PTJA16 – Core Submission Dossier

Venetoclax in combination with a hypomethylating agent for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for intensive chemotherapy

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LIST OF ABBREVIATIONS

AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
ara-C	Cytarabine
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate transaminase
BCL-2	B-cell lymphoma 2
BSC	Best supportive care
BSH	British Society for Haematology
CAG	Cytarabine, aclarubicin, G-CSF
CCR	Conventional care regimens
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CHF	Congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	Complete response
CRD	Centre for Reviews and Dissemination
CRh	Complete response with partial haematological recovery
CRi	Complete response with incomplete bone marrow recovery
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
DARE	Database of Abstracts of Reviews of Effects
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EHA	European Haematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EQ-5D-5L	EuroQol 5-dimension 5-level questionnaire
ESMO	European Society for Medical Oncology
EUnetHTA	European Network for Health Technology Assessment
FAB	French-American-British system
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in one second
GHS/QoL	Global health status/quality of life

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HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HR	Hazard ratio
HRQL	Health-related quality of life
HSCT	Hematopoietic stem cell transplant
HTA	Health technology assessment
IC	Intensive chemotherapy
ICD-10	International Classification of Diseases Version 10
IPD	Individual patient data
IRC	Independent review committee
IRT	Interactive response technology
ITC	Indirect treatment comparison
ITT	Intent to treat
IV	Intravenous
IVRS	Interactive voice response system
IWG	International Working Group
LDAC	Low-dose cytarabine
MCL-1	Myeloid cell leukaemia 1
MDS	Myelodysplastic syndrome
MEC	Mitoxantrone, etoposide, and cytarabine
MedDRA	Medical dictionary for regulatory activities
MFC	Multicolour flow cytometry
MLFS	Morphological leukaemia-free state
MPN	Myeloproliferative neoplasms
MR	Minor response
MRC	Myelodysplasia-related changes
MRD	Minimal/measurable residual disease
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PICO	Population, intervention, comparator, outcome
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRO	Patient-reported outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PSW	Propensity score weighting
RAEB-t	Refractory anaemia with excess blasts in transformation

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RBC	Red blood cells
RCT	Randomised-controlled trial
RFS	Relapse-free survival
R/R	Relapsed/refractory
SAE	Serious adverse event
SC	Subcutaneous
SD	Stable disease
SLL	Small lymphocytic leukaemia
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
TC	Treatment choice
TLS	Tumour lysis syndrome
TTD	Time to deterioration
ULN	Upper limit of normal
WHO	World Health Organization

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EXECUTIVE SUMMARY

Characteristics of the technology

Venetoclax is a first-in-class, highly selective, potent, oral B-cell lymphoma-2 (BCL-2) inhibitor that restores programmed cell death (apoptosis) in cancer cells [1-5]. Overexpression of BCL-2 has been demonstrated in AML cells, where it mediates tumour cell survival and is associated with resistance to chemotherapeutics. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein. This mechanism of action – targeting the BCL-2 protein – is innovative and distinct in the treatment of AML.

The efficacy and safety of venetoclax combinations have been assessed in patients with AML who are ineligible for intensive chemotherapy in an extensive clinical development programme, comprising of two Phase 1b/2 open-label non-randomised studies [6, 7] and two large double-blinded Phase 3 randomised controlled trials, one in comparison with azacitidine alone (VIALE-A) and the other in comparison with LDAC alone (VIALE-C) [8, 9]. Approximately 900 patients with newly diagnosed AML were enrolled in the trials.

Venetoclax in combination with an HMA or LDAC was approved by the FDA for the treatment of newly diagnosed AML in adults aged 75 years or older, or who have comorbidities that preclude use of intensive chemotherapy [10], and is under regulatory review in the EU, Switzerland, and other countries. The anticipated indication in the EU is: venetoclax in combination with an HMA for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

AbbVie was previously granted marketing authorisation for venetoclax in CLL by the European Commission, the FDA, and other regulatory agencies [11, 12]. The FDA also approved venetoclax for the treatment of SLL [12].

Health problem

AML is an aggressive, rapidly fatal, heterogeneous haematologic malignancy characterised by the clonal expansion of myeloid blasts in the bone marrow, peripheral blood, and occasionally extramedullary tissues that disrupts normal production of blood cells and platelets [13, 14]. AML is a rare disease but is one of the most common types of leukaemia in adults [15]. Countries within Europe report varied AML incidence rates per 100,000 population: 2.7 in Serbia, 3.0 in Switzerland and the Netherlands, 4.7 in Italy, 5.1 in the UK, and 5.4 in Denmark [16].

The incidence of AML increases with age, with a median age at diagnosis of 68 years, and approximately one-third of patients are aged ≥75 years at diagnosis [17]. Patients who are ineligible for intensive chemotherapy, often elderly adults with comorbidities, have poor survival, with a 1-year survival rate of 15–20% [18]. Indeed, elderly adults with AML generally face particularly dismal outcomes, with <5% of patients in this age group alive at 5 years post-diagnosis, compared with 40% of younger patients [18, 19].

The HRQL impairment in patients with AML is significant, with deterioration due to AML symptoms, particularly extreme fatigue, anaemia, and infection, which require prolonged hospitalisation, and due to treatment burden [20]. AML can impair normal haematopoiesis, leading to severe cytopenia in one or more cell lineages that can result in bleeding events [21]. The need for repeated blood transfusions contributes to poor HRQL, and leads to substantial clinical burden and healthcare resource use [22, 23]. Complications include transfusion-associated circulatory overload, alloimmunisation, graft versus host disease, and transmission of viral infections (i.e., CMV) [24]. Given the short life expectancy, symptom burden and the need for frequent blood transfusions, HRQL and psychosocial wellbeing are among the most difficult challenges facing patients with AML and their caregivers [22, 23].

Target patient population

The treatment of AML is divided into two phases: induction and consolidation. Both phases involve intensive chemotherapy, which cannot be recommended for certain patients, particularly if they are elderly or have underlying comorbidities [25, 26]. Elderly patients have more unfavourable disease biology and are less likely to tolerate intensive chemotherapy [27]. The population covered in the expected venetoclax indication includes adult patients with newly diagnosed AML who are ineligible for intensive induction chemotherapy. Although there are currently no consensus guidelines to determine ineligibility for intensive chemotherapy, key factors commonly considered include age (≥65 years), poor

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performance status, and significant comorbidities [25, 26]. The assessment of eligibility for intensive/non-intensive chemotherapy is complex and takes place in clinical practice based on a patient-specific risk-benefit analysis [25].

In alignment with the EMA and FDA, modified Ferrara criteria were used to define ineligibility for intensive chemotherapy objectively in the pivotal Phase 3 trial VIALE-A, and Phase 3 VIALE-C trial, of venetoclax in AML [28]. Enrolled patients were ≥ 18 years old and ineligible for intensive chemotherapy due to one or more of the following criteria [8, 9]:

- ≥75 years of age
- ECOG performance status of 2 or 3
- cardiac history of congestive heart failure requiring treatment or ejection fraction ≤50% or chronic stable angina
- diffusing capacity of the lung for carbon monoxide ≤65% or forced expiratory volume in one second ≤65%
- creatinine clearance ≥30 mL/min to <45 mL/min
- moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × upper limit of normal
- any other comorbidity that the physician judges to be incompatible with intensive chemotherapy.

Current clinical practice and comparators

The median expected OS remains <1 year in older patients (age ≥60/65 years) ineligible for intensive chemotherapy [25, 26, 29]. For patients ineligible for intensive chemotherapy, the goal is to prolong OS while preserving HRQL. Currently used treatment options for patients ineligible for intensive chemotherapy are limited to low-intensity therapies (hypomethylating agents [HMA] or LDAC), best supportive care (BSC), or clinical trials with investigational drugs [25, 26]. These treatment options do not provide sufficient clinical benefit in terms of survival [18, 19]. Based on clinical trials, median OS was 7.7 months for patients receiving decitabine, 10.4 months for azacitidine, and 5.0 months for LDAC when given as single agents [25, 26, 30, 31].

Glasdegib in combination with LDAC has recently (26 June 2020) received marketing authorisation from the European Commission for the treatment of newly diagnosed *de novo* or secondary AML in adult patients who are not candidates for standard induction chemotherapy. Glasdegib was granted marketing authorisation based on a limited clinical development programme, including post hoc subgroup analyses of an open-label Phase 2 trial [16, 32].

The comparators for this assessment are azacitidine, decitabine, LDAC, glasdegib in combination with LDAC, and BSC.

Standard of care (SoC) in the majority of European markets is considered to be HMAs [25]. Azacitidine and decitabine are considered to have comparable effectiveness, supported by RCT meta-analysis and real-world evidence [33, 34]. Another group of markets consider LDAC SoC along with HMAs. In a minority of markets LDAC is SoC in situations where the use of azacitidine is restricted [35, 36].

Clinical efficacy

The clinical efficacy and safety of venetoclax in combination with azacitidine in the treatment of newly diagnosed patients with AML who are ineligible for intensive chemotherapy has been assessed in the pivotal Phase 3, randomised, double-blind, placebo-controlled, multicentre study, VIALE-A, supported by a Phase 1b study M14-358 [6, 8]. In the VIALE-A trial, 431 patients were randomised to receive venetoclax plus azacitidine (n=286) or placebo plus azacitidine (n=145). For the EU, Japan, and EU reference countries, VIALE-A had dual primary efficacy endpoints of complete remission + complete remission with incomplete marrow recovery (CR + CRi) rate and OS [8].

