24 September 2015
EMA/757391/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Vidaza

International non-proprietary name: AZACITIDINE

Procedure No. EMEA/H/C/000978/II/0030

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
BM	Bone marrow
BSC	Best supportive care
CALGB	Cancer and Leukemia Group B
CCR	Conventional care regimens
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRF	Case report form
CRi	Complete remission with incomplete blood count recovery
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic acid
DMC	Data Monitoring Committee
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EU	European Union
FAB	French-American-British
GCP	Good clinical practice
GI	gastro-intestinal
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
HSCT	Haematopoietic stem cell transplantation
ICH	International Conference on Harmonisation
IIT	Investigator-initiated trial
ILD	Interstitial lung disease
IPCW	Inverse Probability of Censoring Weighted
IPSS	International Prognostic Scoring System
IR	Incidence rate per 100 person-years of exposure
IRC	Independent Review Committee
ITT	Intent-to-treat
IV	Intravenous(ly)
IWG	International Working Group

KM	Kaplan Meier
LDAC	Low-dose cytarabine
MDS	Myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
NCCN	National Comprehensive Cancer Network
OR	Odds ratio
OS	Overall survival
PB	Peripheral blood
PH	Proportional hazards
PR	Partial response/remission
PS	Performance status
PSUR	Periodic Safety Update Report
PT	Preferred term
QoL	Quality of life
RBC	Red blood cell
RFS	Relapse-free survival
RIC-HSCT	Reduced-intensity conditioning- haematopoietic stem cell transplantation
RMP	Risk management plan
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous(ly)
SD	Stable disease
SmPC	Summary of product characteristics
SMQ	Standardized MedDRA query
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Celgene Europe Limited submitted to the European Medicines Agency on 23 December 2014 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to add treatment of adult patients aged 65 years or older who are not eligible for Haematopoietic stem cell transplantation (HSCT) with Acute myeloid leukemia (AML) with >30% marrow blasts according to the WHO classification, based on the pivotal phase III study AZA-AML-001. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 10.0 was provided as part of the application.

The requested variation proposed amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

Vidaza (azacitidine) was designated as an orphan medicinal product EU/3/07/509 on 29 November 2007. Vidaza was designated as an orphan medicinal product in the following indication:

"Treatment of acute myeloid leukemia (AML)"

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of additional market protection for a new indication.

Protocol assistance

The MAH received Protocol assistance from the CHMP on 25 June 2009. The Protocol assistance

pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Pieter de Graeff Co-Rapporteur: Arantxa Sancho-Lopez

Timetable	Actual dates
Submission date	23 December 2014
Start of procedure	23 January 2015
CHMP Rapporteur Assessment Report	17 March 2015
CHMP Co-Rapporteur Assessment Report	17 March 2015
PRAC Rapporteur Assessment Report	17 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 April 2015
CHMP comments	13 April 2015
1st Request for supplementary information (RSI)	23 April 2015
Submission of responses	24 July 2015
CHMP Rapporteurs' joint response Assessment Report	1 September 2015
CHMP comments	14 September 2015
CHMP Opinion	24 September 2015
The CHMP adopted a report on similarity of Vidaza with Ceplene (histamine dihydrochloride) and Dacogen (decitabine)	24 September 2015
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Vidaza in comparison with existing therapies	24 September 2015

2. Scientific discussion

2.1. Introduction

Problem statement

The disease - AML

Acute myeloid leukaemia (AML) is an aggressive, clonal myeloid neoplasm with maturation arrest of myelopoiesis, leading to an accumulation of myoblasts in bone marrow (BM) and/or blood. AML is the most frequent form of leukaemia, accounting for approximately 25% of all leukaemias in adults in the Western world (Deschler, 2006a). Worldwide, the incidence of AML is the highest in the United States (US), Australia and Western Europe (Redaelli, 2003). The overall annual crude incidence of AML is 3.7 per 100,0000 people (Visser, 2012). More than half of the subjects with newly diagnosed AML in developed countries are over 65 years of age, with a median age at diagnosis of 67 (Colita, 2011; Pollyea, 2011; Smith, 2011).

AML can arise de novo, through transformation of existing myelodysplasia, or be secondary to previous therapy (e.g. cytotoxic chemotherapy). AML is a heterogeneous disease in terms of response to treatment and overall survival (OS). Prognostic factors that contribute to this heterogeneity can be both patient- and disease-related. Patient-related prognostic factors include age, performance score and comorbidities. Disease-related prognostic factors include high leukocyte count, existence of prior MDS or myelodysplasia-related changes, previous cytotoxic therapy, and cytogenetic and molecular/genetic changes in the leukaemic cells at diagnosis. Overall, the 5-year survival rate for AML is 19%, whereas for elderly only 5% of the patients achieve a 5-year survival (Visser, 2012).

The treatment – AML in the elderly

Intensive (induction) chemotherapy

Since the 1970s, the standard initial therapy for patients with AML has consisted of intensive chemotherapy with 7 days of continuous infusion with cytarabine and 3 days with an anthracycline drug (the so-called "7+3" regimen). Published data confirm that also the median overall survival of older patients (median age 70 years) with AML treated with intensive induction therapy was significantly longer (30 weeks) than patients treated with low-intensity therapy (12 weeks) or best supportive care (Deschler, 2006b). However, older patients with AML are more likely to have more numerous and severe comorbidities, contributing to more frequent treatment-related morbidity and mortality (Buchner, 2009; Kantarjian, 2006). Therefore, in clinical practice selection of the appropriate therapeutic approach for the older AML patient is based on patient-specific factors (i.e. his/her "fitness" for chemotherapy) and biological markers of disease predictive of response to various therapeutic interventions. In this respect, the one factor most consistently aligning with clinical outcome after intensive chemotherapy is karyotype in young and elderly patients (Kantarjian, 2006; Krug, 2010; Malfuson, 2008). Older patients with AML characterized by favourable- or intermediate-risk (non-adverse) karyotype have complete remission (CR) rates up to 60% after cytarabine- and anthracycline-based therapy. In contrast, older patients with AML associated with adverse karyotype have remission rates as low as 20%, with an overall survival of 2-3 months (Kantarjian, 2006). (For further reading be referred to the recent review of Wang (Hematology Am Soc Hematol Educ Program, 2014).)

Allogeneic haematopoietic stem cell transplantation (HSCT)

Allogeneic haematopoietic cell transplantation (HSCT) is considered the most effective therapy for addressing resistance in AML. Reduced intensity conditioning (RIC) regimens and the use of donors other than HLA-matched siblings have made HSCT feasible in many older patients. However, there is a lack of knowledge about the relative benefit of HSCT over conventional chemotherapy implying a need for standardized means to help physicians decide which older patients should receive intensive initial chemotherapy and which should subsequently be treated with (RIC-)HSCT (Menzin, 2002; Oran, 2012). Current data from the Centre for International Blood and Marrow Transplant Research (CIBMTR) show that 30% of AML patients > 75 years of age survive for 3 years after allogeneic HSCT (Sorror and Estey, Hematology Am Soc Hematol Educ Program, 2014).

Low-dose cytarabine

Low-dose cytarabine (also known as low-dose Ara-C or LDAC) has been used as a low-intensity therapeutic strategy for the treatment of elderly, "unfit" AML patients for several decades. Recent studies have highlighted the fact that even very small doses of cytarabine (typically given at 20 mg/m^2 administered once or twice daily for 10-14 days per month) can induce CRs in ≈ 8%-18% of patients with AML and can prolong survival (Burnett, 2007; Fenaux, 2010; Kantarjian, 2012). Although these results compare favourably with no remission after hydroxyurea and supportive care,

LDAC is currently considered potentially inferior to other upfront therapies for older patients with AML, in part because no patients with AML with adverse cytogenetic findings achieve remission with this regimen (Burnett, 2007). Despite this fact, LDAC may still be a therapeutic option for geriatric patients with favourable or intermediate risk karyotype AML whose medical issues (such as renal insufficiency) preclude the administration of intensive chemotherapy and who prefer to self-administer drug almost exclusively at home without the need for daily clinic visits or inpatient hospitalization.

Hypomethylating therapy

Over the last several years, hypomethylating therapy with 1 of 2 agents, decitabine and azacitidine, has been increasingly used in place of standard intensive chemotherapy for the treatment of “unfit” elderly patients with AML. Recent studies suggest that, although hypomethylating therapy in AML patients results in lower CR rates (10%-20%) than conventional intensive chemotherapy, an additional 10%-30% of these individuals nevertheless exhibit evidence of some disease response or stabilization and have overall survival rates equivalent or superior to other conventional treatments (Kantarjian, 2012; Quintas-Cardama, 2012). Furthermore, hypomethylating therapy was reported to be well tolerated over long periods of time in unfit elderly individuals, with fewer required hospital days and RBC and platelet transfusions (van der Helm, 2013; Ritchie, 2013). To date, the question of which older patients with AML benefit from intensive versus hypomethylating therapy has been addressed only in retrospective analyses.

Post-remission therapy for older AML patients

The best therapeutic option for older patients with AML after achievement of CR with upfront therapy remains uncertain. Individuals up to the age of 75 years who achieve sufficient disease control after upfront AML therapy and have few comorbidities should be considered for consolidation with allogeneic stem cell transplantation (alloSCT), ideally with reduced intensity conditioning regimens, because this remains the only potential curative therapeutic option for these patients.

For those individuals in remission who are not eligible for alloSCT, the standard approach has been to administer “consolidation” chemotherapy consisting of lower doses of the same agents used in induction therapy. To date, there is no consensus on the number of consolidation chemotherapy cycles (range 1-4), number of agents (cytarabine alone vs cytarabine ± anthracycline), and drug dose (high- vs intermediate-dose cytarabine) needed for the best possible outcomes for older patients with AML. For lack of better information, older patients with favourable- or intermediate-risk AML who achieve CR after upfront cytarabine and anthracycline-based chemotherapy typically are offered 2-4 cycles of intermediate- to high-dose cytarabine. In contrast, patients with adverse karyotype AML who achieve CR have been shown to fare poorly regardless of intensive induction and consolidation chemotherapy and therefore should be referred for investigational therapy in the post-remission setting (Buchner, 2006). (For further reading be referred to the recent review of Wang (Hematology Am Soc Hematol Educ Program, 2014).)

About the product

Azacitidine (Vidaza; 4-amino-1-β-D-ribofuranosyl-s-triazin-2[1H]-one) is an antineoplastic medicinal product, with anatomical Therapeutic Chemical (ATC) Code L01BC07. Azacitidine is an analogue of the naturally occurring pyrimidine nucleoside cytidine that incorporates into ribonucleic acid (RNA) and deoxyribonucleic acid (DNA). Azacitidine is believed to exert its antineoplastic effect by cytotoxicity to abnormal haematopoietic cell in the bone marrow (BM) and hypomethylation of DNA. The cytotoxic effects of azacitidine may be due to inhibition of protein synthesis and activation of DNA damage pathways, upon incorporation into RNA and DNA, respectively. Incorporation of

azacitidine into DNA also results in DNA hypomethylation and may allow the re-expression of genes involved in normal cell cycle regulation and differentiation.

Azacitidine (Vidaza) is currently approved for: "*The treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to the WHO classification*".

With the present variation the Applicant applies for an extension of the indication to: "*The treatment of adult patients age 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification*."

Azacitidine has been extensively studied in MDS and has been shown in a large, randomised Phase 3 trial of higher-risk MDS patients to provide a survival advantage of 9.4 months over conventional care regimens (CCR). The clinical experience of azacitidine in AML is smaller, but efficacy results have been obtained in a subset of 113 patients from the MDS study who are diagnosed with MDS according to the French-American-British (FAB) classification, but who are considered to have AML according to the WHO-definition (20 to 30% blasts). The median survival was 24.5 months (n=55) in the azacitidine arm compared with 16.0 months (n=58) in the conventional care regimen arm. Additionally, the outcome was not significantly different in patients with an unfavourable karyotype, although the sample size was small. The Applicant has now investigated the use of azacitidine in the treatment of elderly patients with AML, in the AZA-AML-001 study. This study included patients with >30% bone marrow blasts, a threshold considered to be diagnostic of AML in both the WHO and FAB classification.

- CHMP guidelines/Scientific Advice
- Orphan indication

Azacitidine was designated an Orphan Medicinal Product in the European Union (EU) for the treatment of Acute Myeloid Leukaemia (AML) (EU/3/07/509), granted on 29 November 2007. The application for the orphan drug designation was based on the following criterion:

- AML was estimated to be affecting less than 2 in 10,000 persons in the Community at the time the application was made;

- the condition is chronically debilitating and life threatening due to the high mortality rate of the refractory or relapsed disease;

- although satisfactory methods of treatment of the condition have been authorized in the Community, justifications have been provided that azacitidine may be of significant benefit to those affected by the condition.

For the newly applied indication, the Applicant has been granted an orphan designation on the same grounds.

Other medicinal products have already been designated as an Orphan medicinal product for a condition relating to the newly applied for azacitidine indication, these products include Ceplene (histamine dihydrochloride) and Dacogen (decitabine). Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

- Paediatric investigation plan

Pursuant to Article 16(1) of the Regulation (EC) No 1901/2006 as amended, the Applicant has submitted in February 2013 an application for a paediatric investigation plan (PIP) for Vidaza and a deferral under Article 20 of said regulation and a waiver under Article 13 of said regulation.

For the AML indication a waiver for the paediatric population from birth to less than 3 months was granted on grounds that clinical studies with the specific medicinal product cannot be expected to be of significant therapeutic benefit to or fulfil a therapeutic need in this patient population.

The indication targeted by the paediatric investigation plan includes the treatment of children with molecular relapse of acute myeloid leukaemia in the first complete remission. The Applicant has agreed to conduct a multicentre, randomized, open-label clinical study to evaluate the safety and pharmacodynamics and efficacy of azacitidine compared to no anti-cancer treatment in children from 3 months to less than 18 years of age (and young adults) in first complete remission after treatment for acute myeloid leukaemia who have increasing molecular signals of aberrations associated with AML. The PDCO agreed that the study should be completed by May 2024.

In addition to the paediatric study on AML, the PIP also included a paediatric study in newly-diagnosed advanced MDS or newly-diagnosed Juvenile myelomonocytic leukemia (JMML) patients. For this indication, a waiver was granted for the paediatric population from birth to less than 1 months on the grounds that the disease or condition does not occur in this patient population..

2.2. Non-clinical aspects

No new non- clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

The Vidaza environmental risk assessment previously submitted (De Roode, 2010) was based on prevalence of MDS in the EU and has been updated to support an application for a new therapeutic indication based on the EMEA/CHMP/SWP/4447/00 guideline and the EMA/CHMP/SWP/44609/2010 Q&A document on ERA.

The initial (Phase I) Predicted Environmental Concentration in surface water ($PEC_{SURFACEWATER}$; assuming no human metabolism and no environmental dissipation) was calculated to be 0.0103 µg/L and hence at the trigger value of 0.01 µg/L. Refinement of the $PEC_{SURFACEWATER}$ calculation (Phase IIB) revealed a concentration of 0.00035 µg/L, which is ~1/30th of the action limit.

Of note: The questions and answers on the EMA guidance (Committee, 2011) indicates that a further refinement of the F_{pen} is possible based on the posology. This further refinement was taken into account in calculating the total $PEC_{SURFACEWATER}$ for both the indications MDS and AML resulting in a lower total $PEC_{SURFACEWATER}$ (0.010 µg/L) compared to the 2010 value calculated for MDS only.

An environmental toxicity, physical-chemical and fate profile (Phase IIA) was established for azacitidine, based on prolonged toxicity studies in aquatic organisms, an activated sewage sludge respiration inhibition test, a ready biodegradability test and a sludge adsorption coefficient (Koc). These studies were all conducted in accordance with GLP and allowed a Predicted No Effect Concentration (PNEC) derivation.

PEC/PNEC ratio for Sewage Treatment Plant (STP) microorganisms, aquatic organisms and groundwater did not exceed the relevant trigger. Hence, the risk to the STP, the aquatic environment and the groundwater compartment is concluded to be low.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of azacitidine.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 1 Overview of studies submitted in support of current application for extension of indication.

Study Identifier Publication	Number of Study Centers Location(s)	Design Control Type	Study and Control Drugs Dose, Route, and Regimen	Study Objectives	Study Start Enrollment Status, Date Planned/Total Enrollment	Duration	Gender Median Age (Years) (Range)	Diagnosis Key Inclusion Criteria	Primary Endpoint
AZA PH GL 2003 CL 001 Supportive study	79 centers US, EU, Australia, Russia	Open-label, prospective, randomized, comparative, controlled, multicenter	AZA SC injection 75 mg/m^2/day x 7 days + BSC. Dose could be decreased based on hematologic or renal toxicity- versus Conventional Care: 1) BSC only; or 2) Cytarabine SC 20 mg/m^2/day x 14 days +BSC; or 3) Standard chemotherapy up to 3 cycles (cytarabine + anthracycline IV) + BSC	Efficacy (survival); Safety, Pharmaco-economics	24 Nov 2003, Completed 24 Jul 2007 354/358	AZA: 7 day dosing every 28 days x 6 cycles minimum. Low-dose cytarabine: 14 day dosing every 28-42 days x 4 cycles minimum. Standard chemotherapy: induction, 1 cycle; consolidation max 2 cycles.	Aza: 132M/47F 69 (42-83) CCR: 119M/60F 70 (38-88)	MDS subtypes RAEB or RAEB-T (FAB)/ AML with 20% to 30 % blasts and multilineage dysplasia (WHO) with International Prognostic Scoring System score of Intermediate-2 or High, ECOG performance status of 0-2, life expectancy ≥3 months	Efficacy: OS

AML = acute myeloid leukemia; ANC = absolute neutrophil count; Ara-C = cytarabine; AZA = azacitidine; BID = twice daily; BSC = best supportive care; C = cycle; CCR = conventional care regimen; CR = complete remission; CRi = CR with incomplete blood count recovery; ECOG = Eastern Cooperative Oncology Group; EU = European Union; F = female; FAB = French American British; IC = intensive chemotherapy; IV = intravenous; LDAC = low-dose cytarabine; M = male; max = maximum; MDS = myelodysplastic syndrome; OS = overall survival; PD = progressive disease; PR = partial remission; PS = performance status; RAEB = refractory anemia with excess blasts; RAEB-T = refractory anemia with excess blasts in transformation; RBC = red blood cell; SC = subcutaneous; UK = United Kingdom; US = United States; vs = versus; WHO = World Health Organization.

[a] Subjects were stratified by CCR selection (IC versus LDAC or BSC), ECOG PS at baseline (0 or 1 vs 2), and cytogenetics (intermediate risk vs poor risk). No crossover between groups was permitted.

[b] Best supportive care included treatment with RBC or whole blood transfusions, fresh frozen plasma transfusions, platelet transfusions, antibiotic and/or antifungal therapy, and nutritional support. Hydroxyurea use was permitted as described in Report AZA-AML-001, Section 9.4.7.

[c] Subjects randomized to AZA, intensive chemotherapy, or LDAC also could receive BSC as needed per investigator discretion.

[d] Subjects who attained CR, CRi, or PR could receive 1 to 2 consolidation cycles; other subjects received BSC only. The first consolidation therapy started between Day 28 and Day 70 from start of induction therapy, upon recovery of ANC to $\geq 1.0 \times 10^9$/L and platelets to $\geq 75 \times 10^9$/L. Similarly, the second consolidation cycle, if given, started between Day 28 and Day 70 from start of the first consolidation therapy. Following consolidation, subjects could receive only BSC, if required.

2.3.2. Pharmacokinetics

For this new indication, no new pharmacokinetic studies were submitted. New pharmacokinetic studies are not necessary, because the dose regimen of 75 mg/m^2/day for 7 days per 28 days recommended for the new indication (i.e. the elderly patients (>=65 yrs) with AML (>30% marrow blasts)) is the same as that for approved indications. Regarding the influence of reduced renal function in elderly patients, this issue was addressed previously for approved indications that no specific dose adjustments were recommended for elderly. Thus, no further pharmacokinetic study in elderly patients is necessary.

2.3.3. Pharmacodynamics

No new clinical pharmacology studies for azacitidine have been conducted in support of the proposed new indication in elderly AML (> 30% blasts). The absence of additional studies is acceptable because of the close relationship between the currently approved indications and the currently proposed indication.

2.3.4. Conclusions on clinical pharmacology

The absence of additional studies pharmacology and pharmacokinetic is acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study(ies)

No new dose-response studies were provided. The dose regimen recommended for the new indication (i.e. the elderly patients (>=65 yrs) with AML (>30% marrow blasts)) is the same as that for approved indications.

2.4.2. Main study

Study AZA-AML-001: A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL, STUDY OF AZACITIDINE (VIDAZA) VERSUS CONVENTIONAL CARE REGIMENS FOR THE TREATMENT OF OLDER SUBJECTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA

Methods

Study participants

The study population consists of subjects who are ⩾ 65 years old with newly diagnosed, histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease with > 30% bone marrow blasts and who are not eligible for haematopoietic stem cell transplantation. The inclusion and exclusion criteria define a heterogeneous intermediate/high risk AML population with adequate organ function and ECOG performance status of 2 or less. A white blood cell (WBC) count of > 15 x 10^9/L at screening and randomization was one of the exclusion criteria. This cut-off value was chosen with guidance from members of the study Steering Committee as an adequate value to limit the possibility that highly proliferative subjects could proliferate out of control before a lower intensity therapy could be effective in controlling the disease.

