PTJA12 - Core Submission Dossier

Glasdegib

Acute myeloid leukaemia

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Abbreviations

Abbreviation	Definition
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike's information criterion
AML	Acute myeloid leukaemia
AMLSG	Study Group Acute Myeloid Leukaemia
APL	Acute promyelocytic leukaemia
AZA	Azacitidine
BIC	Bayesian information criterion
BID	Twice daily
BSC	Best supportive care
CI	Confidence interval
CR	Complete remission
CRc	Cytogenetic complete response
CRF	Case report form
CRi	CR with incomplete haematologic recovery
CRm	Molecular complete response
CRp	CR with incomplete platelet recovery
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
DEC	Decitabine
DSU	Decision Support Unit
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group Performance Status
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
EQ-5D	EuroQoL 5-Dimensional Questionnaire
EU	European Union
FAB	French-American-British
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
G-BA	German Federal Joint Committee (Gemeinsamer Bundesausschuss)
GLAS	Glasdegib
HAS	Haute Autorité de Santé
HLA	Human leukocyte antigen
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Hematopoietic stem cell transplantation
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
ICU	Intensive care unit
IPD	Individual patient data
ITC	Indirect treatment comparison

Abbreviation	Definition
IV	Intravenous
IVRS	Integrated voice response system
KM	Kaplan Meier
LDAC	Low-dose cytarabine
MDS	Myelodysplastic syndrome
MLFS	Morphologic leukaemia-free state
MedDRA	Medical Dictionary for Regulatory Activities
NCCN	National Comprehensive Cancer Network
NGS	Next generation sequencing
NICE	National Institute for Health and Care Excellence
NIH	US National Institutes of Health
NMA	Network Meta-Analysis
NPM1	Nucleophosmin
OS	Overall survival
PCR	Polymerase chain reaction
PFS	Progression-free survival
PH	Proportional hazards
PICO	Patient, intervention, comparison, outcome
PR	Partial response
PT	Preferred term
Q-TWiST	Quality-adjusted Time without symptoms of disease progression or toxicity
QALY	Quality-adjusted life years
QLQ	Quality of Life Questionnaire
QoL	Quality of life
RARECARE	Rare Cancers Registry
RCT	Randomized controlled trial
RFS	Relapse-free survival
RR	Relative risk
SAE	Serious adverse event
SC	Subcutaneous
SLR	Systematic literature review
SMO	Smoothened
SOC	System organ class
STC	Simulated treatment comparison
SmPC	Summary of product characteristics
TC	Treatment choice
UK	United Kingdom
US	United States
VAS	Visual analogue scale
WBC	White blood cell count
WHO	World Health Organisation

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Executive Summary

Health problem

- Acute myeloid leukaemia (AML) is a rare, orphan haematologic cancer.
- AML progresses rapidly and is typically fatal within weeks or months if left untreated.
- Symptoms of AML caused by cytopenia and bone marrow infiltration by myeloblasts (e.g. fatigue, loss of performance and infections) have a severe negative impact on patient-reported health-related quality of life (HRQoL).
- About a third of AML patients are not candidates for standard induction chemotherapy for reasons such as performance status or comorbidities.
- The target population of glasdegib includes adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy.

Current clinical practice

- Patients who are not candidates for standard induction chemotherapy are generally frailer and older with more comorbidities, thus leading to poorer treatment outcomes.
- Given the aggressiveness of AML, the therapeutic goal for these patients is to extend survival.
- The current European treatment guidelines recommend the following non-intensive chemotherapy options for AML patients who are not candidates for standard induction chemotherapy: Low-dose cytarabine (LDAC) or the hypomethylating agents (HMA) azacitidine and decitabine. HMAs have shown numerically but not statistically significantly longer overall survival (OS) than LDAC in AML patients who are not candidates for standard induction chemotherapy, making these three treatment options equivalent in terms of efficacy.

Glasdegib (DAURISMO^{R})

- Glasdegib is an inhibitor of the Hedgehog signal transduction pathway that binds to Smoothened, a Class Frizzled G protein-coupled receptor encoded by the *smoothened* gene.
- Glasdegib is an oral agent given in combination with LDAC (glasdegib + LDAC), which can be self-administered by the patient at home.
- Glasdegib + LDAC is indicated (in the EU) for the 'treatment of newly diagnosed de novo or secondary acute myeloid leukaemia in adult patients who are not candidates for standard induction chemotherapy'.
- The licenced dose of glasdegib in combination with LDAC is 100 mg orally once daily. LDAC is given subcutaneously (SC) with 20 mg twice daily on days 1 to 10 of each 28-day cycle.

- The efficacy and safety of glasdegib + LDAC in the treatment of adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy was demonstrated in BRIGHT AML 1003, a phase 2 randomized, open-label, multicenter study.

Identification and characteristics of relevant studies

- A systematic literature search identified three relevant studies as a basis for this assessment for direct comparison of glasdegib + LDAC vs LDAC alone (BRIGHT AML 1003) and indirect comparison of glasdegib + LDAC vs azacitidine (AZA-AML-001) and vs decitabine (DACO-016).
- The BRIGHT AML 1003 study population included patients with newly diagnosed AML who are not candidates for standard induction chemotherapy; these patients were randomized 2:1 to glasdegib + LDAC or LDAC alone, stratified by cytogenetic risk (good/intermediate or poor).
- Glasdegib 100 mg once daily was administered orally in 28-day cycles on a continuous basis and LDAC was given at a dose of 20 mg administered SC twice daily for 10 days on a 28-day cycle.
- The AZA-AML-001 study evaluated azacitidine efficacy and safety vs conventional care regimens in patients age ≥ 65 years with newly diagnosed AML with > 30 % bone marrow blasts; DACO-016 compared the efficacy and safety of decitabine to treatment choice in older patients with newly diagnosed AML and poor- or intermediate-risk cytogenetics.

Endpoints

- ***Overall survival:*** OS is considered the gold standard primary endpoint of clinical trials by physicians and health regulatory agencies and is therefore the most frequently used primary endpoint in AML clinical trials. OS was measured as time from the date of randomization to the date of death from any cause.
- ***Quality of survival:*** The quality of life of patients is an important component in the evaluation of therapies given the high morbidity (including frequent transfusions and hospitalizations) and mortality associated with AML. In BRIGHT AML 1003, a Q-TWiST analysis (Quality-Adjusted Time Without Symptoms of Disease Progression or Toxicity) was performed, which incorporates quality-of-life considerations into treatment comparisons. The basis of the Q-TWiST method is that patients with no disease symptoms or treatment toxicity have better health-related quality of life than those who have disease symptoms and toxicity. Therefore, the Q-TWiST method provides a tool to assess the net benefits of oncology treatments in terms of quantity (OS, time without symptoms of disease progression or toxicity, and toxicities (i.e. AEs)) and quality (patient health utilities) of survival gained.
- ***Objective response:*** Complete remission (CR) is defined as: neutrophils ≥ 1.000 µl, platelets ≥ 100.000/µl leukemic blasts < 5 % of nucleated bone marrow cells, and transfusion independence. CR with incomplete blood count recovery (CRi) is defined as CR criteria except for residual neutropenia (< 1.000/µL) **or** thrombocytopenia

(< 100.000/µL); morphologic leukaemia-free state (MLFS) as CR criteria except for residual neutropenia (< 1.000/µL) **and** thrombocytopenia (< 100.000/µL).

- ***Transfusion need:*** Transfusion independence is considered a robust indicator for a recovery from AML symptoms and a strong contributor to improving AML patients' HRQoL. In addition, greater transfusion independence and decreased transfusion requirements may have the potential to result in cost reductions for patients and payers. Transfusion need is presented in terms of absolute and relative frequencies of blood product transfusions.
- ***Safety:*** Adverse events (AEs) were collected in a standardised manner as part of the studies. It can be assumed that the AEs are directly noticeable to the patient and have a direct influence on the patient's well-being.

Results on clinical outcomes

- ***The OS benefit associated with glasdegib + LDAC was both statistically significant and clinically meaningful*** (HR [95% CI]: 0.46 [0.30, 0.72]; p = 0.0002; median OS: 8.3 months vs. 4.3 months).

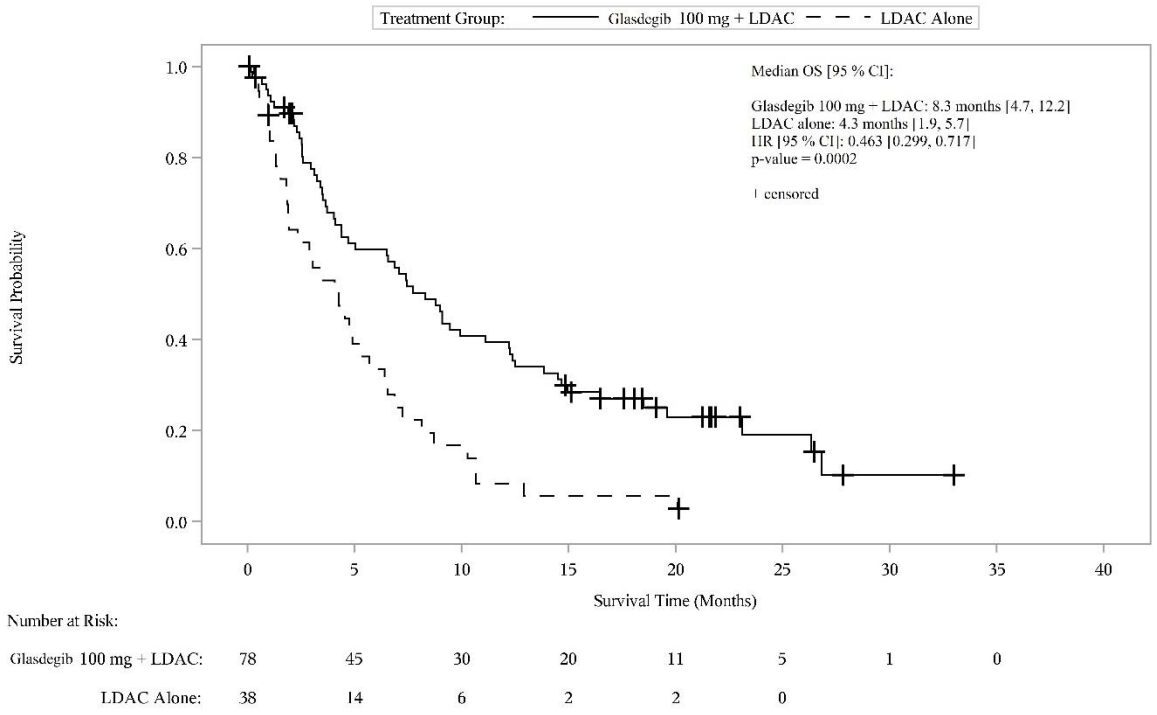


Figure 1: Kaplan-Meier plot of OS for BRIGHT AML 1003

- ***Indirect treatment comparison on overall survival***
  - *Glasdegib + LDAC vs. azacitidine*

    Standard ITC (Bucher) demonstrated a ***statistically significant benefit of glasdegib + LDAC compared to azacitidine*** (HR [95% CI]: 0.51 [0.31, 0.85]) Simulated Treatment Comparisons (STC) were conducted as a supportive

analysis and the results and conclusions were similar to the standard ITC (Bucher) analysis.

- *Glasdegib + LDAC vs. decitabine*

  Standard ITC (Bucher) also demonstrated a ***statistically significant benefit of glasdegib + LDAC compared to decitabine*** (HR [95 % CI]: 0.57 [0.35, 0.91]). STC were conducted as a supportive analysis and the results and conclusions were similar to the standard ITC (Bucher) analysis.

- **Q-TWiST** was 4.0 months longer for glasdegib + LDAC, translating into a statistically significant and clinically meaningful ***75 % relative improvement in quality-adjusted survival compared to LDAC alone***.
- The benefit of glasdegib + LDAC was also substantial with regard to ***objective response*** (including CR, CRi, MLFS): ***Significantly more patients in the glasdegib + LDAC arm achieved CR and objective response (CR + CRi + MLFS) compared to LDAC alone*** (17.9 % vs. 2.6 %; p = 0.0235 and 26.9 % vs. 5.3 %; p = 0.0080, respectively).
  - ***A significantly higher proportion of transfusion-independence was reported with glasdegib + LDAC*** vs. LDAC alone (e.g. transfusion independence ≥ 8 weeks: 28.2 % vs. 5.3 %; p=0.0056), enabling patients to spend more time away from the hospital and improve QoL.

Results on safety outcomes

- Overall ***rates of AEs were comparable between glasdegib + LDAC and LDAC alone***, even though patients were treated for longer time periods with glasdegib + LDAC.
- ***Statistically significant fewer patients had a fatal AE with glasdegib + LDAC***, and fewer patients discontinued treatment with glasdegib + LDAC due to AEs compared to LDAC alone.
- ***No differences between glasdegib + LDAC and LDAC alone were observed regarding AEs commonly expected for antileukemic treatment***: febrile neutropenia, haemorrhage, QT prolongation and infections, incl. pneumonia.

Conclusion

Glasdegib is the first new agent to provide a survival benefit over LDAC in a randomized setting in newly diagnosed AML patients, who are not candidates for standard induction chemotherapy.

Glasdegib + LDAC nearly doubled overall survival compared to LDAC alone and the OS benefit was consistent across demographic and clinical subgroups. Moreover, standard (Bucher) ITC and STC analyses on OS demonstrated ***statistically significant benefit of glasdegib + LDAC over the HMAs azacitidine and decitabine***.

- The Q-TWiST results complemented the efficacy findings and suggest that most of the OS benefit with glasdegib + LDAC is ***added time spent in 'good' health***. ***The OS benefit was further supported by additional clinically meaningful, patient-relevant endpoints*** such as objective response (including CR, CRi, MLFS) and

transfusion independence, especially the latter being strongly correlated with blood count recovery and an alleviation of symptoms. At the same time, the independence of transfusions enables patients to spend more time away from the hospital and thus improves HRQoL, as patients have more time to spend with their families. In addition, greater transfusion independence may result in cost offsets.

Glasdegib + LDAC is tolerable with a manageable safety profile and a relatively low incremental impact on the AE profile.

Glasdegib + LDAC is an innovative, effective, and safe treatment for adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy.

1 Description and technical characteristics of the technology

Summary of the characteristics of the technology

- Glasdegib is the first new agent to provide a survival benefit in a randomized setting in a population of newly diagnosed AML patients who are not candidates for standard induction chemotherapy
- Glasdegib has simple and predictable dosing.
- Glasdegib is an oral agent given in combination with LDAC, which can be self-administered on an out-patient basis.
- Glasdegib, in combination with LDAC, is currently approved for use in AML in the US, and is under regulatory review in the EU, Canada, Switzerland and other countries as shown in Table 4.

1.1 Characteristics of the technology

In Table 1 provide an overview of the technology.

Glasdegib (DAURISMO^{R}) is an oral inhibitor of the Hedgehog signal transduction pathway that binds to Smoothened, a Class Frizzled (Class F) G protein-coupled receptor that is encoded by the *smoothened* (*SMO*) gene. A summary of the pharmaceutical technology is given in Table 1.

Table 1: Features of the technology

Non-proprietary name	Glasdegib
Proprietary name	DAURISMO^{R}
Marketing authorisation holder	Applicant: Pfizer Europe MA EEIG
Class	Small-molecule hedgehog signalling inhibitor
Active substance(s)	PF-04449913-11 (1-((2R,4R)-2-(1H-benzo[d]imidazol-2-yl)-1-methylpiperidin-4-yl)-3-(4-cyanophenyl) urea maleate)
Pharmaceutical formulation(s)	25 mg and 100 mg tablets
ATC code	L01XX63
Mechanism of action	Daurismo^{R} (glasdegib) is an oral inhibitor of the hedgehog pathway. Daurismo^{R} (glasdegib) binds to and inhibits Smoothened, a transmembrane protein involved in hedgehog signal transduction
Abbreviations: ATC code = Anatomical Technical Chemical (classification);	

In Table 2, summarise the information about administration and dosing of the technology.

Glasdegib marketing authorisation application was submitted to EMA in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy. The administration and dosing are described in Table 2.

Table 2: Administration and dosing of the technology

Method of administration	Tablets to be taken orally
Doses	25 mg tablets 100 mg tablets
Dosing frequency	The recommended dose of glasdegib is 100 mg orally once daily
Average length of a course of treatment	Continuously, in combination with LDAC (20 mg subcutaneously twice-daily [BID] on days 1 to 10 of each 28-day cycle), and should be continued as long as the patient is deriving clinical benefit. For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response

Anticipated average interval between courses of treatments	Not applicable
Anticipated number of repeat courses of treatments	A minimum of 6 cycles to allow time for clinical response in patients without unacceptable toxicity
Dose adjustments	Dose modifications may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 50 mg taken orally once daily.

In Table 3 provide information about the different packs available.

Glasdegib will be available in different package sizes; proposed pack size options are given in Table 3. Not all pack sizes may be available.

Table 3: Pack information

	Pack size	Strength	Form	Pack code (if available, for example VnR code or barcode)
Pack 1	60	25 mg	tablets	NA
Pack 2	30	100 mg	tablets	NA
Abbreviations: VnR = Nordic Article Number				

State the context and level of care for the technology (for example, primary healthcare, secondary healthcare, tertiary healthcare, outside health institutions or as part of public health or other).

Glasdegib is a prescription-only medicine and can be used in all treatment settings in primary healthcare, including at home administration, hospital outpatient and inpatient care. Glasdegib should only be prescribed by or under the supervision of a physician experienced in the management of anticancer medicinal products. Glasdegib is formulated as immediate-release tablets for oral administration and may be taken with or without food. LDAC can also be self-administered at home as a subcutaneous injection.

State the claimed benefits of the technology, including whether the technology should be considered innovative.

None of the currently available non-intensive AML treatments have demonstrated statistically significant improvements in OS over LDAC alone, including azacitidine and decitabine (1, 2). Availability of new therapeutic options that extend patient survival remain an important unmet medical need for patients with previously untreated AML who are not candidates for standard induction chemotherapy.

Glasdegib is the first new agent to demonstrate a survival benefit in a randomized setting in an AML population who are not candidates for standard induction chemotherapy. Other recently approved therapies in AML, midostaurin, gemtuzumab ozogamicin, a liposomal combination of cytarabine and daunorubicin, and gilteritinib are limited to only certain AML patients deemed suitable for intensive chemotherapy.

In addition, glasdegib + LDAC provides a major advantage to patient care due to its ease of administration vs. azacitidine and decitabine. While azacitidine and decitabine must be administered on an in-patient basis, glasdegib is an oral agent given in combination with LDAC, which can both be self-administered by the patient at home.

Glasdegib in combination with LDAC chemotherapy demonstrated a clinically meaningful and statistically significant approximate doubling of OS compared to LDAC alone in previously untreated patients with AML who are not candidates for standard induction chemotherapy. The OS benefit associated with glasdegib + LDAC was consistent across demographic and clinical subgroups.

The OS benefit was complemented by the Q-TWiST analysis that demonstrated an increased relative improvement in quality-adjusted survival and further supported by improvements for objective response (including CR, CRi, MLFS) and transfusion independence.

Glasdegib + LDAC is generally well tolerated with a manageable safety profile and a relatively low incremental impact on the AE profile.

1.2 Regulatory status of the technology

Complete Table 4 with the marketing authorisation status of the technology.

The EMA accepted Pfizer's marketing authorisation application for glasdegib in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy for assessment on 29th April 2019, see Table 4.

Glasdegib has been granted full marketing authorisation by the Food and Drug Administration (FDA) on 21st November 2018 in combination with LDAC, for the treatment of newly-diagnosed AML in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy.

Table 4: Regulatory status of the technology ex-US

Organisation/Country issuing approval	Verbatim wording of the (expected) indication(s)	(Expected) Date of approval	Launched (yes/no). If no include proposed date of launch
EMA via the centralised procedure	Proposed indication as submitted: Glasdegib is indicated, in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy	CHMP opinion expected April/May 2020	No From September 2020 (subject to change)
Switzerland	Glasdegib is indicated, in combination with LDAC, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy.	Q3 2020	
Canada	Glasdegib is indicated, in combination with LDAC, for the treatment of adult patients with previously untreated acute myeloid leukaemia (AML) who are not eligible to receive intensive induction chemotherapy.	Q2 2020	

Organisation/Country issuing approval	Verbatim wording of the (expected) indication(s)	(Expected) Date of approval	Launched (yes/no). If no include proposed date of launch
Israel	Glasdegib is a hedgehog pathway inhibitor indicated, in combination with LDAC, for the treatment of newly-diagnosed acute myeloid leukaemia (AML) in adult patients who are > 75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.	September 2020	
Turkey	Glasdegib is indicated, in combination with LDAC, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for intensive induction chemotherapy.	Q1 2021	
Russia	Glasdegib is indicated, in combination with LDAC, for the treatment of adult patients with previously untreated acute myeloid leukaemia (AML) or high-risk myelodysplastic syndrome (MDS).	Q1-2 2021	
Brazil	Glasdegib is indicated, in combination with LDAC, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for intensive induction chemotherapy.	Q1 2022	
Abbreviations: CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency			

State any other indications not included in the assessment for which the technology has marketing authorisation.

None.

State any contraindications or groups for whom the technology is not recommended.

Glasdegib is contraindicated in patients with a hypersensitivity to the active substance or the list of excipients listed in the Summary of Product Characteristics (SmPC).

List the other countries in which the technology has marketing authorisation.

Glasdegib has been granted marketing authorisation by the FDA on 21st November 2018 in combination with LDAC, for the treatment of newly-diagnosed AML in patients who are 75 years old or older or who have comorbidities that preclude intensive induction chemotherapy. Marketing authorisation status of glasdegib in other countries is listed in Table 4.

2 Health problem and current clinical practice

Summary of issues relating to the health problem and current clinical practice

- AML is a rare, orphan haematologic cancer that progresses rapidly and is typically fatal within weeks or months if left untreated.
- Symptoms of AML caused by cytopenia and bone marrow infiltration by myeloblasts (e.g. fatigue, loss of performance and infections) have a negative impact on patient-reported health-related quality of life.
- About a third of AML patients are not candidates for standard induction chemotherapy for reasons such as performance status or comorbidities.
- Patients who are not candidates for standard induction chemotherapy tend to be frailer and older with more comorbidities, thus leading to poorer outcomes. The majority of these AML patients will die within a year of diagnosis.
- Given the aggressiveness of AML, the treatment goal for these patients is to extend survival.
- To date, only single agent treatments are available for AML patients who are not candidates for standard induction chemotherapy, and no single agent alone has significantly extended survival.

2.1 Overview of the disease or health condition

2.1.1 Definition of AML

Define the disease or health condition in the scope of this assessment.

2.1.1.1 Background and risk factors

Acute myeloid leukaemia (AML) (International Classification of Diseases Version 10 [ICD-10] Code: C92.0) is a rare, orphan haematologic malignancy characterized by the clonal expansion of malignant myeloid stem cells in the bone marrow, resulting in proliferation of undifferentiated leukemic cells (“blasts”) in the peripheral blood, bone marrow, and occasionally in other tissues (e.g. spleen and liver) (3). AML is highly aggressive and can progress quickly. If left untreated, AML will prove fatal within a matter of weeks to months (4-6).

Known risk factors that promote the development of AML include exposure to radioactive radiation, to benzene, tobacco, petroleum products, paints, ethylene oxides, herbicides and pesticides. Previous treatments with cytostatics, typically alkylating agents and topoisomerase II inhibitors or drugs such as chloramphenicol and phenylbutazone are also considered to be important triggers of disease (7). Patients with previous haematological conditions (e.g. myelodysplastic syndrome [MDS]) or certain genetic conditions such as Down syndrome (trisomy 21) also have an increased risk of developing AML (8, 9). In addition, smoking has been proven to be a significant risk factor for the development of AML in adults (10).

2.1.1.2 Pathophysiology

AML results from the clonal expansion of undifferentiated myeloid progenitor cells. This expansion is the result of a series of genetic alterations that influence proliferation, maturation and differentiation of the hematopoietic system (6). During normal haematopoiesis, haematopoietic stem cells first develop into myeloid or lymphatic precursor cells and then differentiate. AML leads to the accumulation of myeloblasts in the bone marrow and to an increasing suppression of normal haematopoiesis (see Figure 2) (11). The replacement of normal blood cells in bone marrow and peripheral blood by leukemic blasts results in anaemia, neutropenia, and thrombocytopenia. This is associated with symptoms of fatigue, shortness of breath, impaired wound healing, increased susceptibility to infections and bleeding.

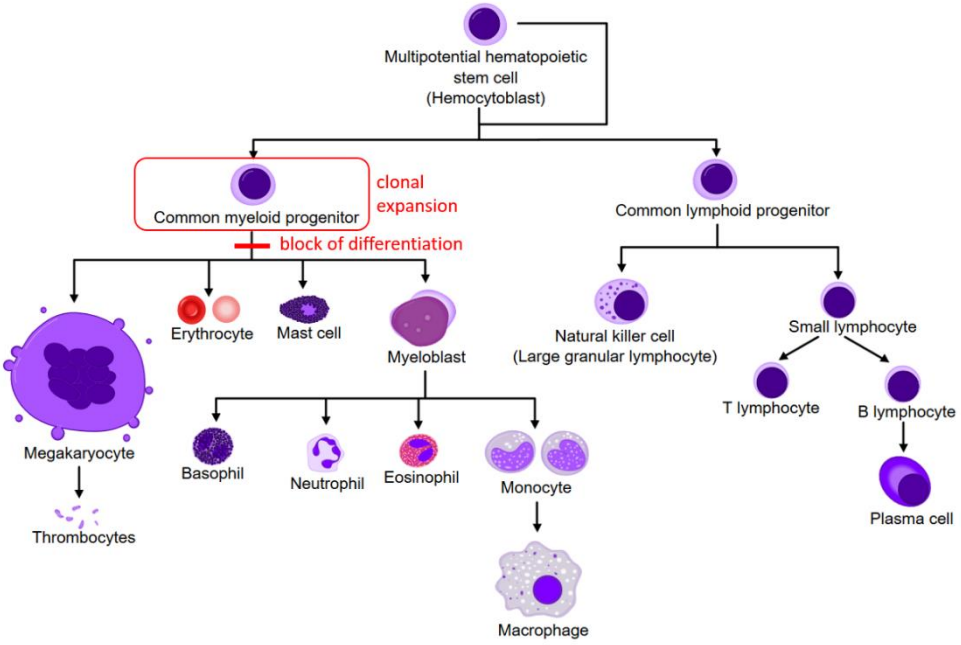


Figure 2: AML results from clonal expansion of myeloid progenitor cells
Reference: (12)

2.1.1.3 Diagnostics

A tentative diagnosis may be made with a presence of > 20 % blasts in a peripheral blood smear (seen in 75 % of AML patients), however a definitive diagnosis requires a bone marrow biopsy with 1) demonstration of a myeloid (as opposed to lymphoid) origin and 2) demonstration of bone marrow infiltration by abnormally differentiated and nonfunctional hematopoietic blasts (13). Cytogenetic analysis and molecular genetics testing are recommended as information from these analyses will help to determine prognosis and recommended treatment approaches based on risk assessment (13). Immunophenotyping, including human leukocyte antigen (HLA) testing, is recommended in newly diagnosed patients who are eligible for allogeneic hematopoietic stem cell transplantation (HSCT), with consideration given to testing in first- and second-degree family members as well (13).

Further evaluations in AML concern the overall fitness of the patient. The main factors that contribute to this assessment are performance status — Eastern Cooperative Oncology Group (ECOG) is frequently used — and comorbidities, renal and liver function, and age (13). The results of this assessment contribute to therapy decisions.

2.1.1.4 Classifications

AML is a highly heterogeneous disease that can be classified by genetic, immunological and morphological characteristics of the leukemic cells. In general, there are two main systems classifying AML in specific subtypes according to certain characteristics: the WHO classification, which considers cyto- and molecular genetic characteristics, and the nowadays less common French-American-British (FAB) classification, which differentiates AML on the basis of morphological characteristics of leukemic blasts.

The WHO classification

The WHO classification system, originally developed in 1999 in collaboration with the Society for Hematopathology and the European Association of Haematopathology, was further refined in 2001 and is currently the most commonly used system for classifying the pathobiology and the associated prognosis of AML (14, 15). It recognizes six broad subtypes based on the presence of antecedent haematologic disorders, cytogenetic abnormalities, and morphological characteristics (14). In the WHO classification, AML is defined with a few exceptions (AML with recurrent genetic changes [t(15;17), t(8;21), inv(16) or t(16;16)], as well as some cases of erythrocyte leukaemia) via a blast percentage of ≥ 20 % in the bone marrow (14). In addition to morphological characteristics, cytogenetic and molecular genetic characteristics of leukemic cells are also considered (see also Appendix A) (14).

2.1.1.5 Prognostic Factors

The prognosis of AML is influenced by both patient-specific and disease-specific factors (16).

Patient-specific factors

Among the most important patient-specific factors are performance status, comorbidities, and age (13, 17).

Performance status

The ECOG performance status grades range from 0 (fully active and able to continue all pre-disease activities without restriction) to 5 (dead) (18). Patients with a poor performance status at diagnosis have worse outcomes (19, 20). A poor performance status is usually the result of a combination of comorbidities and organ dysfunction. It strongly predicts lower CR rates and higher rates of mortality and treatment-related death (21).

Comorbidities

Common comorbidities at the time of diagnosis of older adults with AML are diabetes, liver and kidney disease, or heart failure (20). Several studies specifically investigating older adults have shown a relationship between increased comorbidity burden and worse outcomes including decreased remission rates, increased early mortality, and shorter overall survival times (22, 23)

Age

Advanced age (60 > years) is considered an independent risk factor for poorer prognosis and survival in AML; however, coincident with advanced age are other confounding factors such as increased incidences of higher risk cytogenetics and single-gene mutations, higher proportion of comorbidities, reduced performance and decreased ability to tolerate high-intensity chemotherapy (24).

In adults with AML, treatment results are generally stratified by age for younger (18 – 60 years) patients vs. older patients (> 60 years). Recent studies of population-based registry data indicate that there is generally improvement over the past few decades concerning outcomes in patients > 60 who are able to tolerate intensive chemotherapy and achieve hematopoietic stem cell transplant (HSCT); however, there has not been any similar change in elderly patients who are not candidates for intensive chemotherapy based on performance status, comorbidities, and age (25, 26).

Disease-specific factors

With regard to disease-specific factors, molecular or cytogenetic changes have the strongest prognostic impact (13). Current AML standard of care stratifies patients in different risk categories (favourable, intermediate, unfavourable), with a corresponding prognosis according to the presence or absence of cytogenetic abnormalities (visually detectable chromosomal aberrations under microscopy, or else detectable by fluorescent in situ hybridization—FISH) and according to presence or absence of single-gene mutations detected by PCR or next generation sequencing (NGS). The current (2017) ELN AML Guideline apportions risk and prognosis to known cytogenetic and molecular abnormalities (13). The stratification of these abnormalities into risk categories is presented in Table 5) (13).

Table 5: European LeukemiaNet Risk Stratification by Genetics in Non-APL Acute Myeloid Leukaemia.

Risk category	Genetic alteration
Favourable	*Cytogenetic* t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* inv(16)(p13.1;q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* *Molecular* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}* Biallelic mutated *CEBPA*
Intermediate§	*Cytogenetic* t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favourable or adverse *Molecular* Mutated *NPM1* and *FLT3*-ITD^{high}# Wild type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}* (w/o adverse risk genetic lesions)
Unfavourable	*Cytogenetic* t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL1* inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM* (*EVI1*) Complex karyotype^{A}; monosomal karyotype^{B} *Molecular* Wild-type *NPM1* and *FLT3*-ITD^{high}# Mutated *RUNX1*, *ASXL1* or *TP53*

Reference: (13)
Abbreviations: p = short arm of the chromosome; q = long arm of the chromosome; t(A;B) = used to denote a translocation between chromosome A and chromosome B.
**FLT3*-ITD^{low} = low allelic ratio < 0.5
#*FLT3*-ITD^{high} = high allelic ratio > 0.5
§In the 2017 ELN guideline update, the former risk groups Intermediate-I and Intermediate-II were unified. Intermediate-I included all AMLs with normal karyotype except for those included in the favourable subgroup, Intermediate-II included t(9;11)(p22;q23); *MLLT3-KMT2A* and cytogenetic abnormalities not classified as favourable or adverse.
A: Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions, i.e., t(8;21), inv(16) or t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3) or t(3;3); AML with *BCR-ABL1*.
B: Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core-binding factor AML)

2.1.2 Incidence of AML

Present an estimate of prevalence and/or incidence for the disease or health condition including recent trends.

The target population of glasdegib includes adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy.

Here, only incident patients are taken into consideration since the criterion "newly diagnosed" reflects untreated patients with AML. Moreover, the disease leads to death within a very short time without treatment. Thus, it can be assumed, that the number of incident patients corresponds approximately to the number of prevalent patients.

Generally, AML is a rare disease that mainly affects elderly people; the risk of an AML diagnosis increases with age. Men are affected more frequently than women (27).

In the Information Network on Rare Cancers Registry (RARECARE), incidence estimates for the overall EU region were reported. Data on cancer patients diagnosed up to 2007, archived

in 94 population-based cancer registries in 27 European countries, were analysed. This pool of cancer registries constitutes a representative sample of the total European population (28, 29). A database query on http://www.rarecarenet.eu/analysis.php provides the following age-adjusted incidence rates (European standard population) for the years 2003-2007: 0.32 per 10,000 population (for AML and related precursor neoplasms) and 0.29 per 10,000 population (for AML only), respectively. For 2013, a total number of 19,819 new cases (incidence) of AML in the EU28 was estimated (27). This corresponds to a crude annual incidence rate of 0.35 per 10,000 population (27).

From the years 1995 to 2007 the age-adjusted incidence rates of AML increased slightly from 0.25 to 0.29 per 10,000 population (27). Considering also the demographic ageing, a further slow increase in AML incidence can be expected for the future.

2.1.3 Symptoms and burden of disease of AML

Describe the symptoms and burden of the disease or health condition for patients.

Symptoms of AML

The clinical appearance of AML is largely determined by the increasing hematopoietic insufficiency due to bone marrow infiltration by myeloblasts (30). Symptoms are often non-specific at first, which is why leukaemia is occasionally discovered only during a routine blood test (31). Characteristic symptoms of AML are mostly an expression of anaemia (e.g. fatigue and exhaustion, loss of performance, paleness, etc.), neutropenia (e.g. fever, increased tendency to infection) and thrombocytopenia (e.g. capillary bleeding, nosebleeds, prolonged bleeding) (30). In addition, the disease can lead to leukocytosis, which in turn can lead to hypoxia, pulmonary shadowing, retinal bleeding and neurological impairments (30). Infestation of other organs with myeloblasts often results in organ enlargement and/or pain (30, 31).

Burden of Disease

Overall, AML is the deadliest form of leukaemia (32). Survival in AML patients depends on factors including performance status, comorbidities, age at diagnosis and type of treatment (see section 2.1.1.5 Prognostic factors). Moreover, AML-associated adverse risk genetic abnormalities (both classical cytogenetics and mutations in certain genes) and antecedent hematological disorder are strongly predictors of poor survival as they are predictors of treatment failure or resistance (13). Thus, an adverse cytogenetic risk profile goes along with poorer response to induction therapy and OS compared to an intermediate cytogenetic risk profile (33). With regard to disease history, antecedent haematological disorders are associated with low response rates, high early mortality, and higher risk of early disease relapse (34). Overall survival of patients with AML is generally poor: in five studies of patients from a variety of countries in Europe and Asia, reported median survival ranged from 6.2 months to 9 months. Moreover, 1-year and 5-year survival rates were low. Across five retrospective studies of patients in the US, Spain, and Denmark, patients over age 70 exhibited 1-year survival rates at or below 30 % (35-39).

In the UK, 2,601 people died from AML in 2016 (for reference, there were 3,126 new cases of AML in 2015) (40). Overall, AML made up 1.57 % of all cancer deaths in the UK in 2016 (40).

AML patients suffer from disease symptoms, caused by accumulation of myeloblasts in the bone marrow or peripheral blood and progressive decline of the absolute erythrocyte, neutrophil and platelet counts. Chemotherapy initially leads to a further worsening of blood counts. These haematological adverse events (anaemia, neutropenia and thrombocytopenia) are treated by administration of blood products and the transfusion of erythrocyte and platelet concentrates. Since transfusions are typically administered only in special haematooncological centers and require a minimum stay of several hours, transfusion need directly affects AML patients' HRQoL (41). At the same time, blood transfusions are correlated with the increased risk of infections caused by the transmission of bacteria or viruses, transfusion-associated acute pulmonary insufficiency, immunomodulation and complications caused by mix-up of blood products, thus leading to increased patient morbidity (42).

Symptoms of AML have a significant negative impact on patient-reported HRQoL. A cross-sectional study of 152 patients with AML (further disease characteristics were not reported) examined patient-rated HRQoL measures using the MD Anderson Symptom Inventory, which rates symptoms and how they interfere with life on a scale of 0 to 10 (0 = Not present/no interference; 10 = As bad as imaginable/complete interference) (43).

Inpatients had poorer HRQoL than those people receiving outpatient treatment. Mean symptom rating was significantly higher for AML inpatients than for AML outpatients (2.8 vs 1.8; $p < 0.01$). Similarly, the mean interference rating was significantly higher for AML inpatients than for AML outpatients (4.0 vs 2.7; $P < 0.01$). For all patients with AML (n = 75 inpatients and n = 77 outpatients), the mean symptom ratings were highest for fatigue (4.0), dry mouth (3.4), disturbed sleep (3.3), drowsiness (3.0), and muscle weakness (2.9). Overall, the data suggest that most symptoms were in the mild range (0 to 4) (43).

Additional factors may also contribute to the burden of AML on patients and caregivers. A targeted literature review looking at research on the experiences of patients with AML (or other haematological cancers with short life expectancy) revealed several additional factors that contribute to the burden of the disease on patients and caregivers (44).

- Time spent on medical care away from home left patients with less time for family, work and other activities.
- Transfusion dependence and the threat of infections caused patients to feel trapped either in the hospital or their own home (45, 46).
- Long hospitalization and difficult treatment regimens associated with AML mean that the burden on caregivers can also be significant. The results of a questionnaire given to 163 patients with AML and their family caregivers in China indicated the proportion of caregivers who met criteria for post-traumatic stress symptoms was 36.8 % was significantly higher than the proportion of patients who met the criteria (18.4 %; $P < 0.001$) (47).
- A number of influencing factors were identified when exploring the treatment decisions of patients with AML including potential side effects, difficulty understanding the treatment options available, and the influence of their doctor. Participants were most averse to time in hospital, followed by long-term side effects and short-term side effects (48). Likewise, caregivers also were distressed by the need for their loved one to require care in the hospital (49). Forty-six percent of patients reported being troubled by the time burden of their medical care (50).

- Delaying disease progression and extending survival were most important to patients and their partners based on a social media listening study exploring insights of patients with AML. Patient and partner comments focused on the perceived benefits associated with living longer: reaching personal milestones, being able to attend family events such as holidays and weddings, and limiting the disruption to normal family life (51, 52). Some patients prioritized HRQoL over quantity of life, while others were more determined to explore further treatment options. Desire to be at home and the improved HRQoL patients experience at home was a recurring theme (52).

The reduced HRQoL in patients with AML has been shown in various studies. One study from the Netherlands evaluated HRQoL in 92 AML patients who received induction chemotherapy with cytarabine (plus an anthracycline and/or another agent in some trials) followed by HSCT (in some patients) during a clinical trial (53). The mean EuroQoL 5-dimensional questionnaire (EQ-5D) visual analogue scale (EQ-VAS) score of the AML patients was significantly lower than for the general population (74.6 vs 78.8; p = 0.0333) (53). In addition, the mean scores on the physical functioning, role functioning, cognitive functioning, social functioning, fatigue, dyspnoea, and financial difficulties scales of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) were significantly (and clinically relevant) lower in patients with AML compared with the general population (53).

2.1.4 Aspects of the burden of disease targeted by glasdegib

Describe the aspects of the burden of disease that are targeted by the technology, that is, those that are expected to be reduced by the use of the technology.

AML represents the deadliest form of leukaemia and urgent treatment is required to extend survival and halt disease progression. The BRIGHT AML 1003 study demonstrated that glasdegib + LDAC nearly doubled OS compared with LDAC alone in adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy (HR [95% CI]: 0.46 [0.30, 0.72]; p = 0.0002; median OS: 8.3 months vs. 4.3 months). The resulting survival probability at 1 year was 39.5 % vs 9.5 %.

Q-TWiST analysis, which evaluates the quality of survival during that significantly longer survival time, showed that the added OS was time spent in ‘good’ health (i.e. a significantly longer time without symptoms of disease progression or toxicity), which suggests that the benefits of glasdegib + LDAC vs LDAC alone outweigh the possible risks of treatment (57).

Glasdegib + LDAC not only improved survival, but reduced transfusion requirements: higher rates of transfusion independence were reported with glasdegib + LDAC vs. LDAC alone. Transfusion independence correlates with blood count recovery and alleviation of symptoms. At the same time, the independence from transfusions enables patients to spend more time away from the hospital and thus offer more value time spent with family. Patient and partner responses indicated a desire to survive and to be able to witness important life milestones, including weddings and anniversaries, holiday celebrations, and also maintaining normal family life (51, 52). The improvement in OS offered by glasdegib + LDAC allows patients more opportunities to accomplish these valued milestones, thus improving HRQoL.

In BRIGHT AML 1003, adverse reactions associated with glasdegib + LDAC were generally manageable, with little additional toxicity compared to LDAC alone, even though patients were treated for longer time periods with glasdegib + LDAC.

2.2 Target population

2.2.1 Target population and the proposed position in the pathway of care

Describe the target population and the proposed position of the target population in the patient pathway of care.

The target population is comprised of adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy, but clearly can tolerate and wish antileukemic treatment.

For this group of patients, only limited treatment options are available. They are frailer, have more comorbidities and are older, thus having poorer outcomes. The treatment goal for these patients is to extend survival.

2.2.2 Provide a justification for the proposed positioning of the technology and the definition of the target population.

