Cusatuzumab plus azacitidine in newly diagnosed acute myeloid leukaemia ineligible for intensive chemotherapy (CULMINATE): part one of a randomised, phase 2, dose optimisation study

Thomas Pabst, Cristina Papayannidis, Fatih Demirkan, Vadim Doronin, Laura M Fogliatto, Christina Guttke, Emmanuel Gyan, Nada Hamad, Pilar Herrera, Anna Hultberg, Julie Jacobs, Amy J Johnson, Angélique Langlois, Xuewen Ma, Giovanni Martinelli, Montserrat Arnan, Rouven Müller, Kerri Nottage, Yishai Ofran, Muhit Özcan, Olga Samoilova, Jaszianne A Tolbert, Géralyn C Trudel, Liang Xiu, Norbert Vey, Andrew H Wei*

Lancet Haematol 2023; 10: e902–12

See **Comment** page e868

*Dr Trudel retired in April, 2021

Department of Medical Oncology, Inselspital Bern University Hospital, Bern, Switzerland (Prof T Pabst MD); **IRCCS, Azienda Ospedaliero Universitaria di Bologna, Istituto di Ematologia L e A Seràgnoli, Bologna, Italy** (C Papayannidis MD PhD); **Dokuz Eylul University Division of Hematology, Inciralti Izmir, Turkey** (Prof F Demirkan MD); **Department of Hematology and Chemotherapy, City Clinical Hospital No 40, Moscow, Russia** (V Doronin MD); **Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil** (L M Fogliatto MD); **Janssen Research and Development, Spring House, PA, USA** (C Guttke PhD, A J Johnson PhD, X Ma PhD); **Hematology and Cell Therapy Department, Opale Carnot Institute, University Hospital of Tours, Tours, France** (Prof E Gyan, MD); **Department of Haematology, St Vincent's Hospital Sydney and St Vincent's Clinical School Sydney, University of New South Wales, Sydney, NSW, Australia** (N Hamad MBBS); **Hematology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain** (P Herrera MD); **argenx, Ghent, Belgium** (A Hultberg PhD, J Jacobs PhD); **Janssen Cilag, Paris, France** (A Langlois MSc); **IRCCS Istituto Romagnolo per lo Studio dei Tumori Dino Amadori IRST, Meldola, Italy** (Prof G Martinelli MD); **Hematology Department, Institut Català d'Oncologia**

Summary

Background Cusatuzumab, a high-affinity anti-CD70 antibody, has shown preliminary activity as a treatment for acute myeloid leukaemia when combined with azacitidine. We aimed to determine the optimum dose for future trials of cusatuzumab in combination with azacitidine in patients with previously untreated acute myeloid leukaemia who are not eligible for intensive chemotherapy.

Methods In this randomised, phase 2, open-label, dose-optimisation study we enrolled adult patients aged 18 years or older with newly diagnosed acute myeloid leukaemia not eligible for intensive chemotherapy, and with Eastern Cooperative Oncology Group scores of 0–2, from 40 hospitals and centres across seven countries. In part one of the trial, participants were randomly allocated 1:1 to 10 mg/kg or 20 mg/kg intravenous cusatuzumab on days 3 and 17, combined with subcutaneous or intravenous azacitidine 75 mg/m² on days 1–7 in 28-day cycles. The primary efficacy outcome was the rate of complete remission in the intention-to-treat group. The two dose cohorts were evaluated independently without between-cohort statistical comparison. Safety analyses were performed in all patients who received one dose of study drug. Part two of the trial was planned to be a single-arm expansion to evaluate cusatuzumab plus azacitidine at the cusatuzumab dose level selected in part one (primary hypothesis ≥35% rate of complete remission *vs* null hypothesis of 20%); however, changes in the acute myeloid leukaemia treatment landscape during this trial made it unlikely that enrolment to part two of the study would be clinically feasible, so the study stopped at the end of part one. The trial was registered at ClinicalTrials.gov, NCT04023526.

Findings 103 patients were enrolled between Aug 30, 2019, and Feb 25, 2020, and randomly assigned to either cusatuzumab 10 mg/kg (n=51) or 20 mg/kg (n=52). Median follow-up was 7·2 months (IQR 10·7 months). 57 of 103 (55%) patients were male and 46 (45%) patients were female, 78 (76%) were White, one (1%) was Asian, and 24 (23%) did not report their race. In the 10 mg/kg group, complete remission rate was 12% (six of 51 patients; 95% CI 6–23) and in the 20 mg/kg group was 27% (14 of 52; 17–40). Grade 3 or worse treatment-emergent adverse events (TEAEs) were similar between the cusatuzumab 10 mg/kg (n=51) and 20 mg/kg (n=51) cohorts and included thrombocytopenia (24 patients [47%] *vs* 29 [57%]), anaemia (24 [47%] *vs* 17 [33%]), and neutropenia (20 [39%] in both cohorts). Serious TEAEs were also similar in the two cohorts (44 [86%] *vs* 40 [78%]). Treatment-related TEAEs leading to death were reported in both groups (three patients [6%] in the 10 mg/kg group *vs* one patient [2%] in the 20 mg/kg group); the reported causes of death were pneumonia (n=2) and septic shock (n=2).

Interpretation Although part one of this study was not designed to formally compare the two dose cohorts for efficacy, the totality of clinical data for cusatuzumab studies performed to date indicate that cusatuzumab 20 mg/kg plus azacitidine represents the optimal dose for further studies. A phase 1b study investigating the triple combination of cusatuzumab with venetoclax and azacitidine is underway (NCT04150887).

Funding Janssen Research & Development and argenx.

Introduction

Acute myeloid leukaemia is a heterogeneous malignancy characterised by uncontrolled clonal expansion of haematopoietic myeloid progenitor cells, usually resulting from acquired cytogenetic aberrations, epigenetic changes, and somatic mutations.[1] Incidence of acute myeloid leukaemia increases with age, with a median age at diagnosis of 68–70 years.[2,3] The genomic landscape in older patients is characterised by a higher frequency of poor-risk abnormalities, including *TP53* mutations.[4] Consequently, 5-year overall survival in newly diagnosed acute myeloid leukaemia remains poor

Research in context

Evidence before this study

We searched PubMed using the terms "cusatuzumab" and "acute myeloid leukaemia". No limits on the date of publication or language restrictions were applied. The literature search was ongoing throughout all stages of the trial, up until manuscript preparation. We also searched within the clinicaltrials.gov registry for cusatuzumab trials. The search results confirmed that 5-year survival data in patients with newly diagnosed acute myeloid leukaemia is poor, especially among older patients, owing to the lack of effective therapies for older patients before the approval of venetoclax and a higher frequency of poor-risk genetic features in this population. Until recently, single-agent hypomethylating agents (HMAs) were the standard therapy for patients with newly diagnosed acute myeloid leukaemia who were ineligible for intensive chemotherapy. Treatment with HMAs provide expected rates of complete remission up to 20% and complete remission or complete remission with incomplete haematological recovery (CRi) of up to 28%, and a median overall survival of about 10 months. In 2020, new results from the VIALE-A study for venetoclax, an anti-apoptotic protein B-cell lymphoma 2 inhibitor, were reported and venetoclax plus azacitidine has become the new standard of care, conferring a complete remission rate of 37%, and complete remission or CRi rate of 66%, with an expected median overall survival of about 15 months.