Inclusion criteria:

1. Diagnosis of one of the following:

- Newly diagnosed, histologically confirmed de novo AML or

- Acute myeloid leukemia secondary to prior myelodysplastic disease not treated with azacitidine, decitabine, or cytarabine or

- Acute myeloid leukemia secondary to exposure to potentially leukemogenic therapies or agents (eg, radiation therapy, alkylating agents, topoisomerase II inhibitors) with the primary malignancy in remission for at least 2 years;

2. Bone marrow blasts > 30%;

3. Male or female subjects ⩾ 65 years of age at the time of signing the ICF;

4. Eastern Cooperative Oncology Group performance status of 0, 1, or 2;

5. Adequate organ function, defined as: Serum bilirubin ⩽ 1.5 times the upper limit of normal (ULN); Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ⩽ 2.5 times the ULN; Serum creatinine ⩽1.5 times the ULN;

6. Females of childbearing potential (FCBP)1 had to:

   - Agree to the use of a physician-approved contraceptive method (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) while on azacitidine; and for 3 months following the last dose of azacitidine; and

   - Have a negative serum pregnancy test within 72 hours prior to starting study therapy;

7. Male subjects with a female partner of childbearing potential had to agree to the use of a physician-approved contraceptive method throughout the course of the study and avoid fathering a child during the course of the study and for 3 months (6 months in Canada) following the last dose of azacitidine;

8. Understood and voluntarily signed an informed consent document prior to any study related assessments/procedures being conducted;

9. Able to adhere to the study visit schedule and other protocol requirements.

Exclusion Criteria:

1. Previous cytotoxic (except hydroxyurea which was allowed up to 2 weeks prior to obtaining the Screening hematology sample) or biologic treatment for AML;

2. Previous treatment with azacitidine, decitabine, or cytarabine;

3. Prior use of targeted therapy agents (eg, FLT3 inhibitors, other kinase inhibitors);

4. Suspected or proven acute promyelocytic leukemia (French-American-British [FAB] M3) based on morphology, immunophenotype, molecular assay, or karyotype; or AML with previous hematologic disorder such as chronic myelogenous leukemia or myeloproliferative neoplasms;

5. Acute myeloid leukemia associated with inv(16), t(8;21), t(16;16), t(15;17), or t(9;22) karyotypes or molecular evidence of such translocations;

6. Prior bone marrow or stem cell transplantation;

7. White blood cell count > 15 x 10^9/L at Screening;

a. Hydroxyurea was not allowed to attain a WBC count $\leqslant 15 \times 10^9$/L;

8. Proven central nervous system leukemia;

9. Inaspirable bone marrow;

10. Candidate for allogeneic bone marrow or stem cell transplant;

11. Diagnosis of malignant disease within the previous 12 months (excluding basal cell carcinoma of the skin without complications, “in-situ” carcinoma of the cervix or breast, or other local malignancy excised or irradiated with a high probability of cure);

12. Malignant hepatic tumors;

13. Unstable angina, significant cardiac arrhythmia, or New York Heart Association (NYHA) class 3 or 4 congestive heart failure (Appendix 16.1.1, Study Protocol AZA-AML-001, Appendix D);

14. Pregnant or lactating females;

15. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics or other treatment);

16. Active viral infection with known human immunodeficiency virus (HIV) or viral hepatitis type B or C;

17. Known or suspected hypersensitivity to azacitidine or mannitol;

18. Use of any other experimental drug or therapy within 28 days prior to Day 1 of Cycle 1;

19. Unwilling or unable to complete patient reported outcome assessments without assistance or with minimal assistance from trained site personnel and/or caregiver;

20. Any condition, including the presence of laboratory abnormalities, which placed the subject at unacceptable risk if he/she were to participate in the study;

21. Any significant medical condition, laboratory abnormality, or psychiatric illness that would have interfered or prevented the subject from participating in the study;

22. Any condition that confounded the ability to interpret data from the study.

Treatments

Treatment options for the conventional care regimens were assigned by the investigator before randomisation, based on local practice and on evaluation of the subject’s underlying disease condition.

Following the assignment and documentation of the CCR by the investigator, subjects were to be randomized in a 1:1 ratio into one of two treatment arms in the study:

- Azacitidine SC at 75 mg/m^2/day for 7 days every 28 days; or
- CCR as assigned by the investigator prior to randomization. The 3 CCRs that subjects could be assigned to included:
  - Intensive chemotherapy: intravenous (IV) cytarabine in conjunction with an anthracycline in a “7+3” regimen, plus BSC; or
  - Low-dose cytarabine (LDAC): 20 mg subcutaneously (SC), twice daily (BID) for 10 days, every 28 days, plus BSC; or
  - Best supportive care (BSC) only.

The number of cycles was not fixed. For azacitidine or LDAC treated subjects, the aim was at least 6 or 4 treatment cycles, respectively. For the subjects treated with intensive chemotherapy, the first (induction) cycle should have been followed by a maximum of 2 consolidation cycles. Following the consolidation phase of the intensive chemotherapy regime, the subject could continue in the study, receiving best supportive care, as appropriate.

Objectives

The **primary objective** of the study was to demonstrate superiority in overall survival of azacitidine compared with the combined conventional care regimens in subjects aged 65 years or more who had newly diagnosed AML with more than 30% bone marrow blasts according to WHO, and who were not eligible for HSCT.

The **secondary objectives** of the study were to determine:

- the one-year OS rate in the azacitidine treatment arm compared with the combined conventional care regimens (CCRs)
- the effect of azacitidine compared with the combined CCRs on event-free survival (EFS)
- the effect of azacitidine compared with the combined CCRs on relapse-free survival (RFS)
- the effect of azacitidine compared with the combined CCRs on overall remission rate (CR + morphologic complete remission with incomplete blood count recovery [CRi]) and duration of remission
- the effect of azacitidine compared with the combined CCRs on cytogenetic complete remission rate (CRc)
- the safety and toxicity of azacitidine relative to the CCRs;
- the effect of azacitidine compared with the combined conventional care regimens on health-related quality of life (HRQoL) and healthcare resource utilization (HRU).

The **exploratory objectives** of the study were:

- To identify molecular markers in the bone marrow at baseline that were predictive of response or nonresponse to azacitidine
- To identify molecular markers in the bone marrow during therapy that were associated with response or nonresponse to azacitidine.

Outcomes/endpoints

The primary endpoint of the study was OS, defined as time from randomization to death from any cause. Subjects surviving at the end of the follow-up period or who withdrew consent to follow-up were censored at the date of last contact. Subjects who were lost to follow-up were censored at the date last known alive.

Secondary endpoints were: One-year overall survival rate; Event-free survival (EFS); Relapse-free survival (RFS); Overall remission rate (CR + CRi); Duration of remission (CR + CRi); Cytogenetic complete remission rate (CRc); Safety / tolerability (type, frequency, severity, and relationship of adverse events to study treatments; physical examinations, vital signs; clinical laboratory evaluations, and concomitant medication/therapy); Patient-reported outcomes utilizing the European Organization for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30); and Measures of healthcare resource utilization.

Event-free survival was defined as the interval from the date of randomization to the date of treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or lost to follow-up, whichever occurs first. Subjects who are still alive and in continuous CR/CRi were to be censored at the date of last follow-up.

Relapse-free survival was defined only for subjects that achieve CR and CRi and is measured as the interval from the date of first documented leukemia-free state (defined as less than 5% blasts in an aspirate sample) to the date of disease relapse, death from any cause, or lost to follow-up, whichever occurs first, censoring for subjects alive in continuous CR/CRi.

Disease response was assessed using the Modified IWG AML response criteria (Cheson, 2003).

Progressive Disease (PD) was defined as 1) a > 50% increase in bone marrow blast count percentage from the baseline bone marrow blast count that persists for at least 2 bone marrow assessments separated by at least 1 month, unless the baseline bone marrow blast count is > 70%, in which case, a finding of > 70% blasts that persists for 2 post-baseline bone marrow assessments separated by at least 1 month would be considered progression, or 2) a doubling of the baseline absolute peripheral blood blast count that persists for at least 7 days and the final absolute peripheral blood blast count is > 10 x 10^9/L. The date of progressive disease is defined as the first date that there was either a > 50% increase in bone marrow blast count from baseline, a persistence of bone marrow blasts > 70% in subjects with a baseline bone marrow blast count of > 70%, or a doubling of the peripheral blood blast count.

Sample size

The effect of azacitidine vs CCR was assumed to be 10.5 vs 7.5 months (HR=0.71), for which 374 deaths were required to obtain 90% power at alpha=0.05 two-sided. Given 19 months accrual, 12 month follow-up, 240 vs 240 subjects were planned to be randomized.

Randomisation

Subjects were to be randomised in a 1:1 ratio into 1 of 2 treatment arms in the study.

Subjects were stratified on

- CCR selection: intensive chemotherapy vs (low dose cytarabine or BSC alone) i.e. two levels
- ECOG PS 0-1 vs 2
- Cytogenetics (intermediate v poor-risk)

Stratified blocked randomization was used (based on the above stratification factors) and implemented by IVRS. Blocking was documented but not included in the SAP, since the trial was open-label.
No crossover between any of the treatment groups was permitted.

Blinding (masking)
Study AZA-AML-001 was an open-label study. Central review of haematologic responses and cytogenetic laboratory samples were performed with all central reviewers blinded to subject treatment assignment. The evaluations by central review were used for the statistical efficacy analyses.

Statistical methods
The primary efficacy variable, time to death from any cause, was to be analyzed using a stratified log-rank test, stratifying for treatment, ECOG, and cytogenetic risk. The analysis was to be

performed on the intent-to-treat (ITT) population that includes all subjects randomized. No interim analyses were performed.

Results

Participant flow

The participant flow is presented in Figure 1.

A total of 672 subjects were screened for participation in the study at 107 investigational sites; 184 subjects (27.4%) failed screening. The reasons for screening failure were exclusion criteria met in 94 subjects, with WBC count higher than 15 x 10^9/L (41/672 subjects; 6.1%) as the most frequently met exclusion criteria, and inclusion criteria not met in 98 subjects, with not having BM blasts more than 30% (35/672 subjects; 5.2%) as the most frequent unmet inclusion criteria. The reasons for screening failure mainly concern disease characteristics, thus contributing to the definition of the disease.

The reasons why patients were not eligible for HSCT and why patients were not eligible for intensive chemotherapy were collected. Of the 44 patients in the control group receiving intensive chemotherapy, 43 were not eligible for transplant because of age, other reasons included comorbidities (5), no acceptable donor (1) and/or subject decision (1) (Figure 2).

Figure 1 Investigator conventional care regimen selection

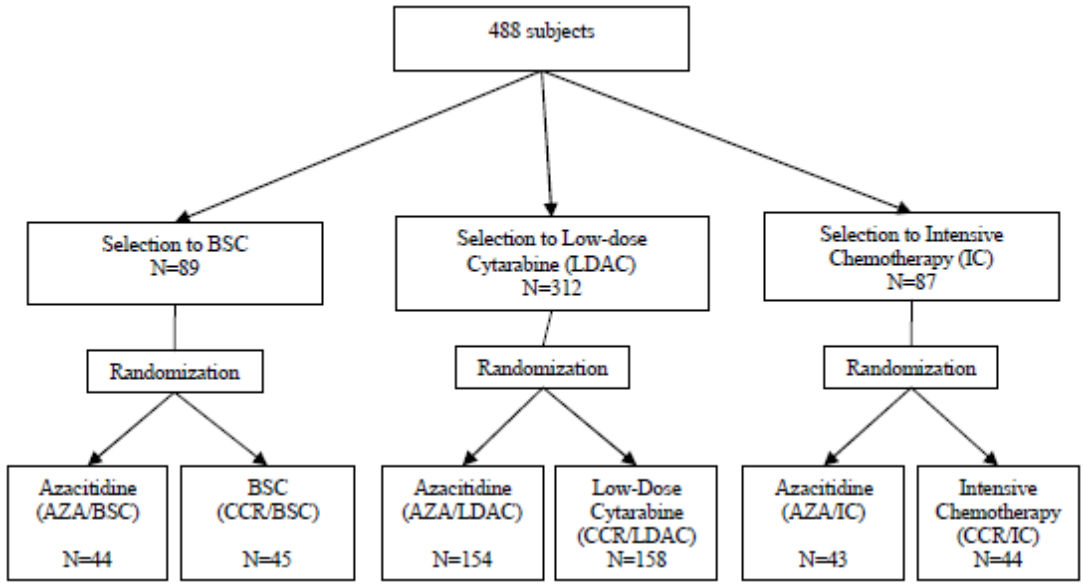
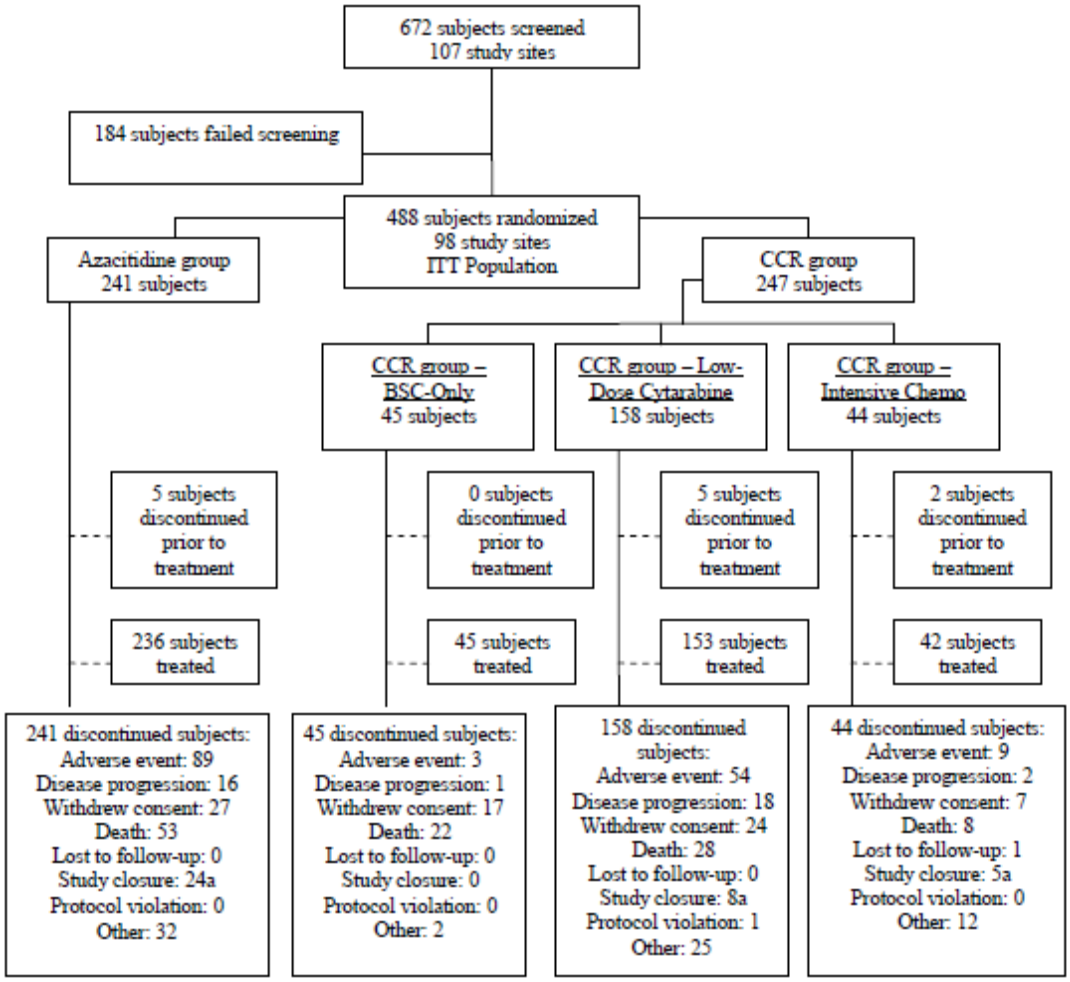


Figure 2 Subject disposition



BSC = best supportive care; CCR = conventional care regimen; Chemo = chemotherapy
a Subjects who were receiving study drug in the Treatment Phase of the study at the time of study closure.

Recruitment

This was a multicentre, international Phase 3 study conducted at 107 investigational sites in 18 countries from different geographic regions. Overall, 107 investigational sites screened subjects and 98 sites randomized subjects. Date first subject screened: 04 Oct 2010; date last subject completed: 22 Jan 2014.

Conduct of the study

The initial study protocol (dated 27 Oct 2009) was amended four times during the study. These amendments mostly concerned administrative and textual modification/clarifications to various sections of the protocol. The amendments are not expected to have significantly impacted the conduct of the study, the population included or the outcome.

In the full ITT population, major protocol violations were observed in the following categories: safety assessments (68 subjects, mainly delayed reporting of an SAE), informed consent (44 subjects, mainly date on consent form or not updating consent form), study drug (29 subjects, mainly (uncertainties on) the refrigeration time or use of an other stock of study drug than specified in the protocol), exclusion criteria (6 subjects), efficacy assessments (5 subjects), inclusion criteria (4 subjects), concomitant medication (1 subject), and other (1 subject). The number of major protocol

violations was generally similar in the azacitidine and CCR treatment groups, except those specifically related to the study drug.

Baseline data

Table 2 Demographic data and baseline characteristics (ITT)

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
Age (years)						
Median	75.0	75.0	78.0	75.0	70.5	75.0
Min, Max	64 [a], 91	65, 89	67, 89	65, 88	65, 81	64, 91
Age Group - n (%)						
< 75 years	103 (42.7)	120 (48.6)	13 (28.9)	75 (47.5)	32 (72.7)	223 (45.7)
≥ 75 years	138 (57.3)	127 (51.4)	32 (71.1)	83 (52.5)	12 (27.3)	265 (54.3)
Sex - n (%)						
Male	139 (57.7)	149 (60.3)	29 (64.4)	94 (59.5)	26 (59.1)	288 (59.0)
Female	102 (42.3)	98 (39.7)	16 (35.6)	64 (40.5)	18 (40.9)	200 (41.0)
Geographic Region - n (%) [b]						
North America / Australia	45 (18.7)	47 (19.0)	13 (28.9)	29 (18.4)	5 (11.4)	92 (18.9)
Western Europe / Israel	116 (48.1)	122 (49.4)	26 (57.8)	74 (46.8)	22 (50.0)	238 (48.8)
Eastern Europe	46 (19.1)	44 (17.8)	0	37 (23.4)	7 (15.9)	90 (18.4)
Asia	34 (14.1)	34 (13.8)	6 (13.3)	18 (11.4)	10 (22.7)	68 (13.9)
Race - n (%)						
White	185 (76.8)	182 (73.7)	37 (82.2)	116 (73.4)	29 (65.9)	367 (75.2)
Black	2 (0.8)	1 (0.4)	0	1 (0.6)	0	3 (0.6)
Asian	37 (15.4)	34 (13.8)	6 (13.3)	18 (11.4)	10 (22.7)	71 (14.5)
Hawaiian/Pacific Islander	1 (0.4)	0	0	0	0	1 (0.2)
American Indian/Alaska Native	0	0	0	0	0	0
Other	1 (0.4)	0	0	0	0	1 (0.2)
Not Applicable	15 (6.2)	30 (12.1)	2 (4.4)	23 (14.6)	5 (11.4)	45 (9.2)

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
Weight (kg)						
Median	71.8	71.0	73.0	70.7	71.1	71.1
Min, Max	36, 141	34, 125	44, 108	34, 125	43, 120	34, 141
BSA (kg/ m²) [c]						
Median	1.8	1.8	1.8	1.8	1.8	1.8
Min, Max	1, 2	1, 2	1, 2	1, 2	1, 2	1, 2

[a] One subject was 64 years and 11 months old at study entry.

[b] North America = United States and Canada; Western Europe = Austria, Belgium, France, Germany, Italy, Spain, The Netherlands, United Kingdom; Eastern Europe = Czech Republic, Poland, and Russia; Asia = China, South Korea, and Taiwan.
[c] BSA (m^2) = weight (kg)0.425 x height (cm)0.725 / 139.2.
Note: Percentages are based on the number of subjects in each treatment group

Table 3 Baseline Disease Characteristics: Acute Myeloid Leukaemia Diagnosis Performance status and prior therapy (ITT)

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
WHO AML Classification - n (%)						
AML with myelodysplasia-related changes	75 (31.1)	83 (33.6)	20 (44.4)	50 (31.6)	13 (29.5)	158 (32.4)
Therapy-related myeloid neoplasms	8 (3.3)	12 (4.9)	2 (4.4)	9 (5.7)	1 (2.3)	20 (4.1)
AML with recurrent genetic abnormalities	5 (2.1)	9 (3.6)	1 (2.2)	4 (2.5)	4 (9.1)	14 (2.9)
AML not otherwise specified	153 (63.5)	143 (57.9)	22 (48.9)	95 (60.1)	26 (59.1)	296 (60.7)
Prior History of MDS - n (%)						
Yes	49 (20.3)	38 (15.4)	11 (24.4)	23 (14.6)	4 (9.1)	87 (17.8)
Primary	46 (19.1)	35 (14.2)	11 (24.4)	20 (12.7)	4 (9.1)	81 (16.6)
Secondary	3 (1.2)	3 (1.2)	0	3 (1.9)	0	6 (1.2)
No	192 (79.7)	209 (84.6)	34 (75.6)	135 (85.4)	40 (90.9)	401 (82.2)
Time Since Original AML Diagnosis (months)						
Median	0.3	0.4	0.7	0.3	0.2	0.4
Min, Max	0 , 19.8	-0.2 [a], 20.2	0 , 20.1	-0.2 [a], 20.2	0 , 4.4	-0.2 [a], 20.2
ECOG Performance Status - n(%) [b]						
Grade 0	54 (22.4)	57 (23.1)	11 (24.4)	36 (22.8)	10 (22.7)	111 (22.7)
Grade 1	132 (54.8)	132 (53.4)	19 (42.2)	87 (55.1)	26 (59.1)	264 (54.1)
Grade 2	55 (22.8)	58 (23.5)	15 (33.3)	35 (22.2)	8 (18.2)	113 (23.2)
Cytogenetic Risk Status, Local - n (%) [b]						
Intermediate	159 (66.0)	159 (64.4)	28 (62.2)	102 (64.6)	29 (65.9)	318 (65.2)
Normal	118 (49.0)	105 (42.5)	22 (48.9)	65 (41.1)	18 (40.9)	223 (45.7)
Poor [c]	82 (34.0)	88 (35.6)	17 (37.8)	56 (35.4)	15 (34.1)	170 (34.8)
Cytogenetic Risk Status, Central - n (%) [b]						
Intermediate	155 (64.3)	160 (64.8)	29 (64.4)	104 (65.8)	27 (61.4)	315 (64.5)
Normal	113 (46.9)	105 (42.5)	23 (51.1)	65 (41.1)	17 (38.6)	218 (44.7)
Poor [d]	44 (18.3)	44 (17.8)	6 (13.3)	29 (18.4)	9 (20.5)	88 (18.0)
Very Poor [e]	41 (17.0)	41 (16.6)	10 (22.2)	25 (15.8)	6 (13.6)	82 (16.8)

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
Prior Therapies - n (%)						
Subjects with at least one prior systemic anti-cancer therapy	8 (3.3)	25 (10.1)	4 (8.9)	19 (12.0)	2 (4.5)	33 (6.8)
Subjects with at least one prior radiation therapy	17 (7.1)	17 (6.9)	2 (4.4)	13 (8.2)	2 (4.5)	34 (7.0)

[a] Two subjects had the formal diagnosis of AML after informed consent was given, but prior to study treatment.
[b] Status at randomization.
[c] Includes -5, -7, 5q-, 7q-, 11q23 abnormalities, inv(3), t(3;3), t(6;9), t(9;22) and complex (≥ abnormalities) that were not considered monosomal karyotype.
[d] Includes -5, -7, 5q-, 7q-, 11q23 abnormalities, inv(3), t(3;3), t(6;9), and complex (≥ abnormalities).
[e] Includes t(9;22), and monosomal karyotype and are included in the poor-risk category based on National Comprehensive Cancer Network guidelines.
Note: Percentages are based on the number of subjects in each treatment group.