The target population of this assessment is the population identified in the marketing authorization: AML patients that are not candidates for standard induction chemotherapy. Patients were defined as not being a candidate for standard induction chemotherapy by having at least one of the following eligibility criteria:

- age ≥75 years
- ECOG PS = 2
- serum creatinine > 1.3 mg/dL
- severe cardiac disease

According to the international expert group European LeukemiaNet (ELN) treatment guideline, the eligibility of AML patients for standard induction chemotherapy depends on several criteria. Factors that determine therapy decisions are age, the general state of health, comorbidities, as well as cytogenetic or molecular genetic characteristics of the patient (13). A biological age of 60 to 65 years or more is a factor that can influence therapy decision-making, since remission rates and long-term remissions both decrease with age and the risk of therapy-associated complications increases at the same time (54-56). For example, the probability of achieving complete remission (CR) is drastically reduced in patients ≥ 50 years of age, and 5-year survival rates significantly decrease in elderly patients (56, 57). According to a study by Kantarjian et al., an age of ≥ 75 years is associated with a high mortality risk in connection with standard induction chemotherapy (58). Regarding the general state of health, studies have shown that older adults who present with poor performance status at the time of diagnosis (ECOG-PS ≥ 2) are more likely to experience toxicity associated with treatment and less likely to benefit (19, 20). For patients with significant comorbidities like heart failure (ejection fraction < 50%) or pulmonary disease, intensive chemotherapy is also not recommended (59). Furthermore, kidney and liver function should be assessed in the context of comorbidities (13). The patient's own perspective is also of great relevance, as some patients place a higher premium on short-term health-related quality of life rather than on the possibility of longer survival (60).

Historically, only single agent treatments were available for patients who are not candidates for standard induction chemotherapy, and no single agent alone has significantly extended survival. Most patients in this group are treated with HMAs or LDAC, but none of these options provide outcomes that are comparable with what can be achieved through intensive

chemotherapy (61). LDAC can improve OS for some patients; however, it is not an effective option for patients with adverse cytogenetics (61). The commonly used HMAs, azacitidine and decitabine, did not demonstrate superiority in terms of improved OS compared with LDAC (1, 2). The European Medicines Agency deemed azacitidine to be similarly effective to LDAC in terms of OS (62). Moreover, in a study of decitabine in older patients with AML and poor/intermediate risk, decitabine showed activity but failed to improve survival when compared to LDAC or BSC (2, 63).

New treatment options are presently in development and in clinical trials to meet this unmet need. These include combination approaches, novel formulations of cytotoxic chemotherapy, novel HMAs and other epigenetic modifiers, antibody-drug conjugates, and agents that target cell cycle and signalling molecules (6, 64, 65). Despite the emergence of several new systemic treatments, significant therapeutic gaps remain in the treatment for AML (65).

Glasdegib has received an orphan drug designation in the EU (since October 2017) for the treatment of AML (66), based on its significant potential benefit for patients with AML who are not candidates for standard induction chemotherapy.

2.2.3 Size of the target population

Estimate the size of the target population. Include a description of how the size of the target population was obtained and whether it is likely to increase or reduce over time.

The estimation of the number of adult patients with newly diagnosed AML who are not candidates for standard induction chemotherapy will be performed in two steps. First, the incidence rates of adult patients suffering from newly diagnosed AML in the EU will be considered (database: RARECARE registry). In a second step, the number of patients will be restricted to patients who are not eligible to receive standard induction chemotherapy.

The RARECARE registry presents data on cancer patients diagnosed up to 2007 originating from 94 population-based cancer registries from 27 European countries. It is considered to represent a good estimate of European-wide data on epidemiology of rare cancers and in this case AML. The RARECARE registry depicts an age-adjusted incidence rate for the years 2003-2007 of 0.29 per 10,000 population for AML patients and predicted 19,819 new cases for AML in the year 2013 for the EU28 (27).

A literature search was conducted to estimate the number of patients who are not candidates for standard induction chemotherapy. In total three publications could be identified that can be applied. First, a publication of the German-Austrian register study AMLSG BiO reports a proportion of 71.12 % of AML patients who received a standard induction chemotherapy. Overall, 3,525 AML patients from Germany and Austria, newly diagnosed between 2012 and 2014 were included. The median age was 65 years (67). Thus 28.9 % of AML patients were not candidates for standard induction chemotherapy.

The second study identified determined how poor risk factors may be used as decision criteria in older patients intensively treated for AML (68). The study included 416 AML patients (median age 72 years) who were prospectively treated in a multicenter trial. The authors used a proposed decisional index that included high-risk cytogenetics (defined as monosomy 7, presence of abnormalities of both chromosomes 5 and 7, 3q26 abnormalities, and complex karyotype with five or more anomalies) and/or the presence of at least two of the following criteria: age ≥ 75 years, performance status ≥ 2, and white cell count ≥ 50 x 10^9/L. Based on

these criteria, 100 out of the 416 AML patients (24 %) were considered as not being candidates for standard induction chemotherapy.

Finally, a retrospective study utilizing Swedish acute leukaemia registry (1997-2005; n = 2,767 AML patients; median age 72 years) reported by age groups and WHO/ECOG PS varying numbers of AML patients that were eligible or non-eligible for intensive chemotherapy (55). The physician was requested to report whether the patient at diagnosis was eligible or not for intensive combination chemotherapy. This decision was based on clinical data and local routine, but not on karyotype, because cytogenetic reports were not available at the time when treatment was initiated (55). This study reported that about 38 % of the patients were not candidates for standard induction chemotherapy. When stratified by age groups, the AML patient population not eligible for standard induction chemotherapy increased with age: 1.8 % for < 50 years; 3.1 % for 50-54 years; 8.8 % for 55-59 years; 7.9 % for 60-64 years; 20.1 % for 65-69 years; 32.9 % for 70-74 years; 54.9 % for 75-79 years; 76.6 % for 80-84 years; and 95.7 % for 85 + years.

Thus, a range between 24 % and 38 % of incident AML patients are considered not to be candidates for standard induction chemotherapy (55, 67, 68). This corresponds to an absolute patient number of 4,757 – 7,531 patients per year in the EU.

2.3 Clinical management of the disease or health condition

2.3.1 Clinical pathway of the disease

Describe the clinical pathway of care for different stages and /or subtypes of the disease being considered in the assessment.

In 2017, ELN published recommendations from a 22-member panel that reviewed literature-based evidence and expert opinions (13). The recommendations cover the following topics: classification of AML, diagnosis, prognostic factors, response criteria, survival outcomes, first-line treatment options based on eligibility for intensive treatment rather than age alone, treatment of relapsed AML, and supportive care.

The recently updated European Society for Medical Oncology (ESMO) Clinical Practice Guideline provides key recommendations on the management of AML in adult patients (69). ESMO recommendations take the approval status of AML drugs in Europe into account until the year 2019.The National Comprehensive Cancer Network (NCCN) is a non-profit alliance of 30 cancer centers across the US. Clinicians from the member institutions meet regularly to update the NCCN guidelines across all tumor types. The guidelines are a statement of evidence and consensus of the professional opinion regarding the currently accepted approaches to treating AML, regardless of the regulatory status of the recommended agents. NCCN Guidelines® - Acute Myeloid Leukemia are comprised of recommendations for the prevention, diagnosis, and management of AML in adult patients (70).

A major factor that influences the prognosis for patients with AML is the type of treatment they receive, if any. While induction with intensive chemotherapy is the preferred line of treatment because it offers the best outcome, it is not appropriate or desirable for all patients with AML.

For patients who are not considered candidates for standard induction chemotherapy, ELN recommends enrolling in a clinical trial if possible, since treatment options are currently limited. Alternatives include low-intensity treatment (LDAC or HMAs such as decitabine or azacitidine); BSC is an alternative for patients who cannot tolerate any antileukemic therapy, or who do not

wish any therapy (Table 6) (13). ESMO guidelines recommend HMAs or LDAC for newly diagnosed AML patients who are not candidates for standard induction therapy (69); BSC or LDAC are remaining options for MDS patients progressing to AML under HMA treatment, if no clinical trial is available (69) (Table 6). The NCCN Guidelines recommend for patients not candidates for or declining intensive remission induction therapy enrolment in a clinical trial for treatment induction. For patients not enrolled in a clinical trial, cytogenetics, overall functional status, and the presence or absence of actionable mutations should guide treatment strategies (Table 6) (70).

BSC includes the use of anti-infectives, transfusion support with blood and blood products, hematopoietic growth factors and hydroxyurea. It is generally accepted that all AML patients who require BSC will receive it in conjunction with their antileukemic therapy. Some patients; however, may choose not to receive any antileukemic therapy and will receive BSC alone as palliative treatment**.** These patients are typically characterized by a worse ECOG PS and significant comorbidities such as end stage congestive heart failure or an uncontrolled neoplasia. Importantly, in a study comparing BSC vs. LDAC, the overall survival was decreased for patients receiving BSC compared to patients receiving LDAC (71). Therefore, BSC is not considered an effective treatment option for the target population of glasdegib. For the scope of this assessment only recommendations on therapy options with European marketing authorisation in newly diagnosed AML patients who are not candidates for standard induction therapy were considered. The current care pathway for treatment of AML patients is shown in Figure 3.

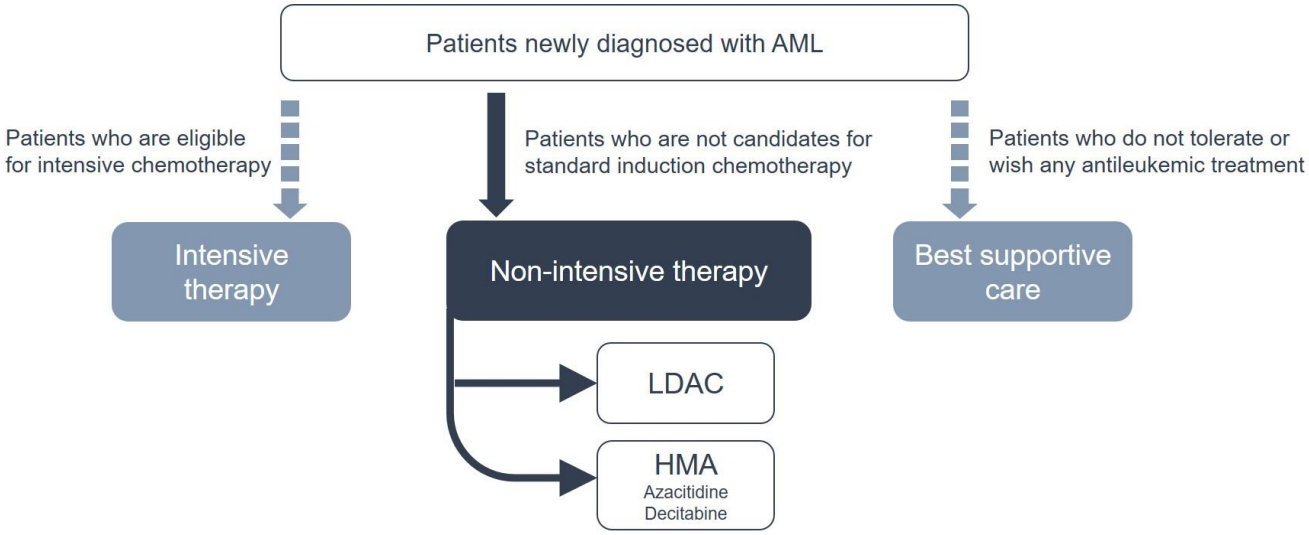


Figure 3: Current care pathway for treatment of AML patients.

Table 6: Relevant guidelines for diagnosis and treatment of AML patients who are not candidates for standard induction chemotherapy

Name of society/organisation issuing guidelines	Date of issue or last update	Country/ies to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)
European LeukemiaNet (ELN)	2017	Europe	**Treatment alternatives for patients who are not candidates for standard induction chemotherapy**: • Azacitidine • Decitabine • LDAC: not recommended in patients with adverse-risk genetics Strong recommendation to enrol these patients in clinical trials.
			Patients who cannot tolerate any antileukemic therapy, or who do not wish any antileukemic therapy: • Best supportive care: including hydroxyurea Strong recommendation to enrol these patients in clinical trials
European Society for Medical Oncology (ESMO)	2020	Europe	**First-line treatment of AML patients not eligible for standard induction and consolidation chemotherapy**: • The HMAs, azacitidine and decitabine, are treatment options in newly diagnosed unfit AML patients [II, B] • Given the moderate effects of HMAs, LDAC remains an alternative to HMAs in the first-line treatment of AML patients who are ineligible for standard induction and consolidation chemotherapy, except in patients with adverse-risk cytogenetics, where LDAC has very poor activity [II, B].
National Comprehensive Cancer Network (NCCN)	2020	USA	**Patient not a candidate for or declines intensive remission induction therapy** *AML without actionable mutations:* • Venetoclax + Decitabine or azacitidine or LDAC • Decitabine • Azacitidine • Glasdegib + LDAC • LDAC • Gemtuzumab ozogamicin • BSC *AML with IDH1 mutation* • Ivosidenib • Azacitidine • Decitabine

Name of society/organisation issuing guidelines	Date of issue or last update	Country/ies to which guideline applies	Summary of recommendations (Level of evidence/grade of recommendation for the indication under assessment)
			• Venetoclax + Decitabine or azacitidine or LDAC *AML with IDH2 mutation* • Enssidenib • Azacitidine • Decitabine • Venetoclax + Decitabine or azacitidine or LDAC *AML with FLT3 mutation* • Azacitidine or Decitabine + Sorafenib • Venetoclax + Decitabine or azacitidine or LDAC Recommendation to enrol these patients in a clinical trial for treatment induction
References: (13, 69, 70)			

2.3.2 Technologies currently used in the clinical pathway

State the technologies currently used in the clinical pathway for which the proposed technology is an alternative, or an additional treatment.

Recent ELN and ESMO Guidelines recommend the following non-intensive chemotherapy options: LDAC, which has been in use for decades as a first-line treatment, and the hypomethylating agents (HMA) azacitidine and decitabine, available since the mid-2000s (13, 61). HMAs have shown numerically but not statistically significantly longer OS than LDAC in AML patients who are not candidates for standard induction chemotherapy (1, 2), making these three treatment options equivalent in terms of efficacy (72, 73).

Table 7 summarises approved therapies for AML patients who are not candidates for standard induction chemotherapy in the EU.

Table 7: Overview of Authorised Medicinal Products for the Treatment of AML patients who are not candidates for standard induction chemotherapy in the EU

Product	Indication in Marketing Authorisation	Dosage and Administration
Non Intensive chemotherapy		
Cytarabine MOA: Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid. It also has antiviral and immunosuppressant properties. Detailed studies on the mechanism of cytotoxicity in vitro suggests that the primary action of Cytarabine is inhibition of deoxycytidine synthesis, although inhibition of cytidylic kinases and incorporation of the compound into nucleic acids may also play a role in its cytostatic and cytocidal actions. ATC code: L01BC01 National approvals, multiple MAHs	For induction of remission in AML in adults and for other acute leukaemias of adults and children. (74)	Low-dose: 20 mg/m^2 daily or 20mg twice daily (13) subcutaneously (SC), days 1-10, every 4 weeks, until progression
Hypomethylating agents		
Azacitidine (Vidaza®) MOA: Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. ATC Code: L01BC07 MAH: Actavis Pharma, Inc, Celgene MA approval: 17 December 2008	Azacitidine is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with: - AML with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification - AML with > 30 % marrow blasts according to the WHO classification. (72)	75 mg/m^2 of body surface area SC, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for at least 6 cycles
Decitabine (Dacogen®) MOA: Decitabine is a cytidine deoxynucleoside analogue that selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can result in reactivation of tumour suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death. ATC Code: L01BC08 MAH: Janssen Pharmaceutica N.V MA approval: 20 September 2012	Decitabine is indicated for the treatment of adult patients with newly diagnosed de novo or secondary AML, according to the WHO classification, who are not candidates for standard induction chemotherapy. (73)	20 mg/m^2 IV over 1 hour repeated daily for 5 consecutive days (i.e. a total of 5 doses per treatment cycle). Total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2.
Abbreviations: AML = acute myeloid leukaemia; ATC = anatomical Therapeutic Chemical; DNA = deoxyribonucleic acid; HSCT = haematopoietic stem transplantation; IV = intravenous; MAH = marketing authorisation holder; MOA = mechanism of action; SC = subcutaneously; WHO = World Health Organisation.		

2.3.3 Pathway of care that incorporates the new technology

Describe the pathway of care that incorporates the new technology if the technology were to be adopted for use.

Based on the ELN and ESMO guidelines, glasdegib will complement the care pathway in the following way (see Figure 4):

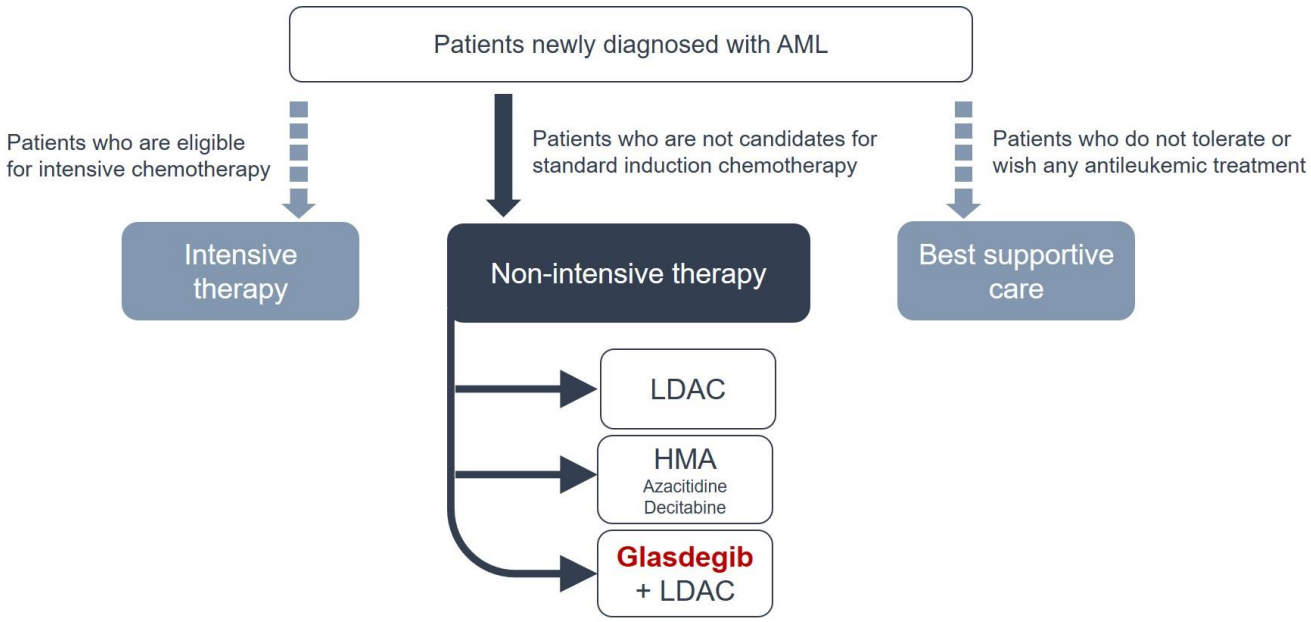


Figure 4: The role of glasdegib in the care pathway for the treatment of AML patients.

2.4 Comparators in the assessment

On the basis of the alternatives presented, identify the technologies to be used as comparator(s) for the assessment.

Based on the ELN and ESMO recommendations, the comparators considered for this assessment are the following non-intensive chemotherapy options: LDAC and the HMAs: azacitidine and decitabine.

3 Current use of the technology

Summary of issues relating to current use of the technology

No information can be given on the current use, availability, and reimbursement of glasdegib as the technology is not yet available on the European market.

3.1 Current use of the technology

Describe the experience of using the technology, for example the health conditions and populations, and the purposes for which the technology is currently used. Include whether the current use of the technology differs from that described in the (expected) authorisation.

At the time of the assessment, the technology was not yet available in Europe.

Indicate the scale of current use of the technology, for example the number of people currently being treated with the technology, or the number of settings in which the technology is used.

At the time of the assessment, the technology was not yet available in Europe.

3.2 Reimbursement and assessment status of the technology

Complete Table 8 with the reimbursement status of the technology in Europe.

At the time of the assessment, the technology was not yet launched in Europe.

Table 8: Overview of the reimbursement status of the technology in European countries

Country and issuing organisation	Status of recommendation (positive/negative/ongoing/not assessed)	If positive, level of reimbursement*
not applicable		
Include a reference to any publicly available guidance documents *For example, full reimbursement or only partial reimbursement. If partial reimbursement give a percentage of reimbursement.		

4 Investments and tools required

Summary of issues relating to the investments and tools required to introduce the technology

- Glasdegib is an oral agent given in combination with LDAC, which can be self-administered by the patient at home provided that patients and carers have been trained, assessed and confirmed competent for self-administration.
- Glasdegib + LDAC should only be prescribed by or under the supervision of a physician experienced in the management of anticancer medicinal products.
- Glasdegib + LDAC achieved a greater proportion of transfusion independence and decreased rate of exposure-adjusted transfusion requirements, which have the potential to achieve cost reductions for patients and payers.
- Glasdegib + LDAC provides a major advance in patient care due to increased ease of administration compared HMAs.

4.1 Requirements to use the technology

If any special conditions are attached to the regulatory authorisation more information should be provided, including reference to the appropriate sections of associated documents (for example, the EPAR and SPC). Include:

- *conditions relating to settings for use, for example inpatient or outpatient, presence of resuscitation facilities*
- *restrictions on professionals who can use or may prescribe the technology*
- *conditions relating to clinical management, for example patient monitoring, diagnosis, management and concomitant treatments.*

Glasdegib is an oral agent given in combination with LDAC, which can be self-administered by the patient at home provided that patients and carers have been trained, assessed and confirmed competent for self-administration (74, 75).

Glasdegib + LDAC should only be prescribed by or under the supervision of a physician experienced in the management of anticancer medicinal products (74, 76).

Clinical management of glasdegib + LDAC

Complete blood counts, electrolytes, renal, and hepatic function should be assessed prior to the initiation of glasdegib and at least once weekly for the first month. Electrolytes and renal function should be monitored once monthly for the duration of therapy. Serum creatine kinase levels should be obtained prior to initiating glasdegib and as indicated clinically thereafter (e.g. if muscle symptoms are reported). Electrocardiograms (ECGs) should be monitored prior to the initiation of glasdegib, approximately one week after initiation, and then once monthly for the next two months to assess for QTc prolongation. ECG should be repeated if abnormal. Certain patients may require more frequent and ongoing ECG monitoring (see section 4.4 of SmPC). Abnormalities should be managed promptly (76).

Patients receiving LDAC must be monitored closely. Frequent platelet and leukocyte counts are mandatory. Suspend or modify therapy when drug-induced marrow depression has resulted in a platelet count under 50,000 or a polymorphonuclear granulocyte count under 1,000 per cubic mm. Counts of formed elements in the peripheral blood may continue to fall after the drug is stopped, and reach lowest values after drug-free intervals of 12 to 24 days. If indicated, restart therapy when definite signs of marrow recovery appear (on successive bone marrow studies). Patients whose drug is withheld until 'normal' peripheral blood values are attained may escape from control (74).

Describe the equipment required to use the technology.

The administration of glasdegib + LDAC does not require any additional equipment.

Describe the supplies required to use the technology.

The administration of glasdegib + LDAC by the patient at home requires the following supplies (specifically for subcutaneous LDAC administration) (77):

- A cytotoxic sharps disposal bin
- Safety guard needles
- Alcohol/chlorhexidine wipes
- Gloves and apron if a carer is to do the injections
- Cytotoxic Spillage kit
- Cotton wool and tape
- Chemotherapy Diary Booklet

4.2 Investments, disinvestments and changes in service organisation

Describe any changes to current services that are needed to introduce the technology. Include:

- *any tests or investigations needed for selecting or monitoring patients that are over and above usual clinical practice*
- *any equipment, or organisational and technical conditions that will require investment before the technology can be introduced;*
- *any investment in infrastructure*
- *any programmes and services that will have to be increased due to introduction of the technology (rehabilitation, nursing etc.)*
- *Consider possible effects on services earlier and later in the care pathway.*

In countries, where LDAC administration by the patient at home is already standard of care, no changes to current services are anticipated to be required in order to introduce glasdegib + LDAC.

In countries, where LDAC administration by the patient at home is not yet standard of care, patients and carers may need to be trained, assessed and confirmed competent for self-administration.

Describe any tests, investigations, interventions, facilities or technologies that would no longer be needed if the technology is introduced.

No tests, investigations, interventions, facilities, or technologies are anticipated to be replaced in order to introduce glasdegib.

Patients receiving glasdegib + LDAC had over three times higher proportion of transfusion independence vs LDAC alone (78). Patients taking glasdegib + LDAC experienced 50 % lower rates of exposure-adjusted transfusions than patients taking LDAC alone, leading to potential cost offsets. Though there is a paucity of data regarding the economic burden associated with transfusion requirements for patients with AML, the high costs and increased healthcare utilization associated with transfusion dependence are well established in patients with MDS (79, 80).

Infusion requirements are increased with sepsis, bacteraemia, inpatient and intensive care unit (ICU) stay, as well as ELN risk. In the BRIGHT AML 1003 trial, patients in the glasdegib + LDAC arm experienced a lower risk of sepsis than patients in the LDAC arm. The most common treatment-related AEs did not include serious infections and generally did not require ICU/hospital stays that might be associated with increased transfusion needs.

Taken together, these results suggest that greater transfusion independence and decreased transfusion requirements have the potential to result in cost reductions for patients with AML and payers. Thus, glasdegib treatment may offer cost offsets based on a greater proportion of transfusion independence and reduced transfusion requirements and the associated decreases in healthcare utilization and costs of acquisition of blood products and administration.

In addition, glasdegib + LDAC provides a major contribution to patient care due to potential differences in the ease of administration vs. azacitidine and decitabine. While azacitidine and decitabine must be administered on an inpatient basis (72, 73), glasdegib is an oral agent given in combination with LDAC, which can be self-administered by the patient at home (69).

5 Clinical effectiveness and safety

Summary of the clinical effectiveness

- Glasdegib + LDAC nearly doubled OS compared to LDAC alone (HR [95 % CI]: 0.46 [0.30, 0.72]; p = 0.0002; median OS: 8.3 months vs. 4.3 months).
- Standard ITC demonstrated a statistically significant benefit in OS of glasdegib + LDAC compared to azacitidine (HR [95 %-CI]: 0.51 [0.31, 0.85]) and decitabine (HR [95 % CI]: 0.57 [0.35, 0.91]). Simulated Treatment Comparisons (STC) were conducted as a supportive analysis and the results and conclusions were similar to the standard ITC analysis.
- Quality-adjusted Time Without Symptoms of Disease Progression or Toxicity (Q-TWiST) was 4.0 months longer for glasdegib + LDAC compared to LDAC alone, translating into a statistically significant and clinically meaningful 75 % relative improvement in quality-adjusted survival compared to LDAC alone.
- The benefit of glasdegib + LDAC was also substantial regarding objective response (including CR, CRi, MLFS): Significantly more patients in the glasdegib + LDAC arm achieved CR and objective response (CR +CRi + MLFS) compared to LDAC alone (17.9 % vs 2.6 %; p = 0.0235 and 26.9 % vs. 5.3 %; p = 0.0080, respectively).
- Statistically significant greater proportion of transfusion-independence were reported with glasdegib + LDAC vs. LDAC alone, enabling patients to spend more time away from the hospital and improving health-related quality of life (e.g. transfusion independence ≥ 8 weeks: 28.2 % vs. 5.3 %; p=0.0056).

Summary of safety

- In general, the rates of AEs were similar between glasdegib + LDAC and LDAC alone, even though patients were treated for longer time periods with glasdegib + LDAC.
- Considering the entire study period, glasdegib + LDAC showed similar rates compared to LDAC alone for SAEs (78.7 % vs. 77.8 %), severe AEs (grade 3 - 5) (92.0 % vs. 97.2 %) and AEs (any CTCAE grade) (100 % vs. 100 %).
- Considering the first 90 days of therapy, glasdegib + LDAC demonstrated a statistically significant benefit over LDAC alone regarding fatal AEs (16.0 % vs. 36.1 %; RR [95 % CI]: 0.44 [0.23, 0.87], p-value = 0.0184) and numerically fewer treatment discontinuations due to AE (20.0 % vs. 33.3 %; RR [95 % CI]: 0.60 [0.31, 1.15], p = 0.1216).
- No differences between glasdegib + LDAC and LDAC alone occurred regarding the regarding the AEs commonly expected for antileukemic treatment: febrile neutropenia (entire study period: 34.7 % vs. 25.0 %; first 90 days: 30.7 % vs. 22.2 %), haemorrhage (entire study period: 48.0 % vs. 50.0 %; first 90 days: 36.0 % vs. 47.2 %), QT prolongation (entire study period: 20.0 % vs. 11.1 %; fist 90 days: 13.3 % vs. 11.1 %) and infections (entire study period: 61.3 % vs. 55.6 %; fist 90 days: 52.0 % vs. 52.8 %) including pneumonia (entire study period: 28.0 % vs. 27.8 %; fist 90 days: 18.7 % vs. 25.0 %).

5.1 Identification and selection of relevant studies

5.1.1 Databases and trial registries

State the databases and trial registries searched and, when relevant, the platforms used to do this.

Literature databases

The key biomedical literature databases were searched according to the methodological guideline "Process of information retrieval for systematic reviews and health technology assessments on clinical effectiveness" published by the EUnetHTA in January 2020 (81). The search strategies were run in the databases MEDLINE, EMBASE and Cochrane library via the OVID platform.

The databases searched for the review are listed in Table 9.

Table 9: Databases to be searched

Database	Interface
Excerpta Medica database (Embase)	Ovid, Advanced search http://ovidsp.ovid.com/
MEDLINE®	Ovid, Advanced search http://ovidsp.ovid.com/
Cochrane Central Register of Controlled Trials	Ovid http://ovidsp.ovid.com/
Abbreviations: EBM: Evidence Based Medicine; Embase = Excerpta Medica database; MEDLINE = Medical Literature Analysis and Retrieval System Online	

The search terms and strategies used to retrieve evidence from these databases are provided in Appendix B-1.

Clinical trials registries

The following clinical trial registries were searched to retrieve a list of trials in patients with AML:

- US National Institutes of Health (NIH) Ongoing Trials Register (www.clinicaltrials.gov)
- European Union Clinical Trials Register (EU CTR)
- The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

The keywords used to retrieve the evidence from these registries are provided in Appendix B-2.

5.1.2 Search date and limitations

State the date the searches were done and any limits (for example date, language) placed on the searches.

The SLR was conducted on 17th January 2020.

Publication time frame

No time restriction was applied in the conducted searches.

Language

No restrictions regarding language were applied, neither in the searches nor in the selection.

5.1.3 Search terms and strategies

Include as an appendix the search terms and strategies used to interrogate each database or registry.

Search terms and keywords used to retrieve evidence from these databases are provided in Appendix B.

5.1.4 Inclusion and exclusion criteria

In Table 10, state the inclusion and exclusion criteria used to select studies and justify these.

The inclusion and exclusion criteria reflect the predefined PICOS criteria as defined in the project scope of EUnetHTA`s project plan. First, studies were searched for the direct comparison of glasdegib + LDAC vs. the respective comparators, defined by the authors (Table 10). Regarding study design, all studies other than RCT were excluded. Comprehensive data on safety including data from non-randomised studies are available in the summary of safety of the EMA CHMP assessment report.

Since only one study comparing the effectiveness of glasdegib + LDAC vs. LDAC alone could be identified, an additional search was performed to identify studies with azacitidine or decitabine suitable for an indirect comparison (see Appendix B). Since only a study assessing glasdegib + LDAC with the comparator LDAC alone was available, LDAC was identified as the only possible common comparator for the indirect comparison of glasdegib + LDAC vs. azacitidine or decitabine. Hence, LDAC was used as a comparator in this selection as well. The inclusion and exclusion criteria for this selection are listed in Table 11 and Table 12.

Table 10: PICOS criteria for selection of studies in the systematic literature review in AML in adult patients who are not candidates for standard induction chemotherapy

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy	• Patients who are candidates for standard induction chemotherapy • Other patient populations not appropriate for the relevant therapeutic area
Interventions	Glasdegib + LDAC	All other treatments
Comparators	LDAC or azacitidine or decitabine	All other comparators
Outcome Measures	Clinically relevant outcomes regarding efficacy and safety reported	No clinically relevant outcomes regarding efficacy and safety reported
Study Design	Randomised controlled trials (RCT)	Studies, other than randomized controlled trials
Setting	Publication delivers adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)	Publication does not deliver adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)
Language	No restriction	
Other search limits or restrictions applied	NA	NA
Abbreviations: AML = acute myeloid leukaemia; LDAC = low-dose cytarabine; RCT = randomized controlled trial		

Table 11: PICOS criteria for selection of studies in the systematic literature review in AML in adult patients who are not candidates for standard induction chemotherapy – Indirect comparison decitabine

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Adult patients newly diagnosed AML who are not candidates for standard induction chemotherapy	• Patients who are candidates for standard induction chemotherapy • Other patient populations not appropriate for the relevant therapeutic area

PICOS	Inclusion Criteria	Exclusion Criteria
Interventions	Decitabine	All other treatments
Comparators	LDAC	Comparators other than LDAC
Outcome Measures	Clinically relevant outcomes regarding efficacy and safety reported	No clinically relevant outcomes regarding efficacy and safety reported
Study Design	Randomised controlled trials (RCT)	Studies, other than randomized controlled trials
Setting	Publication delivers adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)	Publication does not deliver adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)
Language	No restriction	
Other search limits or restrictions applied	NA	NA
Abbreviations: Abbreviations: AML = acute myeloid leukaemia; LDAC = low-dose cytarabine; RCT = randomized controlled trial		

Table 12: PICOS criteria for selection of studies in the systematic literature review in AML in adult patients who are not candidates for standard induction chemotherapy – Indirect comparison azacitidine

PICOS	Inclusion Criteria	Exclusion Criteria
Population	Adult patients newly diagnosed with who are not candidates for standard induction chemotherapy	• Patients who are candidates for standard induction chemotherapy • Other patient populations not appropriate for the relevant therapeutic area
Interventions	Azacitidine	All other treatments
Comparators	LDAC	Comparators other than LDAC
Outcome Measures	Clinically relevant outcomes regarding efficacy and safety reported	No clinically relevant outcomes regarding efficacy and safety reported
Study Design	Randomised controlled trials (RCT)	Studies, other than randomized controlled trials
Setting	Publication delivers adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)	Publication does not deliver adequate information to assess methodology and results (e.g. full publication, report including results from a study register or study report)
Language	No restriction	
Other search limits or restrictions applied	NA	NA
Abbreviations: Abbreviations: AML = acute myeloid leukaemia; LDAC = low-dose cytarabine; RCT = randomized controlled trial		

5.1.5 Study selection and data extraction – literature searches

Implementation and reporting of the clinical systematic literature review followed the recommendations and standards as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) statement (see Figure 5). The SLR was conducted as outlined below:

- First stage: Title/abstract screening was performed by two independent reviewers as per specific PICOS criteria (Table 10, Table 11 or Table 12, respectively).
- Second stage: Full-text articles of titles accepted at first stage were screened by two independent reviewers as per specific PICOS criteria (Table 10).
- Reviewer discrepancies at either stage were resolved by a third reviewer.

  Data were extracted and quality control procedures were applied to verify the accuracy and completeness of each collected data point and to identify any data omissions.

5.1.6 Study selection and data extraction – study registries

The study registry searches listed in Appendix B-2 were performed on the 17th January 2020. The search for glasdegib + LDAC revealed 30 hits (clinical trials: 11, EU CTR: 7, ICTRP: 12 hits), the search for azacitidine 583 hits (clinical trials: 227, EU CTR: 136, ICTRP: 220 hits) and the search for decitabine 434 hits (clinical trials: 170, EU CTR: 61, ICTRP: 203 hits). The identified studies were selected based on the inclusion and exclusion criteria shown in Table 10, Table 11 or Table 12, respectively. As in literature searches, the screening was conducted by two independent reviewers. Studies were included based on the information in the respective registries and were then analysed regarding the provided results. In all cases, the information that was available in the registries was also included in publications retrieved from the literature searches.

5.1.7 PRISMA flow diagram

Provide a flow chart showing the number of studies identified and excluded. The PRISMA statement can be used; the PRISMA flow chart is included below, as an example.

A total of 3 studies were identified from 3 publications. The flow of the studies in the SLR is presented in Figure 5.

Selection of relevant studies

Based on the considerations outlined in Section 2, and the predefined PICO criteria , comparisons were limited to LDAC, decitabine and azacitidine. One study was selected comparing the safety and efficacy of glasdegib + LDAC vs. LDAC alone. Since no study directly comparing glasdegib + LDAC vs. decitabine or azacitidine was available, indirect comparisons were conducted. Therefore, in a first step, LDAC was identified as the only common comparator that could be utilised. In a second step, only studies comparing decitabine or azacitidine with LDAC were selected. Figure 5 summarizes the selection process and depicts the number of studies in- and excluded at the distinct steps.

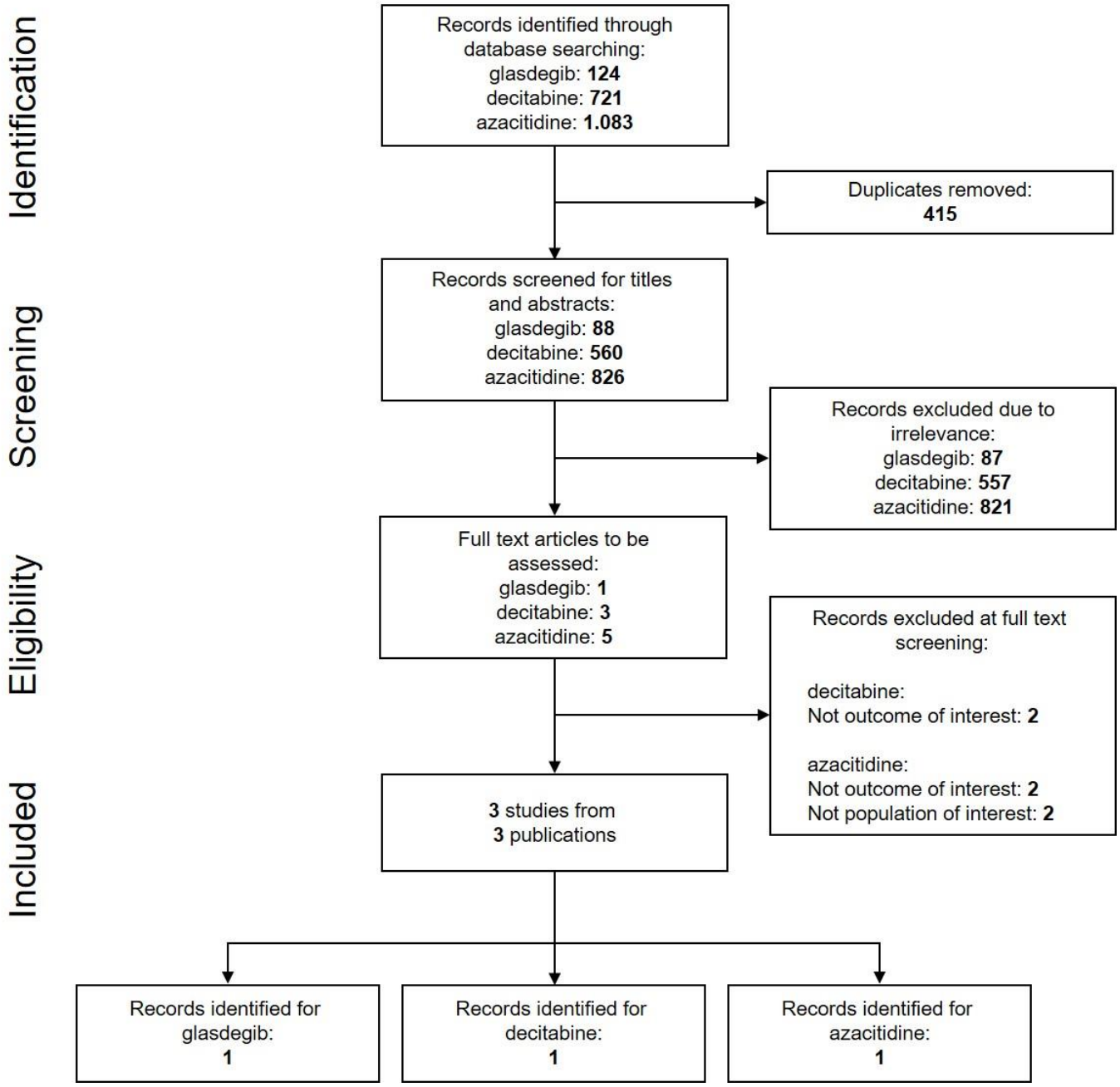


Figure 5: Sequential PRISMA diagram flow depicting the SLR.

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

For glasdegib, of the 124 publications identified in the literature search, one publication for one study met the selected PICOS criteria.

For azacitidine, one publication for one study of the 1,083 publications identified, met the inclusion criteria. Additionally, 721 publications were identified in the search for decitabine; one of them met the inclusion criteria.

All three relevant studies are documented in Table 13.

Data and information on study design of the three trials presented in this submission file were extracted from the publications and corresponding supplementary material, clinical study reports (CSR), and additional analyses conducted for the authorization procedure and HTA reports, respectively.

Table 13: List of all relevant studies

Study reference/ID	Available documentation*	Status (ongoing**/ complete)
Randomised controlled trials		
B1371003[a] NCT01546038 2012-000684-24	*Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome. Leukaemia. 2019;33(2):379-89 (82, 83)*	*completed*
DACO-016 NCT00260832 2005-004503-11	*Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukaemia. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012;30(21):2670-7 (2)*	*completed*
AZA-AML-001 NCT01074047 2009-012346-23	*Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30 % blasts. Blood. 2015;126(3):291-9 (1)*	*completed*
Non-randomized studies		
B1371005 NCT0203877	*A study of PF-04449913 in Japanese Patients with Select Hematologic Malignancies*	*ongoing*
a: the non-intensive phase 2 part of B1371003 is considered relevant for the assessment. *Include references to all linked documents and indicate the expected date of publication for any unpublished clinical studies **Include expected date of completion		

5.2 Relevant studies

As described above, in total three RCTs were considered to be relevant for this assessment according to the selected inclusion criteria.

