Received: 28 June 2024 | Accepted: 21 August 2024

DOI: 10.1111/bjh.19741

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

ORIGINAL PAPER

Haematological Malignancy – Clinical

Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study

Klaus Geissler[1] | **Zdenek Koristek**[2] | **Teresa Bernal del Castillo**[3] | **Jan Novák**[4] | **Gabriela Rodríguez-Macías**[5] | **Stephan K. Metzelder**[6] | **Arpad Illes**[7] | **Jiří Mayer**[8] | **Montserrat Arnan**[9] | **Mary-Margaret Keating**[10] | **Jürgen Krauter**[11] | **Monia Lunghi**[12] | **Nicola Stefano Fracchiolla**[13] | **Uwe Platzbecker**[14] | **Valeria Santini**[15] | **Yuri Sano**[16] | **Aram Oganesian**[16] | **Harold Keer**[16] | **Michael Lübbert**[17]

Correspondence
Klaus Geissler, Sigmund Freud PrivatUniversität, Campus Prater, Freudplatz 1+3, A-1020 Wien, Austria.
Email: geissler.klaus@gmx.at

Funding information
Astex Pharmaceuticals, Inc., now part of Taiho Oncology, Inc.

Summary
This study compared decitabine exposure when administered IV (DEC-IV) at a dose of 20 mg/m^2 for 5-days with orally administered decitabine with cedazuridine (DEC-C), as well as the clinical efficacy and safety of DEC-C in patients with acute myeloid leukaemia (AML) who were ineligible for intensive induction chemotherapy. In all, 89 patients were randomised 1:1 to DEC-IV or oral DEC-C (days 1–5 in a 28-day treatment cycle), followed by 5 days of the other formulation in the next treatment cycle. All patients received oral DEC-C for subsequent treatment cycles until treatment discontinuation. Equivalent systemic decitabine exposures were demonstrated (5-day area under the curve ratio between the two decitabine formulations of 99.64 [90% confidence interval 91.23%, 108.80%]). Demethylation rates also were similar (≤1.1% difference). Median overall survival (OS), clinical response and safety profile with oral DEC-C were consistent with those previously observed with DEC-IV. Next-generation sequencing was performed to identify molecular abnormalities that impact OS and *TP53* mutations were associated with a poor outcome. These findings support the use of oral DEC-C in patients with AML.

KEYWORDS
acute myeloid leukaemia, decitabine/cedazuridine, DNA methyltransferase inhibitors, hypomethylating agents, somatic mutations

INTRODUCTION

Acute myeloid leukaemia (AML) is primarily a disease of older adults; median age at diagnosis is 68 years.[1] The standard treatment is intensive induction therapy for which older adults and those with comorbidities may not be considered candidates.[2]

Either of the DNA methyltransferase inhibitors (DNMTis; azacitidine and decitabine) combined with venetoclax is recommended for adults with AML who are not candidates for intensive induction chemotherapy and have the *IDH1*, *IDH2* or *FLT3* mutation or no actionable mutations.[3] Until recently, both DNMTis were available only in parenteral form, requiring patients to come to a treatment centre daily for 5 or

ClinicalTrials.gov Registry Number: NCT03306264. EudraCT Number: 2018-003395-12.

For affiliations refer to page 1744.

7 consecutive days of every 28-day treatment cycle and imposing a substantial burden on the largely older adult population affected by AML. Decitabine, when administered with cedazuridine (DEC-C), is orally available and was approved in September 2023 in the European Union (EU) for patients with newly diagnosed AML who are ineligible for standard induction chemotherapy.

The oral bioavailability of azacitidine and decitabine is low due to first-pass elimination by the enzyme cytidine deaminase.[4,5] A phase 2 study and a randomised pharmacokinetic (PK) registration study established that a fixed-dose combination of oral decitabine and the cytidine deaminase inhibitor cedazuridine yields systemic exposure, DNA demethylation, efficacy and safety comparable to those seen with intravenous decitabine (DEC-IV) in patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukaemia.[6–8] The present registrational study (ClinicalTrials.gov identifier NCT03306264) in patients with AML compared the intrapatient total systemic exposure of oral DEC-C and DEC-IV over 5 days. Pharmacodynamics (DNA demethylation), clinical response, survival and safety also were assessed.

Initial patient classification was similar to parenteral decitabine trials as the present study bridges to historical data. Updated analyses were performed subsequently to reflect contemporary perspectives. Somatic mutations have been associated with AML development and prognosis,[9] and are incorporated into two risk stratification systems: the International Consensus Classification (ICC) of Myeloid Neoplasms[10] and European LeukemiaNet (ELN) risk stratification.[11] The studies used to validate the 2022 ELN comprised mostly relatively young patients who had received intensive chemotherapy.[12,13] Data from this study investigated whether the ICC classification or ELN risk stratification affected survival.

METHODS

Trial design and oversight

Eligible patients were randomised in a 1:1 ratio to one of two sequences for the first two 28-day treatment cycles: oral DEC-C (one fixed-dose combination tablet once daily: decitabine 35 mg/cedazuridine 100 mg) in cycle 1 and DEC-IV (20 mg/m^2/day, 1-h infusion)[14] in cycle 2 (sequence A) or the reverse (sequence B). Each treatment was given for the first five consecutive days of a 28-day cycle. After cycle 2, patients received treatment with oral DEC-C for the first 5 days of each 28-day cycle until study withdrawal due to disease progression, unacceptable toxicity or other reasons.[7] From cycle 3, dose reduction could be made by reducing the number of treatment days/cycle. According to protocol, dose reduction was to be considered if drug-related rather than disease-related myelosuppression was suspected. Dose delay (delaying the next cycle) to allow recovery of blood count from drug-related myelosuppression was allowed at the discretion of the investigator. Patients were enrolled from January 2020 to April 2021. Patients who benefited from oral DEC-C were offered the option to enter an extension study assessing survival and long-term safety (ClinicalTrials.gov identifier NCT04093570).

The independent ethics committee at each of the 27 participating study centres in Canada and eight European countries (Austria, Czech Republic, France, Germany, Hungary, Italy, Spain and UK) approved the protocol and amendments (sites listed in Table S1). The study was conducted in accordance with the protocol, the International Council for Harmonisation Good Clinical Practice guideline and applicable local requirements. Patients provided informed consent. Clinical response was assessed by an independent review committee. The authors assume responsibility for the accuracy and completeness of the data and analyses.

Randomisation

Patient assignments to treatment sequences were made through a computer-generated randomisation schedule and accessed through an interactive web response system managed by Syneos Health (Morrisville, NC, USA). The study was open label.

Eligibility

Patients aged ≥18 years with de novo or secondary AML (World Health Organization criteria)[15] who were not candidates for standard induction chemotherapy and had not received cytotoxic chemotherapy for AML except hydroxyurea for high white blood cell counts were eligible for inclusion. Those who had received >1 cycle of azacitidine or decitabine were excluded. Other inclusion criteria were Eastern Cooperative Oncology Group performance status 0 or 1 and life expectancy ≥3 months.

Response criteria and end-points

The primary end-point was comparison of decitabine total exposure over 5 days between oral DEC-C and DEC-IV for cycles 1 and 2, measured as area under the curve (AUC). Secondary parameters included other PK parameters, pharmacodynamics (DNA demethylation of oral DEC-C vs. DEC-IV, measured by long interspersed nuclear element-1 [%LINE-1] methylation analysis),[16] safety, clinical response, red blood cell (RBC) and platelet transfusion independence in patients transfusion-dependent at baseline and survival.

Clinical response was assessed as complete response (CR), CR with incomplete blood count recovery (CRi), CR with incomplete platelet recovery or partial response as defined by International Working Group 2006 AML response criteria[17] and the study that led to decitabine marketing authorisation for AML in EU on 20 July 2023.[18] CR with partial haematological recovery was evaluated in a recent study of AML therapy.[19] Survival was evaluated as event-free survival, progression-free survival, overall survival (OS) and survival at 6 months, and

1 and 2 years. Progression-free survival was defined as time to disease progression (including relapse) or death from any cause, whichever came first. Event-free survival was defined as time to disease progression or relapse, treatment discontinuation due to a treatment-related adverse event (AE), use of other anti-leukaemia therapy except haematopoietic cell transplantation or death from any cause, whichever occurred first.