Table 4 Baseline disease characteristics: bone marrow and peripheral blood blasts

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
Bone Marrow Blasts, Local (%) [a]						
n	241	247	45	158	44	488
Mean ± SDev	56.9 ± 20.90	55.4 ± 19.26	51.2 ± 16.79	56.6 ± 19.45	55.6 ± 20.72	56.2 ± 20.08
Median	53.0	50.0	47.0	50.0	55.0	52.0
Min, Max	18 [b] , 100	30 , 99	30 , 90	30 , 99	30 , 90	18 [b] , 100
Bone Marrow Blasts, Local (%) [a]						
≤ 50%	113 (46.9)	125 (50.6)	25 (55.6)	80 (50.6)	20 (45.5)	238 (48.8)
> 50%	128 (53.1)	122 (49.4)	20 (44.4)	78 (49.4)	24 (54.5)	250 (51.2)
Missing	0	0	0	0	0	0
Bone Marrow Blasts, Central (%) [a]						
n	238	243	44	155	44	481
Mean ± SDev	66.6 ± 24.71	70.2 ± 22.28	70.8 ± 22.76	71.3 ± 21.29	65.9 ± 25.11	68.5 ± 23.56
Median	70.0	74.0	76.0	74.0	70.0	72.0
Min [c], Max	2 , 100	4 , 100	9 , 100	4 , 100	6 , 100	2 , 100
Bone Marrow Blasts, Central (%) [a]						
≤ 50%	65 (27.0)	50 (20.2)	8 (17.8)	27 (17.1)	15 (34.1)	115 (23.6)
> 50%	173 (71.8)	193 (78.1)	36 (80.0)	128 (81.0)	29 (65.9)	366 (75.0)
Missing	3 (1.2)	4 (1.6)	1 (2.2)	3 (1.9)	0	7 (1.4)
Peripheral Blood Blasts (%) [a]						
n	228	235	42	153	40	463
Mean ± SDev	16.8 ± 21.75	16.7 ± 22.80	13.5 ± 22.42	17.5 ± 22.52	16.8 ± 24.52	16.7 ± 22.26
Median	6.0	6.0	3.5	6.0	6.5	6.0
Min, Max	0 , 93	0 , 90	0 , 89	0 , 90	0 , 86	0 , 93

Parameter	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
Peripheral Blood Blasts (10^9/L) [a]						
n	228	235	42	153	40	463
Mean ± SDev	1.3 ± 2.61	1.6 ± 6.06	1.1 ± 2.87	1.3 ± 3.81	3.3 ± 12.32	1.4 ± 4.69
Median	0.1	0.1	0.1	0.2	0.1	0.1
Min, Max	0 , 18	0 , 77	0 , 15	0 , 42	0 , 77	0 , 77

[a] Baseline was the last non-missing assessment on or prior to date of randomization.

[b] One subject had acute myelomonocytic leukemia where the bone marrow differential was 18.5% blasts and 21.5 % promonocytes, for a total leukemic cell count of 40%. The CRF did not allow the entry of the bone marrow promonocyte cell count.
[c] Subjects were randomized based on local pathology assessment of baseline bone marrow blast count. Baseline BM slides were retrospectively reviewed by the central pathology reviewer. In some cases, the baseline BM blast count was found to be less than 30% by the central pathology reviewer. These subjects were not removed from the study and were allowed to continue assigned treatment.
Note: Percentages are based on the number of subjects in each treatment group.

Numbers analysed

Table 5 Analysis populations

Analysis Population	Azacitidine				Conventional Care Regimen				Total (N = 488)
	BSC only (N = 44)	Low dose cytarabine (N = 154)	Intensive Chemo (N = 43)	AZA total (N = 241)	BSC only (N = 45)	Low dose cytarabine (N = 158)	Intensive Chemo (N = 44)	CCR total (N = 247)	
Intent to Treat [a]	44 (100.0)	154 (100.0)	43 (100.0)	241 (100.0)	45 (100.0)	158 (100.0)	44 (100.0)	247 (100.0)	488 (100.0)
Safety [b]	42 (95.5)	151 (98.1)	43 (100.0)	236 (97.9)	40 (88.9)	153 (96.8)	42 (95.5)	235 (95.1)	471 (96.5)
Evaluable [c]	35 (79.5)	114 (74.0)	30 (69.8)	179 (74.3)	25 (55.6)	132 (83.5)	34 (77.3)	191 (77.3)	370 (75.8)

[a] Subjects who were randomly assigned to one of the treatment groups.
[b] Randomized subjects who received at least 1 dose of study medication and had at least 1 post-dose safety assessment. BSC subjects were excluded from the safety analysis because they did not have at least 1 post-dose safety assessment.
[c] All ITT subjects who experienced no criteria for removal from Evaluable population during the study, received at least 1 cycle of treatment, and had at least 1 efficacy assessment performed.
Note: Percentages are based on the number of subjects randomized to each treatment group.

Of all subjects who discontinued treatment during the study for reasons other than study closure, 217 (90.0%) subjects discontinued azacitidine treatment compared with 234 (94.7%) subjects who discontinued conventional care treatment. Within the CCR group, the percentage of discontinuations was highest for the BSC only subjects (100%) and lowest for intensive chemotherapy subjects (88.6%).

Table 6. Follow-up treatments (Intent-to-treat population)

ATC1 Dictionary Level / Preferred Name[a]	Azacitidine (N = 241)	CCR total (N = 247)	Conventional Care Regimen			Total (N = 488)
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one follow-up treatment	**69 (28.6)**	**75 (30.4)**	**6 (13.3)**	**51 (32.3)**	**18 (40.9)**	**144 (29.5)**
Antiinfectives for systemic use	**1 (0.4)**	**0**	**0**	**0**	**0**	**1 (0.2)**
Chemotherapeutics	1 (0.4)	0	0	0	0	1 (0.2)
Antineoplastic and immunomodulating agents	**67 (27.8)**	**74 (30.0)**	**6 (13.3)**	**50 (31.6)**	**18 (40.9)**	**141 (28.9)**

Regarding the follow-up treatment within the investigator's choice of CCR subpopulations or within the respective azacitidine subpopulations see table 7 below.

Within the CCR treatment group, the percentage of subjects with at least 1 follow-up treatment was higher in the intensive chemotherapy group (n=18, 41.9%) compared to the low-dose cytarabine group (n=51, 32.3%), or the BSC only group (n=6, 13.3%).

Table 7. Selected follow-up treatments by preselection group (ITT)

ATC1 Dictionary Level / Preferred Name [a]	Preselected to BSC			Preselected to LDAC			Preselected to IC		
	AZA (N = 44)	BSC (N = 45)	Total (N = 89)	AZA (N = 154)	LDAC (N = 158)	Total (N = 312)	AZA (N = 43)	IC (N = 44)	Total (N = 87)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least one follow-up treatment	1 (2.3)	6 (13.3)	7 (7.9)	50 (32.5)	51 (32.3)	101 (32.4)	18 (41.9)	18 (40.9)	36 (41.4)
Antineoplastic and immunomodulating agents	1 (2.3)	6 (13.3)	7 (7.9)	49 (31.8)	50 (31.6)	99 (31.7)	17 (39.5)	18 (40.9)	35 (40.2)

Outcomes and estimation

Overall, 394 deaths (80.7%) occurred in the ITT population. Deaths were reported for 193 (80.1%) subjects in the azacitidine group and 201 (81.4%) subjects in the CCR group.

Primary endpoint: Overall survival

The Kaplan Meier (KM) plot of time to death from any cause for the ITT population is presented in Figure 3. After a median follow-up time of 24.4 months, the median OS was 10.4 months (95% CI = 8.0, 12.7) in the azacitidine group (N = 241) compared with 6.5 months (95% CI = 5.0, 8.6) in the CCR group (see

Table 8). The OS HR for the azacitidine group vs CCR was 0.85 (95% CI = 0.69, 1.03) with an observed difference in median OS of 3.8 months in favour of azacitidine. The difference between survival curves based on the log-rank test did not reach the predefined level of significance (log rank test, with a stratified p = 0.1009).

Figure 3 Kaplan-Meier plot of time to death from any cause (ITT population**)**

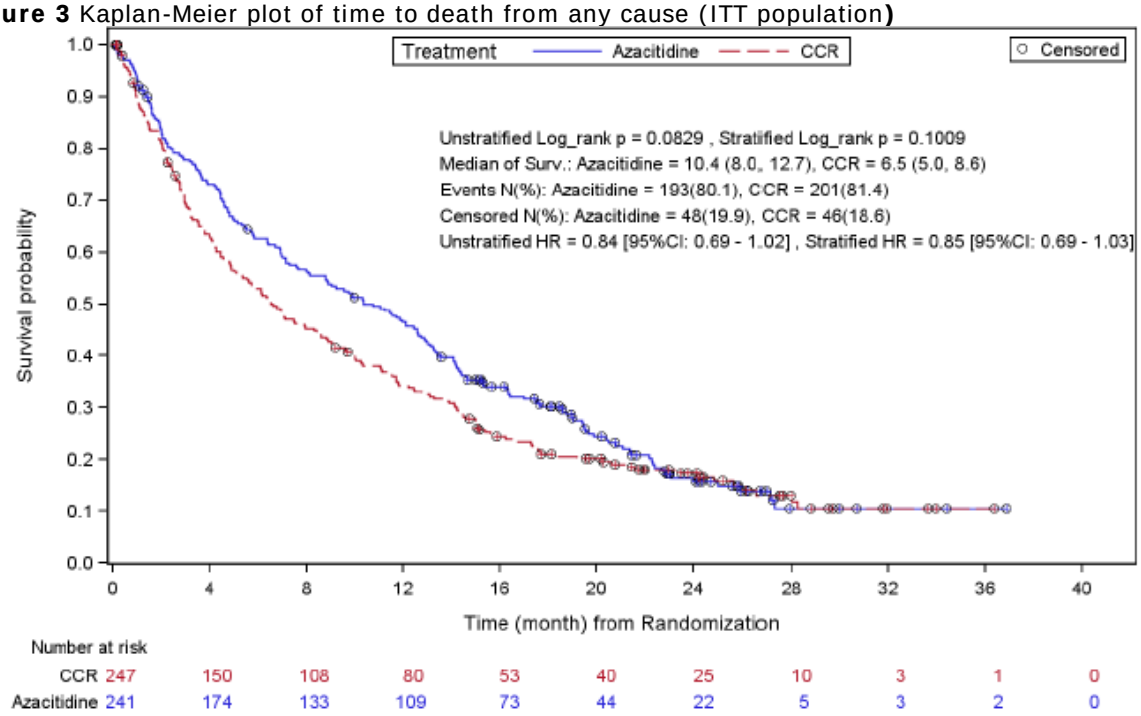


Table 8 Overview of OS in ITT population

	Azacitidine (N = 241)	**CCR (N = 247)**
Event (death), n (%)	193 (80.1)	201 (81.4)
Censored, n (%)	48 (19.9)	46 (18.6)
Median OS (95% CI)[a]	10.4 (8.0, 12.7)	6.5 (5.0, 8.6)
Difference (95% CI)	3.8 (1.0, 6.5)	
HR [AZA:CCR] (95% CI)[b]	0.85 (0.69, 1.03)	
Stratified log-rank test: p-value[c]	0.1009	
HR [AZA:CCR] (95% CI)[d]	0.84 (0.69, 1.02)	
Unstratified log-rank test: p-value[e]	0.0829	

[a] Median estimates are from an unstratified KM analysis. Differences are calculated as AZA - CCR. The CIs for the differences were derived using Kosorok's method (Kosorok, 1999).
[b] The HR is from a Cox proportional hazards model stratified by ECOG PS and cytogenetic risk status.
[c] The p-value is 2-sided from a log-rank test stratified by ECOG PS and cytogenetic risk status.
[d] The HR is from an unstratified Cox proportional hazards model.
[e] The p-value is 2-sided from an unstratified log-rank test.
Note: Unless otherwise indicated, percentages are based on the number of subjects in each treatment group. Overall survival is measured in months.

The most common reason for censoring was the subject being alive at the time of study closure (17.0% of subjects in the azacitidine treatment group and 14.6% of subjects in the CCR treatment group).

Figure 4 Hazard ratio and 95% confidence interval for OS by subgroup for azacitidine versus CCR

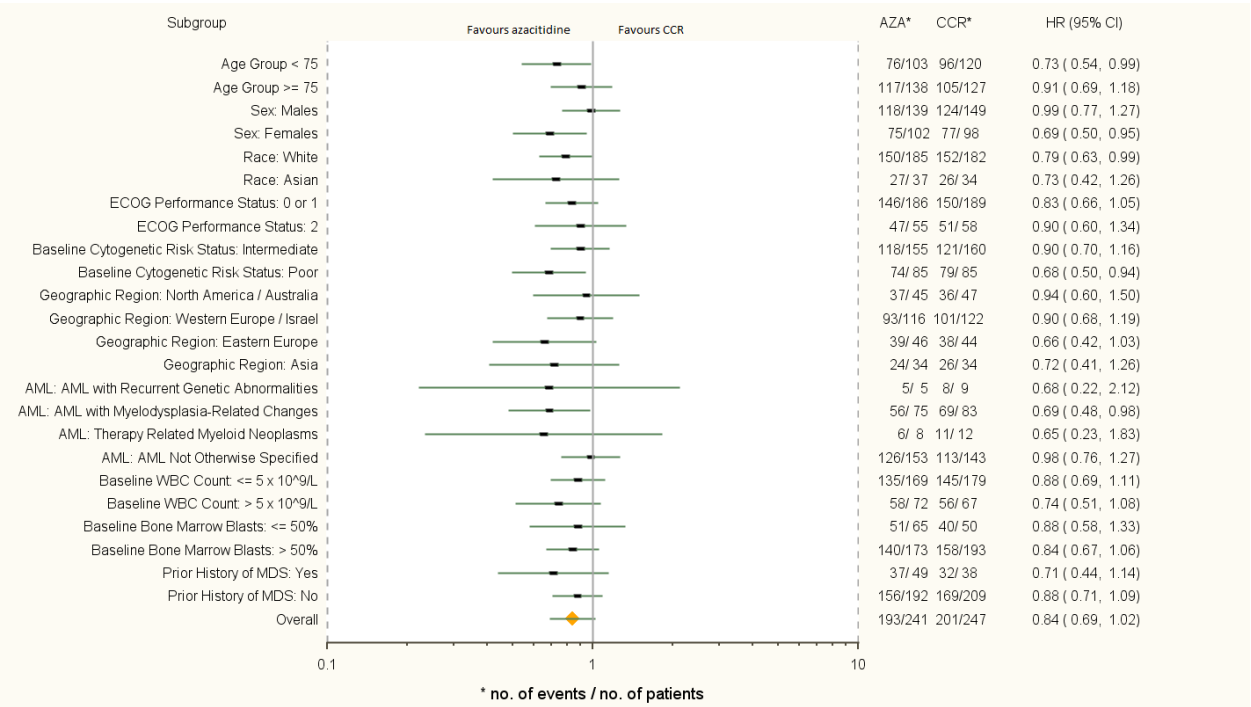


Table 9. OS analysis adjusted for prognostic factiors.

Post Hoc Overall Survival Adjusted for Selected Baseline Factors
(ITT Population)

Variable	Summary of Stepwise Selection [a] Score Chi-Square	P-value	Final Model [b] Hazard Ratio	95% CI	P-value
N=478 [c]					
Treatment (AZA vs CCR)			0.80	0.66,0.99	0.0355
Central Cytogenetic Risk Status (Intermediate vs Poor)	57.52	<0.0001	0.42	0.34,0.52	<0.0001
ECOG Performance Status (0/1 vs 2)	20.05	<0.0001	0.62	0.48,0.79	0.0001
Central Bone Marrow Blasts (%)	17.22	<0.0001	1.01	1.01,1.01	<0.0001
Investigator Pre-selection of CCR	14.36	0.0008			
Best Supportive Care vs Intensive Chemo			1.88	1.32,2.69	0.0005
Low-Dose Cytarabine vs Intensive Chemo			1.14	0.84,1.53	0.3990
Geographic Region	13.29	0.0040			
Asia vs Western Europe			1.19	0.86,1.64	0.2915
Eastern Europe vs Western Europe			1.73	1.30,2.31	0.0002
North American/Australia vs Western Europe			1.16	0.88,1.52	0.3036
Age (years)	5.47	0.0193	1.02	1.00,1.04	0.0219
AML Classification (Myelodysplastic Changes vs All Others)	2.98	0.0841	0.83	0.67,1.03	0.0973

[a] A stepwise selection procedure was employed to select covariates into a Cox model that included treatment. The significance level selecting a covariate into the model was set to 0.25; the significance level for retaining a covariate in the model was set to 0.15 Covariates that were considered but which did not meet the criterion for selection into the model were WBC (log transformed, continuous), prior history of MDS (yes, no), and sex (male, female). No covariates met the criterion for removal from the model after being selected into the model.
Covariates are displayed in the order in which they were selected into the model.
[b] The hazard ratio, 95% confidence intervals and p-value were estimated from a Cox model that included treatment and the covariates selected through the stepwise procedure described in [a].
[c] Subjects with a missing value for any covariate included in the final model are excluded from the analysis.

Sensitivity analysis

Several planned sensitivity analyses were performed to assess the impact on survival of the use of any subsequent therapy for AML, the use of a subsequent hypomethylating agent, and withdrawal from survival follow-up as an event (data not shown).

Secondary endpoints

Table 10 provides a summary of key secondary endpoints which are considered standard measures of activity in AML.

Table 10 Key efficacy secondary endpoints

	Azacitidine (N = 241)	**CCR (N = 247)**
1-year survival estimate (95% CI)	0.465 (0.40, 0.53)	0.343 (0.28, 0.40)
Haematologic Response by IRC (CR + CRi), n (%)	67 (27.8)	62 (25.1)
Morphologic CR by IRC, n (%)	47 (19.5)	54 (21.9)
Median EFS[a], months (95% CI)	6.7 (5.0, 8.8)	4.8 (3.8, 6.0)
Median RFS[b], months (95% CI)	9.3 (6.7, 12.4)	10.5 (7.3, 12.3)
Median Remission Duration[c], months (95% CI)	10.4 (7.2, 15.2) (N=67)	12.3 (9.0, 17.0) (N=62)

CR = complete remission; CRi = complete remission with incomplete blood count recovery; EFS = event-free survival; IRC = Independent Review Committee; RFS = relapse-free survival.
[a] Event = treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or lost to follow-up.
[b] Event = relapse after CR or CRi, or death.
[c] Duration of remission: time from the date CR or CRi was first documented until the date of documented relapse from CR or CRi for subjects who achieved CR or CRi.

Secondary endpoint results within preselected groups

The results for secondary endpoints within the low-dose cytarabine preselection group were consistent with the improvement seen in the primary endpoint of OS. Specifically, there was an increase of 14.5% (48.5% vs 34.0%) in the 1-year survival estimate in azacitidine-treated subjects compared with low-dose cytarabine-treated subjects. Median EFS was longer in azacitidine-treated subjects compared with the low-dose cytarabine-treated subjects (7.3 months vs 4.8 months). Median RFS (8.6 months vs 9.9 months), overall response rate (CR + CRi) were similar between the azacitidine and low-dose cytarabine groups.

Other endpoints

Transfusion (in)dependence

Table 11 Overview of RBC and platelet transfusion status: baseline versus on-treatment status

Baseline Transfusion Status Definition 2	Treatment Group	On-Treatment Transfusion Status			
		Independent		Dependent	
		n (%)	95% CI[a]	n (%)	95% CI[a]
RBC Transfusion Status					
Dependent	Azacitidine	65 (38.5)	(31.1-46.2)	104 (61.5)	(53.8-68.9)
	CCR	45 (27.6)	(20.9-35.1)	118 (72.4)	(64.9-79.1)
Independent	Azacitidine	40 (55.6)	(43.4-67.3)	32 (44.4)	(32.7-56.6)
	CCR	31 (36.9)	(26.6-48.1)	53 (63.1)	(51.9-73.4)
Platelet Transfusion Status					
Dependent	Azacitidine	41 (40.6)	(30.9-50.8)	60 (59.4)	(49.2-69.1)
	CCR	24 (29.3)	(19.7-40.4)	58 (70.7)	(59.6-80.3)
Independent	Azacitidine	101 (72.1)	(63.9-79.4)	39 (27.9)	(20.6-36.1)
	CCR	82 (49.7)	(41.8-57.6)	83 (50.3)	(42.4-58.2)

CCR = conventional care regimen; CI = confidence interval; RBC = red blood cell.
Definition 2: A subject was considered RBC/platelet transfusion independent at baseline if the subject had no RBC/platelet transfusions during the 56 days on or before randomization. A subject was considered RBC/platelet transfusion independent during the treatment period if the subject had no RBC/platelet transfusions during any consecutive 56 days or more (eg, Days 1 through 56, Days 2 through 57, etc.) during the treatment period.
[a] Exact 95% CIs for a proportion.

Growth factor use

According to the protocol, the use of Erythropoiesis-stimulating agents and myeloid growth factors (granulocyte colony-stimulating factor [G-CSF] and granulocyte macrophage colony-stimulating factor [GM-CSF]) was allowed. Given the few subjects who received erythropoiesis-stimulating agents during the study (n=5 in total), no impact on haematological values and/or transfusion dependence was expected.

Table 12: Summary of Subjects who Received Myeloid Growth Factors as a Concomitant Medication (Intent-to-treat Population)

	Azacitidine (N = 241)	CCR (N = 247)	Conventional Care Regimens		
			BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)
	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 myeloid growth factor	**57 (23.7)**	**71 (28.7)**	**4 (8.9)**	**40 (25.3)**	**27 (61.4)**
Number of courses of myeloid growth factor					
0	184 (76.3)	176 (71.3)	41 (91.1)	118 (74.7)	17 (38.6)
1	31 (12.9)	35 (14.2)	2 (4.4)	21 (13.3)	12 (27.3)
2-3	16 (6.6)	28 (11.3)	2 (4.4)	12 (7.6)	14 (31.8)
> 3	10 (4.1)	8 (3.2)	0	7 (4.4)	1 (2.3)

BSC = best supportive care; CCR = conventional care regimens.
Note: Percentages are based on the number of subjects per treatment group.
Source: Section 4, Appendix, Table 1.

Table 13: Cumulative Dose per Subject of Concomitant Myeloid Growth Factors for Subjects who Received Concomitant Myeloid Growth Factors (Intent-to-treat Population)

		Azacitidine (N = 241)	CCR (N = 247)	Conventional Care Regimens		
				BSC only (N = 45)	Low-dose Cytarabine (N = 158)	Intensive Chemotherapy (N = 44)
		n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 myeloid growth factor		**57 (23.7)**	**71 (28.7)**	**4 (8.9)**	**40 (25.3)**	**27 (61.4)**
Cumulative dose/subject						
Filgrastim/G-CSF/ GM-CSF (mcg)	N	45	51	3	26	22
	Mean (std)	4367.2 (5136.63)	3927.5 (4080.20)	800.0 (458.26)	3807.7 (4724.63)	4495.5 (3360.24)
	Median	2400	3000	900	3060	4350
	Min, Max	60, 28500	300, 25500	300, 1200	600, 25500	480, 11400
Lenograstim (mcg)	N	4	7	NA	5	2
	Mean (std)	675.3 (410.10)	2436.3 (2264.67)	NA	2630.0 (2741.78)	1952.0 (214.96)
	Median	699.5	1800	NA	750	1952
	Min, Max	250, 1052	420, 6000	NA	420, 6000	1800, 2104
Pegfilgrastim (mg)	N	5	10	NA	4	6
	Mean (std)	6.0 (0.0)	8.4 (4.16)	NA	10.5 (5.69)	7.0 (2.45)
	Median	6	6	NA	9	6
	Min, Max	6, 6	6, 17.9	NA	6, 17.9	6, 12

BSC = best supportive care; CCR = conventional care regimens; G-CSF = granulocyte colony-stimulating factor; GM-CSF = granulocyte-macrophage colony-stimulating factor; Max = maximum; mcg = microgram; Min = minimum; mg = milligram; NA = not applicable; Std=standard deviation.