One study of the glasdegib development program was included based on the predefined inclusion/exclusion criteria and is considered of primary interest for the assessment. The phase 1b/2, open-label, international, multicenter study B1371003 evaluated safety and efficacy of glasdegib plus intensive chemotherapy (cytarabine and daunorubicin), LDAC or decitabine in previously untreated patients with AML or high-risk MDS. The indication of glasdegib will be 'in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy'. Therefore, only the phase 2, randomized, open-label portion of B1371003 that assesses the efficacy and safety of glasdegib + LDAC vs. LDAC alone in adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy(82) (Cohort E1A in Figure 6, blue box), in the following designated as BRIGHT AML 1003, is relevant for this assessment. Complete data on MDS are provided in the CSR (83).

Two studies used for the indirect comparisons assessing glasdegib + LDAC vs. azacitidine or glasdegib + LDAC vs. decitabine are published by Dombret et al. 2015 (in the following designated as AZA-AML-001) (1) and Kantarjian et al. 2012 (in the following designated as DACO-016) (2).

Study design, endpoints, treatment, patient characteristics, and efficacy and safety results from the RCT included in the evidence base are summarised in the following sections.

5.2.1 Main characteristics of studies

In Table 15, describe the main characteristics of the studies.

Table 15 summarises the characteristics of the studies BRIGHT AML 1003, AZA-AML-001 and DACO-016. All studies were randomized, controlled, open-label, multicenter trials with the aim to evaluate the efficacy and safety of the respective intervention (glasdegib + LDAC, azacitidine or decitabine).

BRIGHT AML 1003

BRIGHT AML 1003 is a phase 2, randomized, open-label, multicenter trial where glasdegib + LDAC was compared to LDAC alone in adult patients newly diagnosed with AML who were not candidates for standard induction chemotherapy. These patients were randomized 2:1 to glasdegib + LDAC or LDAC alone, stratified by cytogenetic risk (good/intermediate or poor). Cytogenetic risk profile was assessed according to ELN 2010 guidelines (see Table 14) (84).

Patient randomization was obtained by the investigator or the designee from an interactive voice response system. Masking was not applicable for this open-label study. BRIGHT AML 1003 was conducted in Europe and North America and started in June 2012; primary completion date was January 2017.

Glasdegib 100 mg once daily was administered orally on a continuous basis and LDAC was given at a dose of 20 mg administered SC twice daily for the first 10 days of a 28-day cycle. Treatment with glasdegib in combination with LDAC or LDAC alone could continue until disease progression or relapse, patient refusal, or occurrence of unacceptable toxicity (whichever came first). All patients were followed up for post-treatment survival status for 4 years from randomization.

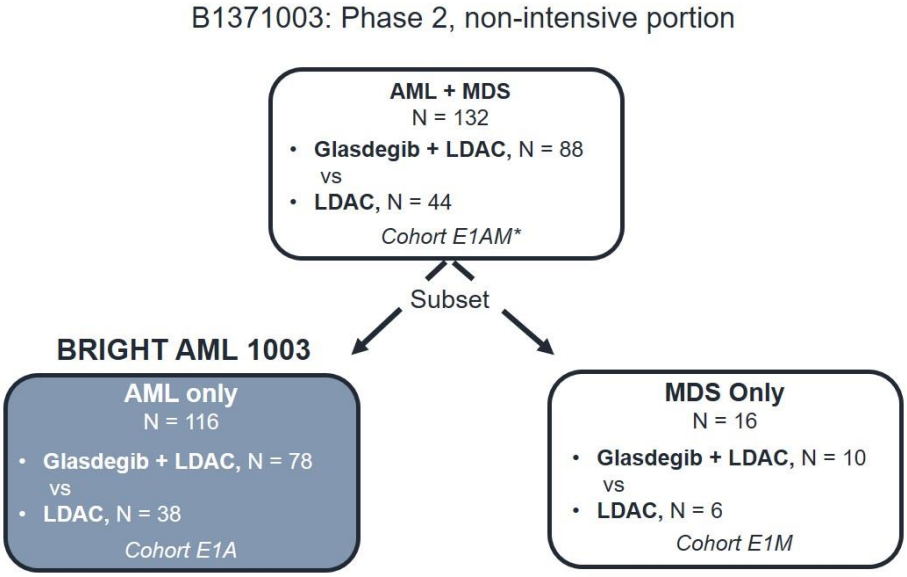


Figure 6: Glasdegib Study Design
Abbreviations: AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; LDAC = low-dose cytarabine;
Reference: adapted from (82)

AZA-AML-001 (Dombret 2015)

This multicenter, randomized, open-label, phase 3 trial evaluated azacitidine efficacy and safety vs. conventional care regimens in patients age ≥ 65 years with newly diagnosed AML presenting with > 30 % bone marrow blasts. It was conducted between October 2010 and January 2016 in 18 countries.

Before randomization, investigators determined which one of three protocol-designated conventional care regimens (BSC, LDAC, or induction chemotherapy) was most appropriate for each patient on the basis of age, ECOG PS, comorbidities, and regional guidelines and/or institutional practice. A central, stratified, and permuted block randomization method with an interactive voice response system were used to randomly assign patients 1:1 to receive azacitidine or conventional care regimen. Randomization was stratified by preselected conventional care regimen (BSC, LDAC, or induction chemotherapy), ECOG PS (0-1 or 2), and cytogenetic risk (intermediate or poor). Cytogenetic risk profile was assessed according to NCCN 2009 criteria (see Table 14) (85).

Patients assigned to a conventional care regimen received their preselected treatment.

Azacitidine 75 mg/m^2 per day was administered subcutaneously for 7 consecutive days per 28-day treatment cycle for at least 6 cycles. The conventional care regimens were as follows: BSC only; subcutaneous LDAC (20 mg twice per day for 10 days per 28-day treatment cycle for at least 4 cycles); or intensive chemotherapy for 1 cycle, followed by up to 2 consolidation cycles for those achieving CR or partial response (PR). Reinduction was not allowed. Azacitidine and LDAC dosing could be reduced or delayed as needed until the blood count recovered. All study participants could receive BSC, including transient use of hydroxyurea (hydroxyurea was not allowed within 72 hours before or after azacitidine administration).

For use in ITC, data were taken from the publication identified in the systematic literature search (Dombret 2015 (1)).

The population of interest for the indirect comparison comprised patients that were preselected for LDAC, as this is the common comparator. Where Dombret 2015 reported data for patients preselected for LDAC, these results were used. If data for this population were not available, the limitations were discussed.

DACO-016 (Kantarjian 2012)

This randomized, open-label, phase 3 study compared the efficacy and safety of decitabine with treatment choice in older patients with newly diagnosed AML and poor- or intermediate-risk cytogenetics and was conducted between January 2006 and April 2009 in 15 countries.

Patients indicated, advised by their physician, their preferred treatment choice, either BSC or LDAC 20mg/m^2 one time per day subcutaneously for 10 consecutive days every 4 weeks. This dose schedule is considered to have comparable drug exposition over time (area under the curve) including any associated cytotoxic effects (86) to twice per day dosing. Patients were randomly assigned 1:1 to receive decitabine or their preferred treatment choice by using a stratified permuted block method. Random assignment was stratified by age, cytogenetic risk, and ECOG PS. Cytogenetic risk profile was assessed according to South West Oncology Classification (see Table 14) (87).

Patients assigned to receive decitabine received 1-hour IV infusions of decitabine 20 mg/m^2 one time per day for five consecutive days every 4 weeks. Treatment continued until relapse or progressive disease, death, unacceptable toxicity, lack of clinical benefit, intercurrent illness preventing treatment, or patient/physician request.

Data were taken from the publication identified in the systematic literature search (Kantarjian 2012 (2)).

The population of primary interest for the indirect comparison comprised patients that were preselected for LDAC, as this is the common comparator. Where Kantarjian 2012 reported data for patients preselected for LDAC, these results were used. If data for this population were not available, the limitations were to be discussed.

Table 14: Overview of cytogenetic and molecular risk stratification tools

Genetic risk group	ELN 2010	NCCN 2009	SWOG 2000
Favourable	**t(8;21)(q22;q22); *RUNX1-RUNX1T1*** **inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*** Mutated *NPM1* without *FLT3*-ITD (normal karyotype)	**t(15;17) with/without secondary aberrations;** **t(8;21) lacking del(9q) or complex karyotypes** **inv(16)/t(16;16)/del(16q),**	**t(8;21)** **inv(16)** **t(16;16)** Normal cytogenetics with isolated *NPM1* mutation

	Mutated *CEBPA* (normal karyotype)		
Intermediate	*Intermediate I* Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype) *Intermediate II* **t(9;11)(p22;q23); *MLLT3-MLL*** **Cytogenetic abnormalities not classified as favorable or adverse**	Normal **+8** **+6** **-Y** **del(12p)**	Normal, **+8 only,** **t(9;11) only** **Other abnormalities not listed with better risk and poor risk cytogenetics and molecular mutations** C-KIT in patients with t(8;21) or inv(16)
Adverse/Poor/ Unfavourable	**-5 or del(5q)** **-7** **abnl(17p)** **inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*** **t(6;9)(p23;q34); *DEK-NUP214*** **t(v;11)(v;q23); *MLL* rearranged** **complex karyotype (≥ 3 abnormalities)**	**-5/ del(5q)** **-7/ del(7q)** **abn 3q, 9q, 11q, 20q, 21q, 17p, t(6;9),** **t(9;22)** **complex karyotypes (≥ 3 unrelated abn)**	**-5/ 5q-** **-7/ 7q-** **Abnormalities of 11q23, excluding t(9;11)** **Inv(3) or t(3;3)** **t(6;9)** **t(9;22)** **complex karyotypes (≥ 3 abnormalities)** Normal cytogenetics with isolated *FLT3*-ITD mutations
Unknown	-	All other abnormalities	-
Abbreviations: Abbreviations: p = short arm of the chromosome; q = long arm of the chromosome; t(A;B) = used to denote a translocation between chromosome A and chromosome B Classical cytogenetic markers are in **bold** References: (84, 85, 87)			

Table 15: Characteristics of the studies BRIGHT AML 1003, AZA-AML-001 (Dombret 2015) and DACO-016 (Kantarjian 2012)

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
BRIGHT AML 1003	To compare the efficacy and safety for glasdegib + LDAC vs. LDAC alone in adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy	phase 2, randomized, open-label, multicenter	<u>Main inclusion criteria:</u> • Aged ≥55 years with newly diagnosed, previously untreated AML according to the WHO 2008 Classification. • Known cytogenetic profile at study entry and considered not suitable for intensive chemotherapy, defined by ≥1 of the following criteria: ○ age ≥75 years ○ serum creatinine > 1.3 mg/dL ○ severe cardiac disease (e.g., left ventricular ejection fraction < 45 % by multi-gated acquisition or echocardiography at screening) ○ ECOG PS = 2. Patients with ECOG PS = 0 or 1 who met ≥1 other inclusion criteria listed above were also eligible <u>Main exclusion criteria:</u> • acute promyelocytic leukaemia, • t(9;22) cytogenetic translocation • active other malignancy	• Treatment phase: ○ Glasdegib (100 mg once daily orally in 28-day cycles on a continuous basis) + LDAC (20 mg s.c. twice daily for 10 days every 28 days) (N = 78) ○ LDAC (20 mg s.c. twice daily for 10 days every 28 days) alone (N = 38) • Follow-up period: patients were followed up for post-treatment survival status for 4 years from randomization	OS (months), defined as duration from the date of randomization to the date of death from any cause.	<u>Secondary outcomes:</u> • CR, defined as those with repeat bone marrow showing ≤5 % myeloblasts, peripheral blood showing neutrophils ≥1000/µL, platelets ≥100,000/µL, 0 % blast and hemoglobin (Hgb) ≥11 g/dL, normal maturation of all cell lines. • Disease specific efficacy endpoints such as CR with incomplete haematologic recovery (CRi), morphologic leukaemia-free state (MLFS), partial remission (PR), PR with incomplete blood count recovery (PRi), minor response (MR), stable disease (SD), cytogenetic complete response (CRc), molecular complete response (CRm) • Type, incidence, severity (graded by the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], Version 4.0), timing, seriousness, and relatedness of adverse events. <u>Additional outcomes:</u> • Quality of Survival evaluated by Q-TWiST analysis (Quality-Adjusted Time Without Symptoms of Disease Progression or Toxicity) which incorporates health-related quality-of-life

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• known active uncontrolled leukaemia of the central nervous system • prior treatment with Hedgehog inhibitor or other investigational agent for the treatment of an antecedent haematologic disease			considerations into treatment comparisons • Transfusion need: Independence from transfusion is presented in terms of absolute and relative frequencies
AZA-AML-001 (Dombret 2015)	To evaluate the efficacy and safety of AZA compared with conventional care regimens (doctor's choice of BSC only, LDAC, or standard IC) in patients age ≥65 years with newly diagnosed AML and > 30 % BM blasts	Phase 3, open-label, international, multicenter, randomized	<u>Main inclusion criteria:</u> • Aged ≥65 years with newly diagnosed, histologically confirmed de novo or secondary AML with > 30 % BM blasts who were not considered eligible for hematopoietic stem cell transplantation • intermediate- or poor-risk cytogenetics (NCCN 2009 criteria 17) • ECOG PS ≤2 • WBC count ≤15 × 10^9/L. <u>Main exclusion criteria:</u> • acute promyelocytic leukaemia t(15;17)(q22;q12) and AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22), t(8;21)(q22;q22), or t(9;22)(q34;q11.2) • AML arising from previous haematologic disorders other than MDS (e.g. myeloproliferative neoplasms); • other malignancies;	Treatment phase: patients were randomly assigned (1:1) to receive AZA or conventional care regimen. • AZA: N = 241 ○ preselected for BSC: N = 44 ○ preselected for LDAC: N = 154 ○ preselected for IC: N = 43 • conventional care regimen: N = 247 ○ BSC: N = 45 ○ LDAC: N = 158 ○ IC: N = 44	OS (months), defined as time from randomization to death as result from any cause	<u>Secondary outcomes:</u> • estimated 1-year survival rate • OS in patient subgroups defined by baseline demographic and disease characteristics: age, gender, race, geographic region, ECOG PS, baseline cytogenetic risk, WHO classification of AML, white blood cell count, BM blasts, and prior history of MDS.

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• uncontrolled systemic infection. • Patients could not have received prior decitabine, azacitidine, or cytarabine treatment; • Prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the screening hematology sample was taken); • any experimental drug within 4 weeks of starting study treatment.			

DACO-016 (Kantarjian 2012)	To compare the efficacy and safety of DEC with patient choice, with physician advice (BSC or LDAC) in older patients with AML	Phase 3, open-label, international, multicenter, randomized	<u>Main inclusion criteria:</u>
			• Aged ≥65 years with newly diagnosed, histologically confirmed de novo or secondary AML (≥20 % blasts) and poor- or intermediate-risk cytogenetics (Southwest Oncology Group categorization)
			• ECOG PS of 0 to 2
			• WBC count ≤40,000/mm
			• bilirubin ≤1.5 × ULN
			• AST or ALT ≤2.5 × ULN
			• creatinine clearance ≥40 mL/min
			• life expectancy ≥12 weeks
			<u>Main exclusion criteria:</u>
			• acute promyelocytic leukaemia
			• t(8;21) or inv(16) karyotype abnormalities
			• CNS leukaemia
			• active systemic malignancies
				Treatment phase: patients were randomly assigned (1:1) to receive DEC or treatment choice.
				• DEC: N = 242
				• treatment choice: N = 243
				  ○ BSC: N = 28
				  ○ LDAC: N = 215
				
				Follow-up: Patients were followed monthly for 2 years post-randomization and then every 2 months for 3 years for OS and PD until death or loss to follow-up.
					OS (months), defined as time from randomization to death as result from any cause	<u>Secondary outcomes:</u>
						• CR
						• CR with incomplete platelet recovery (CRp)
						• Remission (evaluated by using modified 2003 International Working Group criteria)
						• CR with incomplete blood count recovery (CRi)
						• AEs

Study reference/ID	Objective	Study design	Eligibility criteria	Intervention and Comparator (N enrolled)	Primary outcome measure and follow-up time point	Secondary outcome measures and follow-up time points
			• unstable angina or New York Heart Association class 3/4 congestive • heart failure • inaspirable bone marrow, comorbidities or organ dysfunction • uncontrolled active infection, or HIV • previous chemotherapy (except hydroxyurea) for any myeloid disorder or used experimental drugs for 4 weeks pre-randomization • candidates for bone marrow or stem-cell transplantation for 12 weeks prerandomization • received radiotherapy for extramedullary disease for 2 weeks pre-randomization			

Abbreviations: AE = adverse event; ALT = Alanin-Aminotransferase; AST = aspartate aminotransferase; AZA = azacitidine; BM = bone marrow; BSC = best supportive care; CNS = central nervous system; CR = morphologic complete response; CRc = cytogenetic complete response; CRi = CR with incomplete haematologic recovery; CRm = molecular complete response ; CRp = CR with incomplete platelet recovery ; CTCAE = common terminology criteria for adverse events; DEC = decitabine; IC = induction chemotherapy, LDAC = low-dose cytarabine; MDS = myelodysplastic syndrome; MLFS = morphologic leukaemia-free state ; MR = minor response ; NCCN = National Comprehensive Cancer Network; NCI = National Cancer Institute ; OS = overall survival; PD = progressive disease; PR = partial remission ; PRi = PR with incomplete blood count recovery ; PS = performance status; RAEB = refractory anemia with excess blasts; s.c. = subcutaneous; SD = stable disease ; ULN = upper limit of normal; WBC = white blood count; WHO = World Health Organization;
References: (1, 2, 82, 83, 88)

5.2.2 Study flow diagram

For each study provide a flow diagram of the numbers of patients moving through the trial.

In Figure 7, Figure 8, and Figure 9 consolidated standards of reporting trials (CONSORT) flow diagrams of studies BRIGHT AML 1003, AZA-AML-001 and DACO-016 are presented.

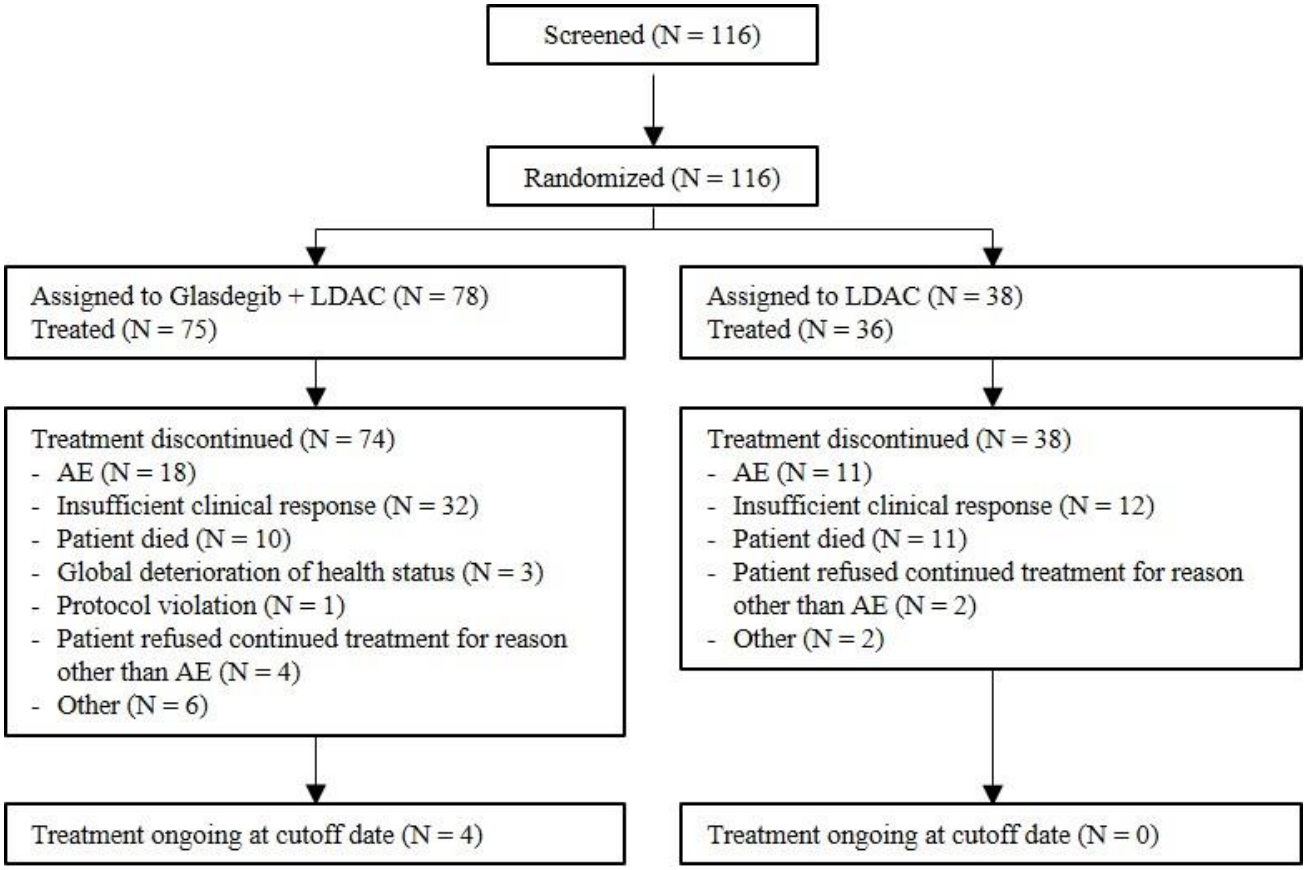
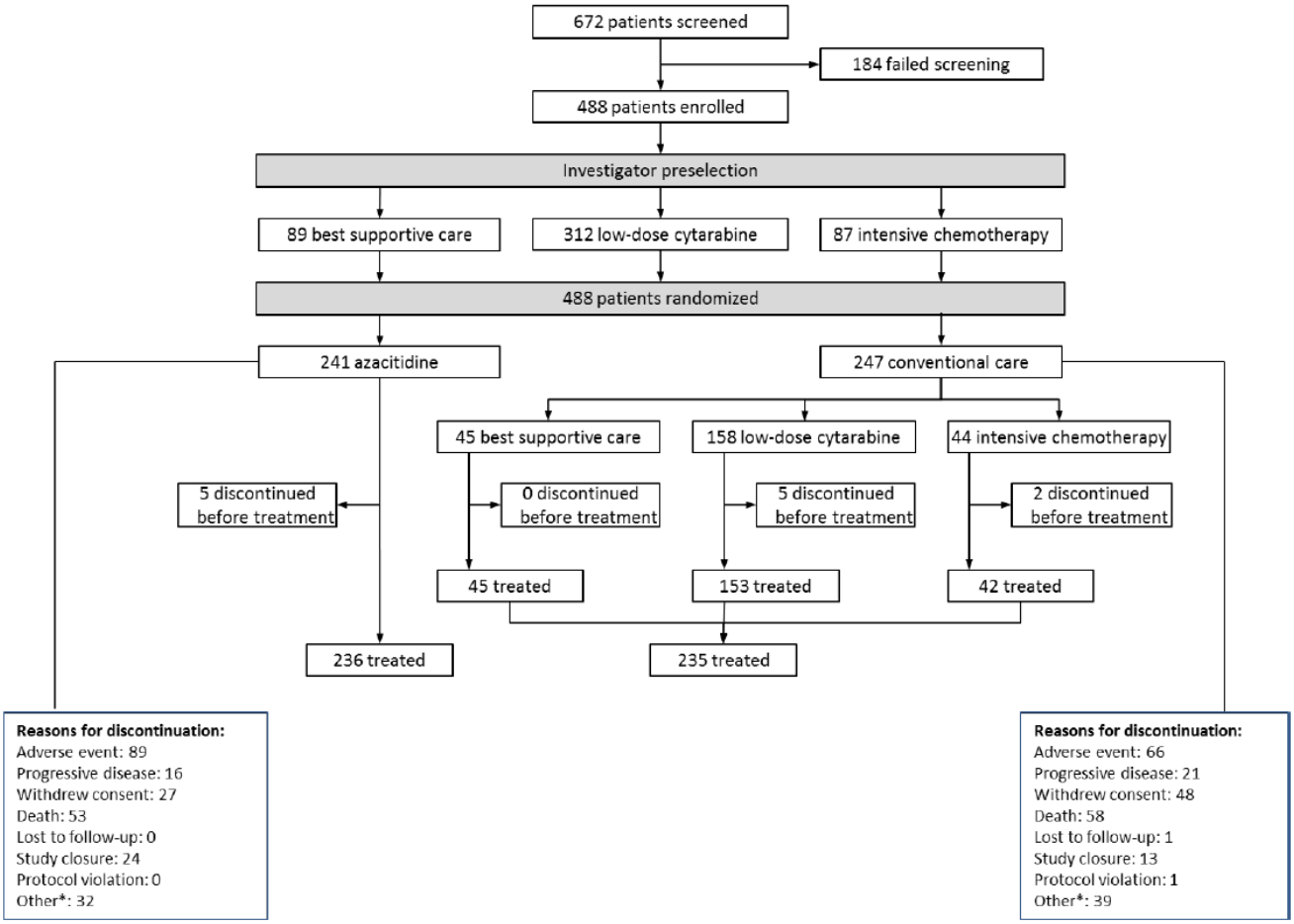


Figure 7: CONSORT Flow Diagram of BRIGHT AML 1003.

Data-cut January 3rd 2017 (primary data-cut). Insufficient clinical response was determined by clinical judgement.

Other reasons for treatment discontinuations for patients assigned to glasdegib + LDAC were “patient randomized but never treated” (N=3), “patient proceeding to donor lymphocyte infusion” (N=1), “patient and P.I. made mutual decision” (N=1) and “patient proceed to bone marrow transplant” (N=1). Other reasons for treatment discontinuations for patients assigned to LDAC alone were “patient randomized but never treated” (N=2),

Reference: (89)



*Of all 71 patients who withdrew due to "Other" reasons, 41 patients (58%) had "relapse" listed on their case report form (CRF). Of the remaining patients, 24 (34%) discontinued due to "investigator decision," and 6 (8%) discontinued for various other reasons.

Figure 8: CONSORT Flow Diagram of AZA-AML-001.

Reference: (1)

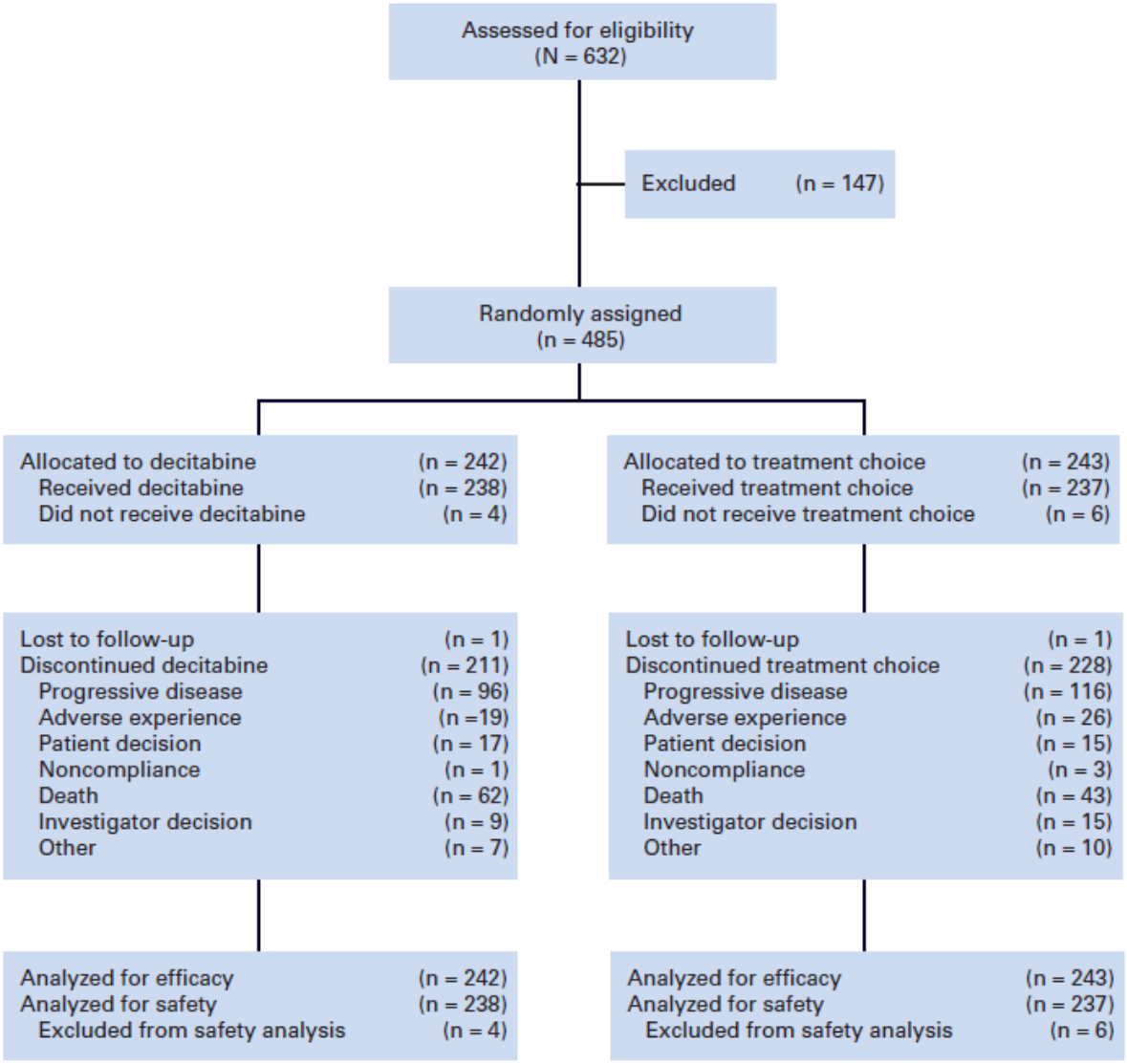


Figure 9: CONSORT Flow Diagram of DACO-016.
Reference: (2)

5.2.3 Key demographic and baseline characteristics

For each study provide a comparison of patients (including demographic, clinical and social information [if applicable]) in treatment arms at baseline.

Analysis sets

The analysis set for BRIGHT AML 1003 comprised all randomized patients with AML who were not candidates for standard induction chemotherapy.

Dombret 2015 reported baseline patient demographics and clinical characteristics for patients receiving LDAC, but not separately for LDAC preselected patients in the azacitidine arm. Therefore, the azacitidine arm comprised all patients randomized to azacitidine, regardless of their preselected care regimen (BSC, LDAC or intensive chemotherapy).

Kantarjian 2012 reported efficacy results based on all randomized patients in the decitabine and treatment choice arm, regardless of their preselected treatment choice (BSC or LDAC). To ensure consistency with the individual study results, baseline patient demographics and clinical characteristics were also presented for all randomized patients in the decitabine and treatment choice arm.

Results

Key demographic and baseline characteristics are summarised in Table 16 for all RCT.

BRIGHT AML 1003

Overall, both treatment arms were generally comparable, both in terms of demographic characteristics and disease-specific features. The majority of patients were male (glasdegib + LDAC: 75.6 %; LDAC alone: 60.5 %). The median age at study entry was 77 years in the glasdegib + LDAC arm and 76 years in the LDAC alone arm. The majority of patients showed good or intermediate cytogenetic risk according to ELN 2010 criteria: 62.8 % (according to IVRS[1]) and 67.9 % (according to CRF[2]) of the patients in the glasdegib + LDAC arm and 55.3 % (according to IVRS) and 57.9 % (according to CRF) of the patients in the LDAC alone arm had good/intermediate cytogenetic risk profile. De novo and secondary AML was nearly balanced in both treatment arms: 48.7 % in the glasdegib + LDAC arm and 47.4 % of the patients in the LDAC alone arm had de novo AML. Accordingly, 51.3 % in the glasdegib + LDAC arm and 52.6 % in the LDAC alone arm had secondary AML. The proportion of patients with ECOG PS 0 - 1 and ECOG PS ≥ 2 distributed almost equally between glasdegib + LDAC and LDAC alone (ECOG PS of 0 or 1: 46.2% vs. 52.6%; ECOG PS of 2: 52.6% vs. 47.4%). The median peripheral blood white cell count was 2.47 $10^3/mm^3$ and 4.07 $10^3/mm^3$ in the glasdegib + LDAC or LDAC arm, respectively. The median bone marrow blasts were comparable between both treatment arms (41 % vs. 46 %). The duration since the histopathological diagnosis was comparable between the treatment arms (median approximately two weeks).

AZA-AML-001

Baseline demographic and disease characteristics were generally balanced between treatment arms. The majority of patients were male (AZA: 57.7 %; LDAC: 59.5 %). The median age at study entry was 75 years in both arms. The majority of patients showed good or intermediate cytogenetic risk, as defined by NCCN 2009 criteria: 64.3 % in the AZA arm and 65.8 % in the LDAC arm. The majority of patients enrolled in the study had de novo AML: 79.7 % in the AZA arm vs. 85.4 % in the LDAC arm. Regarding ECOG-PS, the majority of patients in the study had ECOG PS 0 - 1 (ECOG PS of 0 or 1: 77.2 % in the AZA arm vs. 77.9 % in the LDAC arm; ECOG PS of 2: 22.8 % in the AZA arm vs. 22.2 % in the LDAC arm). The median peripheral blood white cell count was 3.1 $10^3/mm^3$ and 2.3 $10^3/mm^3$ in the AZA and LDAC arm, respectively. The median bone marrow blasts were comparable between both treatment arms (70 % vs. 74 %).

DACO-016

Patient demographics and baseline clinical characteristics were balanced. The majority of patients were male (DEC: 56.6 %; Treatment choice: 62.1 %). The median age at study entry was 73 years in both arms. The majority of patients showed good or intermediate cytogenetic risk, as defined by South West Oncology Classification: 63.1 % in the DEC arm and 63.6 % in the treatment choice arm. The majority of patients enrolled in the study had de novo AML: 64.0 % in the DEC arm vs. 64.6 % in the treatment choice arm. Regarding ECOG-PS, the majority of patients in the study had ECOG PS 0 - 1 (ECOG PS of 0 or 1: 76.0

[1] The investigator or designee provided cytogenetic risk profile prior enrolment within the IVRS to enable the stratification of the randomization by cytogenetic risk (good/intermediate or poor). Any one of the following cytogenetic features (which were required prior to enrollment) classified the patient as having poor risk disease: inv(3), t(6;9), 11q23, -5, -5q, -7, abnl (17p), complex karyotype (≥3 clonal abnormalities). Patients with none of the features described above were classified as having good/intermediate risk disease. This approach reflected the ELN 2010 guidelines (see Table 14).

[2] The cyctogenetic riks profile was derived from the information regarding ELN genetic risk groups (shown in Table 14) provided via the CRF according to a prespecified algorithm: If genetic risk group = ‘adverse’ then cytogenetic risk = ‘poor cytogenetic risk’, if genetic risk group = (‘favorable’ or ‘intermediate-I’ or ‘intermediate-II’) then cytogenetic risk = ‘good/intermediate cytogenetic risk’.

% in the DEC arm vs. 75.3 % in the treatment choice arm; ECOG PS of 2: 24.0 % in the DEC arm vs. 24.7 % in the treatment choice arm). The median peripheral blood white cell count was 3.1 $10^3/mm^3$ and 3.7 $10^3/mm^3$ in the DEC or treatment choice arm, respectively. The median bone marrow blasts percentage was not reported, however, the majority of patients had bone marrow blasts ≤ 50 % (54.8 % in both arms).

BRIGHT AML 1003 vs AZA-AML-001 and DACO-016

The majority of patients were male, but the proportion of male patients was slightly higher in BRIGHT AML 1003 compared to AZA-AML-001 and DACO-016 (75.6 % or 60.5 % compared to 57.7 % or 59.5 % and 56.6 % or 62.1 %, respectively). The median age at study entry across treatment arms ranged from 73 to 77 years. Most patients were enrolled in Europe (between 81.6 % and 60.5 %), but there were no Asian study centres in BRIGHT AML 1003. The majority of patients showed good or intermediate cytogenetic risk (between 55.3 % and 65.8 %). De novo and secondary AML was nearly balanced in both treatment arms of BRIGHT AML 1003, whereas in the AZA-AML-001 study and in the DACO-016 study the majority of patients had de novo AML (79.7 % and 85.4 % or 64.0 % and 64.6 % of patients, respectively). In BRIGHT AML 1003 the proportion of patients with ECOG PS 0 - 1 and ECOG PS ≥ 2 distributed almost equally, in AZA-AML-001 and DACO-016 most patients showed ECOG PS 0-1 (between 76.0 % and 77.9 % of patients). The median peripheral blood white cell count in the BRIGHT AML 1003 study was 2.74 $10^3/mm^3$ and 4.07 $10^3/mm^3$ in the glasdegib + LDAC or LDAC arm, respectively. In AZA-AML-001 and DACO-016 it ranged from 2.3 $10^3/mm^3$ to 3.69 $10^3/mm^3$. The bone marrow blasts were comparable between the treatment arms but differed between the studies: In BRIGHT AML 1003 and DACO-016 less patients had bone marrow blasts > 50 % (39.8 % or 47.4 % and 43.69 % or 41.9 %, respectively), whereas in AZA-AML-001 the majority of patients had bone marrow blasts > 50 % (71.8 % and 81.0 % respectively). The median haemoglobin level ranged from 9.1 g/dL to 9.5 g/dL. The duration since the histopathological diagnosis was comparable between the treatment arms of BRIGHT AML 1003 and DACO-016 (median approximately two weeks), this duration was not reported in Dombret 2015.

Table 16: Summary of baseline patient demographics and clinical characteristics for BRIGHT AML 1003, AZA-AML-001 (Dombret 2015) and DACO-016 (Kantarjian 2012)

	BRIGHT AML 1003		AZA-AML-001 (Dombret 2015)		DACO-016 (Kantarjian 2012)	
	Glasdegib + LDAC N = 78	**LDAC N = 38**	**AZA N = 241[a]**	**LDAC N = 158**	**DEC N = 242[b]**	**Treatment choice, including BSC (N = 28) and LDAC (N = 215) N = 243[c]**
Demographic Characteristics						
Sex, n (%)						
Male	59 (75.6)	23 (60.5)	139 (57.7)	94 (59.5)	137 (56.6)	151 (62.1)
Female	19 (24.4)	15 (39.5)	102 (42.3)	64 (40.5)	105 (43.4)	92 (37.9)
Age (years)						
Mean (std)	76.4 (6.0)	74.8 (4.9)	n.r.	n.r.	n.r.	n.r.
Median (range)	77 (64-92)	76 (58-83)	75 (64-91)	75 (65-88)	73 (64-89)	73 (64-91)
Age categories, n (%)						
< 75 years	30 (38.5)	15 (39.5)	103 (42.7)	75 (47.5)	< 70 years: 71 (29.3)	< 70 years: 70 (28.8)
≥ 75 years	48 (61.5)	23 (60.5)	138 (57.3)	83 (52.5)	≥ 70 years: 171 (70.7)	≥ 70 years: 173 (71.2)
BMI (kg/m^2)						
Mean (std)	27.3 (4.2)	28.3 (5.7)	n.r.	n.r.	n.r.	n.r.
Median (range)	27.1 (17.5-41.9)	26.9 (20.0-48.2)	n.r.	n.r.	n.r.	n.r.
Geographic region, n (%)						
Europe[d]	50 (64.1)	31 (81.6)	162 (67.2)	111 (70.3)	160 (66.1)	147 (60.5)
North America/Australia	28 (35.9)	7 (18.4)	45 (18.7)	29 (18.4)	51 (21.1)	69 (28.4)
Asia	0	0	34 (14.1)	18 (11.4)	31 (12.8)	27 (11.1)
Race, n (%)						
White	75 (96.2)	38 (100.0)	n.r.	n.r.	n.r.	n.r.
Black	1 (1.3)	0	n.r.	n.r.	n.r.	n.r.
Asian	2 (2.6)	0	n.r.	n.r.	n.r.	n.r.
Clinical characteristics						
Type of AML, n (%)						

	BRIGHT AML 1003		AZA-AML-001 (Dombret 2015)		DACO-016 (Kantarjian 2012)	
	Glasdegib + LDAC N = 78	**LDAC N = 38**	**AZA N = 241[a]**	**LDAC N = 158**	**DEC N = 242[b]**	**Treatment choice, including BSC (N = 28) and LDAC (N = 215) N = 243[c]**
De novo	38 (48.7)	18 (47.4)	192 (79.7)	135 (85.4)	155 (64.0)	157 (64.6)
Secondary	40 (51.3)	20 (52.6)	49 (20.3)	23 (14.6)	87 (36.0)	84 (34.6)
ECOG PS, n (%)						
0-1	36 (46.2)	20 (52.6)	186 (77.2)	123 (77.9)	184 (76.0)	183 (75.3)
≥2	41 (52.6)	18 (47.4)	55 (22.8)	35 (22.2)	58 (24.0)	60 (24.7)
missing	1 (1.3)	0	0	0	0	0
History of severe cardiac disease, n (%)						
no	26 (33.3)	18 (47.4)	n.r.	n.r.	n.r.	n.r.
yes	52 (66.7)	20 (52.6)	n.r.	n.r.	n.r.	n.r.
Serum creatinine, n (%)						
≤1,3 mg/dL	62 (79.5)	32 (84.2)	n.r.	n.r.	n.r.	n.r.
> 1,3 mg/dL	15 (19.2)	5 (13.2)	n.r.	n.r.	n.r.	n.r.
missing	1 (1.3)	1 (2.6)	n.r.	n.r.	n.r.	n.r.
Cytogenetic risk n (%)	**(according to IVRS, per ELN 2010 guidelines)**		**(per central review, per modified NCCN Clinical Practice Guidelines)**		**(per South West Oncology Classification)**	
Good/intermediate	49 (62.8) [e]	21 (55.3) [e]	155 (64.3)[f]	104 (65.8)[f]	152 (63.1)[g]	154 (63.6)[g]
Poor	29 (37.2) [e]	17 (44.7) [e]	85 (35.3)[f]	54 (34.2)[f]	87 (36.1)[g]	87 (36.0)[g]
Cytogenetic risk n (%)	**(according to CRF, per ELN 2010 guidelines)**					
Good/intermediate	53 (67.9) [e]	22 (57.9) [e]	-	-	-	-
Poor	25 (32.1) [e]	16 (42.1) [e]	-	-	-	-
ELN risk stratification						
Favourable	5 (6.4)	3 (7.9)	n.r.	n.r.	n.r.	n.r.
Intermediate-I	27 (34.6)	11 (28.9)	n.r.	n.r.	n.r.	n.r.
Intermediate-II	21 (26.9)	8 (21.1)	n.r.	n.r.	n.r.	n.r.