Cusatuzumab, our study drug, is a high-affinity, anti-CD70 antibody with multiple mechanisms of action. CD70 antigen is a tumour necrosis factor-receptor ligand expressed on most acute myeloid leukaemia bone marrow blasts, leukaemic stem cells (LSCs), and leukaemic progenitor cells, but not haematopoietic stem cells or most normal tissues. Resistance to HMAs has been posited to occur through upregulation of CD70 expression on LSCs; hence, combining HMAs with cusatuzumab might enhance efficacy and overcome HMA resistance. In preclinical experiments, cusatuzumab and HMAs showed synergy in eliminating patient-derived LSCs. A phase 1/2 dose-escalation study demonstrated the feasibility of combining cusatuzumab 1–20 mg/kg every 2 weeks with azacitidine (following an initial cusatuzumab monotherapy phase) in patients with acute myeloid leukaemia ineligible for intensive chemotherapy (NCT03030612). Preliminary data suggested promising activity, with durable complete remissions at doses 10 mg/kg or greater. However, as no dose-limiting toxicities were observed (across the range 1–20 mg/kg), the optimal dose of cusatuzumab plus azacitidine remained uncertain. Our study was designed as a randomised, phase 2 study of cusatuzumab plus azacitidine to determine the rate of complete remission at two cusatuzumab dose levels (10 mg/kg and 20 mg/kg) and evaluate other efficacy outcomes and safety in patients with newly diagnosed acute myeloid leukaemia not eligible for intensive chemotherapy.

Added value of this study

Our study findings confirm that cusatuzumab is clinically active when given in combination with azacitidine. Cusatuzumab dosed at 20 mg/kg provided numerically higher complete remission and overall response rates and prolonged median overall survival in comparison to 10 mg/kg cusatuzumab. Therefore, we recommend a cusatuzumab dose of 20 mg/kg for future studies. Based on the safety profile and novel mechanism of action of this drug, cusatuzumab could be a valuable addition to the choice of drugs available to treat acute myeloid leukaemia in this patient population.

Implications of all the available evidence

Based on the currently available clinical data for studies with cusatuzumab, there is an indication that cusatuzumab is clinically active. Moreover, as the combination of cusatuzumab and azacitidine is generally well tolerated and toxicities are clinically manageable, further studies are warranted to examine if the novel mechanism of action associated with cusatuzumab could further enhance clinical outcomes associated with the current standard of care—venetoclax plus azacitidine. A phase 1b study is in progress investigating the triple combination of cusatuzumab with venetoclax and azacitidine (NCT04150887).

Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), Hospitalet, Barcelona, Spain (M Arnan MD); **Department of Medical Oncology and Hematology, University Hospital Zurich, Zurich, Switzerland** (R Müller Dr med); **Janssen Research and Development, Raritan, NJ, USA** (K Nottage MD, J A Tolbert MD, G C Trudel MSc PhD, L Xiu PhD); **Department of Hematology Shaare Zedek Medical Center, Faculty of Medicine, Hebrew University of Jerusalem, Israel** (Y Ofran MD); **Ankara University School of Medicine, Department of Hematology, Ankara, Turkey** (Prof M Özcan MD); **Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod, Russia** (O Samoilova MD); **Institut Paoli-Calmettes, CRCM, Aix-Marseille Université, Marseille, France** (Prof N Vey MD); **Peter MacCallum Cancer Centre, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia** (Prof A H Wei PhD); **The Alfred Hospital and Monash University, Melbourne VIC, Australia** (Prof A H Wei)

Correspondence to:
Prof Andrew H Wei, Department of Haematology, Peter MacCallum Cancer Centre, Melbourne, VIC 3000, Australia
andrew.wei@petermac.org

(17–29% across all age groups), especially among older patients.[2,5]

At the time that this study was initiated in Europe and Australia, single-agent hypomethylating agents (HMAs) were the standard therapy for newly diagnosed patients not eligible for intensive chemotherapy,[6–9] with expected rates of complete remission of up to 20%, and complete remission or complete remission with incomplete haematological recovery (CRi) of up to 28%, and median overall survival of about 10 months.[8] More recently, during the course of this study, the VIALE-A study results were reported and venetoclax (a B-cell lymphoma 2 inhibitor) plus azacitidine has become the new standard of care, conferring a complete remission rate of 37%, a complete remission or CRi rate of 66%, and an expected median overall survival of approximately 15 months.[10]

Cusatuzumab is a high-affinity, anti-CD70 antibody with multiple mechanisms of action, including Fc-mediated effector functions (especially enhanced antibody-dependent cell-mediated cytotoxicity) and blockade of CD70/CD27 antigen signalling, leading to leukaemic stem cell (LSC) and acute myeloid leukaemia blast cytotoxicity and cell death.[11–13] CD70 is a tumour necrosis factor-receptor ligand expressed on most acute myeloid leukaemia bone marrow blasts, LSCs, and leukaemic progenitor cells, but not haematopoietic stem cells or most normal tissues, making it an attractive therapeutic target.[11,12,14] CD70 is also recognised as a promising target antigen for chimeric antigen receptor T-cell therapy for acute myeloid leukaemia.[15] In acute myeloid leukaemia, CD70 binds to CD27 to initiate a cascade that activates gene-expression programmes, stimulating tumour-cell

proliferation, maintaining self-renewal of LSCs, and promoting symmetrical cell division, leading to release of soluble CD27.[11–14] Soluble CD27, a marker of CD70/CD27 interactions, is elevated in the sera of patients with newly diagnosed acute myeloid leukaemia and is inversely correlated with overall survival.[11]

Resistance to HMAs has been posited to occur through upregulation of CD70 expression on LSCs;[11] hence, combining HMAs with cusatuzumab might enhance efficacy and overcome resistance by targeting distinct pathways of myeloblast propagation. In non-clinical experiments, cusatuzumab and HMAs showed synergy in eliminating patient-derived LSCs.[12] A phase 1/2 dose-escalation study showed the feasibility of combining cusatuzumab 1–20 mg/kg every 2 weeks with azacitidine (following an initial cusatuzumab monotherapy phase) in patients with acute myeloid leukaemia ineligible for intensive chemotherapy.[12] Preliminary data suggested promising activity, with durable complete remissions at doses greater than or equal to 10 mg/kg. However, as no dose-limiting toxicities were observed (across the range 1–20 mg/kg), the optimal dose of cusatuzumab plus azacitidine remained uncertain.

CULMINATE is a randomised, phase 2 study of cusatuzumab plus azacitidine to determine the rate of complete remission at two cusatuzumab dose levels (10 mg/kg and 20 mg/kg), and to evaluate other efficacy outcomes and safety in patients with newly diagnosed acute myeloid leukaemia not eligible for intensive chemotherapy.

Methods

Study design and participants

CULMINATE was a randomised, phase 2, open-label, dose-optimisation study, designed to be conducted in eight countries and 54 centres (appendix pp 7–8). Part one was a randomised study to determine which of two cusatuzumab doses (10 mg/kg or 20 mg/kg every 2 weeks, plus azacitidine) was optimal for further development. A three-stage monitoring approach (stage one after enrolment of 15 patients, stage two after 30 patients, and stage three after 50 patients in each group) was used to determine—at each stage and for each dose cohort independently—if the observed complete remission rate and other outcomes warranted the respective dose to be continued into the next stage or into part two. Patients on cusatuzumab 10 mg/kg were escalated to 20 mg/kg after selection of the higher dose at the end of part one. Part two was a single-arm expansion to evaluate cusatuzumab plus azacitidine at the cusatuzumab dose level selected in part one. Due to changes in the acute myeloid leukaemia treatment landscape, the findings of part one no longer seemed advantageous. Enrolment was stopped at the end of part one, and part two was not initiated, as venetoclax plus azacitidine became a new standard of care. Patients aged 18 years or older, with newly diagnosed, de novo, or secondary acute myeloid leukaemia not eligible for intensive chemotherapy, according to criteria outlined by Ferrara and colleagues,[16] and with Eastern Cooperative Oncology Group (ECOG) performance status scores of 0–2 were eligible for recruitment. Patients were excluded if they had acute promyelocytic leukaemia; active leukaemic involvement of the CNS; other active malignancies or systemic infection; previous treatment with an HMA for acute myeloid leukaemia or myelodysplastic syndromes; or had received immunosuppressive agents within the past 4 weeks (see appendix pp 3–4 for full inclusion and exclusion criteria).