Note: N reflects the number for subjects who received at least 1 myeloid growth factor and who had all data available for determining cumulative dose for at least 1 occurrence.

Source: Section 4, Appendix, Table 2.

Health-related Quality of Life

Health-related Quality of Life (HRQoL) assessment was complicated by a small sample size, a reduced number of evaluations received for the combined CCR group after Cycle 3, and a large variation in responses within treatment groups.

Within each treatment group, mean changes from baseline to the end-of-study visit varied, with wide distributions and standard deviations for the Fatigue, Dyspnoea, Physical Functioning, and Global Health Status/QoL domains, making it challenging to establish whether there were any true differences between treatment groups. In both groups, these domains appeared to improve slightly over time during treatment, but worsened or remained unchanged compared with baseline at end-of-study.

Thus, no firm conclusions can be drawn other than that the data seems to indicate that there is no detrimental effect of azacitidine on HRQoL when compared to combined CCR.

Table 14. EORTC QLQ-C30 assessment rates over all cycles for azacitidine and CCR - all subjects (ITT population)

Assessments	CCR (n=247)			AZA (n= 241)
	Best Supportive Care (n=45)	Intensive Chemotherapy (n=44)	Low Dose Cytarabine (n=158)	
Cycle 1 (Baseline) QoL Assessment	32/41 (78.0%)	40/42 (95.2%)	138/153 (90.2%)	210/237 (88.6%)
Cycle 3 QoL Assessment	14/21 (66.7%)	19/21 (90.5%)	80/89 (89.9%)	152/174 (87.4%)
Cycle 5 QoL Assessment	4/10 (40.0%)	13/16 (81.3%)	55/60 (91.7%)	127/146 (87.0%)
Cycle 7 QoL Assessment	2/4 (50.0%)	9/12 (75.0%)	47/51 (92.2%)	105/118 (89.0%)
Cycle 9 QoL Assessment	1/2 (50.0%)	8/9 (88.9%)	29/38 (76.3%)	89/98 (90.8%)
EOS QoL Assessment	4/34 (11.8%)	21/44 (47.7%)	60/147 (40.8%)	94/223 (42.2%)

Note: The PRO study population includes any ITT study participants with =1 active treatment and =1 PRO measurement item completed. ITT population includes all study participants randomized to the study. The evaluable population includes all mITT participants with successful HRQL assessment cycle assignment defined by time windows. NE is not estimable. a) QoL assessment rates are calculated as the number of patients having an EORTC QLQ-C30 assessment divided by the total number of patients receiving treatment at the scheduled treatment visit.
Abbreviations: AZA, Azacitidine; CCR, Conventional Care Regimen; EOS, End of Study

Table 15. Mean (Standard Deviation) Absolute Score Change from Baseline for Primary and Secondary Health-related Quality of Life Endpoints (HRQoL Evaluable Population)

Azacitidine Treatment Group
Mean Score Change from Baseline (SDev)

Domain	Cycle 3	Cycle 5	Cycle 7	Cycle 9	EOS
Fatigue	n=135	n=112	n=94	n=80	n=87
	−1.5 (24.69)	−2.8 (27.36)	−6.1[a] (26.90)	−9.0[a] (27.90)	8.9[a] (33.54)
Dyspnea	n=136	n=112	n=94	n=81	**n=87**
	5.1[a] (26.88)	3.9 (27.49)	0.4 (29.93)	−4.9 (26.93)	**12.6[a] (31.43)**
Physical Function	n=136	n=112	n=94	n=81	**n=87**
	−4.2[a] (17.98)	−4.4[a] (19.25)	1.6 (18.75)	3.5 (18.26)	**−13.0[a] (26.74)**
Global Health Status / QoL	n=134	n=112	n=94	n=80	n=87
	0.9 (20.97)	1.6 (22.50)	5.1 (25.84)	7.8[a] (27.28)	−4.4 (29.20)

CCR Treatment Group
Mean Score Change from Baseline (SDev)

Domain	Cycle 3	Cycle 5	Cycle 7	Cycle 9	EOS
Fatigue	n=101	n=66	**n=53**	**n=36**	n=80
	−1.9 (27.54)	−7.1[a] (27.61)	**−12.2[a] (30.45)**	**−10.2 (33.85)**	6.1 (34.19)
Dyspnea	n=101	n=66	n=53	n=36	n=80
	−1.7 (30.69)	−6.6 (28.18)	−8.8[a] (28.61)	−2.8 (26.87)	6.3 (35.22)
Physical Function	n=102	n=67	n=54	n=36	n=81
	−0.3 (18.85)	−1.3 (20.41)	1.5 (23.08)	−0.4 (22.81)	−9.4[a] (26.43)
Global Health Status / QoL	n=101	n=66	n=52	**n=36**	n=80
	3.8 (26.42)	9.0[a] (24.82)	8.7[a] (27.91)	**10.4[a] (23.09)**	−6.1 (27.90)

CCR = conventional care regimen; EOS = end of study; QoL = quality of life; SDev = standard deviation.
[a] Indicates within-group change ($p < 0.05$); p value was calculated using the paired t-test on the observed domain score, comparing each with baseline. **Bold text** indicates meaningful change (ie, group level change of at least 10 points between baseline and subsequent assessments). Negative change from baseline score on functional scale and Global Health Status/QoL indicates worsening functioning/global health status. Positive change from baseline on symptom scale indicates worsening symptoms. n-values indicated the number of assessments evaluable for a change-from-baseline calculation at the indicated domain and cycle.
Note: numbers in table are number of respondents (n) and mean (SDev).

Ancillary analyses

Post Hoc Analyses - influence of subsequent therapy on azacitidine vs combined CCR group

Three post-hoc analyses were performed to adjust for the effect of subsequent therapies using a stepwise variable selection procedure, which consisted of a series of forward selection and backward

elimination steps. This included a Cox-PH analyses and an IPCW model that was created to study the effect subsequent therapies (see Table 12).

Table 16 Post-hoc OS survival estimates adjusted for subsequent therapy

Estimation Method	Hazard Ratio (AZA versus CCR)	95% CI for Hazard Ratio	p value
Cox-PH unadjusted for baseline factors			
Adjusted for subsequent therapy (time dependent)	0.75	0.59, 0.94	0.0130
IPCW Cox-PH Models			
Unadjusted for baseline characteristics	0.77	0.61, 0.98	0.0310

IPCW = Inverse Probability of Censoring Weighted; ITT = intent-to-treat; PH = proportional hazards.

Post Hoc Overall Survival with IPCW [a] Adjustment for Subsequent Therapy
(ITT Population)

	Univariate Model			Multivariate Model [b]		
Variable	Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
N=488 [c]						
Treatment (AZA vs CCR)	0.77	0.61,0.98	0.0310	0.71	0.56,0.90	0.0047
Central Cytogenetic Risk Status (Intermediate vs Poor)				0.40	0.31,0.51	<0.0001
ECOG Performance Status (0/1 vs 2)				0.58	0.44,0.77	0.0002
Central Bone Marrow Blasts (%)				1.01	1.01,1.02	<0.0001
Investigator Pre-selection of CCR						
Best Supportive Care vs Intensive Chemo				2.64	1.74,4.01	<0.0001
Low-Dose Cytarabine vs Intensive Chemo				1.23	0.83,1.80	0.3029
Geographic Region						
Asia vs Western Europe				1.24	0.84,1.81	0.2812
Eastern Europe vs Western Europe				1.99	1.44,2.75	<0.0001
North American/Australia vs Western Europe				1.15	0.84,1.58	0.3752
Age (years)				1.03	1.00,1.05	0.0281
AML Classification (Myelodysplastic Changes vs All Others)				0.87	0.68,1.11	0.2501

[a] IPCW = Inverse probability of censoring weighted

[b] Baseline covariates included in the multivariate model were selected through the stepwise selection procedure

[c] Subjects with missing values for continuous covariates were assigned the mean value for the entire ITT population; missing values for centrally assessed cytogenetic risk and percentage bone marrow blasts were replaced with the local assessment.

Exploratory Analyses

OS results within preselected groups

In support of the primary efficacy analysis, planned exploratory analyses were conducted based on investigator selection to CCR using the same methods as for the primary analysis, without stratification.

Table 67 Summary of OS within investigator selection (ITT)

	BSC Only Selection		Low-dose cytarabine Selection		Intensive Chemotherapy Selection	
	Azacitidine (N = 44)	CCR (N = 45)	Azacitidine (N = 154)	CCR (N = 158)	Azacitidine (N = 43)	CCR (N = 44)
Events, n (%)	38 (86.4)	42 (93.3)	124 (80.5)	126 (79.7)	31 (72.1)	33 (75.0)

Median OS, months (95% CI)[a]	5.8 (3.6, 9.7)	3.7 (2.8, 5.7)	11.2 (8.8, 13.4)	6.4 (4.8, 9.1)	13.3 (7.2, 19.9)	12.2 (7.5, 15.1)
Hazard ratio (95% CI)[b]	0.60 (0.38, 0.95)		0.90 (0.70, 1.16)		0.85 (0.52, 1.38)	
Unstratified log-rank test: p-value[c]	0.0288		0.4270		0.5032	

[a] Median, 25th, and 75th percentile estimates of OS are from an unstratified Kaplan-Meier analysis. Differences are calculated as AZA - CCR. The CIs for the differences were derived using Kosorok's method.
[b] The hazard ratio is from an unstratified Cox proportional hazards model.
[c] The p-value is two-sided from an unstratified log-rank test.

Secondary endpoints – analyses within CCR subgroups

The Applicant also performed an analysis (post-hoc) of the secondary endpoints within the investigator selection subpopulations. The results are depicted in Table 14.

Table 78 Key secondary endpoints within investigator selection group

	BSC		**Low-dose cytarabine**		**IC**	
	AZA (N=44)	**CCR (N =45)**	**AZA (N=154)**	**CCR (N =158)**	**AZA (N=43)**	**CCR (N =44)**
1-year survival estimate (95% CI)	30.3% (17.5, 44.2)	18.6% (8.7, 31.4)	48.5% (40.3, 56.2)	34.0% (26.6, 41.6)	55.8% (39.8, 69.1)	50.9% (35.2, 64.6)
Haematologic Response by IRC (CR + CRi), n (%)	7 (15.9)	0	42 (27.3)	41 (25.9)	18 (41.9)	21 (47.7)
Morphologic CR by IRC, n (%)	6 (13.6)	0	28 (18.2)	38 (24.1)	13 (30.2)	16 (36.4)
Median EFS[a], months (95% CI)	4.5 (2.1, 7.6)	3.1 (2.6, 4.0)	7.3 (4.6, 9.5)	4.8 (3.8, 6.1)	8.1 (4.5, 12.3)	9.7 (5.0, 13.7)
Median RFS[b], months (95% CI)	n.d.	n.d.	8.6 (6.7, 12.4)	9.9 (5.4, 12.3)	10.8 (3.7, 18.1)	12.1 (4.9, 19.8)
Median Remission Duration[c], months (95% CI)	n.d.	n.d.	9.2 (6.7, 12.8)	11.2 (5.7, 16.8)	17.3 (3.7, DNE)	19.8 (8.2, 26.3)

[a] Event = treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or lost to follow-up.
[b] Event = relapse after CR or CRi, or death.
[c] Duration of remission: time from the date CR or CRi was first documented until the date of documented relapse from CR or CRi for subjects who achieved CR or CRi.

The results of the 1-year survival endpoint for the investigator's choice of CCR subpopulations are in line with that observed for the combined CCR study population. A suggestion of an improved median EFS in the azacitidine treated subjects is seen within the BSC subpopulation and the low dose cytarabine subpopulation. In contrast, in the subjects selected to receive intensive chemotherapy results of the EFS were in favour of the intensive chemotherapy group. As with the combined CCR study population, also the other key secondary endpoints show no substantial difference between the benefit of treatment of intensive chemotherapy or azacitidine. Notably, there are clear differences in secondary endpoints between the subgroups of azacitidine treated subjects (e.g. 1 year survival estimate is 30% within the BSC-selected azacitidine treated patients, while it is 56% in the intensive

chemotherapy selected azacitidine subjects). This confirms the notion that the investigator's choice of therapy encompasses different patient populations.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 89 Summary of efficacy for trial AZA-AML-001

Title: A Phase 3, Multicenter, Randomized, Open-Label, Study of Azacitidine (Vidaza®) versus Conventional Care Regimens for the Treatment of Older Subjects with Newly Diagnosed Acute Myeloid Leukemia. Protocol AZA-AML-001.			
Study identifier	AZA-AML-001		
Design	This was an international, multicenter, controlled, Phase 3 study with an open-label, randomized (1:1), parallel group design.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		28-day cycles[a] Day -28 to 1 n.a.
Hypothesis	For the primary efficacy analysis of OS, AZACITIDINE will be compared to CCR using the log-rank test in order to assess superiority.		
Treatments groups	Experimental arm		azacitidine (75 mg/m²/day administered SC for 7 days, every 28 days) (N= 241)
	Control arm		combined conventional care regimen (N=247) - including intensive chemotherapy (IV cytarabine in conjunction with an anthracycline in a "7 + 3" regimen) (N= 44) - low dose cytarabine (cytarabine SC 20 mg, twice daily for 10 days, every 28 days) (N= 158) - BSC alone (N=45)
Endpoints and definitions	Primary endpoint	Overall survival	time from randomization to death from any cause
	Secondary endpoint	1-year overall survival rate	
	Secondary endpoint	Event-free survival	the interval from the date of randomization to the date of treatment failure, progressive disease, relapse after CR or CRi, death from any cause, or lost to follow-up, whichever occurs first
	Secondary endpoint	Relapse-free survival	Date from first documented CR/Cri to date of relapse, death, lost to follow-up
	Secondary endpoint	Overall remission rate	Haematologic response (CR, CRi, and relapse after CR or CRi) will be based on IWG response criteria

	Secondary endpoint	Duration of remission	time from the date CR or CRi was first documented until the date of documented relapse from CR or CRi for subjects who achieved CR or CRi
	Secondary endpoint	Cytogenetic complete remission rate	(CRc) is defined morphologic complete remission with reversion to a normal karyotype for those with an abnormal karyotype at baseline
	Secondary endpoint	Safety / tolerability	type, frequency, severity, and relationship of adverse events to study treatments; physical examinations, vital signs; clinical laboratory evaluations, and concomitant medication/therapy
	Secondary endpoint	Patient-reported outcomes	Cancer Quality-of-Life questionnaire (EORTC QLQ-C30)
Database lock	21 March 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	subjects who are ⩾ 65 years old with newly diagnosed, histologically confirmed de novo AML or AML secondary to prior myelodysplastic disease with > 30% bone marrow blasts and who are not eligible for haematopoietic stem cell transplantation		
Descriptive statistics and estimate variability	Treatment group	azacitidine	combined conventional care regimens (CCR)
	Number of subject	241	247
	Overall survival (months)	10.4	6.5
	95% CI	[8.0, 12.7]	[5.0, 8.6]
	1-year overall survival rate	0.465	0.343
	95% CI	[0.40, 0.53]	[0.28, 0.40]
	Event-free survival 95% CI	6.7 [5.0, 8.8]	4.8 [3.8, 6.0]
	Relapse-free survival 95% CI	9.3 [6.7, 12.4]	10.5 [7.3, 12.3]
	Overall remission rate (n) %	67 27.8	62 25.1
	Duration of remission (months)	10.4	12.3

	95% CI	[7.2, 15.2]	[9.0, 17.0]
	Cytogenetic complete remission rate %	47 19.5	54 21.9

Effect estimate per comparison	Overall survival	Comparison groups	Azacitidine vs CCR
		Difference in OS (months)	3.8
		95% CI	[1.0, 6.5]
		Hazard Ratio (95% CI)	0.85 (0.69, 1.03)
		P-value	0.1009
	1-year overall survival rate	Comparison groups	Azacitidine vs CCR
		Difference in 1-year survival estimate (%)	12.3
		95% CI	[3.5, 21.0]
		P-value	not found
Notes			

Analysis description	**Ancillary analysis**		
OS azacitidine vs combined CCR group	OS results adjusted for key-baseline characteristics (Cox-PH analysis)		
	HR	0.80	
	95% CI	0.66, 0.99	
	p-value	0.0355	
	Exploratory analysis		
OS within investigator selection	**BSC only selection** in ITT		
	Treatment group	azacitidine	(CCR)
	Number of subject	44	45
	Overall survival (months)	5.8	3.7
	95% CI	(3.6, 9.7)	(2.8, 5.7)
	Hazard ratio (95% CI)	0.60 (0.38, 0.95)	
	P-value	0.0288	
	Low-dose cytarabine Selection in ITT		
	Treatment group	azacitidine	(CCR)
	Number of subject	154	158
	Overall survival (months)	11.2	6.4
	95% CI	(8.8, 13.4)	(4.8, 9.1)
	Hazard ratio (95% CI)	0.90 (0.70, 1.16)	
	P-value	0.4270	
	Intensive Chemotherapy Selection in ITT		
	Treatment group	azacitidine	(CCR)

	Number of subject	43	44
	Overall survival (months)	13.3	12.2
	95% CI	(7.2, 19.9)	(7.5, 15.1)
	Hazard ratio (95% CI)	0.85 (0.52, 1.38)	
	P-value	0.5032	

[a]Azacitidine group: at least 6 cycles, a median of 6 cycles (range: 1 to 28 cycles); Low-dose cytarabine: at least 4, a median of 4 cycles (range: 1 to 25 cycles); Intensive chemotherapy: max 3 cycles, a median of 2 cycles; BSC-only: median was 3 cycles (range: 1 to 20 cycles).

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled and meta-analysis were performed.

Clinical studies in special populations

There are no data on use in renal or hepatic impaired patients. This is acknowledged by the Applicant, and noted as important missing information in the RMP.

Supportive studies

In addition to the pivotal study, this Application is supported by the results from the original registration study (Study AZA PH GL 2003 CL 001), and a subpopulation of this study with 20% to 30% BM blast count and multi-lineage dysplasia. In addition, reports of 4 registry or compassionate use studies in AML patients treated with azacitidine were provided. Furthermore, a summary of 3 prospective studies and 3 retrospective analyses of azacitidine in elderly patients with newly diagnosed AML was provided (data not shown).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The primary objective of the study was to demonstrate superiority in overall survival of azacitidine compared with the combined conventional care regimens. The primary analyses were performed on the intent to treat (ITT) population. The primary endpoint was overall survival (OS). The primary analysis seems to be defined as two analyses: stratified and unstratified. As the randomization was stratified, it is recommended that the primary analysis would be stratified as well and this is in accordance with the protocol specified analysis.

The pivotal trial was open-label. All central reviewers (pathology and cytogenetic) were blinded to subject treatment assignment, and evaluations by central review were used for the statistical efficacy analyses.

Regular bone biopsies/aspirates were not planned at the same points within a cycle for each group (e.g. cycle 3, 5, 7 for azacitidine and low dose cytarabine; cycle 4, 7, 10 for BSC; every two cycles for intensive chemotherapy). Nevertheless, it is not likely that differences in BM collection plans have impacted the results of the secondary endpoints EFS and RFS considering that best supportive care and the low dose cytarabine group have a similar sampling plan and the limited duration of the intensive chemotherapy treatment (median 2 cycles (max 3 cycles) of each median 63.5 days)) in relation to the median EFS and the RFS that are well above 8 months.

During the study 4 protocol amendments were made, it is agreed with the Applicant that these amendments are not expected to have significantly impacted the conduct of the study, the population included or the outcome. Several major protocol violations were noted, however, it is considered unlikely that these violations had significant impact on the safety or the validity of the efficacy assessments.

Patient population (demographics, disease characteristics at baseline)

The AZA-AML-001 ITT study population was a high risk AML population: 54.3% of subjects were at least 75 years of age (median age, 75.0), 32.4% had AML with myelodysplasia-related changes, 17.8% had a prior history of MDS, 34.8% had a poor cytogenetic risk AML (of whom 16.8% had a very poor cytogenetic risk), 23.2% had ECOG PS of 2, and 71.5% presented at least 1 comorbidity at baseline. Moreover, median baseline BM blasts was 72.0% and median PB values at baseline were 2.5 x 10^9/L for WBCs, 0.3 x 10^9/L for absolute neutrophil count (ANC), and 53.0 x 10^9/L for platelets.

The baseline characteristics for the ITT appeared generally well balanced between the azacitidine-treated patients and the combined CCR population. The only obvious difference between the treatment groups seems to be the percentage of subjects who received prior systemic anti-cancer treatment, which was higher in the combined CCR group (10.1%) compared to the azacitidine group (3.3%). Also the demographic disposition appeared generally well balanced between the azacitidine and the combined CCR group.

In the CCR population, subjects receiving intensive chemotherapy group had better patient-related prognostic factors with a lower median age (median age, 70.5), fewer comorbidities (61.4% of subjects with at least 1 comorbidity), and better disease-related prognostic factors compared to the low-dose cytarabine and BSC-only groups. Subjects in the BSC-only group had the worst patient- and disease-related prognostic factors. The differences seen in baseline characteristics between the CCR subpopulations are as expected, and are a reflection of the heterogeneity of the intended patient population. As part of the consistency assessment of the results across subpopulations comparisons are made between the subpopulations based on investigator's choice of CCR.

Formally cross over between the treatment groups was not allowed, however, within the CCR group, 28 (11%) patients received azacitidine as follow-up treatment subsequent to study discontinuation, while 40 (17%) of the azacitidine-treated patients received cytarabine as one of the CCR treatment options.

Outcomes

Overall, 394 deaths (80.7%) occurred in the ITT population. Deaths were reported for 193 (80.1%) subjects in the azacitidine group and 201 (81.4%) subjects in the combined CCR group. The data are considered mature. After a median follow-up time of 24.4 months, the median OS was 10.4 months (95% CI = 8.0, 12.7) in the azacitidine group (N = 241) compared with 6.5 months (95% CI = 5.0, 8.6) in the CCR group with an observed difference in median OS of 3.8 months. The OS HR for the azacitidine group vs CCR was 0.85 (95% CI = 0.69, 1.03), but was not statistically significant. A multivariate Cox proportional hazards (PH) model adjusting for established patient- and disease-related, pre-specified baseline prognostic factors defined a HR for azacitidine versus CCR of 0.80 (95% CI: 0.66, 0.99), with a 20% reduction of the risk of death and a nominal p-value below 0.05 (p = 0.0355).