	BRIGHT AML 1003		AZA-AML-001 (Dombret 2015)		DACO-016 (Kantarjian 2012)	
	Glasdegib + LDAC N = 78	**LDAC N = 38**	**AZA N = 241[a]**	**LDAC N = 158**	**DEC N = 242[b]**	**Treatment choice, including BSC (N = 28) and LDAC (N = 215) N = 243[c]**
Adverse	25 (32.1)	16 (42.1)	n.r.	n.r.	n.r.	n.r.
Peripheral white blood cell count ($10^3/mm^3$)						
Median (range)	2.47 (0.6-64.0)	4.07 (1.1-45.2)	3.1 (0-33)	2.3 (0-73)	3.10 (0.3-127.0)	3.69 (0.5-80.9)
Bone marrow blasts (%)						
Median (range)	41 (16-100)	46 (13-95)	70 (2-100)	74 (4-100)	-	-
Bone marrow blasts, n (%)						
< 20 %	3 (3.8)	1 (2.6)	n.r.	n.r.	n.r.	n.r.
≥ 20 - ≤30 %	21 (26.9)	9 (23.7)	n.r.	n.r.	65 (27.0)	58 (24.1)
> 30 - ≤50 %	20 (25.6)	8 (21.1)	n.r.	n.r.	67 (27.8)	74 (30.7)
> 50 %	31 (39.7)	17 (44.7)	173 (71.8)	128 (81.0)	105 (43.7)	101 (41.9)
Not reported	3 (3.8)	3 (7.9)	n.r.	n.r.	n.r.	n.r.
Hemoglobin (g/dL)						
Median (range)	9.1 (6.4-14.0)	9.3 (6.0-14.6)	9.5 (5.0-13.4)	9.3 (5.6-14.4)	9.3 (5.2-15.0)	9.4 (5.0-12.6)
Duration since histopathological diagnosis (months)					**(days)**	
Median (range)	0.57 (0.0-3.5)	0.51 (0.1-3.8)	n.r.	n.r.	14.0 (3.0-346.0)	15.0 (0.0-398.0)

	BRIGHT AML 1003		AZA-AML-001 (Dombret 2015)		DACO-016 (Kantarjian 2012)	
	Glasdegib + LDAC N = 78	**LDAC N = 38**	**AZA N = 241[a]**	**LDAC N = 158**	**DEC N = 242[b]**	**Treatment choice, including BSC (N = 28) and LDAC (N = 215) N = 243[c]**

a: Comprised all patients in the azacitidine arm, regardless of their preselected care regimen. Of these 241 patients, 44 were preselected for BSC, 43 were preselected for intensive chemotherapy and 154 were preselected for LDAC.

b: Comprised all patients in the azacitidine arm, regardless of their preselected care regimen. The number of patients preselected for LDAC was not published by Kantarjian 2012.

c: Comprised all patients in the treatment choice arm, regardless of their preselected care regimen. Of these 243 patients, 28 received BSC and 215 received LDAC. Baseline and disease characteristics for LDAC were available in the publication of Kantarjian 2012, but the complete treatment choice arm is relevant for the indirect comparison.

d: Including Israel

e: According to ELN 2010 guidelines: Patients were classified as having poor-risk disease if they had one of the following cytogenetic features: inv(3), t(6;9), 11q23, –5, –5q, –7, abnormal (17p), or complex karyotype (≥3 clonal abnormalities). Patients with none of these features were classified as having good/intermediate- risk disease (good/intermediate cytogenetic risk=favourable, intermediate-I and intermediate-II risk groups according to ELN 2010 (84).

f: According to NCCN 2009 criteria: intermediate-risk category: +8, t(9;11), normal karyotype. Poor risk category: inv(3), t(3;3), t(6;9), t(9;22),11q23, –5, –5q, –7, -7q or complex karyotype (≥3 clonal abnormalities)(85).

g: According to South West Oncology Classification; intermediate risk category: 18, 2Y, 16, del(12p), or normal karyotype. Unfavourable risk category: presence of one or more of 25/del(5q), 27/del(7q), inv(3q), abn 11q, 20q, or 21q, del(9q), t(6;9), t(9;22), abn 17p, and complex karyotype defined as 3 or more abnormalities (87).

Abbreviations: AML = acute myeloid leukaemia; AZA = azacitidine; BMI = body mass index ; CRF = case report form; DEC = decitabine; ELN = European LeukaemiaNet; IVRS = interactive voice response system ; LDAC = low-dose cytarabine; PS = performance status; n.r. = not reported;

References: (1, 2, 82, 83, 88)

5.3 Individual study results (clinical outcomes)

5.3.1 Relevant endpoints

Describe the relevant endpoints, including the definition of the endpoint, and method of analysis (Table 17).

Table 17 gives an overview of methods of data collection and analysis of endpoints.

Table 17: Methods of data collection and analysis of endpoints

Endpoint	Definition	Study reference/s	Method of analysis
OS			
	Time from the date of randomization to the date of death from any cause	BRIGHT AML 1003 AZA-AML-001 (Dombret 2015) DACO-016 (Kantarjian 2012)	OS was the primary endpoint in BRIGHT AML 1003 and in the studies AZA-AML-001 and DACO-016 published by Dombret et al. 2015 and Kantarjian et al. 2012. In BRIGHT AML 1003, patients not known to have died at the last follow-up were censored on the date they were last known to be alive. **Analysis sets** In BRIGHT AML 1003, analysis for OS was based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). IN AZA-AML-001, analysis for OS was based on all randomized patients, who were preselected for LDAC before randomization. In DACO-016, analysis for OS was based on all randomized patients, regardless of their preselected care regimen. **Glasdegib + LDAC vs. LDAC** OS was analysed and displayed graphically for each arm using the Kaplan-Meier method. A stratified log-rank test (one-sided, α = 5 %) was used to compare OS between the treatment arms. The hazard ratio (HR) and its 95 % CI was estimated. Stratification variable was cytogenetic risk based on IVRS. The median event time for each treatment arm with corresponding two-sided 95 % CI was provided for OS. In addition, the survival rates at month 6 and 12 were presented. ***Sensitivity analyses*** - Sensitivity analyses of the primary endpoint of OS were prespecified by censoring patients upon receiving transplant. - Additional sensitivity analyses for OS included derivations for the stratification variables (CRF instead of IVRS). ***Subgroup analyses*** Prespecified subgroup analysis included stratification by cytogenetic risk (good/intermediate vs. poor). Additionally, subgroups by age, gender, race, region, baseline ECOG, baseline white blood cells count, baseline bone marrow blast count, prognostic risk factors and disease history were presented. **Glasdegib + LDAC vs. AZA and glasdegib + LDAC vs. DEC (indirect comparisons)** The Kaplan-Meier plots were displayed for OS for the comparison of AZA vs. LDAC and DEC vs. LDAC. A standard unadjusted ITC, a

Endpoint	Definition	Study reference/s	Method of analysis
			multivariate ITC, a stepwise exponential STC and a full exponential STC were conducted. Regarding these indirect comparisons, Kaplan-Meier plots and corresponding HRs with 95 % CIs are presented.
Health-related quality of life			
Quality of survival	Quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST analysis)	BRIGHT AML 1003	**Analysis sets** Analysis was based on all randomized AML patients, regardless of whether they have received the study drugs. **Primary analysis** This analysis assessed the possible trade-offs between time with adverse events (toxicities) and after relapse/progression (with symptoms of disease) as compared to 'good' survival (time without toxicities or symptoms of progression) when comparing glasdegib + LDAC vs. LDAC.
Objective response			
CR	neutrophils ≥1.000/µL, platelets ≥100.000/µL, bone marrow blasts < 5 % with spicules present, no Auer rods, transfusion independence (defined as free from platelets or PRBC transfusion for at least one week) no EMD • Investigator responses are the Investigator's assessment of morphologic disease response per patient based on locally analyzed bone marrow aspirates or biopsies, blood samples, and other clinical assessments. Based on clinical judgment, the investigator entered a disease response for each patient in the CRF according to the criteria noted above. • Derived responses are the Sponsor's assessment of morphologic disease responses determined programmatically. Algorithms based on AML response criteria used the same patient data in the CRF recorded by the	BRIGHT AML 1003	CR was a secondary endpoint in BRIGHT AML 1003. **Analysis sets** Analyses for objective response endpoints were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). **Primary analysis** CR (Investigator-reported) was presented in terms of absolute and relative frequencies. The p-value of the unstratified Pearson chi-square test as well as the relative risk incl. its 95 % CI and the p-value based on the CMH stratified by prognosis stratum (IVRS based cytogenetic risk) were calculated. **Sensitivity analyses** Sensitivity analyses for CR included a different derivation for the stratification variables (CRF instead of IVRS) and a different derivation for response (derived response from disease assessments instead of investigator-reported response). **Subgroup analysis** The prespecified subgroup analysis for CR stratified by cytogenetic risk (poor vs. good/intermediate) were presented.

Endpoint	Definition	Study reference/s	Method of analysis
	investigator to derive each patient's response. Additional information about the derived responses is provided in the SAP.		
CRi	neutrophils < 1.000/µL or platelets < 100.000/µL, bone marrow blasts < 5 %, either neutrophils or platelets not recovered, no EMD	BRIGHT AML 1003	CRi was a secondary endpoint in BRIGHT AML 1003. **Analysis sets** Analyses for objective response endpoints were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). **Analysis** CRi was presented in terms of absolute and relative frequencies. The relative risk incl. its 95 % CI and the p-value based on the CMH stratified by prognosis stratum (IVRS based cytogenetic risk) were calculated.
MLFS	neutrophils < 1.000/µL and platelets < 100.000/µL, bone marrow blasts < 5 % in BM with spicules and no blasts with Auer rods, neutrophils and platelets not recovered, flow cytometry negative, no EMD	BRIGHT AML 1003	MLFS was a secondary endpoint in BRIGHT AML 1003. **Analysis sets** Analyses for objective response endpoints were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). **Analysis** MLFS was presented in terms of absolute and relative frequencies. The relative risk incl. its 95 % CI and the p-value based on the CMH stratified by prognosis stratum (IVRS based cytogenetic risk) were calculated.
CR + CRi + MLFS	Meet one of the criteria mentioned above.	BRIGHT AML 1003	**Analysis sets** Analyses for objective response endpoints were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). **Analysis** CR + CRi + MLFS was presented in terms of absolute and relative frequencies. The relative risk incl. its 95 % CI and the p-value based on the CMH stratified by prognosis stratum (IVRS based cytogenetic risk) were calculated.
Transfusion need			
Transfusion independence	No transfusions for ≥ 8, 12, 16, 20 and 24 consecutive weeks during treatment phase.	BRIGHT AML 1003	**Analysis sets** Analyses were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS).

Endpoint	Definition	Study reference/s	Method of analysis
	Transfusion independency was not measured at baseline. Rather transfusions received by each patient were recorded throughout the treatment period. Transfusion independency (> 8 weeks) is defined as a period of at least 56 consecutive days in which patients did not receive any type of blood transfusion - if patients achieved this during any time of their treatment, thy were counted as responders for this endpoint. "No transfusion" means neither red blood cell transfusions nor platelet transfusions nor any other types of blood transfusions.		**Analysis** Transfusion independence was presented in terms of absolute and relative frequencies. The relative risk incl. its 95 % CI and the p-value based on the CMH stratified by prognosis stratum (IVRS based cytogenetic risk) were calculated.
Transfusion rates per month of treatment	number of transfusion during treatment phase / (last active therapy date -first active therapy date + 1)/30.4375 "Transfusions" includes any type of transfusion (red blood cell transfusions, platelets transfusions, etc.).	BRIGHT AML 1003	**Analysis sets** Analyses were based on all randomized AML patients, regardless of whether they have received the study drugs (FAS). **Analysis** Transfusion rates per month of treatment were presented as mean with standard deviation and median with range.
Transfusion days per months of treatment	number of transfusion days during treatment phase / (last active therapy date -first active therapy date + 1)/30.4375 "Transfusions" includes any type of transfusion (red blood cell transfusions, platelets transfusions, etc).	BRIGHT AML 1003	**Analysis sets** Analyses were based on all AML randomized patients, regardless of whether they have received the study drugs (FAS). **Analysis** Transfusion days per month of treatment were presented as mean with standard deviation and median with range.

Abbreviations: ANC = absolute neutrophil count; AZA = azacitidine; BM = bone marrow ; CI = confidence interval; CMH = Cochran–Mantel–Haenszel test; CR = morphologic complete remission; CRF = case report form; CRi = CR with incomplete blood count recovery; DEC = decitabine; EMD = extramedullary disease; FAS = full analysis set; HR = hazard ratio ; ITC = indirect treatment comparison; ITT = intention to treat; IVRS = interactive voice response system; LDAC = low-dose cytarabine; MLFS = morphologic leukaemia-free state; MR = minor response; OS = overall survival; PB = peripheral blood; PR = partial remission; PRi = PR with incomplete blood count recovery; SD = stable disease; STC = simulated treatment comparison;
References: (1, 2, 82, 83, 88)

5.3.2 Overall survival

OS is considered the gold standard primary endpoint of clinical trials by physicians and health regulatory agencies and is therefore the most common primary endpoint used in AML clinical trials. OS is universally recognized as being unambiguous, unbiased, with a defined end point of paramount clinical relevance, and positive results provide confirmatory evidence that a given treatment extends the life of a patient (90).

5.3.2.1 Glasdegib + LDAC vs LDAC

Analysis set

The analysis set for BRIGHT AML 1003 comprised all randomized adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy, regardless of whether they have received the study drugs.

Results

The median follow-up duration for OS was 156.5 (range: 2 – 1005) days in total, thereof 226.0 (range: 5 – 1005) days in the glasdegib + LDAC arm and 115.0 (range: 2 – 613) days in the LDAC alone arm.

Glasdegib + LDAC was shown to have superior OS (HR [95 %-CI]: 0.46 [0.30, 0.72]; p = 0.0002) compared to LDAC alone (median OS: 8.3 months vs. 4.3 months) (Table 18, Figure 18). Sensitivity analyses showed almost identical results.

Table 18: Results summary for OS for BRIGHT AML 1003

OS	Glasdegib + LDAC N = 78		LDAC N = 38		HR [95 % CI][b] p-value[c]
	n/N (%)	Median (months) [95 % CI][a]	n/N (%)	Median (months) [95 % CI][a]	
Primary analysis (stratified by IVRS based cytogenetic risk)					
	59/78 (75.6)	8.3 [4.7, 12.2]	35/38 (92.1)	4.3 [1.9, 5.7]	0.46 [0.30, 0.72] 0.0002
Sensitivity analysis					
Censoring patients upon receiving transplant					
	58/78 (74.4)	8.3 [4.7, 12.2]	35/38 (92.1)	4.3 [1.9, 5.7]	0.46 [0.30, 0.71] 0.0002
Stratified by CRF based cytogenetic risk					
	59/78 (75.6)	8.3 [4.7, 12.2]	35/38 (92.1)	4.3 [1.9, 5.7]	0.47 [0.30, 0.72] 0.0002

a: Based on the Brookmeyer und Cowley Method

b: Based on the Cox Proportional hazards model

c: 1-sided p-value from the stratified log-rank test. stratified by prognosis stratum.

Abbreviations: LDAC = low-dose cytarabine; OS = overall survival
References: (89)

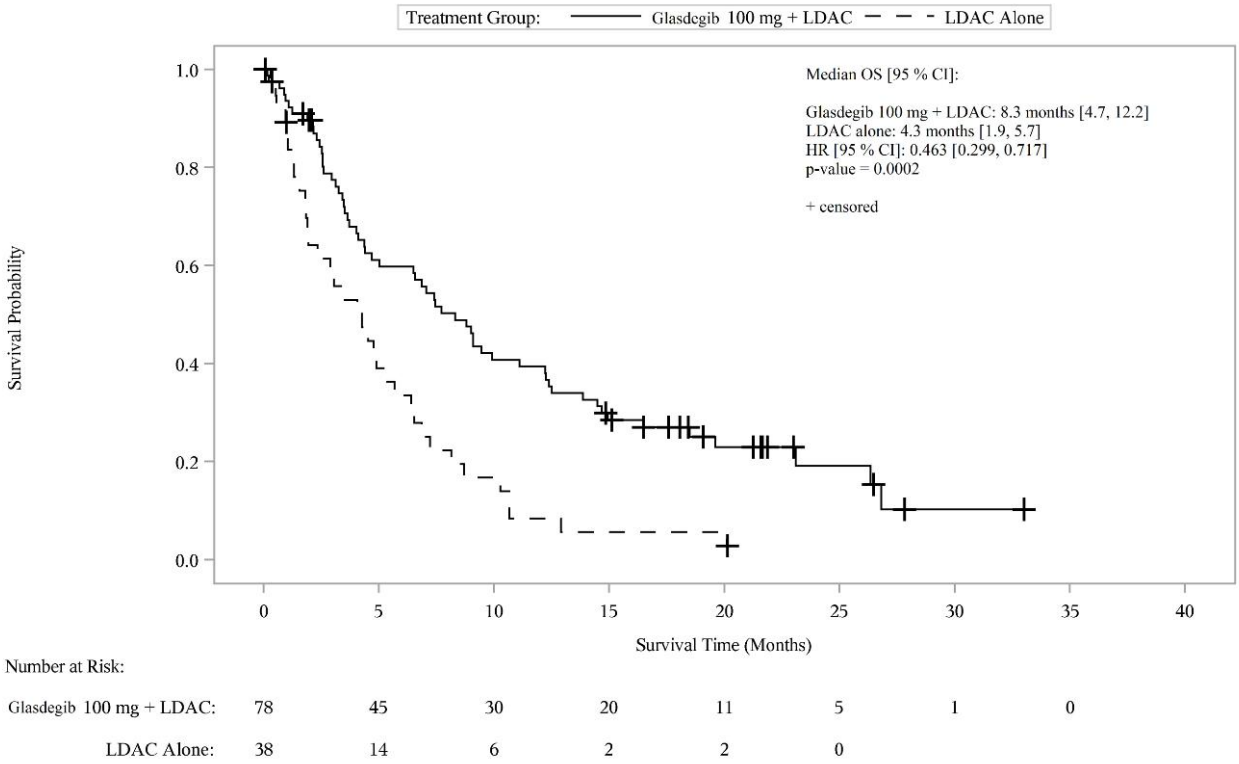


Figure 10: Kaplan-Meier plot of OS for BRIGHT AML 1003

Abbreviations: CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine; OS = overall survival.
Reference:(76)

Survival rates and survival probabilities at day 30, day 60, month 6, and month 12 are presented in Table 19. At each time point considered in the analyses, the survival probabilities in the glasdegib + LDAC arm were higher than in the LDAC arm.

Improvement in OS was also consistent across prespecified cytogenetic risk subgroups and other demographic and clinical subgroups including age, gender, cytogenetic risk (good/intermediate vs. poor), disease history (de novo vs. secondary AML) and baseline ECOG PS (Figure 11).

Table 19: Results summary for survival rates and survival probabilities for BRIGHT AML 1003

Survival rates and survival probabilities	Glasdegib + LDAC N = 78			LDAC N = 38		
	Survival rates		Survival probabilities (%) [95 % CI]	Survival rates		Survival probabilities (%) [95 % CI]
	patients died	patients ongoing		patients died	patients ongoing	
At day 30						
	5	72	93.5 [85.2, 97.3]	4	32	89.2 [73.7, 95.8]
At day 60						
	17	57	77.4 [66.2, 85.3]	15	21	58.5 [40.9, 72.6]

Survival rates and survival probabilities	Glasdegib + LDAC N = 78			LDAC N = 38		
	Survival rates		Survival probabilities (%) [95 % CI]	Survival rates		Survival probabilities (%) [95 % CI]
	patients died	patients ongoing		patients died	patients ongoing	
At month 6						
	30	44	59.8 [47.7, 69.9]	24	12	33.5 [18.9, 48.7]
At month 12						
	45	29	39.4 [28.3, 50.3]	33	3	8.4 [2.2, 20.1]

Abbreviations: CI = confidence interval, LDAC = low-dose cytarabine
References: (83, 89)

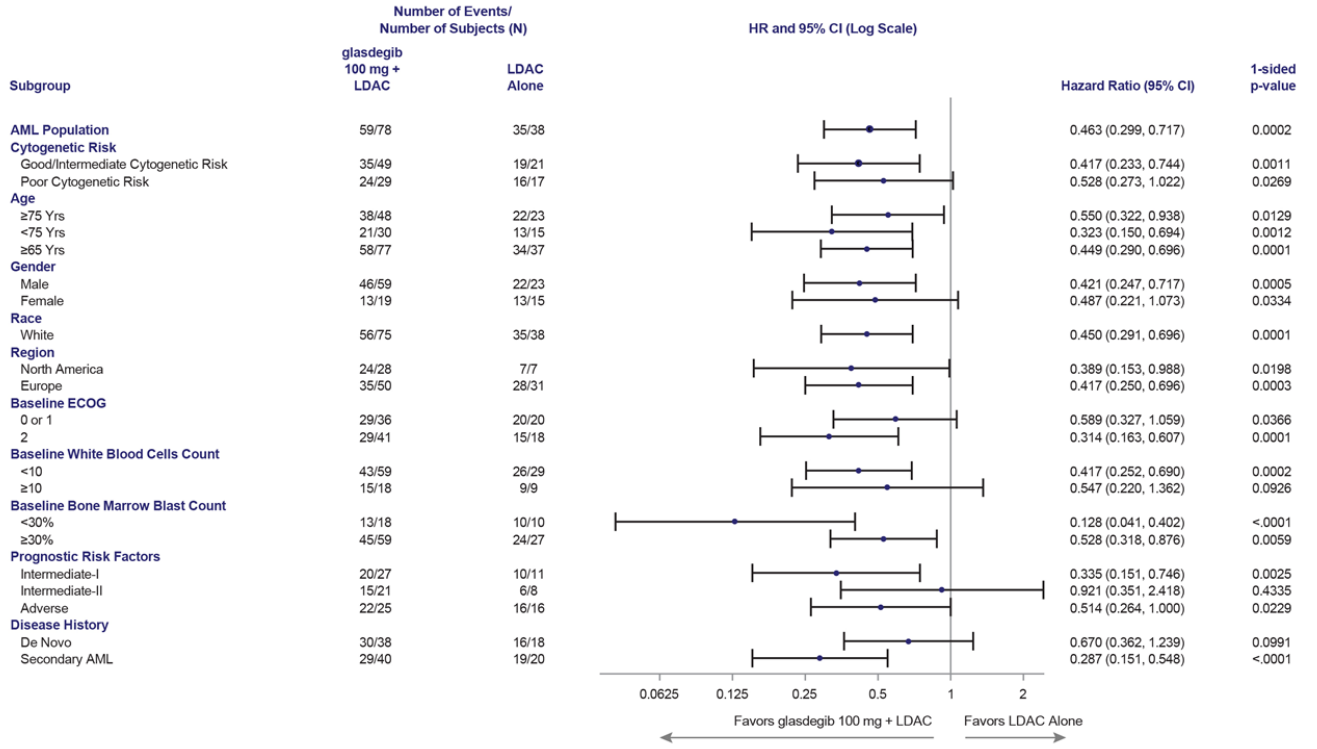


Figure 11: Forest plot of OS for BRIGHT AML 1003

The sample sizes for the subgroups of baseline age < 65 years old, race other than white and the prognostic risk factor as favourable were too small (n ≤ 10) for analysis. The HR and p-value presented were based on the unstratified analysis for all subgroups except for AML population. Prognostic risk factor (good/intermediate vs. poor) from IVRS was used as a stratification factor in the stratified analysis for AML population
Abbreviations: AML = acute myeloid leukaemia; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; LDAC = low-dose cytarabine; N = number of subjects; Yrs = years.
Reference: (88)

Patients censored and therefore no longer being followed for OS within the first 12 months are summarized in Table 20.

Table 20: Patients censored until month 12 for BRIGHT AML 1003

Treatment arm	Study day of censoring	Reason for censoring
glasdegib + LDAC	11	Subject refused further follow-up
glasdegib + LDAC	52	Lost to follow-up
glasdegib + LDAC	60	Subject refused further follow-up
glasdegib + LDAC	63	Subject refused further follow-up

Treatment arm	Study day of censoring	Reason for censoring
LDAC alone	2	Subject refused further follow-up
LDAC alone	30	Subject refused further follow-up

Abbreviations: LDAC = low-dose cytarabine
References: (89)

5.3.2.2 Glasdegib + LDAC vs. azacitidine

Since no direct evidence of glasdegib + LDAC vs. the comparator azacitidine is available, an indirect comparison was conducted to evaluate the relative efficacy in terms of OS of glasdegib + LDAC vs. azacitidine.

The systematic literature searches revealed, that LDAC could be used as a common comparator for indirect comparisons, other common comparators were not available. With the selected studies, a network of RCT was established that utilized the LDAC treatment arm as the common comparator (Figure 12).

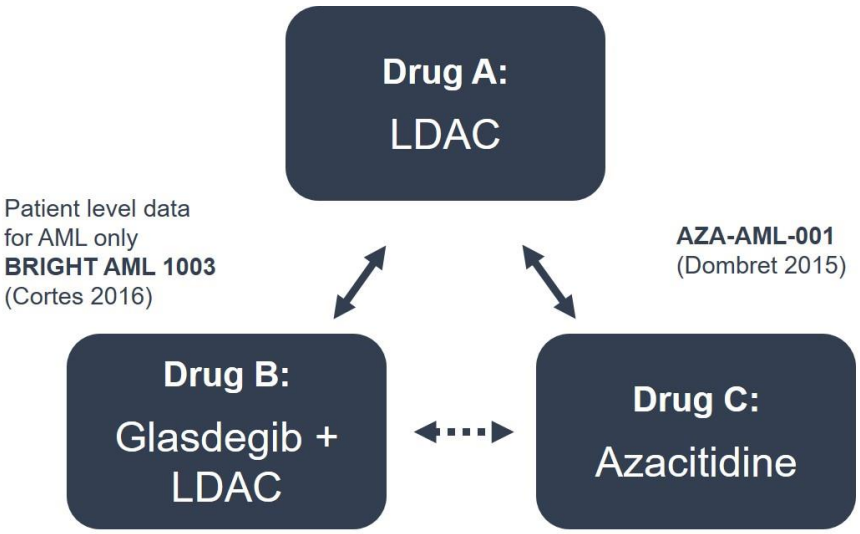


Figure 12: Indirect comparison network for glasdegib + LDAC vs. azacitidine
Abbreviations: LDAC: low-dose cytarabine
Reference: (91)

Analysis sets

OS for glasdegib + LDAC vs. LDAC alone in adult patients newly diagnosed with AML who were not candidates for standard induction chemotherapy was evaluated in BRIGHT AML 1003. OS results for azacitidine vs. LDAC could be derived from AZA-AML-001 (published by Dombret 2015). The OS results from AZA-AML-001 were based on all patients who were preselected for LDAC (N = 154 within the azacitidine arm and N = 158 within the conventional care regimen arm), no patients preselected for BSC or intensive chemotherapy were included. Therefore, all patients considered for this indirect comparison are part of the target population relevant for this assessment.

Baseline demographics and disease characteristics are described in chapter 5.2.3 and shown in Table 16.

Assessment of cytogenetic risk profile

Cytogenetic risk profile in BRIGHT AML 1003 was assessed according to ELN 2010 guidelines, in AZA-AML-001 according to NCCN 2009 guidelines. The cytogenetic features utilized are both based on the WHO definition of recurrent cytogenetic abnormalities present in AML and do not differ greatly. This is why

there has recently been a convergence of the risk classification systems used in AML along with the addition of mutations associated with outcomes.

Study treatment

In both the BRIGHT AML 1003 and AZA-AML-001 trial, LDAC was administered as 20 mg twice per day.

Definition of OS

In both the BRIGHT AML 1003 and AZA-AML-001 trial, OS was defined as time from the date of randomization to the date of death from any cause.

Overall, BRIGHT AML 1003 and AZA-AML-001 showed sufficient similarity regarding analysis population, study treatment, outcome and study design to conduct a valid indirect treatment comparison.

Methodology

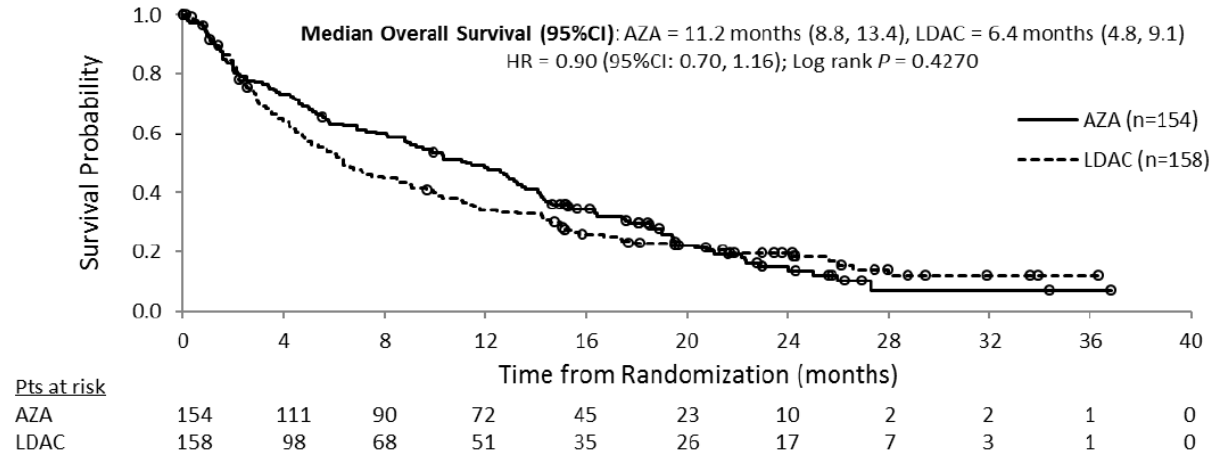
Primary analysis methodology for indirect comparisons is the standard (Bucher) ITC approach (92), as this is widely accepted and follows a straight forward and robust method. It is also recommended by the EUnetHTA guideline on direct and indirect comparisons (87).

The methodological principles and the OS results for the indirect comparisons of glasdegib + LDAC vs. azacitidine have been published by Tremblay 2019 (91). Although the baseline populations are considered to be sufficiently similar between the studies to avoid bias, a simulated treatment comparison (STC) was conducted as a supportive analysis to investigate the potential impact of baseline differences such as age, gender, de novo vs secondary AML, cytogenic risk, performance status, and hemoglobin level at baseline. STC allows to adjust for baseline differences between trials. For this purpose, covariates that may influence outcome, were selected and an optimal model to estimate the treatment effects of glasdegib + LDAC vs. LDAC alone was explored. STCs were performed following general guidance published by the DSU (Decision Support Unit) of the NICE as well as using a propensity weighted approach (weighted for within-trial mean cytogenetic risk) (93).

An overview of the methodological principles for STC as well as rationales for the variable and model selections can be found in Appendix C.

Results for AZA-AML-001 (Dombret 2015)

In Dombret 2015, OS data were provided separately for the patients according to their preselected therapies: BSC, LDAC or intensive chemotherapy. A total of 312 patients were preselected for LDAC before randomization (N = 154 in the azacitidine arm and N = 158 in the LDAC arm). Among these patients, the median survival was 11.2 months (95 % CI [8.8, 13.4]) for azacitidine (N = 154) and 6.4 months (95 % CI [4.8, 9.1]) for LDAC (N = 158); HR demonstrated no statistically significant difference between the treatment arms (HR [95 % CI]: 0.90 [0.70, 1.16], p-value from log rank test = 0.4270) (Figure 13).



Pts at risk											
AZA	154	111	90	72	45	23	10	2	2	1	0
LDAC	158	98	68	51	35	26	17	7	3	1	0

Figure 13: Kaplan-Meier plot of OS for AZA-AML-001 (Dombret 2015)

Abbreviations: AZA = azacitidine, CI = confidence interval; HR = hazard ratio; LDAC = low-dose cytarabine;
Reference: (1)

Variable selection for STC

The full covariate model for the glasdegib + LDAC vs. azacitidine comparisons included all of the baseline characteristics available for both studies: age, sex, disease history, proportion of bone marrow blasts > 50 %[3], ECOG PS, cytogenetic risk, and hemoglobin level. Decisions for variable selection for the stepwise model are summarized in in the following:

- Mean age at baseline: Included due to significant treatment effect for subgroup age < 75 years but not age ≥75 years in Dombret 2015.
- Sex, male: Included due to significant treatment effect for females but not males in Dombret 2015, prognostic in the literature, large imbalance between trials.
- Disease history, de novo: Excluded for lack of significance in glasdegib + LDAC vs. LDAC individual patient data (IPD) regression and no subgroup analysis in Dombret 2015.
- Bone marrow blasts, > 50 %: Excluded for lack of significance in glasdegib + LDAC vs. LDAC IPD regression and no subgroup analysis in Dombret 2015.
- ECOG PS, 0 or 1 vs. 2: Excluded for lack of significance in glasdegib + LDAC vs. LDAC IPD regression and no subgroup analysis in Dombret 2015.
- Cytogenetic risk, poor vs. good/intermediate: Included due to being a stratification factor in both trial protocols
- Median baseline hemoglobin level (g/dL): Excluded for lack of significance in glasdegib + LDAC vs. LDAC IPD regression and no subgroup analysis in Dombret 2015.

Thus, the stepwise model included age, sex, and cytogenetic risk.

[3] The calculation of the proportion of bone marrow blasts for glasdegib + LDAC vs. LDAC differed slightly in comparison to the a priori analysis: To reduce the number of missing values, bone marrow blasts at baseline were merged with bone marrow blasts during screening, resulting in 18 patients having bone marrow blasts > 50 % in the LDAC alone arm (compared to 17 patients, see Table 16)

Model selection for STC

Visual assessment of the log-cumulative hazard plots and the Schoenfeld test of proportionality for the full and stepwise Cox models indicated no statistically significant deviation from the PH assumption.

Based on fit statistics AIC and BIC, the visual inspection of graphs of the survival curves and the survival estimates, the exponential model (DSU approach) and the Weibull model (propensity weighted approach) were chosen as it provided the best fit. For a detailed description and rationales for model selection please see Appendix C.

Results for the indirect comparisons of glasdegib + LDAC vs. azacitidine

Table 21 summarizes results from all ITC. All models show that glasdegib + LDAC was statistically significantly associated with longer OS when compared with azacitidine (two rightmost columns). Compared with the result using only the standard (Bucher) ITC (HR [95 %CI]: 0.51 [0.31, 0.85]), adjusting for population covariates resulted in slightly stronger treatment effects of glasdegib + LDAC in comparison to azacitidine.

Table 21: Results summary for OS for the indirect comparisons of glasdegib + LDAC vs. azacitidine

Glasdegib + LDAC vs azacitidine	glasdegib + LDAC vs. LDAC		azacitidine vs. LDAC		glasdegib + LDAC vs. azacitidine	
	HR	[95 % CI]	HR	[95 % CI]	HR	[95 % CI]
Primary analysis (standard [Bucher] ITC)						
Cox unadjusted	0.46	[0.30, 0.72]	0.90	[0.70, 1.16]	0.51	[0.31, 0.85]
Supportive analyses						
STC following general guidance published by the DSU of the NICE						
Cox full (Multivariate ITC)[a]	0.42	[0.22, 0.78]	0.90	[0.70, 1.16]	0.46	[0.24, 0.91]
Stepwise Exponential (STC)	0.38	[0.22, 0.67]	0.90	[0.70, 1.16]	0.42	[0.23, 0.79]
Full Exponential (STC)	0.40	[0.22, 0.74]	0.90	[0.70, 1.16]	0.45	[0.23, 0.86]
STC using a propensity weighted approach.						
Cox full (Multivariate ITC)[a]	0.43	[0.22, 0.78]	0.90	[0.70, 1.16]	0.47	[0.24, 0.93]
Stepwise Weibull (STC)	0.37	[0.20, 0.68]	0.90	[0.70, 1.16]	0.41	[0.21, 0.79]
Full Exponential (STC)	0.40	[0.22, 0.73]	0.90	[0.70, 1.16]	0.44	[0.23, 0.85]

a: This row performs a covariate-adjusted ITC.
Abbreviations: CI = confidence interval; DSU: Decision Support Unit; HR = Hazard Ratio; ITC = indirect treatment comparison; LDAC = low-dose cytarabine; NICE: National Institute for Health and Care Excellence; OS = Overall survival; STC = simulated treatment comparison
Reference: (91)

5.3.2.3 Glasdegib + LDAC vs. decitabine

Since no direct evidence of glasdegib + LDAC vs. the comparator decitabine is available, an indirect comparison was conducted to evaluate the relative efficacy in terms of OS of glasdegib + LDAC vs. decitabine.

The systematic literature searches revealed, that LDAC could be used as a common comparator for indirect comparisons, other common comparators were not available. With the selected studies, a network of RCT was established that utilized the LDAC treatment arm as the common comparator (Figure 14).

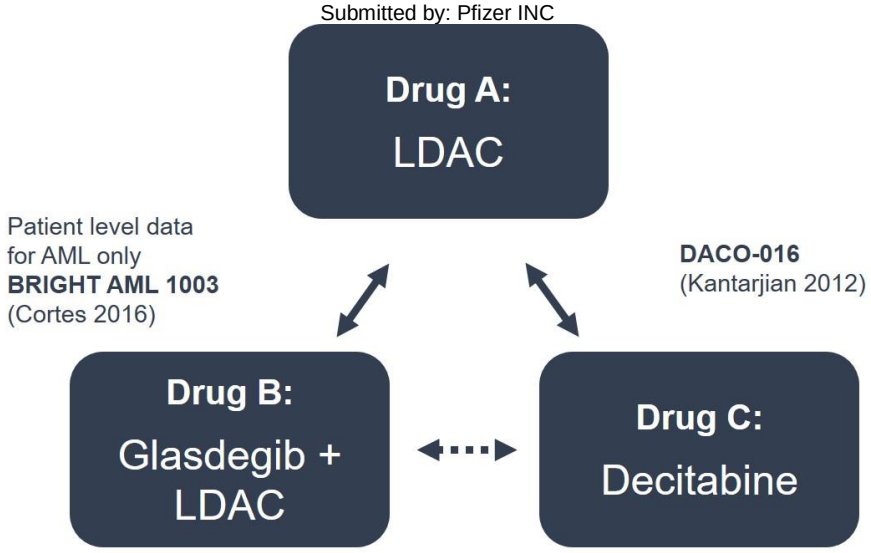


Figure 14: Indirect comparison network for glasdegib + LDAC vs. decitabine
Abbreviations: LDAC: low-dose cytarabine
Reference: (91)

Analysis sets

OS for glasdegib + LDAC vs. LDAC alone in adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy was evaluated in BRIGHT AML 1003 AML. OS results for decitabine vs. LDAC could be derived from DACO-016 (published by Kantarjian 2012). These results were only available based on all patients who were randomized to decitabine or treatment choice, regardless of their preselected treatment choice (BSC or LDAC). In consequence, patients that had received BSC are included for the comparison of decitabine vs. LDAC. It is assumed, that the comparison is nevertheless valid:

(I) In the treatment choice arm, the proportion of patients receiving BSC is relatively low compared to the proportion of patients receiving LDAC (BSC: N = 28 and LDAC: N = 215).

(II) As patients with BSC within the treatment choice arm did not receive any antileukemic therapy, it can be assumed that these BSC patients were not contributing to an extended survival in the treatment choice arm. Therefore, the effect of decitabine would appear stronger than in a comparison of decitabine vs. LDAC, thus the glasdegib + LDAC vs. decitabine comparison is estimated more conservatively from the perspective of glasdegib + LDAC.

Baseline demographics and disease characteristics are described in chapter 5.2.3 and shown in Table 16.

Assessment of cytogenetic risk profile

Cytogenetic risk profile in BRIGHT AML 1003 was assessed according to ELN 2010 guidelines, in DACO-016 according to SWOG 2000 guidelines. The cytogenetic features utilized are both based on the WHO definition of recurrent cytogenetic abnormalities present in AML and do not differ greatly. This is why there has recently been a convergence of the risk classification systems used in AML along with the addition of mutations associated with outcomes.

Study treatment

In BRIGHT AML 1003, LDAC was administered as 20 mg twice per day. In the DACO-016 trial, LDAC was administered as 20 mg/m^2 once daily. Either dose schedule is considered to result in comparable drug concentrations over time (area under the curve) which includes any associated cytotoxic effects (86).

Definition of OS

In both the BRIGHT AML 1003 and DACO-016 trial, OS was defined as time from the date of randomization to the date of death from any cause.

Overall, the studies BRIGHT AML 1003 and DACO-016 showed sufficient similarity to conduct a valid indirect treatment comparison.

Methodology

Primary analysis method for indirect comparisons is the standard (Bucher) ITC approach (92), as this is widely accepted and follows a straight forward and robust method. It is also recommended by the EUnetHTA guideline on direct and indirect comparisons (87).

The methodological principles and the OS results for the indirect comparisons of glasdegib + LDAC vs. decitabine have been published by Tremblay 2019 (91). Although the baseline populations are considered to be sufficiently similar between the studies to avoid bias, a simulated treatment comparison (STC) was conducted as a supportive analysis to investigate the potential impact of baseline differences such as age, gender, de novo vs secondary AML, cytogenic risk, performance status, and hemoglobin level at baseline. STC allows to adjust for baseline differences between trials. For this purpose, covariates that may influence outcome, were selected and an optimal model to estimate the treatment effects of glasdegib + LDAC vs. LDAC alone was explored. STCs were performed following general guidance published by the DSU of the NICE as well as using a propensity weighted approach (weighted for within-trial mean cytogenetic risk). (93)

An overview of the methodological principles for STC as well as rationales for the variable and model selections can be found in Appendix C.