The study was conducted in accordance with the principles originating in the Declaration of Helsinki, Good Clinical Practice guidelines, and all applicable local laws and regulations. An Independent Ethics Committee or Institutional Review Board at each site (or a central site for France) approved the protocol and other required pre-study documentation. All patients provided written informed consent. The study protocol is shown in the appendix (from p 28).

See Online for appendix

Randomisation and masking

In part one of this open-label study, patients were stratified by disease type (de novo *vs* secondary) and ECOG performance status (0–1 *vs* 2), and randomly allocated in a 1:1 ratio to the two dose-level groups by use of an Interactive Web Response System with a block size of two.

Procedures

Following random allocation, patients received cusatuzumab (10 mg/kg or 20 mg/kg) intravenously on days 3 and 17, plus azacitidine 75 mg/m² on days 1–7 subcutaneously or intravenously (per local practice) in 28-day cycles. Cusatuzumab (active ingredient) was manufactured by Lonza Biologics (Slough, UK) and cusatuzumab (finished dosage form) was manufactured by Patheon Italia SPA (Ferentino, Italy). Cusatuzumab dose modifications were not allowed; toxicities attributed to cusatuzumab were managed by modifying the infusion rate in the case of infusion-related reactions (IRRs), temporarily stopping cusatuzumab, or discontinuing cusatuzumab altogether (appendix pp 2–3). Patients were treated and continued in the study until either progressive disease, relapse, unacceptable toxicity, withdrawal of consent, or withdrawal due to investigator discretion. Premedications are described in the appendix (p 2).

Response status was assessed by trained haematopathologists at each participating trial site. Blood samples from patients were collected weekly during the first 28 day cycle for clinical laboratory assessments in haematology and serum chemistry. Adverse events and special reporting situations were reported from the time a signed and dated informed consent form was obtained until 30 days following the last dose of study intervention,

or until the start of subsequent anti-acute myeloid leukaemia therapy, if earlier. Special reporting situations meeting the criteria of a serious adverse event were recorded in the electronic case report form.

Outcomes

The primary endpoint was rate of complete remission for both dose levels. Secondary endpoints were rate of complete remission with partial haematological recovery (CRh); rate of complete remission plus CRh; rate of CRi; overall response rate (complete remission plus CRh plus CRi); rate of complete remission without minimal residual disease ($<10^{-3}$ by flow cytometry; appendix pp 5–6); rate of minimal residual disease among participants achieving complete remission, CRh, CRi, or morphological leukaemia-free state; time to and duration of first response (complete remission, CRh, or CRi); transfusion independence (red blood cells or platelets; ≥8 weeks with no transfusion between first and last dose plus 30 days); safety profile of adverse events and serious adverse events; pharmacokinetics; and immunogenicity and antidrug antibody testing. Exploratory endpoints included overall survival, progression-free survival, change in bone marrow blasts, and biomarkers of response. Other exploratory endpoints that were defined in the protocol but are not reported here were CD70+ LSCs, natural killer cells, patient-reported outcomes using the functional assessment of cancer therapy–leukaemia and EQ-5D-5L questionnaires, duration of hospitalisation, and outpatient medical encounters and treatments. These exploratory endpoints were deemed to be outside the scope of this publication as we chose to focus on the key endpoints; however, they might be included in future publications.

Clinical response was determined by modified European LeukemiaNet (ELN) Response Criteria in acute myeloid leukaemia,[6] with inclusion of CRh (<5% blasts in bone marrow; no circulating blasts; no blasts with Auer rods, or extramedullary disease; absolute neutrophil count $>0{\cdot}5\times10^9$ cells per L; and platelet count $>50\times10^9$ cells per L). CRh was programmatically determined by the study sponsor. All patients who reached CRh also met the criteria for CRi. Response status was assessed at every alternate cycle, starting at cycle 1, until complete remission, CRh, CRi, or progressive disease; then every fourth cycle until relapse in patients with complete remission, CRh, or CRi. Patients were deemed not assessable if they had no post-baseline disease evaluations to determine response. TEAEs were monitored throughout the study until 30 days after the last dose of study medication; severity was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. Other assessments including pharmacokinetic, immunogenicity, and pharmacodynamic analyses are described in the appendix (p 5–6).

Statistical analysis

At each stage of study part one, data were evaluated in an informal interim analysis by a Data Review Committee to determine if either or both dose cohorts should continue into the next stage, but without intention of rejecting the null hypothesis. For each analysis, data were reviewed after patients had received three or more cycles. By design, each of the two dose cohorts were to be evaluated independently without between-cohort statistical comparison; therefore, any comparative presentation of the results are exploratory.

For the primary endpoint, the number and percentage of participants reaching complete remission were summarised by treatment group along with 95% CIs based on the Wilson Score without continuity correction. The primary hypothesis was that cusatuzumab at 10 mg/kg or 20 mg/kg plus azacitidine could lead to a rate of complete

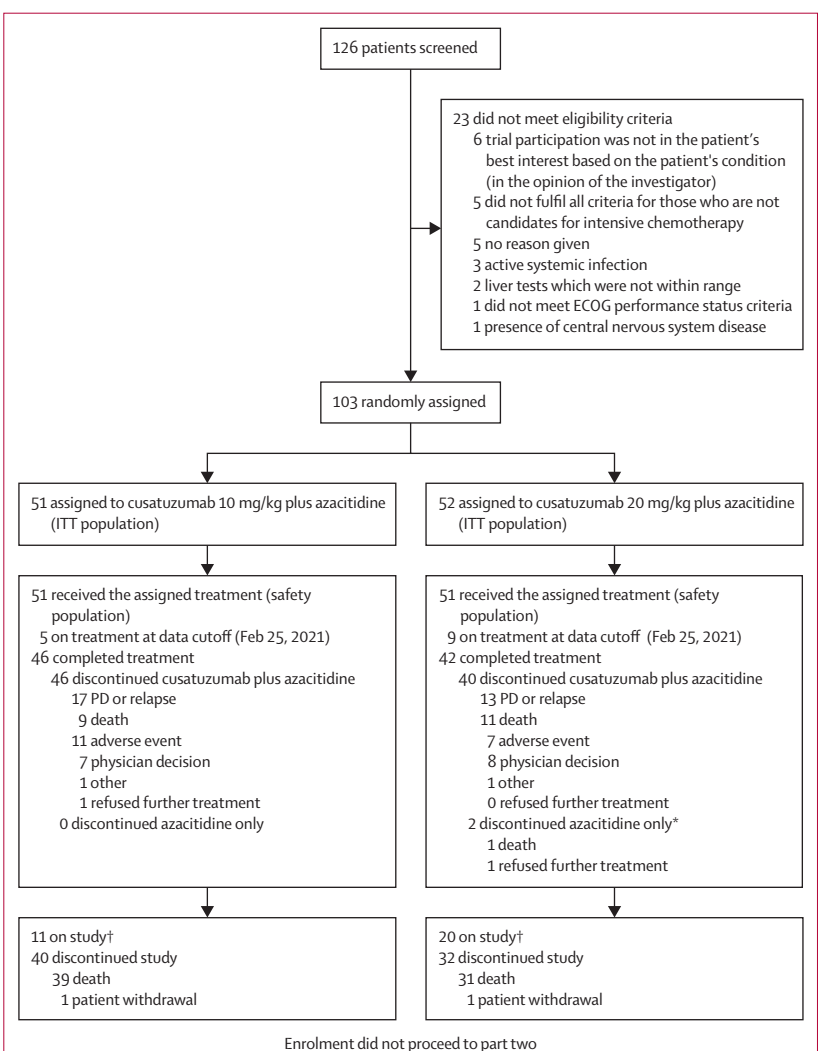

Figure 1: **Trial profile**
ITT=intention-to-treat. PD=progressive disease. ECOG=Eastern Cooperative Oncology Group. *Patients who discontinued azacitidine did so without receiving cusatuzumab. †Currently on treatment or in follow-up for survival.