In support of the primary efficacy analysis, planned exploratory analyses were conducted based on investigator's preselection for CCR using the same methods as for the primary analysis, without stratification. When considering investigator pre-selection, the KM median time to death was longer in each of the azacitidine treated groups when compared with the BSC (5.8 versus 3.7 months; p =

0.0288), or low-dose cytarabine, but the latter was not significant (11.2 versus 6.4 months; p = 0.4270). The OS HR of 0.6 in the BSC choice subpopulation reached statistical significance and was in favour of azacitidine.

Regarding the impact of baseline factors on OS results in subgroups within the preselection groups, the number of subjects in the individual prespecified subgroups based on baseline factors within the preselection groups is small. This implies that caution should be applied when drawing conclusions, but the following results were observed:

Best supportive care - there was a consistent trend in OS benefit (as measured in OS HR) across the subgroups in favour of azacitidine compared with best supportive care;

Low dose cytarabine - there was a consistent trend in OS benefit (as measured in OS HR) across the subgroups in favour of azacitidine compared with low-dose cytarabine when looking at the OS HR point-estimates, though the trend was weaker as observed in the best-supportive care group. The pattern was more or less similar to what was observed with the ITT population.

Intensive chemotherapy - the results are very difficult to interpret due to the low patient numbers per subgroup.

Secondary endpoints

The most clear difference between the study arms in terms of the secondary endpoints results is observed in the 1-year survival rate. There was a clinically meaningful improvement of 12.3% (95% CI = 3.5, 21.0) in the 1-year survival estimate for the azacitidine group (46.5% [95% CI = 40.1, 52.7]) versus the combined CCR group (34.3% [95% CI = 28.3, 40.3]). In addition, there was a suggestion towards an improved median EFS with azacitidine compared with the combined CCR treatment group (6.7 months versus 4.8 months respectively). Differences between experimental and control arm in the other secondary endpoints are not substantial. In this respect, there is a trend towards longer duration of remission in the control group and the rate of haematological remission was rather similar between the two arms of the study.

The 1-year survival rate for the investigator's choice of CCR subpopulations is in line with what was seen for OS in these populations, with a higher survival rate in the azacitidine group compared with the CCR group for those subjects selected for BSC or low-dose cytarabine, and a similar survival rate for the azacitidine and CCR groups for those subjects selected to receive intensive chemotherapy.

As with the analysis in the ITT, the other key secondary endpoints showed no substantial difference between the azacitidine or CCR treatment groups within each of the investigator's choice subpopulations, apart from EFS, where azacitidine treated subjects tended to have a longer EFS in the BSC and the low-dose cytarabine choice of CCR subgroup. In the patients selected for intensive chemotherapy, EFS seemed shorter in the azacitidine treated patients.

There was a trend in favour of azacitidine when comparing the rates of conversion of subjects from RBC transfusion dependence to RBC transfusion independence, and from platelet transfusion dependence to platelet transfusion independence. However, the median duration of transfusion independence for RBCs or platelets was somewhat shorter in the azacitidine treatment group compared the CCR treatment.

Regarding growth factor use as supportive measure, given the few subjects who received erythropoiesis-stimulating agents during the study (n=5 in total), no impact on haematological values and/or transfusion dependence is expected. No meaningful differences in the number of courses or cumulative dose of myeloid growth factor was observed between the azacitidine and

combined CCR treatment group. As expected, the number of courses and cumulative dose of myeloid growth factor was lower in the BSC-only group and higher in the intensive chemotherapy group. Given the similarity of myeloid growth factor use between the groups, it is unlikely that there was a differential effect on hematologic values.

Finally, concerning HRQoL, no firm conclusions can be drawn other than that the data seems to indicate that there is no detrimental effect of azacitidine on HRQoL when compared to CCR.

Supportive studies and cross study concordance

A survival benefit of azacitidine treatment is also noted in the AML population of the registration study (AZA PH GL 2003 CL 001). Moreover, the survival seen in the registries and in published studies with azacitidine in AML population differs between studies, as it is affected by the included AML patient population, but is within the same range as here reported in the pivotal study (data not shown).

2.4.1. Conclusions on the clinical efficacy

Overall, the study was well designed and conducted for this purpose. Although the primary OS analysis for the effect of azacitidine in comparison to combined CCR did not show a statistically significant difference, a prognostic-factor adjusted Cox-PH model showed a HR of 0.80 and p-value <0.05. The treatment effect in terms of the point-estimates of the OS HR in the various CCR preselection groups, in several of the pre-specified subpopulations and in a post-hoc defined patient subpopulation with the worst disease, i.e. AML subjects who had either myelodysplasia-related changes in the BM and/or adverse cytogenetics at diagnosis, are in favour of azacitidine to a variable extent. Support was provided by the results from several of the secondary endpoints. Finally, results from the additional (sensitivity) analyses to correct for subsequent AML therapy imply overall anti-disease activity of azacitidine relative to CCR. In conclusion, the efficacy is considered established.

2.5. Clinical safety

2.5.1. Introduction

Azacitidine is a nucleoside analogue designed to incorporate into RNA and DNA in place of cytidine, with a mechanism of action that is related to demethylation and cytotoxicity. Since rapidly dividing cells are most sensitive to a cell cycle-specific agent, like azacitidine, adverse event characteristics of such compounds most commonly include BM suppression (anaemia, thrombocytopenia, leukopenia, neutropenia), adverse consequences of BM suppression (infection, haemorrhage), and gastrointestinal events (nausea, vomiting, diarrhoea). In addition to the potential cytotoxic effects, demethylating agents have been shown to affect spermatogenesis and embryo development in animals. As a result, precaution should be taken to avoid the use of azacitidine in pregnant women. In addition, animal data suggest that the liver and kidney may be target organs. Non-clinical studies indicate that the toxicology profile of azacitidine is generally consistent with that of other pyrimidine analogues of the antimetabolite class.

The evaluation of safety focuses on data from 471 elderly AML subjects treated in the AZA-AML-001 Phase 3 study. In further support of the safety of azacitidine, additional safety information is summarized from:

- the Phase 3 Study AZA PH GL 2003 CL 001 in high-risk MDS patients and AML patients with 20% to 30% BM blasts and multi-lineage dysplasia, including a descriptive comparison of the

safety data in the approved indication of higher risk MDS with that from the elderly AML population in AZA AML 001,

- from AML investigator-initiated trials (IITs) (serious AEs reported to Celgene from cases received through 18 May 2014), and
- from post-marketing data from the most recent azacitidine (Vidaza) Periodic Safety Update Report (PSUR) covering the reporting period 19 May 2013 through 18 May 2014 (PSUR, 16 Jul 2014).

Patient exposure

In the pivotal trial a total of 471 patients received at least 1 dose of study drug and had at least 1 post-dose safety assessment (at least 1 post-randomization safety assessment for BSC only), and were thus evaluable for safety analyses. This safety population included 236 subjects in the azacitidine group, 40 subjects in the BSC-only group, 153 subjects in the low-dose cytarabine group, and 42 subjects in the intensive chemotherapy group. The median duration of exposure was longer in the azacitidine group (191.5 days) compared with low-dose cytarabine treated subjects (125.0 days) and intensive chemotherapy treated subjects (124.5 days). The median number of cycles that was administered per treatment option was the highest in the azacitidine group, i.e.:

- azacitidine was given for a median of 6.0 cycles (range: 1 to 28 cycles) (planned was at least 6 cycles), with 124 (52.5%) subjects who received at least 6 cycles and 76 (32.2%) subjects who received at least 12 cycles;
- low-dose cytarabine was given for a median of 4 cycles (range: 1 to 25 cycles) (planned was at least 4 cycles), with 79 (51.6%) subjects receiving at least 4 cycles;
- intensive chemotherapy was given for a median of 2.0 cycles (planned was max 3 cycles) with 59.5% (25/42) of subjects who received at least 2 cycles of intensive chemotherapy while 42.9% (18/42) of subjects received 3 cycles;
- in the BSC-only group, the median number of cycles was 3.0 (range: 1 to 20 cycles).

When calculated as person-years of exposure, this was 174.9 for SC azacitidine, 82.9 for low-dose cytarabine, 14.1 for intensive chemotherapy, and 9.6 for BSC-only. Thus, as expected, the duration of exposure in person-years in the azacitidine group was also longer than in the other treatment subgroups.

Dose modifications

The very most of the patients receiving azacitidine did not have a dose modification. Indeed, of the 236 subjects in the azacitidine treatment group, 207 (87.7%) remained on 75 mg/m^2 throughout the study with no dose adjustments. Of the other patients at least 1 dose modification was reported in 29 (12.3%) with the very most patients in this subgroup having only 1 dose adjustment, i.e. twenty-five subjects (10.6%). Even lower frequencies of dose modifications were observed in the CCR treatment groups, with at least 1 dose modification to be reported in 7 (4.6%) subjects for low-dose cytarabine. For intensive chemotherapy at least one dose modification was reported in 2 (4.8%) subjects for cytarabine, in 1 (4.8%) subject for daunorubicin, and in 2 (9.5%) subjects for idarubicin.

In the azacitidine treatment group, the main reason for dose modifications was haematological toxicity for 21 (8.9%) subjects. The main reason was “other ” for the low-dose cytarabine and intensive chemotherapy treatment groups (percentages were as described as frequency of dose modification). This concerned only few patients in absolute terms for these CCR subgroups (i.e. 2 to 7 patients per study drug).

Patient demographics and disease characteristics of the safety population at baseline

In the safety population (N = 471), the median age was 75.0 years (range 64.0 to 91.0 years) with approximately half (53.3%) of the subjects ⩾ 75 years, the majority of the patients were White (75.2%), and 59.2% of the subjects were male. Furthermore, the majority of subjects in the overall study population (60.1%) were classified as AML not otherwise specified. The other WHO AML subtypes were AML with myelodysplasia-related changes (32.7%), therapy-related myeloid neoplasms (4.2%), and AML with recurrent genetic abnormalities (3.0%) (7). Together, these data show that the overall safety population adequately represents the elderly patient with AML.

As expected, within the CCR treatment groups, subjects who received intensive chemotherapy were slightly younger than any of the other treatment groups, with a median age of 70.5 years and 73.8% of the subjects < 75 years. Subjects in the BSC-only group were slightly older than subjects in any of the other treatment groups with a median age of 77.5 years and 32.5% of the subjects < 75 years. These differences are as expected considering the divergent safety risks associated with the respective therapy choices. Finally, baseline demographic characteristics of subjects in the low-dose cytarabine treatment group were similar to those of the subjects in the azacitidine treatment group.

Table 20 Baseline Demographics (Study AZA-AML-001: Safety Population)

		Conventional Care Regimen (CCR)				
Parameter	**Azacitidine (N = 236)**	**CCR total (N = 235)**	**BSC-only (N = 40)**	**Low-dose Cytarabine (N = 153)**	**Intensive Chemo (N = 42)**	**Total (N = 471)**
Age (years)						
Median	75.0	75.0	77.5	75.0	70.5	75.0
Min, Max	64, 91	65, 89	67, 89	65, 88	65, 79	64, 91
Age group - n (%)						
< 75 years	103 (43.6)	117 (49.8)	13 (32.5)	73 (47.7)	31 (73.8)	220 (46.7)
≥ 75 years	133 (56.4)	118 (50.2)	27 (67.5)	80 (52.3)	11 (26.2)	251 (53.3)
Sex - n (%)						
Male	136 (57.6)	143 (60.9)	26 (65.0)	92 (60.1)	25 (59.5)	279 (59.2)
Female	100 (42.4)	92 (39.1)	14 (35.0)	61 (39.9)	17 (40.5)	192 (40.8)
Geographic Region n(%)[a]						
North America/Australia	42 (17.8)	44 (18.7)	10 (25.0)	29 (19.0)	5 (11.9)	86 (18.3)
Western Europe/Israel	114 (48.3)	119 (50.6)	25 (62.5)	72 (47.1)	22 (52.4)	233 (49.5)
Eastern Europe	46 (19.5)	42 (17.9)	0	35 (22.9)	7 (16.7)	88 (18.7)
Asia	34 (14.4)	30 (12.8)	5 (12.5)	17 (11.1)	8 (19.0)	64 (13.6)
Race - n (%)						
White	180 (76.3)	174 (74.0)	33 (82.5)	112 (73.2)	29 (69.0)	354 (75.2)
Black	2 (0.8)	1 (0.4)	0	1 (0.7)	0	3 (0.6)
Asian	37 (15.7)	30 (12.8)	5 (12.5)	17 (11.1)	8 (19.0)	67 (14.2)
Hawaiian/Pacific Islander	1 (0.4)	0	0	0	0	1 (0.2)
American Indian/Alaska Native	0	0	0	0	0	0
Other	1 (0.4)	0	0	0	0	1 (0.2)
Not applicable	15 (6.4)	30 (12.8)	2 (5.0)	23 (15.0)	4 (9.5)	45 (9.6)
Weight (kg)						
Median	71.4	71.0	72.0	70.5	71.3	71.0
Min, Max	36, 141	34, 125	44, 108	34, 125	45, 120	34, 141
BSA (kg/m^2)[b]						
Median	1.8	1.8	1.8	1.8	1.8	1.8
Min, Max	1, 2	1, 2	1, 2	1, 2	1, 2	1, 2

BSA = body surface area; BSC = best supportive care; chemo = chemotherapy; CCR = conventional care regimens; Min = minimum; Max = maximum.

[a] North America = US and Canada; Western Europe = Austria, Belgium, France, Germany, Italy, Spain, The Netherlands, United Kingdom; Eastern Europe = Czech Republic, Poland, and Russia; Asia = China, South Korea, and Taiwan.

[b] BSA (m^2) = weight $(kg)^{0.425}$ × height $(cm)^{0.725}$/139.2.

Note: Percentages were based on the number of subjects in each treatment group. There was 1 subject who was 64 years and 11 months old at study entry.

Source: Report AZA-AML-001, Table 14.1.6.2.

As one of the parameters of interest for prognosis, the percentage of subjects with AML with myelodysplasia-related changes was similar between the azacitidine (31.4%) and the combined CCR groups (32.7%). Furthermore, within the CCR treatment groups, the intensive chemotherapy treatment group had a smaller percentage of subjects with a previous history of MDS (9.5%) and ECOG of 2 (19.0%) compared to the other treatment groups, although the difference for these parameters between the intensive chemotherapy group and the low dose cytarabine group (LDAC) is not substantial. For comparison, prior MDS concerned 13.1% of the LDAC group and 25.0% of the BSC-only patients and ECOG 2 concerned 22.2% of the LDAC group and 32.5% of the BSC-only patients.

Regarding prior therapy, only 7.0% of subjects in the safety population (N = 471) received at least 1 prior systemic anti-cancer therapy and 7.0% received at least 1 prior radiation therapy. The percentage of subjects who received prior systemic anti-cancer treatment was higher in the combined CCR treatment group (10.6%) compared to the azacitidine treatment group (3.4%). This seems to be the only obvious difference between the azacitidine and the CCR arm regarding baseline disease characteristics.

Other key baseline disease characteristics, including peripheral blood cell counts (bone marrow blasts, haemoglobin, platelets, absolute neutrophil count, white blood cells), and the number of red blood cell (RBC) and platelet transfusions were similar between the azacitidine treatment group and the combined CCR treatment groups. Of note, peripheral blood cell counts were low at baseline as to be expected for subjects with AML.

Table 21 Baseline Disease Characteristics (Study AZA-AML-001: Safety Population)

		Conventional Care Regimen (CCR)				
Parameter	Azacitidine (N = 236)	CCR total (N = 235)	BSC-only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemo (N = 42)	Total (N = 471)
AML WHO Classification, n (%)						
AML with recurrent genetic abnormalities	5 (2.1)	9 (3.8)	1 (2.5)	4 (2.6)	4 (9.5)	14 (3.0)
AML with myelodysplasia-related changes	74 (31.4)	80 (34.0)	18 (45.0)	49 (32.0)	13 (31.0)	154 (32.7)
Therapy-related myeloid neoplasms	8 (3.4)	12 (5.1)	2 (5.0)	9 (5.9)	1 (2.4)	20 (4.2)
AML not otherwise specified	149 (63.1)	134 (57.0)	19 (47.5)	91 (59.5)	24 (57.1)	283 (60.1)
Prior History of MDS, n (%)						
Yes	48 (20.3)	37 (15.7)	10 (25.0)	23 (15.0)	4 (9.5)	85 (18.0)
Primary	45 (19.1)	34 (14.5)	10 (25.0)	20 (13.1)	4 (9.5)	79 (16.8)
Secondary	3 (1.3)	3 (1.3)	0	3 (2.0)	0	6 (1.3)
No	188 (79.7)	198 (84.3)	30 (75.0)	130 (85.0)	38 (90.5)	386 (82.0)
Time Since Initial AML Diagnosis (months)						
Mean ± SDev	0.7 ± 1.48	0.8 ± 2.07	1.3 ± 3.15	0.7 ± 1.95	0.4 ± 0.72	0.7 ± 1.80
Median	0.3	0.4	0.7	0.3	0.2	0.3
Min, Max	0, 19.8	-0.2[a], 20.2	0, 20.1	-0.2 , 20.2	0, 4.4	-0.2 , 20.2
ECOG Performance Status, n(%)[b]						
Grade 0	54 (22.9)	54 (23.0)	11 (27.5)	33 (21.6)	10 (23.8)	108 (22.9)
Grade 1	129 (54.7)	126 (53.6)	16 (40.0)	86 (56.2)	24 (57.1)	255 (54.1)
Grade 2	53 (22.5)	55 (23.4)	13 (32.5)	34 (22.2)	8 (19.0)	108 (22.9)
Cytogenetic Risk Status, Local, n (%)[b]						
Intermediate	155 (65.7)	149 (63.4)	24 (60.0)	97 (63.4)	28 (66.7)	304 (64.5)
Normal	115 (48.7)	98 (41.7)	18 (45.0)	62 (40.5)	18 (42.9)	213 (45.2)
Poor	81 (34.3)	86 (36.6)	16 (40.0)	56 (36.6)	14 (33.3)	167 (35.5)
Cytogenetic Risk Status, Central, n (%)[b]						
Intermediate	152 (64.4)	150 (63.8)	24 (60.0)	99 (64.7)	27 (64.3)	302 (64.1)
Normal	111 (47.0)	97 (41.3)	18 (45.0)	62 (40.5)	17 (40.5)	208 (44.2)
Poor[c]	43 (18.2)	44 (18.7)	6 (15.0)	29 (19.0)	9 (21.4)	87 (18.5)
Very Poor[d]	41 (17.4)	40 (17.0)	10 (25.0)	25 (16.3)	5 (11.9)	81 (17.2)

Table 21 **Baseline Disease Characteristics (Study AZA-AML-001: Safety Population)(continued)**

		Conventional Care Regimen (CCR)				
Parameter	**Azacitidine (N = 236)**	**CCR total (N = 235)**	**BSC-only (N = 40)**	**Low-dose Cytarabine (N = 153)**	**Intensive Chemo (N = 42)**	**Total (N = 471)**
Prior therapies, n (%)						
Subjects with at least 1 prior systemic anti-cancer therapy	8 (3.4)	25 (10.6)	4 (10.0)	19 (12.4)	2 (4.8)	33 (7.0)
Subjects with at least 1 prior radiation therapy	17 (7.2)	16 (6.8)	2 (5.0)	12 (7.8)	2 (4.8)	33 (7.0)

AML = acute myeloid leukemia; BSC = best supportive care; chemo = chemotherapy; CCR = conventional care regimens; ECOG = Eastern Cooperative Oncology Group; MDS = myelodysplastic syndrome; Min = minimum; Max = maximum; SDev = standard deviation; WHO = World Health Organization.

[a] Two subjects had a diagnosis of AML after informed consent was given, but prior to study treatment.

[b] Status at randomization

[c] Includes -5, -7, 5q-, 7q-, 11q23 abnormalities, inv(3), t(3;3), t(6;9), and complex (≥ abnormalities) that were not considered monosomal karyotype.

[d] Includes t(9;22), and monosomal karyotype and are included in the poor-risk category based on National Comprehensive Cancer Network guidelines.

Note: Percentages were based on the number of subjects in each treatment group.

Source: Report AZA-AML-001, Table 14.1.7.2, Table 14.1.11.2, Table 14.1.12.2.

Adverse events

Table 23 Summary of Treatment-emergent Adverse Events (Study AZA-AML-001: Safety Population)

TEAE Categories[a]	Azacitidine (N = 236)	Conventional Care Regimen		
		BSC-only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemo (N = 42)
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 TEAE	234 (99.2)	36 (90.0)	153 (100.0)	42 (100.0)
Subjects with at least 1 TEAE related to study drug[b]	188 (79.7)	0	124 (81.0)	39 (92.9)
Subjects with at least 1 Grade 3 or 4 TEAE	207 (87.7)	26 (65.0)	141 (92.2)	37 (88.1)
Subjects with at least 1 Grade 3 or 4 TEAE related to study drug	125 (53.0)	0	90 (58.8)	29 (69.0)
Subjects with at least 1 Grade 5 TEAE	56 (23.7)	23 (57.5)	38 (24.8)	9 (21.4)
Subjects with at least 1 serious TEAE	188 (79.7)	30 (75.0)	118 (77.1)	27 (64.3)
Subjects with at least 1 serious TEAE related to study drug	87 (36.9)	0	56 (36.6)	14 (33.3)
Subjects with at least 1 TEAE leading to discontinuation of study drug	110 (46.6)	0	68 (44.4)	11 (26.2)
Subjects with at least 1 study drug-related TEAE leading to discontinuation of study drug	22 (9.3)	0	20 (13.1)	5 (11.9)
Subjects with at least 1 TEAE leading to study drug dose reduction only	8 (3.4)	0	2 (1.3)	2 (4.8)
Subjects with at least 1 TEAE leading to study drug dose interruption only	116 (49.2)	0	61 (39.9)	4 (9.5)
Subjects with at least 1 TEAE leading to study drug dose reduction and interruption	13 (5.5)	0	7 (4.6)	0

BSC = best supportive care; chemo = chemotherapy; CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event.

[a] Treatment-emergent adverse events included adverse events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and low-dose cytarabine (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for intensive chemotherapy (3) between the date of randomization and the date of discontinuation from the treatment period for BSC-only. Also, any adverse event that started outside the treatment-emergent period and assessed as related to study drug was considered treatment-emergent.

[b] Related = suspected by investigator to be related.

Note: Percentages were based on the number of subjects in each treatment group. Severity was graded per CTCAE (Version 4.0); for any adverse events not defined in the CTCAE, the severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life-threatening [Grade 4], or death [Grade 5]) was assessed by the investigator.

Source: Report AZA-AML-001, Table 38.