Results for DACO-016 (Kantarjian 2012)

Kantarjian 2012 reported OS data as pooled treatment choice (N = 243) for LDAC (N = 215) and supportive care (N = 28). 219 (90 %) patients receiving decitabine (N = 242) and 227 (93 %) patients treated according to the preselected treatment choice died within the study. In an unplanned analysis one year after the protocol-specified clinical cutoff analysis, the median survival was 7.7 months (95 % CI [6.2, 9.2]) for decitabine and 5.0 months (95 % CI [4.3, 6.3]) for pooled LDAC and supportive care.

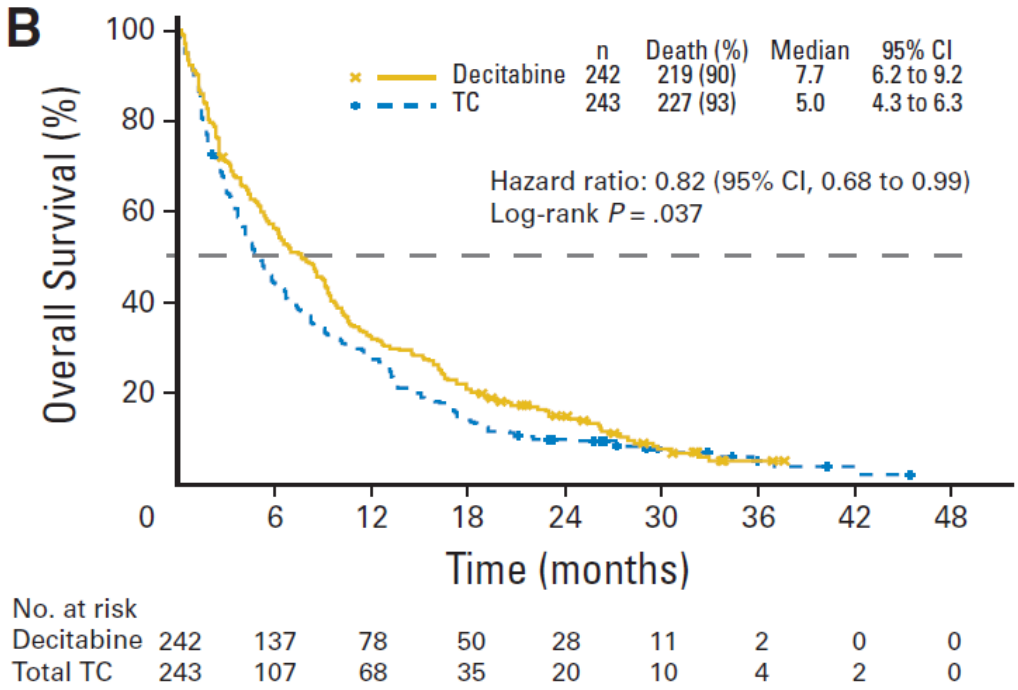


Figure 15: Kaplan-Meier plot of OS for DACO-016 (Kantarjian 2012)

Abbreviations: CI = confidence interval; TC = treatment choice;
Reference: (2)

Variable selection for STC

The full covariate model for the glasdegib + LDAC vs. decitabine comparisons included all of the baseline characteristics available for both studies: age, sex, disease history, proportion of bone marrow blasts > 50 %[4], ECOG PS, cytogenetic risk, and hemoglobin level. Decisions for variable selection for the stepwise model are summarized in in the following:

- Mean age at baseline: Included due to significant treatment effect for only subgroup age ≥ 75 years in Kantarjian 2012, potentially prognostic as advised by clinical expertise.
- Sex, male: Excluded for lack of subgroup analysis in Kantarjian 2012.
- Disease history, de novo: Significant treatment effect for de novo but not secondary AML in Kantarjian 2012, large imbalance between trials.
- Bone marrow blasts > 50 %: Included due to significant treatment effect for subgroup > 30 % in Kantarjian 2012, large imbalance between trials.
- ECOG PS 0 or 1 vs. 2: Included due to significant treatment effect for subgroup ECOG = 2 in Kantarjian 2012, large imbalance between trials.
- Cytogenetic risk poor vs. good/intermediate: Included due to being a stratification factor in both trial protocols

[4] The calculation of the proportion of bone marrow blasts for glasdegib + LDAC vs. LDAC differed slightly in comparison to the a priori protocol: To reduce the number of missing values, bone marrow blasts at baseline were merged with bone marrow blasts during screening, resulting in 18 patients having bone marrow blasts > 50 % in the LDAC alone arm (compared to 17 patients, see Table 16)

- Median baseline hemoglobin level (g/dL): Excluded for lack of significance in glasdegib + LDAC vs. LDAC IPD regression and no subgroup analysis in Kantarjian 2012.

Thus, the stepwise model included age, disease history, bone marrow blasts, ECOG PS and cytogenetic risk.

Model selection for STC

The glasdegib + LDAC vs. decitabine STC also involved visual assessment of the hazard plots and the Schoenfeld test for the Cox stepwise model. As in the glasdegib + LDAC vs. azacitidine STC, no significant deviations from the PH assumption was found.

Based on the comparison of fit statistics AIC and BIC, the visual inspection of graphs of the survival curves and the comparison of survival estimates, the exponential model (DSU approach) and the Weibull model (propensity weighted approach) were chosen as it provided the best fit. For a detailed description and rationales please see Appendix C.

Results for the indirect comparisons of glasdegib + LDAC vs. decitabine

Results in Table 22 summarize all ITC performed. All ITC including STC approaches found glasdegib + LDAC to have significantly longer OS relative to decitabine. Compared with the result using standard ITC (HR [95 % CI]: 0.57 [0.35, 0.91]), overall trends found that adjustment for population covariates resulted in slightly stronger treatment effects of glasdegib + LDAC vs. decitabine.

Table 22: Results summary for OS for the indirect comparisons of glasdegib + LDAC vs. decitabine

Glasdegib + LDAC vs decitabine	glasdegib + LDAC vs. LDAC		decitabine vs. LDAC		glasdegib + LDAC vs. decitabine	
	HR	[95 % CI]	HR	[95 % CI]	HR	[95 % CI]
Primary analysis (standard (Bucher) ITC)						
Cox unadjusted	0.46	[0.30, 0.72]	0.82	[0.68, 0.99]	0.57	[0.35, 0.91]
Supportive analyses						
STC following general guidance published by the DSU of the NICE						
Cox full (Multivariate ITC)[a]	0.42	[0.22, 0.78]	0.82	[0.68, 0.99]	0.51	[0.27, 0.98]
Stepwise Exponential (STC)	0.41	[0.23, 0.76]	0.82	[0.68, 0.99]	0.51	[0.27, 0.95]
Full Exponential (STC)	0.40	[0.22, 0.74]	0.82	[0.68, 0.99]	0.49	[0.26, 0.92]
STC using a propensity weighted approach.						
Cox full (Multivariate ITC)[a]	0.42	[0.23, 0.79]	0.82	[0.68, 0.99]	0.51	[0.27, 0.99]
Stepwise Weibull (STC)	0.40	[0.20, 0.77]	0.82	[0.68, 0.99]	0.51	[0.24, 0.97]
Full Exponential (STC)	0.40	[0.22, 0.73]	0.82	[0.68, 0.99]	0.49	[0.23, 0.91]

a: This row performs a covariate-adjusted ITC.
Abbreviations: CI = confidence interval; DSU: Decision Support Unit, HR = hazard ratio; ITC, indirect treatment comparison; LDAC, low-dose cytarabine; NICE = National Institute for Health and Care Excellence; OS = overall survival; STC, simulated treatment comparison.
Reference: (91)

Summary of results for the indirect comparisons

The results of the indirect treatment comparisons for OS are illustrated in Figure 16 (according to guidance from DSU of NICE) and Figure 17 (according to a propensity weighted approach). All methods of ITC clearly demonstrate a significant advantage of glasdegib + LDAC with regard to OS over the comparators

azacitidine and decitabine. Glasdegib + LDAC significantly prolongs OS relative to both HMA, azacitidine and decitabine.

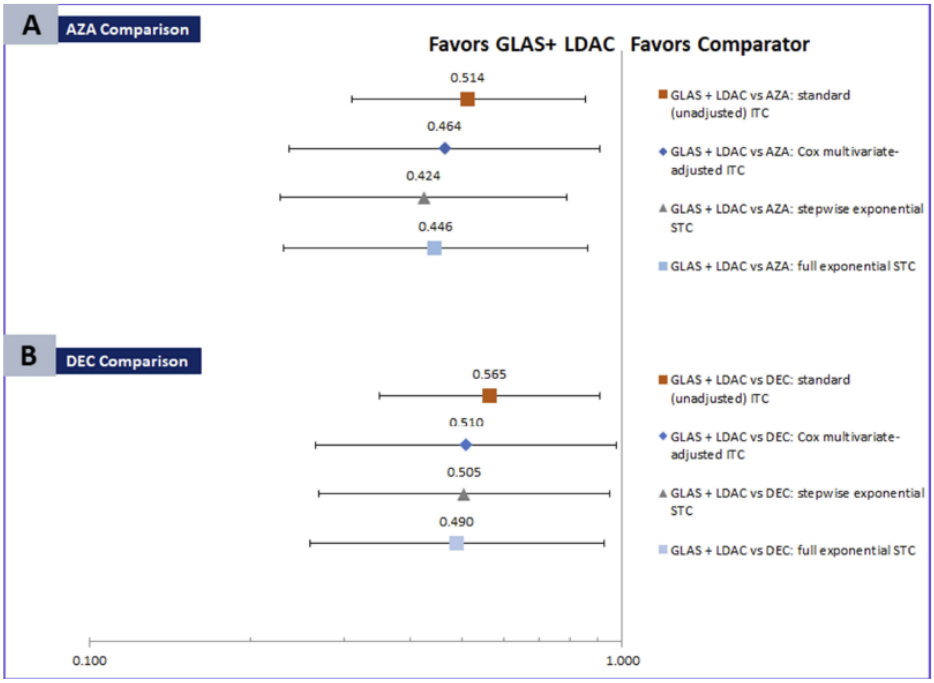


Figure 16: Forest plot of indirect comparisons for OS (according to guidance from DSU of NICE)

The forest plots (95 % confidence intervals) demonstrate glasdegib + LDAC superiority vs (A) azacitidine and (B) decitabine, and provide a simple visualization of the comparable HR results among each set of models. The x-axis is presented on the log scale.

Abbreviations: AZA = azacitidine; DEC = decitabine; GLAS = glasdegib; ITC = indirect treatment comparison; LDAC = low-dose cytarabine; STC = simulated treatment comparison.

Reference: (91)

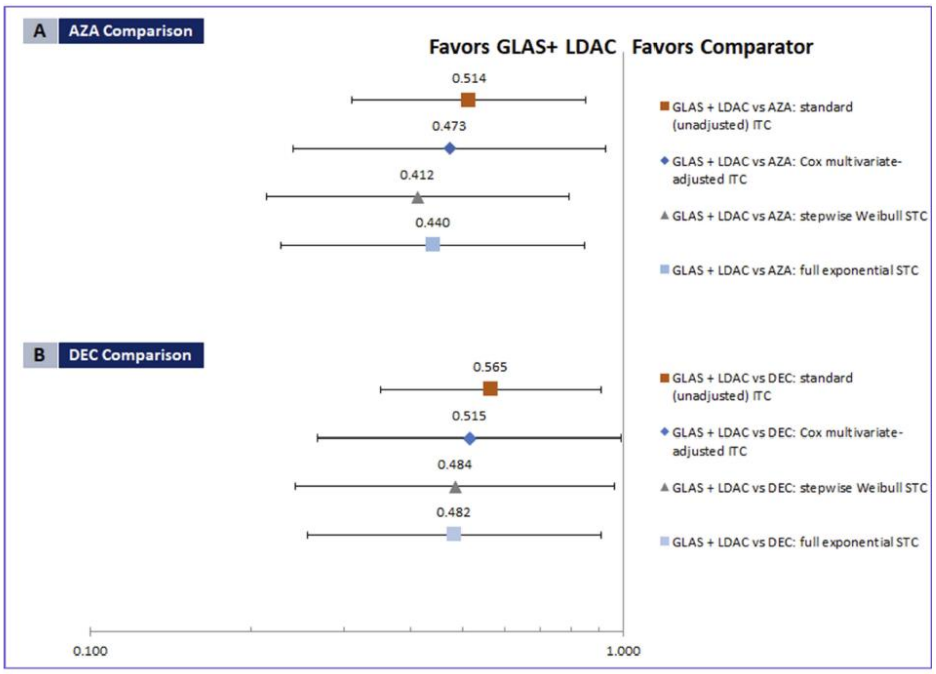


Figure 17: Forest plot of indirect comparisons for OS (according to a propensity weighted approach)

The forest plots (95 % confidence intervals) demonstrate glasdegib + LDAC superiority vs (A) azacitidine and (B) decitabine, and provide a simple visualization of the comparable HR results among each set of models. The x-axis is presented on the log scale.

Abbreviations: AZA = azacitidine; DEC = decitabine; GLAS = glasdegib; ITC = indirect treatment comparison; LDAC = low-dose

cytarabine; STC = simulated treatment comparison.
Reference: (91)

5.3.3 Progression-free survival (PFS)

5.3.3.1 Glasdegib + LDAC vs. LDAC

PFS was not collected in BRIGHT AML 1003. PFS is defined as the time from randomization until objective tumour progression or death, whichever occurs first (88). PFS serves as a valuable end point in oncology since it can represent a valid surrogate marker for OS (89). Since BRIGHT AML 1003 has mature OS data, the PFS endpoint would not add any value to the clinical interpretation of survival as a surrogate marker for OS is no longer needed. In addition, given the relatively high rate of non-evaluable patients due to a lack of bone marrow biopsies, which is not unexpected in a patient population with AML who are not candidates for standard induction chemotherapy, it is not practical to measure PFS.

5.3.4 Health-related Quality of Life (HRQoL)/Quality of Survival

5.3.4.1 Glasdegib + LDAC vs. LDAC

Patient reported outcomes (PRO) were not proactively collected because Study B1371003 was a phase 1b/2 study initially designed as a dose finding and proof of concept study. Given the statistically significant and clinically meaningful OS benefit in BRIGHT AML1003, it was decided to bring glasdegib + LDAC forward in the regulatory process to make it available to patients with AML who are not candidates for standard induction chemotherapy.

While BRIGHT AML 1003 OS results clearly demonstrate a survival advantage of glasdegib + LDAC vs. LDAC alone, this endpoint does not provide information on the HRQoL during this time. To examine the benefit-risk tradeoff that may be associated with additional side effects of treatment vs. an extension of life, it is thus important to determine whether extension of survival results in more time with symptoms of disease progression or toxicity, or whether it may be “good” additional survival time. The quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) method provides a tool to assess the net benefits of oncology treatments in terms of quantity (OS, time without symptoms of disease progression or toxicity, and toxicities (i.e. AEs)) and quality (patient health utilities) of survival gained.

The methodological approach and the results for the Q-TWiST analysis of glasdegib + LDAC vs. LDAC alone have been published by Kwon et al. 2019 (94).

For this Q-TWiST analysis, based on 20-month follow up data, OS was partitioned into

- TOX: Time with toxicity, defined as AEs grade ≥ 3 prior to progression;
- TWiST: Time without symptoms of disease progression or toxicity, this is considered the most desirable time period (i.e. “good” health);
- REL: Time post-progression, where progression was defined as treatment discontinuation due to insufficient clinical response or death; patients who discontinued for other reasons (including AEs) were censored at the date of discontinuation unless death occurred within 28 days of discontinuation.

Figure 18 depicts the Kaplan-Meier survival curves (magenta) as well as the curve representing the time without symptoms of disease progression or toxicity (orange) and the total days with grade ≥ 3 AEs (green), which are used to partition survival into TOX, TWiST, and REL health states in the calculation of Q-TWiST. The area under each of these curves is equal to the mean time in each state.

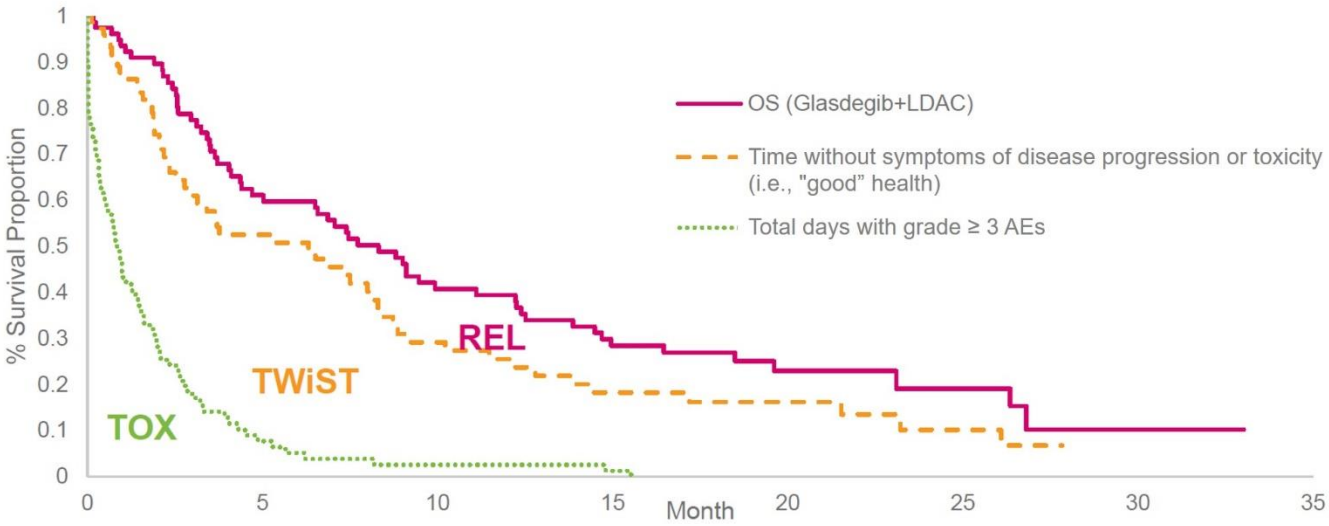


Figure 18: Partitioned Survival Curve for glasdegib + LDAC

Abbreviations: LDAC = low-dose cytarabine; OS = overall survival; REL = time after progression/relapse; TOX = time with grade ≥ 3 toxicity; TWiST = time without symptoms of disease progression or toxicity (i.e., “good” health).
Reference: adapted from (94)

Q-TWiST was calculated by multiplying restricted mean time in each state by respective utilities (U) and then summing up the utility-adjusted time. Base case analysis used U(TOX) = U(REL) = 0.5 and U(TWiST) = 1.0; threshold analyses were performed varying U(TOX) and U(REL) jointly each from 0 to 1 (Table 23). Relative gains (calculated as Q-TWiST difference/overall survival in LDAC arm) of ≥ 15 % were considered clinically meaningful per the clinical literature (95).

At 20 months of follow-up, the survival rates in the glasdegib + LDAC and LDAC arms were 28.2 % and 7.9 %, respectively. Glasdegib + LDAC patients (n = 78) had significantly longer mean time in TWiST (+ 3.4 [95 % CI]: [1.8, 5.2] months) and TOX (+ 0.4 [0.1, 0.8] months), and longer but non-significant REL (+ 0.2 [-1.0, 1.2] months) when compared to LDAC patients (n = 38) (

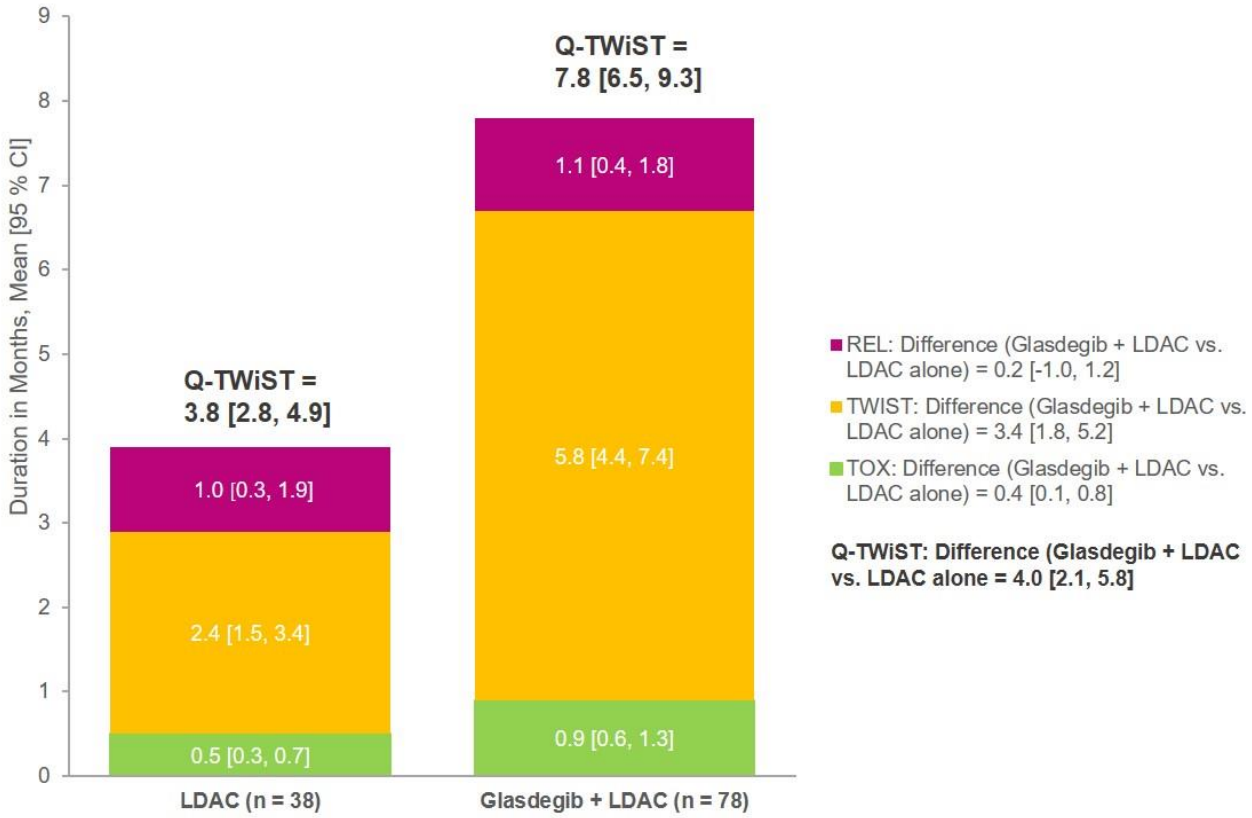


Figure 19). These mean times were multiplied by the respective utilities for TOX*0.5, REL*0.5 and TWIST*1.0 (i.e., the base case).

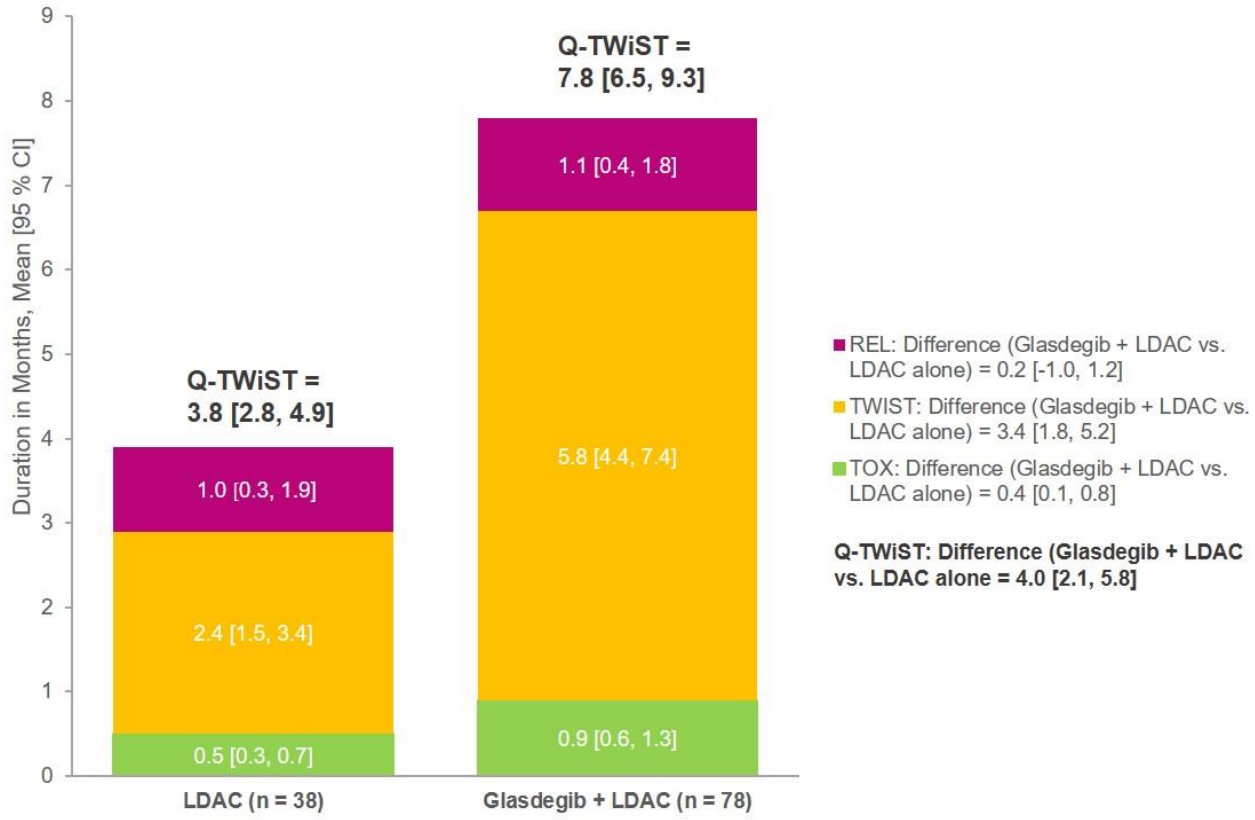


Figure 19: Restricted Mean Duration of Health States

Abbreviations: CI: Confidence interval; LDAC = low-dose cytarabine; REL = time after progression; TOX = time with grade ≥ 3 toxicity; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity.
Reference: adapted from (94)
* Due to rounding, the sum/difference may differ from the individual results

Table 23 depicts quality-adjusted survival (Q-TWiST) for glasdegib + LDAC, LDAC alone, and the difference between these cohorts using a range of utilities. Quality-adjusted survival results were robust to utilities used for TOX and REL states. Relative gains, calculated as difference in quality-adjusted survival relative to overall survival in the LDAC group were calculated.

Table 23: Q-TWiST Threshold Analysis

Q-TWiST Utility Values		LDAC Mean [95 %-CI] (months)	glasdegib + LDAC Mean [95 %-CI] (months)	Difference Mean [95 %-CI] (months)	Relative Gain %
TOX	REL				
0	0	2.4 [1.5, 3.4]	5.9 [4.4, 7.4]	3.50 [1.77, 5.19]	66
0	0.5	3.3 [2.4, 4.5]	6.9 [5.7, 8.3]	3.60 [1.77, 5.23]	68
0	1	4.3 [2.8, 6.1]	8.0 [6.6, 9.6]	3.70 [1.43, 5.87]	70
0.5	0	2.9 [2.0, 3.8]	6.8 [5.2, 8.4]	3.90 [2.08, 5.69]	74
0.5	**0.5**	**3.8 [2.8, 4.9]**	**7.8 [6.5, 9.3]**	**4.00 [2.11, 5.78]**	**75**
0.5	1	4.8 [3.4, 6.6]	8.9 [7.4, 10.6]	4.10 [1.72, 6.35]	77
1	0	3.4 [2.4, 4.4]	7.6 [6.0, 9.4]	4.20 [2.37, 6.34]	79
1	0.5	4.3 [3.3, 5.5]	8.7 [7.3, 10.3]	4.40 [2.45, 6.36]	83
1	1	5.3 [3.9, 7.1]	9.8 [8.2, 11.5]	4.50 [2.04, 6.86]	85

The green row represents base case results. Base case analysis: U[TOX] = U[REL] = 0.5 and U[TWiST] = 1.0. A bootstrap procedure was used to obtain 95 % confidence intervals [95 % CI].
Abbreviations: LDAC = low-dose cytarabine; Q-TWiST = quality-adjusted time without symptoms of disease progression or toxicity; REL = utility of time after progression; TOX = utility of time with grade ≥ 3 toxicity.

Reference: (94)

Base case Q-TWiST (base case analysis used U[TOX] = U[REL] = 0.5 and U[TWiST] = 1.0) was 4.0 ([95 % CI]: [2.1, 5.8]) months longer for glasdegib + LDAC, translating into a 75 % relative improvement in quality-adjusted survival relative to LDAC alone. In threshold analyses, absolute and relative Q-TWiST gains ranged from 3.5 to 4.5 months and 66 % to 85 %, respectively. These results exceeded the clinically meaningful threshold for gains in Q-TWiST and were statistically significant across all combinations of the utility values of TOX and REL. Sensitivity analysis varied the length of follow-up (6 to 24 month) and AE definitions (including all adverse events regardless of grade) and showed robust results; subgroup analyses were also performed and showed consistent effects.

Glasdegib is an add-on therapy to LDAC that has demonstrated significant survival benefits for newly diagnosed AML patients who are not candidates for standard induction chemotherapy. While patients can experience a longer time with toxicities from receiving glasdegib + LDAC (as expected since it is given as an add-on therapy), the treatment can overall still be favourable as it provides additional time spent in 'good' health (i.e. a significantly longer time in Q-TWiST). In the BRIGHT AML 1003 trial, the relative gains in OS far exceeded previously established thresholds (≥ 15 % as stated in clinical literature (95)) for being clinically meaningful, which suggests that the benefits of glasdegib + LDAC treatment outweigh its risks.

5.3.4.2 Glasdegib + LDAC vs. azacitidine/decitabine

No PRO were proactively collected in BRIGHT AML 1003, therefore an indirect comparison is not possible.

5.3.5 Objective response

Objective disease responses were defined according to international and widely used standards. While achieving CR is a therapeutic goal in the intensive treatment of AML patients, non-intensive chemotherapy rather aims at altering the natural course of the disease and not necessarily achieving CR (59). CR (defined

as: leukemic blasts < 5 % of nucleated bone marrow cells, platelets ≥ 100.000/µl and neutrophil granulocytes ≥ 1.000/µl in peripheral blood (13)) is by definition associated with partial regeneration of peripheral blood cell counts, so that transfusion of thrombocyte concentrates and hospitalization due to the high risk of infection (possibly including the so-called obligation to protective isolation) is no longer required. Both the independence from blood transfusions and the possibility of patient discharge from the hospital and subsequent outpatient therapy are clearly patient-relevant. The rate of CR has also been shown to correlate with OS (54). Therefore, the endpoint CR is considered as patient-relevant. Other response criteria regarded as clinically relevant include CR with incomplete blood count recovery (CRi), defined as CR criteria except for residual neutropenia (< 1.000/µL) **or** thrombocytopenia (< 100.000/µL) and morphologic leukaemia-free state (MLFS) defined as CR criteria except for residual neutropenia (< 1.000/µL) **and** thrombocytopenia (< 100.000/µL).(13).

5.3.5.1 Glasdegib + LDAC vs. LDAC

Analysis set

The analysis set for BRIGHT AML 1003 comprised all randomized AML patients, regardless of whether they had received the study drugs. Disease response was determined by bone marrow evaluation based on the "International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukaemia" response criteria for AML. Therefore, patients who did not have a bone marrow evaluation performed during treatment were non-evaluable. All non-evaluable patients were counted as non-responders for disease response.

Results

The primary analysis of CR (CR based on investigator-reported response from disease assessments, stratification factors based on IVRS) is summarized in Table 24. Significantly more patients in the glasdegib + LDAC arm (n = 14, 17.9 %) achieved CR compared with LDAC alone (n = 1, 2.6 %) (RR [95 % CI]: 7.10 [0.89, 56.83]; p = 0.0235).

Sensitivity analyses showed very similar results (Table 60 in Appendix D): Using the stratification factors from CRF instead of IVRS, slightly more patients showed good/intermediate cytogenetic risk. CR based on derived response showed the identical results to those based on the investigator assessment.

Table 24: Results summary for CR for BRIGHT AML 1003 – primary analysis

	Glasdegib + LDAC	LDAC
Investigator-reported response		
Total		
Number of patients randomized	78	38
Number (%) with CR	14 (17.9)	1 (2.6)
95 % CI[a]	[9.4, 26.5]	[0.0, 7.7]
Good/Intermediate cytogenetic risk (stratification factors based on IVRS)		
Number of patients randomized	49	21
Number (%) with CR	10 (20.4)	0 (0.0)
95 % CI[b]	[10.2, 34.3]	[0.0, 16.1]
Poor cytogenetic risk (stratification factors based on IVRS)		
Number of patients randomized	29	17
Number (%) with CR	4 (13.8)	1 (5.9)
95 % CI[b]	[3.9, 31.7]	[0.1, 28.7]
Pearson Chi-Square test (unstratified)		

	Glasdegib + LDAC	LDAC
p-value	0.0210	
CMH Stratified by Prognosis Stratum		
RR [95 % CI]	7.10 [0.89, 56.83]	
p-value	0.0235	

a. Using normal approximation.
b. Using exact method based on binomial distribution.
Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel test; CR = morphologic complete remission; IVRS = interactive voice response system; LDAC = low-dose cytarabine; RR = relative risk
Reference: (89)

Table 25 summarizes the objective response rates in terms of CR, CRi, MLFS and the composite endpoint CR + CRi + MLFS. The benefit for glasdegib + LDAC was substantial regarding objective response: Results for CR are comprehensively presented in Table 24. Glasdegib + LDAC demonstrated statistically significant better objective response assessed as CR + CRi + MLFS when compared to LDAC alone (RR [95 % CI]: 4.94 [1.19, 20.52], p = 0.0080).

There was a relatively high number of patients that could not be evaluated (30.8 % of patients with glasdegib + LDAC and 42.1 % of patients with LDAC alone). The decision to not perform a bone marrow evaluation was based on clinical judgment and is not unexpected in patients experiencing disease progression or complications of AML. Main reasons for patients not being evaluated for response include AEs leading to study termination or death prior to on-study bone marrow sampling and withdrawal of consent.

Table 25: Results summary for Objective response for BRIGHT AML 1003

	Glasdegib + LDAC N = 78		LDAC N = 38		RR [95 % CI], p-value from CMH
	n (%)	[95 % CI][a]	n (%)	[95 % CI][a]	
Morphologic complete remission (CR)	14 (17.9)	[10.2, 28.3]	1 (2.6)	[0.1, 13.8]	7.10 [0.89, 56.83] 0.0235
Morphologic complete remission with incomplete blood count recovery (CRi)	5 (6.4)	[2.1, 14.3]	1 (2.6)	[0.1, 13.8]	2.14 [0.27, 17.24] 0.4593
Morphologic leukaemia-free state (MLFS)	2 (2.6)	[0.3, 9.0]	0 (0.0)	[0.0, 9.3]	n. e. 0.3510
CR + CRi + MLFS	21 (26.9)	[17.5, 38.2]	2 (5.3)	[0.6, 17.7]	4.94 [1.19, 20.52] 0.0080
Not evaluable	24 (30.8)	[20.8, 42.2]	16 (42.1)	[26.3, 59.2]	-

a. Using exact method based on binomial distribution.
b. Not evaluable is defined as patients that were not assessed for response.
Response is Investigator-reported.

Abbreviations: CI = confidence interval, CR = morphologic complete remission; CRi = CR with incomplete blood count recovery; LDAC = low-dose cytarabine; MLFS = morphologic leukaemia-free state; n. e. = not estimable.
Reference: (89)

5.3.5.2 Glasdegib + LDAC vs. azacitidine/decitabine

No direct evidence of glasdegib + LDAC vs. the comparators azacitidine or decitabine for response was available.

Indirect comparisons in terms of CR and CR + CRi have been published by Westley et al. 2018. For glasdegib + LDAC vs. azacitidine, the standard unadjusted ITC as well as the stepwise STC demonstrated a statistically significant superiority of glasdegib + LDAC in terms of CR and CR + CRi (standard unadjusted ITC: RR [95 % CI]: 7.67 [1.02, 57.87] and 4.33 [1.02, 18.29], respectively) (96). For glasdegib + LDAC vs. decitabine, the standard unadjusted ITC as well as the STC showed numerical

trends in favour of glasdegib + LDAC in terms of CR and CR + CRi (standard unadjusted ITC: 3.43 [0.44, 27.00] and 1.94 [0.46, 8.43], respectively).

Indirect comparisons of objective response have certain limitations:

- Indirect comparisons could not be conducted for objective response (CR + CRi + MLFS), as results for MLFS are not available for azacitidine vs. LDAC and decitabine vs. LDAC from the publications of Dombret 2015 and Kantarjian 2012, respectively.
- Response outcomes CR and CRi within the control arm of AZA-AML-001 in the Dombret 2015 publication were reported as pooled conventional care regimens LDAC (N = 158), BSC (N = 45), or intensive chemotherapy (N = 44). Data for LDAC alone was not available, so the common comparator comprised LDAC in BRIGHT AML 1003 but LDAC + BSC + intensive chemotherapy in AZA-AML-001.
- Kantarjian 2012 did not separately report CR and CRi for LDAC preselected patients in the decitabine arm. Therefore, patients that were preselected for BSC also contribute to the analysis.

5.3.6 Transfusion need

AML patients suffer from worsening disease symptoms caused by the accumulation of myeloblasts in the bone marrow or peripheral blood and a progressive decline of the absolute erythrocyte, neutrophil and platelet counts. Standard chemotherapy typically leads to a further deterioration of blood counts. These haematological adverse events (anaemia, neutropenia and thrombocytopenia) are therefore treated by administration of blood products (transfusion of erythrocyte and platelet concentrates). If there are no or only minor haematological adverse events, transfusions are not required. This is referred to as transfusion independence and is considered an indicator for a recovery from AML symptoms. The independence from blood transfusions has also been shown to be a strong positive prognostic factor in adult and unfit AML patients.

A study by Cannas et al demonstrated that high transfusion intensity during induction therapy negatively influenced treatment outcome: it was associated with lower response rates and reduced median OS (97). There is also evidence that unfit AML patients who are transfusion independent during therapy have a significantly longer OS compared to transfusion dependent patients (98, 99).

Moreover, transfusion independence of AML patients is a criterion for achieving complete remission (100). The recovery of the bone marrow during the remission phase leads to a sufficient production of erythrocytes and thrombocytes and thus to independence from transfusions.

Furthermore, transfusion independence reduces the risk of infections caused by the transmission of bacteria or viruses, transfusion-associated acute pulmonary insufficiency, immunomodulation and complications caused by mix-up of blood products, thus leading to reduced patient morbidity (42). Since transfusions are typically administered only in special haematooncological centers and require a minimum stay of several hours, transfusion independence directly contributes to improving AML patients' health-related quality of life (41).

Though there is a paucity of data regarding the economic burden associated with transfusion requirements for patients with AML, the high costs and increased healthcare utilization associated with transfusion dependence are well established in patients with MDS (79, 80). Therefore, decreased transfusion requirements may have the potential to result in cost reductions for both patients with AML and payers.

Transfusion independency is therefore considered as a patient-relevant endpoint.

5.3.6.1 Glasdegib + LDAC vs. LDAC

Analysis set

The analysis set for BRIGHT AML 1003 comprised all randomized AML patients, regardless of whether they had received the study drugs.

Results

Transfusion independence data for ≥ 8, 12, 16, 20 and 24 weeks as well as exposure-adjusted transfusion rates per month of treatment and transfusion days per month of treatment are presented in Table 26 and Table 27. In BRIGHT AML 1003, statistically significant more patients receiving glasdegib + LDAC than patients receiving LDAC alone were transfusion independent for all durations considered (e.g. transfusion independence ≥ 8 weeks: 28.2 % vs. 5.3 %; p=0.0056). The mean exposure-adjusted transfusion rate per month of treatment was 4.83 in the glasdegib + LDAC arm vs. 8.07 in the LDAC alone arm. Patients with glasdegib + LDAC received transfusions on average over 3.93 days, whereas patients with LDAC alone received transfusions on average over 5.93 days.

Table 26: Results summary for transfusion independence for BRIGHT AML 1003

Duration of transfusion independence[a]	**Glasdegib + LDAC N = 78**	**LDAC N = 38**	**RR [95 % CI], p-value from CMH**
≥ 8 weeks	22 (28.2)	2 (5.3)	5.17 [1.25, 21.41]; 0.0056
≥ 12 weeks	18 (23.1)	2 (5.3)	4.27 [1.02, 17.86] 0.0214
≥ 16 weeks	16 (20.5)	2 (5.3)	3.82 [0.91, 16.08] 0.0396
≥ 20 weeks	16 (20.5)	2 (5.3)	3.82 [0.91, 16.08] 0.0396
≥ 24 weeks	14 (17.9)	0 (0.0)	n. e. 0.0067

a: No transfusions for ≥8, 12, 16, 20 and 24 consecutive weeks during treatment phase.

Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel test; LDAC = low-dose cytarabine; n. e.: not estimable; RR = relative risk
Reference: (89)

Table 27: Results summary for exposure-adjusted transfusion rates for BRIGHT AML 1003

	Glasdegib + LDAC N = 78	**LDAC N = 38**
Transfusion rate per month of treatment		
n (missing)	75 (3)	36 (2)
mean (std)	4.83 (4.386)	8.07 (7.799)
median (range)	4.06 (0-25.1)	5.80 (0-30.4)
Transfusion days per month of treatment		
n (missing)	75 (3)	36 (2)
mean (std)	3.93 (3.428)	5.93 (5.831)
median (range)	3.27 (0-19.7)	3.81 (0-25.4)

Transfusion rate is calculated as
number of transfusion during treatment phase / (last active therapy date - first active therapy date + 1)/30.4375.

Transfusion days is calculated as
number of transfusion days during treatment phase / (last active therapy date - first active therapy date + 1)/30.4375.

Abbreviations: LDAC = low-dose cytarabine
Reference: (89)

5.3.6.2 Glasdegib + LDAC vs. azacitidine/decitabine

In the AZA-AML-001 and DACO-006 trials, data on transfusion independence was available for azacitidine and the pooled conventional care regimen (BSC, LDAC or intensive chemotherapy), and decitabine and the pooled treatment choice regimen (supportive care or LDAC) respectively. No data on transfusions were available for LDAC preselected patients receiving azacitidine/decitabine and patients receiving LDAC alone. Therefore, transfusion data for azacitidine/decitabine and LDAC from AZA-AML-001 trial and DACO-006 trials is not considered for indirect comparison vs. glasdegib + LDAC.