	Cusatuzumab 10 mg/kg plus azacitidine (n=51)	Cusatuzumab 20 mg/kg plus azacitidine (n=52)
Median age, years (range)	74 (54–88)	75 (59–88)
Age ≥75 years	23 (45%)	27 (52%)
Sex		
Male	28 (55%)	29 (56%)
Female	23 (45%)	23 (44%)
Race		
White	40 (78%)	38 (73%)
Asian	1 (2%)	0
Not reported*	10 (20%)	14 (27%)
ECOG performance status		
0	4 (8%)	7 (13%)
1	16 (31%)	12 (23%)
2	31 (61%)	33 (63%)
Median time from initial diagnosis, days (range)	14 (1–86)	16 (4–75)
Type of acute myeloid leukaemia		
De novo	39 (76%)	40 (77%)
Secondary	12 (24%)	12 (23%)
ELN 2017 genetic risk stratification†		
Favourable	4 (8%)	8 (15%)
Intermediate	20 (39%)	14 (27%)
Adverse	24 (47%)	24 (46%)
Incomplete assessment	3 (6%)	6 (12%)
Cytogenetic abnormality‡		
Yes†	17 (33%)	23 (44%)
del(5q)	10 (20%)	9 (17%)
Complex karyotype	7 (14%)	9 (17%)
Monosomal karyotype	3 (6%)	7 (13%)
Somatic mutations‡		
Yes§	34 (67%)	36 (69%)
NPM1	10 (20%)	9 (17%)
TP53	8 (16%)	7 (13%)
FLT3-ITD	9 (18%)	5 (10%)
ASXL1	6 (12%)	7 (13%)
RUNX1	4 (8%)	9 (17%)
IDH2	0	2 (4%)
Median % blasts, range		
Bone marrow aspirate	58 (21–95)	52 (8–90)
Peripheral blood	25 (0–90)	25 (0–99)

Data are n (%) unless otherwise stated. Details of acute myeloid leukaemia classifications are provided in the appendix (p 9). ECOG=Eastern Cooperative Oncology Group. ELN=European LeukemiaNet. FISH=fluorescence in situ hybridisation. NGS=next-generation sequencing. *Not all countries permit race reporting. †As per ELN. ‡Baseline testing for cytogenetic abnormalities and somatic mutations was conducted initially at local sites using various methods, including NGS, FISH, real-time PCR, karyotyping, and other tools. Central testing by NGS was subsequently employed, which involved retrospective sampling for some patients. §Abnormalities observed in ≥5% of all patients are shown plus *IDH2*.

Table 1: **Baseline characteristics**

remission of greater than or equal to 35% against the null hypothesis of 20%. This hypothesis was based on the complete remission rate for HMAs approximating 20%,[8,9] and a 15% improvement was considered clinically meaningful. The overall study had more than 90% power to reject the null hypothesis of a complete remission rate of 20% under the alternative hypothesis of 35%. Part one of the study was not powered for rejection of the null hypothesis; the sample size of 50 patients for part one of the study was based on the single-arm Wilson Score test without continuity correction at an overall one-sided type 1 error rate of less than 2·5%. Efficacy outcomes were assessed within the intention-to-treat (ITT) population (all patients randomly allocated in part one). Post-hoc efficacy analyses were also performed in a modified ITT population (mITT; those randomly allocated in part one who received ≥1 dose of both study drugs). Safety outcomes were assessed within the safety analysis set (those in the ITT population who received ≥1 dose of study drug).

Overall response rate, minimal residual disease negativity, and rate of transfusion independence were analysed using the same method as for the primary endpoint. Time to first or best response was calculated as the time from randomisation to documented first or best response among patients who reached complete remission, CRh, or CRi. Duration of first or best response was calculated as time from documented first or best response (complete remission, CRh, or CRi) in patients who reached such responses to relapse, death, or date of last disease evaluation. Planned subgroup analyses are provided for overall response rate as forest plots. The number and percentage of patients reaching progression-free survival events (overall, disease progression, relapse, or death) and overall survival were summarised. Kaplan-Meier estimates of time-to-event endpoints are presented graphically, and median estimates and associated 95% CIs are provided.

Statistical analyses were performed using SAS version 9.4. This trial is registered with ClinicalTrials.gov, NCT04023526.

Role of the funding source

The funders were involved in study conception and design, data collection, data analysis and interpretation, and drafting and writing of the report.

Results

Between Aug 30, 2019, and Feb 25, 2020, 103 patients from 40 hospital and academic centres across seven countries (Australia, France, Italy, Russia, Spain, Switzerland, and Turkey, appendix pp 7–8) were enrolled into part one and randomly allocated to cusatuzumab 10 mg/kg (n=51) or 20 mg/kg (n=52), plus azacitidine (figure 1, table 1). 14 centres (one in Australia, three each in Switzerland, Spain, and Israel, and two each in Italy and Turkey) did not recruit any patients as no eligible participants were present during the period between site enrolment and the end of study enrolment. One patient in the 20 mg/kg group did not receive any study medication due to an adverse event (pneumonia) on

cycle 1 day 1 and was excluded from the safety population (n=102); an additional three patients did not receive cusatuzumab (20 mg/kg) due to an adverse event, withdrawal of consent, and death, respectively (mITT set: 51 patients in the 10 mg/kg group and 48 in the 20 mg/kg group). Although enrolment was progressed throughout all three stages of part one of the study, enrolment was stopped per sponsor decision at the end of part one (July 10, 2020), and part two did not take place. 12 (24%) of 51 patients on cusatuzumab 10 mg/kg were escalated to 20 mg/kg after selection of the higher dose at the end of part one; all analyses are presented according to randomisation group. As of the clinical data cutoff (Feb 25, 2021), median follow-up was 7·2 months (IQR 10·7). Major protocol deviations were: received a disallowed concomitant treatment (4 [4%] of 103), received wrong treatment or incorrect dose (4 [4%] of 103), entered but did not satisfy criteria (2 [2%] of 103), developed withdrawal criteria but not withdrawn (2 [2%] of 103), and other (1 [1%] of 103).

At the time of data cutoff, 31 patients (11 in the 10 mg/kg group and 20 patients in the 20 mg/kg group) of 103 patients were still on treatment or being followed up for survival (figure 1). Among the 86 patients who had discontinued cusatuzumab–azacitidine (46 patients in the 10 mg/kg group and 40 patients in the 20 mg/kg group), the most common reason was progressive disease or relapse (17 patients in the 10 mg/kg group, 13 patients in the 20 mg/kg group). Of the 72 patients who had permanently discontinued the study (40 on 10 mg/kg, 32 on 20 mg/kg), 70 had died (39 on 10 mg/kg and 31 on 20 mg/kg, including two people who had reached complete remission before death) and two people (one in each cohort) who had withdrawn consent.

The rate of complete remission in the ITT population was 12% (six of 51 patients; 95% CI 6–23) in the 10 mg/kg group and 27% (14 of 52 patients; 95% CI 17–40) in the 20 mg/kg group (table 2). In the 10 mg/kg group overall response rate was 29% (15 of 51; 95% CI 19–43), and 40% (21 of 52; 28–54) in the 20 mg/kg group (table 2). Responses were observed across patient subgroups (appendix p 20). Of 12 patients who escalated from 10 mg/kg to 20 mg/kg after enrolment was stopped (after a mean of 8·9 [SD 1·4] cycles of combination treatment), two converted from partial remission and CRi, to complete remission.