Common adverse events

Table 24 Treatment-emergent Adverse Events Reported in at Least 10% of Subjects (in the Azacitidine Group) by System Organ Class and Preferred Term (Study AZA-AML-001: Safety Population)

System Organ Class / Preferred Term[a]	Azacitidine (N = 236)	Conventional Care Regimen		
		BSC only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemotherapy (N = 42)
	n (%)	n (%)	n (%)	n (%)
Subject with at least 1 TEAE[b]	**234 (99.2)**	**36 (90.0)**	**153 (100.0)**	**42 (100.0)**
Blood and lymphatic system disorders	**175 (74.2)**	**17 (42.5)**	**115 (75.2)**	**31 (73.8)**
Anaemia	48 (20.3)	4 (10.0)	39 (25.5)	7 (16.7)
Febrile neutropenia	76 (32.2)	12 (30.0)	51 (33.3)	17 (40.5)
Neutropenia	71 (30.1)	2 (5.0)	44 (28.8)	14 (33.3)
Thrombocytopenia	64 (27.1)	2 (5.0)	46 (30.1)	9 (21.4)
Gastrointestinal disorders	**191 (80.9)**	**20 (50.0)**	**107 (69.9)**	**34 (81.0)**
Abdominal pain	31 (13.1)	3 (7.5)	16 (10.5)	7 (16.7)
Constipation	99 (41.9)	9 (22.5)	42 (27.5)	16 (38.1)
Diarrhoea	87 (36.9)	5 (12.5)	35 (22.9)	21 (50.0)
Nausea	94 (39.8)	3 (7.5)	43 (28.1)	24 (57.1)
Vomiting	53 (22.5)	3 (7.5)	24 (15.7)	8 (19.0)
General disorders and administration site conditions	**200 (84.7)**	**27 (67.5)**	**109 (71.2)**	**32 (76.2)**
Asthenia	55 (23.3)	9 (22.5)	32 (20.9)	5 (11.9)
Fatigue	54 (22.9)	10 (25.0)	20 (13.1)	5 (11.9)
Injection site erythema	29 (12.3)	0	0	0
Injection site reaction	31 (13.1)	0	0	0
Oedema peripheral	55 (23.3)	7 (17.5)	33 (21.6)	9 (21.4)
Pyrexia	89 (37.7)	9 (22.5)	61 (39.9)	23 (54.8)
Infections and infestations	**184 (78.0)**	**24 (60.0)**	**108 (70.6)**	**31 (73.8)**
Pneumonia	57 (24.2)	3 (7.5)	36 (23.5)	6 (14.3)
Investigations	**60 (25.4)**	**5 (12.5)**	**35 (22.9)**	**8 (19.0)**
Weight decreased	30 (12.7)	3 (7.5)	3 (2.0)	1 (2.4)
Metabolism and nutrition disorders	**136 (57.6)**	**18 (45.0)**	**80 (52.3)**	**22 (52.4)**
Decreased appetite	61 (25.8)	8 (20.0)	33 (21.6)	7 (16.7)
Hypokalaemia	55 (23.3)	6 (15.0)	45 (29.4)	16 (38.1)

Table 25 Treatment-emergent Adverse Events Reported in at Least 10% of Subjects (in the Azacitidine Group) by System Organ Class and Preferred Term (Study AZA-AML-001: Safety Population (continued)

System Organ Class / Preferred Term[a]	Azacitidine (N = 236)	Conventional Care Regimen		
		BSC only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemotherapy (N = 42)
	n (%)	n (%)	n (%)	n (%)
Musculoskeletal and connective tissue disorders	**105 (44.5)**	**11 (27.5)**	**55 (35.9)**	**9 (21.4)**
Arthralgia	33 (14.0)	2 (5.0)	11 (7.2)	3 (7.1)
Back pain	37 (15.7)	5 (12.5)	22 (14.4)	2 (4.8)
Pain in extremity	26 (11.0)	3 (7.5)	11 (7.2)	2 (4.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**55 (23.3)**	**13 (32.5)**	**40 (26.1)**	**1 (2.4)**
Acute myeloid leukaemia	49 (20.8)	13 (32.5)	37 (24.2)	1 (2.4)
Nervous system disorders	**105 (44.5)**	**12 (30.0)**	**53 (34.6)**	**14 (33.3)**
Dizziness	45 (19.1)	3 (7.5)	15 (9.8)	4 (9.5)
Headache	31 (13.1)	1 (2.5)	19 (12.4)	6 (14.3)
Psychiatric disorders	**75 (31.8)**	**12 (30.0)**	**32 (20.9)**	**8 (19.0)**
Insomnia	36 (15.3)	2 (5.0)	11 (7.2)	4 (9.5)
Respiratory, thoracic and mediastinal disorders	**127 (53.8)**	**20 (50.0)**	**87 (56.9)**	**18 (42.9)**
Cough	54 (22.9)	6 (15.0)	36 (23.5)	6 (14.3)
Dyspnoea	46 (19.5)	7 (17.5)	36 (23.5)	5 (11.9)
Epistaxis	30 (12.7)	5 (12.5)	21 (13.7)	2 (4.8)
Skin and subcutaneous tissue disorders	**109 (46.2)**	**9 (22.5)**	**60 (39.2)**	**20 (47.6)**
Pruritus	25 (10.6)	1 (2.5)	10 (6.5)	6 (14.3)
Rash	26 (11.0)	0	14 (9.2)	8 (19.0)

BSC = best supportive care; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] System organ classes and preferred terms are coded using the MedDRA dictionary (Version 16.1). A subject with multiple occurrences of a TEAE is counted only once in each TEAE category.

[b] TEAEs include adverse events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and low-dose cytarabine (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for intensive chemotherapy (3) between the date of randomization and the date of discontinuation from the treatment period for BSC only. Also, any adverse event that started outside the treatment-emergent period and assessed as related to study drug is considered treatment-emergent.

Note: Percentages are based on the number of subjects in each treatment group.

Source: Report AZA-AML-001, Table 41.

Common Adverse Events by Cycle of Onset

Table 96 First Occurrence of the Most Frequently Reported Treatment-emergent Adverse Events (in at Least 10.0% in the Azacitidine Treatment Group) by Cycle of Onset in Azacitidine Treatment Group (Study AZA-AML-001: Safety Population)

	Azacitidine					
	Cycles 1-2 (N = 236)	Cycles 3-4 (N = 171)	Cycles 5-6 (N = 146)	Cycles 7-12 (N = 116)	Cycles 13-24 (N = 68)	Cycle > 24 (N = 11)
SOC/PT[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 TEAE in the cycle category[b]	**227 (96.2)**	**139 (81.3)**	**107 (73.3)**	**107 (92.2)**	**59 (86.8)**	**10 (90.9)**
Blood and Lymphatic System Disorders	**134 (56.8)**	**33 (19.3)**	**19 (13.0)**	**28 (24.1)**	**14 (20.6)**	**1 (9.1)**
Anaemia	35 (14.8)	5 (2.9)	3 (2.1)	2 (1.7)	3 (4.4)	0
Febrile neutropenia	58 (24.6)	7 (4.1)	3 (2.1)	6 (5.2)	1 (1.5)	1 (9.1)
Neutropenia	38 (16.1)	12 (7.0)	8 (5.5)	8 (6.9)	5 (7.4)	0
Thrombocytopenia	43 (18.2)	11 (6.4)	4 (2.7)	4 (3.4)	2 (2.9)	0
Gastrointestinal Disorders	**150 (63.6)**	**58 (33.9)**	**35 (24.0)**	**47 (40.5)**	**18 (26.5)**	**5 (45.5)**
Abdominal pain	13 (5.5)	6 (3.5)	4 (2.7)	7 (6.0)	1 (1.5)	0
Constipation	69 (29.2)	13 (7.6)	6 (4.1)	8 (6.9)	3 (4.4)	0
Diarrhoea	58 (24.6)	9 (5.3)	6 (4.1)	9 (7.8)	5 (7.4)	0
Nausea	67 (28.4)	13 (7.6)	6 (4.1)	6 (5.2)	2 (2.9)	0
Vomiting	32 (13.6)	9 (5.3)	2 (1.4)	9 (7.8)	0	1 (9.1)
General Disorders and Administration Site Conditions	**163 (69.1)**	**51 (29.8)**	**32 (21.9)**	**33 (28.4)**	**22 (32.4)**	**4 (36.4)**
Asthenia	32 (13.6)	7 (4.1)	7 (4.8)	4 (3.4)	5 (7.4)	0
Fatigue	41 (17.4)	7 (4.1)	0	1 (0.9)	4 (5.9)	1 (9.1)
Injection site erythema	19 (8.1)	3 (1.8)	4 (2.7)	1 (0.9)	2 (2.9)	0
Injection site reaction	27 (11.4)	1 (0.6)	1 (0.7)	1 (0.9)	1 (1.5)	0
Oedema peripheral	34 (14.4)	8 (4.7)	8 (5.5)	3 (2.6)	2 (2.9)	0
Pyrexia	58 (24.6)	15 (8.8)	5 (3.4)	7 (6.0)	4 (5.9)	0
Infections and Infestations	**117 (49.6)**	**52 (30.4)**	**36 (24.7)**	**49 (42.2)**	**27 (39.7)**	**4 (36.4)**
Pneumonia	32 (13.6)	10 (5.8)	3 (2.1)	9 (7.8)	1 (1.5)	2 (18.2)

Table 27 First Occurrence of the Most Frequently Reported Treatment-emergent Adverse Events (in at Least 10.0% in the Azacitidine Treatment Group) by Cycle of Onset (Study AZA-AML-001: Safety Population)(continued)

	Azacitidine					
	Cycles 1-2 (N = 236)	Cycles 3-4 (N = 171)	Cycles 5-6 (N = 146)	Cycles 7-12 (N = 116)	Cycles 13-24 (N = 68)	Cycle > 24 (N = 11)
SOC/PT[a]	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Investigations	**31 (13.1)**	**14 (8.2)**	**8 (5.5)**	**11 (9.5)**	**5 (7.4)**	**0**
Weight decreased	17 (7.2)	4 (2.3)	2 (1.4)	5 (4.3)	2 (2.9)	0
Metabolism and Nutrition Disorders	**95 (40.3)**	**26 (15.2)**	**22 (15.1)**	**23 (19.8)**	**10 (14.7)**	**1 (9.1)**
Decreased appetite	44 (18.6)	6 (3.5)	9 (6.2)	2 (1.7)	0	0
Hypokalaemia	33 (14.0)	7 (4.1)	8 (5.5)	6 (5.2)	1 (1.5)	0
Musculoskeletal and Connective Tissue Disorders	**59 (25.0)**	**28 (16.4)**	**24 (16.4)**	**35 (30.2)**	**12 (17.6)**	**1 (9.1)**
Arthralgia	13 (5.5)	6 (3.5)	4 (2.7)	7 (6.0)	3 (4.4)	0
Back pain	14 (5.9)	9 (5.3)	4 (2.7)	7 (6.0)	2 (2.9)	1 (9.1)
Pain in extremity	13 (5.5)	1 (0.6)	6 (4.1)	5 (4.3)	1 (1.5)	0
Neoplasms Benign, Malignant and Unspecified (Incl Cysts and Polyps)	**14 (5.9)**	**7 (4.1)**	**7 (4.8)**	**16 (13.8)**	**12 (17.6)**	**0**
Acute myeloid leukaemia	14 (5.9)	7 (4.1)	6 (4.1)	12 (10.3)	10 (14.7)	0
Nervous System Disorders	**60 (25.4)**	**26 (15.2)**	**12 (8.2)**	**25 (21.6)**	**13 (19.1)**	**1 (9.1)**
Dizziness	26 (11.0)	11 (6.4)	1 (0.7)	5 (4.3)	2 (2.9)	0
Headache	13 (5.5)	5 (2.9)	6 (4.1)	4 (3.4)	2 (2.9)	1 (9.1)
Psychiatric Disorders	**49 (20.8)**	**12 (7.0)**	**10 (6.8)**	**5 (4.3)**	**5 (7.4)**	**2 (18.2)**
Insomnia	20 (8.5)	6 (3.5)	5 (3.4)	1 (0.9)	3 (4.4)	0
Respiratory, Thoracic and Mediastinal Disorders	**85 (36.0)**	**23 (13.5)**	**26 (17.8)**	**24 (20.7)**	**17 (25.0)**	**1 (9.1)**
Cough	29 (12.3)	6 (3.5)	8 (5.5)	8 (6.9)	3 (4.4)	0
Dyspnoea	28 (11.9)	3 (1.8)	8 (5.5)	3 (2.6)	3 (4.4)	1 (9.1)
Epistaxis	16 (6.8)	2 (1.2)	3 (2.1)	4 (3.4)	4 (5.9)	1 (9.1)
Skin and Subcutaneous Tissue Disorders	**73 (30.9)**	**24 (14.0)**	**19 (13.0)**	**17 (14.7)**	**13 (19.1)**	**2 (18.2)**
Pruritus	10 (4.2)	4 (2.3)	2 (1.4)	4 (3.4)	4 (5.9)	1 (9.1)
Rash	14 (5.9)	7 (4.1)	3 (2.1)	2 (1.7)	0	0

MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] System organ classes and PTs were coded using the MedDRA dictionary (Version 16.1). Only the first occurrence of a TEAE preferred term for a subject was counted.

[b] Treatment-emergent adverse events included adverse events that started between the date of first dose of study drug and 28 days after the date of last dose of azacitidine. Also, any adverse event that started outside the treatment-emergent period and assessed as related to study drug is considered treatment-emergent.

Note: Percentages were based on the number of subjects in each treatment group.

Source: Report AZA-AML-001, Table 43.

Grade 3 or 4 adverse events

In the Safety population, the percentages of subjects with at least 1 Grade 3 or 4 TEAE was reported in 87.7% of azacitidine subjects, 65.0% of the BSC-only subjects, 92.2% of low-dose cytarabine subjects, and 88.1% of intensive chemotherapy subjects .

In azacitidine subjects, the most frequently reported Grade 3 or 4 TEAEs were febrile neutropenia (28.0%), neutropenia (26.3%), and thrombocytopenia (23.7%). These events were reported at similar or lower rates in the azacitidine group as compared to the 2 other active treatment groups, i.e. for low-dose cytarabine these rates were 30.1%, 24.8% and 27.5%, respectively, and for intensive chemotherapy these were 31.0%, 33.3% and 21.4%, respectively. In comparison to the BSC-only

group, the most frequent Grade 3 or 4 haematological TEAEs were higher in the azacitidine group, except for febrile neutropenia, which was observed in 27.5% in the BSC-only patients. Indeed, neutropenia and thrombocytopenia were observed in only 5% of the BSC-only subjects.

Table 28 Grade 3 or 4 Treatment-emergent Adverse Events Reported in at Least 10% of Subjects (in the Azacitidine Group) by System Organ Class and Preferred Term (Study AZA-AML-001: Safety Population)

System Organ Class/ Preferred Term[a]	Azacitidine (N = 236)	Conventional Care Regimen		
		BSC only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemotherapy (N = 42)
	n (%)	n (%)	n (%)	n (%)
Subjects with at least 1 Grade 3 or 4 TEAE[b]	**207 (87.7)**	**26 (65.0)**	**141 (92.2)**	**37 (88.1)**
Blood and lymphatic system disorders	**156 (66.1)**	**14 (35.0)**	**103 (67.3)**	**28 (66.7)**
Anaemia	37 (15.7)	2 (5.0)	35 (22.9)	6 (14.3)
Febrile neutropenia	66 (28.0)	11 (27.5)	46 (30.1)	13 (31.0)
Neutropenia	62 (26.3)	2 (5.0)	38 (24.8)	14 (33.3)
Thrombocytopenia	56 (23.7)	2 (5.0)	42 (27.5)	9 (21.4)
Infections and infestations	**119 (50.4)**	**14 (35.0)**	**70 (45.8)**	**21 (50.0)**
Pneumonia	45 (19.1)	2 (5.0)	29 (19.0)	2 (4.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	45 (19.1)	8 (20.0)	29 (19.0)	1 (2.4)
Acute myeloid leukaemia	42 (17.8)	8 (20.0)	28 (18.3)	1 (2.4)

BSC = best supportive care; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a] System organ classes and preferred terms are coded using the MedDRA dictionary (Version 16.1). A subject with multiple occurrences of a TEAE is counted only once in each TEAE category.

[b] TEAEs include adverse events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and low-dose cytarabine, (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for intensive chemotherapy, or (3) between the date of randomization and the date of discontinuation from the treatment period for BSC only. Also, any adverse event that started outside the treatment-emergent period and was assessed as related to study drug is considered treatment-emergent.

Notes: Percentages are based on the number of subjects in each treatment group. Severity was graded per CTCAE (Version 4.0); for any adverse events not defined in the CTCAE, the severity (mild [Grade 1], moderate [Grade 2], severe [Grade 3], life-threatening [Grade 4], or death [Grade 5]) was assessed by the investigator.

Source: Report AZA-AML-001, Table 52.

When adjusting for duration of exposure, the most frequently reported Grade 3 or 4 TEAEs remained haematological disorders in the azacitidine group: febrile neutropenia (37.7), neutropenia (35.4), and thrombocytopenia (32.0). However, in comparison to the 2 other active treatment groups, these events occurred at 1.3- to 3-fold lower rates in the azacitidine group compared to the low-dose cytarabine or intensive chemotherapy groups. When compared to BSC, the incidence rate for Grade 3 or 4 febrile neutropenia was 3-fold lower in the azacitidine group, whereas the incidence rates for Grade 3 or 4 neutropenia and thrombocytopenia remained higher in the azacitidine group.

Regarding the occurrence of neoplasms (either benign, malignant or unspecified), this is predominantly AML and is the lowest in the intensive chemotherapy CCR subgroup, i.e. 17.8% for azacitidine, 20.0% for BCS-only, 18.3% for LDAC and 2.4% for intensive chemotherapy. In case the AML as reported was a relapse or worsening of the underlying AML, these numbers may either represent a difference in the baseline chance for relapse for the intensive chemotherapy patients, indicate the stronger ability of the intensive chemotherapy regimen to eradicate the leukaemia or a combination thereof. The apparent difference in occurrence of AML between the individual groups,

may have been impacted by several factors, including differences between the study groups in the duration of treatment and due to AE documentation rules. When all information is combined, the overall frequency of all AML events was similar between all treatment groups. It was previously concluded that the baseline disease characteristics were similar between the azacitidine and the combined CCR groups, except for the number of prior treatments. This was in favour of the azacitidine group, but it should be noted that a similar percentage of patients in the azacitidine group had previous treatment as in the intensive chemotherapy arm (though low absolute number), i.e. 3.4% (n=8) vs 4.8% (n=2), respectively.

Treatment-related adverse events

In the safety population, at least 1 treatment-related adverse events (TEAE) considered related to study drug was reported in 79.7% of subjects treated with azacitidine, 81.0% of subjects treated with low-dose cytarabine, and 92.9% of subjects treated with intensive chemotherapy (Table 221).

In the azacitidine group, the most frequently reported treatment-related TEAEs included nausea (27.1%), neutropenia (19.9%), and thrombocytopenia (17.4%). The events of neutropenia and thrombocytopenia were less frequently reported in the azacitidine group compared to the low dose cytarabine (22.9% and 22.2%, respectively) and intensive chemotherapy (31.0% and 21.4%, respectively) groups. Nausea was less frequently reported in low-dose cytarabine subjects (22.2%) as compared to azacitidine subjects, but was more frequently observed in intensive chemotherapy (42.9%) treated subjects as compared to azacitidine subjects.

The percentages of subjects with at least 1 Grade 3 or 4 treatment-related TEAE was higher in the intensive chemotherapy group (69.0%) compared to the other 2 active treatment groups (53.0% for azacitidine subjects and 58.8% for low-dose cytarabine subjects). In the azacitidine group, the most frequently reported Grade 3 or 4 treatment-related TEAEs were neutropenia (17.4%), thrombocytopenia (14.4%), and febrile neutropenia (12.7%). The frequency of these Grade 3 or 4 events was lower in the azacitidine group compared to the 2 other active treatment groups, i.e. for the LDAC patients these rates were 20.9%, 20.9% an 18.3%, respectively, and for the intensive chemotherapy subgroup these were 31.0%, 21.4% and 23.8%, respectively.

Thus, the type of AEs designated as treatment-related (including Grade 3 or 4) are similar to the commonly-reported AEs. Furthermore, the most frequently reported treatment-related TEAEs across the 3 active treatment groups were known effects of the active study drugs (haematological and gastrointestinal disorders).

Table 29 Treatment-emergent Adverse Events Related to Study Treatment Reported in at Least 10% of Subjects (in the Azacitidine Group) by System Organ Class and Preferred Term (Study AZA-AML-001: Safety Population)

		Conventional Care Regimen		
	Azacitidine (N = 236)	BSC-only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemo (N = 42)
SOC/PT[a]	n (%)	n (%)	n (%)	n (%)
Subject with at least 1 related TEAE[b]	**188 (79.7)**	**0**	**124 (81.0)**	**39 (92.9)**
Blood and Lymphatic System Disorders	**105 (44.5)**	**0**	**79 (51.6)**	**26 (61.9)**
Febrile neutropenia	35 (14.8)	0	31 (20.3)	13 (31.0)
Neutropenia	47 (19.9)	0	35 (22.9)	13 (31.0)
Thrombocytopenia	41 (17.4)	0	34 (22.2)	9 (21.4)
Gastrointestinal Disorders	**102 (43.2)**	**0**	**60 (39.2)**	**24 (57.1)**
Constipation	31 (13.1)	0	10 (6.5)	5 (11.9)
Diarrhoea	29 (12.3)	0	8 (5.2)	9 (21.4)
Nausea	64 (27.1)	0	34 (22.2)	18 (42.9)
Vomiting	34 (14.4)	0	16 (10.5)	3 (7.1)
General Disorders and Administration Site Conditions	**122 (51.7)**	**0**	**49 (32.0)**	**17 (40.5)**
Injection site erythema	28 (11.9)	0	0	0
Injection site reaction	30 (12.7)	0	0	0
Pyrexia	29 (12.3)	0	24 (15.7)	10 (23.8)
Metabolism and Nutrition Disorders	**46 (19.5)**	**0**	**24 (15.7)**	**12 (28.6)**
Decreased appetite	32 (13.6)	0	14 (9.2)	5 (11.9)

BSC = best supportive care; chemo = chemotherapy; MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.

[a] System organ classes and PTs were coded using the MedDRA dictionary (Version 16.1). A subject with multiple occurrences of a TEAE is counted only once in each TEAE category.

[b] Treatment-emergent adverse events included adverse events that started (1) between the date of first dose of study drug and 28 days after the date of last dose of study drug for azacitidine and low-dose cytarabine (2) between the date of first dose of study drug and 70 days after the date of last dose of study drug for intensive chemotherapy (3) between the date of randomization and the date of discontinuation from the treatment period for BSC-only. Also, any adverse event that started outside the treatment-emergent period and assessed as related to study drug was considered treatment-emergent.

Note: Percentages were based on the number of subjects in each treatment group.

Source: Report AZA-AML-001, Table 54.

Other significant events

The earlier described data indicate that the important identified AEs (risks) associated with the use of azacitidine are commonly related to the blood and lymphatic system (neutropenia, thrombocytopenia, anaemia). Other common important identified risks include haemorrhagic events and infections. Less common AEs (risks) identified with the use of azacitidine include renal failure, hepatic failure, interstitial lung disease (ILD), and tumour lysis syndrome (TLS). Events considered as important potential risks in the AML setting described in this section include cardiac events and ischemic colitis.