5.4 Individual study results (safety outcomes)

5.4.1 Relevant endpoints

Describe the relevant endpoints, including the definition of the endpoint and methods of analysis (Table 28).

An overview of relevant endpoints, including the definition of the endpoint and methods of analysis is given in Table 28. Adverse events were collected in a standardised manner as part of the studies. It can be assumed that the adverse events are directly noticeable to the patient and have a direct influence on the patient's well-being.

Table 28: Methods of data collection and analysis of adverse events

Endpoint	Definition	Study reference/ID	Method of analysis

AEs	The following outcomes were covered:
	• SAEs
	• Severe AEs (grade 3 - 5)
	• Fatal AEs
	• AEs (any CTCAE grade)
	• AEs commonly expected for antileukemic treatment:
	  ○ febrile neutropenia
	  ○ haemorrhage
	  ○ QT prolongation
	  ○ Infections incl. pneumonia
	• Treatment discontinuation due to AE
		BRIGHT AML 1003	**Analysis set**
			In BRIGHT AML 1003, safety analyses were based on all randomized AML patients who received at least one dose of any of the study medications (safety analysis set).
			
			AE reporting
			Within this submission, treatment-emergent AEs are presented, those with initial onset or increasing in severity after the first dose of study medication. Reporting period was through and including 28 calendar days after the last administration of study medication. SAEs that occurred to a subject after the active reporting period had ended were to be reported if the investigator had become aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to investigational products were to be reported.
			
			AE Grading for severity
			AEs were graded for severity by investigator in accordance with National Cancer Institute CTCAE version 4.03.
			
			Analysis
			Total patients with at least one AE outcome in terms of absolute and relative frequencies are shown.
			
			SAEs, severe AEs (grade 3-5) and treatment discontinuations due to AE occurring in ≥ 2 % of patients are presented separately by MedDRA SOC and PT. All SAEs and all severe AEs (grade 3-5) separately by MedDRA SOC

Endpoint	Definition	Study reference/ID	Method of analysis
			and PT are included in Attachment A (101). AEs (any CTCAE grade) occurring in ≥ 20 % of patients are presented separately by MedDRA SOC and PT. AEs (any CTCAE grade) occurring in ≥ 10 % patients separately by MedDRA SOC and PT are included in Attachment A (101). AEs were evaluated for the entire study period and at day 90.
Abbreviations: (S)AE = (serious) Adverse event; AZA = azacitidine; CTCAE = Common Terminology Criteria for Adverse Events; DEC = decitabine; LDAC = Low-dose cytarabine; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred term; SOC = System organ class; References: (1, 2, 82, 83, 88, 89)			

5.4.2 Results on safety outcomes

For the technology, and the comparator, tabulate the total number of adverse events, frequency of occurrence (as a %), absolute and relative risk and 95 % CI reported in each of the clinical studies. Categorise the adverse events by frequency, severity and system organ class.

5.4.2.1 Glasdegib + LDAC vs. LDAC

According to the EMA guidelines on the evaluation of anti-cancer medicinal products in human patients, information on AEs with or without a causal relationship to the drug(s) should always be collected and graded by severity in clinical trials (102). The tolerability of a drug is often defined as the degree to which the AEs are acceptable to a patient. This includes adverse drug reactions that affect the patient's quality of life or activities of daily living, often over a large proportion of the treatment time.

Treatment duration in BRIGHT AML 1003

Analysis set

In BRIGHT AML 1003, safety analyses were based on all randomized AML patients who received at least one dose of any of the study medications (safety analysis set).

Results

Table 29 summarizes the treatment duration in BRIGHT AML 1003 for the direct comparison of glasdegib + LDAC vs. LDAC alone. In the glasdegib + LDAC arm, the median treatment duration was 83.0 days vs. 40.5 days for the LDAC alone arm. 37.3 % of patients in the glasdegib + LDAC arm and 5.6 % of patients in the LDAC alone arm received at least 6 cycles of treatment.

Overall, the mean relative dose intensities for glasdegib and LDAC were 87.3 % and 94.2 % respectively, for the glasdegib + LDAC arm, and 95.7 % for LDAC for the LDAC alone arm (Table 30 and Table 31).

Table 29: Results summary for treatment duration for BRIGHT AML 1003

	Glasdegib + LDAC N = 75	LDAC N = 36
Duration category (days)		
≤ 1	0	0

	Glasdegib + LDAC N = 75	LDAC N = 36
2 - 7	3	2
8 - 14	4	10
15 - 28	8	0
29 - 60	15	10
61 - 90	11	4
≥ 91	34	10
Median duration (range)	**83.0 (3 - 972)**	**40.5 (6- 239)**
Patients receiving at least 6 cycles of treatment	**28 (37.3)**	**2 (5.6)**

The duration was defined as (last dosing date - Cycle 1 Day 1 + 1), where last dosing date is last non-0 mg dose date. It is including the missed doses on unknown dates in treatment duration.

Abbreviations: LDAC = low-dose cytarabine
Reference: (89)

Table 30: Results for dose exposure summary of glasdegib in BRIGHT AML 1003

	Glasdegib + LDAC N = 75
Days on glasdegib	
Median (range)	72.0 (3, 954)
Average glasdegib dose per cycle (mg/day)	
Median (range)	89.5 (19, 101)
Relative glasdegib dose intensity (%)	
Median (range)	92.3 (19, 101)
Subjects with glasdegib dose reduction [n (%)]	13 (17.3)
Time to first glasdegib dose reduction (days)	
n	13
Median (range)	76.0 (41, 377)
Subjects with temporary dose delay for glasdegib [n (%)]	3 (4.0)
Average duration of temporary dose delay for glasdegib (days/delay)	
n	3
Median (range)	33.0 (33, 41)
Time to first temporary dose delay for glasdegib (days)	
n	3
Median (range)	56.0 (29, 427)
Subjects with dose interruption for glasdegib [n (%)]	59 (78.7)
Average duration of dose interruption for glasdegib (days/interruption)	
n	58
Median (range)	5.7 (1, 49)
Time to first dose interruption for glasdegib (days)	
n	59
Median (range)	26.0 (1, 308)

A cycle delay was defined as >=8 weeks apart between cycles (from Day 1 of the previous cycle).
A dose reduction was defined as a day when the prescribed dose is less than the previous prescribed dose for any reason with the exception that a day with total dose administered of 0mg is not considered a dose reduction.
A dose interruptions/missed dose was defined as a planned dosing day with 0 mg total dose administered.
Any day with total daily dose of 0 mg was not counted in 'Days on Glasdegib'.

	Glasdegib + LDAC N = 75
Average Dose per Cycle = Actual total dose in this cycle (exclude 0 mg and dose missed on unknown days) / Actual dosing days in this cycle (include 0 mg and dose missed on unknown days) Abbreviations: LDAC = low-dose cytarabine Reference: (89)	

Table 31: Results for dose exposure summary of LDAC in BRIGHT AML 1003

	Glasdegib + LDAC N = 75	LDAC N=36
Average LDAC dose per cycle (mg/day)		
Median (range)	40.0 (8, 40)	40.0 (24, 40)
Relative LDAC dose intensity (%)		
Median (range)	100.0 (20, 106)	100.0 (60, 100)
Subjects with LDAC dose reduction [n (%)]	12 (16,0)	0
Time to first glasdegib dose reduction (days)		
n	12	0
Median (range)	143.5 (45, 667)	-
Subjects with temporary dose delay for LDAC [n (%)]	3 (4,0)	0
Average duration of temporary dose delay for glasdegib (days/delay)		
n	3	-
Median (range)	33.0 (33, 40)	-
Time to first temporary dose delay for LDAC (days)		
n	3	-
Median (range)	56.0 (29, 427)	-
A cycle delay was defined as >=8 weeks apart between cycles (from Day 1 of the previous cycle). A dose reduction was defined as a day when the prescribed dose is less than the previous prescribed dose for any reason with the exception that a day with total dose administered of 0mg is not considered a dose reduction. A dose interruptions/missed dose was defined as a planned dosing day with 0 mg total dose administered. Any day with total daily dose of 0 mg was not counted in 'Days on Glasdegib'. Average Dose per Cycle = Actual total dose in this cycle (exclude 0 mg and dose missed on unknown days) / Actual dosing days in this cycle (include 0 mg and dose missed on unknown days) Abbreviations: LDAC = low-dose cytarabine Reference: (89)		

The relative risk (RR) was primarily used to make conclusions about the statistical significance of AEs. Risk differences (RD) were presented for sake of completeness. AEs that showed statistically significant differences between the treatment arms according to RD but not RR and occurred in a higher amount of patients were those related to either receiving an oral therapy (e.g. nausea, vomiting of any grade) or SMOi (e.g. muscle spasms or dizziness (103)).

Summary for total AEs

Table 32 summarizes the total AE endpoints for BRIGHT AML 1003, for the entire study period and for the first 90 days of therapy.

Considering the entire study period, glasdegib + LDAC showed comparable rates compared to LDAC alone for SAEs (78.7 % vs. 77.8 %), severe AEs (grade 3 - 5) (92.0 % vs. 97.2 %) and AEs of any CTCAE grade (100 % vs. 100 %). Patients receiving glasdegib + LDAC had numerical but not statistically significant lower risks for fatal AEs (29.3 % vs. 44.4 %; RR [95 % CI]: 0.66 [0.40, 1.10], p-value = 0.1080),

and AEs leading to permanent discontinuation of all study drugs (30.7 % vs. 47.2 %; RR [95 % CI]: 0.65 [0.40, 1.05], p-value = 0.0810).

To account for imbalances in treatment duration between the glasdegib + LDAC and LDAC alone arms, AEs are presented separately for the first 90 days of therapy. Considering the first 90 days of therapy, glasdegib + LDAC demonstrated a statistically significant advantage over LDAC alone regarding fatal AEs (16.0 % vs. 36.1 %; RR [95 % CI]: 0.44 [0.23; 0.87], p-value = 0.0184) and numerically fewer treatment discontinuations due to AE (20.0 % vs. 33.3 %; RR [95 % CI]: 0.60 [0.31, 1.15], p-value = 0.1216).

No statistically significant differences between glasdegib + LDAC and LDAC alone occurred regarding the AEs commonly expected for antileukemic treatments such as febrile neutropenia (entire study period: 34.7% vs. 25.0%; first 90 days: 30.7 % vs. 22.2 %), haemorrhage (entire study period: 48.0 % vs. 50.0 %; first 90 days: 36.0 % vs. 47.2 %), QT prolongation (entire study period: 20.0 % vs. 11.1 %; first 90 days: 13.3 % vs. 11.1 %), and infections (entire study period: 61.3 % vs. 55.6 %; first 90 days: 52.0 % vs. 52.8 %) including pneumonia (entire study period: 28.0 % vs. 27.8 %; first 90 days: 18.7 % vs. 25.0 %).

SAEs separately by MedDRA SOC and PT

Table 33 lists the SAEs occurring in ≥ 2 % of patients separately by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) for BRIGHT AML 1003. No statistically significant differences according to the RD between glasdegib + LDAC and LDAC alone occurred, neither for the entire study period nor for the first 90 days of therapy. A list of all SAEs by MedDRA SOC and PT is given in Attachment A (101).

Severe AEs (grade 3 - 5) separately by MedDRA SOC and PT

Table 34 lists the severe AEs (grade 3 - 5) occurring in ≥ 2 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003. No statistically significant differences according to the RR between glasdegib + LDAC and LDAC alone occurred, neither for the entire study period nor for the first 90 days of therapy. A list of all severe AEs (grade 3 - 5) by MedDRA SOC and PT is given in Attachment A (101).

AEs (any CTCAE grade) separately by MedDRA SOC and PT

Table 35 lists the AEs occurring in ≥ 20 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003, for the entire study period and for the first 90 days of treatment.

Considering the entire study period, statistically significant more patients (according to the RR) receiving glasdegib + LDAC had nausea (PT, 36.0 % vs. 11.1 %; RR [95 % CI]: 3.24 [1.23, 8.56]; p-value = 0.0178), decreased appetite (PT, 32.0 % vs. 11.1 %; RR [95 % CI]: 2.88 [1.08, 7.68]; p-value = 0.0346), musculoskeletal and connective tissue disorders (SOC, 56.0 % vs. 30.6 %; RR [95 % CI]: 1.83 [1.08, 3.12]; p-value = 0.0256) and nervous system disorders (SOC, 58.7 % vs. 22.2 %; 2.64 [1.39, 5.01]; p-value = 0.0029), including dysgeusia (PT, 24.0 % vs. 2.8 %; RR [95 % CI]: 8.64 [1.20, 62.21]; p-value = 0.0323). Most of these AEs were mild to moderate.

Considering the first 90 days of therapy, statistically significant more patients (according to the RR) receiving glasdegib + LDAC had nervous system disorders (SOC, 50.7 % vs. 19.4 %; RR [95 % CI]: 2.61 [1.29, 5.25]; p-value = 0.0074).

A list of AEs (any CTCAE grade) occurring in ≥ 10 % by MedDRA SOC and PT is given in Attachment A (101).

Treatment discontinuations due to AE separately by MedDRA SOC and PT

Table 36 lists the treatment discontinuations due to AE occurring in ≥ 2 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003. No statistically significant differences between glasdegib + LDAC and LDAC alone according to the RR occurred, neither for the entire study period nor for the first 90 days of therapy. A list of all treatment discontinuations due to AEs by MedDRA SOC and PT is given in Attachment A (101).

Table 32: Results summary for total AEs for BRIGHT AML 1003

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95 %-CI]; p-value	RD [95 %-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95 %-CI]; p-value	RD [95 %-CI]; p-value
Total patients with at least one								
SAEs	59 (78.7)	28 (77.8)	1.01 [0.82, 1.25]; 0.9158	0.01 [-0.16, 0.17]; 0.9156	49 (65.3)	26 (72.2)	0.90 [0.70, 1.17]; 0.4519	-0.07 [-0.25, 0.11]; 0.4574
Severe AEs (grade 3-5)	69 (92.0)	35 (97.2)	0.95 [0.87, 1.03]; 0.2116	-0.05 [-0.13, 0.03]; 0.2095	65 (86.7)	33 (91.7)	0.95 [0.83, 1.08]; 0.4070	-0.05 [-0.17, 0.07]; 0.4087
Fatal AEs	22 (29.3)	16 (44.4)	0.66 [0.40, 1.10]; 0.1080	-0.15 [-0.34, 0.04]; 0.1234	12 (16.0)	13 (36.1)	0.44 [0.23, 0.87]; 0.0184	-0.20 [-0.38, -0.02]; 0.0264
AEs (any CTCAE grade)	75 (100.0)	36 (100.0)	n. e.	n. e.	74 (98.7)	36 (100.0)	0.99 [0.96, 1.01]; 0.3173	-0.01 [-0.04, 0.01]; 0.3141
AEs commonly expected for antileukemic treatments								
Febrile neutropenia (PT)	26 (34.7)	9 (25.0)	1.39 [0.73, 2.64]; 0.3209	0.10 [-0.08; 0.27]; 0.2866	23 (30.7)	8 (22.2)	1.38 [0.69, 2.78]; 0.3668	0.08 [-0.09, 0.26]; 0.3339
Haemorrhage (SMQ)	36 (48.0)	18 (50.0)	0.96 [0.64, 1.44]; 0.8425	-0.02 [-0.22, 0.18]; 0.8436	27 (36.0)	17 (47.2)	0.76 [0.48, 1.21]; 0.2462	-0.11 [-0.31, 0.08]; 0.2616
QT prolongation (SMQ)	15 (20.0)	4 (11.1)	1.80 [0.64, 5.04]; 0.2628	0.09 [-0.05, 0.23]; 0.2031	10 (13.3)	4 (11.1)	1.20 [0.40, 3.57]; 0.7429	0.02 [-0.11, 0.15]; 0.7342
Infections (SOC)	46 (61.3)	20 (55.6)	1.10 [0.78, 1.56]; 0.5718	0.06 [-0.14; 0.24]; 0.5638	39 (52.0)	19 (52.8)	0.99 [0.68, 1.44]; 0.9386	-0.01 [-0.21, 0.19]; 0.9388
Pneumonia (PT)	21 (28.0)	10 (27.8)	1.01 [0.53, 1.91]; 0.9805	0.00 [-0.18; 0.18]; 0.9805	14 (18.7)	9 (25.0)	0.75 [0.36, 1.56]; 0.4373	-0.06 [-0.23, 0.10]; 0.4565
Treatment discontinuations due to AE	23 (30.7)	17 (47.2)	0.65 [0.40, 1.05]; 0.0810	-0.17 [-0.36, 0.03]; 0.0937	15 (20.0)	12 (33.3)	0.60 [0.31, 1.15]; 0.1216	-0.13 [-0.31, 0.05]; 0.1435

Abbreviations: (S)AEs = (serious) adverse event; CI = Confidence interval; LDAC = Low-dose cytarabine; n.e. = not estimable; RD = risk difference; RR = risk ratio
References: (89)

Table 33: Results summary for SAEs occurring in ≥ 2 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Infections and infestations								
All PT	26 (34.7)	13 (36.1)	0.96 [0.56; 1.64]; 0.8809	-0.01 [-0.20; 0.18]; 0.8817	18 (24.0)	13 (36.1)	0.66 [0.37; 1.20]; 0.1765	-0.12 [-0.31; 0.06]; 0.1977
Pneumonia	16 (21.3)	7 (19.4)	1.10 [0.50; 2.43]; 0.8191	0.02 [-0.14; 0.18]; 0.8160	10 (13.3)	7 (19.4)	0.69 [0.28; 1.65]; 0.4009	-0.06 [-0.21; 0.09]; 0.4259
Sepsis	3 (4.0)	5 (13.9)	0.29 [0.07; 1.14]; 0.0760	-0.10 [-0.22; 0.02]; 0.1103	2 (2.7)	4 (11.1)	0.24 [0.05; 1.25]; 0.0901	-0.08 [-0.19; 0.02]; 0.1287
Lung infection	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Septic shock	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Cystitis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pseudomembranous colitis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Urogenital infection bacterial	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Blood and lymphatic system disorders								
All PT	26 (34.7)	9 (25.0)	1.39 [0.73; 2.64]; 0.3209	0.10 [-0.08; 0.27]; 0.2866	21 (28.0)	8 (22.2)	1.26 [0.62; 2.56]; 0.5239	0.06 [-0.11; 0.23]; 0.5044
Febrile neutropenia	21 (28.0)	6 (16.7)	1.68 [0.74; 3.80]; 0.2125	0.11 [-0.05; 0.27]; 0.1613	18 (24.0)	5 (13.9)	1.73 [0.70; 4.28]; 0.2375	0.10 [-0.05; 0.25]; 0.1826
Anaemia	5 (6.7)	0 (0.0)	5.36 [0.30; 94.29]; 0.2515	0.07 [0.01; 0.12]; 0.0206	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Leukocytosis	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Pancytopenia	0 (0.0)	2 (5.6)	0.10 [0.00; 1.98]; 0.1295	-0.06 [-0.13; 0.02]; 0.1456	0 (0.0)	2 (5.6)	0.10 [0.00; 1.98]; 0.1295	-0.06 [-0.13; 0.02]; 0.1456

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Disseminated intravascular coagulation	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: General disorders and administration site conditions								
All PT	14 (18.7)	6 (16.7)	1.12 [0.47; 2.67]; 0.7985	0.02 [-0.13; 0.17]; 0.7943	10 (13.3)	4 (11.1)	1.20 [0.40; 3.57]; 0.7429	0.02 [-0.11; 0.15]; 0.7342
Disease progression	7 (9.3)	4 (11.1)	0.84 [0.26; 2.69]; 0.7688	-0.02 [-0.14; 0.10]; 0.7751	6 (8.0)	3 (8.3)	0.96 [0.25; 3.62]; 0.9519	0.00 [-0.11; 0.11]; 0.9523
Pyrexia	3 (4.0)	1 (2.8)	1.44 [0.16; 13.37]; 0.7484	0.01 [-0.06; 0.08]; 0.7308	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Fatigue	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Sudden death	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	0 (0.0)	0 (0.0)	n. e.	n. e.
General physical health deterioration	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Gastrointestinal disorders								
All PT	8 (10.7)	3 (8.3)	1.28 [0.36; 4.54]; 0.7023	0.02 [-0.09; 0.14]; 0.6887	7 (9.3)	2 (5.6)	1.68 [0.37; 7.68]; 0.5036	0.04 [-0.06; 0.14]; 0.4575
Gastrointestinal haemorrhage	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Nausea	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Vomiting	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Diarrhoea	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Lower gastrointestinal haemorrhage	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Cardiac disorders								
All PT	6 (8.0)	3 (8.3)	0.96 [0.25; 3.62]; 0.9519	0.00 [-0.11; 0.11]; 0.9523	4 (5.3)	2 (5.6)	0.96 [0.18; 5.00]; 0.9613	0.00 [-0.09; 0.09]; 0.9616
Atrial fibrillation	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Cardiac arrest	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Myocardial infarction	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Acute myocardial infarction	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Cardiogenic shock	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Nervous system disorders								
All PT	8 (10.7)	1 (2.8)	3.84 [0.50; 29.55]; 0.1962	0.08 [-0.01; 0.17]; 0.0793	6 (8.0)	1 (2.8)	2.88 [0.36; 23.04]; 0.3187	0.05 [-0.03; 0.13]; 0.2095
Haemorrhage intracranial	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Syncope	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
SOC: Injury, poisoning and procedural complications								
All PT	4 (5.3)	1 (2.8)	1.92 [0.22; 16.57]; 0.5530	0.03 [-0.05; 0.10]; 0.4982	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Splenic rupture	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Respiratory, thoracic and mediastinal disorders								
All PT	2 (2.7)	3 (8.3)	0.32 [0.06; 1.83]; 0.2005	-0.06 [-0.15; 0.04]; 0.2540	1 (1.3)	3 (8.3)	0.16 [0.02; 1.49]; 0.1069	-0.07 [-0.16; 0.02]; 0.1442

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Pleural effusion	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Cough	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Respiratory arrest	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Metabolism and nutrition disorders								
All PT	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
Hyponatraemia	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
SOC: Musculoskeletal and connective tissue disorders								
All PT	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
SOC: Renal and urinary disorders								
All PT	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Acute kidney injury	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
SOC: Skin and subcutaneous tissue disorders								
All PT	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
SOC: Investigations								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Laboratory test abnormal	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Squamous cell carcinoma of skin	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

Abbreviations: (S)AEs = (serious) adverse event; CI = Confidence interval; LDAC = Low-dose cytarabine; n.e. = not estimable; PT = preferred term; RD = risk difference; RR = risk ratio; SOC = system organ class

References: (89)

Table 34: Results summary for severe AEs (grade 3 - 5) occurring in ≥ 2 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Blood and lymphatic system disorders								
All PT	51 (68.0)	23 (63.9)	1.06 [0.80; 1.42]; 0.6740	0.04 [-0.15; 0.23]; 0.6701	48 (64.0)	22 (61.1)	1.05 [0.77; 1.43]; 0.7710	0.03 [-0.16; 0.22]; 0.7690
Anaemia	32 (42.7)	13 (36.1)	1.18 [0.71; 1.96]; 0.5195	0.07 [-0.13; 0.26]; 0.5050	31 (41.3)	13 (36.1)	1.14 [0.69; 1.91]; 0.6047	0.05 [-0.14; 0.24]; 0.5948
Febrile neutropenia	26 (34.7)	9 (25.0)	1.39 [0.73; 2.64]; 0.3209	0.10 [-0.08; 0.27]; 0.2866	23 (30.7)	8 (22.2)	1.38 [0.69; 2.78]; 0.3668	0.08 [-0.09; 0.26]; 0.3339
Thrombocytopenia	24 (32.0)	8 (22.2)	1.44 [0.72; 2.88]; 0.3034	0.10 [-0.07; 0.27]; 0.2652	23 (30.7)	8 (22.2)	1.38 [0.69; 2.78]; 0.3668	0.08 [-0.09; 0.26]; 0.3339
Neutropenia	9 (12.0)	5 (13.9)	0.86 [0.31; 2.39]; 0.7785	-0.02 [-0.15; 0.12]; 0.7836	5 (6.7)	4 (11.1)	0.60 [0.17; 2.10]; 0.4244	-0.04 [-0.16; 0.07]; 0.4572
Leukocytosis	3 (4.0)	3 (8.3)	0.48 [0.10; 2.26]; 0.3534	-0.04 [-0.14; 0.06]; 0.3985	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963
Leukopenia	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Pancytopenia	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961
Splenomegaly	0 (0.0)	2 (5.6)	0.10 [0.00; 1.98]; 0.1295	-0.06 [-0.13; 0.02]; 0.1456	0 (0.0)	2 (5.6)	0.10 [0.00; 1.98]; 0.1295	-0.06 [-0.13; 0.02]; 0.1456
Disseminated intravascular coagulation	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Infections and infestations								
All PT	29 (38.7)	15 (41.7)	0.93 [0.57; 1.50]; 0.7604	-0.03 [-0.23; 0.17]; 0.7632	21 (28.0)	14 (38.9)	0.72 [0.42; 1.24]; 0.2393	-0.11 [-0.30; 0.08]; 0.2586
Pneumonia	17 (22.7)	9 (25.0)	0.91 [0.45; 1.83]; 0.7849	-0.02 [-0.19; 0.15]; 0.7882	11 (14.7)	8 (22.2)	0.66 [0.29; 1.50]; 0.3203	-0.08 [-0.23; 0.08]; 0.3476
Sepsis	5 (6.7)	6 (16.7)	0.40 [0.13; 1.22]; 0.1083	-0.10 [-0.23; 0.03]; 0.1441	4 (5.3)	5 (13.9)	0.38 [0.11; 1.34]; 0.1344	-0.09 [-0.21; 0.04]; 0.1759
Device related infection	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Lung infection	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Septic shock	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Cystitis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pharyngitis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pseudomembranous colitis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Urogenital infection bacterial	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: General disorders and administration site conditions								
All PT	24 (32.0)	10 (27.8)	1.15 [0.62; 2.14]; 0.6554	0.04 [-0.14; 0.22]; 0.6465	16 (21.3)	8 (22.2)	0.96 [0.45; 2.03]; 0.9150	-0.01 [-0.17; 0.16]; 0.9156

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Disease progression	7 (9.3)	4 (11.1)	0.84 [0.26; 2.69]; 0.7688	-0.02 [-0.14; 0.10]; 0.7751	6 (8.0)	3 (8.3)	0.96 [0.25; 3.62]; 0.9519	0.00 [-0.11; 0.11]; 0.9523
Fatigue	9 (12.0)	2 (5.6)	2.16 [0.49; 9.49]; 0.3077	0.06 [-0.04; 0.17]; 0.2286	7 (9.3)	2 (5.6)	1.68 [0.37; 7.68]; 0.5036	0.04 [-0.06; 0.14]; 0.4575
Pyrexia	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Asthenia	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Sudden death	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	0 (0.0)	0 (0.0)	n. e.	n. e.
General physical health deterioration	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Multiple organ dysfunction syndrome	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Oedema peripheral	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Systemic inflammatory response syndrome	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Investigations								
All PT	23 (30.7)	11 (30.6)	1.00 [0.55; 1.83]; 0.9905	0.00 [-0.18; 0.18]; 0.9905	20 (26.7)	10 (27.8)	0.96 [0.50; 1.83]; 0.9015	-0.01 [-0.19; 0.17]; 0.9022
Platelet count decreased	12 (16.0)	4 (11.1)	1.44 [0.50; 4.15]; 0.5000	0.05 [-0.08; 0.18]; 0.4679	11 (14.7)	4 (11.1)	1.32 [0.45; 3.86]; 0.6121	0.04 [-0.09; 0.17]; 0.5925
Neutrophil count decreased	8 (10.7)	1 (2.8)	3.84 [0.50; 29.55]; 0.1962	0.08 [-0.01; 0.17]; 0.0793	4 (5.3)	1 (2.8)	1.92 [0.22; 16.57]; 0.5530	0.03 [-0.05; 0.10]; 0.4982
White blood cell count decreased	8 (10.7)	1 (2.8)	3.84 [0.50; 29.55]; 0.1962	0.08 [-0.01; 0.17]; 0.0793	6 (8.0)	1 (2.8)	2.88 [0.36; 23.04]; 0.3187	0.05 [-0.03; 0.13]; 0.2095
C-reactive protein increased	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963
Electrocardiogram QT prolonged	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Blood fibrinogen decreased	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Blood creatinine increased	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Laboratory test abnormal	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pseudomonas test positive	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
White blood cell count increased	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Metabolism and nutrition disorders								
All PT	15 (20.0)	4 (11.1)	1.80 [0.64; 5.04]; 0.2628	0.09 [-0.05; 0.23]; 0.2031	12 (16.0)	3 (8.3)	1.92 [0.58; 6.38]; 0.2871	0.08 [-0.05; 0.20]; 0.2204
Hyponatraemia	5 (6.7)	0 (0.0)	5.36 [0.30; 94.29]; 0.2515	0.07 [0.01; 0.12]; 0.0206	5 (6.7)	0 (0.0)	5.36 [0.30; 94.29]; 0.2515	0.07 [0.01; 0.12]; 0.0206
Decreased appetite	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Hypokalaemia	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
Hyperglycaemia	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Acidosis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Hypercholesterolaemia	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Hypoalbuminaemia	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
SOC: Respiratory, thoracic and mediastinal disorders								
All PT	11 (14.7)	7 (19.4)	0.75 [0.32; 1.78]; 0.5206	-0.05 [-0.20; 0.10]; 0.5380	9 (12.0)	7 (19.4)	0.62 [0.25; 1.52]; 0.2955	-0.07 [-0.22; 0.07]; 0.3266

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Dyspnoea	4 (5.3)	2 (5.6)	0.96 [0.18; 5.00]; 0.9613	0.00 [-0.09; 0.09]; 0.9616	4 (5.3)	2 (5.6)	0.96 [0.18; 5.00]; 0.9613	0.00 [-0.09; 0.09]; 0.9616
Hypoxia	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Pleural effusion	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Respiratory distress	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Respiratory failure	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Acute pulmonary oedema	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Cough	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pulmonary oedema	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Respiratory arrest	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Gastrointestinal disorders								
All PT	12 (16.0)	3 (8.3)	1.92 [0.58; 6.38]; 0.2871	0.08 [-0.05; 0.20]; 0.2204	9 (12.0)	2 (5.6)	2.16 [0.49; 9.49]; 0.3077	0.06 [-0.04; 0.17]; 0.2286
Diarrhoea	3 (4.0)	1 (2.8)	1.44 [0.16; 13.37]; 0.7484	0.01 [-0.06; 0.08]; 0.7308	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Nausea	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Vomiting	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Gastrointestinal haemorrhage	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Lower gastrointestinal haemorrhage	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Nervous system disorders								
All PT	13 (17.3)	1 (2.8)	6.24 [0.85; 45.87]; 0.0720	0.15 [0.04; 0.25]; 0.0048	8 (10.7)	1 (2.8)	3.84 [0.50; 29.55]; 0.1962	0.08 [-0.01; 0.17]; 0.0793
Syncope	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
Haemorrhage intracranial	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Loss of consciousness	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Headache	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Cardiac disorders								
All PT	8 (10.7)	3 (8.3)	1.28 [0.36; 4.54]; 0.7023	0.02 [-0.09; 0.14]; 0.6887	6 (8.0)	2 (5.6)	1.44 [0.31; 6.79]; 0.6448	0.02 [-0.07; 0.12]; 0.6206
Atrial fibrillation	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Cardiac arrest	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Cardiac failure	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Myocardial infarction	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Acute myocardial infarction	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Cardiogenic shock	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Renal and urinary disorders								
All PT	7 (9.3)	2 (5.6)	1.68 [0.37; 7.68]; 0.5036	0.04 [-0.06; 0.14]; 0.4575	7 (9.3)	2 (5.6)	1.68 [0.37; 7.68]; 0.5036	0.04 [-0.06; 0.14]; 0.4575

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Acute kidney injury	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
Chronic kidney disease	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961
SOC: Musculoskeletal and connective tissue disorders								
All PT	7 (9.3)	1 (2.8)	3.36 [0.43; 26.29]; 0.2482	0.07 [-0.02; 0.15]; 0.1304	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Muscle spasms	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398	0 (0.0)	0 (0.0)	n. e.	n. e.
Back pain	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Bone pain	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Injury, poisoning and procedural complications								
All PT	5 (6.7)	2 (5.6)	1.20 [0.24; 5.89]; 0.8223	0.01 [-0.08; 0.10]; 0.8163	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961
Fracture	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	0 (0.0)	0 (0.0)	n. e.	n. e.
Allergic transfusion reaction	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Splenic rupture	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Vascular disorders								
All PT	6 (8.0)	0 (0.0)	6.33 [0.37; 109.36]; 0.2044	0.08 [0.02; 0.14]; 0.0107	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398
Hypertension	4 (5.3)	0 (0.0)	4.38 [0.24; 79.25]; 0.3172	0.05 [0.00; 0.10]; 0.0398	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771
Hypotension	3 (4.0)	0 (0.0)	3.41 [0.18; 64.27]; 0.4132	0.04 [0.00; 0.08]; 0.0771	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Skin and subcutaneous tissue disorders								
All PT	3 (4.0)	2 (5.6)	0.72 [0.13; 4.12]; 0.7121	-0.02 [-0.10; 0.07]; 0.7260	3 (4.0)	2 (5.6)	0.72 [0.13; 4.12]; 0.7121	-0.02 [-0.10; 0.07]; 0.7260
Rash	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Ecchymosis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Erythema	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Ear and labyrinth disorders								
All PT	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
Hypoacusis	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	1 (1.3)	0 (0.0)	1.46 [0.06; 34.99]; 0.8152	0.01 [-0.01; 0.04]; 0.3141
SOC: Psychiatric disorders								
All PT	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349	1 (1.3)	1 (2.8)	0.48 [0.03; 7.46]; 0.6000	-0.01 [-0.07; 0.05]; 0.6349
Agitation	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Delirium	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Squamous cell carcinoma of skin	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

Abbreviations: AEs = adverse event; CI = Confidence interval; LDAC = Low-dose cytarabine; n. e. = not estimable; PT = preferred term; RD = risk difference; RR = Risk ratio; SOC = system organ class
References: (89)

Table 35: Results summary for AEs (any CTCAE grade) occurring in ≥ 20 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Gastrointestinal disorders								
All PT	58 (77.3)	24 (66.7)	1.16 [0.89; 1.51]; 0.2659	0.11 [-0.07; 0.29]; 0.2476	51 (68.0)	23 (63.9)	1.06 [0.80; 1.42]; 0.6740	0.04 [-0.15; 0.23]; 0.6701
Nausea	27 (36.0)	4 (11.1)	3.24 [1.23; 8.56]; 0.0178	0.25 [0.10; 0.40]; 0.0011	22 (29.3)	4 (11.1)	2.64 [0.98; 7.09]; 0.0542	0.18 [0.04; 0.33]; 0.0141
Diarrhoea	21 (28.0)	9 (25.0)	1.12 [0.57; 2.19]; 0.7411	0.03 [-0.14; 0.20]; 0.7357	13 (17.3)	9 (25.0)	0.69 [0.33; 1.47]; 0.3393	-0.08 [-0.24; 0.09]; 0.3635
Constipation	19 (25.3)	6 (16.7)	1.52 [0.66; 3.48]; 0.3212	0.09 [-0.07; 0.24]; 0.2779	15 (20.0)	5 (13.9)	1.44 [0.57; 3.65]; 0.4426	0.06 [-0.08; 0.21]; 0.4080
Vomiting	18 (24.0)	3 (8.3)	2.88 [0.91; 9.15]; 0.0729	0.16 [0.02; 0.29]; 0.0203	15 (20.0)	3 (8.3)	2.40 [0.74; 7.77]; 0.1439	0.12 [-0.01; 0.24]; 0.0737
SOC: General disorders and administration site conditions								
All PT	57 (76.0)	24 (66.7)	1.14 [0.88; 1.48]; 0.3301	0.09 [-0.09; 0.28]; 0.3143	52 (69.3)	22 (61.1)	1.13 [0.84; 1.53]; 0.4110	0.08 [-0.11; 0.27]; 0.3973
Fatigue	21 (28.0)	8 (22.2)	1.26 [0.62; 2.56]; 0.5239	0.06 [-0.11; 0.23]; 0.5044	19 (25.3)	6 (16.7)	1.52 [0.66; 3.48]; 0.3212	0.09 [-0.07; 0.24]; 0.2779
Pyrexia	20 (26.7)	8 (22.2)	1.20 [0.59; 2.46]; 0.6183	0.04 [-0.12; 0.21]; 0.6056	15 (20.0)	8 (22.2)	0.90 [0.42; 1.93]; 0.7860	-0.02 [-0.19; 0.14]; 0.7896
Oedema peripheral	19 (25.3)	7 (19.4)	1.30 [0.60; 2.81]; 0.5007	0.06 [-0.10; 0.22]; 0.4775	17 (22.7)	7 (19.4)	1.17 [0.53; 2.56]; 0.7020	0.03 [-0.13; 0.19]; 0.6936
SOC: Blood and lymphatic system disorders								
All PT	53 (70.7)	23 (63.9)	1.11 [0.83; 1.47]; 0.4890	0.07 [-0.12; 0.26]; 0.4791	49 (65.3)	22 (61.1)	1.07 [0.79; 1.46]; 0.6711	0.04 [-0.15; 0.23]; 0.6669
Anaemia	35 (46.7)	15 (41.7)	1.12 [0.71; 1.77]; 0.6262	0.05 [-0.15; 0.25]; 0.6183	33 (44.0)	15 (41.7)	1.06 [0.66; 1.68]; 0.8177	0.02 [-0.17; 0.22]; 0.8158
Febrile neutropenia	26 (34.7)	9 (25.0)	1.39 [0.73; 2.64]; 0.3209	0.10 [-0.08; 0.27]; 0.2866	23 (30.7)	8 (22.2)	1.38 [0.69; 2.78]; 0.3668	0.08 [-0.09; 0.26]; 0.3339
Thrombocytopenia	24 (32.0)	9 (25.0)	1.28 [0.66; 2.46]; 0.4601	0.07 [-0.11; 0.25]; 0.4370	23 (30.7)	9 (25.0)	1.23 [0.63; 2.37]; 0.5442	0.06 [-0.12; 0.23]; 0.5275

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Infections and infestations								
All PT	46 (61.3)	20 (55.6)	1.10 [0.78; 1.56]; 0.5718	0.06 [-0.14; 0.25]; 0.5638	39 (52.0)	19 (52.8)	0.99 [0.68; 1.44]; 0.9386	-0.01 [-0.21; 0.19]; 0.9388
Pneumonia	21 (28.0)	10 (27.8)	1.01 [0.53; 1.91]; 0.9805	0.00 [-0.18; 0.18]; 0.9805	14 (18.7)	9 (25.0)	0.75 [0.36; 1.56]; 0.4373	-0.06 [-0.23; 0.10]; 0.4565
SOC: Investigations								
All PT	45 (60.0)	18 (50.0)	1.20 [0.82; 1.75]; 0.3410	0.10 [-0.10; 0.30]; 0.3208	40 (53.3)	17 (47.2)	1.13 [0.75; 1.69]; 0.5560	0.06 [-0.14; 0.26]; 0.5459
Weight decreased	15 (20.0)	1 (2.8)	7.20 [0.99; 52.40]; 0.0513	0.17 [0.07; 0.28]; 0.0013	11 (14.7)	1 (2.8)	5.28 [0.71; 39.33]; 0.1044	0.12 [0.02; 0.22]; 0.0156
SOC: Respiratory, thoracic and mediastinal disorders								
All PT	38 (50.7)	22 (61.1)	0.83 [0.59; 1.17]; 0.2844	-0.10 [-0.30; 0.09]; 0.2947	30 (40.0)	19 (52.8)	0.76 [0.50; 1.15]; 0.1906	-0.13 [-0.32; 0.07]; 0.2041
Dyspnoea	16 (21.3)	11 (30.6)	0.70 [0.36; 1.35]; 0.2837	-0.09 [-0.27; 0.08]; 0.3065	13 (17.3)	9 (25.0)	0.69 [0.33; 1.47]; 0.3393	-0.08 [-0.24; 0.09]; 0.3635
Cough	16 (21.3)	6 (16.7)	1.28 [0.55; 2.99]; 0.5692	0.05 [-0.11; 0.20]; 0.5500	12 (16.0)	5 (13.9)	1.15 [0.44; 3.02]; 0.7737	0.02 [-0.12; 0.16]; 0.7678
SOC: Metabolism and nutrition disorders								
All PT	43 (57.3)	13 (36.1)	1.59 [0.99; 2.56]; 0.0572	0.21 [0.02; 0.40]; 0.0309	35 (46.7)	11 (30.6)	1.53 [0.88; 2.64]; 0.1303	0.16 [-0.03; 0.35]; 0.0932
Decreased appetite	24 (32.0)	4 (11.1)	2.88 [1.08; 7.68]; 0.0346	0.21 [0.06; 0.36]; 0.0054	15 (20.0)	3 (8.3)	2.40 [0.74; 7.77]; 0.1439	0.12 [-0.01; 0.24]; 0.0737
SOC: Musculoskeletal and connective tissue disorders								
All PT	42 (56.0)	11 (30.6)	1.83 [1.08; 3.12]; 0.0256	0.25 [0.07; 0.44]; 0.0079	33 (44.0)	11 (30.6)	1.44 [0.83; 2.51]; 0.1976	0.13 [-0.05; 0.32]; 0.1605
Muscle spasms	16 (21.3)	2 (5.6)	3.84 [0.93; 15.81]; 0.0624	0.16 [0.04; 0.28]; 0.0094	11 (14.7)	2 (5.6)	2.64 [0.62; 11.29]; 0.1905	0.09 [-0.02; 0.20]; 0.1032

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Skin and subcutaneous tissue disorders								
All PT	40 (53.3)	13 (36.1)	1.48 [0.91; 2.39]; 0.1138	0.17 [-0.02; 0.37]; 0.0808	33 (44.0)	12 (33.3)	1.32 [0.78; 2.24]; 0.3026	0.11 [-0.08; 0.30]; 0.2727
SOC: Nervous system disorders								
All PT	44 (58.7)	8 (22.2)	2.64 [1.39; 5.01]; 0.0029	0.36 [0.19; 0.54]; <0.0001	38 (50.7)	7 (19.4)	2.61 [1.29; 5.25]; 0.0074	0.31 [0.14; 0.48]; 0.0004
Dizziness	16 (21.3)	3 (8.3)	2.56 [0.80; 8.23]; 0.1145	0.13 [0.00; 0.26]; 0.0490	13 (17.3)	3 (8.3)	2.08 [0.63; 6.84]; 0.2280	0.09 [-0.03; 0.21]; 0.1564
Dysgeusia	18 (24.0)	1 (2.8)	8.64 [1.20; 62.21]; 0.0323	0.21 [0.10; 0.32]; 0.0002	15 (20.0)	1 (2.8)	7.20 [0.99; 52.40]; 0.0513	0.17 [0.07; 0.28]; 0.0013
SOC: Vascular disorders								
All PT	23 (30.7)	12 (33.3)	0.92 [0.52; 1.63]; 0.7758	-0.03 [-0.21; 0.16]; 0.7787	16 (21.3)	12 (33.3)	0.64 [0.34; 1.21]; 0.1679	-0.12 [-0.30; 0.06]; 0.1907
SOC: Psychiatric disorders								
All PT	23 (30.7)	9 (25.0)	1.23 [0.63; 2.37]; 0.5442	0.06 [-0.12; 0.23]; 0.5275	17 (22.7)	8 (22.2)	1.02 [0.49; 2.14]; 0.9582	0.00 [-0.16; 0.17]; 0.9580
SOC: Renal and urinary disorders								
All PT	19 (25.3)	7 (19.4)	1.30 [0.60; 2.81]; 0.5007	0.06 [-0.10; 0.22]; 0.4775	16 (21.3)	5 (13.9)	1.54 [0.61; 3.86]; 0.3617	0.07 [-0.07; 0.22]; 0.3181
SOC: Cardiac disorders								
All PT	19 (25.3)	5 (13.9)	1.82 [0.74; 4.49]; 0.1913	0.11 [-0.04; 0.26]; 0.1344	16 (21.3)	4 (11.1)	1.92 [0.69; 5.33]; 0.2105	0.10 [-0.04; 0.24]; 0.1475
SOC: Injury, poisoning and procedural complications								
All PT	17 (22.7)	5 (13.9)	1.63 [0.65; 4.07]; 0.2938	0.09 [-0.06; 0.24]; 0.2433	11 (14.7)	5 (13.9)	1.06 [0.40; 2.81]; 0.9132	0.01 [-0.13; 0.15]; 0.9123

Abbreviations: AEs = adverse event; CI = Confidence interval; LDAC = Low-dose cytarabine; PT = preferred term; RD = risk difference; RR = Risk ratio; SOC = system organ class

References: (89)

Table 36: Results summary for treatment discontinuations due to AE occurring in ≥ 2 % of patients separately by MedDRA SOC and PT for BRIGHT AML 1003

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
SOC: Infections and infestations								
All PT	9 (12.0)	3 (8.3)	1.44 [0.41; 5.00]; 0.5659	0.04 [-0.08; 0.15]; 0.5371	6 (8.0)	1 (2.8)	2.88 [0.36; 23.04]; 0.3187	0.05 [-0.03; 0.13]; 0.2095
Pneumonia	4 (5.3)	1 (2.8)	1.92 [0.22; 16.57]; 0.5530	0.03 [-0.05; 0.10]; 0.4982	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Sepsis	1 (1.3)	2 (5.6)	0.24 [0.02; 2.56]; 0.2374	-0.04 [-0.12; 0.04]; 0.2961	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Blood and lymphatic system disorders								
All PT	3 (4.0)	4 (11.1)	0.36 [0.09; 1.52]; 0.1653	-0.07 [-0.18; 0.04]; 0.2126	2 (2.7)	4 (11.1)	0.24 [0.05; 1.25]; 0.0901	-0.08 [-0.19; 0.02]; 0.1287
Febrile neutropenia	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963	2 (2.7)	2 (5.6)	0.48 [0.07; 3.27]; 0.4535	-0.03 [-0.11; 0.05]; 0.4963
Leukocytosis	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Pancytopenia	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: General disorders and administration site conditions								
All PT	4 (5.3)	2 (5.6)	0.96 [0.18; 5.00]; 0.9613	0.00 [-0.09; 0.09]; 0.9616	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Disease progression	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Sudden death	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	0 (0.0)	0 (0.0)	n. e.	n. e.
Pyrexia	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
SOC: Investigations								
All PT	3 (4.0)	1 (2.8)	1.44 [0.16; 13.37]; 0.7484	0.01 [-0.06; 0.08]; 0.7308	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value	Glasdegib + LDAC N = 75 n (%)	LDAC N = 36 n (%)	RR [95%-CI]; p-value	RD [95%-CI]; p-value
Pseudomonas test positive	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Gastrointestinal disorders								
All PT	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732	2 (2.7)	1 (2.8)	0.96 [0.09; 10.24]; 0.9730	0.00 [-0.07; 0.06]; 0.9732
Nausea	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517	2 (2.7)	0 (0.0)	2.43 [0.12; 49.43]; 0.5625	0.03 [-0.01; 0.06]; 0.1517
Lower gastrointestinal haemorrhage	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Cardiac disorders								
All PT	0 (0.0)	2 (5.6)	0.10 [0.00; 1.98]; 0.1295	-0.06 [-0.13; 0.02]; 0.1456	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Acute myocardial infarction	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Cardiogenic shock	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Myocardial infarction	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Injury, poisoning and procedural complications								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Splenic rupture	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Signet-ring cell carcinoma	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105

AE Outcome	Study period				Within the first 90 days of therapy			
	Glasdegib + LDAC N = 75 n (%)	**LDAC N = 36 n (%)**	**RR [95%-CI]; p-value**	**RD [95%-CI]; p-value**	**Glasdegib + LDAC N = 75 n (%)**	**LDAC N = 36 n (%)**	**RR [95%-CI]; p-value**	**RD [95%-CI]; p-value**
SOC: Nervous system disorders								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
Haemorrhage intracranial	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105
SOC: Renal and urinary disorders								
All PT	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.
Renal failure	0 (0.0)	1 (2.8)	0.16 [0.01; 3.89]; 0.2618	-0.03 [-0.08; 0.03]; 0.3105	0 (0.0)	0 (0.0)	n. e.	n. e.