Median time to first response (complete remission, CRh, or CRi) was 2·8 months (95% CI 2·6–3·5) for the 10 mg/kg cohort and 3·0 months (2·8–3·9) for the 20 mg/kg cohort. Median duration of first response was 5·6 months (0·7–not estimable [NE]) for the lower dose and 13·6 months (6·3–NE; table 2 and figure 2A) for the higher dose. Median overall survival was 5·1 months (3·3–11·3; 39 events) in the 10 mg/kg group, and 9·9 months (5·5–16·2; 31 events; figure 2B) in the 20 mg/kg group. Median progression-free survival was 4·4 months (2·5–5·5; 41 events) in the 10 mg/kg group and 6·7 months (3·8–9·9; 36 events) in the 20 mg/kg group (appendix p 21). At time of cutoff, 13 (25%) of 51 patients in the 10 mg/kg group and 17 (33%) of 51 patients in the 20 mg/kg group had received one or more subsequent therapies; most commonly venetoclax (seven [14%] of 51 and nine [18%] of 51), azacitidine (five [10%] and nine [18%]), or cytarabine (five [10%] and six [12%]). Two patients, both in the 20 mg/kg cohort, went on to receive haematopoietic stem-cell transplantation. Before receiving transplantation, one patient had a best response of progressive disease and the other patient had CRi for 6·5 months.

The proportion of patients reaching transfusion independence was 15 (29%) of 51 in the 10 mg/kg group and 22 (42%) of 52 for the 20 mg/kg group for red blood cells, 20 (39%) of 51 and 27 (52%) of 52 for platelets, and 14 (27%) of 51 and 19 (37%) of 52 for both, respectively (appendix p 10). Median duration of transfusion independence was not reached in the 20 mg/kg dose level (NE [95% CI 37·0–NE]) versus 50·6 weeks (19·1–NE) in the 10 mg/kg dose level.

The mean number of cusatuzumab and azacitidine cycles received by patients enrolled in the 10 mg/kg group was 3·1 (SD 2·6) and for 20 mg/kg cohorts was 6·4 (5·0). 12 patients in the 10 mg/kg cohort underwent dose escalation after a mean of 8·9 (1·4) cycles and received 4·2 (2·3) cycles at 20 mg/kg. Dose reductions

	Cusatuzumab 10 mg/kg plus azacitidine (n=51)	Cusatuzumab 20 mg/kg plus azacitidine (n=52)
Best response, n (%, 95% CI)*		
Complete remission	6 (12%, 6–23)	14 (27%, 17–40)
Complete remission without minimal residual disease	1 (2%)	4 (8%)
CRi	9 (18%)	7 (13%)
CRh	5 (10%)	4 (8%)
ORR (complete remission + CRh + CRi)	15 (29%, 19–43)	21 (40%, 28–54)
Morphological leukaemia-free state	1 (2%)	1 (2%)
Partial remission	1 (2%)	1 (2%)
Stable disease	20 (39%)	19 (37%)
Progressive disease	5 (10%)	3 (6%)
Not evaluable	9 (18%)	7 (13%)
Median time to response, months (95% CI)		
First response	2·8 (2·6–3·5)	3·0 (2·8–3·9)
Best response	2·8 (2·6–4·9)	4·4 (2·9–5·4)
Median duration of response, months (95% CI)		
First response	5·6 (0·7–NE)	13·6 (6·3–NE)
Best response	5·6 (0·7–NE)	11·6 (4·0–NE)

CRh=complete remission with partial haematological recovery. CRi=complete remission with incomplete haematological recovery. NE=not estimable. ORR=overall response rate. *15 patients did not have a post-baseline disease evaluation: eight patients died before the first evaluation; one patient withdrew consent before the first evaluation and then died; six patients did not have a first evaluation performed due to their site's misinterpretation of the protocol but then died before the second disease evaluation. One patient remained on study treatment after response of progressive disease at first disease evaluation, reaching response of stable disease at five subsequent disease evaluations.

Table 2: **Best response per investigator assessment (intention-to-treat population)**

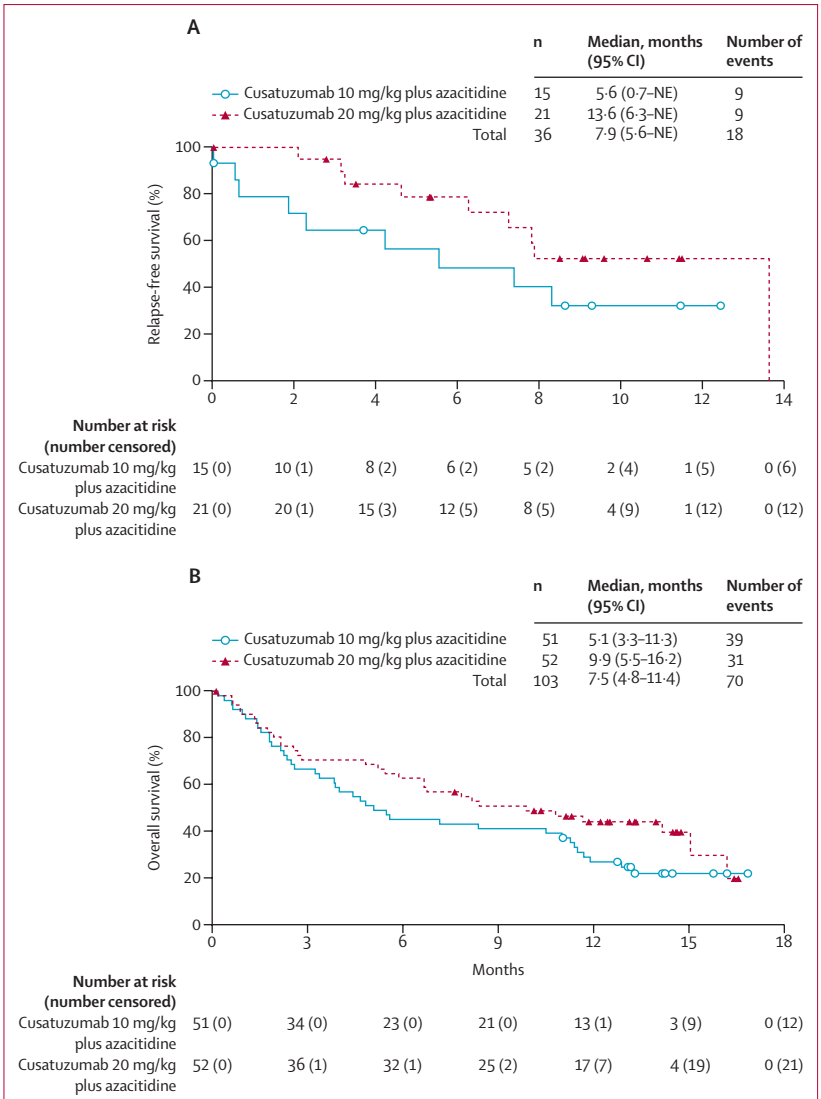

Figure 2: **Kaplan-Meier estimates of (A) duration of first response among patients who reached complete remission, CRh, or CRi and (B) overall survival**
CRh=complete remission with partial haematological recovery. CRi=complete remission with incomplete haematological recovery. NE=not estimable.

were not permitted for cusatuzumab; four patients required an azacitidine dose reduction.

Incidence and nature of TEAEs were similar between the two cohorts (table 3 and appendix p 13); consequently, safety data are described here for all patients combined. Nearly all patients (101 [99%] of 102) had one or more TEAE, with 56 (55%) of 102 having a treatment-related TEAE. COVID-19 pneumonia was reported as a TEAE in eight (8%) of 102 patients, and SARS-CoV-2 infection in one (2%) of 102 patients, respectively. Grade 3 or worse TEAEs (≥20% incidence) were reported by 101 (99%) of 102 patients and included thrombocytopenia (53 [52%] of 102), anaemia (41 [40%] of 102) neutropenia (40 [39%] of 102), leucopenia (29 [28%] of 102), and pneumonia (25 [25%] of 102). Serious TEAEs were observed in 84 (82%) of 102 patients (44 [86%] in the 10 mg/kg group *vs* 40 [78%] in the 20 mg/kg group); 18 [18%] of 102 were treatment-related (10 [20%] of 51 in the 10 mg/kg group *vs* 8 [16%] of 51 in the 20 mg/kg group). TEAEs led to discontinuation of any drug in 23 (23%) of 102 patients. Serious adverse events occurring in more than 5 percent of patients were pneumonia (19 [19%] of 102), febrile neutropenia (14 [14%] of 102), and COVID-19 pneumonia (eight [8%] of 102). Further detailed TEAE data stratified by grade are presented in table 3.

Of 102 patients, 18 (18%) developed IRRs, most commonly (≥2% incidence) hypotension (five [5%] of 102), chills (four [4%] of 102), dyspnoea (two [2%] of 102), nausea (two [2%] of 102), and tremor (two [2%] of 102). One (1%) of 102 patients had grade 3 hypoxia; all other IRRs were grade 1–2. Most IRRs occurred with the first dose and only one patient had more than one IRR (three events). All patients who had IRRs had received premedication and all were able to receive more than one dose of cusatuzumab. IRRs were managed as per protocol, by interrupting infusion and administering symptomatic therapies. No patients discontinued treatment due to an IRR.

34 (33%) of 102 patients died because of a TEAE, including two due to COVID-19: one due to COVID-19 pneumonia and one due to SARS-CoV-2 infection; in four (4%) patients, fatal TEAEs were considered as probably or possibly treatment-related by the investigator (pneumonia n=2, septic shock n=2). Nine (9%) of 102 patients died within 30 days of first dosing because of a TEAE (five [10%] of 51 at 10 mg/kg, and four [8%] of 51 at 20 mg/kg); eight of the nine deaths (four per group) occurred before first disease response assessment and one after CRi was reached.

Among 59 evaluable patients, mean serum exposure parameters for cusatuzumab increased with dose (appendix pp 18, 22). The mean concentrations at 24 h, 96 h, and 336 h after the first dose of cusatuzumab were compared with values obtained after 20 mg/kg dose of cusatuzumab. The mean ratios at these times post dose ranged from 1·8 to 1·9 when 20 mg/kg was compared with 10 mg/kg. There was no obvious change in dose-normalised parameters with increasing dose, suggesting that cusatuzumab exposure increased in an approximately dose-proportional manner over the range 10–20 mg/kg. Mean elimination half-life was 8·1 days (SD 2·3) at 10 mg/kg and 10·6 days (3·8) at 20 mg/kg.

Nine (10%) of 93 patients with evaluable samples were positive for antibodies to cusatuzumab post-dose (seven [15%] of 47 at 10 mg/kg, two [4%] of 46 at 20 mg/kg). There was no apparent relationship between immunogenicity status and cusatuzumab exposure, although interpretation is limited by the small sample size and low number of patients with antidrug antibodies.

A decrease in acute myeloid leukaemia bone marrow blasts was observed at 10 mg/kg and 20 mg/kg in most patients following cusatuzumab–azacitidine treatment

	Cusatuzumab 10 mg/kg plus azacitidine (n=51)					Cusatuzumab 20 mg/kg plus azacitidine (n=51)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Death	Any grade	Grade 1–2	Grade 3	Grade 4	Death
Patients with ≥1 TEAEs	51 (100%)	2 (4%)	1 (2%)	30 (59%)	18 (35%)	50 (98%)	1 (2%)	8 (16%)	25 (49%)	16 (31%)
Thrombocytopenia	26 (51%)	2 (4%)	5 (10%)	19 (37%)	0	30 (59%)	1 (2%)	9 (18%)	20 (39%)	0
Anaemia	24 (47%)	0	24 (47%)	0	0	18 (35%)	1 (2%)	16 (31%)	1 (2%)	0
Neutropenia	20 (39%)	0	1 (2%)	19 (37%)	0	21 (41%)	1 (2%)	2 (4%)	18 (35%)	0
Constipation	18 (35%)	18 (35%)	0	0	0	19 (37%)	18 (35%)	1 (2%)	0	0
Nausea	16 (31%)	15 (29%)	1 (2%)	0	0	19 (37%)	18 (35%)	1 (2%)	0	0
Pyrexia	16 (31%)	13 (25%)	3 (6%)	0	0	15 (29%)	11 (22%)	4 (8%)	0	0
Diarrhoea	15 (29%)	12 (24%)	3 (6%)	0	0	14 (27%)	11 (22%)	3 (6%)	0	0
Pneumonia	15 (29%)	1 (2%)	9 (18%)	1 (2%)	4 (8%)	13 (25%)	2 (4%)	6 (12%)	1 (2%)	4 (8%)
Hypokalaemia	14 (27%)	4 (8%)	7 (14%)	3 (6%)	0	8 (16%)	5 (10%)	2 (4%)	1 (2%)	0
Leukopenia	13 (25%)	0	4 (8%)	9 (18%)	0	16 (31%)	0	6 (12%)	10 (20%)	0
Lymphopenia	13 (25%)	2 (4%)	8 (16%)	3 (6%)	0	7 (14%)	0	6 (12%)	1 (2%)	0
Febrile neutropenia	11 (22%)	0	7 (14%)	4 (8%)	0	9 (18%)	1 (2%)	5 (10%)	3 (6%)	0
Vomiting	9 (18%)	9 (18%)	0	0	0	11 (22%)	10 (20%)	1 (2%)	0	0
Asthenia	8 (16%)	6 (12%)	2 (4%)	0	0	11 (22%)	9 (18%)	2 (4%)	0	0
Hypomagnesaemia	7 (14%)	6 (12%)	1 (2%)	0	0	5 (10%)	4 (8%)	0	1 (2%)	0
Cough	6 (12%)	6 (12%)	0	0	0	8 (16%)	8 (16%)	0	0	0
Sepsis*	5 (10%)	0	2 (4%)	2 (4%)	1 (2%)	6 (12%)	1 (2%)	0	2 (4%)	3 (6%)
Hypotension	4 (8%)	2 (4%)	2 (4%)	0	0	10 (20%)	8 (16%)	1 (2%)	1 (2%)	0
Death or sudden death	4 (8%)	0	0	0	4 (8%)	0	0	0	0	0
COVID-19 or COVID-19 pneumonia	3 (6%)	0	2 (4%)	1 (2%)	0	7 (14%)	1 (2%)	4 (8%)	0	2 (4%)
Atrial fibrillation	3 (6%)	0	2 (4%)	1 (2%)	0	4 (8%)	2 (4%)	2 (4%)	0	0
Hyponatraemia	3 (6%)	2 (4%)	0	1 (2%)	0	3 (6%)	2 (4%)	1 (2%)	0	0
Cardiac arrest or ventricular fibrillation	3 (6%)	0	0	1 (2%)	2 (4%)	0	0	0	0	0
Diverticulitis	3 (6%)	1 (2%)	1 (2%)	0	1 (2%)	0	0	0	0	0
General physical health deterioration	2 (4%)	1 (2%)	0	0	1 (2%)	3 (6%)	0	1 (2%)	0	2 (4%)
Multiple organ dysfunction syndrome	2 (4%)	0	0	0	2 (4%)	2 (4%)	0	0	0	2 (4%)
Soft tissue infection	2 (4%)	0	2 (4%)	0	0	2 (4%)	1 (2%)	0	1 (2%)	0
Hyperkalaemia	2 (4%)	0	1 (2%)	1 (2%)	0	1 (2%)	0	1 (2%)	0	0
Pulmonary oedema	2 (4%)	0	1 (2%)	0	1 (2%)	0	0	0	0	0
Hyperuricaemia	1 (2%)	0	0	1 (2%)	0	2 (4%)	2 (4%)	0	0	0
Acute kidney injury	1 (2%)	1 (2%)	0	0	0	2 (4%)	0	0	2 (4%)	0
Acute myocardial infarction	1 (2%)	0	0	1 (2%)	0	1 (2%)	0	0	0	1 (2%)
Haemorrhage intracranial or cerebral haematoma	1 (2%)	0	0	0	1 (2%)	1 (2%)	0	0	0	1 (2%)
Differentiation syndrome	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Cardiac failure acute	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Large intestine perforation	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Mucosal inflammation	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Cholecystitis	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Cerebrovascular accident	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Major depression	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Pulmonary haemorrhage	1 (2%)	0	0	0	1 (2%)	0	0	0	0	0
Splenic rupture	1 (2%)	0	0	1 (2%)	0	0	0	0	0	0
Respiratory disorder or failure	0	0	0	0	0	2 (4%)	0	0	1 (2%)	1 (2%)

Safety analysis set included all patients who received at least one dose of the study drugs, azacitidine or cusatuzumab. Patients were counted only once for any given event, regardless of the number of times they had the event. The event with the worst toxicity is used. If a patient had missing toxicity for a specific adverse event, that adverse event is excluded from the table. A detailed breakdown of the TEAEs are shown in the appendix (pp 14–17). TEAE=treatment-emergent adverse event. *Sepsis is a grouped term including sepsis, pseudomonal sepsis, septic shock, and staphylococcal sepsis.

Table 3: **TEAEs stratified by grade (safety population)**

(appendix p 23–24). Additionally, mean change from baseline in peripheral blood blasts by the end of cycle 6 was –96% (SD 8) at 10 mg/kg and –91% (25) at 20 mg/kg.

CD70 expression was detectable by flow cytometry on peripheral blood blasts in 64% of the patient samples tested at baseline. The biomarker data suggested a possible association between CD27 or CD70 expression and response, with responders who reached complete remission (including complete remission without minimal residual disease), CRh, or CRi appearing to have higher baseline expression of these markers than non-responders, although there was wide variability in the data (appendix p 19). As a result, we cannot rule out that the antibody staining used for the study was suboptimal; therefore, more studies need to be performed to determine if association between CD70 expression and response to antibody targeting exists. There was no difference in baseline soluble CD27 levels between responders and non-responders (appendix p 19) and there was also no difference after one cycle of treatment (appendix p 22). Analysis of baseline cytogenetic risk (ELN 2017) by response indicated that responses (complete remission, CRh, or CRi) were reached across both dose levels and all risk categories (appendix p 26).

A mITT population was analysed post hoc that excluded patients who never received cusatuzumab treatment. Four (4%) of 103 patients met this criterion, and all were in the 20 mg/kg cohort. In this group, the complete remission rate was 29% (14 of 48; 95% CI 18–43) and overall response rate was 44% (21 of 48; 95% CI 31–58; appendix p 11). Median overall survival was 10·8 months (6·7–16·2; 28 events; appendix p 12).

Discussion

The CULMINATE study is part of a programme to assess the benefit of adding the CD70 targeting antibody cusatuzumab to current acute myeloid leukaemia therapies. In this Article, newly diagnosed patients with acute myeloid leukaemia ineligible for intensive chemotherapy who had received cusatuzumab and azacitidine before the cutoff date of Feb 25, 2021 reached a complete remission rate of 12% (95% CI 6–23) at cusatuzumab 10 mg/kg and 27% (17–40) at 20 mg/kg, rising to overall response rate of 29% (95% CI 19–43) at 10 mg/kg and 40% (28–54) at 20 mg/kg, when CRh and CRi were also considered. Median overall survival was 5·1 months (95% CI 3·3–11·3; 39 events) and 9·9 months (95% CI 5·5–16·2; 31 events) in the 10 mg/kg and 20 mg/kg cohorts, respectively. Although the study was not continued into part two to formally test the null hypothesis of a complete remission rate of 20% versus the target of 35%, the 40% overall response rate observed at the highest 20 mg/kg dose suggested clinical activity, and based on the totality of the data, the 20 mg/kg dose was selected for further study. A future study to explore further dose escalation is under consideration.

We recognise the limitations of this work, including the generalisability of the results, and that this was an elderly population with poor-risk features enrolled within the early stages of the COVID-19 pandemic, which resulted in altered outpatient clinic schedules, doses being delayed, and in rare cases, evaluations being missed. Moreover, disease responses were measured locally and assessed by the investigator which might introduce heterogeneity and bias. In addition, this trial used an open-label design. These are all factors that could have affected the findings. In addition, small sample sizes limited our ability to assess response by cytogenetic (ELN 2017) risk features as well as interpretation of the relationship between immunogenicity status and cusatuzumab exposure data.

Cusatuzumab 20 mg/kg was associated with numerically higher response rates, more durable responses, longer progression-free survival and overall survival than the 10 mg/kg dose and more frequent red cell and platelet transfusion independence, with minimal additional toxicity, although this part of the trial was not powered to compare the two doses statistically. The complete remission rate for the 10 mg/kg dose was lower than anticipated based on early data (n=3) from a phase 1/2 trial of cusatuzumab 10 mg/kg plus azacitidine[12] and lower than would be expected for azacitidine alone.[8] This observation could be due to the high proportion of patients with adverse cytogenetic risk features (48 [47%] of 103) and poor performance status (64 [62%] of 103 with ECOG performance status 2). There were also fewer patients with isocitrate dehydrogenase 2 (*IDH2*) mutant acute myeloid leukaemia (two [2%] of 103) enrolled in this study than reported in other acute myeloid leukaemia studies involving older populations (eg, 25% in VIALE-A[10]). The low enrolment of patients with mutated *IDH2* was likely related to preferential enrolment to competing IDH inhibitor studies enrolling at the same time. These differences in patient baseline characteristics and the larger sample size in this trial compared with the earlier phase 1/2 trial have contributed to the lower than anticipated efficacy outcomes.

CULMINATE was initiated before venetoclax–azacitidine being established as the new standard for patients aged 75 years or older or with medical conditions that prevent use of standard chemotherapy. The goal of this study was to optimise the dose of cusatuzumab and it was administered in combination with azacitidine because at the time the study began, azacitidine was considered the standard of care; the VIALE-A study had not yet been published. Our study design included a 20% complete remission rate for azacitidine which was considered reliable historical control data, as such, a control group was not considered in order to simplify the design. During the CULMINATE study, the VIALE-A data showed that median overall survival was longer with venetoclax–azacitidine than azacitidine alone (14·7 months *vs* 9·6 months, respectively).[10] As our

part one findings did not seem advantageous in the context of the VIALE-A results, enrolment was stopped, with ongoing patients eligible to continue with, or escalate to, the 20 mg/kg dose. At the cutoff date, nine patients were continuing treatment with this higher dose where two patients converted to complete remission (one from partial remission and one from CRi). Notably, high rates of infections and prolonged pancytopenia have been reported during treatment with venetoclax combination therapy,[17–19] indicating the importance of careful patient management when prescribing venetoclax-containing combinations. The favourable risk–benefit profile for cusatuzumab–azacitidine at 20 mg/kg, including durable complete remissions and the notable transfusion independence in a considerable number of patients (22 [42%] of 52 for red blood cells, 27 [52%] of 52 for platelets in the 20 mg/kg group), provides a rationale for further exploration of cusatuzumab with venetoclax with or without azacitidine Preclinical data have shown synergy between cusatuzumab and venetoclax in eliminating LSCs in vitro,[20] and a phase 1b study of cusatuzumab plus venetoclax or cusatuzumab plus venetoclax and azacitidine is underway in newly diagnosed patients with acute myeloid leukaemia ineligible for intensive chemotherapy (ELEVATE; NCT04150887). Despite the modest efficacy findings in this study, long-term follow-up data from studies incorporating venetoclax–azacitidine suggest that most patients will eventually experience post-remission relapse. This result supports the clinical rationale to explore the cusatuzumab–venetoclax–azacitidine triplet strategy, which incorporates an agent with a complimentary mechanism of action and a non-overlapping toxicity profile.

Cusatuzumab–azacitidine had an acceptable safety profile in this study, consistent with previous reports,[12] with the most common grade 3 or worse TEAEs being haematological toxicities and pneumonia. The safety profile of this combination was also comparable with single-agent azacitidine,[7,8] except for IRRs, which are common TEAEs associated with immunotherapies.[21] IRRs with cusatuzumab–azacitidine tended to be mild or moderate and manageable through dose interruption, symptomatic treatment, and a reduced infusion rate. Procedures were also taken to prevent IRRs through premedication and slowly increasing the cusatuzumab infusion rate. Premedications were per protocol and were consistent across countries and sites.

The pharmacokinetic data for cusatuzumab were consistent with previous clinical investigations,[22] demonstrating approximate dose proportionality and a terminal half-life of 8–11 days. Analysis of biomarkers suggested the potential of baseline CD70 expression as a marker of response to cusatuzumab–azacitidine, although further confirmatory studies are needed as the data were highly variable. Serum soluble CD27 were in line with the data from Reither and colleagues,[11] which showed elevated levels at baseline in patients with acute myeloid leukaemia versus healthy control participants.[11]

In conclusion, considering the totality of clinical data for cusatuzumab studies to date, this study indicates that cusatuzumab was clinically active when given in combination with azacitidine at the recommended dose of 20 mg/kg. As cusatuzumab–azacitidine is generally well tolerated and toxicities are clinically manageable, further studies are warranted to examine if the novel mechanism of action associated with cusatuzumab could further enhance clinical outcomes associated with venetoclax–azacitidine. Clinical studies exploring this possibility are already in progress (eg, NCT04150887).[23]

Contributors

All authors confirm that they had full access to all the data in the study; GCT contributed to the conception and design of the study and protocol and study conduct; AH and JJ contributed to design of study and protocol, and interpretation of results; TP, CP, FD, VD, LMF, EG, NH, PH, GM, MA, RM, YO, MÖ, OS, NV, and AHW were study investigators and collected data for the analysis; CK, CG, AJJ, AL, XM, KN, JAT, and LX contributed to study protocol and interpretation of results. AHW and KN have directly accessed and verified the underlying data reported in the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Declaration of interests

CG is an employee of Johnson & Johnson and has stock options. EG has received consulting fees and research funding from Novartis. AH is an employee of argenx which includes stock options and patents. AJJ is an employee and has stock options in Janssen. AL is an employee of Janssen R&D and has stock options in Johnson & Johnson. MA has received consulting fees from BMS-Celgene, Novartis, Astellas, Jazz Pharmaceuticals, and Pfizer; and is an advisory board member for BMS-Celgene and Novartis. KN is an employee of Janssen R&D; and has stock options in Johnson & Johnson. MÖ has received a research grant from Janssen; received grant funding or contracts from AbbVie, Bayer, Janssen, Acerta, Beddy's, Merck Sharp & Dohme, Roche, and Takeda; and has received meeting support from AbbVie, Jazz Pharmaceuticals, and Roche. GCT has stock options in Johnson & Johnson. NV has received honoraria payment from Amgen, argenx, BMS, Janssen, and Roche; and received meeting support from Novartis, Amgen, and BMS. AHW has received research funding from Novartis, AbbVie, Servier, BMS, Syndax, Astex, AstraZeneca, and Amgen; is an employee of Walter and Eliza Hall Institute of medical research which receives milestone and royalty payments related to venetoclax and is eligible for financial benefits associated with these payments; has received consulting fees from Shoreline, Servier, Novartis, and AbbVie; has served on speaker's bureaus for AbbVie, Novartis, BMS, and Astellas; and has served on advisory boards for Novartis, Astellas, Janssen, Amgen, Roche, Pfizer, AbbVie, Servier, Gilead, BMS, Macrogenics, and Agios. XM was an employee of Janssen at the time the study was completed. All other authors declare no competing interests.

Data sharing

The data-sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. Janssen has an agreement with the Yale Open Data Access (YODA) Project who act as independent review panel for evaluation of data requests. To make a request, please visit http://yoda.yale.edu.

Acknowledgments

This study was sponsored by Janssen Research & Development in collaboration with argenx. Medical writing support for the development of this manuscript, under the direction of the authors, was provided by Ranjana Whitlock, PhD, of Ashfield MedComms, an Inizio company, and funded by Janssen Research & Development and argenx.

References

1 Ley TJ, Miller C, Ding L, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med* 2013; **368:** 2059–74.

2 National Cancer Institute. SEER stat fact sheets: acute myeloid leukemia (AML). 2022. http://seer.cancer.gov/statfacts/html/amyl.html (accessed March 9, 2022).

3 Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31:** 697–712.

4 Prassek VV, Rothenberg-Thurley M, Sauerland MC, et al. Genetics of acute myeloid leukemia in the elderly: mutation spectrum and clinical impact in intensively treated patients aged 75 years or older. *Haematologica* 2018; **103:** 1853–61.

5 De Angelis R, Minicozzi P, Sant M, et al. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000–2007: results of EUROCARE-5 population-based study. *Eur J Cancer* 2015; **51:** 2254–68.

6 Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood* 2017; **129:** 424–47.

7 Fenaux P, Mufti GJ, Hellström-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; **28:** 562–69.

8 Dombret H, Seymour JF, Butrym A, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 2015; **126:** 291–99.

9 Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol* 2012; **30:** 2670–77.

10 DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med* 2020; **383:** 617–29.

11 Riether C, Schürch CM, Bührer ED, et al. CD70/CD27 signaling promotes blast stemness and is a viable therapeutic target in acute myeloid leukemia. *J Exp Med* 2017; **214:** 359–80.

12 Riether C, Pabst T, Höpner S, et al. Targeting CD70 with cusatuzumab eliminates acute myeloid leukemia stem cells in humans. *Nat Med* 2020; **26:** 1459–67.

13 Silence K, Dreier T, Moshir M, et al. ARGX-110, a highly potent antibody targeting CD70, eliminates tumors via both enhanced ADCC and immune checkpoint blockade. *MAbs* 2014; **6:** 523–32.

14 Nolte MA, van Olffen RW, van Gisbergen KP, van Lier RAW. Timing and tuning of CD27-CD70 interactions: the impact of signal strength in setting the balance between adaptive responses and immunopathology. *Immunol Rev* 2009; **229:** 216–31.

15 Sauer T, Parikh K, Sharma S, et al. CD70-specific CAR T cells have potent activity against acute myeloid leukemia without HSC toxicity. *Blood* 2021; **138:** 318–30.

16 Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* 2013; **27:** 997–99.

17 Winters AC, Gutman JA, Purev E, et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. *Blood Adv* 2019; **3:** 2911–19.

18 Morsia E, McCullough K, Joshi M, et al. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. *Am J Hematol* 2020; **95:** 1511–21.

19 Apel A, Moshe Y, Ofran Y, et al. Venetoclax combinations induce high response rates in newly diagnosed acute myeloid leukemia patients ineligible for intensive chemotherapy in routine practice. *Am J Hematol* 2021; **96:** 790–95.

20 Riether C, Chiorazzo T, Johnson AJ, et al. The combination of the BCL-2 antagonist venetoclax with the CD70-targeting antibody cusatuzumab synergistically eliminates primary human leukemia stem cells. *Blood* 2019; **134** (suppl 1)**:** 3918 (abstr).

21 Cáceres MC, Guerrero-Martín J, Pérez-Civantos D, Palomo-López P, Delgado-Mingorance JI, Durán-Gómez N. The importance of early identification of infusion-related reactions to monoclonal antibodies. *Ther Clin Risk Manag* 2019; **15:** 965–77.

22 Aftimos P, Rolfo C, Rottey S, et al. Phase I dose-escalation study of the anti-CD70 antibody ARGX-110 in advanced malignancies. *Clin Cancer Res* 2017; **23:** 6411–20.

23 Roboz G, Pabst T, Aribi A, et al. Safety and efficacy of cusatuzumab in combination with venetoclax and azacitidine (CVA) in patients with previously untreated acute myeloid leukemia (AML) who are not eligible for intensive chemotherapy; an open-label, multicenter, phase 1b study. *Blood* 2021; **138** (suppl 1)**:** 369 (abstr).