, Novartis, and Janssen. Kensuke Usuki has received research grants and personal fees from Novartis, Kyowa Kirin, LabCorp Drug Development, Symbio, Astellas-Amgen-Biopharma, Otsuka, Apellis, Takeda, Nippon Shinyaku, AbbVie, Janssen, Ono, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, MSD, Alexion, Gilead, Pfizer, Incyte, Celgene, Sumitomo-Dainippon, Mundi, Yakult, Eisai, Astellas, Pharma Essentia, Sanofi, and Alnylam Japan. Takahiro Yamauchi has received research grants and personal fees from AbbVie, Astellas, Pfizer, and Nippon Shinyaku; and research grants from Amgen, Janssen, Chugai, and Sumitomo-Dainippon. Kensuke Aida, Tomoyoshi Hatayama, and Toru Shirahase are employees of Janssen.

DATA AVAILABILITY STATEMENT

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

ETHICS STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The investigational review board at each study site approved the protocol.

Informed Consent: Informed consent was obtained from all participants prior to the enrollment.

Animal Studies: N/A

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