Abbreviations: AEs = adverse event; CI = Confidence interval; LDAC = Low-dose cytarabine; n. e. = not estimable; PT = preferred term; RD = risk difference; RR = risk ratio; SOC = system organ class
References: (89)

5.4.2.2 Glasdegib + LDAC vs. azacitidine/decitabine

Indirect treatment comparison for AEs for the assessment of glasdegib + LDAC vs. azacitidine and decitabine respectively was not conducted due to substantial differences in reporting of AEs and treatment duration between the three studies.

5.5 Conclusions

Provide a general interpretation of the evidence base considering the benefits associated with the technology relative to those of the comparators.

The indication of glasdegib will be 'in combination with low-dose cytarabine, for the treatment of newly diagnosed de novo or secondary acute myeloid leukaemia (AML) in adult patients who are not candidates for standard induction chemotherapy'. Therefore only the phase 2, randomized, open-label portion of B1371003 - BRIGHT AML 1003 - that assesses the efficacy and safety of glasdegib + LDAC vs. LDAC alone in adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy is relevant for this assessment. Full data on MDS patients are provided in the CSR (83).

Overall survival

Glasdegib + LDAC vs. LDAC

The survival benefit associated with glasdegib + LDAC was both clinically meaningful and statistically significant, as OS was nearly doubled compared to LDAC alone (HR [95 % CI]: 0.46 [0.30, 0.72]; p = 0.0002; median OS: 8.3 months vs. 4.3 months). Sensitivity analyses showed almost identical results in favour of glasdegib + LDAC.

Improvement in OS was also consistent across pre-specified cytogenetic risk subgroups and other demographic and clinical subgroups including age, gender, cytogenetic risk (good/intermediate vs. poor), disease history (de novo vs. secondary AML) and baseline ECOG PS.

In BRIGHT AML 1003, survival probabilities in the glasdegib + LDAC arm were higher than in the LDAC arm at day 30, day 60, month 6 and month 12.

Glasdegib + LDAC vs. azacitidine

The primary standard (Bucher) ITC analysis demonstrated a statistically significant benefit of glasdegib + LDAC compared to azacitidine (HR [95 % CI]: 0.51 [0.31, 0.85]). The results and conclusions of the supportive STC were similar to the primary ITC analysis.

Glasdegib + LDAC vs. decitabine

The primary standard (Bucher) ITC analysis also demonstrated a statistically significant benefit of glasdegib + LDAC compared to decitabine (HR [95 % CI]: 0.57 [0.35, 0.91]). The results and conclusions of the supportive STC were similar to the primary ITC analysis.

Health-related quality of life, assessed as quality of survival

Glasdegib + LDAC vs. LDAC

Q-TWiST was 4.0 ([95 % CI]: [2.1, 5.8]) months longer for glasdegib + LDAC, translating into a statistically significant 75 % relative improvement in quality-adjusted survival compared to LDAC alone, which greatly exceeded the previously established thresholds of ≥ 15 % for being clinically meaningful. This clearly

shows that the added OS was time spent in ‘good’ health (i.e. a significantly longer time without symptoms of disease progression or toxicity), which suggests that the benefits of glasdegib + LDAC vs. LDAC alone outweigh the risks of treatment.

Objective response

Glasdegib + LDAC vs. LDAC

The benefit of glasdegib + LDAC was substantial regarding objective response: Significantly more patients in the glasdegib + LDAC arm achieved CR compared with LDAC alone (RR [95 % CI]: 7.10 [0.89, 56.83]; p = 0.0235; 17.9 % vs. 2.6 %). Sensitivity analyses showed almost identical results.

The glasdegib + LDAC arm also demonstrated a statistically significant better objective response rate assessed as CR + CRi + MLFS when compared to LDAC alone (RR [95 % CI]: 4.94 [1.19, 20.52], p = 0.0080; 26.9 % vs. 5.3 %).

Transfusion need

Glasdegib + LDAC vs. LDAC

In BRIGHT AML 1003, significantly more patients receiving glasdegib + LDAC than patients receiving LDAC alone were transfusion independent for ≥ 8, 12, 16, 20 and 24 weeks (e.g. transfusion independence ≥ 8 weeks: 28.2 % vs. 5.3 %; p = 0.0056). The mean exposure-adjusted transfusion rate per month of treatment was 4.83 in the glasdegib + LDAC arm vs. 8.07 in the LDAC alone arm. Patients with glasdegib + LDAC received transfusions on average over 3.93 days per month of treatment, whereas patients with LDAC alone received transfusions on average over 5.93 days per month of treatment.

Overall efficacy conclusion

Glasdegib + LDAC nearly doubled overall survival of adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy compared to LDAC alone. This improvement, that was both clinically meaningful and statistically significant, was also consistent across demographic and clinical subgroups. Moreover, standard (Bucher) ITC and STC analyses on OS demonstrated statistically significant benefit of glasdegib + LDAC over the HMAs azacitidine and decitabine. The Q-TWiST results further extended the efficacy findings and suggest that most of the OS benefit with glasdegib + LDAC is added time spent in 'good' health’. The OS benefit was further supported by additional clinically meaningful, patient-relevant endpoints such as objective response (including CR, CRi, MLFS) and transfusion independence, especially the latter being correlated with blood count recovery and alleviation of symptoms. At the same time, the independence of transfusions enables patients to spend more time away from the hospital and thus improves health-related quality of life, as patients have more value time spent with family. Moreover, glasdegib + LDAC treatment may offer cost offsets based on increased transfusion independence and reduced transfusion requirements and the resulting decreases in healthcare utilization and costs of acquisition of blood products and administration.

Glasdegib + LDAC is an innovative and effective treatment for adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy. To this currently underserved patient group with limited therapeutic options and an exceptionally high medical need, glasdegib + LDAC offers a realistic prospect of extending the duration and quality of survival.

Provide a general interpretation of the evidence base considering the harms associated with the technology relative to those of the comparators.

Glasdegib + LDAC vs. LDAC

In BRIGHT AML 1003, glasdegib + LDAC treatment was associated with an almost 3 times longer mean duration of treatment than LDAC alone. The substantial longer duration of safety follow-up for patients in the glasdegib + LDAC arm compared to the patients in the LDAC alone arm did not necessarily lead to higher overall rates of AEs for patients receiving glasdegib + LDAC.

To account for imbalances in treatment duration between the glasdegib + LDAC and LDAC alone arms, AEs are presented separately for the first 90 days of therapy. Regarding SAEs and severe AEs (grade 3 - 5), no statistically significant differences between glasdegib + LDAC and LDAC alone occurred, neither for the entire study period nor for the first 90 days of therapy.

The relative risk (RR) was primarily used to make conclusions about the statistical significance of AEs. Risk differences (RD) were presented for sake of completeness.

Considering the first 90 days of therapy, glasdegib + LDAC demonstrated a statistically significant benefit over LDAC alone regarding fatal AEs (16.0 % vs. 36.1 %; RR [95 % CI]: 0.44 [0.23, 0.87], p-value = 0.0184) and numerically fewer treatment discontinuations due to AE (20.0 % vs. 33.3 %; RR [95 % CI]: 0.60 [0.31, 1.15], p-value = 0.1216).

The proportion of patients with at least one AE (any CTCAE grade) is 100 % in every study arm. Considering the first 90 days of treatment, statistically significant more patients receiving glasdegib + LDAC had nervous system disorders (SOC, 50.7 % vs. 19.4 %; RR [95 % CI]: 2.61 [1.29, 5.25]; p-value = 0.0074), which were mostly due mild to moderate dizziness (PT) and dysgeusia (PT).

No statistically significant differences between glasdegib + LDAC and LDAC alone occurred regarding AEs commonly expected for antileukemic treatments febrile neutropenia (entire study period: 34.7 % vs. 25.0 %; first 90 days: 30.7 % vs. 22.2 %), haemorrhage (entire study period: 48.0 % vs. 50.0 %; first 90 days: 36.0 % vs. 47.2 %), QT prolongation (entire study period: 20.0 % vs. 11.1 %; fist 90 days: 13.3 % vs. 11.1 %) and infections (entire study period: 61.3 % vs. 55.6 %; fist 90 days: 52.0 % vs. 52.8 %) including pneumonia (entire study period: 28.0 % vs. 27.8 %; first 90 days: 18.7 % vs. 25.0 %).

Treatment with glasdegib + LDAC was associated with an acceptable safety profile in patients with AML, with little additional toxicity seen with the combination of glasdegib + LDAC versus LDAC alone. Furthermore, the combination is not associated with substantial marrow suppression and attendant cytopenic complications as seen with other therapies in AML.

Glasdegib + LDAC is an innovative and safe treatment for adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy.

5.6 Strengths and limitations

Summarise the internal validity of the evidence base, taking into account the study quality, the validity of the endpoints used as well as the overall level of evidence. Include a statement about the consistency of the results in the evidence base.

The exploration of the internal validity was based on the framework developed by the Cochrane Collaboration to assess the risk of bias for RCT, which was revised in 2019 (104). It consists of 5 domains:

- bias arising from the randomization process;
- bias due to lack of blinding and deviations from intended interventions;
- bias due to missing outcome data;
- bias in measurement of the outcome;
- bias in selection of the reported result.

The domain "bias due to missing outcome data" was explored within the discussion of validity on endpoint-level, whereas the other domains were explored on study- and endpoint-level. The risk-of-bias assessment for each endpoint via the RoB Excel tool provided by the Cochrane Collaboration is presented in Attachment C (105).

Validity of the evidence base

Glasdegib + LDAC vs. LDAC: Direct comparison via BRIGHT AML 1003

In BRIGHT AML 1003, AML patients were centrally randomized at a ratio of 2:1 to receive either glasdegib + LDAC or LDAC alone. Randomization was stratified by cytogenetic risk factor (good/intermediate vs. poor). The randomization scheme and codes were provided in the appendix of the CSR. Thus, the generation of the allocation sequence was adequate. An IVRS was used as a central mechanism to assign patients to study treatment, ensuring adequate allocation concealment. The baseline differences between the intervention groups do not suggest a problem with the randomization process, so, the risk of bias is considered low regarding the randomization process.

Patients and investigators were not blinded during the trial. There is no indication that there are deviations from the intended interventions due to the open-label design. The potential for a substantial impact on the results due to open label is assumed to be minor, especially for the objectively measured endpoints like OS and CR.

Outcome reporting was objective. All outcomes were analysed and reported in accordance to a priori protocols. Furthermore, established and patient-relevant outcomes for AML were used for benefit and risk assessment.

No other aspects which could potentially increase the risk of bias were identified. Therefore, based on the randomized controlled design of the BRIGHT AML 1003 trial, the risk of bias on study level is considered low.

Glasdegib + LDAC vs. azacitidine and decitabine: Indirect comparisons via BRIGHT AML 1003 AML, AZA-AML-001 and DACO-016

In the AZA-AML-001 trial, a central, stratified, and permuted block randomization method and IVRS were used to randomly assign patients 1:1 to receive azacitidine or conventional care regimen. Randomization was stratified by preselected conventional care regimen (BSC, LDAC, or intensive chemotherapy), ECOG PS (0-1 or 2), and cytogenetic risk (intermediate or poor). There is no indication of bias arising from the randomization process.

In the DACO-016 trial, patients were randomly assigned 1:1 to receive decitabine or treatment choice by using a stratified permuted block method. Random assignment was stratified by age, cytogenetic risk, and ECOG PS. There is no indication of bias arising from the randomization process.

In AZA-AML-001 and DACO-016, patients and investigators were not blinded during the trial. Like for BRIGHT AML 1003, the potential for a substantial impact on the results due to the open label design is assumed to be minor, especially for the objectively measured endpoints like OS and CR. There is no indication that there are deviations from the intended interventions due to the open-label design.

Due to the limited information given in the publications of Dombret 2015 and Kantarjian 2012, no reliable conclusions could be drawn regarding missing values and selective outcome reporting. Established and patient-relevant outcomes for AML were used for benefit and risk assessment, so there was no indication of bias arising from missing values and selective outcome reporting.

No other aspects which could potentially increase the risk of bias were identified. Therefore, based on the randomized controlled design, the risk of bias on study level and especially for the endpoint OS is considered low for both the AZA-AML-001 and DACO-016 trials.

The comparability of the BRIGHT AML 1003, AZA-AML-001 and DACO-016 was discussed in detail in sections 5.3 and 5.4: Overall, BRIGHT AML 1003 and AZA-AML-001 as well as BRIGHT AML 1003 and DACO-016 showed sufficient similarity regarding analysis population, study treatment, outcome and study design to conduct a valid indirect treatment comparison for OS. The risk of bias for the indirect comparisons was considered low.

Validity of the endpoints

Overall survival (OS)

The validity of the endpoint OS is given by the clear and objective definition: OS is defined as time from the date of randomization to the date of death from any cause.

All randomized patients were included in the analyses of OS in BRIGHT 1003, AZA-AML-001 and DACO-16. In BRIGHT AML 1003, OS was analysed and reported in accordance to the a priori protocol, for AZA-AML-001 and DACO-16 there is too little information to assess the potential of selective outcome reporting. Although all participants and investigators were aware of their assigned treatment, the risk of bias is considered low as OS is a highly objectively measured endpoint (see also Attachment C; (105)). ENREF 105

Quality of Survival

Q-TWiST (Quality-adjusted Time Without Symptoms of Disease Progression or Toxicity) analysis represents a quality-adjusted life years (QALY) metric, with explicit definitions of the discrete health states in cancer therapy: toxicity, defined as AEs grade ≥ 3 prior to progression; time without symptoms of disease progression or toxicity, and relapse, defined as treatment discontinuation due to insufficient clinical response or death (106, 107).

All randomized AML patients were included in the analyses of quality of survival, there was no selective reporting. The participants and investigators were aware of their assigned treatment, but the potential for a substantial impact on the results due to open label is assumed to be minor as the analysis of quality of survival is based on objectively measured endpoints. This analysis was done ad hoc, but as this approach highly reflected the patient relevance and the same procedures were used in both treatment arms, no risk of bias arose.

Objective response

In BRIGHT AML 1003 the evaluation and classification of objective response was performed in accordance with the recommendations of the "International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukaemia", which are nationally and internationally recognized recommendations for the collection of these parameters (100). The primary analysis for the objective response outcomes is based on the reportings of the investigator. Sensitivity analyses, where the objective response outcomes were derived by sponsor, showed identical results.

All randomized AML patients were included in the analyses of the objective response criteria CR, CRi and MLFS in BRIGHT 1003. The participants and investigators were aware of their assigned treatment, but the potential for a substantial impact on the results due to open label is assumed to be minor as objective response is an objectively measured endpoint. The objective response criteria were analysed and reported in accordance to the a priori protocol, there was no selective reporting. Missing outcome data was an issue in the evaluation of objective response criteria. 30.8 % of patients in the glasdegib + LDAC arm and 42.1 % of patients in the LDAC alone arm were not evaluable for these criteria. The majority of these patients were not evaluable due to AEs or patient death prior to on-study bone marrow sampling. It is not unexpected that when a patient with AML is experiencing disease progression or complications of AML, a potentially painful and invasive procedure like a scheduled bone marrow biopsy to document disease progression is often not performed. All non-evaluable patients were included in the denominator when calculating response rates and were counted as “non-responders”. Due to this conservative, medically justified imputation of missing values, the potential impact on the analysis of response rates is considered low.

Transfusions

In BRIGHT AML 1003, administration of blood products should be consistent with institutional guidelines. The following were suggested for patients enrolled:

- Red blood cell and platelet transfusions may be utilized throughout the study as clinically indicated.
- The haemoglobin should be maintained at a safe level (e.g., haemoglobin >8-10 g/dL), especially in severely thrombocytopenic patients or those with co-morbid diseases.
- Efforts should be made to maintain the platelet counts above 10 $x10^9$/L in asymptomatic patients. In the presence of fever or hypertension, platelet transfusion to 20 $x10^9$/L is recommended. In the presence of active haemorrhage or suspected gastrointestinal bleeding, platelet transfusion to a minimum count of 50 $x10^9$/L is recommended.

Due to the well-defined criteria for the administration of transfusion, endpoints describing the transfusion need is considered valid.

All randomized AML patients were included in the analyses of transfusion independence and transfusion rates, there was no selective reporting. The participants and investigators were aware of their assigned treatment, but the potential for a substantial impact on the results due to open label is assumed to be minor as transfusion independence and transfusion rates are objectively measured endpoints. The definition of transfusion differs from the a priori protocol, because all types of transfusions were taken into consideration. As this approach reflected the patient relevance and the same criteria were used in both treatment arms, no risk of bias arose.

Adverse Events

For all AEs, the investigator had to pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it met the criteria for classification as serious. Additionally, the investigator was required to assess causality. The safety analysis was performed separately for each treatment group

using MedDRA (version 19.1) in accordance with good clinical practice (GCP). The classification of severity was performed according to CTCAE version 4.0. The presentation according to standardized MedDRA terminology complies with international standards and is therefore considered valid.

All randomized AML patients who received at least one dose of any of the study medications were included in the analyses of AEs in BRIGHT AML 1003. AEs were analysed and reported in accordance to the a priori protocol, there was no selective outcome reporting. The participants and investigators were aware of the assigned treatment, so there were some concerns regarding the risk of bias due to open-label. In BRIGHT AML 1003, glasdegib + LDAC treatment was associated with an almost 3 times longer mean duration of treatment than LDAC alone leading to a substantial longer duration of safety follow-up for patients in the glasdegib + LDAC arm compared to the patients in the LDAC alone arm and thus, causing potential bias in the analyses of AEs to the disadvantage of glasdegib + LDAC. To account for imbalances in treatment duration between the glasdegib + LDAC and LDAC alone arms, AEs are also presented separately for the first 90 days of therapy.

Consistency of results

The substantial improvement in OS in patients receiving glasdegib + LDAC compared to patients receiving LDAC alone was consistent across demographic and clinical subgroups. This benefit was also demonstrated by other clinically meaningful, patient-relevant endpoints such as objective response (including CR, CRi, MLFS) and transfusion independence.

Strengths and limitations

In summary, the following strengths and limitations of the evidence base have been identified:

Strengths of the evidence base

- Glasdegib + LDAC vs. LDAC: Direct comparison via BRIGHT AML 1003
    - The assessment of efficacy and safety for glasdegib + LDAC compared to LDAC alone was based on RCT of the highest evidence level.
    - BRIGHT AML 1003 covered directly the PICO criteria of this assessment.
    - BRIGHT AML 1003 had a low risk of bias.
    - The duration of follow-up was adequate to gain reliable (i.e. mature) results for OS.
- Glasdegib + LDAC vs. azacitidine and decitabine: Indirect comparison of OS via BRIGHT AML 1003, AZA-AML-001 and DACO-016
    - The indirect comparison for OS is based on RCT of the highest evidence level with low risk of bias.
    - The studies showed sufficient similarity regarding analysis population, study treatment, outcome and study design to conduct valid indirect treatment comparisons for OS.
    - Results are consistent across the different approaches for indirect comparisons (standard ITC, multivariate ITC, stepwise STC or full STC), regardless of the adjustment for baseline differences between trials.

Limitations of the evidence base

- Glasdegib + LDAC vs. LDAC: Direct comparison via BRIGHT AML 1003

- As expected for a rare disease, the sample size was relatively low (N = 78 for glasdegib + LDAC and N = 38 for LDAC alone).
- The open label design may cause potential bias. However, the impact on results due to the open label design is assumed to be minor, especially for the objectively measured endpoints like OS and objective response.
- No patient reported outcomes were proactively collected via PRO tools. However, a Q-TWiST analysis was used to assess the quality of survival.

- Glasdegib + LDAC vs. azacitidine and decitabine: Indirect comparison of OS via BRIGHT AML 1003, AZA-AML-001 and DACO-016
  - Regarding OS, to date, no direct comparison is available for glasdegib + LDAC vs. azacitidine or glasdegib + LDAC vs. decitabine
  - For OS, the common comparator comprised BSC + LDAC in DACO-016 but LDAC alone in BRIGHT AML 1003.

Provide a brief statement of the relevance of the evidence base to the scope of the assessment.

The results of BRIGHT AML 1003 demonstrate the significant clinical benefit of glasdegib. The bias potential of study BRIGHT AML 1003 is classified as low (see section 5.6).

The study population included adult patients newly diagnosed with AML who are not candidates for standard induction chemotherapy. This corresponds to the target population of glasdegib according to the proposed label indication and is transferable to the European health care context with regard to both general patient characteristics and disease-specific criteria (see section 5.2).

The clinical effectiveness and safety of glasdegib + LDAC was compared to LDAC alone, azacitidine and decitabine, which represent the current reference treatment according to high-quality European clinical practice guidelines. As there is no direct OS evidence available comparing glasdegib + LDAC vs. azacitidine or decitabine, the current submission has presented an indirect comparison of OS in the form of a standard (Bucher) ITC as the primary analysis and a STC as a supportive analysis.

All endpoints used for the presentation of efficacy and safety in this assessment are patient-relevant (see sections 5.3 - 5.4). The endpoints were collected using valid instruments and analysed using adequate methods.

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7 Appendices

Appendix A AML Classification according to WHO

A total of 9 balanced cytogenetic changes are listed as separate entities, including AML with translocations and inversions: AML with *NPM1* (nucleophosmin) mutation, AML with biallelic mutations of the transcription factor CEBPA (CCAAT/enhancer binding protein alpha), and acute promyelocytic leukaemia (APL) with the fusion gene PML-RARA. In addition, two molecular genetic entities were included in the classification: AML with the fusion gene *BCR-ABL1* and AML with mutation of the transcription factor *RUNX1* (Runt-related Transcription Factor 1) (14)

Table 37: WHO classification of AML and related neoplasms

WHO Classification
AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1* AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* APL with t(15;17)(q22;q12); *PML-RARA* AML with t(9;11)(p22;q23); *MLLT3-KMT2A* AML with t(6;9)(p23;q34); *DEK-NUP214* AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1* *Provisional entity: AML with BCR-ABL1* AML with mutated *NPM1* AML with biallelic mutation of *CEBPA* *Provisional entity: AML with mutated RUNX1*
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, not otherwise specified
AML with minimal differentiation AML without maturation AML with maturation Acute myelomonocytic leukaemia Acute monoblastic/monocytic leukaemia Pure erythroid leukaemia Acute megakaryoblastic leukaemia Acute basophilic leukaemia Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis Myeloid leukaemia associated with Down syndrome
Reference (14) AML = acute myeloid leukaemia; APL = acute promyelocytic leukaemia; *BCR-ABL1* = B-cell-receptor and tyrosinkinase ABL1 (fusiongen); *CBFB-MYH11* = core binding factor subunit beta and myosin-11 (fusiongen); *CEBPA* = CCAAT/enhancer-binding protein alpha (gene); *DEK-NUP214* = DEK-oncogene and nucleoporin 214 (fusiongen); inv() = inversion; MECOM = MDS1 and EVI1 complex locus (Gen); *MLLT3-KMT2A* = myeloid/lymphoid or mixed-lineage leukaemia translocated to chromosome 3 protein and histone-lysine N-methyltransferase 2A (fusiongen); *NPM1* = nucleophosmin (gene); p = short arm of chromosome; *PML-RARA* = promyelocytic leukaemia and retinoic acid receptor alpha (fusiongen); q = long arm of chromosome; *RBM15-MKL1* = Putative RNA-binding protein 15 and megakaryoblastic leukaemia 1 (fusiongen); *RUNX1* = runt-related transcription factor 1 (Gen); *RUNX1-RUNX1T1* = RUNX1 and RUNX1 translocation partner 1 (fusiongen); t() = translocation; WHO = World Health Organisation

Appendix B Search Strategy

B.1 Literature searches

Table 38: MEDLINE® Search for Glasdegib via Ovid (searched on 17th January 2020)

Database name	Ovid MEDLINE® and Epub Ahead of Print , In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1946 to January 16, 2020
Search filter	(108)

#	Searches	Results
1	Glasdegib.mp.	46
2	Daurismo.mp.	1
3	(PF-04449913 or PF04449913 or PF 04449913 or PF-4449913 or PF4449913 or PF 4449913 or PF-913 or PF913 or PF 913).mp.	22
4	(1095173-27-5 or 1095173-64-0).rn.	0
5	(1095173-27-5 or 1095173-64-0).mp.	1
6	1 or 2 or 3 or 4 or 5	57
7	randomi#ed controlled trial.pt.[5]	498866
8	randomi#ed.mp.5	856721
9	placebo.mp.	211104
10	7 or 8 or 9	914748
11	6 and 10	11

Table 39: Embase Search for Glasdegib via Ovid (searched on 17th January 2020)

Database name	Excerpta Medica database (Embase), EMBASE Classic + Embase
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1947 to 2020 January 16
Search filter	(108)

#	Searches	Results
1	exp Glasdegib/	200
2	Glasdegib.mp.	209
3	Daurismo.mp.	7
4	exp PF-04449913	200
5	(PF-04449913 or PF04449913 or PF 04449913 or PF-4449913 or PF4449913 or PF 4449913 or PF-913 or PF913 or PF 913).mp.	185
6	(1095173-27-5 or 1095173-64-0).rn.	179
7	(1095173-27-5 or 1095173-64-0).mp.	0
8	1 or 2 or 3 or 4 or 5 or 6 or 7	303
9	random*.tw.	1507106
10	placebo*.mp.	458106
11	double-blind*.tw.	211030
12	9 or 10 or 11	1772554
13	8 and 12	65

[5] The RCT-Filter according to Wong et al. was adapted in steps 7 and 8 („randomi#ed“ instead of „randomized“) to identify results with English and American spelling.

Table 40: Cochrane Central Register of Controlled Trials Search for Glasdegib (searched on 17th January 2020)

Database name	Cochrane Central Register of Controlled Trials
Search interface	Ovid http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1991 to December 2019
Search filter	NA

#	Searches	Results
1	Glasdegib.mp.	44
2	Daurismo.mp.	1
3	(PF-04449913 or PF04449913 or PF 04449913 or PF-4449913 or PF4449913 or PF 4449913 or PF-913 or PF913 or PF 913).mp.	24
4	(1095173-27-5 or 1095173-64-0).mp.	0
5	1 or 2 or 3 or 4	48

Table 41: MEDLINE® Search for decitabine via Ovid (searched on 17th January 2020)

Database name	Ovid MEDLINE® and Epub Ahead of Print , In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1946 to January 16, 2020
Search filter	(108)

#	Searches	Results
1	exp Leukaemia, Myeloid, Acute/	54135
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	54852
3	(leuk?emia? adj1 myeloid adj1 acute).mp	54863
4	(AML or AMLs).mp.	31257
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	13382
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	13373
7	1 or 2 or 3 or 4 or 5 or 6	79045
8	Decitabine.mp	3962
9	exp Decitabine/	3252
10	Dacogen.mp	40
11	2-deoxy-5-azacytidine.mp	59
12	5-aza-2-deoxycytidine.mp	3615
13	5-azadeoxycytidine.mp	114
14	5-deoxyazacytidine.mp	9
15	(Nsc127716 or Nsc-127716 or Nsc 127716).mp	6
16	(JNJ-30979754 or JNJ30979754 or JNJ 30979754).mp	0
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	5894
18	randomi#ed controlled trial.pt.[6]	498866
19	randomi#ed.mp.	856721
20	placebo.mp.	211104
21	18 or 19 or 20	914748
22	7 and 17 and 21	70

[6] The RCT-Filter according to Wong et al. was adapted in steps 18 and 19 („randomi#ed“ instead of „randomized“) to identify results with English and American spelling.

Table 42: Embase Search for decitabine via Ovid (searched on 17th January 2020)

Database name	Excerpta Medica database (Embase), EMBASE Classic + Embase
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1947 to 2020 January 16
Search filter	(108)

#	Searches	Results
1	exp acute myeloid leukaemia/	39367
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	62092
3	(leuk?emia? adj1 myeloid adj1 acute).mp.	62099
4	(AML or AMLs).mp.	62509
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	75935
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	75933
7	1 or 2 or 3 or 4 or 5 or 6	133016
8	Exp Decitabine	4111
9	Decitabine.mp	6138
10	Dacogen.mp	475
11	2-deoxy-5-azacytidine.mp	82
12	5-aza-2-deoxycytidine.mp	9461
13	5-azadeoxycytidine.mp	144
14	5-deoxyazacytidine.mp	11
15	(Nsc127716 or Nsc-127716 or Nsc 127716).mp	13
16	(JNJ-30979754 or JNJ30979754 or JNJ 30979754).mp	0
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	12923
18	random*.tw.	1507106
19	placebo*.mp.	458106
20	double-blind*.tw.	211030
21	18 or 19 or 20	1772554
22	7 and 17 and 21	383

Table 43: Cochrane Central Register of Controlled Trials Search for decitabine (searched on 17th January 2020)

Database name	Cochrane Central Register of Controlled Trials
Search interface	Ovid http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1991 to December 2019
Search filter	NA

#	Searches	Results
1	exp Leukaemia, Myeloid, Acute/	1393
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	4065
3	(leuk?emia? adj1 myeloid adj1 acute).mp.	4064
4	(AML or AMLs).mp.	3821
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	1361
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	1364
7	1 or 2 or 3 or 4 or 5 or 6	5781
8	Decitabine.mp	408
9	Dacogen.mp	22
10	2-deoxy-5-azacytidine.mp	1
11	5-aza-2-deoxycytidine.mp	48
12	5-azadeoxycytidine.mp	0
13	5-deoxyazacytidine.mp	0
14	(Nsc127716 or Nsc-127716 or Nsc 127716).mp	0
15	(JNJ-30979754 or JNJ30979754 or JNJ 30979754).mp	1
16	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	414
17	7 and 16	268

Table 44: MEDLINE® Search for azacitidine via Ovid (searched on 17th January 2020)

Database name	Ovid MEDLINE® and Epub Ahead of Print , In-Process & Other Non-Indexed Citations, Daily and Versions(R)
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1946 to January 16, 2020
Search filter	(108)

#	Searches	Results
1	exp Leukaemia, Myeloid, Acute/	54135
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	54852
3	(leuk?emia? adj1 myeloid adj1 acute).mp	54863
4	(AML or AMLs).mp.	31257
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	13382
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	13373
7	1 or 2 or 3 or 4 or 5 or 6	19045
8	exp Azacitidine/	6715
9	azacytidine.mp	3396
10	vidaza.mp	63
11	azacitidine.mp	7050
12	5-azacytidine.mp	3066
13	5-azacitidine.mp.	186
14	ladakamycin.mp	1
15	(Nsc-102816 or Nsc102816 or Nsc 102816).mp	20
16	320-67-2.mp	1
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	8493
18	randomi#ed controlled trial.pt.[7]	498866
19	randomi#ed.mp.	856721
20	placebo.mp.	211104
21	18 or 19 or 20	914748
22	7 and 17 and 21	135

Table 45: Embase Search for azacitidine via Ovid (searched on 17th January 2020)

Database name	Excerpta Medica database (Embase), EMBASE Classic + Embase
Search interface	Ovid, Advanced search http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1947 to 2020 January 16
Search filter	(108)

#	Searches	Results
1	exp acute myeloid leukaemia/	39367
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	62092
3	(leuk?emia? adj1 myeloid adj1 acute).mp.	62099
4	(AML or AMLs).mp.	62509
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	75935
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	75933
7	1 or 2 or 3 or 4 or 5 or 6	133016
8	azacytidine.mp	5250
9	Vidaza.mp	718
10	Exp azacitidine	13531

[7] The RCT-Filter according to Wong et al. was adapted in steps 18 and 19 („randomi#ed“ instead of „randomized“) to identify results with English and American spelling.

#	Searches	Results
11	Azacitidine.mp	13705
12	5-azacytidine.mp	4355
13	5-azacitidine.mp.	606
14	ladakamycin	2
15	(Nsc-102816 or Nsc102816 or Nsc 102816).mp	46
16	320-67-2.mp	1
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	14581
18	random*.tw.	1507106
19	random*.tw.	1507106
20	double-blind*.tw.	211030
21	18 or 19 or 20	1560168
22	7 and 17 and 21	484

Table 46: Cochrane Central Register of Controlled Trials Search for azacitidine (searched on 17th January 2020)

Database name	Cochrane Central Register of Controlled Trials
Search interface	Ovid http://ovidsp.ovid.com/
Search date	17th January 2020
Period covered	1991 to December 2019
Search filter	NA

#	Searches	Results
1	exp Leukaemia, Myeloid, Acute/	1393
2	(acute adj1 myeloid adj1 leuk?emia?).mp.	4065
3	(leuk?emia? adj1 myeloid adj1 acute).mp.	4064
4	(AML or AMLs).mp.	3849
5	(acute adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 leuk?emia?).mp	1419
6	(leuk?emia? adj1 (myeloblastic or myelocytic or myelogenous or nonlymphoblastic or non lymphoblastic or non-lymphoblastic or nonlymphocytic or non lymphocytic or non-lymphocytic or granulocytic) adj1 acute).mp.	1420
7	1 or 2 or 3 or 4 or 5 or 6	5825
8	exp Azacitidine/	253
9	Azacytidine.mp	111
10	vidaza.mp	58
11	azacitidine.mp	685
12	5-azacytidine.mp	64
13	5-azacitidine.mp.	44
14	ladakamycin.mp	0
15	(Nsc-102816 or Nsc102816 or Nsc 102816).mp	2
16	320-67-2.mp	29
17	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	739
18	7 and 17	464

B.2 Study registries

Table 47: Clinical Trials (US) Search for glasdegib (https://clinicaltrials.gov) as searched on 17th January 2020

Database name	US National Institutes of Health (NIH) Ongoing Trials Register
Search interface	https://clinicaltrials.gov/ct2/search/advanced
Search date	17th January 2020

Searches	Results
AML or acute myeloid leukaemia or acute myeloid leukaemia [condition or disease] Glasdegib OR Daurismo OR PF-04449913 OR PF04449913 OR PF 04449913 OR PF-4449913 OR PF4449913 OR PF 4449913 OR PF-913 OR PF913 OR PF 913 [intervention]	11

Table 48: Clinical Trials (EU) Search for glasdegib (https://clinicaltrialsregister.eu) as searched on 17th January 2020

Database name	European Union Clinical Trials Register (EU CTR)
Search interface	https://www.clinicaltrialsregister.eu/ctr-search/search
Search date	17th January 2020

Searches	Results
Glasdegib OR daurismo OR PF-04449913 OR PF04449913 OR "PF 04449913" OR PF-4449913 OR PF4449913 OR "PF 4449913" OR PF-913 OR PF913 OR "PF 913"	7

Table 49: The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for glasdegib as searched on 17th January 2020

Database name	ICTRP Search Portal (WHO) (ICTRP)
Search interface	http://apps.who.int/trialsearch/AdvSearch.aspx
Search date	17th January 2020

Searches	Results
AML or acute myeloid leukaemia or acute myeloid leukaemia [condition] AND Glasdegib OR Daurismo OR PF-04449913 OR PF04449913 OR PF 04449913 OR PF-4449913 OR PF4449913 OR PF 4449913 OR PF-913 OR PF913 OR PF 913 [intervention] Recruitment status is ALL and Phases are All	26 records for 12 trials found

Table 50: Clinical Trials (US) Search for decitabine (https://clinicaltrials.gov) as searched on 17th January 2020

Database name	US National Institutes of Health (NIH) Ongoing Trials Register
Search interface	https://clinicaltrials.gov/ct2/search/advanced
Search date	17th January 2020

Searches	Results
AML or acute myeloid leukaemia or acute myeloid leukaemia [condition or disease] and decitabine OR dacogen OR 2'-deoxy-5-azacytidine OR 5-aza-2'-deoxycytidine OR 5-azadeoxycytidine OR 5-deoxyazacytidine OR nsc-127716 OR nsc127716 OR nsc 127716 OR JNJ-30979754 OR JNJ30979754 OR JNJ 30979754 [intervention]	170

Table 51: Clinical Trials (EU) Search for decitabine (https://clinicaltrialsregister.eu) as searched on 17th January 2020

Database name	European Union Clinical Trials Register (EU CTR)
Search interface	https://www.clinicaltrialsregister.eu/ctr-search/search
Search date	17th January 2020

Searches	Results
decitabine OR 2'-deoxy-5-azacytidine OR 5-aza-2'-deoxycytidine OR 5-azadeoxycytidine OR 5-deoxyazacytidine OR nsc-127716 OR nsc127716 OR "nsc 127716" OR JNJ-30979754 OR JNJ30979754 OR "JNJ 30979754"	61

Table 52: The World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for decitabine as searched on 17th January 2020

Database name	ICTRP Search Portal (WHO) (ICTRP)
Search interface	http://apps.who.int/trialsearch/AdvSearch.aspx
Search date	17th January 2020

Searches	Results
AML or acute myeloid leukaemia or acute myeloid leukaemia [condition] AND decitabine OR dacogen OR 5-aza-2-deoxycytidine OR nsc-127716 OR nsc127716 OR nsc 127716 OR JNJ-30979754 OR JNJ30979754 OR JNJ 30979754 [intervention] Recruitment status is ALL and Phases are ALL	295 records for 203 trials found

Table 53: Clinical Trials (US) Search for azacitidine (https://clinicaltrials.gov) as searched on 17th January 2020

Database name	US National Institutes of Health (NIH) Ongoing Trials Register
Search interface	https://clinicaltrials.gov/ct2/search/advanced
Search date	17th January 2020

Searches	Results
AML OR acute myeloid leukaemia OR acute myeloid leukaemia [condition or disease] | azacytidine OR vidaza OR azacitidine OR 5-azacytidine OR ladakamycin OR 320-67-2 OR nsc-102816 OR nsc102816 OR nsc 102816 [intervention]	227

Table 54: Clinical Trials (EU) Search for azacitidine (https://clinicaltrialsregister.eu) as searched on 17th January 2020

Database name	European Union Clinical Trials Register (EU CTR)
Search interface	https://www.clinicaltrialsregister.eu/ctr-search/search
Search date	17th January 2020

Searches	Results
azacytidine OR vidaza OR azacitidine OR 5-azacytidine OR ladakamycin OR 320-67-2 OR "nsc 102816" OR nsc-102816 OR nsc102816	136

Table 55: The World Health Organization for azacitidine (WHO) International Clinical Trials Registry Platform (ICTRP) as searched on 17th January 2020

Database name	ICTRP Search Portal (WHO) (ICTRP)
Search interface	http://apps.who.int/trialsearch/AdvSearch.aspx
Search date	17th January 2020

Searches	Results
AML OR acute myeloid leukaemia OR acute myeloid leukaemia [condition] AND azacytidine OR vidaza OR azacitidine OR 5-azacytidine OR ladakamycin OR 320-67-2 OR nsc-102816 OR nsc102816 OR nsc 102816 [intervention] Recruitment status is ALL and Phases are ALL	383 records for 220 trials found

Appendix C Simulated treatment comparison: Methodological principles and rationales for the variable and model selections

Since no direct evidence of glasdegib + LDAC vs. the comparators azacitidine or decitabine is available, indirect comparisons were conducted to evaluate the relative efficacy of glasdegib + LDAC vs. azacitidine and glasdegib + LDAC vs. decitabine.