The Applicant described that the most frequent reported TEAEs of special interest in the azacitidine group were infections (78.0%) and myelosuppression (69.5%). Furthermore, the overall percentages of subjects who experienced TEAEs and Grade 3 or 4 TEAEs of infection and myelosuppression appeared to be similar in the 3 active treatment groups and lower in the BSC-only group.

Other frequently reported TEAEs of special interest in the azacitidine group were cardiac disorders reported in 44.1% of subjects, mainly peripheral oedema (23.3%), and haemorrhagic events in 39.8% of subjects, mostly epistaxis (12.7%). The frequency of Grade 3 or 4 and serious cardiac TEAEs was similar across the 3 active treatment groups. The occurrence of haemorrhagic TEAEs was similar across the 4 treatment groups.

Table 30 Summary of Treatment-emergent Adverse Events of Special Interest (AZA-AML-001: Safety population)

Events of Special Interest	Any Grade				Grade 3 or 4			
	Azacitidine (N = 236)	BSC only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemo (N = 42)	Azacitidine (N = 236)	BSC only (N = 40)	Low-dose Cytarabine (N = 153)	Intensive Chemo (N = 42)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Infection	184 (78.0)	24 (60.0)	108 (70.6)	31 (73.8)	119 (50.4)	14 (35.0)	70 (45.8)	21 (50.0)
Myelosuppression	164 (69.5)	17 (42.5)	110 (71.9)	30 (71.4)	151 (64.0)	14 (35.0)	101 (66.0)	28 (66.7)
Cardiac disorders	104 (44.1)	12 (30.0)	59 (38.6)	20 (47.6)	29 (12.3)	3 (7.5)	21 (13.7)	7 (16.7)
Hemorrhagic events	94 (39.8)	16 (40.0)	56 (36.6)	16 (38.1)	19 (8.1)	6 (15.0)	15 (9.8)	3 (7.1)
Renal failure	26 (11.0)	7 (17.5)	19 (12.4)	6 (14.3)	10 (4.2)	3 (7.5)	9 (5.9)	1 (2.4)
ILD	6 (2.5)	0	2 (1.3)	0	3 (1.3)	0	2 (1.3)	0
Hepatic failure	4 (1.7)	0	5 (3.3)	1 (2.4)	3 (1.3)	0	4 (2.6)	0
TLS	2 (0.8)	0	1 (0.7)	0	0	0	1 (0.7)	0
Ischemic colitis	0	0	0	0	0	0	0	0

BSC = best supportive care; Chemo = chemotherapy; ILD = interstitial lung disease; TLS = tumor lysis syndrome.
Percentages are based on the number of subjects in each treatment group.
Sources: Report AZA-AML-001, Table 56, Table 58, Table 60, Table 62, Table 64, Table 14.3.1.3.2.1, Table 66, Table 14.3.1.6, Table 14.3.1.19, Table 68.

Serious adverse event / deaths

In the Safety population, at least 1 serious TEAE was reported in 79.7% of subjects in the azacitidine group, 75.0% of subjects in the BSC group, 77.1% of subjects in the low-dose cytarabine group, and 64.3% of subjects in the intensive chemotherapy group (**Error! Reference source not found.**3).

The most common serious TEAEs reported in azacitidine subjects included febrile neutropenia (25.0%), pneumonia (20.3%), AML (11.0%), and pyrexia (10.6%). Serious febrile neutropenia, pneumonia, and AML events were mainly of Grade 3 or 4 severity (22.9%, 17.8%, and 8.9% of subjects). Similar trends were observed in low-dose cytarabine subjects with the most frequently reported serious TEAEs being febrile neutropenia (24.8%), pneumonia (19.0%), AML (11.1%), and pyrexia (10.5%). The percentage of subjects with serious TEAEs was lower in the intensive chemotherapy group with the most frequently reported serious TEAE being febrile neutropenia (16.7%). In the BSC-only group the most frequently reported serious TEAEs were AML (30.0%), febrile neutropenia (30.0%), and cellulitis (10.0%).

The most frequently reported Grade 3 or 4 serious TEAE was febrile neutropenia in the 4 treatment groups, which was more frequently observed in the BSC-only group (25.0%), in a similar percentage in low-cytarabine group (22.9%) and less frequently observed in the intensive chemotherapy group (16.7%) compared to the azacitidine group (22.9%).

When adjusted for duration of exposure, the rate per person-year of serious TEAEs was lower in the azacitidine group (107.5) compared to the 3 other treatment groups (312.8 for BSC only, 142.3 for low-dose cytarabine, and 191.2 for intensive chemotherapy groups).

Deaths in ITT

On-treatment deaths were defined as deaths that occurred from the date of first dose of study drug through 28 days after the date of last dose of azacitidine and low-dose cytarabine, or from the date of first dose of study drug through 70 days after the date of last dose of intensive chemotherapy, or from the date of randomization through the date of treatment period discontinuation for best supportive care only.

Similar pre-treatment, on-treatment and post-treatment death rates were reported in the 3 active treatment groups despite the longer treatment duration for azacitidine subjects. The data show that:

- post-treatment death for azacitidine was 54.8%, for LDAC was 53.2%, for intensive chemotherapy 50.0%,
- on treatment death for azacitidine was 23.2%, for LDAC was 24.7%, and for intensive chemotherapy 22.7% and that
- pre-treatment death for azacitidine was 2.1%, for LDAC was 1.9%, and for intensive chemotherapy 2.3%.

The rate of on-treatment deaths was 2-fold higher in the BSC-only group as compared to the active treatment groups. This is as expected as no active treatment has been put into place (Table).

Table 31 Summary of Deaths (Study AZA-AML-001: All Subjects)

	Screen failures (N = 184)	Azacitidine (N = 241)	Conventional Care Regimens		
			BSC-only (N = 45)	Low-Dose Cytarabine (N = 158)	Intensive Chemo (N = 44)
Time to Death	n (%)	n (%)	n (%)	n (%)	n (%)
Screening	24 (13.0)	-	-	-	-
Total Deaths After Randomization	-	193 (80.1)	42 (93.3)	126 (79.7)	33 (75.0)
Pretreatment deaths	-	5 (2.1)	0	3 (1.9)	1 (2.3)
On-treatment deaths	-	56 (23.2)	22 (48.9)	39 (24.7)	10 (22.7)
Posttreatment deaths	-	132 (54.8)	20 (44.4)	84 (53.2)	22 (50.0)

BSC = best supportive care; chemo = chemotherapy; CCR = conventional care regimen.
Note: Percentages were based on the number of subjects in each treatment group. The treatment period was defined as the period from date of first dose through (1) date of last dose + 28 days for azacitidine and low-dose cytarabine (2) date of last dose + 70 days for intensive chemotherapy. For CCR/BSC, the treatment period was defined as the period from date of randomization through date of discontinuation from the treatment period. The pretreatment period was defined as the period beginning on the date of randomization to the date of first dose. The posttreatment period was the period subsequent to the end of the treatment period.
Source: Report AZA-AML-001, Table 70.

Regarding the percentages of subjects with at least one Grade 5 TEAE (=TEAE leading to death), these were similar across the 3 active treatment groups, i.e. 23.7% of azacitidine subjects, 24.8% of low-dose cytarabine subjects, and 21.4% of intensive chemotherapy subjects, and higher in the BSC-only group (57.5% of subjects).

In the azacitidine group, the primary causes of on-treatment death were categorized by the investigator as “death from other cause” in 35 (14.8%) subjects, of whom death was attributed to pneumonia in 13 subjects, and death from “malignant disease” in 14 (5.9%) subjects, with AML in 13 subjects. Furthermore, the investigator categorized 2 deaths due to toxicity, which included pneumonia and viral pneumonia reported as the primary cause of death.

In the CCR subgroups, the primary causes of on-treatment death were categorized by the investigator as “death from other cause”:

- 14 (35.0%) subjects of whom death was attributed to pneumonia in 3 subjects in the BSC-only group,
- 17 (11.1%) subjects of whom death was attributed to septic shock in 4 subjects in the LDAC group, and
- 5 (11.9%) subjects in the intensive chemotherapy group.

In the azacitidine group, the most common TEAEs leading to death were pneumonia (6.4%) and AML (5.1%). In the other treatment groups, the Grade 5 TEAEs reported in at least 5% of subjects were AML (25.0%), pneumonia (7.5%), and cerebral haemorrhage (5.0%) in subjects receiving BSC only and AML (6.5%) in low-dose cytarabine treated subjects. In the intensive chemotherapy group, the most frequently reported Grade 5 TEAE was respiratory failure occurring in 2 subjects (4.8%).

Table 32 Primary causes of death by death category during treatment by treatment group preselection (Study AZA-AML-001: Safety Population)

Cause of Death Category (as reported by the investigator in the CRF Death Form)	AZA (N = 236)	CCR (N = 235)	Preselected to BSC		Preselected to LDAC		Preselected to IC	
			AZA (N = 42)	BSC (N = 40)	AZA (N = 151)	LDAC (N = 153)	AZA (N = 43)	IC (N = 42)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Death from malignant disease	14 (5.9)	23 (9.8)	2 (4.8)	8 (20.0)	9 (6.0)	14 (9.2)	3 (7.0)	1 (2.4)
Death from toxicity	2 (0.8)	9 (3.8)	2 (4.8)	0	0	6 (3.9)	0	3 (7.1)
Death because of other cause	35 (14.8)	36 (15.3)	6 (14.3)	14 (35.0)	25 (16.6)	17 (11.1)	4 (9.3)	5 (11.9)
Unknown (not assessable or insufficient data)	5 (2.1)	3 (1.3)	1 (2.4)	0	4 (2.6)	2 (1.3)	0	1 (2.4)

AZA = azacitidine; BSC = best supportive care; CCR = conventional care regimen; CRF = case report form; IC = intensive chemotherapy; LDAC = low-dose cytarabine.
Percentages are based on the number of subjects in each treatment group.
The treatment period is defined as the period from date of first dose through (1) date of last dose + 28 days for azacitidine and low-dose cytarabine (2) date of last dose + 70 days for intensive chemotherapy. For CCR/BSC, the treatment period is defined as the period from date of randomization through date of discontinuation from the treatment period.
Source: Table 2.1.8.1 and Table 2.1.8.2.

Death from malignant disease was most prominent in the best supportive care group (20%) and the lowest in the intensive chemotherapy subgroup (2.4%) within the CCR preselection group. The percentage of subjects dying in the azacitidine groups was more or less similar across the CCR preselection groups.

Laboratory findings

Haematology

Across all cycles for haemoglobin, the majority of subjects (54.9%) treated with azacitidine reached their lowest peripheral blood counts between Day 8 and Day 14 and the median time reach this point across all cycles was 12 days. For platelets, the majority of subjects (54.0%) reached their lowest blood counts between Day 8 and Day 14 and the median time to the lowest value across all cycles was 14 days. This would mean that the 28-day cycle generally allowed for a sufficient amount of time for patients to recover before starting the next cycle.

Overall, the median haemoglobin and platelet values in subjects treated with azacitidine improved over time. This would mean that the haematology data fit with the trend toward normalization for haemoglobin and platelets, and for transfusion independency. However, when comparing the results of azacitidine with LDAC or intensive chemotherapy, the haematological profile that was better at cycle 1 in the azacitidine group, more or less similar between the groups at cycle 2, but into favour of LDAC and intensive chemotherapy at cycle 3 and onward in case of LDAC (there were only 3 cycles of intensive chemotherapy). Regarding the BSC-only arm, also the haematological profile of these subjects steadily improved during the course of the supportive treatment, even up to cycle 6, and was better as compared to azacitidine from cycle 2 on.

Chemistry and vital signs

No important changes were noted for serum chemistry parameters and the analysis of vital sign data demonstrated no changes or trends over time.

Safety in special populations

No relevant differences were observed by gender, race or extrinsic factors upon exposure to azacitidine. Overall , TEAEs reported more often with a ⩾ 10% difference in subjects ⩾ 75 years compared to < 75 years included asthenia (30.8% compared to 13.6%) and pneumonia (28.6% compared to 18.4%). Events reported with a ⩾ 10% difference in subjects < 75 years compared to ⩾ 75 years included diarrhoea (42.7% compared to 32.3%), neutropenia (35.9% compared to 25.6%), fatigue (30.1% compared to 17.3%), and back pain (22.3% compared to 10.5%). For information, in the azacitidine treatment group, 43.6% of subjects were < 75 years of age while 56.4% of subjects were ⩾75 years of age with less than 10% of subjects were ⩾ 85 years (azacitidine n = 14).

Furthermore, the Applicant provided the safety data related to age within the azacitidine and the CCR subgroups.

Table 33. Summary of safety data according to European Medicines Agency-specified age groups (safety population)

TEAE Category	Azacitidine (N = 236)			Conventional Care Regimen (N = 235)								
				BSC only (N = 40)			Low-dose Cytarabine (N = 153)			Intensive Chemotherapy (N = 42)		
	65-74 yrs[a]	75-84 yrs	≥ 85 yrs	65-74 yrs	75-84 yrs	≥ 85 yrs	65-74 yrs	75-84 yrs	≥ 85 yrs	65-74 yrs	75-84 yrs	≥ 85 yrs
	n (%) 103 (43.6)	n (%) 119 (50.4)	n (%) 14 (5.9)	n (%) 13 (32.5)	n (%) 24 (60.0)	n (%) 3 (7.5)	n (%) 73 (47.7)	n (%) 70 (45.8)	n (%) 10 (6.5)	n (%) 31 (73.8)	n (%) 11 (26.2)	n (%) 0
Subject with at least 1 TEAE	102 (99.0)	118 (99.2)	14 (100.0)	12 (92.3)	22 (91.7)	2 (66.7)	73 (100.0)	70 (100.0)	10 (100.0)	31 (100.0)	11 (100.0)	-
Subject with at least 1 serious TEAE	78 (75.7)	99 (83.2)	11 (78.6)	9 (69.2)	19 (79.2)	2 (66.7)	57 (78.1)	52 (74.3)	9 (90.0)	18 (58.1)	9 (81.8)	-
Subjects with at least 1 fatal TEAE	21 (20.4)	29 (24.4)	6 (42.9)	6 (46.2)	16 (66.7)	1 (33.3)	22 (30.1)	13 (18.6)	3 (30.0)	6 (19.4)	3 (27.3)	-
Subjects with at least 1 TEAE leading to discontinuation of study drug	37 (35.9)	64 (53.8)	9 (64.3)	NA	NA	NA	33 (45.2)	32 (45.7)	3 (30.0)	8 (25.8)	3 (27.3)	-
Psychiatric disorders SOC	32 (31.1)	36 (30.3)	7 (50.0)	3 (23.1)	8 (33.3)	1 (33.3)	21 (28.8)	10 (14.3)	1 (10.0)	5 (16.1)	3 (27.3)	-
Nervous system disorders SOC	51 (49.5)	45 (37.8)	9 (64.3)	4 (30.8)	8 (33.3)	0 (0.0)	26 (35.6)	24 (34.3)	3 (30.0)	9 (29.0)	5 (45.5)	-
Accidents and injuries[b]	24 (23.3)	16 (13.4)	2 (14.3)	1 (7.7)	4 (16.7)	0 (0.0)	11 (15.1)	7 (10.0)	0 (0.0)	1 (3.2)	2 (18.2)	-
Cardiac disorders SOC	23 (22.3)	33 (27.7)	1 (7.1)	3 (23.1)	3 (12.5)	0 (0.0)	15 (20.5)	14 (20.0)	2 (20.0)	8 (25.8)	4 (36.4)	-
Vascular disorders SOC	29 (28.2)	41 (34.5)	5 (35.7)	2 (15.4)	7 (29.2)	0 (0.0)	22 (30.1)	17 (24.3)	5 (50.0)	8 (25.8)	2 (18.2)	-
Cerebrovascular disorders[b]	6 (5.8)	3 (2.5)	2 (14.3)	1 (7.7)	1 (4.2)	0 (0.0)	2 (2.7)	2 (2.9)	1 (10.0)	1 (3.2)	1 (9.1)	-
Infections and infestations SOC	81 (78.6)	93 (78.2)	10 (71.4)	9 (69.2)	14 (58.3)	1 (33.3)	59 (80.8)	42 (60.0)	7 (70.0)	23 (74.2)	8 (72.7)	-
Anticholinergic syndrome[b]	60 (58.3)	70 (58.8)	9 (64.3)	6 (46.2)	12 (50.0)	1 (33.3)	45 (61.6)	37 (52.9)	3 (30.0)	20 (64.5)	10 (90.9)	-
PT Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	-
Sum of Postural hypotension, falls, black outs syncope, dizziness, ataxia, and fractures[b]	36 (35.0)	36 (30.3)	3 (21.4)	1 (7.7)	4 (16.7)	0 (0.0)	17 (23.3)	12 (17.1)	2 (20.0)	3 (9.7)	3 (27.3)	-

BSC = best supportive care; MedDRA = Medical Dictionary for Regulatory Activities; NA = not applicable; PT = preferred term; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event; yrs = years.

[a] One subject was 64 years and 11 months old at study entry.

[b] Accidents and injuries defined as SMQ of Accidents and injuries, narrow scope; Cerebrovascular disorders consists of 4 Sub-SMQ: Hemorrhagic Cerebrovascular Conditions; Ischemic Cerebrovascular Conditions; Central nervous system hemorrhages and cerebrovascular accident events; and Cerebrovascular disorders, not Specified as Hemorrhagic or Ischemic, narrow scope; Anticholinergic syndrome defined as SMQ of Anticholinergic syndrome, broad scope; Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, and fracture events are defined as the MedDRA high level group term of bone and joint injuries and ad hoc preferred terms.

Note: Percentages are based on the number of subjects in each treatment group.

Sources: Appendix 4.1, Tables 16.1.1.1 to 16.1.1.3, Tables 16.1.2.1 to Table 16.1.2.3, Tables 16.1.3.1 to 16.1.3.3, Tables 16.1.4.1 to 16.1.4.3, Tables 16.1.5.1 to 16.1.5.3, Tables 16.1.6.1 to 16.1.6.3, Tables 16.1.7.1 to 16.1.7.3, Tables 16.1.8.1 to 16.3.8.3, Tables 16.1.9.1 to 16.1.9.3, Tables 16.1.10.1 to 16.1.10.3, Tables 16.1.11.1 to 16.1.11.3, Tables 16.1.12.1 to 16.1.12.3.

There is limited safety information available with azacitidine in patients ⩾85 years (with 14 [5.9%] patients ⩾85 years in AZA-AML-001 study; see SmPC section 4.8).

Safety related to drug-drug interactions and other interactions

As clinically significant inhibitory or inductive effects of azacitidine on CYPs are unlikely, drug-drug interactions are not expected to influence the safety profile of azacitidine.

Discontinuation, dose interruptions and dose reduction due to adverse events

In the azacitidine group, treatment was permanently discontinued for 46.6% of subjects, the dose was reduced for 3.4% of subjects, the treatment was interrupted for 49.2% of subjects, and the treatment was reduced and interrupted for 5.5% of subjects. Similar results were observed with low-dose cytarabine, with treatment permanently discontinued for 44.4% of subjects, the dose was reduced for 1.3% of subjects, the treatment was interrupted for 39.9% of subjects, and the treatment was reduced and interrupted for 4.6% of subjects. In the intensive chemotherapy group, the percentages of subjects who experienced TEAEs leading to discontinuation of study drug, to dose interruption and dose reduction and/or interruption was lower than in the other active treatment groups, being 26.2%, 4.8% and 9.5%, respectively (Table 7).

Table 34 Summary of Significant Treatment-emergent Adverse Events in AZA AML 001 Study

		Conventional Care Regimen	
	Azacitidine (N=236)	Low-dose Cytarabine (N=153)	Intensive Chemotherapy (N=42)
Criteria	n (%)	n (%)	n (%)
Subject with at least one TEAE leading to discontinuation	110 (46.6)	68 (44.4)	11 (26.2)
Subject with at least one TEAE leading to dose reduction	8 (3.4)	2 (1.3)	2 (4.8)
Subject with at least one TEAE leading to dose interruption	116 (49.2)	61 (39.9)	4 (9.5)
Subject with at least one TEAE leading to dose interruption and reduction	13 (5.5)	7 (4.6)	0

TEAE = treatment-emergent adverse event.
Percentages are based on the number of subjects in each treatment group.
Sources: Report AZA-AML-001, Table 77, Table 78, Table 79, and Table 80.

The most frequent TEAEs leading to azacitidine study drug discontinuation were AML (16.1%) and pneumonia (7.6%). For these subjects the frequency of haematological or gastrointestinal TEAEs leading to study drug discontinuation was 4.2% and 0.8% (from clinical study report), respectively.

In the LDAC group the pattern of study drug discontinuation was more or less similar as for the azacitidine group with 5.9% discontinuations due to pneumonia and 18.3% due to AML. In the intensive chemotherapy group, the incidence of AEs leading to drug discontinuation was (more than) 2-fold lower compared to other active treatment groups and the pattern of TEAEs somewhat different. In this respect, the TEAEs that led to study drug discontinuation in the intensive chemotherapy group were primarily the infections and infestations (7.1%), but not pneumonia and no cases of AML was reported. In the BSC-only group there were no discontinuations reported. Action taken with study medication was not recorded for TEAEs occurring within the BSC only treatment group; thus there are no TEAEs reported as leading to Discontinuation in this treatment group.

Treatment-emergent AEs leading to dose reduction and/or interruption of azacitidine treatment were primarily haematological disorders, mainly neutropenia. Similar trends regarding pattern and incidence were noted for subjects treated with low-dose cytarabine. Relatively few or no dose reductions and/or interruptions were observed in the BSC-only and the intensive chemotherapy group, this is as expected considering the purpose and/or the duration of the treatments.

Discontinuation within the CCR preselection groups

Best supportive care preselection group

Action taken with study medication was not recorded for TEAEs occurring within the best supportive care only treatment group, and thus there are no TEAEs reported as leading to discontinuation in this treatment group.

Low-dose cytarabine preselection group

Within the low-dose cytarabine preselection group, the most frequently reported TEAEs leading to study discontinuation (≥ 5% of subjects) reported in subjects included pneumonia and AML. All TEAEs leading to study discontinuation were reported at comparable frequencies (<10% difference) between the azacitidine-treated subjects and the low-dose cytarabine treated subjects.

Intensive chemotherapy preselection group

Within the intensive chemotherapy preselection group the most frequently reported TEAEs leading to study discontinuation (≥ 5% of subjects) included AML, which was reported in 20.9% of azacitidine-treated subjects vs 0% in intensive chemotherapy-treated subjects. As described previously, subjects treated with intensive chemotherapy were unlikely to have an event of AML resulting in discontinuation of study treatment due to the relatively short treatment duration. All other TEAEs leading to study discontinuation were reported at comparable frequencies between the two treatment groups.