Pharmacokinetic and pharmacodynamic end-points were assessed during the first two cycles only. Efficacy and safety end-points were calculated using all data through final cut-off on May 25, 2023.

Next-generation sequencing (NGS) was performed to identify molecular abnormalities. Prevalence of mutations with variant allele frequency (>2%) and the effect of somatic mutations (eg, *ASXL1*, *BCOR*, *RUNX1*, *SRSF2*, *STAG2* and *TP53*) were assessed, as well as the impact of the number of mutations (≤ or >4) on survival. Eighty-six patients were classified according to 2022 ELN genetic risk classification and ICC 2022. Relationships to survival of clinical parameters, ELN risk and ICC categories were evaluated.

Statistical analysis

The primary analysis was comparison of total 5-day AUC over the last 24-h dosing interval (AUC_{0-24}) exposures of decitabine after treatment with oral DEC-C versus DEC-IV. Oral DEC-C and DEC-IV were considered equivalent if the 2-sided 90% confidence interval (CI) of the 5-day AUC_{0-24} ratio of geometric least-squares means for oral DEC-C versus DEC-IV was within 0.80–1.25. A 70-patient sample was estimated to provide 90% power at a 0.05 statistical significance level, presuming the true ratio of geometric means is 1.0, intrapatient coefficient of variation (CV) on an unlogged scale is 0.41, and equivalence limits of the mean ratio are 0.80 and 1.25. A total of 85 patients was planned to yield ~70 evaluable patients, assuming that 20% would not be evaluable. An intrapatient CV of 0.41 was chosen as a conservative value, as the estimated intrapatient CV from PK studies of oral DEC-C versus DEC-IV in patients with MDS and chronic myelomonocytic leukaemia was ~0.32.[7]

Pharmacokinetic statistical analyses were performed with Phoenix™ WinNonlin® (version 8.3 or higher; Certara, Princeton, NJ, USA).

The primary end-point analysis was based on data from patients who received full doses of oral and IV therapy with evaluable 5-day AUC_{0-24} for both oral DEC-C and DEC-IV (paired cycles). Oral treatment had to occur within 3 h of intended dosing time, with no vomiting within 6 h of dosing. Decitabine AUC_{0-24} had to be evaluable for day 1 and day 2 or 5 of oral dosing. Other PK parameters were analysed in patients who received any study treatment with sufficient samples to measure drug concentrations.

Maximum %LINE-1 methylation was analysed in all patients who received any study treatment and had LINE-1 methylation data at day 1 of cycle 1 or 2 and on day 8 or 15 of the same cycle. The 95% CIs for the differences in mean maximal %LINE-1 demethylation between oral DEC-C and DEC-IV in cycles 1 and 2 were generated based on analysis of variance with treatment as a factor.

Clinical response, survival and safety were assessed with descriptive statistics in all patients who received any amount of study treatment. All statistical tests and CIs were two-sided with α of 0.05, unless otherwise specified. An SAS® statistical package (version 9.4 or later; SAS Institute, Inc., Cary, NC, USA) was used for the analysis. No comparison between treatment sequences was performed. Survival parameters were evaluated using Kaplan–Meier analysis. Effect of covariates on survival was evaluated using Cox proportional hazard model. Length of follow-up was estimated using reverse Kaplan–Meier method.

RESULTS

Patients and treatment

Eighty-nine patients were randomised 1:1 between the two treatment sequences (Figure 1). Two patients received no treatment, and the 87 who received treatment were included in efficacy and safety analyses. NGS samples were available for 76 patients. Seven patients received only DEC-IV, 8 received only oral DEC-C, and 80 received ≥1 dose of oral DEC-C. Median duration of follow-up was 23.6 months (range 20.5–24.5). Sixty-nine patients had samples from cycles 1 and 2 and were evaluable for PK analysis.

Median age was 78 years (range 61–92); baseline characteristics generally were balanced between treatment sequences (Table 1). Eight patients were pretreated for an antecedent haematological disorder or with cytoreductive therapy. Two patients received prior DNMTi therapy with 1 cycle of azacitidine.

Patients received a median of five treatment cycles (range 1–20). Median treatment duration was 4.5 months (range 0–7.8), with 35% of patients treated for ≥6 months and 6% for >12 months. Nearly two-thirds of patients (63%) had ≥1 dose-delayed cycle and 8% had ≥1 dose-reduced cycle. Death was the most common reason for treatment discontinuation (26%; Figure 1).

After eliminating patients with insufficient data or data quality issues, 69 patients had paired PK samples and were included in the primary end-point analysis. Seventy-eight patients were included in pharmacodynamic analyses.

Pharmacokinetics and pharmacodynamics

The primary end-point, the geometric least-squares mean ratio of decitabine 5-day AUC_{0-24} between oral DEC-C and DEC-IV, was 99.64 (90% CI 91.23%, 108.80%; Table 2). The CIs were contained within the prespecified range of 80%–125%. Secondary PK parameters supported these findings (Table S2). Peak plasma concentrations of decitabine were higher following IV versus oral administration. Plasma

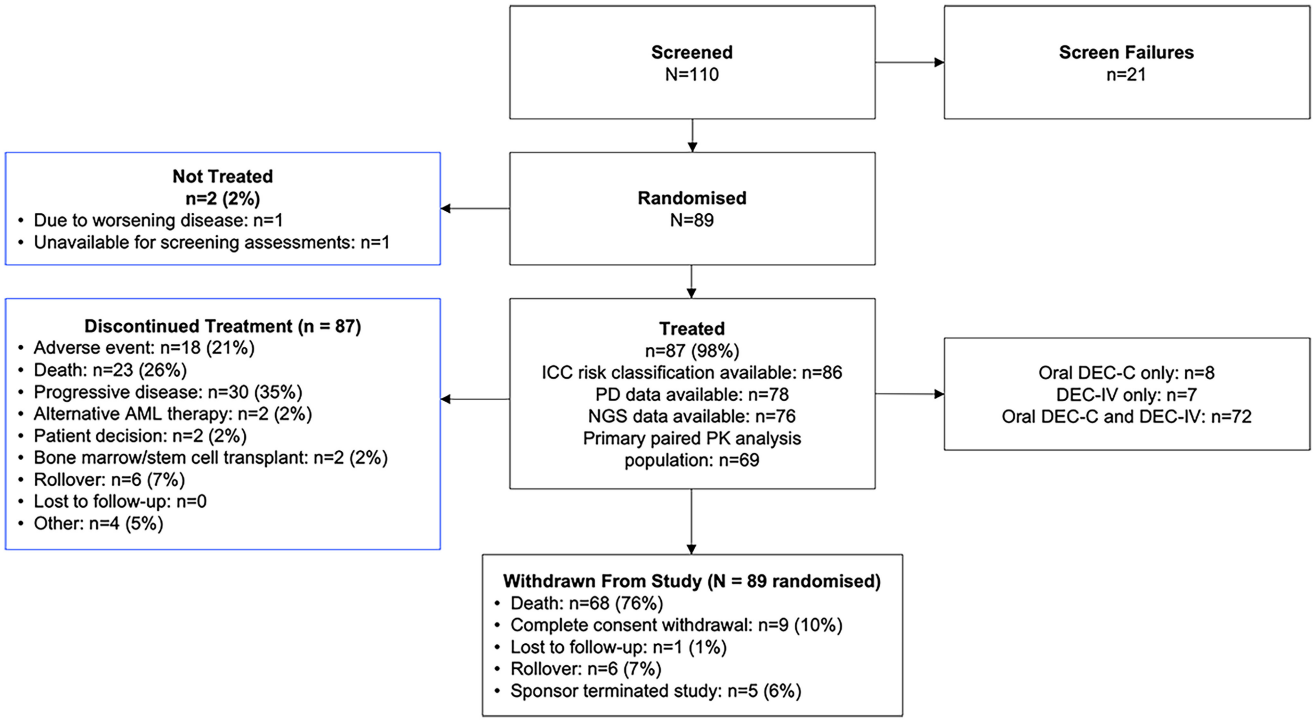


FIGURE 1 Patient disposition. AML, acute myeloid leukaemia; DEC-C, decitabine/cedazuridine; ICC, International Consensus Classification; IV, intravenous; NGS, next generation sequencing; PD, pharmacodynamic; PK, pharmacokinetic.

decitabine concentrations were higher following multiple doses of oral DEC-C on days 2 and 5 versus a single dose on day 1 (Figure 2). Plasma concentrations remained above the lower limit of quantification for up to 4 h in most patients after IV therapy and up to 6 h in most following oral administration.

Steady state was achieved with the second dose of oral therapy. Geometric mean terminal half-life was higher following oral versus IV therapy, with a wide range and variability: 1.07 h (31.6% CV) on day 1, 1.36 h (35.0% CV) on day 2, and 1.45 h (34.0% CV) on day 5 versus 1.16 h (56.7 CV%) on day 1 and 1.18 h (49.0% CV) on day 5. PK variability was similar between oral DEC-C and IV decitabine.

Differences in maximal %LINE-1 demethylation between oral DEC-C and DEC-IV were 1.1% in cycle 1 and −0.12% in cycle 2, with 95% CIs including 0, consistent with treatments having similar pharmacodynamic values (Table 3).

Clinical efficacy

Complete response occurred in 21.8% (19/87) of patients and composite response (CR + CRi + partial response) was observed in 32.2% (28/87; Table 4). Median time to CR was 3.0 months (range 1.8–7.4) and median duration of CR was 6.9 months. Median time to first response was 2.9 months (range 1.9–6.5); median time to best response was 3.5 months (range 1.9–7.5). Median duration of combined CR and CR with partial haematological recovery was 9.0 months (95% CI 3.4, 11.5).

In all, 38% (14/37) of patients RBC transfusion dependent at baseline became RBC transfusion independent for 8 weeks and 24% (9/37) for 16 weeks. More than a third of patients who were platelet transfusion dependent at baseline (36% [5/14]) attained platelet transfusion independence for 8 weeks and 29% (4/14) for 16 weeks.

Median event-free survival was 5.9 months (95% CI 3.8, 8.5), median progression-free survival was 6.1 months (95% CI 4.8, 8.7), and median OS was 8.9 months (95% CI 6, 13.1; Figure 3). Estimated survival rates at 6 months, and 1 and 2 years were 61% (95% CI 50%, 71%), 44% (95% CI 33%, 54%) and 16% (8%, 26%), respectively.

Somatic mutations and survival

Figure S1 displays the mutations detected at ≥2% variant allele frequency in the study population. *ASXL1*, *DNMT3A*, *TET2*, *TP53* and *RUNX1* were present in ≥20% of the 76 patients for whom NGS could be performed.

Figure S2 shows the relative frequency and relationship of gene mutations, indicating that mutations occur concurrently in the same patient. The number of mutations (≤ or >4) was not, however, significantly associated with survival (Figure 4). Mutated *TP53* negatively impacted OS and was the only 1 of 10 mutations evaluated to display a significant association with survival (Figure 4; Figure S3). Higher platelet count (> vs. $\leq 50 \times 10^9$/L) was significantly associated with better survival. Other factors assessed (baseline Eastern Cooperative Oncology Group performance status [0 vs. 1], treatment-related AML, complex karyotype and grade 4 neutropenia) were not significantly associated with survival.

TABLE 1 Baseline characteristics.

Baseline characteristic	Oral DEC-C ($n=80$)	All treated patients ($N=87$)
Age, *n*		
Mean (SD)	76.3 (6.77)	76.7 (6.71)
Median (range)	76.5 (61, 92)	78.0 (61, 92)
Age ≥75 years, *n* (%)	23 (62.2)	56 (64)
Male sex, *n* (%)	49 (61)	53 (61)
Median weight, kg (range)[a]	74.0 (46.2, 117.0)	73.7 (46.2, 117.0)
Mean BSA, m^2 (SD)[a]	1.84 (0.18)	1.84 (0.20)
Study disease, *n* (%)		
De novo AML	51 (64)	55 (63)
Secondary AML	29 (36)	32 (37)
MDS	17 (21)	18 (21)
Other haematological disorder	6 (8)	7 (8)
Therapy-related AML	6 (8)	7 (8)
ECOG performance status, *n* (%)		
0	33 (41)	35 (40)
1	46 (58)	51 (59)
2	1 (1)	1 (1)
Cytogenetic risk classification, *n* (%)		
Poor	30 (38)	33 (38)
Intermediate	43 (54)	45 (52)
Not evaluable/missing	7 (9)	5 (6)
>30% Bone marrow blasts, *n* (%)	39 (49)	45 (52)
2022 ELN risk category, *n* (%)		
Favourable	4 (5)	4 (5)
Intermediate	18 (23)	19 (22)
Adverse	57 (71)	63 (72)
Not evaluable	1 (1)	1 (1)
ICC classification of AML, *n* (%)		
AML not otherwise specified	16 (20)	16 (18)
AML with mutated TP53	13 (16)	16 (18)
AML with MDS-related cytogenetic abnormality	6 (8)	6 (7)
AML with MDS-related gene mutation	36 (45)	39 (45)
AML with recurrent genetic abnormalities	8 (10)	9 (10)
Not evaluable	1 (1)	1 (1)
Prior therapy for antecedent haematological disorder or cytoreduction, *n* (%)	8 (10)	8 (9)
Prior DNMTi, *n* (%)	2 (3)	2 (2)
Azacitidine	0	0
RBC transfusion dependent, *n* (%)[b]	34 (43)	37 (42)
Platelet transfusion dependent, *n* (%)[b]	12 (15)	14 (16)
Median haemoglobin, g/L (range)	89 (61.0, 137.0)	89 (61.0, 137.0)
<80, *n* (%)	19 (24)	23 (26)
80 to <100, *n* (%)	46 (58)	49 (56)
100 to <110, *n* (%)	3 (4)	3 (3)
≥110, *n* (%)	12 (15)	12 (14)
Median neutrophils, 10^9/L (range)	0.490 (0.00, 12.68)	0.475 (0.00, 12.68)
$<0.5\times10^9$/L, *n* (%)	42 (53)	46 (53)
0.5 to $<1.0\times10^9$/L, *n* (%)	15 (19)	15 (17)
$1.0–1.5\times10^9$/L, *n* (%)	2 (3)	3 (3)
$>1.5\times10^9$/L, *n* (%)	20 (25)	22 (25)
Missing	1 (1)	1 (1)
Median platelets, 10^9/L (range)	63.0 (3399)	62.0 (3, 399)
$<25\times10^9$/L, *n* (%)	15 (19)	16 (18)
25 to $<50\times10^9$/L, *n* (%)	13 (16)	16 (18)
50 to $<75\times10^9$/L, *n* (%)	20 (25)	22 (25)
75 to $<100\times10^9$/L, *n* (%)	8 (10)	8 (9)
$\geq100\times10^9$/L, *n* (%)	24 (30)	25 (29)

Abbreviations: AML, acute myeloid leukaemia; BSA, body surface area; DNMTi, DNA methyltransferase inhibitor; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; ICC, International Consensus Classification; MDS, myelodysplastic syndromes; RBC, red blood cell.

[a]For patients with valid data.

[b]Defined as ≥2 units within 56 days of first dose of study treatment.

TABLE 2 Pharmacokinetics: 5-day decitabine AUC_{0-24} for oral and IV formulations.

Analysis	5-day decitabine AUC_{0-24} LSM, h × ng/mL (*n*)		Ratio, % (90% CI)	Intrapatient CV (%)
	IV decitabine	Oral DEC-C		
Primary end-point				
Paired	907.39 (69)	904.13 (69)	99.64 (91.23, 108.8)	31.55
Sensitivity				
Unpaired	908.77 (71)	893.00 (71)	98.26 (90.11, 107.2)	31.56
Paired	896.46 (78)	885.66 (79)	98.80 (90.81, 107.5)	31.31

Abbreviations: AUC_{0-24}, area under curve over last dosing interval; CI, confidence interval; CV, coefficient of variation; DEC-C, decitabine/cedazuridine; IV, intravenous; LSM, least-squares mean.

Figure 5 displays the impact of ICC categories on survival. Patients who had 'AML with *TP53* mutations' had a poor prognosis: median OS 5.5 months and 2-year OS of 13%. According to the 2022 ELN risk classification, most patients were classified in the adverse-risk group (72%, $n=63$), followed by the

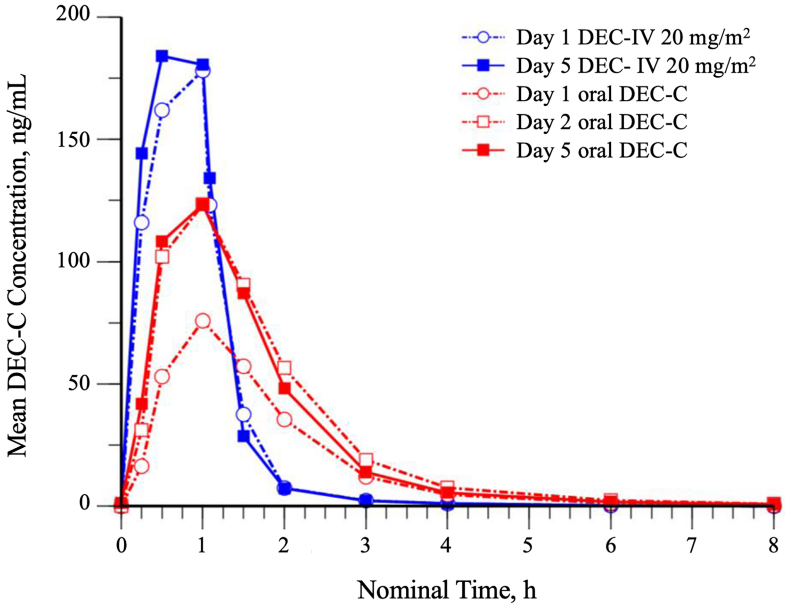


FIGURE 2 Mean plasma decitabine concentration-time profiles following single and multiple doses of intravenous decitabine (DEC-IV) decitabine and oral decitabine/cedazuridine (DEC-C) on days 1, 2 (oral only), and 5; linear scale.

TABLE 3 Pharmacodynamics: Mean maximal %LINE-1 demethylation.

Cycle	*n*	Treatment	Mean baseline	Maximal %LINE-1 demethylation, LSM (95% CI)	Difference between oral and IV therapy, estimate (95% CI)
1	33	Oral DEC-C	75.884	9.357 (7.288, 11.426)	1.113 (−1.698, 3.925)
	39	IV decitabine	76.502	8.243 (6.340, 10.147)	
2	34	Oral DEC-C	74.764	8.037 (6.258, 9.816)	−0.116 (−2.738, 2.507)
	29	IV decitabine	74.640	8.153 (6.226, 10.079)	

Abbreviations: CI, confidence interval; DEC-C, decitabine/cedazuridine; IV, intravenous; LINE-1, long interspersed nuclear element-1; LSM, least-squares mean.

intermediate- (22% [*n* = 19]) and favourable-risk (5% [*n* = 4]) groups. Favourable intermediate- versus adverse-risk group survival curves were largely overlapping (Figure 6), indicating 2022 ELN classification did not provide clinically meaningful prognostic value in determining survival.

Safety

In all, 86 of 87 patients in the safety/efficacy population reported ≥1 AE during the study (Table 5). AEs in the first two treatment cycles occurred at similar rates with IV (91%) and oral (90%) therapy. Most common AEs were cytopaenias (anaemia, thrombocytopenia and neutropenia), febrile neutropenia, pneumonia and pyrexia. More than half of patients had an AE of grade ≥3 severity. Most common grade ≥3 AEs were cytopaenias (thrombocytopenia, anaemia and neutropenia), febrile neutropenia and pneumonia.

Rates of treatment-related AEs are presented in Table 5. Most common treatment-related AEs in the study were

TABLE 4 Analysis of best response.

	Efficacy set (*n* = 87)		Oral DEC-C (*n* = 80)	
Analysis	*n* (%)	95% CI	*n* (%)	95% CI
Best response				
CR	19 (21.8)	13.7, 32.0	19 (23.8)	14.9, 34.6
CRi	5 (5.7)	1.9, 12.9	5 (6.3)	2.1, 14.0
CRp	2 (2.3)	0.3, 8.1	2 (2.5)	0.3, 8.7
PR	4 (4.6)	1.3, 11.4	4 (5.0)	1.4, 12.3
SD	33 (37.9)	27.7, 49.0	32 (40.0)	29.2, 51.6
NE	26 (29.9)	20.5, 40.6	20 (25.0)	16.0, 35.9
Composite response rates				
CR + CRi + PR	28 (32.2)	22.6, 43.1	28 (35.0)	24.7, 46.5
CR + CRh	21 (24.1)	15.6, 34.5	21 (26.3)	17.0, 37.3
CRh	2 (2.3)	0.3, 8.1	2 (2.5)	0.3, 8.7

Abbreviations: CI, confidence interval; CR, complete response; CRh, CR with partial haematological recovery; CRi, CR with incomplete blood count recovery; CRp, complete response with incomplete platelet recovery; DEC-C, decitabine/cedazuridine; NE, not evaluable; PR, partial response; SD, stable disease.

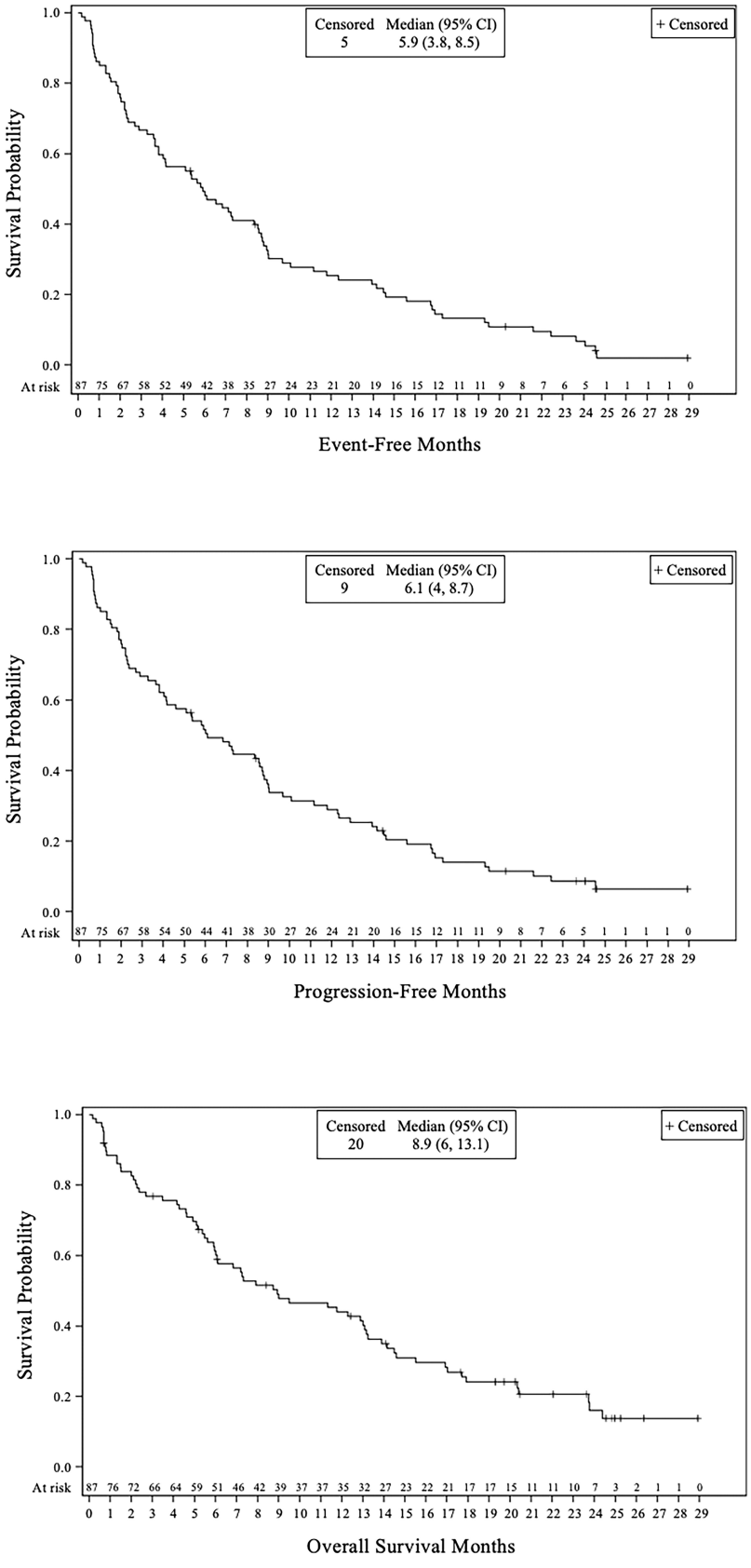


FIGURE 3 Kaplan–Meier curves for event-free, progression-free and overall survival. CI, confidence interval.

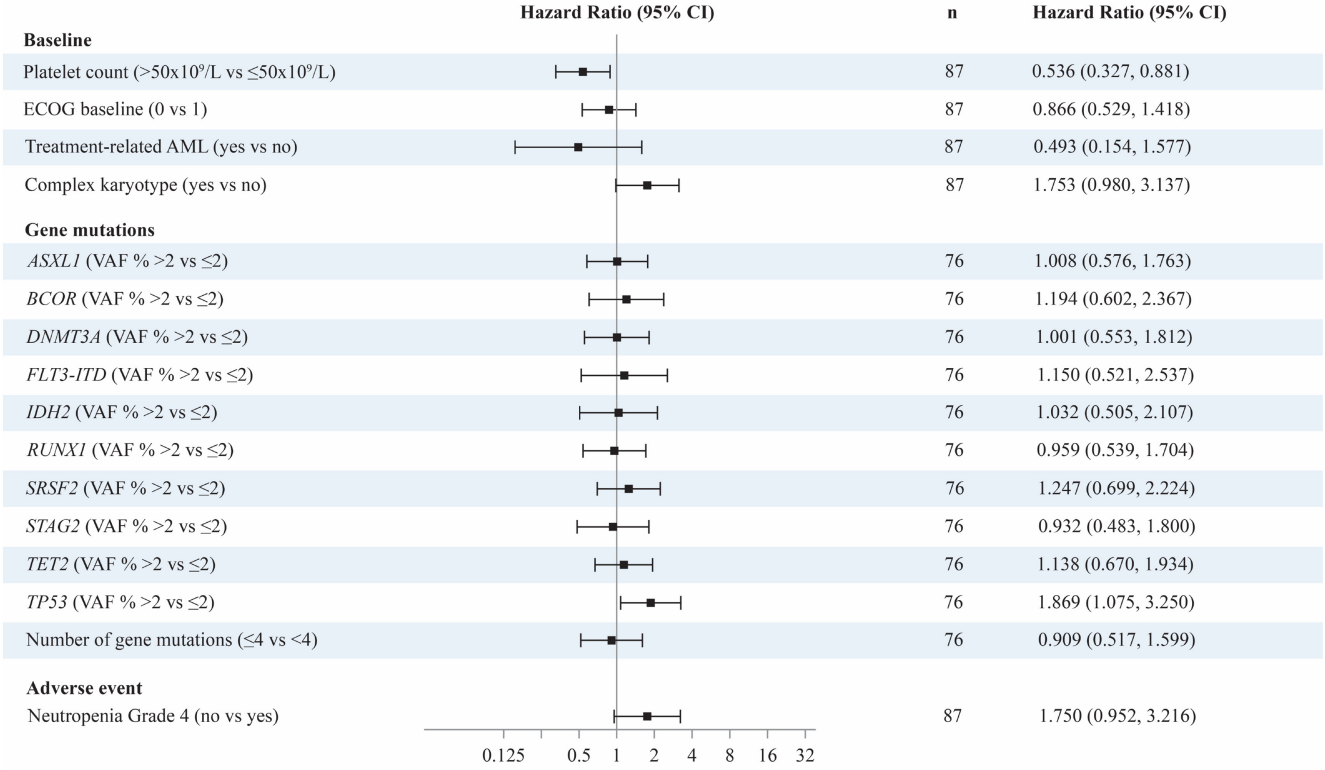


FIGURE 4 Relationship of baseline characteristics, gene mutations and adverse event to overall survival. AML, acute myeloid leukaemia; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; VAF, variant allele frequency.

similar to most common AEs regardless of treatment relation: thrombocytopenia, neutropenia and anaemia.

Most patients (81% [70/87]) experienced a serious AE during the study; 25% (22/87) developed a serious treatment-related AE. In all, 29% (25/87) of patients died due to an AE during the study; only one of these deaths, due to intracerebral bleeding, was deemed oral DEC-C related.

Of the 87 patients who received any of the study drugs, 55 (63%) experienced ≥1 dose-delayed cycle and 7 (8%) experienced ≥1 dose-reduced cycle. The proportion of dose-delayed cycles was 22%, whereas the proportion of dose-reduced cycles was 2%. In the cohort of 80 patients receiving DEC-C, dose delay or reduction due to AEs occurred in 47.5%. The most common AEs (≥5% of patients) leading to dose delay or reduction while receiving DEC-C were neutropenia (12.5%), haematological toxicity (7.5%), febrile neutropenia (5%) and pneumonia (5%). Dose delay or reduction was required due to neutropenia in 13% of patients in cycle 3 or later. The reasons for and frequency of dose delays or reductions did not differ from those reported in the safety report for DEC-IV.

In all, 18% (16/87) of patients discontinued treatment due to AEs. Two patients had serious treatment-related (oral DEC-C) AEs (asthaenia and mucositis) leading to treatment discontinuation. Twenty-eight serious oral DEC-C-related AEs were reported in 20 patients; most common were pneumonia and febrile neutropenia (7 cases each). One serious oral DEC-C-related AE resulted in death (noted previously).

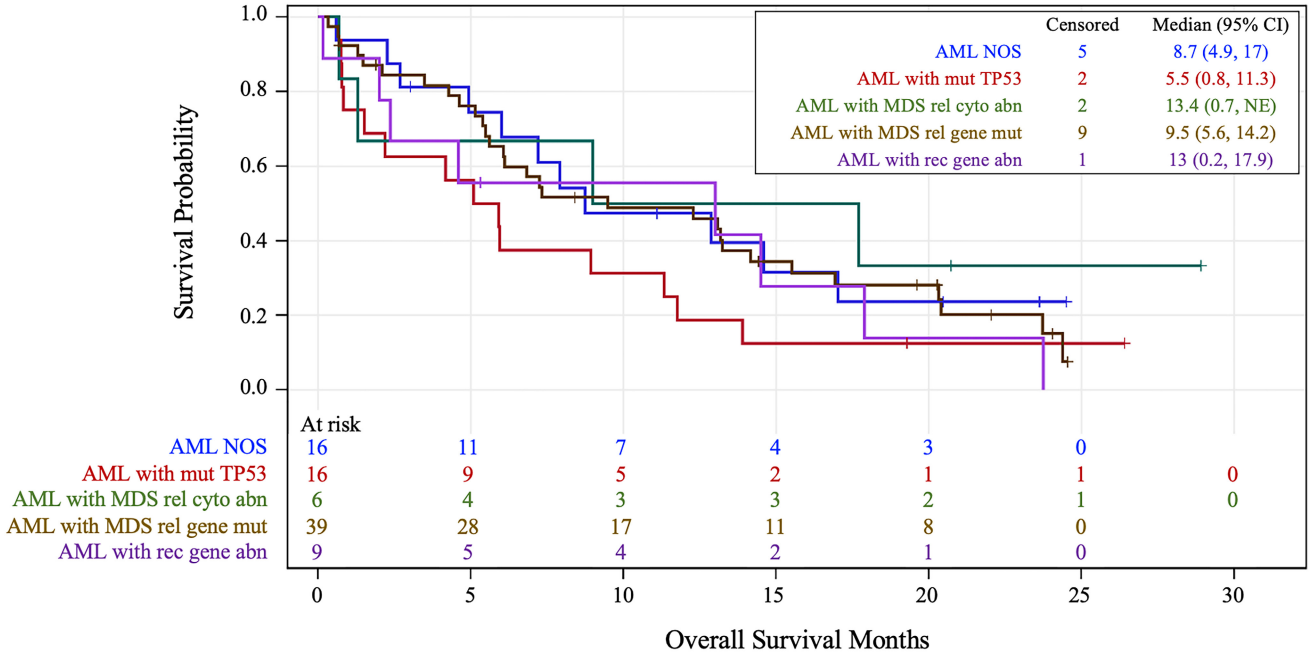
DISCUSSION

This study confirms the findings of a registration trial in MDS,[7] demonstrating equivalent PK AUC systemic exposures and demethylation rates between oral DEC-C and DEC-IV in an AML population. Safety and efficacy profiles of oral DEC-C were consistent with those of DEC-IV in AML.[18] In the phase 3 DEC-IV AML study[18] and the present study, respectively, median OS was 7.7 and 8.9 months, CR plus CR with incomplete platelet recovery rates were 18% and 24%, and CR plus CRi rates were 26% and 30%.

For comparison, a real-world study of Medicare beneficiaries with AML who were ineligible for intensive induction therapy and were receiving parenteral DNMTi reported similar median survival (8.2 months from diagnosis) and RBC transfusion independence (33% of those transfusion dependent when initiating DNMTi) rates.[20]

Oral therapy for older, often infirm patients with AML ineligible for intensive chemotherapy may provide significant benefit over parenteral treatment requiring daily trips to a treatment centre for 5 or 7 days/month. Patients may require transportation to a centre and visits can last hours. Oral therapy may reduce some of the treatment-associated burden of AML therapy and improve adherence.[21]

Intravenous decitabine is indicated in the EU for treatment of adults with newly diagnosed de novo or secondary AML who are not candidates for induction chemotherapy. Decitabine or azacitidine plus venetoclax is the standard



ICC AML Type	n†	Median OS, mo	Time	Survival, %	95% CI
NOS	16	8.8	1-year OS	47	22, 69
			2-year OS	24	6, 48
Mutated *TP53**	16	5.5	1-year OS	19	5, 40
			2-year OS	13	2, 33
MD-rel cyto abn	6	13.4	1-year OS	50	11, 80
			2-year OS	33	5, 68
MD-rel gene mut	39	9.5	1-year OS	49	32, 64
			2-year OS	15	5, 31
Rec gene abn	9	13.0	1-year OS	56	20, 80
			2-year OS	0	

FIGURE 5 Overall survival (OS) by International Consensus Classification (ICC) criteria. *Any somatic *TP53* mutation (variant allele frequency >10%); †One patient was not evaluable for ICC category; ICC categories are mutually exclusive. abn, abnormal; AML, acute myeloid leukaemia; CI, confidence interval; cyto, cytokine; MD, myelodysplasia; MDS, myelodysplastic syndromes; mut, mutation; NE, not evaluable; NOS, not otherwise specified; rec, recurrent; rel, related.

therapy for patients with AML who are ineligible for intensive therapy and have *FLT3*, or *IDH1* or *-2* mutation, or no actionable mutations.[2,19,22,23] Oral DEC-C is approved in the EU for adults newly diagnosed with AML aged ≥65 years or ineligible for standard induction therapy. The availability of oral DEC-C makes an all-oral regimen possible for patients receiving concomitant venetoclax.[24]

Preliminary results from a study assessing the PK and drug interactions of oral DEC-C with venetoclax in patients with newly diagnosed AML ineligible for intensive chemotherapy report that each therapy's AUC was unaffected by coadministration with the other agent.[25] The phase 1/2 study is ongoing to assess the efficacy, safety and PK of this combination (NCT04657081).

An oral form of azacitidine is available and approved in EU and USA as maintenance therapy for adults with AML who achieve CR or CRi following induction chemotherapy and not proceeding to haematopoietic cell transplantation.[26,27] It is not pharmacologically equivalent to parenteral azacitidine and not indicated for the same population of AML patients as parenteral azacitidine. Of interest, a combination of azacitidine and cedazuridine to allow orally available azacitidine that provides equivalent PK exposure is in development (NCT04256317).

The genomic landscape of AML in older patients deemed unfit for intensive chemotherapy differs from that of younger patients who have received intensive chemotherapy.[28–30] Most common mutations in this study are broadly similar to those most frequently isolated in ASTRAL-1, the largest study performed in older patients with AML receiving less intensive chemotherapy.[29]

This study confirms earlier findings that ELN risk categories are not significantly related to survival in patients not receiving intensive therapy.[28,29,31] This is consistent with data from VIALE-A and its preceding phase 1 trials, which reported that in patients treated with azacitidine and

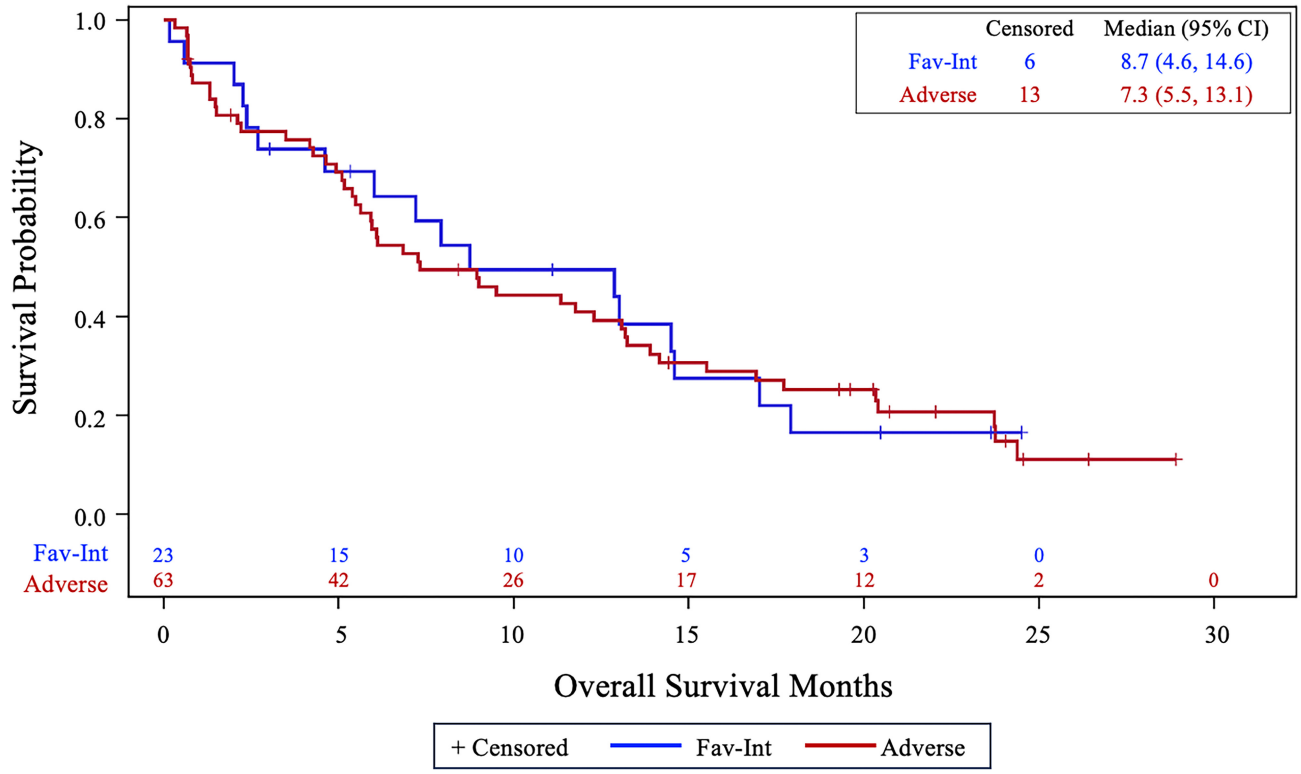


FIGURE 6 Overall survival for acute myeloid leukaemia by 2022 European Leukaemia Net risk stratification. CI, confidence interval; Fav-Int, favourable-intermediate.

TABLE 5 Most common TEAEs.[a]

Patients, *n* (%)	Efficacy set (*n* = 87)	Oral DEC-C (*n* = 80)
≥1 TEAE regardless of relation to treatment[b]	86 (99)	80 (100)
Thrombocytopenia	50 (58)	47 (59)
Anaemia	45 (52)	44 (55)
Neutropenia	28 (32)	28 (35)
Febrile neutropenia	26 (30)	25 (31)
Asthenia	22 (25)	22 (28)
Pneumonia	22 (25)	19 (24)
Pyrexia	19 (22)	19 (24)
Diarrhoea	18 (21)	18 (23)
Nausea	17 (20)	17 (21)
Peripheral oedema	16 (18)	16 (20)
Constipation	17 (20)	15 (19)
Hypokalaemia	15 (17)	15 (19)
Decreased appetite	12 (14)	12 (15)
≥1 Grade ≥3 TEAE regardless of relation to treatment[b]	52 (66)	43 (55)
Thrombocytopenia	43 (49)	41 (51)
Anaemia	33 (38)	33 (41)
Neutropenia	26 (30)	26 (32)
Febrile neutropenia	24 (28)	23 (29)
Pneumonia	21 (24)	18 (23)
Treatment-related TEAEs[b]		
≥1 TEAE	60 (69)	57 (71)
Thrombocytopenia	27 (31)	26 (33)
Neutropenia	20 (23)	20 (25)
Anaemia	17 (20)	17 (21)

[a]Treatment-emergent adverse events (TEAEs) were coded using Medical Dictionary for Regulatory Activities Version 22.0 and are listed in descending order of incidence in oral decitabine/cedazuridine (DEC-C) population.
[b]Events occurring in ≥15% of patients.

venetoclax, ELN risk category is not an effective predictor of patient outcome.[32]

A limitation of this study includes the open-label design, which has the potential to introduce bias to investigators and patients. The design should not have affected the PK and efficacy results, however, because all patients received a pharmacokinetically equivalent form of decitabine and PK assessments were the same.

In conclusion, this study met its primary objective to demonstrate pharmacologic equivalence between DEC-IV and oral decitabine in patients with AML. Clinical safety and efficacy were consistent with those reported for DEC-IV. Oral DEC-C enables home-based therapy, and thus may reduce treatment burden and improve adherence, which would be of particular value in older patients.

AUTHOR CONTRIBUTIONS

All authors reviewed the final manuscript, had full access to all the data in the study, were involved with the acquisition, analysis or interpretation of data, take responsibility for the integrity of the data and the accuracy of the data analysis, and provided critical revision of the manuscript for important intellectual content. Klaus Geissler: Patient enrolment, data acquisition and interpretation, and manuscript review. Zdenek Koristek, Uwe Platzbecker and Montserrat Arnan: Data acquisition and manuscript review. Teresa Bernal del Castillo, Gabriela Rodríguez-Macías, Mary-Margaret Keating and Jürgen Krauter: Data acquisition, interpretation, and verification, and manuscript review. Stephan K.

Metzelder and Monia Lunghi: Data acquisition, interpretation, and verification, and manuscript drafting and review. Jan Novák and Nicola Stefano Fracchiolla: Data acquisition and interpretation, and manuscript review. Arpad Illes: Data acquisition and verification, and manuscript drafting and review. Jiří Mayer and Valeria Santini: Data acquisition and interpretation, and manuscript drafting and review. Aram Oganesian: Study design, data acquisition and analysis, and manuscript review. Yuri Sano: In study design, data acquisition, interpretation, and verification, and manuscript drafting and review. Harold Keer: Study concept and design, data acquisition and analysis, and manuscript drafting and review. Michael Lübbert: Patient care and manuscript review.

AFFILIATIONS

[1]Sigmund Freud PrivatUniversität, Wien, Austria
[2]Department of Haematooncology, University Hospital Ostrava, Ostrava, Czech Republic
[3]Hospital Universitario Central de Asturias, Instituo de Investigación Sanitaria del Principado de Asturias, Instituto Universitario de Oncología del Principado de Asturias, Oviedo, Spain
[4]Department of Haematology, Third Faculty of Medicine, Charles University and Faculty Hospital University, Hospital Královské Vinohrady, Prague, Czech Republic
[5]Hospital General Universitario Gregorio Marañón, Madrid, Spain
[6]Philipps University Marburg and University Hospital Gießen and Marburg, Marburg, Germany
[7]Division of Hematology, Department of Internal Medicine, Faculty of Medicine, University of Debrecen, Hungary
[8]Fakultní Nemocnice Brno and Masaryk University, Brno, Czech Republic
[9]Institut Català d'Oncologia-Hospital Duran i Reynals, Barcelona, Spain
[10]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada
[11]Städtisches Klinikum Braunschweig, Klinik für Hämatologie und Onkologie, Braunschweig, Germany
[12]Azienda Ospedaliero-Universitaria Maggiore Della Carità Novara, Novara, Italy
[13]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, SC Ematologia, Milan, Italy
[14]Universitätsklinikum Leipzig, Leipzig, Germany
[15]MDS Unit, Hematology, AOUC, DMSC, Università degli Studi di Firenze, Firenze, Italy
[16]Taiho Oncology, Inc., Pleasanton, California, USA
[17]Department of Haematology, Oncology, and Stem Cell Transplantation, University of Freiburg Medical Center, University of Freiburg Faculty of Medicine, Freiburg, Germany

ACKNOWLEDGEMENTS

Editorial support for this manuscript was provided by Eileen McCaffrey and Geoff Marx of BioScience Communications, New York, NY, USA, and funded by Astex Pharmaceuticals, Inc., now part of Taiho Oncology, Inc.

CONFLICT OF INTEREST STATEMENT

Klaus Geissler is a speaker for and has received consultancy honoraria from AbbVie, Celgene, Jazz, Novartis and Otsuka. Zdenek Koristek has received consultancy honoraria from AbbVie, BMS, CSL Behring, Kite Pharma, Novartis and Swixx. Teresa Bernal del Castillo has served on advisory boards for AbbVie and Otsuka. Jan Novak has served on advisory boards for AbbVie, Astellas, BMS and Servier. Gabriela Rodríguez-Macías is a speaker for and has received consultancy honoraria from AbbVie, Astellas, BMS-Celgene, Jazz, Otsuka and Servier. Stephan K. Metzelder, Jürgen Krauter and Monia Lunghi have nothing to declare. Arpad Illes has received consultancy honoraria from Celgene, Janssen, Novartis, Pfizer, Roche and Takeda. Jiří Mayer has received research support from AbbVie and Astex. Montserrat Arnan has served on advisory boards for AbbVie, BMS, Novartis and Otsuka, and received consultancy honoraria from AbbVie, BMS, Jazz and Otsuka. Mary-Margaret Keating has served on advisory boards for AbbVie, AstraZeneca, Beigene, Incyte, Roche, Sobi and Taiho. Nicola Stefano Fracchiolla is a speaker for and has received consultancy honoraria from AbbVie, Amgen, Gilead, Incyte, Jazz and Pfizer. Uwe Platzbecker is a speaker for and/or has received consultancy honoraria from AbbVie, Akeso, Blueprint, BMS, Celgene, Curis, Geron, Gilead, GSK, Janssen, Jazz, Novartis, Pierre Fabre, Servier, Silence and Syros. Valeria Santini has served on advisory boards for AbbVie, Ascentage, BMS, CTI, Keros, Novartis, Servier and Syros, and received travel grants from AbbVie and Jazz. Yuri Sano, Aram Oganesian and Harold Keer are employed by Taiho. Michael Lübbert has served on boards of directors or advisory committees for AbbVie, Astex, Otsuka, and Syros, and received research funding from Janssen-Cilag.

DATA AVAILABILITY STATEMENT

The clinical data can be requested by any qualified researchers who engage in rigorous independent scientific research. Data requests can be submitted to medicalinformation@taihooncology.com for review and approval.

ORCID

Klaus Geissler https://orcid.org/0000-0003-1921-7034
Teresa Bernal del Castillo https://orcid.org/0000-0002-2338-513X
Valeria Santini https://orcid.org/0000-0002-5439-2172
Harold Keer https://orcid.org/0000-0003-0753-4921
Michael Lübbert https://orcid.org/0000-0003-1186-1650

REFERENCES

1. Shallis RM, Wang R, Davidoff A, Ma X, Zeidan AM. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev. 2019;36:70–87.
2. National Comprehensive Cancer Network. Clinical practice guidelines in oncology (NCCN guidelines®). Acute myeloid leukemia. Version 2.2024—March 22, 2024.
3. National Comprehensive Cancer Network. Acute myeloid leukemia. Version 6.2023—October 24, 2023.
4. Mistry B, Jones MM, Kubiak P, Garcia-Manero G, Litzow MR, Mesa RA, et al. A phase 1 study to assess the absolute bioavailability and safety of an oral solution of decitabine in subjects with myelodysplastic syndromes (MDS). Blood. 2011;118(21):3801.
5. Garcia-Manero G, Gore SD, Cogle C, Ward R, Shi T, Macbeth KJ, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. J Clin Oncol. 2011;29(18):2521–7.
6. Garcia-Manero G, Griffiths EA, Steensma DP, Roboz GJ, Wells R, McCloskey J, et al. Oral cedazuridine/decitabine for MDS and CMML: a phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. Blood. 2020;136(6):674–83.
7. Garcia-Manero G, McCloskey J, Griffiths EA, Yee KWL, Zeidan AM, Al-Kali A, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study. Lancet Haematol. 2024;11(1):e15–e26.

8. Savona MR, McCloskey JK, Griffiths EA, Yee KWL, Zeidan AM, Al-Kali A, et al. Efficacy and safety of oral decitabine/cedazuridine (ASTX727) in the CMML subpopulation from phase 2 and ASCERTAIN phase 3 studies. Hemasphere. 2023;7(Suppl):e1342620.
9. Patel JP, Gönen M, Figueroa ME, Fernandez H, Sun Z, Racevskis J, et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. N Engl J Med. 2012;366(12):1079–89.
10. Arber DA, Orazi A, Hasserjian RP, Borowitz MJ, Calvo KR, Kvasnicka H-M, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200–28.
11. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140(12):1345–77.
12. Lo MY, Tsai XC, Lin CC, Tien FM, Kuo YY, Lee WH, et al. Validation of the prognostic significance of the 2022 European LeukemiaNet risk stratification system in intensive chemotherapy treated aged 18 to 65 years patients with de novo acute myeloid leukemia. Am J Hematol. 2023;98(5):760–9.
13. Rausch C, Rothenberg-Thurley M, Dufour A, Schneider S, Gittinger H, Sauerland C, et al. Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia. 2023;37(6):1234–44.
14. Dacogen. Prescribing information. Princeton, NJ: Otsuka America Pharmaceutical, Inc.; 2021.
15. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.
16. Yang AS, Estécio MR, Doshi K, Kondo Y, Tajara EH, Issa JP. A simple method for estimating global DNA methylation using bisulfite PCR of repetitive DNA elements. Nucleic Acids Res. 2004;32(3):e38.
17. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al. Revised recommendations of the International Working Group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol. 2003;21(24):4642–9.
18. Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, 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(21):2670–7.
19. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617–29.
20. Zeidan AM, Wang R, Wang X, Shallis RM, Podoltsev NA, Bewersdorf JP, et al. Clinical outcomes of older patients with AML receiving hypomethylating agents: a large population-based study in the United States. Blood Adv. 2020;4(10):2192–201.
21. Gupta A, Eisenhauer EA, Booth CM. The time toxicity of cancer treatment. J Clin Oncol. 2022;40(15):1611–5.
22. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17.
23. Pollyea DA, Pratz K, Letai A, Jonas BA, Wei AH, Pullarkat V, et al. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a phase 1b study. Am J Hematol. 2021;96(2):208–17.
24. Bazinet A, Garcia-Manero G, Short N, Alvarado Y, Bataller A, Abuasab T, et al. Oral decitabine and cedazuridine plus venetoclax for older or unfit patients with acute myeloid leukaemia: a phase 2 study. Lancet Haematol. 2024;11(4):e276–e286.
25. Mannis GN, Griffiths EA, Savona MR, Odenike O, Roboz GJ, O'Connell CL, et al. A phase 1 study evaluating ASTX727 (decitabine and cedazuridine) and venetoclax combination therapy in newly diagnosed AML patients unfit for intensive induction chemotherapy. Presented at the American Society of Hematology Annual Meeting. Atlanta, GA; December 11–13, 2021. Abstract 1245, 138.
26. Onureg. Prescribing information. Princeton, NJ: Bristol-Myers Squibb Co; 2022.
27. Onureg. Summary of Product Characteristics [Internet]. Available from: https://www.ema.europa.eu/en/documents/product-information/onureg-epar-product-information_en.pdf
28. Jahn E, Saadati M, Fenaux P, Gobbi M, Roboz GJ, Bullinger L, et al. Clinical impact of the genomic landscape and leukemogenic trajectories in non-intensively treated elderly acute myeloid leukemia patients. Leukemia. 2023;37(11):2187–96.
29. Jahn E, Saadati M, Fenaux P, Gobbi M, Roboz GJ, Bullinger L, et al. Genomic landscape and prognosis in older acute myeloid leukemia patients not eligible for intensive chemotherapy. HemaSphere. 2023;7:677–8.
30. Silva P, Neumann M, Schroeder MP, Vosberg S, Schlee C, Isaakidis K, et al. Acute myeloid leukemia in the elderly is characterized by a distinct genetic and epigenetic landscape. Leukemia. 2017;31(7):1640–4.
31. Silva P, Badiola J, Martín-Rojas RM, Gómez-Centurión I, Rodríguez-Macias G, Gómez-Llobell M, et al. Patients with acute myeloid leukemia on non-intensive therapy: applicability of the European Leukemia Net Risk Classification. Blood. 2021;138:3382.
32. Döhner H, Pratz KW, DiNardo CD, Jonas BA, Pullarkat VA, Thirman MJ, et al. ELN risk stratification is not predictive of outcomes for treatment-naïve patients with acute myeloid leukemia treated with venetoclax and azacitidine. Blood. 2022;140(Suppl 1):1441–4.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Geissler K, Koristek Z, del Castillo TB, Novák J, Rodríguez-Macías G, Metzelder SK, et al. Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study. Br J Haematol. 2024;205(5):1734–1745. https://doi.org/10.1111/bjh.19741