The methodological principles and the OS results for the indirect comparisons of glasdegib + LDAC vs. azacitidine and vs. decitabine have been published by Tremblay 2019 (91).

Indirect analyses using a Bayesian NMA (Network Meta Analysis) do not provide additional information regarding the relative efficacy of glasdegib + LDAC vs. azacitidine and decitabine compared to the classical ITC (Bucher) approach or STC. In this case, the network is quite simple, so the point estimates would differ only marginally and different conclusions from NMA are not expected. Bayesian NMAs is expected to provide more information in the presence of mixed evidence, informative priors, or complex networks. As none of these conditions are met here, using the frequentist approach allows a comprehensive assessment of glasdegib + LDAC vs. the comparators.

C.1 Methodological aspects on STC

While the standard (Bucher) ITC approach compares aggregate trial data, STC adjusts for covariates within the available individual patient data (IPD) (93, 109). For this assessment, IPD were extracted from the BRIGHT AML 1003 trial for glasdegib + LDAC vs. LDAC alone for adult patients with previously untreated AML. Two different STCs, glasdegib + LDAC vs. azacitidine and glasdegib + LDAC vs. decitabine, were performed to provide population-specific estimates of OS.

STCs were performed following general guidance published by the DSU of the NICE (93). Justification for STC, as discussed by the DSU, requires the presence of within-trial effect modification and different distributions of effect modifiers across studies. In this context, effect modifiers are defined as covariates that modify the effect of treatment, so that estimates of treatment efficacy vary across strata of the effect modifier. Additionally, the DSU encourages adjustment for additional effect modifiers and prognostic factors (affecting survival outcomes directly) to produce more precise estimates of relative treatment effects. These effect modifiers and prognostic variables can be identified in the IPD, relevant disease literature, and by clinician expertise. Rationales for the selection of the covariates incorporated into the STCs are listed in detail within the presentation of the results.

An overview of the multi-stepped criteria to conduct and evaluate STCs is given in Figure 20. First, exploration of parametric models (including proportional and non-proportional hazards models) was conducted to determine the optimal modelling of efficacy for glasdegib + LDAC vs. LDAC. Variable selection to develop the optimal models explored mutually available covariates first between the glasdegib + LDAC IPD and the azacitidine trial, and second between the same glasdegib + LDAC IPD and the decitabine trial. After including key covariates as described in criterion 1 (Figure 20), the resultant fit statistics (criterion 2), graphs of the survival curves (criterion 3) and survival estimates (criterion 4) glasdegib + LDAC vs. LDAC were compared between models for comparability and predictive ability using the unadjusted Cox regression and Kaplan-Meier estimates as references. These unadjusted analyses replicated intent-to-treat protocol estimates. Once an optimal model was selected from the glasdegib + LDAC trial with IPD, the published mean (aggregate) covariate values from each of the comparator study populations were substituted into that model. Covariate adjustment of the optimal models allowed estimation of efficacy between glasdegib + LDAC vs. LDAC in each of the comparator (azacitidine or decitabine) populations. Visual inspection (criterion 3) and prediction validation (criterion 4)

were repeated for the covariate-adjusted results. New, adjusted OS HRs estimating glasdegib + LDAC were obtained for each of the comparator populations azacitidine and decitabine. These OS HRs with simulated azacitidine or decitabine populations were compared against adjusted Cox models, which included the same set of covariates. As a last step in STC, the new, covariate-adjusted HRs for OS were entered into ITC against the published HRs for azacitidine vs. LDAC, and decitabine vs. LDAC. These final standard ITCs separately estimated indirect OS HRs for glasdegib + LDAC vs. azacitidine and glasdegib + LDAC vs. decitabine. All standard ITCs utilized the Bucher method with 95 % CIs.

Tremblay et al. 2019 also presented another STC approach using propensity-weighted data for within-trial mean cytogenetic risk. As this initial step was not specified in the DSU, results from the STC approach using propensity-weighted data was also presented.

All analyses were performed using Microsoft Excel 2016 and Stata (version 15.1; StataCorp LLC, College Station, TX, USA).

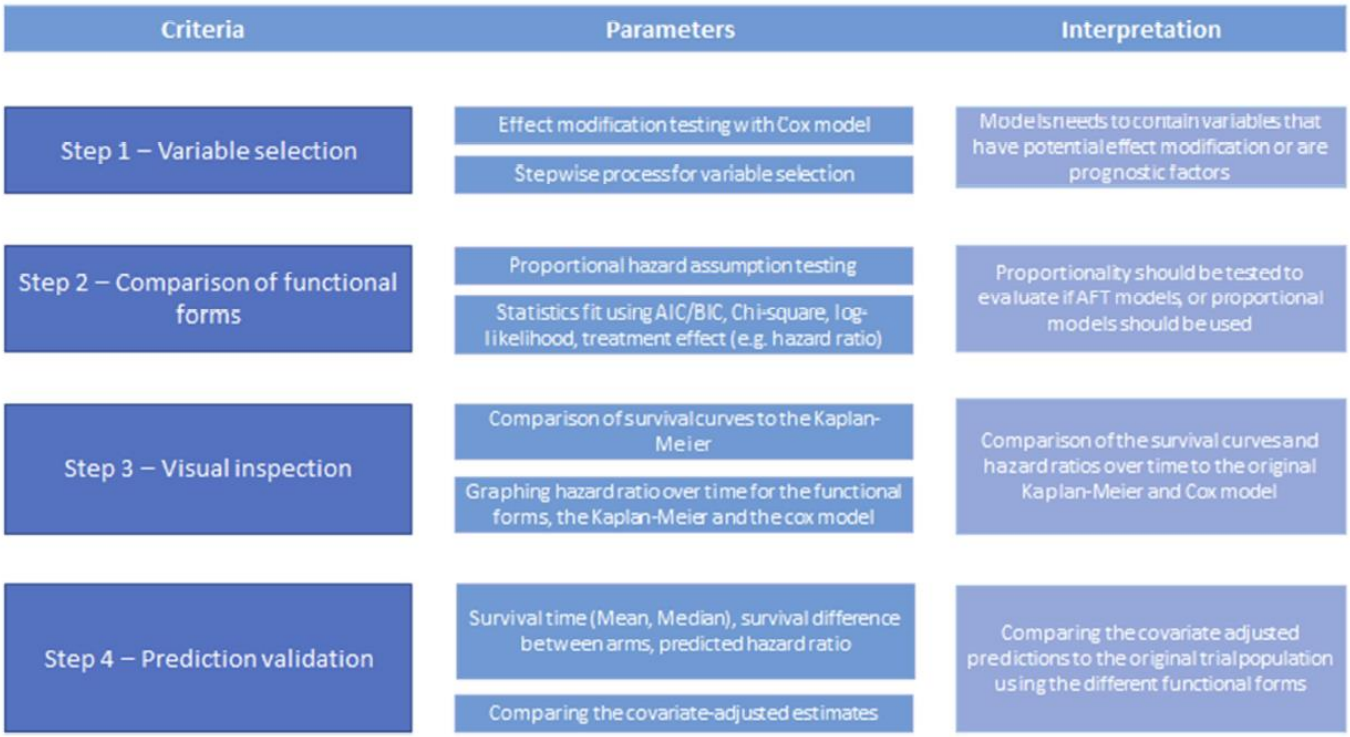

Figure 20: Multi-stepped criteria to conduct and evaluate STCs
Abbreviations: AFT = accelerated failure time; AIC = Akaike's information criterion; BIC = Bayesian information criterion.

Reference: (91)

Variable selection (criterion 1)

The full covariate models comprised all baseline variables available for both BRIGHT AML 1003 and AZA-AML-001 or BRIGHT AML 1003 and DACO-016, respectively. Based on DSU guidance, exploration was repeated with reduced models (designated as stepwise models), including variables that met at least one "stepwise" criterion: the presence of a statistically significant covariate from both the full and reduced models, identification as an effect modifier in at least one of the trials, or being retained as a stratification factor (e.g. cytogenetic risk factor) from the original three trials. Of note, the set of stepwise variables could be different for glasdegib + LDAC vs. azacitidine and glasdegib + LDAC vs. decitabine comparisons, based on each trial's design and reporting of results. Rationales for the selection of the covariates incorporated into the stepwise models are listed in detail within the presentation of the results.

Model exploration and comparison of functional forms (criterion 2)

Tremblay et al. explored six different model techniques to estimate treatment effects of glasdegib + LDAC vs. LDAC: parametric modelling of proportional hazards (PHs; exponential, Weibull, Gompertz) and nonproportional, accelerated failure time (AFT) models (loglogistic, lognormal, gamma). Both a stepwise and a full model were explored based on each of these six model techniques. To obtain HRs at the median OS (duration) for the AFT models, the hazard rates within each trial arm were constructed from the difference in the natural log of the survival between each month. These hazard rates were then summed and divided between trial arms to obtain the HR for each month. In addition, Cox regression models were evaluated.

Appropriate use of Cox regression modelling was tested by visual assessment of the log-cumulative hazard plots, as well as the Schoenfeld global test of proportionality. Model fit statistics, including Akaike's information criterion (AIC), Bayesian information criterion (BIC), the loglikelihood, and chi-square, were compared between all models, to inform of optimal stepwise and full adjustments. Results for the Schoenfeld test are included within the presentation of the results.

Visual inspection and prediction validation (criteria 3 and 4)

In order to assess the comparability of each model's predictive ability, continuous survival outcomes were estimated with each of the six models, which were compared with original KM estimates for glasdegib + LDAC vs. LDAC. Post-regression predictions in Stata were performed to estimate average survival (proportion alive), median OS (months) and extended mean OS (months) for both glasdegib + LDAC and LDAC alone. Additionally, OS HRs derived from Cox unadjusted and fully adjusted multivariate models were compared against OS HRs estimated from the three PH and three AFT models. Survival curves graphed separately for glasdegib + LDAC and LDAC arms were visually compared with the original trial's (unadjusted) KM curves. To further evaluate visual evidence for selecting the optimal model, each model's HR, including the proportional models producing static HRs, was plotted over 20 months (maximum duration of survival in the LDAC treatment group). While an exact match of adjusted and unadjusted estimates was not expected, reasonably similar results were desired.

Covariate adjustment

Once an optimal model was selected, the mean covariate values of the azacitidine treatment arm were entered into the optimal model to simulate the glasdegib + LDAC vs. LDAC comparison being performed among the azacitidine patients. New predictions including covariate-adjusted survival curves (criterion 3), survival times (criterion 4) and OS HR (criterion 4) were generated and compared with the original IPD population estimates. The same covariate adjustment was performed substituting the decitabine population to simulate the glasdegib + LDAC vs. LDAC comparison among decitabine patients.

Indirect treatment comparisons

ITCs were separately conducted for glasdegib + LDAC vs. azacitidine and glasdegib + LDAC vs. decitabine. First, standard (Bucher) ITC compared unadjusted OS HRs from original publications. The second ITC approach applied Cox multivariate regression of glasdegib + LDAC vs. LDAC IPD against azacitidine or decitabine published OS HRs. Finally, as the last step in STC, the STC-derived estimates glasdegib + LDAC vs. LDAC efficacy entered final ITC against azacitidine or decitabine. Optimal models from the STC model exploration were selected into the final ITC, which included full and stepwise adjustments.

C.2 Glasdegib + LDAC vs. azacitidine: Rationale for model selection

Model exploration and comparison of functional forms

Fit statistics AIC and BIC were similar between full (615 resp. 637) and stepwise (617 resp. 628) Cox models, with the next best fit statistics resulting from the stepwise exponential model (343 reps. 359). For all full and stepwise model parametrizations, the Chi-square tests for the log likelihood demonstrated significance for at least one of the included variables in the OS HR regression, and the exponential and Weibull stepwise models had the smallest associated p-values (p = 0.0002 and p = 0.0001, respectively) (Table 56).

Table 56: STC for glasdegib + LDAC vs. azacitidine: Fit statistics using BRIGHT AML 1003 data

	Exponential	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Model Metric	PH with treatment covariate	PH with treatment covariate	PH with treatment covariate	AFT with treatment covariate	AFT with treatment covariate	AFT with treatment covariate
Full model						
Log-likelihood	-163.90	-163.61	-163.89	-162.77	-163.55	-162.30
Chi2	0.0023	0.0022	0.0073	0.0105	0.0105	0.0085
AIC/BIC	348/375	349/379	350/380	348/378	348/377	349/382
Stepwise model						
Log-likelihood	-165.42	-165.08	-165.42	-165.95	-166.62	-164.47
Chi2	0.0002	0.0001	0.0006	0.0038	0.0063	0.0012
AIC/BIC	343/359	344/363	344/364	346/365	347/367	345/367

Abbreviations: AFT = accelerated failure time; AIC = Akaike information criterion; BIC = Bayesian information criterion.PH = proportional hazard

References: (110)

Visual inspection and prediction validation

Following DSU guidance with glasdegib + LDAC vs. LDAC IPD, lognormal and loglogistic appeared to have the strongest visual fits early in the analysis time. However, over all trial time, the exponential model showed strong visual fit (Figure 21). After applying weighted trial data, the exponential model continued to demonstrate close visual comparison to the KM. However, among the stepwise models, the Weibull distribution demonstrated a somewhat stronger visual fit. With either approach, the graphs of the HRs over 20 months (maximum survival in the LDAC alone arm) all had comparable estimates of glasdegib + LDAC superiority over LDAC, with strong overlap between parametrizations and the Cox regression estimate (Figure 22).

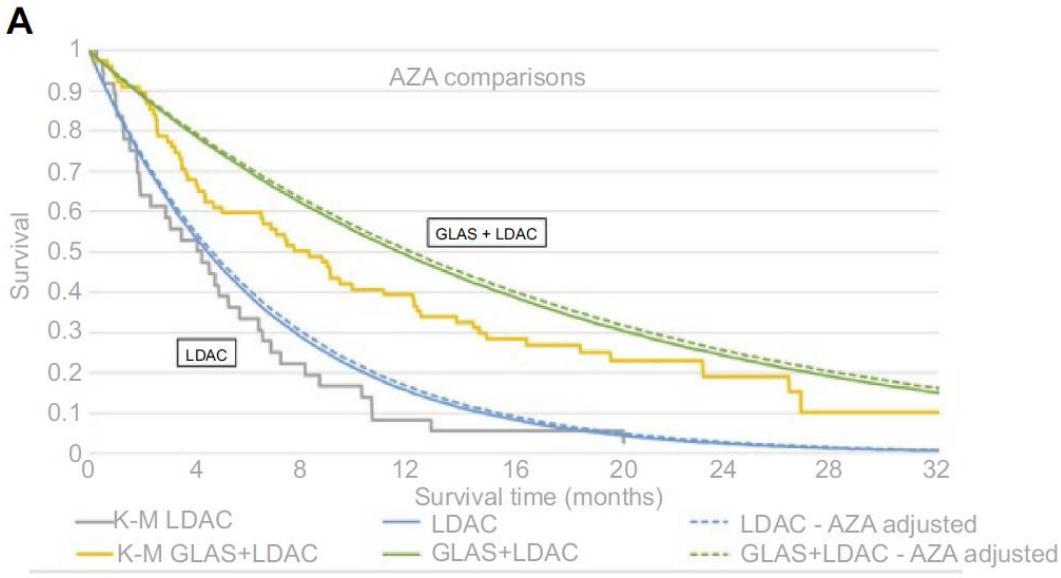

Figure 21: STC for glasdegib + LDAC vs. azacitidine: Overlay of Kaplan-Meier with exponential parametrization adjusting trial IPD

The grey (KM) and both blue (exponential) curves represent OS in the LDAC alone treatment arm. The orange and green lines estimate survival time in the glasdegib + LDAC arm. The solid curves apply the average covariate values from the IPD population, while the dashed curves model the mean covariates from the comparator trials.

Abbreviations: AZA = azacitidine; GLAS = glasdegib; KM = Kaplan-Meier; LDAC = low-dose cytarabine; IPD = individual patient data; OS = overall survival.

Reference: (91)

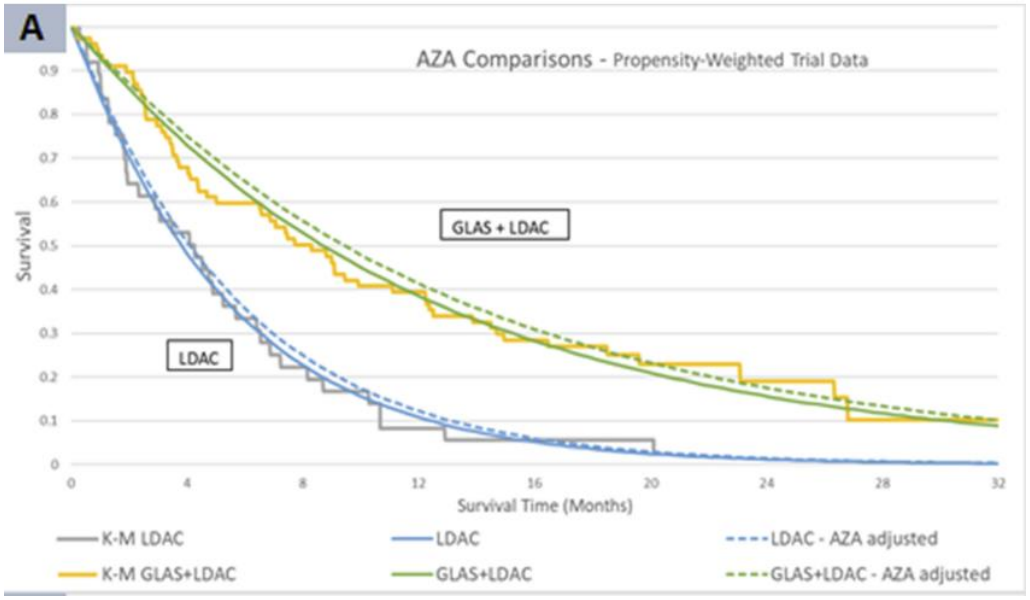

Figure 22: Weighted STC for glasdegib + LDAC vs. azacitidine: Overlay of Kaplan-Meier with Weibull parametrization adjusting trial IPD

The grey (KM) and both blue (Weibull) curves represent OS in the LDAC alone treatment arm. The orange and green lines estimate survival time in the glasdegib + LDAC arm. The solid curves apply the average covariate values from the IPD population, while the dashed curves model the mean covariates from the comparator trials.

Abbreviations: AZA = azacitidine; GLAS = glasdegib; KM = Kaplan-Meier; LDAC = low-dose cytarabine; IPD = individual patient data; OS = overall survival.

Reference: (91)

In estimating OS with glasdegib + LDAC vs. LDAC IPD, among the PH models, exponential and Gompertz distributions produced the most similar OS HR, OS median, and OS estimates to Cox regression estimates, for both stepwise and full model comparisons (Table 57). The exponential model, over Gompertz, had slightly better model fit statistics; therefore, exponential was considered the optimal PH model. Among the AFT models, gamma had the most reasonable survival estimates, although AIC and BIC were somewhat higher due to a more complex model than PH. All model results (PH and AFT) demonstrated glasdegib + LDAC superiority over LDAC. In conclusion, the exponential model (DSU guidance) and Weibull model (weighted STC approach) was chosen as it provided the best fit, respectively.

Table 57: STC for glasdegib + LDAC vs. azacitidine: OS estimates and model prediction,

DSU guided						
Full models						
Cox Hazard Ratio (adjusted for covariates)	0.418 (0.224 - 0.779)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.401 (0.219-0.736)	0.386 (0.209-0.715)	0.406 (0.218-0.753)	0.503 (0.262-0.838)	0.503 (0.271- 0.843)	0.436 (0.225- 0.782)
Predicted hazard ratio at median OS[b]	0.401 (0.219-0.736)	0.386 (0.209-0.715)	0.406 (0.218-0.753)	0.404 (0.12- 0.712)	0.468 (0.077- 0.733)	0.401 (0.149- 0.725)
Predicted median (glasdegib + LDAC vs. LDAC)	9.31 vs. 3.92	9.53 vs. 4.09	9.22 vs. 3.89	8.34 vs. 3.69	8.24 vs. 3.71	8.71 vs. 3.76
Stepwise models						
Cox Hazard Ratio (adjusted for covariates)	0.395 (0.219 - 0.712)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.382 (0.217 - 0.673)	0.366 (0.206 - 0.651)	0.385 (0.215 - 0.688)	0.452 (0.223 - 0.794)	0.441 (0.215 - 0.795)	0.371 (0.193 - 0.681)
Predicted hazard ratio at median OS[b]	0.382 (0.217 - 0.673)	0.366 (0.206 - 0.651)	0.385 (0.215 - 0.688)	0.356 (0.154 - 0.740)	0.387 (0.158 - 0.775)	0.345 (0.171 - 0.663)
Predicted median (glasdegib + LDAC vs. LDAC)	9.30 vs 3.89	9.54 vs 4.08	9.24 vs 3.87	8.44 vs 3.64	8.05 vs 3.54	9.02 vs 3.82
Weighted STC Approach						
Full models						
Cox Hazard Ratio (adjusted for covariates)	0.418 (0.224 - 0.779)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.396 (0.216 - 0.725)	0.383 (0.207 - 0.71)	0.399 (0.215 - 0.741)	0.580 (0.348 - 0.857)	0.548 (0.329 - 0.843))	0.432 (0.235 - 0.758)
Predicted hazard ratio at median OS[b]	0.396 (0.216 - 0.725)	0.383 (0.207 - 0.71)	0.399 (0.215 - 0.741)	0.530 (0.272 - 0.854)	0.546 (0.311 - 0.849)	0.414 (0.215 - 0.75)
Predicted median (glasdegib + LDAC vs. LDAC)	9.24 vs 3.96	9.44 vs 4.12	9.17 vs 3.93	8.40 vs 3.63	8.14 vs 3.61	8.92 vs 3.80
Stepwise models						
Cox Hazard Ratio (adjusted for covariates)	0.395 (0.222 - 0.702)					

Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.383 (0.217 - 0.676)	0.371 (0.203 - 0.677)	0.387 (0.217 - 0.692)	0.491 (0.247 - 0.838)	0.458 (0.233 - 0.804)	0.386 (0.205 - 0.698)
Predicted hazard ratio at median OS[b]	0.383 (0.217 - 0.676)	0.371 (0.203 - 0.677)	0.387 (0.217 - 0.692)	0.402 (0.174 - 0.802)	0.415 (0.18 - 0.79)	0.363 (0.184 - 0.683)
Predicted median (glasdegib + LDAC vs. LDAC)	9.29 vs 3.88	9.50 vs 4.03	9.21 vs 3.85	8.44 vs 3.64	8.08 vs 3.54	9.00 vs 3.80

a: Hazard ratio for non-proportional hazard models were predicted over the period 0 to the maximum trial follow-up.
b: Median rounded up at 9 months from 8.8 months for GLAS+LDAC arms.

Abbreviations: AFT = accelerated failure time; AIC = Akaike information criterion; BIC = Bayesian information criterion.PH = proportional hazard

References: (110)

Covariate adjustment

Results from applying the mean covariate values from the azacitidine population to glasdegib + LDAC vs. LDAC comparison continued to demonstrate significant treatment effects among the simulated azacitidine population. As the chosen optimal model from following DSU guidance, the stepwise exponential approach estimated slightly improved glasdegib + LDAC efficacy vs. LDAC (HR [95 % CI]: 0.382 [0.217, 0.673]) compared with estimates from the Cox stepwise covariate model (HR [95 % CI]: 0.395 [0.219, 0.712]). Likewise, in the weighted trial data for glasdegib + LDAC vs. LDAC the stepwise Weibull model estimated a slightly lower OS HR (HR [95 % CI]: 0.371 [0.203, 0.677]) compared with the Cox stepwise model (HR [95 % CI]: 0.395 [0.222, 0.702]).

An overlay (see Figure 21 and Figure 22) of the original Kaplan-Meier and stepwise exponential survival curves applying either the glasdegib + LDAC vs. LDAC IPD population (solid lines) or simulated azacitidine population (dashed lines) demonstrates similarity between the populations when graphing glasdegib + LDAC vs. LDAC.

C.3 Glasdegib + LDAC vs. decitabine: Rationale for model selection

Model exploration and comparison of functional forms

The stepwise approach for both Cox and parametric models demonstrated improved AIC and BIC values compared with the full models, resulting in a more robust model measuring greater significance in treatment effects. Across all parametrizations (PH and AFT models), the Chi-square tests for the log likelihood demonstrated significance for at least one of the included variables, and the exponential and Weibull models had the smallest associated p-values (p = 0.0008 for both). Again, while the exponential, stepwise parametrization demonstrated numerically superior AIC/BIC fit statistics (345/367), all of the tested stepwise model forms demonstrated comparable fit.

Table 58: STC for glasdegib + LDAC vs. decitabine: Fit statistics using BRIGHT AML 1003 data

	Exponential	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Model Metric	PH with treatment covariate	PH with treatment covariate	PH with treatment covariate	AFT with treatment covariate	AFT with treatment covariate	AFT with treatment covariate
Full model						
Log-likelihood	-163.90	-163.60	-163.88	-162.45	-162.77	-162.30

Chi2	0.002	0.002	0.007	0.008	0.010	0.008
AIC/BIC	348/375	349/379	350/380	347/377	348/378	349/382
Stepwise model						
Log-likelihood	-164.29	-164.03	-164.27	-163.11	-163.65	-162.78
Chi2	0.0008	0.0008	0.0028	0.0040	0.0061	0.0035
AIC/BIC	345/367	346/370	347/371	344/369	345/370	346/373

Abbreviations: AFT = accelerated failure time; AIC = Akaike information criterion; BIC = Bayesian information criterion.PH = proportional hazard

References: (110)

Visual inspection and prediction validation

Following DSU guidance with glasdegib + LDAC vs. LDAC IPD, lognormal and loglogistic appeared to have the strongest visual fits early in the analysis time. However, over all trial time, the exponential model showed strong visual fit (Figure 23). After applying weighted trial data, the exponential model continued to demonstrate close visual comparison to the KM. However, among the stepwise models, the Weibull distribution demonstrated a somewhat stronger visual fit. With either approach, the graphs of the HRs over 20 months (maximum survival in the LDAC alone arm) all had comparable estimates of glasdegib + LDAC superiority over LDAC with strong overlap between parametrizations and the Cox regression estimate (Figure 24).

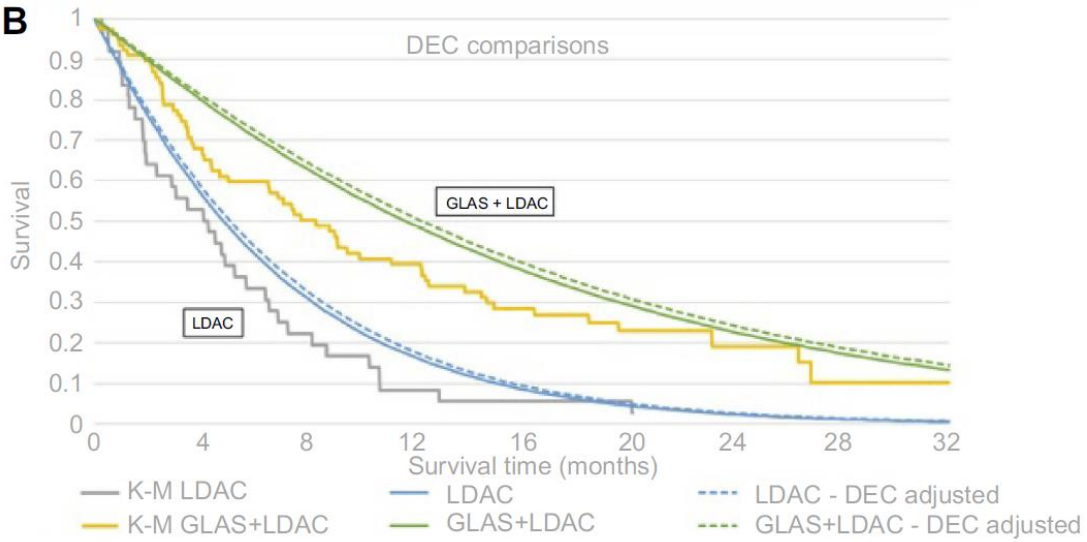

Figure 23: STC for glasdegib + LDAC vs. decitabine Overlay of Kaplan-Meier with exponential parametrization adjusting trial IPD

The grey (KM) and both blue (exponential) curves represent OS in the LDAC alone treatment arm. The orange and green lines estimate survival time in the glasdegib + LDAC arm. The solid curves apply the average covariate values from the IPD population, while the dashed curves model the mean covariates from the comparator trials.
Abbreviations: DEC = decitabine; GLAS = glasdegib; KM = Kaplan-Meier; LDAC = low-dose cytarabine; IPD = individual patient data; OS = overall survival.
Reference: (91)

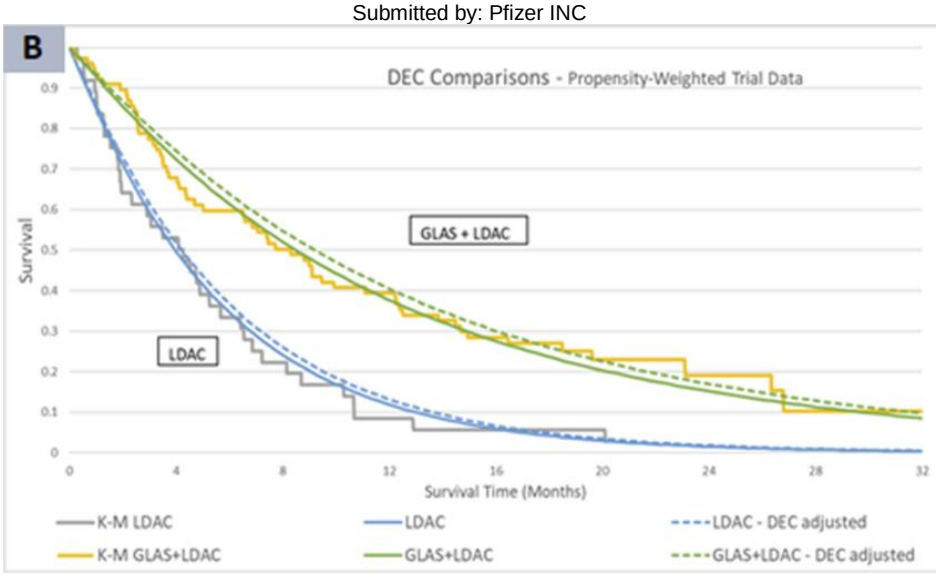

Figure 24: Weighted STC approach for glasdegib + LDAC vs. decitabine Overlay of Kaplan-Meier with Weibull parametrization adjusting trial IPD

The grey (KM) and both blue (Weibull) curves represent OS in the LDAC alone treatment arm. The orange and green lines estimate survival time in the glasdegib + LDAC arm. The solid curves apply the average covariate values from the IPD population, while the dashed curves model the mean covariates from the comparator trials.
Abbreviations: DEC = decitabine; GLAS = glasdegib; KM = Kaplan-Meier; LDAC = low-dose cytarabine; IPD = individual patient data; OS = overall survival.
Reference: (91)

Relative to the unadjusted Cox OS HR and Kaplan-Meier survival outcomes, exponential and Gompertz stepwise models had the closest HR estimates to those of the Cox regression model. With full models, exponential (PH) and gamma (AFT) models provided the most comparable values for average survival rates and median OS (Table 59). All models demonstrated significantly higher survival with glasdegib + LDAC over LDAC alone. After applying the three criteria for determining the optimal model (statistical fit, visual inspection, prediction estimation), it was determined that the exponential stepwise parametrization provided the optimal fit for estimating glasdegib + LDAC vs. LDAC efficacy in the decitabine population when using the glasdegib + LDAC vs. LDAC IPD. With propensity-weighted trial data for glasdegib + LDAC vs. LDAC, the Weibull distribution among the stepwise models was considered optimal.

Table 59: STC for glasdegib + LDAC vs. decitabine: OS estimates and model prediction

DSU guided						
Full models						
Cox Hazard Ratio (adjusted for covariates)	0.418 (0.224 - 0.779)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.401 (0.219-0.736)	0.386 (0.208-0.715)	0.406 (0.218-0.753)	0.503 (0.262–0.838)	0.503 (0.271–0.843)	0.436 (0.225–0.782)
Predicted hazard ratio at median OS[b]	0.401 (0.219-0.736)	0.386 (0.208-0.715)	0.406 (0.218-0.753)	0.404 (0.179 - 0.796)	0.468 (0.22 - 0.836)	0.401 (0.189 - 0.767)
Predicted median (glasdegib + LDAC vs. LDAC)	9.31 vs 3.92	9.53 vs 4.09	9.22 vs 3.89	8.34 vs 3.69	8.24 vs 3.71	8.71 vs 3.75
Stepwise models						

Cox Hazard Ratio (adjusted for covariates)	0.431 (0.233 - 0.800)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.414 (0.227-0.757)	0.400 (0.217-0.869)	0.419 (0.227-0.774)	0.370 (0.160–0.767)	0.367 (0.145–0.784)	0.390 (0.186–0.769)
Predicted hazard ratio at median OS[b]	0.414 (0.227-0.757)	0.400 (0.217-0.869)	0.419 (0.227-0.774)	0.305 (0.123-0.718)	0.288 (0.086-0.746)	0.354 (0.155-0.74)
Predicted median (glasdegib + LDAC vs. LDAC)	9.21 vs. 3.94	9.42 vs. 4.10	9.11 vs. 3.90	8.42 vs. 3.63	8.18 vs. 3.61	8.76 vs. 3.74
Weighted STC Approach						
Full models						
Cox Hazard Ratio (adjusted for covariates)	0.404 (0.219 - 0.748)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.395 (0.215 - 0.725)	0.382 (0.206 - 0.709)	0.398 (0.214 - 0.740)	0.578 (0.345 - 0.856)	0.546 (0.327 - 0.843)	0.403 (0.208 - 0.742)
Predicted hazard ratio at median OS[b]	0.395 (0.215 - 0.725)	0.382 (0.206 - 0.709)	0.398 (0.214 - 0.740)	0.524 (0.268 - 0.852)	0.544 (0.307 - 0.848)	0.379 (0.186 - 0.728)
Predicted median (glasdegib + LDAC vs. LDAC)	9.24 vs 3.96	9.44 vs 4.12	9.17 vs 3.93	8.40 vs 3.63	8.14 vs 3.61	8.92 vs 3.80
Stepwise models						
Cox Hazard Ratio (adjusted for covariates)	0.422 (0.225 - 0.792)					
Kaplan-Meier Median OS (months) (glasdegib + LDAC vs. LDAC)	8.31 vs. 4.27					
Model prediction	**Exponential**	**Weibull**	**Gompertz**	**Log-logistic**	**Log-normal**	**Gamma**
Predicted hazard ratio[a]	0.408 (0.218 - 0.766)	0.397 (0.204 - 0.772)	0.412 (0.217 - 0.782)	0.448 (0.208 - 0.831)	0.435 (0.202 - 0.817)	0.405 (0.203 - 0.766)
Predicted hazard ratio at median OS[b]	0.408 (0.218 - 0.766)	0.397 (0.204 - 0.772	0.412 (0.217 - 0.782)	0.305 (0.123 - 0.718)	0.385 (0.149 - 0.800)	0.383 (0.182 - 0.782)
Predicted median (glasdegib + LDAC vs. LDAC)	9.16 vs 3.95	9.34 vs 4.10	9.07 vs 3.91	8.40 vs 3.61	8.09 vs 3.55	9.00 vs 3.80

a: Hazard ratio for non-proportional hazard models were predicted over the period 0 to the maximum trial follow-up.
b: Median rounded up at 9 months from 8.8 months for GLAS+LDAC arms.

Abbreviations: AFT = accelerated failure time; AIC = Akaike information criterion; BIC = Bayesian information criterion.PH = proportional hazard

References: (110)

Covariate adjustment

Following DSU guidance, after covariate adjustment to the glasdegib + LDAC vs. LDAC IPD to simulate the decitabine population, glasdegib + LDAC continued to demonstrate significantly improved survival gains relative to LDAC (HR [95 % CI]: 0.414 [0.227, 0.757]) for the stepwise exponential model. Applying

weighted glasdegib + LDAC vs. LDAC trial data in the decitabine covariate adjustment, the stepwise Weibull model generated similar results (HR [95 % CI]: 0.397 [0.204, 0.772]) (Table 22).

Appendix D Sensitivity analyses for CR

Table 60: Results summary for CR for BRIGHT AML 1003 – sensitivity analysis

	Glasdegib + LDAC	LDAC
Investigator-reported response		
Total		
Number of patients randomized	78	38
Number (%) with CR	14 (17.9)	1 (2.6)
95 % CI[a]	[9.4, 26.5]	[0.0, 7.7]
Good/Intermediate cytogenetic risk (stratification factors based on CRF)		
Number of patients randomized	53	22
Number (%) with CR	11 (20.8)	0 (0.0)
95 % CI[b]	[10.8, 34.1]	[0.0, 15.4]
Poor cytogenetic risk (stratification factors based on CRF)		
Number of patients randomized	25	16
Number (%) with CR	3 (12.0)	1 (6.3)
95 % CI[b]	[2.5, 31.2]	[0.2, 30.2]
Pearson Chi-Square test (unstratified)		
p-value	0.0210	
CMH Stratified by Prognosis Stratum		
Relative risk [95 % CI]	7.22 [0.86, 60.52]	
p-value	0.0249	
Derived response[c]		
Total		
Number of patients randomized	78	38
Number (%) with CR	14 (17.9)	1 (2.6)
95 % CI[a]	[9.4, 26.5]	[0.0, 7.7]
Good/Intermediate cytogenetic risk (stratification factors based on IVRS)		
Number of patients randomized	49	21
Number (%) with CR	10 (20.4)	0 (0.0)
95 % CI[b]	[10.2, 34.3]	[0.0, 16.1]
Poor cytogenetic risk (stratification factors based on IVRS)		
Number of patients randomized	29	17
Number (%) with CR	4 (13.8)	1 (5.9)
95 % CI[b]	[3.9, 31.7]	[0.1, 28.7]
Pearson Chi-Square test (unstratified)		
p-value	0.0210	
CMH Stratified by Prognosis Stratum		
Relative risk [95 % CI]	7.10 [0.89, 56.83]	
p-value	0.0235	

	Glasdegib + LDAC	LDAC
Derived response[c]		
Total		
Number of patients randomized	78	38
Number (%) with CR	14 (17.9)	1 (2.6)
95 % CI[a]	[9.4, 26.5]	[0.0, 7.7]
Good/Intermediate cytogenetic risk (stratification factors based on CRF)		
Number of patients randomized	53	22
Number (%) with CR	11 (20.8)	0 (0.0)
95 % CI[b]	[10.8, 34.1]	[0.0, 15.4]
Poor cytogenetic risk (stratification factors based on CRF)		
Number of patients randomized	25	16
Number (%) with CR	3 (12.0)	1 (6.3)
95 % CI[b]	[2.5, 31.2]	[0.2, 30.2]
Pearson Chi-Square test (unstratified)		
p-value	0.0210	
CMH Stratified by Prognosis Stratum		
Relative risk [95 % CI]	7.21 [0.86, 60.52]	
p-value	0.0249	

a. Using normal approximation.
b. Using exact method based on binomial distribution.
c. Derived by the sponsor.
Abbreviations: CI = confidence interval; CMH = Cochran–Mantel–Haenszel test; CR = morphologic complete remission; CRF = case report form; LDAC = low-dose cytarabine; RR = relative risk
Reference: (89)