Post-marketing experience

The results from the PSUR indicate that the important identified risks are myelosuppression, haemorrhagic events, infections, renal failure, ischemic colitis, hepatic failure, ILD, anxiety, confusional state and insomnia, and tumour lysis syndrome. The important potential risks are other psychiatric disorders, malignancies (including injection site tumours), male infertility, prenatal developmental toxicity and cardiac events.

As acknowledged by the Applicant, the important missing information for azacitidine are use in renal impairment, use in hepatic impairment, use in cardiac impairment, effect on QT-interval, interactions with other drugs (including cytotoxic), and use in children.

- Investigator-initiated trials

The safety profile observed with azacitidine in Study AZA-AML-001 and in the investigator-initiated trials is consistent with that previously observed and reported for Vidaza in the currently approved indications. In this respect, the events reported were generally similar, although differences in frequency were observed. This may be related to the fact that Celgene does not have access to the safety databases for these trials. In addition, the study designs, patient populations (inclusion/exclusion criteria), data collection methods, and treatment regimens varied widely with most of the studies evaluating azacitidine at various doses in various combinations with other treatments.

Nevertheless, it can be agreed that the general pattern of SAEs reported from these non-Celgene sponsored AML studies appear to be consistent with the safety profile of azacitidine and do not suggest any new safety issues with azacitidine.

2.5.2. Discussion on clinical safety

Azacitidine has been marketed and widely used for the approved indications of higher-risk MDS and AML 20% to 30% blasts since 2004, with an estimated 216,066 patients treated. In the pivotal trial of this MAA, a total of 471 patients received at least 1 dose of study drug and had at least 1 post-dose

safety assessment (at least 1 post-randomization safety assessment for BSC only), and were thus evaluable for safety analyses. This safety population included 236 subjects in the azacitidine group, 40 subjects in the BSC-only group, 153 subjects in the low-dose cytarabine group, and 42 subjects in the intensive chemotherapy group. The majority of subjects in the overall study population (60.1%) were classified as AML not otherwise specified. The other WHO AML subtypes were AML with myelodysplasia-related changes (32.7%), therapy-related myeloid neoplasms (4.2%), and AML with recurrent genetic abnormalities (3.0%). Furthermore, the duration of exposure (in person-years) was longer in the azacitidine group than in the other treatment subgroups. Within each of the investigator's choice preselection treatment groups, the median duration of exposure, median duration of treatment, and treatment exposure in person-years were also longer in the azacitidine-treated subjects compared to each individual CCR treatment group (i.e., best supportive care, low-dose cytarabine, or intensive chemotherapy).

Most of the patients included in the study did not have a dose modification, irrespective of the type of study arm/CCR subgroup. In the azacitidine treatment group, the main reason for dose modifications was haematological toxicity and for the CCR subgroups, this was classified as "other". Overall, the azacitidine and combined CCR treatment groups were comparable for baseline demographic and disease characteristics, except for the number of prior anti-cancer systemic therapies, which was in favour of the azacitidine arm.

Regarding the most common TEAEs, in the azacitidine group these involved gastrointestinal disorders (mainly constipation, nausea, and diarrhoea), general disorders and administration site conditions (mainly pyrexia), and haematological disorders (mainly febrile neutropenia and neutropenia). This would be consistent with the underlying disease and the known pharmacology of azacitidine.

Regarding the occurrence of AML during the study, apparently this was the lowest in the intensive chemotherapy CCR subgroup. However, when all information was combined, the overall frequency of all AML events appeared similar between all treatment groups.

The risks for infection and myelosuppression were not unexpected considering the known safety profile of azacitidine and the patient population at hand. Also, the events appeared manageable with dose adjustment, dose delay, and supportive treatment.

The pattern of serious TEAEs, of Grade 3 or 4 serious TEAEs, of common AEs and treatment-related AEs was more or less the same between the azacitidine and the individual CCR, also between the respective treatment groups, with the most frequently occurring events being febrile neutropenia, pneumonia and AML.

Within the investigator choice preselection CCR subgroups, the data further show that in azacitidine-treated subjects, the TEAEs from these SOCs were reported at a higher frequency (>10% difference) compared to the best supportive care only subjects, and at a similar frequency compared to low-dose cytarabine subjects, except for Skin and subcutaneous tissue disorders (i.e. 50.3% azacitidine vs 39.2% low-dose cytarabine),Gastrointestinal disorders (i.e. 81.5% azacitidine vs 69.9% low- dose cytarabine) and General Disorders (i.e. 82.8% azacitidine vs 71.2% low- dose cytarabine).

Compared to intensive chemotherapy subjects, TEAES were reported:

- at similar frequencies (<10% difference) for the SOCs Blood and lymphatic system disorders, Gastrointestinal Disorders, Infections and infestations, Investigations, Skin and subcutaneous tissue disorders, Vascular disorders, Metabolism and nutrition disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders, and

-more frequently (>10% difference) for the SOCs General disorders and administration site conditions, Musculoskeletal and connective tissue disorders, Neoplasms benign, malignant and unspecified (incl cysts and polyps), Nervous system disorders, Psychiatric disorders, relative to the azacitidine treatment group.

It is acknowledged that when adjusted for duration of exposure, the incidence rates for TEAEs in these SOCs in the azacitidine-treated subjects were either similar (vs low-dose cytarabine) or lower (vs best supportive care or intensive chemotherapy). However, correction for the duration of the treatment/exposure does not seem to be appropriate when comparing the safety profile between study treatments as this does not represent the actual incidence of (TE)AES in relation to the respective treatment and thereby the clinical situation.

Similar pre-treatment, on-treatment and post-treatment death rates were reported in the 3 active treatment groups despite the longer treatment duration for azacitidine subjects. Furthermore, the pattern of primary causes of death as reported by the investigator's in the azacitidine vs the individual CCR groups is similar as observed for the TEAEs leading to death and this points at these data being consistent. The causes of death were seemingly similar between the azacitidine and the CCR subgroups.

Treatment-emergent AEs leading to reduction and/or interruption of azacitidine treatment were primarily haematological disorders, mainly neutropenia. Similar trends regarding pattern and incidence were noted for subjects treated with low-dose cytarabine. Relatively few or no dose reductions and/or interruptions were observed in the BSC-only and the intensive chemotherapy group. These data indicate that the treatments were tolerable for the patients studied.

Regarding the safety data from other sources, the risks of azacitidine treatment seem to remain consistent across all sources and relate primarily to the known pharmacology of azacitidine and include myelosuppression and associated infections and gastrointestinal toxicities.

2.5.3. Conclusions on clinical safety

Azacitidine was generally well tolerated in elderly patients with newly diagnosed AML, with bone marrow blast count > 30%, and who were not eligible for HSCT. No new risks of azacitidine were identified. Based on the available data, azacitidine showed a well-known safety profile of azacitidine that although acceptable, may be less favourable in comparison to best supportive care, comparable to low dose cytarabine and less favourable or similar to the intensive chemotherapy regimen.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

ON 10 April 2015, the PRAC considered that the RMP version 10 (dated 09 December 2014) is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

Further to the MAH's responses to the CHMP request for supplementary information, the CHMP endorsed the RMP version 12 (dated 23 September 2015) with the following content (changes between version 10 and 12 of the RMP are pointed out in bold:

Safety concerns

Table 35: Summary of safety concerns

Summary of safety concerns	
Important identified risks	- Myelosuppression - Haemorrhagic events - Infections - Renal failure - Hepatic failure - Interstitial lung disease - Anxiety, confusional state, insomnia - Tumour lysis syndrome
Important potential risks	- Ischaemic colitis - Other psychiatric disorders - Malignancies (including injection site tumours) - Male infertility - Prenatal development toxicity - Cardiac events
Missing information	- Use in renal impairment - Use in hepatic impairment - Use in cardiac impairment - Effect on QT interval - Interactions with other drugs (including cytotoxics) - Use in children - Use in very elderly (≥ 85 years) patients

Pharmacovigilance plan

Table 36: Ongoing, planned and completed studies in the PhV development plan

Activity / Study title	Objectives	Safety concerns addressed	Status Planned, started, completed	Date for submission of interim or final reports (planned or actual)
AZA PH US 2007 PK 006	To assess the safety and tolerability of azacitidine given SC in patients with varying degrees of renal impairment	Use in Patients with Renal Impairment	Completed	27 Jun 2014
AZA PH US 2007 CL 005	Evaluate the safety, PK, and PD of oral azacitidine	Use in Patients with Renal Impairment (PK analysis of patients with varying degree of renal function/part 1 in patients receiving SC azacitidine)	Completed	27 Jun 2014

The PRAC, having considered the updated data submitted, was of the opinion that routine pharmacovigilance remains sufficient to identify and characterise the risks of the product.
The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Table 37: Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Myelosuppression	• Section 4.2 of the SmPC - Recommendations on dose adjustments and delay based on haematology laboratory values to reduce the risk. • Section 4.4 of the SmPC - Warnings regarding haematological toxicity and how to monitor this risk. • Section 4.8 of the SmPC - Listed as ADRs and details on the frequency and severity for thrombocytopenia, neutropenia and leukopenia.	• None
Haemorrhagic Events	• Section 4.2 of the SmPC - Recommendations on dose adjustments and delay based on haematology laboratory values including platelet count, to reduce the risk. • Section 4.4 of the SmPC - Warnings regarding thrombocytopenia and how to monitor this risk. • Section 4.8 of the SmPC - Details on haemorrhagic ADRs.	• None
Infections	• Section 4.2 of the SmPC - Recommendations on dose adjustments and delay based on haematology laboratory values including ANC, to reduce the risk. • Section 4.4 of the SmPC - Warnings regarding	• None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	neutropenia and how to monitor this risk. • **Section 4.4 of the SmPC - Warnings regarding necrotising fasciitis.** • ADRs of infections, **including necrotising fasciitis,** listed in Section 4.8 of the SmPC.	
Renal Failure	• Section 4.2 of the SmPC - Recommendations on dose adjustments based on renal function and serum electrolytes. • Section 4.4 of the SmPC - Warnings regarding renal abnormalities. • Listed as ADRs in Section 4.8 of the SmPC.	• None
Hepatic failure	• Section 4.2 of the SmPC - Recommendations for monitoring liver chemistries and for monitoring patients with severe hepatic organ impairment. • Section 4.3 of the SmPC - Contraindication in patients with advanced malignant hepatic tumours. • Section 4.4 of the SmPC - Warning in patients with severe hepatic impairment.	• None
Interstitial Lung Disease	• Listed as an ADR in Section 4.8 of the SmPC.	• None
Anxiety, Confusional State, Insomnia	• Listed as an ADR in Section 4.8 of the SmPC.	• None
Tumour Lysis Syndrome	• Listed as an ADR in Section	• None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	4.8 of the SmPC.	
Important Potential Risks		
Ischaemic Colitis	• Ischaemic colitis is not a confirmed safety signal for azacitidine treatment. • Gastrointestinal events (such as constipation, abdominal pain and gastrointestinal haemorrhage) listed as ADRs in Section 4.8 of the SmPC.	• None
Other Psychiatric Disorders	• Anxiety, confusional state, insomnia are listed as ADRs in Section 4.8 of the SmPC.	• None
Malignancies (including injection site tumours)	• Studies have shown that azacitidine is carcinogenic and mutagenic in rats and mice (Section 5.3 of the SmPC).	• None
Male Infertility	• Section 4.6 of the SmPC - Men should be advised not to father a child while receiving treatment. Before starting treatment, male patients should be advised to seek counselling on sperm storage.	• None
Prenatal Development Toxicity	• Section 4.6 of the SmPC - Azacitidine should not be used during pregnancy unless clearly necessary. • Due to the potential serious adverse reactions in the nursing child, breastfeeding is contraindicated during azacitidine therapy (Sections 4.3 and 4.6 of the SmPC).	• None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardiac Events	• Section 4.4 of the SmPC – Warning for patients with cardiac and pulmonary disease • Increased incidence in Vidaza-treated patients with newly diagnosed AML and known history of CV or pulmonary disease described in Section 4.8 of the SmPC	• None
Missing Information		
Use in renal impairment	• Section 4.2 of the SmPC - Recommendations for monitoring AEs in patients with severe renal impairment. • Section 4.4 of the SmPC - Warning for patients with severe renal impairment.	• None
Use in Hepatic Impairment	• Section 4.2 of the SmPC - Recommendations for monitoring AEs in patients with severe hepatic impairment. • Section 4.3 of the SmPC - Contraindication in patients with advanced malignant hepatic tumours. • Section 4.4 of the SmPC – Warning for patients with severe hepatic impairment	• None
Use in Cardiac Impairment	• Section 4.4 of the SmPC - Warning for patients with cardiac impairment.	• None
Effects on QT Interval	• None	• None
Interactions with Other Drugs	• Section 4.5 and 5.2 of the SmPC - Details of potential	• None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
(including cytotoxics)	interactions	
Use in Children	• Section 4.2 of the SmPC - Indicates that azacitidine is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.	• None
Use in Very Elderly (≥ 85 years) Patients	• Section 4.2 of the SmPC - Recommendations for elderly patients. • Section 4.8 of the SmPC - Mention of limited safety information in very elderly (≥ 85 years) patients.	• None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- the changes to the patient information leaflet are minimal and do not constitute any of the categories that require a new consultation in addition to the testing that have already been performed (in accordance with Articles 59(3) and 61(1) of Directive 2001/83/EC as amended).

3. Benefit-Risk Balance

Benefits

Beneficial effects

The current Type II variation seeks approval for a new indication: “Vidaza is indicated for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to WHO classification.”

The efficacy claims of this application are supported by the efficacy results of a Phase 3, international, multicenter, controlled study with an open-label, randomized, parallel-group design conducted by the MAH (Study AZA-AML-001).

The primary objective of the pivotal study was to demonstrate superiority in overall survival of azacitidine (n=241) compared to combined conventional care regimens (CCR) (n=247) as treatment of elderly AML patients (⩾ 65 years of age) with > 30% bone marrow blasts (according to WHO criteria) that were not eligible for HSCT. The secondary endpoints were 1-year overall survival rate,

event free survival (EFS), relapse free survival (RFS), remission rate (CR + CRincomplete (CRi)), duration of remission (CR + CRi), cytogenetic complete remission rate (CRc), Safety / tolerability, EORTC QLQ-C30), and Measures of healthcare resource utilization. The chosen primary and secondary endpoints fit the overall aim of the study.

Together, the design of the study served the objectives of the study and the patient and disease characteristics define an appropriate patient population to evaluate the efficacy of azacitidine vs CCR in the pivotal study.

After a median follow-up time of 24.4 months, the median OS was 10.4 months (95% CI = 8.0, 12.7) in the azacitidine group (N = 241) compared with 6.5 months (95% CI = 5.0, 8.6) in the combined CCR group with an observed difference in median OS of 3.8 months. The OS HR for the azacitidine group vs CCR was 0.85 (95% CI = 0.69, 1.03). The difference between survival curves based on the log-rank test did not reach the predefined level of significance (log rank test, with a stratified p = 0.1009). Analysis of pre-specified subgroups showed a consistent trend for OS advantage in favour of azacitidine across subgroups, which reached statistical significance in patients with poor cytogenetic risk, patients with AML with myelodysplasia-related changes, patients younger than 75 years, female, or white.

The clearest difference between the study arms in terms of the secondary endpoints was observed in the 1-year survival rate with an improvement of 12.3% (95% CI = 3.5, 21.0) in the estimate for the azacitidine group (46.5% [95% CI = 40.1, 52.7]) versus the combined CCR group (34.3% [95% CI = 28.3, 40.3]). In addition, there was a suggestion of a trend towards an improved median EFS with azacitidine compared to the combined CCR treatment group (6.7 months versus 4.8 months respectively). No differences were noted between the experimental and the control arm for the other secondary endpoints on disease control, i.e. haematologic response, morphologic response, RFS and duration of remission. Rates of conversion of subjects from RBC transfusion dependence to RBC transfusion independence, and from platelet transfusion dependence to platelet transfusion independence tended to be in favour of azacitidine.

Planned exploratory analyses based on investigator's preselection for CCR showed that, within the treatment selection group, the median OS was longer in the azacitidine treated groups for the subjects selected for BSC (5.8 versus 3.7 months; p = 0.0288), or low-dose cytarabine, but the latter was not significant (11.2 versus 6.4 months; p = 0.4270). Survival was similar in the intensive chemotherapy choice groups (13.3 for azacitidine versus 12.2 months for chemotherapy; p = 0.5032).

Considering the heterogeneity of the study population, the slight imbalances of the key baseline characteristics within the CCR treatment groups and the fact that several of these baseline characteristics are interdependent, a multivariate Cox proportional hazards (PH) model was applied to adjust for established patient- and disease-related, pre-specified baseline prognostic factors. The analysis resulted in an OS HR for azacitidine versus CCR of 0.80 (95% CI: 0.66, 0.99), with a 20% reduction of the risk of death and a nominal p-value below 0.05 (p = 0.0355).

Regarding the impact of baseline factors on OS results in subgroups within the preselection groups, the following results were observed:

Best supportive care - there was a consistent trend in OS benefit (as measured in OS HR) across the subgroups in favour of azacitidine compared with best supportive care; this was seemingly a more favourable pattern as observed in the ITT;

Low dose cytarabine - there seems to be a consistent trend in OS benefit (as measured in OS HR) across the subgroups in favour of azacitidine compared with low-dose cytarabine when looking at the

OS HR point-estimates, though the trend was weaker as observed in the best-supportive care group. The pattern was more or less similar to what was observed with the ITT population.

The number of subjects in the individual prespecified subgroups relating to baseline factors within the preselection groups is small. This implies that caution should be applied when drawing conclusions on the OS HR results in this setting. This is in particular relevant for the preselection group of intensive chemotherapy. Nevertheless, in view of the consistent effect, it is possible to conclude that efficacy has been established and that the effect on OS associated with azacitidine is of a similar magnitude compared to low-dose cytarabine and intensive chemotherapy, and improved compared to best supportive care.

Uncertainty in the knowledge about the beneficial effects

Due to the (inherent) limitations that accompany HRQoL assessment (i.e. patient not completing the questionnaires as scheduled) and because the decrease in number of evaluations in time differed between treatment groups, clear conclusions cannot be drawn. Thus, the impact of treatment on HRQoL remains uncertain. This has been adequately reflected in the SmPC (see section 5.1).

Risks

Unfavourable effects

The most common serious adverse reactions (⩾10%) noted from AZA-AML-001 within the azacitidine treatment arm included febrile neutropenia (25.0%), pneumonia (20.3%), and pyrexia (10.6%). Other less frequently reported serious adverse reactions in the azacitidine treatment arm included sepsis (5.1%), anaemia (4.2%), neutropenic sepsis (3.0%), urinary tract infection (3.0%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%) and dyspnoea (2.1%).

The most commonly reported (⩾30%) adverse reactions with azacitidine treatment were gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhoea (36.9%), (usually Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; usually Grade 1-2) and haematological events, including febrile neutropenia (32.2%) and neutropenia (30.1%), (usually Grade 3-4).

Regarding the occurrence of AML during the study, this is the lowest in the intensive chemotherapy CCR subgroup (i.e. 2.4% vs 20.8% azacitidine vs 32.5% BSC vs 24.2% LDAC).

The review of the TEAEs of special interest showed that the risks for infection and myelosuppression were not unexpected considering the known safety profile of azacitidine and the patient population at hand. Also, the events appeared manageable with dose adjustment, dose delay, and supportive treatment.

The pattern of serious TEAEs, of Grade 3 or 4 serious TEAEs, of common AEs and treatment-related AEs was more or less the same between the Azacitidine and the individual CCR, also between the respective treatment groups, with the most frequently occurring events being febrile neutropenia, pneumonia and AML.

Most TEAEs were reported in the SOCs General disorders and administration site conditions, Gastrointestinal disorders, Infections and infestations, and Blood and lymphatic system disorders.

Compared to intensive chemotherapy subjects, TEAEs were reported similar to more frequent in differential SOCs. Not adjusting for the duration of treatment showed a safety profile of azacitidine to be less favourable in comparison to best supportive care, comparable to low dose cytarabine and less favourable to similar to the intensive chemotherapy regimen.

Regarding the safety data from other sources, the risks of azacitidine treatment seem to remain consistent across all sources and relate primarily to the known pharmacology of azacitidine and include gastrointestinal toxicities and myelosuppression and associated infections.

Uncertainty in the knowledge about the unfavourable effects

The interpretation of the data regarding the fatal TEAE and TEAE in the azacitidine group in the oldest age group (>85 years), is hampered by the limited number of patients in this category (this has been adequately reflected in the SmPC (see section 4.8).

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The majority of older patients with AML should be offered definitive anti-leukaemic therapy to prolong both duration and quality of life remaining. Performance status, comorbidities, disease biology, quality of life (QoL), and long-term treatment goals should all be considered in the selection of the most appropriate therapeutic approach for each patient. OS is an important endpoint in this disease. Based on the data submitted, it is possible to conclude that efficacy has been established and that the effect on OS associated with azacitidine is of a similar magnitude compared to low-dose cytarabine and intensive chemotherapy, and improved compared to best supportive care.

Azacitidine was generally well tolerated in elderly patients with newly diagnosed AML, with bone marrow blast count > 30%, and who were not eligible for HSCT. No new risks of azacitidine were identified. Based on the available data, azacitidine showed the well-known safety profile of azacitidine that, although acceptable, may be less favourable in comparison to best supportive care, comparable to low dose cytarabine and less favourable or similar to the intensive chemotherapy regimen. Although some of the toxicity associated with azacitidine was higher compared to intensive chemotherapy, azacitidine was generally well-tolerated.

Benefit-risk balance

Based on the effect on OS associated with azacitidine, which is of a similar magnitude compared to low-dose cytarabine and intensive chemotherapy, and improved compared to best supportive care, and the fact that azacitidine is generally well-tolerated and has a well-known and manageable safety profile, the benefits outweigh the risks for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification.

Discussion on the Benefit-Risk Balance

Acute myeloid leukaemia is a heterogeneous disease in terms of response to treatment and overall survival. Prognostic factors that contribute to this heterogeneity can be both patient and disease related, including blasts counts. The new indication for azacitidine aims to extend the current indication into elderly AML patients with >30% blasts. This population would represent patients with a different stage of the disease and who have a greater incidence of poor prognostics factors, implying a greater severity of disease with poorer outcomes, as compared to the authorized AML indication for Vidaza in the EU.

Given the poor overall outcome and high treatment-related mortality in older AML patients, some physicians do not pursue aggressive induction therapy, opting for less aggressive therapies. Treatment options are few for patients who choose not to receive intensive chemotherapy or are considered ineligible (unfit) to receive intensive chemotherapy by their physician. Patients considered ineligible for intensive chemotherapy are generally patients older than 75 years or those

60 to 75 years old with significant co-morbidities, poor performance status, or with complex cytogenetic abnormalities.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to add treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the WHO classification, based on the pivotal phase III study AZA- AML-001. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. A revised RMP version 12.0 was agreed during the procedure.

Similarity with authorised orphan medicinal products

The CHMP is by consensus of the opinion that Vidaza is not similar to Ceplene and Dacogen within the meaning of Article 3 of Commission Regulation (EC) No. 847/200..

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies