Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study

Courtney D DiNardo, Keith W Pratz, Anthony Letai, Brian A Jonas, Andrew H Wei, Michael Thirman, Martha Arellano, Mark G Frattini, Hagop Kantarjian, Relja Popovic, Brenda Chyla, Tu Xu, Martin Dunbar, Suresh K Agarwal, Rod Humerickhouse, Mack Mabry, Jalaja Potluri, Marina Konopleva, Daniel A Pollyea**

Summary

Background Elderly patients (aged ≥65 years) with acute myeloid leukaemia have poor outcomes and no effective standard-of-care therapy exists. Treatment with hypomethylating agents such as azacitidine and decitabine is common, but responses are modest and typically short-lived. The oral anti-apoptotic B-cell lymphoma 2 protein inhibitor, venetoclax, has shown promising single-agent activity in patients with relapsed or refractory acute myeloid leukaemia and preclinical data suggested synergy between hypomethylating agents and venetoclax, which led to this combination phase 1b study.

Methods Previously untreated patients aged 65 years and over with acute myeloid leukaemia who were ineligible for standard induction therapy were enrolled into this non-randomised, open-label, phase 1b study. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–2 and either intermediate-risk or poor-risk cytogenetics. Patients were enrolled into one of three groups for the dose-escalation phase of this study: group A (venetoclax and intravenous decitabine 20 mg/m^2 [days 1–5 of each 28-day cycle]), group B (venetoclax and subcutaneous or intravenous azacitidine 75 mg/m^2 [days 1–7 of each 28-day cycle]), and group C (a venetoclax and decitabine substudy with the oral CYP3A inhibitor posaconazole, 300 mg twice on cycle 1, day 21, and 300 mg once daily from cycle 1, days 22–28, to assess its effect on venetoclax pharmacokinetics). Dose escalation followed a standard 3+3 design with at least three evaluable patients enrolled per cohort; daily target doses of venetoclax for groups A and B were 400 mg (cohort 1), 800 mg (cohorts 2 and 3), and 1200 mg (cohort 4), and 400 mg for group C. The primary endpoints were the safety and pharmacokinetics of venetoclax plus decitabine or azacitidine, and to determine the maximum tolerated dose and recommended phase 2 dose. Secondary endpoints included the preliminary anti-leukaemic activity of venetoclax with decitabine or azacitidine through the analysis of overall response, duration of response, and overall survival. We analysed safety, pharmacokinetics, and anti-leukaemic activity in all patients who received one or more venetoclax doses. The expansion phase of the study is ongoing but is closed to accrual. This trial is registered with ClinicalTrials.gov, number NCT02203773.

Findings 57 patients were enrolled in the study. 23 patients in group A and 22 patients in group B were enrolled between Nov 19, 2014, and Dec 15, 2015, and 12 patients in group C were enrolled between June 14, 2015, and Jan 16, 2016. As of data cutoff on June 15, 2016, the most common grade 3–4 treatment-emergent adverse events were thrombocytopenia (27 [47%] of 57 patients; nine in group A, 13 in group B, and five in group C), febrile neutropenia (24 [42%] of 57; 11 in group A, ten in group B, and three in group C), and neutropenia (23 [40%] of 57; 12 in group A, eight in group B, and three in group C). The most common serious treatment-emergent adverse event in groups A and B was febrile neutropenia (seven [30%] of 23 patients *vs* seven [32%] of 22), whereas in group C it was lung infection (four [33%] of 12 patients). 49 (86%) of 57 patients had treatment-related adverse events; the most common in groups A and B included nausea (12 [52%] patients *vs* seven [32%] patients), fatigue (six [26%] patients *vs* seven [32%]), and decreased neutrophil count (six [26%] patients *vs* six [27%]), whereas in group C the most common were nausea (seven [58%] of 12 patients), leucopenia (six [50%]), vomiting (five [42%]), and decreased platelet count (five [42%]). The maximum tolerated dose was not reached. The recommended phase 2 dose was 400 mg once a day or 800 mg with an interrupted dosing schedule (safety expansion). In total, four (7%) of 57 patients had died within 30 days of the first venetoclax dose caused by sepsis (group B), bacteraemia (group A), lung infection (group C), and respiratory failure (group A). Tumour lysis syndrome was not observed. Decitabine and azacitidine did not substantially affect venetoclax exposures. Overall, 35 (61%; 95% CI 47·6–74·0) of 57 patients achieved complete remission or complete remission with incomplete marrow recovery. In groups A and B, 27 (60%; 95% CI 44·3–74·3) of 45 patients had complete remission or complete remission with incomplete marrow recovery.

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*These authors contributed equally

University of Texas MD Anderson Cancer Center, Houston, TX, USA (C D DiNardo MD, Prof H Kantarjian MD, Prof M Konopleva MD); **Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA** (K W Pratz MD); **Dana-Farber Cancer Institute, Boston, MA, USA** (A Letai MD); **UC Davis Comprehensive Cancer Center, Sacramento, CA, USA** (B A Jonas MD); **The Alfred Hospital and Monash University, Melbourne, VIC, Australia** (A H Wei MBBS); **University of Chicago Medical Center, Chicago, IL, USA** (M Thirman MD); **Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA, USA** (M Arellano MD); **Columbia University Medical Center, New York, NY, USA** (M G Frattini MD); **AbbVie Inc, North Chicago, IL, USA** (R Popovic PhD, B Chyla PhD, T Xu PhD, M Dunbar DRPH, S K Agarwal PhD, R Humerickhouse MD, M Mabry MD, J Potluri MD); **and University of Colorado School of Medicine, Aurora, CO, USA** (D A Pollyea MD)

Correspondence to:
Dr Daniel A Pollyea, University of Colorado School of Medicine, Aurora, CO 80045, USA
daniel.pollyea@ucdenver.edu

Interpretation Venetoclax plus hypomethylating agent therapy seems to be a novel, well-tolerated regimen with promising activity in this underserved patient population. Evaluation of expansion cohorts is ongoing at 400 mg and 800 mg doses using both hypomethylating agent combinations.

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Introduction

Acute myeloid leukaemia is predominant in elderly patients (aged ≥65 years), with a median age of 68 years at diagnosis.[1] These patients are more frequently refractory than younger patients to cytotoxic intensive induction chemotherapy because of biological disease-related factors such as increased frequency of adverse-risk cytogenetic and molecular features, secondary acute myeloid leukaemia, and increased expression of multidrug resistance phenotypes.[2] Elderly patients also present with more comorbidities and compromised organ function than young patients, which decreases tolerance to intensive therapies and leads to unacceptably high treatment-related mortality.[3–5] Thus, a crucial need exists to develop more effective, well tolerated therapies for elderly patients with acute myeloid leukaemia.

The anti-apoptotic B-cell lymphoma 2 (BCL-2) protein is overexpressed in the leukaemia stem cell compartment[6] and BCL-2 overexpression is associated with chemo-therapy resistance and poor outcomes in patients with acute myeloid leukaemia.[7] Myeloblasts associated with this disease are dependent on BCL-2 to promote cell survival and are sensitive to BCL-2 inhibition in vitro and in vivo.[8] Venetoclax, a potent, selective, orally bioavailable small-molecule inhibitor of BCL-2, has shown modest single-agent clinical activity, with 16 (19%) of 32 patients with relapsed and refractory acute myeloid leukaemia achieving an overall response in a phase 2 trial.[9] Venetoclax synergises with hypomethylating agents such as decitabine and azacytidine in preclinical models, suggesting that this drug combination might be a promising therapeutic approach for acute myeloid leukaemia therapy.[10] Furthermore, studies suggest azacitidine could reduce concentrations of MCL-1, an anti-apoptotic protein crucial for survival in acute myeloid leukaemia and a possible source of resistance to venetoclax.[11,12] These data provide a strong clinical rationale for the combination of venetoclax with hypomethylating agents for the treatment of this disease.

Methods

Study design and participants

See Online for appendix

This analysis is part of a phase 1b, open-label, multicentre, two-stage study. A list of the participating sites is provided in the appendix (p 1). Eligible patients had histologically confirmed acute myeloid leukaemia by WHO criteria,[13]

Research in context

Evidence before this study

Elderly patients (aged ≥65 years) with newly diagnosed acute myeloid leukaemia are often not eligible for standard induction therapy and have few available treatment options and poor outcomes. We searched PubMed for clinical trial reports (with no start date and up to Oct 15, 2016) to identify new agents used to treat this patient population. Terms used in the search were "acute myelogenous leukemia", "acute myeloid leukemia", "AML", "older", "elderly", "≥65 years", "treatment naive", "standard induction therapy", and "novel therapy". The published literature showed that the DNA hypomethylating agents, decitabine and azacitidine, hold promise for treating this population and the European Medicines Agency has approved both these agents for the treatment of acute myeloid leukaemia. Low-dose cytarabine is another commonly used agent in elderly patients with acute myeloid leukaemia who are not eligible for clinical trials of standard induction therapy. However, responses achieved with these agents when used alone are modest and not durable. Therefore, novel therapeutic approaches are urgently needed.

Added value of this study

Our results show that venetoclax in combination with hypomethylating agent therapy is well tolerated in newly diagnosed patients with acute myeloid leukaemia who are aged 65 years or older and not eligible for standard induction therapy. The combination of venetoclax with hypomethylating agents had a higher proportion of and more rapid objective responses than observed in historical studies using single-agent hypomethylating agents. To our knowledge, this study is the first time that a drug that specifically targets the anti-apoptotic BCL-2 protein has been combined with hypomethylating agents in elderly patients with acute myeloid leukaemia. The observed overall responses and duration of responses are promising, and the observed toxicity profile seems acceptable. These data strongly support clinical development of the BCL-2 inhibitor venetoclax in combination with hypomethylating agents in this patient population.

Implications of all the available evidence

These results support further evaluation of the combination of venetoclax with hypomethylating agents as an option to treat elderly patients with newly diagnosed acute myeloid leukaemia who are not eligible for standard induction therapy.

were aged 65 years or older, had a projected life expectancy of at least 12 weeks, were not eligible for standard induction chemotherapy, had not received any previous therapy for acute myeloid leukaemia or a previous hypomethylating agent for any indication, had adequate renal and hepatic function, and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were defined as not eligible for intensive induction therapy on the basis of investigator assessment of age, ECOG performance status, comorbidities, regional guidelines, or institutional practice, or all these. At enrolment, white cell count was required to be 25×10^9 per L or lower; use of leukapheresis or hydroxyurea was permitted to achieve this concentration. Patients with favourable-risk cytogenetics or known active CNS involvement from acute myeloid leukaemia were ineligible. The cytogenetic risk categories were based on the National Comprehensive Cancer Network Guidelines from 2014.[14] Coadministration of strong or moderate CYP3A inducers or inhibitors was not allowed within 7 days before or during study participation (except for patients in group C of the trial who received posaconazole on cycle 1, days 21–28, as part of the trial design). Other exclusion criteria included patients with: t(8;21), inv(16), or t(15;17) chromosomal abnormalities; acute promyelocytic leukaemia; positivity for HIV; cardiovascular disability status of New York Heart Association Class 2 or above; substantial history of renal, neurological, psychiatric, endocrine, metabolic, immunological, hepatic, or cardiovascular disease, or any other medical condition that in the opinion of the investigator would adversely affect participation in the study; chronic respiratory disease that requires continuous oxygen use; malabsorption syndrome or other conditions that preclude enteral route of administration; and evidence of other clinically significant uncontrolled conditions. Further details on inclusion and exclusion criteria are provided in the appendix (p 1).

The study was done according to applicable regulations and guidelines governing clinical study conduct and ethical principles provided by the Declaration of Helsinki, and was approved by the independent ethics committee and institutional review board of all participating institutions. All patients voluntarily provided written informed consent.

Procedures

The study included a dose-escalation stage evaluating the safety and pharmacokinetics of venetoclax plus decitabine or azacitidine, which was followed by a dose-expansion stage assessing safety and preliminary activity of both combinations. The dose-escalation phase consisted of two primary groups: group A (venetoclax plus decitabine) and group B (venetoclax plus azacitidine). A third group (C) was a drug–drug interaction substudy, which was done at MD Anderson Cancer Center and was designed to assess the safety and pharmacokinetics of venetoclax coadministered with posaconazole—a strong CYP3A inhibitor—plus decitabine.

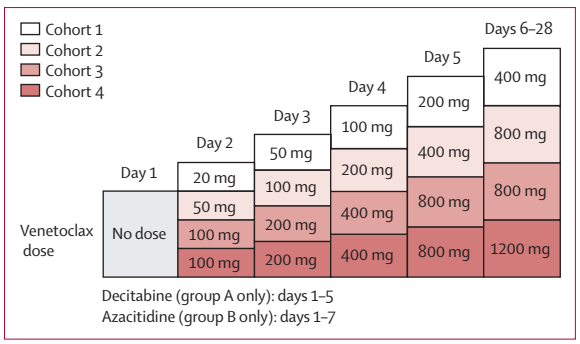

Figure 1: **Dosing schedule for group A (venetoclax and decitabine) and group B (venetoclax and azacitidine)**

Dose escalation followed a standard 3 + 3 design with a minimum of three evaluable patients enrolled per cohort. Oral administration of venetoclax began on day 2 of cycle 1, with a mandated daily increase to reach the final cohort dose to mitigate potential tumour lysis syndrome. In cohort 1, the starting dose of venetoclax was 20 mg and the target dose was 400 mg. Cohorts 2 and 3 escalated to 800 mg (from a starting dose of 50 mg in cohort 2 and 100 mg in cohort 3) by use of different dose ramp-up schedules. Cohort 4 escalated from a starting dose of 100 mg venetoclax to 1200 mg venetoclax (figure 1). For patients who received 800 mg and 1200 mg doses and remained on the study, the duration of venetoclax treatment or dose was reduced to mitigate neutropenia. Since no guidelines exist for growth factor use in acute myeloid leukaemia, recommendations were not provided in the study protocol.

When the cohort-designated maximum dose was reached, the target dose of venetoclax was continued daily in 28-day cycles. For group A, decitabine (20 mg/m²) was administered intravenously on days 1–5 of each cycle. For group B, azacitidine (75 mg/m²) was administered intravenously or subcutaneously on days 1–7 of each cycle. Details of group C (the substudy to evaluate the effect of posaconazole on the safety and pharmacokinetics of venetoclax) have been reported previously.[15] In brief, patients in group C received decitabine intravenously on days 1–5 and venetoclax daily from cycle 1, on days 2–20 with a target dose of 400 mg (appendix p 5). Once the anticipated steady-state dose of venetoclax was reached, 300 mg oral posaconazole was administered twice on cycle 1, day 21, and 300 mg once per day from cycle 1, days 22–28, with concurrent reduction in venetoclax dose to either 100 mg or 50 mg daily during cycle 1, days 21–28. Patients who achieved disease control and tolerable side-effects received treatment until discontinuation criteria were met. These criteria included consent withdrawal, investigator recommendation, disease progression while on the study drug, dose interruption for more than one cycle, administration of

radiotherapy or alternate antineoplastic agents during study period, adverse events that precluded further treatment, and non-compliance with the study protocol.

All patients received prophylaxis for tumour lysis syndrome during cycle 1 beginning at least 72 h before venetoclax dosing with an oral uric acid-reducing agent (eg, allopurinol) and hydration (1·5–2 L/day orally and intravenous administration commencing 24 h before venetoclax dosing on admission to hospital). Admission to hospital was required starting the night before cycle 1, day 1, and for at least 24 h after the maximum dose of venetoclax was reached. All patients were admitted to hospital for the first week of venetoclax dosing (or longer if needed) for management of potential disease complications during the dose escalation of venetoclax or bone marrow recovery, or both. Tumour lysis syndrome was monitored in the laboratory predose and 6 h and 12 h post dose for each dose escalation, and hours 24, 48, and 72 post administration of the maximum venetoclax dose. All patients received supportive care measures according to institutional guidelines and could receive prophylactic non-azole antifungals in groups A and B.

Per protocol, any dose-limiting toxicities required interruption and possible discontinuation of venetoclax, azacitidine, or decitabine. Venetoclax could be reintroduced at a reduced dose if the toxicity grade returned to grade 1 or lower, or to baseline if grade 2 at study entry. The dose could be increased thereafter on assessment of the patient but was not to exceed the highest tolerated dose. For patients in complete remission with incomplete marrow recovery or who had a morphologically leukaemia-free state at the end of cycle 1, and persistent neutropenia after completion of the assessment period for dose-limiting toxicities, venetoclax dosing could be interrupted to allow neutrophil recovery to at least 500 cells per μL before initiation of the next cycle of study treatment. Decitabine or azacitidine was also delayed. Treatment with venetoclax and decitabine or azacitidine resumed once peripheral blood counts had improved for all patients. Venetoclax dosing was adjusted during posaconazole administration during cycle 1.

Treatment-emergent adverse events and treatment-related adverse events assessed by the investigator were summarised as per the Medical Dictionary for Regulatory Activities and the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Laboratory chemistry assessments were done at hours 24, 48, and 72 after administration of the highest scheduled venetoclax dose. Persistent cytopenias at the same CTCAE grade as at baseline were not reported as adverse events unless they had an identifiable cause other than underlying disease, fulfilled seriousness criteria, or resulted in interruption or permanent discontinuation of a study drug. Blood counts were analysed on days 1–7 of cycle 1, day 1 of each cycle, and as clinically indicated while on study treatment. All patients with a reported adverse event of neutropenia or decreased neutrophil count after enrolment were included in the safety analysis regardless of their baseline neutropenia.

Blood samples for pharmacokinetic assessments were collected at hours 0, 2, 4, 6, 8, and 24 post-dose on cycle 2, day 5. Venetoclax predose samples were collected on day 5 of cycles 3, 4, 6, and 8. Non-compartmental methods were used to determine venetoclax pharmacokinetic parameters including maximum observed plasma concentration, time to reach this concentration, and area under the plasma concentration-time curve from 0 h to 24 h dose interval. Patients who discontinued prematurely before the intensive pharmacokinetic visit or those who were missing two or more pharmacokinetic samples on the visit were not included in the analysis. Pharmacokinetic assessments in group C have been published previously.[15]

Bone marrow aspirate and biopsies were taken at screening, at the end of cycle 1, and every third cycle thereafter for anti-leukaemic activity assessments, which were done at the investigator sites as per the International Working Group criteria for acute myeloid leukaemia.[16] Per investigator discretion, additional bone marrow samples were collected if there was peripheral blood count recovery suggestive of an improved response or in patients at risk of relapsed or resistant disease.

Peripheral blood or bone marrow specimens, or both, were collected from patients at baseline for biomarker analysis, which was an exploratory endpoint. Recurrent mutations associated with acute myeloid leukaemia were detected by next-generation sequencing through use of the Foundation One Heme panel (Foundation Medicine, Cambridge, MA, USA) or the TruSight Myeloid panel (Illumina, San Deigo, CA). Status of *FLT3*-internal tandem duplication (*FLT*–ITD) was done by fragment amplification and separation by capillary electrophoresis.[17] This phase 1b study is now in the expansion phase and biomarker samples are still under analysis.

Outcomes

The primary endpoints were to evaluate the safety and pharmacokinetics of venetoclax in combination with decitabine and azacitidine, as well as determine the maximum tolerated dose and recommended phase 2 dose of venetoclax in combination with these hypomethylating agents. Dose-limiting toxicities were determined during cycle one (4 weeks) of study treatment. Patients who entered the study with grade 3 or 4 anaemia, neutropenia, or thrombocytopenia were not evaluable for haematology-related dose-limiting toxicities. Any of the following events were considered dose-limiting toxicities if they could not be attributed by the investigator to a clearly identifiable cause (eg, tumour progression, underlying or concurrent illness, or concomitant medication): grade 3 or worse non-haematological toxicity possibly related to the study drug, and grade 3 or worse anaemia, neutropenia, or thrombocytopenia with hypocellular bone marrow and less than 5% marrow blasts lasting for 42 days or longer.

The maximum tolerated dose for each group (excluding group C) was defined as the highest dose (and corresponding ramp-up period regimen, if applicable) for which the probability of a dose-limiting toxicity is less than 0·33. The recommended phase 2 dose was defined as the maximum tolerated dose or less. Secondary endpoints were preliminary activity of venetoclax in combination with decitabine or azacitidine through analysis of overall response, duration of response, and overall survival. Per study protocol, overall response was defined as complete remission, complete remission with incomplete marrow recovery, and partial remission. Duration of response was defined as the number of days from the date of first response (complete remission, complete remission with incomplete marrow recovery, or partial remission) to the earliest evidence of relapse, and overall survival was defined as the number of days from date of first dose to the date of death. The effect of posaconazole on the pharmacokinetic properties of venetoclax was a secondary endpoint (appendix p 9). Correlative studies to identify biomarkers that might serve as surrogates for clinical endpoints in future studies was a prespecified exploratory objective.

Statistical analysis

The number of patients required for the dose-escalation phase was dependent on toxicities observed as the trial progressed. No formal power calculations were done. In the dose-escalation phase, up to 48 patients were planned for enrolment. Enrolment of up to 12 additional patients was planned in the drug–drug interaction substudy (group C). Complete data from 12 patients would provide 90% power for the test on the dose-normalised pharmacokinetic parameters if the true ratio of central values is 1·7 (70% increase). Safety, pharmacokinetics, and anti-leukaemic activity analyses were done per protocol on all patients who received at least one dose of venetoclax. Demographics were analysed by descriptive statistics. Overall response was defined as the proportion of patients who achieve complete remission, complete remission with incomplete marrow recovery, or partial remission per the International Working Group criteria for acute myeloid leukaemia. 95% CIs were calculated based on the binomial distribution. Duration of response and overall survival were analysed by Kaplan-Meier methods with median values and corresponding 95% CI calculated. For patients in remission, duration of response data were censored on the date of the last available disease assessment. For non-responding patients, duration of response data were not included unless otherwise indicated. All statistical analyses were done with SAS version 9.3 or higher.

This study is registered with ClinicalTrials.gov, number NCT02203773.

Role of the funding source

The funders of the study participated in the design, study conduct, analysis and interpretation of data, as well as the writing, review, and approval of this manuscript. All

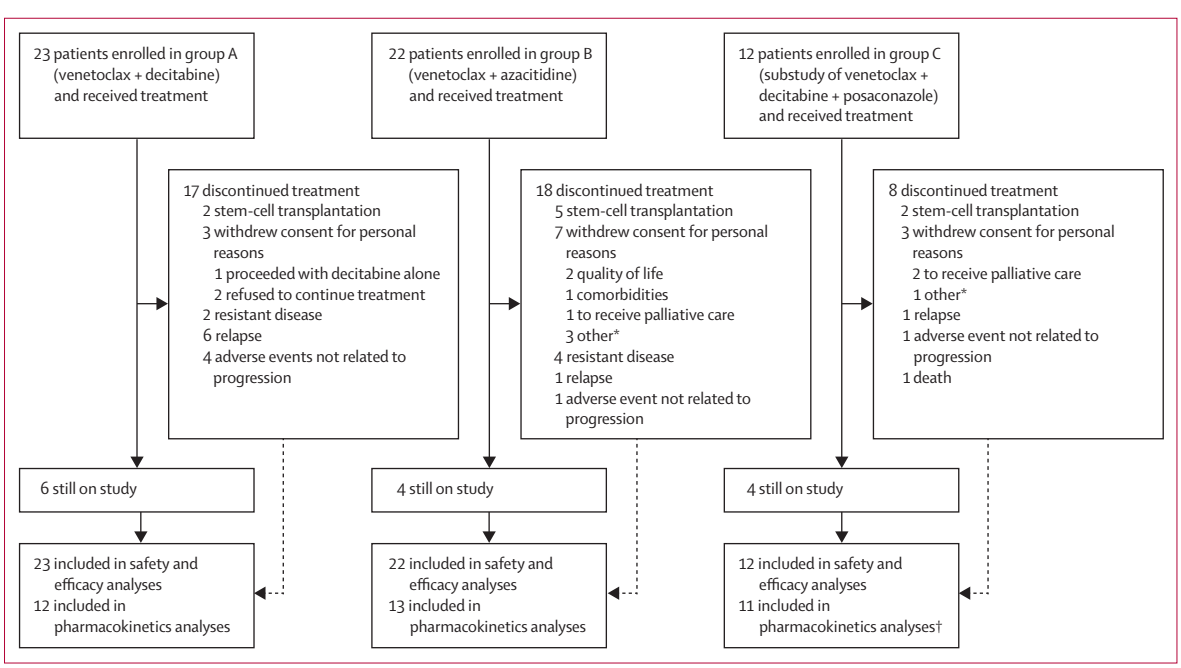

Figure 2: **Trial profile**

Patients who discontinued prematurely before the intensive pharmakokinetics visit or those who were missing two or more pharmacokinetic samples on the visit were not included in the analysis as the pharmacokinetic parameters could not be estimated accurately.*Other reasons include patient choosing to seek treatment from a local physician (n=1), and unknown personal reasons (n=3). †One patient discontinued prematurely.

	Group A (n=23)	Group B (n=22)	Group C (n=12)
Age (years)	74 (71·5–79·0)	75 (71·0–80·0)	74 (69·0–79·5)
Age ≥75 years	11 (48%)	12 (55%)	6 (50%)
Sex			
Male	9 (39%)	11 (50%)	8 (67%)
Female	14 (61%)	11 (50%)	4 (33%)
ECOG performance status			
0	2 (9%)	4 (18%)	5 (42%)
1	17 (74%)	14 (64%)	5 (42%)
2	4 (17%)	4 (18%)	2 (17%)
Cytogenetics*			
Intermediate risk	17 (74%)	13 (59%)	5 (42%)
Poor risk	6 (26%)	9 (41%)	6 (50%)
Mutation†			
FLT3	6 (26%)	1 (5%)	0
FLT3–ITD	4 (17%)	0	0
FLT3–ITD and *FLT3*–TKD	1 (4%)	0	0
FLT3–TKD	2 (9%)	0	0
FLT3 amplification	0	1 (5%)	0
IDH1/2	7 (30%)	7 (33%)	3 (30%)
TP53	3 (13%)	3 (14%)	5 (50%)
Antecedent haematological disorder	2 (9%)	3 (14%)	3 (25%)
Baseline bone marrow blast count			
20–30%	6 (26%)	6 (27%)	4 (33%)
31–50%	7 (30%)	9 (41%)	4 (33%)
>50%	10 (43%)	7 (32%)	4 (33%)
Median	42 (30–65)	41 (25–60)	47 (28–52)
White blood cells (10^9 per L)	2·9 (1·6–7·7)	2·2 (1·3–4·0)	2·4 (1·5–5·5)
Hydroxyurea before study initiation	6 (26%)	2 (9%)	2 (17%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *FLT3*=FMS-like tyrosine kinase 3. *FLT3*–ITD=*FLT3*-internal tandem duplication. *FLT3*–TKD=*FLT3*-tyrosine kinase domain. *IDH1/2*=isocitrate dehydrogenases 1 and 2. *TP53*=tumour protein p53. *One patient in group C had insufficient sample size for cytogenetics testing. †n=54; data were not available for three patients (one in group B and two in group C); patients might be counted more than once regarding each marker from the myeloid panel.

Table 1: **Patient demographics and baseline characteristics**

authors had access to the raw data. The corresponding author had full access to all the data and had the final responsibility to submit for publication.

Results

Of 57 patients enrolled in the study, 45 were enrolled in the dose-escalation cohorts (23 in group A and 22 in group B) and 12 in group C for the drug–drug interaction substudy (figure 2). In group A, six patients were enrolled in cohort 1 (400 mg venetoclax), 12 in cohorts 2 and 3 (800 mg venetoclax), and five patients in cohort 4 (1200 mg venetoclax). In group B, four patients were enrolled in cohort 1, 12 in cohorts 2 and 3, and six in cohort 4.

For groups A and B, enrolment began on Nov 19, 2014, and ended on Dec 15, 2015, and for group C, enrolment occurred from June 14, 2015, to Jan 16, 2016. The data cutoff for all groups was June 15, 2016. Median duration of follow-up was 12·4 months (IQR 8·3–15·8) for the overall trial population, and 15·2 months (10·8–16·5) for group A, 12·7 months (9·0–15·8) for group B, and 7·9 months (5·9–10·0) for group C. Baseline characteristics and demographics are summarised in table 1. Median age was 75 years (IQR 71–80). 46 (81%) of 57 patients had an ECOG performance status of 1–2, 21 (37%) had poor-risk cytogenetics,[14] and eight (14%) had an antecedent haematological disorder. Some heterogeneity in cytogenetic risk was noted between groups, with six (50%) of 12 patients in group C having poor-risk cytogenetics, compared with six (26%) of 23 patients and nine (41%) of 22 patients in groups A and B, respectively.

At baseline, 41 (72%) of 57 patients had grade 3 or worse neutropenia (15 in group A, 18 in group B, and eight in group C), 34 (60%) had grade 4 thrombocytopenia (12 in group A, 14 in group B, and eight in group C), 16 (28%) had grade 3 or worse anaemia (six in group A and ten in group B), and 40 (70%) received transfusion support (20 in group A, 12 in group B, and eight in group C).

The most common any-grade treatment-emergent adverse events in all groups were gastrointestinal events, of which most were grade 1–2, and cytopenias (appendix pp 2–3). The most common grade 3–4 treatment-emergent adverse events were thrombocytopenia (27 [47%] of 57 patients; nine in group A, 13 in group B, and five in group C), febrile neutropenia (24 [42%] of 57; 11 in group A, ten in group B, and three in group C), and neutropenia (23 [40%] of 57; 12 in group A, eight in group B, and three in group C). 15 (33%) of 45 patients in groups A and B (ten in group A and five in group B) and eight (67%) of 12 patients in group C had grade 3 or 4 infections. In group C, the most common treatment-emergent adverse events in six patients receiving 100 mg versus six patients receiving the 50 mg dose were diarrhoea (three [50%] *vs* one [17%]), nausea (three [50%] *vs* two [33%]), vomiting (one [17%] *vs* one [17%]), febrile neutropenia (two [33%] *vs* 0), and lung infection (0 *vs* one [17%]).

No events of laboratory or clinical tumour lysis syndrome were reported and no dose-limiting toxicities were recorded in any dosing cohort. Although the maximum tolerated dose was not reached in any cohort, the 1200 mg dose caused frequent gastrointestinal adverse events including nausea in nine (82%; four in group A and five in group B) of 11 patients, diarrhoea in seven (64%; three in group A and four in group B), constipation in six (55%; two in group A and four in group B), and vomiting in five (45%; three in group A and two in group B), which restricted continuous dosing

	Group A (n=23)				Group B (n=22)				Group C (n=12)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any event	4 (17%)	2 (9%)	13 (57%)	0	5 (23%)	2 (9%)	12 (55%)	1 (5%)	1 (8%)	0	9 (75%)	0
Anaemia	0	3 (13%)	0	0	1 (5%)	1 (5%)	0	0	0	3 (25%)	0	0
Febrile neutropenia	0	1 (4%)	1 (4%)	0	0	3 (14%)	0	0	0	0	0	0
Neutropenia*	0	0	11 (48%)	0	0	0	7 (32%)	0	0	0	3 (25%)	0
Pancytopenia	0	0	0	0	0	0	1 (5%)	0	0	0	0	0
Thrombocytopenia†	0	0	5 (22%)	0	0	2 (9%)	9 (41%)	0	1 (8%)	0	5 (42%)	0
Diarrhoea	8 (35%)	1 (4%)	0	0	3 (14%)	0	0	0	3 (25%)	0	0	0
Gastrointestinal haemorrhage	0	0	0	0	0	1 (5%)	0	0	0	0	0	0
Nausea	12 (52%)	0	0	0	7 (32%)	0	0	0	7 (58%)	0	0	0
Proctitis	0	0	0	0	0	1 (5%)	0	0	0	0	0	0
Vomiting	4 (17%)	0	0	0	2 (9%)	0	0	0	5 (42%)	0	0	0
Fatigue	5 (22%)	1 (4%)	0	0	6 (27%)	1 (5%)	0	0	2 (17%)	0	0	0
Candida infection	0	0	0	0	3 (14%)	0	0	0	0	0	0	0
Escherichia bacteraemia	0	0	0	0	0	1 (5%)	0	0	0	0	0	0
Mucosal infection	0	0	0	0	0	1 (5%)	0	0	0	0	0	0
Sepsis	0	0	0	0	0	0	0	1 (5%)	0	0	0	0
Increased alanine aminotransferase	0	1 (4%)	0	0	1 (5%)	0	0	0	0	0	0	0
Increased blood bilirubin	1 (4%)	1 (4%)	0	0	0	1 (5%)	0	0	0	0	0	0
Decreased lymphocyte count	0	0	0	0	1 (5%)	0	0	0	2 (17%)	1 (8%)	0	0
Decreased white blood cell count	0	2 (9%)	2 (9%)	0	0	0	4 (18%)	0	0	0	6 (50%)	0
Decreased appetite	3 (13%)	0	0	0	6 (27%)	0	0	0	1 (8%)	0	0	0
Hyperphosphataemia	4 (17%)	0	0	0	0	0	0	0	0	0	0	0
Pruritus	0	0	0	0	3 (14%)	0	0	0	0	0	0	0

Data are n (%). Shown are adverse events of grade 1–2 occurring in ≥10% patients in any group and all grade 3, 4, and 5 events. *Includes neutropenia and decreased neutrophil count. †Includes thrombocytopenia and decreased platelet count.

Table 2: **Treatment-related adverse events**

and led to dose reduction to 800 mg daily in five of eight patients (three of 11 patients had discontinued treatment before dose reduction). Because the maximum tolerated dose was not reached, recommended phase 2 dose was 400 mg day or 800 mg with an interrupted dosing schedule (safety expansion).

Treatment-emergent adverse events of grade 3–4 neutropenia occurred in 11 (27%) of 41 patients who had grade 3–4 neutropenia at baseline, indicating haematological improvement in 30 (73%) patients. Treatment-emergent adverse events of grade 3–4 thrombocytopenia occurred in 15 (44%) of 34 patients who had grade 3–4 thrombocytopenia at baseline, indicating haematological improvement in 19 (56%) patients (appendix p 2).

Overall, 38 (67%) of 57 patients (15 in group A, 14 in group B, and nine in group C) had serious treatment-emergent adverse events. Febrile neutropenia (14 [31%] of 45 patients in groups A and B; seven [30%] of 23 patients in group A *vs* seven [32%] of 22 in group B) was the most common serious treatment-emergent adverse event in groups A and B and lung infection was the most common in group C (four [33%] of 12 patients).

Overall, four (7%) of 57 patients died within 30 days of the first dose of study drug. The causes of death were sepsis (one patient in group B), bacteraemia (one in group A), lung infection (one in group C), and respiratory failure (one in group A). Nine (16%) of 57 patients died within 60 days. The causes of death were malignant neoplasm progression (one in group A and one in group B), sepsis (one in group B and one in group C), bacteraemia (one in group A), volvulus (one in group C), lung infection (one in group C), respiratory failure (one in group A), and disease progression (one in group B).

Of 26 patients who had died at the time of data cutoff (ten in group A, nine in group B, and seven in group C), ten (38%) died from adverse events (four in group A, two in group B, and four in group C) and 16 (62%) died during survival follow-up. The adverse events leading to death were from progression of acute myeloid leukaemia (two in group A, one in group B, and one in group C), bacteraemia (one in group A), respiratory failure (one in group A), volvulus (one in group C), sepsis (one in group B and one in group C), and lung infection (one in group C). The patient's death caused by sepsis in group B

was considered treatment-related. 14 (88%) of 16 patients who died during survival follow-up (>30 days after study drug discontinuation) died from progressive disease (six in group A, five in group B, and three in group C) and two (13%) of 16 (in group B) died of an unknown cause.

49 (86%) of 57 patients had a treatment-related adverse event (table 2). The most common treatment-related adverse events of any grade in patients in groups A and B were nausea (19 [42%] of 45 patients), neutropenia (18 [40%]), thrombocytopenia (16 [36%]), fatigue (13 [29%]), diarrhoea (12 [27%]), and decreased appetite (nine [20%]). For patients in group C, the most common treatment-related adverse events were nausea (seven [58%] of 12 patients), thrombocytopenia (six [50%]), vomiting (five [42%]), diarrhoea (three [25%]), and anaemia (three [25%]).

25 (44%) of 57 patients received intermittent granulocyte colony-stimulating factor support after bone marrow confirmation of leukaemia clearance (16 in group A and nine in group B), and, in groups A and B, 24 (53%) of 45 patients (16 in group A and eight in group B) received prophylactic non-azole antifungal agents. Broncho-pulmonary aspergillosis (n=1) and hepatic candidiasis (n=1) were the only documented grade 3 fungal infections; both cases occurred in patients in group A receiving 1200 mg venetoclax.

Venetoclax dose reductions due to treatment-emergent adverse events were required for four (17%) of 23 patients in group A, three (14%) of 22 in group B, and one (8%) of 12 in group C. In group C, when oral posaconazole administration was initiated, the dose of venetoclax was reduced by 75·0% (to 100 mg) in six patients and by 87·5% (to 50 mg) in five patients because co-administration of venetoclax with azole antifungal agents increases venetoclax exposures. To match the exposures from 400 mg alone, the second set of six patients were dose reduced to 50 mg of venetoclax when given with posaconazole after results from the 100 mg dose with posaconazole were available. One patient with a lung infection event from day 4 discontinued use of venetoclax on day 21 and posaconazole on day 22 because of difficulty with oral intake and inability to swallow oral medications.

Venetoclax dosing interruptions caused by adverse events occurred in 29 (51%) of 57 patients overall (15 in group A, 13 in group B, and one in group C), with 15 of these occurring between cycle 1 and cycle 2 per protocol due to absolute neutrophil count recovery; the most common reasons for dose interruptions at any point during the study were neutropenia (n=13; seven in group A, five in group B, and one in group C), febrile neutropenia (n=5; three in group A and two in group B), and thrombocytopenia (n=5; two in group A and three in group B). Six (60%) of ten patients treated at 400 mg in groups A and B (four in group A and two in group B) had venetoclax dose interruptions (one in group A and one in group B had subsequent venetoclax reduction to 200 mg); 17 (71%) of 24 patients treated with 800 mg venetoclax had venetoclax dose interruptions (nine in group A and eight in group B), and two (8%) of these subsequently required dose reduction (in group A, one patient had the dose reduced to 400 mg and the other to 600 mg and then 400 mg). The median duration of venetoclax interruptions was 0·5 months (IQR 0·4–0·8).

Ten (43%) of 23 patients who had a treatment-emergent adverse event of neutropenia (20 in groups A and B, three in group C) required venetoclax interruption (six in group A, three in group B, and one in group C; median duration of interruption 12·5 days [IQR 10·0–17·0]) and dose delay between cycles 1 and 2 due to failure of neutrophil recovery to $0·5\times10^9$ per L. Seven (70%) of these ten patients required venetoclax dose interruptions during subsequent cycles. Median duration of treatment-emergent adverse events of neutropenia was 1·3 months (IQR 0·6–3·2). Median time on study treatment at the time of analysis was 4·0 months (IQR 2·3–6·6) for groups A and B, and 2·3 months (0·9–5·9) for group C. The median number of cycles of treatment in groups A and B was 4·0 (IQR 2·0–6·0), with responders (those achieving complete remission, complete remission with incomplete recovery, or partial remission) receiving a median of 5·0 (3·0–7·5) cycles of treatment and non-responders receiving a median of 2·0 (1·0–4·0) cycles. In group C, patients received a median of 2·0 (1·0–4·5) treatment cycles (3·0 [IQR 1·5–5·5] for responders *vs* 1·0 [1·0–1·0] for non-responders). Across all three groups overall, responding patients received a median of five cycles (IQR 3–7) of hypomethylating agent therapy. Overall, 43 (75%) of 57 patients discontinued study treatment (figure 2). Median time to study treatment discontinuation for these 43 patients was 2·8 months (IQR 1·3–4·8). The main reasons for treatment discontinuation were disease relapse or resistant disease (n=14), withdrawal of consent (n=13; for various personal reasons), and proceeding to stem cell transplantation (n=9; figure 2). The median time to consent withdrawal was 2·2 months (IQR 0·8–2·6). The nine patients who discontinued study treatment to receive stem cell transplant did so after completion of three to four cycles of therapy. Six patients discontinued study treatment because of adverse events not related to disease progression (figure 2). No patients discontinued treatment because of gastrointestinal treatment-emergent adverse events, including nausea. Treatment-emergent adverse events that led to study treatment discontinuation were acute embolic stroke (one in group A), lung infection (one in group A), sepsis (one in group B), volvulus (one in group C), respiratory failure (one in group A), and hepatic candidiasis (one in group A). The sepsis event was considered to have a reasonable possibility of being treatment-related. One patient in group C discontinued study treatment because of death (figure 2). As of data cutoff, 14 (25%) of 57 patients

	Group A (n=12)			Group B (n=13)		
	400 mg (n=3)	800 mg (n=6)	1200 mg (n=3)	400 mg (n=3)	800 mg (n=8)	1200 mg (n=2)*
T_{max} (h)	4 (3·3–8·0)	6 (4·0–8·0)	6·2 (4·0–8·1)	4 (4·0–8·0)	6·3 (5·4–8·0)	7 (6·0, 8·0)
C_{max} (μg/mL)	3·36 (2·45)	3·15 (1·39)	6·22 (3·07)	1·00 (0·88)	3·07 (1·57)	3·38 (1·60, 5·15)
C_{max}/dose (μg/mL per mg)	0·008 (0·006)	0·004 (0·002)	0·005 (0·003)	0·003 (0·002)	0·004 (0·002)	0·003 (0·001, 0·004)
AUC_{24} (μg×h/mL)	57·6 (39·7)	47·2 (26·0)	99·7 (72·7)	14·6 (14·0)	47·1 (22·0)	52·8 (21·5, 84·2)
AUC_{24}/dose (μg×h/mL per mg)	0·144 (0·099)	0·059 (0·033)	0·083 (0·061)	0·036 (0·035)	0·059 (0·027)	0·044 (0·018, 0·070)

Data are median (IQR) or mean (SD). Pharmacokinetic parameters for group C have been reported previously.[15] T_{max}=time to maximum observed plasma concentration. C_{max}=maximum observed plasma concentration. AUC_{24}=area under the plasma concentration–time curve from 0 h to 24 h dose interval. *n=2 presented as mean (individual values).

Table 3: **Venetoclax pharmacokinetic parameters for groups A and B in cycle 2, day 5**

remain on study, including six patients in group A, four in group B, and four in group C.

In pharmacokinetic assessments, peak venetoclax concentrations were attained 4–8 h post dose. Venetoclax half-life could not be estimated because of insufficient sampling after time to maximum observed plasma concentration. Venetoclax exposure parameters after coadministration with decitabine or azacitidine (table 3, appendix p 5) were within the exposure range of those observed for venetoclax alone,[18,19] indicating that decitabine and azacitidine did not substantially affect venetoclax exposures. Average venetoclax exposures at 800 mg were similar in groups A and B. Although the average exposures at 400 mg and 1200 mg were higher in group A than in group B, the sample size at these doses was small (n≤3). Results from group C (which have been reported previously) showed that posaconazole was estimated to increase venetoclax maximum observed plasma concentration by 7·1 times and area under the plasma concentration–time curve from 0 h to 24 h dose interval by 8·8 times, which is consistent with inhibition of CYP3A-mediated metabolism of venetoclax.[15]

The proportion of patients achieving an overall response to treatment with venetoclax was similar whether it was given in combination with decitabine or azacitidine (table 4). Nine (18%) of 51 patients evaluable for response had additional bone marrow assessments between the end of cycle 1 and cycle 4 (six in group A, two in group B, and one in group C); all nine patients showed improved responses between end of cycle 1 and cycle 2 (data not shown). Overall, 43 (75%; 95% CI 62·2–85·9) of 57 patients achieved an overall response or a morphologically leukaemia-free state response. 35 (61%; 95% CI 47·6–74·0) of 57 patients had complete remission or complete remission with incomplete marrow recovery. Of the 45 patients in groups A and B, 28 (62%; 95% CI 46·5–76·2) had an overall response and 27 (60%; 44·3–74·3) had complete remission (n=14) or complete remission with incomplete marrow recovery (n=13). Seven (16%) of 45 patients had morphologically leukaemia-free state with recovery of counts not meeting criteria for complete remission with incomplete marrow recovery. Of 12 patients in group C, eight (67%; 95% CI 34·9–90·1) achieved an overall response and eight (67%) achieved complete remission with incomplete marrow recovery. Median time to complete remission or complete remission with incomplete marrow recovery was 1·0 month (IQR 0·9–1·8) in group A, 1·2 months (1·0–2·4) in group B, and 0·9 months (0·8–1·5) in group C. The median duration of response was 8·4 months (95% CI 4·2–not reached) in 15 responding patients in group A, 12·3 months (7·9–12·9) in 13 responders in group B, and 4·3 months (1·1–not reached) in eight responders in group C. In the dose-escalation groups (groups A and B combined), the overall median duration of response was 11·0 months (95% CI 6·8–12·9; n=28), compared with 8·4 months (4·7–11·7; n=36) for all responding patients in the entire study.

	Group A (n=23)	Group B (n=22)	Group C (n=12)
Complete remission	8 (35%)	6 (27%)	0
CRi	6 (26%)	7 (32%)	8 (67%)
Partial remission	1 (4%)	0	0
MLFS*	2 (9%)	5 (23%)	0
Resistant disease	3 (13%)	2 (9%)	3 (25%)
Non-evaluable†	3 (13%)	2 (9%)	1 (8%)
Complete remission and CRi	14 (61%)	13 (59%)	8 (67%)
Overall response‡	15 (65%)	13 (59%)	8 (67%)
Overall outcome§	17 (74%)	18 (82%)	8 (67%)

Data are n (%). CRi=complete remission with incomplete marrow recovery. MLFS=morphologically leukaemia-free state. *Less than 5% blasts in an aspirate sample with marrow spicules and a count of 200 or more nucleated cells. †Includes five patients who discontinued before end of cycle 1 because of adverse events of infections; one patient was found to have CNS leukaemia on day 7. ‡Including complete remission, CRi, and partial remission. §Including overall response and MLFS.

Table 4: **Responses to treatment**

Median overall survival for the 45 patients in groups A and B combined was 15·2 months (95% CI 10·2–not reached; 19 deaths) and 12·3 months (9·3–not reached; 26 deaths) for all 57 patients (appendix p 6). Median overall survival in group A was 15·2 months (95% CI 8.0–not reached) and median overall survival in group B was 14·2 months (9·3–not reached). We did not

assess overall survival separately in group C. Four (44%) of the nine patients (two in group A, five in B, and two in C) who received allogeneic stem cell transplantation were alive at the time of data cutoff. Median overall survival in these patients was 12·3 months (95% CI 5·2–not reached; five deaths).

Because five (45%) of 11 patients in the 1200 mg cohort (two in group A and three in group B) had their dose reduced to 800 mg, the 400 mg and 800 mg dose cohorts were analysed further. 22 (65%) of 34 patients achieved complete remission or complete remission with incomplete marrow recovery in these cohorts in arms A and B (11 in both groups). The median overall survival was the same as that observed for all patients treated in the dose escalation groups A and B (n=45; data not shown here). Bone marrow blast counts were evaluated in 51 (89%) of 57 patients (three in group A, two in group B, and one in group C did not complete cycle 1, and therefore were unevaluable). In total, 43 (84%) of 51 patients had more than 80% reduction in bone marrow blasts, compared with baseline (appendix p 7); for those in the 400 mg and 800 mg cohorts of groups A and B, 27 (79%) of 34 patients had more than 80% bone marrow blast reduction. Best response per patient is shown in the appendix (p 4). Across the study, median time to best response was 1·6 months (IQR 0·9–3·4). Details of time to best response and duration of response per patient are included in the appendix (p 4).

In our exploratory biomarker analysis, results of site-reported cytogenetics were used to categorise patients as intermediate or poor risk. Data in the appendix (p 8) show that responses to venetoclax plus hypomethylating agents correlated with National Comprehensive Cancer Network risk categories. 23 (66%) of 35 patients with intermediate-risk cytogenetics achieved a complete remission or complete remission with incomplete marrow recovery, whereas 11 (52%) of 21 patients with poor-risk cytogenetics achieved this status. For patients treated with 400 mg or 800 mg venetoclax in groups A and B, 17 (68%) of 25 patients with intermediate-risk cytogenetics and five (56%) of nine patients with poor-risk cytogenetics had complete remission or complete remission with incomplete marrow recovery. Data on mutations were available for 54 (95%) of 57 patients; a sample was not available for one patient and two others had incomplete sequencing data. Of the 17 of 54 patients with *IDH1/2* mutations (seven in group A, seven in group B, and three in group C), ten (59%) had complete remission or complete remission with incomplete marrow recovery (four in group A, four in group B, and two in group C) and three (18%; all in group B) achieved morphologically leukaemia-free state (appendix p 8). *FLT3* abnormalities were observed in seven patients (six in group A and one in group B); three had *FLT3*–ITD only mutations, one had *FLT3*–ITD mutations, one had *FLT3*–ITD and *FLT3*–TKD mutations, two had *FLT3*–TKD mutations, and one had *FLT3* amplification (table 1). For patients with *FLT3*–ITD mutations (all in group A), three (75%) of four patients had complete remission or complete remission with incomplete marrow recovery and one patient achieved morphologically leukaemia-free state. In patients with *FLT3*–TKD only mutations (both in group A), one (50%) of two patients achieved complete remission (the other had resistant disease), and the patient with *FLT3* amplification (group B) achieved complete remission with incomplete marrow recovery. For patients with *TP53* mutations, four (36%) of 11 patients (two in group B and two in group C) had complete remission with incomplete marrow recovery and one (9%) patient (in group A) achieved morphologically leukaemia-free state (appendix p 8). Further outcomes of the biomarker analysis, which is still ongoing in the expansion phase of this study, will be reported in a future publication.

Discussion

Results from this dose-escalation study of venetoclax plus decitabine or azacitidine show that these drug combinations are well tolerated, with low early mortality and promising clinical activity in terms of overall response and overall survival in a patient population for whom treatment outcomes have been historically poor. Groups A and B both showed similar safety profiles. No dose-limiting toxicities were recorded and the maximum tolerated dose was not reached. However, dose escalation was halted at 1200 mg because of gastrointestinal toxicity, perhaps related to the high pill burden, thus limiting continuous therapy and resulting in dose reduction to 800 mg. Evaluations of dose-expansion cohorts are ongoing at 400 mg daily and 800 mg with an interrupted dosing schedule with both hypomethylating agents. By contrast with the observation of tumour lysis syndrome with venetoclax in patients with chronic lymphocytic leukaemia,[20] no laboratory or clinical events of tumour lysis syndrome were noted in this patient population with acute myeloid leukaemia. As a precautionary measure, all patients were required to have a white cell count below 25×10^9 per L at study start to mitigate this potential risk. In cycle 1, admission to hospital during venetoclax dose ramp-up was mandated for close monitoring of potential risk of tumour lysis syndrome. However, the number of days spent in hospital is difficult to report because they varied according to institutional practices, and patients being treated at times at hospitals outside of the investigator sites for adverse events. None of the patients required admission to hospital beyond cycle 1 to receive therapy because of underlying acute myeloid leukaemia. The most common treatment-emergent adverse event causing interruption of venetoclax dose was neutropenia, with an increased incidence observed at high doses of venetoclax; however, this association did not correlate with increased incidence of clinically relevant infectious complications. The most common grade 3 or 4 treatment-emergent adverse events were thrombocytopenia (47%), febrile neutropenia (42%), and neutropenia (40%), which

is similar to previous reports of treatment-emergent adverse events for hypomethylating agent monotherapy: thrombocytopenia (24–40%), febrile neutropenia (28–32%), and neutropenia (26–32%).[21,22] Febrile neutropenia was the most common serious treatment-emergent adverse in our study (31%) and in the decitabine (24%) and azacitidine (25%) monotherapy phase 3 trials.[21,22] Early mortality (30-day mortality 7%; 60-day mortality 16%) was lower than would be expected in an age-matched population receiving intensive therapy and similar to hypomethylating agent monotherapy (9% and 20% with decitabine[21] and 7% and 16% with azacitidine[22] monotherapy). Study treatment withdrawal for personal reasons was higher than anticipated. Causes included logistical and financial constraints in continuation of travel to the trial centre to receive hypomethylating agent therapy and attend study-mandated assessments, patient preference to cease study therapy and revert to supportive care, and emergent non-acute myeloid leukaemia and non-study-related comorbidities compromising the safety of ongoing therapy. Responding patients received a median of five cycles (IQR 3–7·5) of hypomethylating agent therapy. Disease was not assessed during the survival follow-up and therefore no data exist for patients who relapsed after final study visit.

Patients with acute myeloid leukaemia are susceptible to life-threatening fungal infections. Anti-fungal prophylaxis with agents such as posaconazole is widely used and shows a survival benefit in these patients.[23] Because venetoclax is a CYP3A substrate and posaconazole is a strong CYP3A inhibitor, group C was designed to assess the effect of posaconazole on the safety and pharmacokinetic properties of venetoclax. Results support the use of anti-fungal prophylaxis with posaconazole in patients with the disease who are receiving venetoclax after reducing the venetoclax dose by at least 75%.[15] Few fungal infections were documented despite exclusion of anti-fungal azoles in groups A and B, possibly because many patients received an alternative anti-fungal prophylaxis that was not CYP3A inhibitors.

Pharmacokinetic parameters of venetoclax in this study, as well as the variability in observed venetoclax exposures, were consistent with those reported for the drug alone,[18,19] indicating that their exposures were not affected by coadministration with decitabine or azacitidine.

Combinations of venetoclax and hypomethylating agents showed promising activity; similar proportions of patients achieving a response were recorded with either combination. 27 (60%) of 45 patients achieved complete remission or complete remission with incomplete marrow recovery at all dose levels in the dose-escalation cohorts of groups A and B, and 22 (65%) of 34 patients in the 400 mg and 800 mg dose cohorts with either hypomethylating agent. Responses were rapid and durable, with a median duration of response of 11·0 months and a median overall survival of 15·2 months in groups A and B. Median overall survival was shorter (12·3 months) in the overall study population than groups A and B combined, which is possibly due to shorter median duration of follow-up in group C (7·9 months) than in groups A (15·2 months) and B (12·7 months). Since group C consisted of a small population of patients receiving two doses of venetoclax and had a shorter follow-up than groups A and B, overall survival outcomes were not analysed separately. The proportion of patients with a complete remission or complete remission with incomplete marrow recovery and median overall survival in our study seem to compare favourably with those reported in phase 3 trials of hypomethylating agent monotherapy (26% of patients with complete remission or complete remission with incomplete marrow recovery and median overall survival of 7·7 months for decitabine[21] and 28% and 10·4 months for azacitidine[22]). However, cross-trial comparisons are difficult and probably unreliable because of the different study designs and the small number of patients in our trial. More than an 80% reduction in bone marrow blast count was recorded in 79% of all patients assessed in groups A and B. Additionally, nine patients in this trial proceeded to allogeneic stem cell transplantation while in remission because of their improved clinical status, suggesting that venetoclax plus hypomethylating agent might provide a tolerable bridge to a curative strategy. These outcomes warrant further investigation of the combination regimens versus hypomethylating agent monotherapy in randomised trials to fully elucidate the benefits of combination therapy.

Preliminary results also suggest promising activity in patients with intermediate-risk and poor-risk cytogenetics. Although the sample size is small, patients with high-risk molecular abnormalities achieved complete remission or complete remission with incomplete marrow recovery (three [75%] of four patients with *FLT3*–ITD mutations; four [36%] of 11 patients with *TP53* mutations). Moreover, a high proportion of patients with *IDH1/2* mutations achieved complete remission, complete remission with incomplete marrow recovery, or a morphologically leukaemia-free state, which is in agreement with previous data suggesting that patients with isocitrate dehydrogenase mutations might have increased sensitivity to a BCL-2 inhibitor.[24] However, these data should be interpreted with caution because some of the molecular data were provided by the sites and were not evaluated consistently at each site because some data were not uniformly available.

Limitations of our study include the availability of molecular data from the central laboratory at the time of the analysis and the small number of patients who were treated across different venetoclax dose-level cohorts and with two different hypomethylating agents. Overall survival and duration of response analyses by subset (eg, cytogenetic risk group and specific unfavourable mutations), although important, were not feasible

because this would require a larger cohort of patients treated in a uniform manner. The reported outcomes from our phase 1b study need to be confirmed in larger and randomised trials. Nevertheless, our data indicate that targeting of BCL-2 might be a promising option in patients with adverse disease features that are historically associated with poor outcomes.

To our knowledge, this phase 1b trial is the first study of venetoclax in combination with decitabine or azacitidine in acute myeloid leukaemia and the first to assess venetoclax in previously untreated patients with the disease. Venetoclax in combination with hypomethylating agents seems to be a well tolerated regimen with low early mortality and promising anti-leukaemic activity in elderly, treatment-naive patients with acute myeloid leukaemia. Further evaluation of the 400 mg and 800 mg doses of venetoclax in an expansion phase of this study is ongoing and will provide additional insight into the safety and efficacy of these combinations.

Contributors

CDD participated in data collection, data analysis, data interpretation, and writing of the manuscript. KWP collected, analysed, and interpreted the data, edited the manuscript, and approved the final version of the manuscript. AL participated in data interpretation and writing of the manuscript. BAJ served as a site principal investigator, contributed patients, collected and reviewed patient data and data queries, participated in data analysis and interpretation, and edited the manuscript. AHW participated in data generation and collection, interpretation and editing of the tables and figures, and editing of the manuscript. MT participated in data collection, interpretation and analysis, and carefully reviewed drafts of the manuscript, and approved the final version. MA participated in data collection, data interpretation, review and approval of the manuscript. MGF participated in patient recruitment, patient treatment, data analysis and interpretation, reviewing and editing of the manuscript. HK participated in study design, data analysis and data interpretation, and writing of the manuscript. RP and BC were responsible for the biomarker data generation and analysis, participated in biomarker data interpretation, and reviewed and edited the manuscript. TX contributed to data analysis and interpretation, and development and review of the manuscript. MD contributed to data analysis and interpretation, and development and review of the manuscript. SKA participated in data collection, analysis and interpretation, and in writing and approval of the final manuscript. RH contributed to data analysis and interpretation, and development and review of the manuscript. MM contributed to study design, data analysis and interpretation, and development and review of the manuscript. JP contributed to study design, monitoring, data review and interpretation, and development and review of the manuscript. MK participated in study design, data collection, analysis, data interpretation, and writing of the manuscript. DAP participated in data collection and interpretation, and in writing of the manuscript.

Declaration of interests

CDD reports personal fees for speaking and lecturing from AbbVie outside the submitted work. KWP reports grants from AbbVie during the conduct of this study. AL has served as a consultant for and has received research funding from AbbVie during the conduct of this study, and has served as a consultant for and received research funding from AbbVie, TetraLogic, and AstraZeneca not related to any aspect of this study. BAJ reports grants from AbbVie during the conduct of the study, personal fees from Rigel, Celgene, Amgen, and Incyte, grants from Daiichi Sankyo, Pharmacyclics, Genentech/Roche, Esanex, and Kalobios, and grants and personal fees from Glycomimetics outside the submitted work. AHW reports grants and personal fees from AbbVie, Servier, Amgen, and Novartis outside the submitted work. MT reports grants from AbbVie, Gilead, Merck, and Pharmacyclics during the conduct of the study. MK has served as a consultant for and reports grants from AbbVie outside the submitted work, has served as a consultant for Genentech and reports grants from Genentech outside the submitted work, has served as a consultant for F Hoffman-LaRoche outside the submitted work, and reports grants from Eli Lilly, Cellectis, Calithera, Stemline, Threshold, Flexus Biosciences, and Novartis outside the submitted work. DAP has received research funding from Pfizer and Agios and has been an advisory board member for Pfizer, Curis, Takeda, Servier, Celgene, Jazz, Gilead, Pharmacyclics, and Alexion outside the submitted work. BC, RP, SKA, TX, MD, RH, MM, and JP are employees of AbbVie and might own stock. All other authors declare no competing interests.

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