<u>Overall survival (OS)</u>

In the VIALE-A trial, venetoclax in combination with azacitidine led to a statistically significant and clinically meaningful reduction in the risk of death (hazard ratio [HR] 0.66 [95% confidence interval (CI): 0.52, 0.85]; p<0.001), after a median follow-up of 20.5 months (range: <0.1–30.7) [8]. The median OS was 14.7 months in patients randomised to receive venetoclax plus azacitidine compared with 9.6 months in the azacitidine only arm. This improvement in OS was consistent across the majority of prognostic subgroups including blast count, type of AML (*de novo*, secondary) as well as a number of

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molecular and cytogenic subgroups [8]. Similarly, venetoclax (400 mg) in combination with decitabine, in the Phase 1b M14-358 trial in patients aged ≥65 years, resulted in a median OS of 16.2 months (95% CI: 9.1, 27.8) after a median follow-up of 40 months [37].

Remission rates

In VIALE-A, venetoclax in combination with azacitidine resulted in increases in the remission rates (CR + CRi [composite CR], CR, and CR + CRh) compared with patients treated with azacitidine alone. Venetoclax plus azacitidine more than doubled CR + CRi compared with azacitidine alone (66.4% versus 28.3%, p<0.001) [8, 38]. In the Phase 1b M14-358 trial, venetoclax (400 mg) in combination with decitabine demonstrated a CR + CRi rate of 74%, comparable to that achieved by venetoclax in combination with azacitidine (71%) [37].

Rapid achievement of CR + CRi, CR, and CR + CRh was observed in VIALE-A, as measured by the high response rates by the initiation of Cycle 2 [8].

Responses were also durable; patients showed sustained long-term benefit with ongoing treatment. The median duration for composite CR for venetoclax plus azacitidine was 17.5 months (95% CI: 13.6, NR) compared with 13.4 months (95% CI: 5.8, 15.5) in the azacitidine arm [8]

Venetoclax plus azacitidine showed an improvement in CR + CRi for all patient subgroups stratified by various prognostic factors including AML subtype, bone marrow blasts and the presence of molecular mutations [8].

Transfusion independence

Rates of post-baseline long-term transfusion independence, for red blood cells (RBC) or platelets, of at least 56 days were improved by ≥19% in patients treated with venetoclax plus azacitidine compared with azacitidine alone in VIALE-A [8]. RBC transfusion independence occurred in 60% (95% CI: 54, 66) of the patients in the venetoclax in combination with azacitidine arm and in 35% (95% CI: 27, 44) of those in the azacitidine arm (p<0.001), and platelet transfusion independence occurred in 69% (95% CI: 63, 74) and 50% (95% CI: 41, 58) (p<0.001), respectively [8].

Minimal/measurable residual disease (MRD)

A reduction in MRD levels has been shown to be prognostic for OS and risk of relapse after intensive chemotherapy and therefore, a reduction below 1 leukaemic cell in 1,000 ($<10^{-3}$) was considered a relevant metric to evaluate the quality of remission (CR, CRi, or CRh) in response to treatment regimens [8, 39].

Among patients who achieved a remission of CR + CRi in the VIALE-A trial, MRD negativity was achieved in 23.4% of those receiving venetoclax plus azacitidine compared with 7.6% in the azacitidine arm [8].

Event-free survival (EFS)

Venetoclax in combination with azacitidine significantly improved EFS compared with azacitidine alone in the VIALE-A trial (HR 0.63 [95% CI: 0.50, 0.80]; p<0.001). Median EFS was 9.8 months versus 7.0 months, respectively [8].

Health-related quality of life (HRQL)

In VIALE-A, treatment with venetoclax plus azacitidine delayed time to deterioration (TTD) on the EORTC-QLQ-C30 General Health Status/Quality of Life (GHS/QOL) scale by 7.2 months more than azacitidine alone, although the difference was not statistically significant (median TTD: 16.5 months versus 9.3 months; HR: 0.81 [95% CI: 0.55, 1.18]; p=0.07).

Clinical safety

Overall, results from the Phase 3 VIALE-A trial and the Phase 1b M14-358 trial demonstrate that the safety profile of venetoclax in combination with HMAs is well-characterised and manageable in newly diagnosed patients with AML who are ineligible for intensive chemotherapy [8, 37]. This is also supported by VIALE-C, which indicated a similar safety profile for venetoclax in combination with LDAC [9, 40]. Adverse events (AEs) reported in the trials were consistent with the known safety profiles of each agent and within expectations for a population with AML ineligible for intensive chemotherapy. No new risks associated with venetoclax at proposed doses in combination with HMAs (or LDAC) among

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patients with AML were identified [6-8, 40, 41]. Early mortality was similar between arms in VIALE-A, with 30-day mortality rates for venetoclax plus azacitidine versus azacitidine of 7% versus 6%, respectively [8]. The discontinuation rates seen in VIALE-A showed that the percentage of patients discontinuing treatment due to AEs was similar for venetoclax plus azacitidine versus azacitidine alone (24% versus 20%) [8]. Consistently, early mortality was also similar between arms in VIALE-C and the discontinuation rates reported were comparable to VIALE-A [40].

Indirect comparison

In addition to the direct evidence, individual patient data from the VIALE-A and VIALE-C trials were used to indirectly compare venetoclax plus azacitidine with LDAC alone using a propensity score weighting technique, considering this is a relevant comparison in countries where azacitidine is restricted. The propensity score analyses demonstrated that venetoclax plus azacitidine was associated with significantly prolonged OS, EFS and significantly higher rates CR + CRi compared with LDAC. Similar results were obtained within a subpopulation of patients with >30% bone-marrow blasts. Taken together with direct evidence, these results support the efficacy profile for venetoclax in combination with an HMA for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy. The results of a network meta-analysis (NMA) feasibility assessment demonstrated that the systematic differences between VIALE-A and the trials providing comparison with other comparators (such as BSC and glasdegib in combination with LDAC) are of a magnitude that would risk producing misleading results, rendering an NMA invalid and non-informative for decision-making [42].

Conclusions

AML is an aggressive, rapidly fatal, heterogeneous hematologic malignancy. Survival for patients with AML decreases markedly with increasing age of diagnosis, with 5-year OS rates of 7% for patients ≥65 years [43]. AML can impair normal haematopoiesis, leading to severe cytopenia that can result in symptoms such as extreme fatigue, infections, and bleeding events all of which have a substantial negative impact on HRQL [20]. Current SoC (first choice HMAs, followed by LDAC) for patients who are ineligible for intensive chemotherapy have not provided long-term clinical benefit. These patients have extremely poor prognoses, and most will die within 1 year of diagnosis [25, 26].

Venetoclax is a first-in-class, highly selective, potent, oral BCL-2 inhibitor that has been studied in well-designed, large, double-blind, randomised Phase 3 studies, supported by Phase 1b/2 studies, in combination with azacitidine or LDAC [1-5]. The pivotal Phase 3 VIALE-A trial has shown venetoclax in combination with HMAs (azacitidine or decitabine) to provide considerably improved clinical outcomes in patients with AML who are ineligible for intensive therapy compared with azacitidine monotherapy. Benefits were largely consistent across all subpopulations [8, 37].

Venetoclax in combination with HMAs resulted in prolonged OS, rapid and durable remissions (CR + CRi), greater transfusion independence rates and longer EFS. This superior efficacy throughout all patient relevant and clinically meaningful endpoints was achieved without a negative impact on HRQL. Furthermore, the safety profile of venetoclax in combination with HMAs is well-characterised and manageable in a newly diagnosed AML patient population. AEs reported in the clinical trials were consistent with the known safety profiles of each agent and within expectations for a population with AML ineligible for intensive chemotherapy. No new risks associated with venetoclax at the proposed doses in combination with HMAs were identified during the development program [6, 8, 38].

The prognosis in patients with AML who are ineligible to receive intensive chemotherapy has been dismal. Venetoclax in combination with HMAs addresses a high therapeutic need by providing an innovative, highly effective, range of treatment options for this challenging patient population.

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1 DESCRIPTION AND TECHNICAL CHARACTERISTICS OF THE TECHNOLOGY

1.1 Summary of the characteristics of the technology

- Venetoclax is a first-in-class, highly selective, oral BCL-2 inhibitor that, in synergistic combination with SoC therapy, induces apoptosis in AML cells [44, 45].

- Venetoclax in combination with HMAs offers improved treatment outcomes in the first-line treatment of AML in patients who are ineligible for intensive chemotherapy [6, 8]. In the pivotal Phase 3 clinical trial, VIALE-A, venetoclax in combination with azacitidine demonstrated clinically meaningful improvements in OS, response rates, and rates of long-term transfusion independence over azacitidine monotherapy [8].

- Venetoclax in combination with azacitidine delayed deterioration in patients' global health status and physical functioning compared with either treatment alone, leading to a longer preservation of HRQL [46].

- Venetoclax combinations have a well-characterised and manageable safety profile that is consistent across clinical trials [6-8, 40, 41].

- Venetoclax in combination with HMAs or LDAC is approved by the FDA for the treatment of newly diagnosed AML in adults 75 years of age or older, or who have comorbidities that preclude use of intensive chemotherapy [12], having already been approved in over 25 countries worldwide for the treatment of AML (as shown in section 1.3).

1.2 Characteristics of the technology

Venetoclax is a first-in-class, highly selective, potent, oral B-cell lymphoma 2 (BCL-2) inhibitor that induces apoptosis in acute myeloid leukaemia (AML) cells in synergistic combination with other therapeutic agents [44, 45]. A summary of the pharmaceutical technology is provided in Table 1.1 and Table 1.2.

Table 1.1 Features of the technology

Non-proprietary name	Venetoclax
Proprietary name	Venclyxto, Venclexta
Marketing authorisation holder	AbbVie
Class	Selective small-molecule BCL-2 inhibitor
Active substance(s)	4-[4-[[2-(4-chlorophenyl)-4,4-dimethylcyclohexen-1-yl]methyl]piperazin-1-yl]-N-[3-nitro-4-(oxan-4-ylmethylamino) phenyl]sulfonyl-2-(1H-pyrrolo[2,3-b]pyridin-5-yloxy) benzamide
Pharmaceutical formulation(s)	10 mg, 50 mg, and 100 mg tablets
ATC code	L01XX52
Mechanism of action	Venetoclax is a highly selective, potent, oral BCL-2 inhibitor that induces apoptosis in AML cells in combination with other therapeutic agents.

Abbreviations: AML, acute myeloid leukaemia, ATC, Anatomical Therapeutic Chemical; BCL-2, B-cell lymphoma 2.
Source:[11, 12]

Venetoclax is administered orally, once daily, with food [11]. The administration and dosing of venetoclax in combination with a hypomethylating agent (HMA) for the treatment of adult patients with AML who are ineligible for intensive chemotherapy are described in Table 1.2.

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Table 1.2 Administration and dosing of the technology

<table>
<tr><td>Method of administration</td><td>Tablets to be taken orally</td></tr>
<tr><td>Doses</td><td>10 mg, 50 mg, and 100 mg tablets</td></tr>
<tr><td>Dosing frequency</td><td>Recommended dose is once daily</td></tr>
<tr><td>Average length of a course of treatment</td><td>100 mg on Day 1, 200 mg on Day 2, 400 mg on Day 3 and beyond. This should be continued until disease progression or unacceptability toxicity is observed.</td></tr>
<tr><td>Anticipated average interval between courses of treatments</td><td>Not applicable</td></tr>
<tr><td>Anticipated number of repeat courses of treatments</td><td>Not applicable</td></tr>
<tr><td>Dose adjustments</td><td>When venetoclax must be given concomitantly with a strong CYP3A inhibitor the dose during the initial dose-titration phase should conform to the regimen summarised in the table below.
<table>
<tr><th>Inhibitors</th><th>Initiation and dose-titration phase</th><th>Steady daily dose (after dose-titration phase)</th></tr>
<tr><td>Strong CYP3A inhibitor</td><td>Day 1 – 10 mg
Day 2 – 20 mg
Day 3 – 50 mg
Day 4 – 100 mg or less</td><td>Reduce venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons)</td></tr>
<tr><td>Moderate CYP3A inhibitor</td><td colspan="2">Reduce venetoclax dose by at least 50%</td></tr>
</table></td></tr>
</table>

Abbreviations: CYP3A, Cytochrome P450 family 3 subfamily A; HMA, hypomethylating agent.
Source: [47]

1.2.1 Technology context and level of care

Venetoclax is a prescription-only medicine and can be used in all treatment settings, including at-home administration, hospital outpatient, and inpatient care. Treatment with venetoclax should be initiated and supervised by a physician experienced in the use of anticancer medicinal products [47]. Venetoclax is given in the form of immediate-release tablets for oral administration and should be taken within 30 minutes after completion of a meal (preferably breakfast) [47]. Azacitidine must be administered by a doctor or trained nurse via subcutaneous injection as per the label [48].

1.2.2 Claimed benefits of technology

Certain patients with newly diagnosed with AML are deemed unfit or ineligible for intensive chemotherapy due to factors such as advanced age, higher prevalence of comorbidities, and/or unfavourable cytogenetics [25, 26, 49, 50]. Current treatment options for these patients are limited to low-intensity therapies (HMAs or LDAC), best supportive care (BSC), or clinical trials with investigational drugs [25, 26]. Glasdegib was also recently approved by the European Commission (EC) in combination with LDAC [16]. Despite the availability of these treatment options, prognosis remains poor. In this population, the median overall survival (OS) is 7.7 months for patients receiving decitabine, 10.4 months for azacitidine, and 5.0 months for LDAC, when given as single agents [23, 25, 30, 31]. Azacitidine and decitabine failed to demonstrate a statistically significant OS improvement in their registrational trials [30, 31]. A substantial unmet need therefore exists for therapies that can provide survival benefits without compromising quality of life for patients with AML who are ineligible for intensive chemotherapy.

Venetoclax is an oral, first-in-class, highly selective, potent, small molecule, BCL-2 inhibitor that restores programmed cell death (apoptosis) in cancer cells [1-5]. Overexpression of BCL-2 has been demonstrated in AML cells, where it mediates tumour cell survival and is associated with resistance to chemotherapeutics [51]. Venetoclax helps restore the process of apoptosis by binding directly to the BCL-2 protein. This innovative mechanism of action – targeting the BCL-2 protein – is a novel and completely distinct principal mechanism of action in the treatment of AML. In contrast to venetoclax, products currently used to treat patients with AML who are ineligible for intensive chemotherapy (i.e., azacitidine, decitabine, and LDAC), are pyrimidine analogues acting as antimetabolites interfering with DNA synthesis and thus leading to cell death [48, 52, 53]. Venetoclax provides a synergistic effect in

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combination with other therapeutic agents as a factor of a novel mechanism of action thereby improving efficacy versus monotherapy with azacitidine, decitabine or LDAC [44, 45]. HMAs (e.g., azacitidine and decitabine) indirectly increase sensitivity to BCL-2 inhibition in AML cells by modifying the relative levels of BCL-2 family members [54-56].

Venetoclax in combination with HMAs or LDAC has been assessed in patients with AML ineligible for intensive chemotherapy in an extensive clinical development program comprising two open-label non-randomised Phase 1b/2 trials and two large Phase 3 double-blind randomised controlled trials in direct comparison with recommended therapies [6-9, 37].

The Phase 1b trial, M14-358, was designed to evaluate the safety, pharmacokinetics, and efficacy of venetoclax in combination with HMAs (azacitidine or decitabine) that are considered to be the standard of care (SoC) for patients ineligible for intensive chemotherapy. M14-358 demonstrated that each combination produced favourable and durable response rates (complete response [CR] and CR with incomplete marrow recovery [CRi]) and had manageable safety profiles across patient subgroups [6].

The two Phase 3, multicentre, randomised, double-blind, placebo-controlled trials, investigated venetoclax in combination with azacitidine compared with azacitidine alone (VIALE-A) and venetoclax in combination with LDAC compared with LDAC alone (VIALE-C).

The pivotal VIALE-A trial showed venetoclax in combination with azacitidine provided a clinically meaningful and significant improvement in OS compared with azacitidine monotherapy [8]. Venetoclax in combination with azacitidine also provided rapid and more durable remissions (CR + CRi) compared with azacitidine monotherapy. Composite CR rates (CR + CRi) were more than twofold higher for venetoclax in combination with azacitidine compared with azacitidine alone [8]. More patients also achieved transfusion independence during treatment with venetoclax plus azacitidine compared with azacitidine alone [8]. Lower rates of transfusion dependence have a positive impact on the health-related quality of life (HRQL) of patients with AML due to reduced patient burden, and meaningful cost offsets due to reduced hospitalisation time [57]. Importantly, venetoclax has a well-characterised and manageable safety profile in adults with newly diagnosed AML who are ineligible for intensive chemotherapy [6, 8, 9, 37]. Venetoclax in combination with azacitidine preserved HRQL while resulting in improved efficacy outcomes when compared with SoC [46].

1.3 Regulatory status of the technology

AbbVie has filed a Type II variation application with the European Medicines Agency (EMA) to extend the indication for venetoclax to include the addition of venetoclax in combination with an HMA for the treatment of adults with AML who are ineligible for intensive chemotherapy. The opinion of the Committee for Medicinal Products for Human Use (CHMP) will be available before publication of this document.

The US Food and Drug Administration (FDA) granted orphan drug status for venetoclax in AML on 4 February 2016. In addition, the agency granted Breakthrough Therapy Designations for venetoclax in combination with HMAs (azacitidine or decitabine) and for venetoclax in combination with LDAC for the treatment of patients with newly diagnosed AML who are ineligible for intensive chemotherapy, on 25 January 2016 and 21 July 2017, respectively [58].

On 21 November 2018, the FDA granted accelerated approval of venetoclax in combination with azacitidine, decitabine, or LDAC for the treatment of newly diagnosed AML in adults 75 years of age or older, or who have comorbidities that preclude the use of intensive chemotherapy [10]. The pivotal Phase 3 trials, VIALE-A and VIALE-C, were listed as post-marketing requirements to verify clinical benefit. On 22 May 2020, the FDA accepted a supplemental new drug application to be reviewed under the new Project Orbis initiative. In addition, the FDA confirmed the participation of Canada, Australia, Switzerland, and Brazil in the Project Orbis review of the application [59]. On 16 October 2020, the FDA granted regular approval to venetoclax in combination with azacitidine, decitabine, or LDAC for newly diagnosed AML in adults 75 years or older, or who have comorbidities precluding intensive induction chemotherapy [59].

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AbbVie was previously granted a marketing authorisation for venetoclax in chronic lymphocytic leukaemia (CLL) by the EC, the FDA, and other regulatory agencies [11, 12]. The FDA also approved venetoclax for the treatment of small lymphocytic leukaemia (SLL) (see Table 1.3 for further details).

Table 1.3 Regulatory status of the technology in Europe and the US

Organisation issuing approval	Verbatim wording of the indication(s)	Date of Approval	Launched (yes/no) *If no: include proposed date of launch*
EMA [11]	Venclyxto monotherapy in: ▪ in the presence of 17p deletion or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or ▪ in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor	4 December 2016 (first approval)	Yes
EMA [11]	Venclyxto in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least one prior therapy	29 October 2018	Yes
EMA [11]	Venclyxto in combination with obinutuzumab is indicated for the treatment of adult patients with previously untreated CLL	9 March 2020	Yes
EMA	Venclyxto in combination with an HMA is indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy	*[Expected]* May-June 2021	No: Expected Q2/Q3 2021
FDA [12]	VENCLEXTA is indicated for the treatment of adult patients with CLL or SLL	CLL (initial approval): 11 April 2016 SLL: 15 May 2019	Yes
FDA [10, 59]	VENCLEXTA is indicated in combination with azacitidine, or decitabine, or LDAC for the treatment of newly diagnosed AML in adults who are age 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy	16 October 2020	Yes

Abbreviations: AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; EMA, European Medicines Agency; FDA, Food and Drug Administration; HMA, hypomethylating agent; LDAC, low-dose cytarabine; SLL, small lymphocytic leukaemia.

Other locations where venetoclax is approved in combination with an HMA and/or in combination with LDAC for the treatment of AML are Argentina, Aruba, Bahrain, Belarus, Brazil, Canada, Chile, Dominican Republic, Ecuador, Egypt, El Salvador, Guatemala, Honduras, Israel, Japan, Kazakhstan, Kuwait, Lebanon, Mexico, New Zealand, Panama, Paraguay, Peru, Puerto Rico, Qatar, Russia, Saudi Arabia, Singapore, South Korea, Switzerland, the United Arab Emirates, and Uruguay. Venetoclax is also provisionally approved for the treatment of AML in: Australia, China, and Taiwan.

1.3.1 Contraindications

Concomitant use of preparations containing St. John's wort is contraindicated. Hypersensitivity to the active substance or to any of the excipients is contraindicated [47].

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2 HEALTH PROBLEM AND CURRENT CLINICAL PRACTICE

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

- AML is a rare, rapidly fatal, and fast-growing clonal hematologic cancer that primarily affects the elderly with the average patient being 68 years old at diagnosis [13, 14, 60].

- Patients who are ineligible for intensive chemotherapy, often elderly adults with comorbidities, have poor survival, with a 1-year survival rate of 15–20% [18]. Indeed, elderly adults with AML generally face particularly dismal outcomes, with <5% of patients in this age group alive at 5 years post-diagnosis, compared with 40% of younger patients [18, 19].

- AML results from uncontrolled proliferation of abnormal myeloblasts, most commonly in the bone marrow, leading to rapid health deterioration in patients [61]. The HRQL impairment in patients with AML is significant, with deterioration both due to AML symptoms, particularly fatigue, anaemia, and infection, which requires prolonged hospitalisation, and due to treatment [62-64]. The need for repeated blood transfusions due to thrombocytopenia also leads to substantial clinical burden and healthcare resource use [24, 62, 65, 66].

- Current treatment options for patients ineligible for intensive chemotherapy are few, have poor response rates and, as a result, increase the likelihood of relapse after initial remission [23]. This means survival outcomes are poor and median OS is low, ranging from 5.0 to 10.5 months [25, 30, 31].

- There is a need for new treatments that improve survival and provide durable response rates while preserving HRQL in patients with AML who are ineligible for intensive chemotherapy [67].

2.2 Overview of the disease or health condition

2.2.1 Pathogenesis of AML

AML (International Classification of Diseases Version 10 [ICD-10] Code: C92.0) is a cancer characterised by the clonal expansion of myeloid blasts in the peripheral blood, bone marrow, and/or other tissues [14]. Genetic alterations in myeloid progenitor stem cells alter normal growth and differentiation of myeloblasts [68]. Despite poor differentiation, AML cells can continue to divide and proliferate indefinitely [69]. Accumulated mutations promote transformation of leukemic cells and development of malignant characteristics. The malignant characteristics include evasion of apoptosis (BCL-2 overexpression and P53 dysregulation); loss of differentiation (fusion transcription factors and retinoic acid receptors); increased self-renewal (β-catenin mutations and Wnt activation); loss of cell-cycle control (P53 mutations); dissemination (tumour necrosis factor secretion); and autonomous proliferation (FLT3, Ras, C-Kit, C-FMS, Jak2, PTPN11). Unlike normal progenitor cells, leukaemic cells from patients with AML have differing capacities to undergo self-renewal, rather than lineage-specific commitment. A leukaemic cell's ability to resist programmed cell death via apoptosis is critical to the development of a malignancy [69].

2.2.2 Risk factors for developing AML

The exact cause of AML is unknown, but risk factors include age, sex, smoking, presence of certain genetic syndromes and/or blood disorders, and exposure to chemicals and/or radiation, as summarised in Table 2.1 [70].

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Table 2.1 Risk factors for AML

Risk factor	Causes
Demographics	• Increasing age (≥65 years) • Male gender
Past medical history	• Previous anti-cancer treatments • Other blood disorders (e.g., myelodysplasia or myeloproliferative disorders)
Environmental exposure	• Exposure to chemicals/radiation (e.g., benzene)
Lifestyle behaviour	• Smoking
Genetic	• Concomitant genetic disorder (e.g., Down's syndrome)

Source: [70].

2.2.3 AML diagnosis and classification

The diagnostic workup of AML involves a combination of procedures and tests intended to assess patient history, cytology of nucleated cells in blood and bone marrow, immunophenotyping, cytochemistry, and cytogenetics markers [71]. Originally, the French-American-British (FAB) system developed in the mid-1970s relied upon diagnostic criteria predicated on myeloid and monocytic differentiation and ≥30% blasts. Over time the criteria have evolved; the most recent developments in the diagnosis of AML are reflected in the 2016 World Health Organisation (WHO) update of criteria [25].

According to the WHO, the diagnostic criteria of AML are based on any of the following:

- ≥20% blasts in blood or marrow (based on 200 nucleated cells from blood and 500 nucleated cells from bone marrow)
- clonal, recurring cytogenetic abnormalities t(8;21)(q22;q22), inv(16)(p13q22) or t(16;16)(p13;q22), and t(15;17)(q22;q12) (regardless of blast percentage)
- myeloid sarcoma (regardless of blast percentage).

Similar outcomes data have been observed at the differing blasts thresholds (FAB ≥30% and WHO ≥20%) and provided the rationale for the WHO's lower threshold [14]. Clinical practice and medical researchers have since transitioned away from the FAB system and subsequently adopted the WHO classification system as the standard for diagnosing and classifying AML [72].

The WHO classification system incorporates meaningful clinical subcategories of AML. Table 2.2 details the four major types of AML currently recognised using the 2016 WHO classification system [71].

Table 2.2 2016 WHO classification of AML

AML with recurrent genetic abnormalities	AML with t(8;21)(q22;q22.1); RUNX1-RUNX1T1
	AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	APL with PML-RARA
	AML with t(9;11)(p21.3;q23.3); MLLT3-KMT2A
	AML with t(6;9)(p23;q34.1);DEK-NUP214
	AML with inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM
	AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1
	Provisional entity: AML with BCR-ABL1
	AML with mutated NPM1
	AML with biallelic mutations 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

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	Pure erythroid leukaemia
	Acute megakaryoblastic leukaemia
	Acute basophilic leukaemia
	Acute panmyelosis with myelofibrosis

Abbreviations: AML, acute myeloid leukaemia; WHO, World Health Organisation.
Source: [71]

2.2.4 Prognostic factors

Overall, prognostic factors in AML can be subdivided into two categories [68]:

- disease-related factors, which include white-cell count, prior myelodysplastic syndrome or cytotoxic therapy for another disorder, and leukaemic-cell genetic changes; current treatment guidelines recognise validated prognostic groups categorised as favourable, intermediate, and adverse cytogenetics and molecular abnormalities (Table 2.3) [14, 25, 26].
- patient-associated factors, which include increasing age, coexisting conditions, and poor performance status.
    - Age and the presence of a comorbid disease are significantly associated with overall mortality in patients with AML [73]. For elderly patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or 3, age had a dramatic effect, with 82% of patients >75 years with a performance status of 3 dying within 30 days of the initiation of induction [49]. Overall, patient-related factors are important for characterising tolerability to intensive chemotherapy in the adult population when choosing a treatment strategy [25, 26, 28, 72]. Treatments suitable for older and frail patients include HMAs, LDAC, and BSC. OS ranges from 5 to 10 months in patients who are ineligible for intensive chemotherapy treated with existing treatment options [68].

Age and performance status in addition to chromosomal and molecular aberrations remain the most important tools for outcome prediction in AML [72].

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Table 2.3 Risk status associated with cytogenetics and molecular abnormalities

Risk status	Cytogenetics			Molecular abnormalities		
	NCCN	**ELN**	**ESMO**	**NCCN**	**ELN**	**ESMO**
Favourable	t(8;21)(q22;q22.1); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11	t(8;21); RunX1-RUNX1T1, inv(16) or t(16;16); CBFB-MYH11	t(8;21)(q22;q22.1); RUNX1-RUNX1T1, inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11)	Normal cytogenetics: NPM1 mutation in the absence of FLT3-ITD or presence of FLT3-ITD^{low} or isolated biallelic (double) CEBPA mutation	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Biallelic mutated CEBPA	Mutated NPM1 without FLT3-ITD or with FLT3-ITD^{low} Biallelic mutated CEBPA
Intermediate	t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favourable or adverse	t(9;11); MLLT3-KMT2A Cytogenetic abnormalities not classified as favourable or adverse	t(9;11)(p21.3;q23.3); MLLT3-KMT2A Cytogenetic abnormalities not classified as favourable or adverse	Core binding factor with KIT mutation Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low}7 (without poor-risk genetic lesions)	Mutated NPM1 and FLT3-ITD^{high} Wild type NPM1 without FLT3-ITD or with FLT3-ITD^{low} (without adverse risk genetic lesions	Mutated NPM1 and FLT3-ITD^{high} Wild-type NPM1 without FLT3-ITD or with FLT3-ITD^{low} a (without adverse risk genetic lesions)
Adverse	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1	t(6;9); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22); BCR-ABL1 inv(3) or t(3;3); GATA2, MECOM (EVI1)	t(6;9)(p23;q34.1); DEK-NUP214 t(v;11q23.3); KMT2A rearranged t(9;22)(q34.1;q11.2); BCR-ABL1	Wild-type NPM1 and FLT3-ITD^{high} Mutated RUNX1 Mutated ASXL1 Mutated TP53#	Wild type NPM1 and FLT3-ITD^{high} Mutated RUNX1, mutated ASXL1, mutated TP53	Wild type NPM1 and FLT3- ITD^{high} Mutated RUNX1d Mutated ASXL1d Mutated TP53

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	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)-5 or del(5q); -7; -17/abn(17p) Monosomal karyotype	-5 or del(5q); -7 -17/abn (17p) Complex karyotype (≥3) Monosomal karyotype	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2, MECOM (EVI1) -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype			

Abbreviations: AML, acute myeloid leukaemia; ELN, European LeukemiaNet; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network.
Source: [14, 25, 26]

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2.2.5 Incidence and prevalence

The annual incidence of AML in European adults is 0.37 cases per 10,000 individuals. When glasdegib was granted orphan designation in 2020, the AML prevalence for 2019 was projected to be 1.3 per 10,000 population in the EU; this was equivalent to a total of around 69,000 people [13].

2.2.6 Clinical presentation of AML

AML has a rapid onset and progression [74]. The signs and symptoms of AML reflect the impaired bone marrow function and can include fatigue, fever, weakness, dizziness, headache, and shortness of breath due to anaemia [20]. Consequent development of leukopenia and neutropenia can cause an increased susceptibility to infections. Bleeding disorders resulting from thrombocytopenia, such as frequent or severe nose bleeds, bleeding gums, and excess bruising, are also common. Patients with AML who are ineligible for intensive chemotherapy have a high risk of developing anaemia and thrombocytopenia, which require treatment with blood products and may result in transfusion dependence. At least 85% of patients ineligible for intensive chemotherapy will require a transfusion [62]. Complications related to transfusion include transfusion-associated circulatory overload, transfusion-related acute lung injury, alloimmunisation, graft versus host disease, and transmission of viral infections (e.g., cytomegalovirus) [65]. By the time a patient presents with symptoms related to anaemia, infection, or bleeding, immediate medical intervention is required [64]. AML can be fatal within months from diagnosis if left untreated [75].

2.2.7 Mortality

AML is rare but rapidly fatal if left untreated, and is responsible for 62% of all leukaemia deaths [76, 77]. Survival is particularly poor in patients ineligible for intensive chemotherapy, with a 1-year survival rate of 15–20% and a 5-year survival rate of just 5% [78, 79].

Current treatment options for patients ineligible for intensive induction chemotherapy are limited to low-intensity therapies (particularly HMAs or LDAC) and BSC [25, 26], and these treatments offer poor survival outcomes. Although HMAs are considered the SoC, these treatments failed to demonstrate statistically significant OS improvements in their registrational trials (azacitidine: HR: 0.85, 95% CI: 0.69–1.03; decitabine: HR: 0.85; 95% CI: 0.69–1.04). Based on clinical trials, median OS was 7.7 months for patients receiving decitabine, 10.4 months for azacitidine, and 5.0 months for LDAC, when given as single agents [23, 25, 30, 31].

A US retrospective observational study using data from the Surveillance, Epidemiology, and End Results (SEER) program (2010–2015) and from Medicare (up to 2016) found that survival outcomes in patients with AML ineligible for intensive chemotherapy remain poor. Median OS was comparable between those treated with azacitidine and decitabine (6.3 months versus 7.4 months), while median OS was lowest with BSC (1.0 month) [80].

2.2.8 HRQL

AML affects many aspects of a patient's life throughout diagnosis, treatment, and recovery. HRQL and psychosocial wellbeing are among the most difficult challenges facing patients with AML and their caregivers [23]. Psychological distress can derive from the need for rapid treatment and the subsequent cognitive demand required to understand treatment pathways and options [81]. Fatigue and physical function are commonly diminished in patients with AML and, given the short life expectancy, particularly for older adults, patients are likely to prioritise general wellbeing and quality of life over length of life [82]. Irrespective of the treatment stage or disease status, fatigue symptoms are reportedly the most burdensome to patients [83]. Severe fatigue prior to first-line induction therapy is prognostic for shorter survival, regardless of the patient's age [84]. One study found that symptom burden with regards to fatigue, anxiety, and inability to engage in hard work or activity worsened with proximity to death [22].

HRQL usually worsens with an increased number of comorbid medical conditions, with disease progression, and at disease relapse [63]. HRQL is poor in patients with AML who are ineligible for standard induction therapy and poor HRQL at diagnosis is associated with poor OS [67]. Frequent and repeated red blood cell (RBC) transfusions, which are required during AML treatment, contribute to poor HRQL due to the hospitalisation, transfusion procedures, and associated adverse events [85]. Reducing anaemia symptoms and transfusion requirements may improve HRQL in patients with AML who are ineligible for intensive chemotherapy [67, 86].

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2.2.9 Societal burden

In 2016, the global age standardised years of life lost due to AML were 36.5 (range 33.7–38.9) per 100,000 [87]. The societal cost of AML is high, mainly due to healthcare resource use during induction treatment, but also from the burden of sick leave and early retirement in patients with AML [88]. A Swedish study of 2,954 adult patients diagnosed with AML between 2007 and 2015 estimated the 5-year cost per patient at €80,669: €57,250 from hospitalisations, €8,936 from outpatient visits, €3,391 from prescribed drugs, and €11,092 from sick leave and early retirement [88]. Similarly, a US retrospective observational study found that total cost of care for patients with AML ineligible for intensive chemotherapy is driven by hospitalisation (≥60%), followed by drug costs and costs related to transfusions. The mean total cost of care for this patient population ranges from $18,080.35 to $26,691.00 per patient per month [80]. Furthermore, another US observational study (administrative claims data 2009-2017) found that during first-line treatment (HMA or LDAC), 53.1% of patients (≥60 years) had ≥ 1 hospitalisation with a mean (median; range) length of inpatient stay of 10.9 (7.0; 1-97) days [89].

Transfusion requirement amongst older patients with AML receiving low-intensity treatment is a burden not only on patients and caregivers but also on healthcare systems. A US retrospective observational study of older (≥60 years) patients with AML who received first-line treatment with an HMA found that 76% required ≥1 RBC transfusion and 45% required ≥1 platelet transfusion in the first month of treatment [90]. Furthermore, transfusion dependence may be prognostic for induction chemotherapy. A French observational, longitudinal, and retrospective study conducted in 1067 patients (>15 years of age) with AML between 1985 and 2006 found that high packed RBC and platelet transfusion intensities during induction chemotherapy were associated with significantly lower response rates, higher rates of early death and poorer OS [91].

A US study in 1,492 patients ≥65 years diagnosed with AML not receiving intensive chemotherapy found that about a third of patients went untreated (i.e., no chemotherapy, blood transfusion, or stem cell transplant) and these patients incurred more healthcare resource use after diagnosis. Compared with treated patients, untreated patients had fewer days of follow-up (106 versus 263), more days of hospitalisation (4.8 versus 3.2), more days of hospice care (0.4 versus 0.1), and fewer office visits (3.8 versus 5.8) per month (all $P < 0.01$). This suggests major unmet needs for well-tolerated treatment options for patients ineligible for intensive chemotherapy [92].

2.3 Target population

2.3.1 Definition of target population and proposed positioning in the treatment pathway

The target population for treatment with venetoclax in combination with an HMA is adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

The European Society for Medical Oncology (ESMO) guidelines for AML indicate that age, ECOG performance status, and pre-existing heart, lung, kidney, or liver conditions are the key factors in determining whether a patient is unfit for intensive chemotherapy. Alongside these factors, several other clinical parameters are mentioned as important considerations when assessing the risk of intensive chemotherapy to a patient, such as body temperature, *de novo* versus secondary leukaemia, haemoglobin level, platelet count, fibrinogen level, and serum concentration of lactate dehydrogenase [25].

According to European LeukemiaNet (ELN) recommendations, factors that suggest a patient is not eligible for intensive induction chemotherapy include age (≥65 years), poor performance status, significant comorbidities and, in the case of conventional regimens such as 7+3, adverse ELN cytogenetics/molecular genetics (see Table 2.3) [26].

In 2013, a group of experts came together with the aim of developing a consensus-based, objective definition of unfitness to intensive and non-intensive chemotherapy in AML, which became known as the Ferrara criteria. After consultation with international AML clinical investigators, AbbVie collaborated with the EMA and FDA to operationalize objective criteria for VIALE-A and VIALE-C, using the Ferrara criteria as a starting point [28, 47]. These objective criteria to define ineligibility for intensive chemotherapy are similar to that used by other recently approved agents for newly diagnosed AML who are ineligible for intensive chemotherapy, glasdegib and ivosidenib [93, 94].

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The inclusion criteria for the VIALE-A and VIALE-C trials were developed and defined as follows [8, 40]:

- ≥75 years of age, or
- 18–74 years of age and fulfil at least one of the following criteria associated with lack of fitness for intensive induction chemotherapy:
    - ECOG performance status of 2 or 3
    - cardiac history of congestive heart failure requiring treatment or ejection fraction ≤50% or chronic stable angina
    - diffusing capacity of the lungs for carbon monoxide ≤65% or forced expiratory volume in one second≤65%
    - creatinine clearance ≥30 mL/min to <45 mL/min
    - moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 times the upper limit of the normal range
    - other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy, which must be reviewed and approved by the study medical monitor before study enrolment.

2.3.2 Justification for proposed positioning of the technology

The proposed positioning of venetoclax in combination with an HMA is in line with its EU marketing authorisation: the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

Venetoclax is positioned to address a population with high unmet need for which there has been limited innovation: the treatment pathway of AML has remained largely unchanged for around 20 years [95]. Within this context, European guidelines strongly recommend enrolling these patients in clinical trials [26]. Single agent, low-intensity therapies (first choice HMAs, followed by LDAC) offered to patients ineligible for intensive chemotherapy provide unsatisfactory OS benefit [25, 26, 30, 31]. Likewise, low-intensity therapy has been shown to maintain, but not improve HRQL, highlighting the need for new treatments that improve quality of life and extend survival for patients with AML ineligible for intensive chemotherapy [67].

The mechanism of action of venetoclax is synergistic with the first-line treatment for this population, HMAs, and also with LDAC. Azacitidine and cytarabine have shown the ability to down-regulate myeloid leukaemia cell 1 (MCL-1), an anti-apoptotic protein related to BCL-2 that can act as a resistance factor for BCL-2 family inhibitors, which results in a synergistic effect [44, 45]. For this reason, an extensive clinical development program comprising of two open-label non-randomised Phase 1b/2 studies and two large Phase 3 double-blind randomised controlled studies has been conducted with venetoclax in combination with HMAs and LDAC [7, 8, 37, 40].

Venetoclax in combination with azacitidine provides a clinically meaningful and significant improvement in OS and rapid, more durable rates of CR compared with azacitidine monotherapy in the pivotal VIALE-A clinical trial [8]. Treatment with venetoclax plus azacitidine significantly prolonged survival by 5.1 months from 9.6 to 14.7 months, compared with azacitidine alone. Composite CR rates (CR + CRi) were more than twofold higher (38%) for venetoclax in combination with azacitidine compared with azacitidine alone. More patients also achieved transfusion independence during treatment with venetoclax plus azacitidine compared with azacitidine alone [8]. Furthermore, venetoclax in combination with azacitidine appears to have a positive impact on the HRQL, leading to a longer preservation of functioning and overall health status compared with azacitidine alone [46]. Importantly, venetoclax has a well-characterised and manageable safety profile in a population that is ineligible for intensive chemotherapy [6-8, 40].

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Based on its efficacy and safety data, venetoclax in combination with an HMA provides a substantial benefit, consistent across the majority of prognostic subgroups, compared with existing treatments [8]. Venetoclax in combination with azacitidine provides an alternative treatment option with a distinct mechanism of action, addressing the high unmet need of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy.

2.3.3 Size of the target population

When glasdegib was granted orphan designation in 2020, the AML prevalence for 2019 was projected to be 1.3 per 10,000 population in the EU; this was equivalent to a total of around 69,000 people [13]. Approximately 30–50% of patients are ineligible for intensive chemotherapy [96-98]. Therefore, a total of approximately 20,700-34,500 people would be ineligible for intensive chemotherapy across Europe.

2.4 Clinical management of the disease or health condition

2.4.1 AML treatment overview

The general therapeutic strategy in patients with AML has not changed substantially in recent years. The treatment of AML is divided into two phases: induction and consolidation. Treatment decision for type of induction therapy is based on multiple criteria including age, fitness, risk of treatment-related mortality and cytogenic risk [26]. During the induction phase, chemotherapy aims to reduce the leukaemic burden and restore normal haematopoiesis to produce CR. A favourable response to induction therapy should be followed by consolidation therapy. Consolidation therapy typically consists of intermediate- or high-dose cytarabine-based therapy, allogeneic hematopoietic stem cell transplant or continuation of first-line therapy, to eradicate residual disease (detectable or nondetectable) and aid in achieving lasting remission [23].

Certain patients will be ineligible for intensive chemotherapy (Figure 2.1). Treatment alternatives per guidelines for these “unfit or ineligible” patients are limited to low-intensity treatment, BSC, or clinical trials with investigational drugs. Low-intensity options are either therapy with an HMA (azacitidine or decitabine) as first choice followed by LDAC [25, 26]. Initial assessment determines whether a patient is eligible for intensive induction chemotherapy and the risks/benefits of such therapy by assessing likelihood of treatment-related mortality. Treatment guidance and assessment of treatment-related mortality should not be based solely on chronological age, but rather the combination of performance status, the presence of significant medical comorbidities, and adverse ELN cytogenetic/molecular genetics [26].

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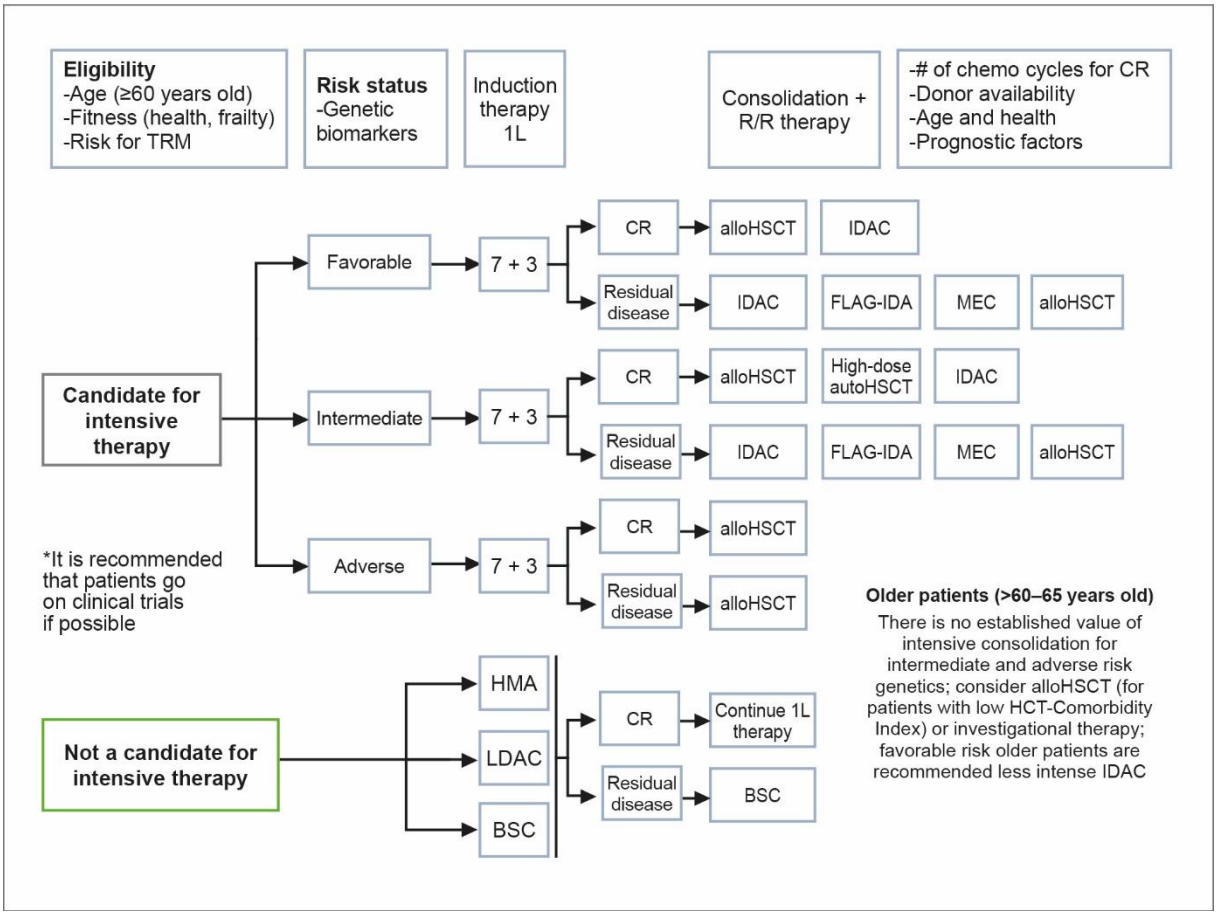
Figure 2.1 Current treatment pathway for patients with AML



Abbreviations: 1L, first line; alloHSCT, allogeneic hematopoietic stem cell transplant; AML, acute myeloid leukaemia; BSC, best supportive care; CR, complete response; ELN, European LeukemiaNet; FLAG-IDA, fludarabine + cytarabine + granulocyte-colony-stimulating factor + idarubicin; HCT, hematopoietic cell transplantation; HMA, hypomethylating agent.; IDAC/LDAC, intermediate/low dose cytarabine; MEC, mitoxantrone, etoposide, and cytarabine; R/R, relapsed/refractory; TRM, treatment-related mortality.
Source: [26]

2.4.2 Guidance documents for the management of patients with AML ineligible for intensive chemotherapy

Key guidelines for the management of AML from 2020 recommend low-intensity chemotherapy agents in patients ineligible for standard, intensive chemotherapy (Table 2.4). In Europe, HMAs are preferred to LDAC as the first-choice of therapy [25].

Of note, venetoclax in combination with an HMA or LDAC is already recommended by the 2020 guidelines of the National Comprehensive Cancer Network (NCCN) for the first-line treatment of patients aged ≥60 years and who are not candidates for intensive chemotherapy, without actionable mutations (preferred regimen) or with IDH1, IDH2, or FLT3 mutation [14].

In addition, venetoclax in combination with an HMA or LDAC is included in the ESMO guidelines for the first-line treatment of patients ineligible for intensive chemotherapy (Category III, A), including patients with prior HMA treatment (Category III, B) [25]. Although venetoclax combinations are considered to be superior to currently available first-line treatments in this patient population based on promising preliminary data, results of ongoing randomised trials are awaited before its use can be recommended with confidence [25].

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Table 2.4. Relevant guidelines for diagnosis and management

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)
ESMO	17 Mar 2020	Europe	**First-line treatment of AML patients not eligible for standard induction and consolidation chemotherapy:** <u>For those pre-treated with HMAs for MDS:</u> • HMA + venetoclax if available [III, B] • LDAC, 6-mercaptopurine or melphalan or hydroxycarbamide [III, C] <u>All others:</u> • The HMAs, azacitidine and decitabine, are treatment options in newly diagnosed unfit AML patients [II, B] (combine with venetoclax if available [III, A]) 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].
ELN	26 Jan 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 • BSC
NCCN	12 Nov 2020	USA	**Patient not a candidate for or declines intensive remission induction therapy** <u>AML without actionable mutations</u> • Venetoclax + decitabine or azacitidine (preferred) • Venetoclax + LDAC • Decitabine • Azacitidine • Glasdegib + LDAC • LDAC • Gemtuzumab ozogamicin • BSC <u>AML with *IDH1/2* mutation</u> • Ivosidenib (*IDH1* only) (preferred) • Enasidenib (*IDH2* only) (preferred)

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			• Venetoclax + decitabine or azacitidine (preferred) • Azacitidine • Decitabine • Venetoclax + LDAC <u>AML with *FLT3* mutation</u> • Venetoclax + decitabine or azacitidine (preferred) • Azacitidine or decitabine + sorafenib • Venetoclax + LDAC

Abbreviations: AML, acute myeloid leukaemia; BSC, best supportive care; ELN, European LeukemiaNet; ESMO, European Society for Medical Oncology; HMA, hypomethylating agent; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; NCCN, National Comprehensive Cancer Network.
Source: [25] [26] [14]

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2.4.3 Technologies currently used in the clinical pathway for patients with AML ineligible for intensive chemotherapy

Due to a lack of improvements in available treatments in recent years, the ELN emphasises that treatment of unfit and most older patients with AML is currently unsatisfactory and strongly recommends enrolling these patients in clinical trials [26]. ESMO recommends the HMAs azacitidine and decitabine as first-choice treatments in patients with newly diagnosed unfit AML. Other options are LDAC and BSC, which includes the use of anti-infectives, transfusion support with blood and blood products, 6-mercaptopurine, and hydroxyurea [25, 26]. Glasdegib was recently approved by the EC on 26 June 2020 in combination with LDAC to treat newly diagnosed (*de novo* or secondary) AML in adult patients who are not candidates for standard chemotherapy [99].

Table 2.5 summarises approved therapies for AML patients who are ineligible for intensive chemotherapy in Europe.

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Table 2.5 Summary of products with marketing authorisation as treatments for patients with AML who are not eligible for intensive chemotherapy in the EU

Treatment	Mechanism of action	Indication per marketing authorisation	Dosage and administration
HMAs			
Azacitidine	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.	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 WHO classification • AML with >30% marrow blasts according to the WHO classification.	75 mg/m^2 per day subcutaneously on days 1–7 every 4 weeks, until progression.
Decitabine	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.	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.	20 mg/m^2 per day intravenously on days 1–5 every 4 weeks, until progression.
Non-intensive chemotherapy			
Low-dose cytarabine	Cytarabine, a pyrimidine nucleoside analogue, is an antineoplastic agent which inhibits the synthesis of deoxyribonucleic acid. It also has antiviral and immunosuppressant properties.	For induction of remission in AML in adults and for other acute leukaemias of adults and children.	• 20 mg twice daily subcutaneously for 10 days every 4 weeks, until progression. • In some countries, low-dose cytarabine is used in a dosage of 20 mg/m^2 per day subcutaneously.
Other drugs			
Glasdegib	Glasdegib is an 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.	Glasdegib is indicated, in combination with LDAC, for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy.	100 mg orally once daily on days 1–28 in combination with LDAC (20 mg subcutaneously twice daily on days 1–10 of each 28-day cycle) continued in the absence of unacceptable toxicity until progression. For patients without unacceptable toxicity, treat for a minimum of 6 cycles to allow time for clinical response.

Abbreviations: AML, acute myeloid leukaemia; DNA, deoxyribonucleic acid; EU, European Union; HMA, hypomethylating agent; RNA, ribonucleic acid; WHO, World Health Organisation.
Source:[26, 48, 52, 93, 100].

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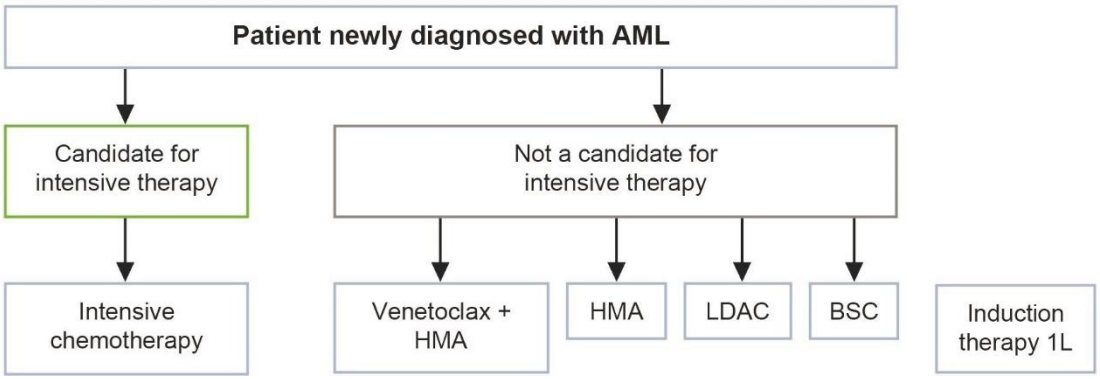
2.4.4 Pathway of care incorporating the new technology

Based on the current treatment pathway according to the ELN and ESMO, venetoclax in combination with an HMA will be incorporated into the pathway as a first-choice non-intensive therapy for newly diagnosed patients with AML who are ineligible for intensive chemotherapy (Figure 2.2).

Figure 2.2 Proposed positioning of venetoclax in the treatment pathway of patients with AML



Abbreviations: 1L, first-line; AML, acute myeloid leukaemia; BSC, best supportive care; CR, complete response; HMA, hypomethylating agent; LDAC, low-dose cytarabine; R/R, relapsed/refractory.

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3 COMPARATORS IN THE ASSESSMENT

3.1 Choice of comparators

Based on ELN and ESMO guidelines, appropriate comparators for venetoclax for this assessment include those recommended as first-line non-intensive therapies in the treatment of newly diagnosed AML (i.e., HMAs and LDAC) and BSC [25, 26]. Of these, the HMAs, azacitidine and decitabine, are currently recommended as the first-choice in unfit patients with newly diagnosed AML, with LDAC recommended as an alternative to HMA treatment [25].

Although not represented in guidelines, glasdegib in combination with LDAC is also considered a comparator for this assessment given its recent (26 June 2020) approval for the treatment of newly diagnosed de novo or secondary AML in adult patients who are not candidates for standard induction chemotherapy [16].

Therefore, the comparators for this assessment are azacitidine, decitabine, LDAC, glasdegib in combination with LDAC, and BSC.

3.1.1 Rationale for comparator selection in venetoclax development program

The proposed indication for venetoclax in AML is in combination with the current first-choice SoC, HMAs. The Phase 1b trial (M14-358, venetoclax in combination with azacitidine or decitabine) confirmed the safety and efficacy of this combination in the population of interest [6].

The Phase 3 trial, VIALE-A, was designed to be as robust as possible: a randomised, double-blind, placebo-controlled study versus a comparator considered to be the current first-choice SoC, azacitidine. This trial investigated venetoclax in combination with one HMA (azacitidine). Only one HMA was taken forward to Phase 3 due to the comparability of the azacitidine and decitabine combinations, consistent with their similar mechanisms of action [8, 48, 52]. Specifically:

- Similarities in efficacy and safety profiles were reported across all subgroups evaluated with azacitidine and decitabine combination therapies in the non-randomised study, M14-358 [6]. Long-term follow-up data indicated not only a comparable median OS of 16.4 months and 16.2 months but also a comparable CR + CRi rate (71% versus 74%) for venetoclax in combination with azacitidine and decitabine, respectively [37]. Key grade ≥3 adverse events were also comparable across combinations: febrile neutropenia (39% and 65%), anaemia (30% and 26%), thrombocytopenia (25% and 23%), and neutropenia (20% and 10%) for venetoclax in combination with azacitidine and decitabine, respectively [37].

- The similar profiles between the two HMAs is also supported by network meta-analyses of randomised controlled trials. The authors concluded that neither shows superiority; both demonstrated enhanced outcomes in mortality, overall response rate, and haematological parameters compared with traditional treatments [33].

- The comparability of the two HMAs is further confirmed by real-world evidence from >2,000 elderly patients who were treated with either HMA. The authors reported no clinically meaningful differences in the context of prolonging OS or independence from RBC transfusions [34].

The azacitidine combination, and therefore azacitidine as a comparator, was chosen for Phase 3 in part due to the ELN guidelines favouring azacitidine over decitabine. Although ESMO guidelines recommend HMAs as the first-choice treatment for this patient population, ELN guidelines state that azacitidine may be particularly advantageous in AML with adverse cytogenetics [26].

3.2 Comparator pivotal trials

3.2.1 HMAs (azacitidine and decitabine) versus conventional care regimens (LDAC or BSC)

Azacitidine and decitabine have been evaluated in three randomised open-label Phase 3 trials in comparison with conventional care regimens (CCR), namely AZA-AML-001, AZA-001, and DACO-016

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[30, 31, 101]. LDAC was the most used conventional care treatment in the pivotal studies of azacitidine (AZA-AML-001) and decitabine (DACO-016) [30, 31].

For AZA-AML-001 and AZA-001, before randomisation, investigators determined which protocol-designated CCR (BSC, LDAC, or intensive chemotherapy) was most appropriate for each patient on the basis of age, ECOG PS, comorbidities, and regional guidelines and/or institutional practice. Therefore, patients were 'preselected' for either BSC, LDAC or intensive chemotherapy [30, 101].

The registrational AZA-AML-001 trial evaluated azacitidine versus CCR in older patients with newly diagnosed AML with >30% blasts. Median OS and CR + CRi rate were numerically improved by azacitidine compared with CCR (see Table 3.1 and Table 3.2) [30].

Table 3.1 Median OS data by preselected population from AZA-AML-001

Overall population	Median OS (months [95% CI])	HR (95% CI)	P value
Azacitidine	10.4 (8.0-12.7)	0.85 (0.69-1.03)	0.1009
CCR	6.5 (5.0-8.6)		
Preselected for BSC only			
Azacitidine (n = 44)	5.8 (3.6-9.7)	0.60 (0.38-0.95)	0.0288
BSC (n = 45)	3.7 (2.8-5.7)		
Preselected for LDAC			
Azacitidine (n = 154)	11.2 (8.8-13.4)	0.9 (0.70-1.16)	0.4270
LDAC only (n = 158)	6.4 (4.8-9.1)		
Preselected for IC			
Azacitidine (n = 43)	13.3 (7.2-19.9)	0.85 (0.52-1.38)	0.5032
IC (n = 44)	12.2 (7.5-15.1)		

Abbreviations: BSC, best supportive care; CCR, conventional care regimens; HR, hazard ratio; IC, intensive chemotherapy; LDAC, low-dose cytarabine; OS, overall survival.
Source: [30].

Table 3.2 Overall response data for azacitidine and CCR from AZA-AML-001

	Overall response (CR + CRi)
Azacitidine (n = 241)	27.8%
CCR (n = 247)	25.1%
BSC	0%
LDAC	25.9%
IC	47.7%

Abbreviations: BSC, best supportive care; CCR, conventional care regimen; CR, complete response; CRi, complete response with incomplete marrow recovery; IC, intensive chemotherapy; LDAC, low-dose cytarabine.
Source: [30].

The benefit of azacitidine over CCR is further supported by a subgroup analysis of AZA-001 that included only patients with AML and 20–30% blasts. The 2-year OS rates were higher with azacitidine versus CCR in patients considered unfit for intensive chemotherapy [101].

In the registrational DACO-016 trial, decitabine resulted in a CR rate of 15.7% and a CRi rate of 9.9%, compared with 7.9% and 2.8%, respectively, for LDAC and 3.6% for each for BSC. The primary analysis with 396 deaths (81.6%) showed a nonsignificant increase in median OS with decitabine (7.7 months; 95% CI, 6.2 to 9.2) versus treatment choice (5.0 months; 95% CI, 4.3 to 6.3; p = 0.108; hazard ratio [HR]: 0.85; 95% CI, 0.69 to 1.04) [31].

The registrational trials of both HMAs failed to show statistically significant OS improvement compared with standard treatment (including LDAC and BSC) [30, 31].

3.2.2 Glasdegib in combination with LDAC versus LDAC

Glasdegib in combination with LDAC has recently been granted marketing authorisation by the EC for the treatment of newly diagnosed *de novo* or secondary AML in patients who are ineligible for intensive chemotherapy [16]. No randomised double-blind Phase 3 trials have been conducted with glasdegib in combination with LDAC. The key trial supporting glasdegib plus LDAC in patients with AML is the

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open-label Phase 2 study, BRIGHT-AML 1003. BRIGHT-AML 1003 trial was a subgroup of the larger B1371003 trial that enrolled patients with either previously untreated AML or high-risk myelodysplastic syndrome (MDS) who were considered ineligible for intensive chemotherapy. Analyses of the AML patient subgroup were not pre-planned and randomization was stratified by cytogenetic risk (but not formally stratified by AML or MDS) [32]. The median OS among the 78 patients with AML who received glasdegib in combination with LDAC was 8.3 months (80% CI: 6.6, 9.5). For the 38 patients receiving LDAC monotherapy, the median OS was 4.3 months (80% CI: 2.9, 4.9), resulting in an HR of 0.46 (80% CI: 0.35, 0.62). Fourteen (17.0%) patients with AML who received glasdegib in combination with LDAC achieved a CR, compared with one (2.3%) who received LDAC. The CR + CRi rate in the AML population was 24.3% (19/78) with glasdegib in combination with LDAC and 5.3% (2/38) with LDAC [102].

3.3 Limitations of clinical evidence for comparators

Important limitations regarding the quality of the pivotal studies and corresponding evidence for the relevant comparators warrant noting, since they make interpretation of benefit and cross-trial comparisons challenging.

- **Open-label design:** The pivotal trials of azacitidine, decitabine, and glasdegib in combination with LDAC were all open-label designs meaning bias may have been introduced, which could have impacted the estimated treatment effect [30, 31, 101, 102].

- **Definition of ineligibility for intensive chemotherapy:** Enrolment of patients eligible for intensive induction chemotherapy was allowed in the pivotal trials of azacitidine and decitabine, with unclear definitions of ineligibility [30, 31]. Patients enrolled in AZA-AML-001 and DACO-016 were ≥65 years of age, but as set out above (see section 2.3.1), this is not the only factor used to determine ineligibility for intensive chemotherapy. In AZA-AML-001, patients preselected for intensive chemotherapy were included in the azacitidine arm. Therefore, patients who were eligible for intensive chemotherapy (i.e., those considered fit and with a better prognosis) were included in the trial and thus it does not reflect the population of interest. For DACO-016, it remains unclear whether patients eligible for intensive chemotherapy were included and therefore the trial may not completely reflect the population of interest.

- **Pre-selection:** In AZA-AML-001 and AZA-001, patients in the control groups were pre-selected by the investigator using subjective criteria [30, 101]. In DACO-016, patients indicated, with physician's advice, their preferred treatment choice and so were not randomised to LDAC or BSC [31]. The unblinded and non-transparent nature of the treatment selection criteria may have resulted in selection bias.

- **Restriction of blast count:** The azacitidine trials included only patients with a particular bone marrow blast count; >30% for AZA-AML-001 and 20–30% for AZA-001. These patient restrictions limit the applicability of this evidence to the entire population of interest; patients who are ineligible for intensive chemotherapy [30, 101].

- ***Post hoc* analysis:** Another limitation of BRIGHT-AML 1003 (glasdegib in combination with LDAC), other than it being a small, Phase 2 trial, is the requirement for *post hoc* subgroup analyses for AML due to the inclusion of patients with MDS in the trial [102]. These analyses were not pre-planned and were underpowered for the primary endpoint (OS) and did not control for multiple testing [32]. Additionally, randomization was stratified by cytogenetic risk but not formally stratified by AML or MDS.

- **Certainty of evidence:** For BRIGHT-AML 1003, the certainty of evidence according to GRADE is considered low for OS and safety outcomes by EUnetHTA [32].

Assessment regarding risk of bias in relevant trials is further explored in section 7.6.1.

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4 CURRENT USE OF THE TECHNOLOGY

4.1 Summary of issues relating to current use of the technology

- Venetoclax was initially approved and launched as a monotherapy for the treatment of CLL, first in the US and later in Europe, and has since been approved and launched for further indications in CLL (in combination with rituximab) by the majority of jurisdictions worldwide (see section 1.3 for more details) [11, 12, 103-112].

- On 21 November 2018, venetoclax in combination with HMAs (azacitidine or decitabine) or LDAC was granted accelerated approval by the FDA and launched as a treatment of newly diagnosed AML in adults 75 years of age or older, or who have comorbidities that preclude the use of intensive chemotherapy [10]. Subsequently, on 16 October 2020 the FDA granted full approval for venetoclax in this indication. Venetoclax in combination with HMAs or LDAC is also approved in over 30 countries worldwide for the treatment of AML and is under review in a number of others (see section 1.3 for more details) [59].

- Early real-world evidence from the US indicates that venetoclax combinations achieve high response rates and increase survival rates (OS and EFS) at 6, 12 and 24 months compared with matched control patients who received a range of treatments, including low- and high-intensity therapy (i.e., HMA, intensive chemotherapy) [113, 114].

- For patients with AML who are ineligible for intensive chemotherapy, venetoclax is included as part of the NCCN and ESMO guidelines as the preferred and a promising treatment, respectively. In the NCCN guidelines for AML, venetoclax is a preferred treatment for use in patients without actionable mutations or with IDH1, IDH2, or FLT3 mutations, and in patients who are not candidates for intensive chemotherapy. Furthermore, venetoclax in combination with an HMA or LDAC is considered to be superior to current first-line treatments for AML in ESMO guidelines, despite not yet being licensed in Europe [14, 25, 32].

4.2 Current use of the technology in EUnetHTA countries

- Venetoclax is available in multiple indications in all countries that are part of EUnetHTA as shown in Table 4.1.

- For CLL, venetoclax is used as monotherapy or in combination with rituximab or obinutuzumab. It is widely reimbursed as monotherapy and in combination with rituximab. It is also reimbursed in combination with obinutuzumab (including in Germany and the UK), with assessments of this combination ongoing in several additional countries [11, 103-112, 115].

- For AML:

    - In Italy, venetoclax has been included in the 648 list (Law 648/96) since 10 March 2020, under the indication of venetoclax in combination with azacitidine or decitabine for the treatment of newly diagnosed AML in adults who are not eligible for intensive induction chemotherapy, or who are 75 years or older [116].

    - In the UK, venetoclax has been included in a “COVID-friendly” cancer treatments program as an oral alternative to more toxic standard chemotherapy for patients with AML [117].

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4.3 Reimbursement and assessment status of the technology

Table 4.1 Overview of the reimbursement status of venetoclax in CLL in European countries

Country	Indication(s)	Status of recommendation (positive/negative/ongoing/not assessed)	If positive, level of reimbursement
Austria	R/R and 1L	Positive	Reimbursed
Belgium[14]	R/R	Positive	Reimbursed
Bulgaria	R/R	Positive	Reimbursed
Croatia	R/R	Positive	Reimbursed
Czech Republic	R/R	Positive	Reimbursed with restrictions
Denmark[11]	R/R	Positive	Reimbursed
Finland	R/R and 1L	Positive	Reimbursed
France	R/R	Positive	Reimbursed
Germany[1-4]	R/R	Positive	Reimbursed
Greece*[13]	R/R and 1L	Positive	Reimbursed
Hungary	R/R	Positive	Reimbursed
Italy[5,6]	R/R	Positive	Reimbursed
Netherlands[12]	R/R	Positive	Reimbursed
Norway	R/R	Positive	Reimbursed
Poland	R/R	Positive	Reimbursed with restrictions
Portugal	R/R	Positive	Reimbursed
Romania	R/R	Positive	Reimbursed
Slovenia	R/R	Positive	Reimbursed
Spain[7,8]	R/R	Positive	Reimbursed
Sweden[15]	R/R and 1L	Positive	Reimbursed
Switzerland	R/R	Positive	Reimbursed
United Kingdom[9,10]	R/R and 1L	Positive	Reimbursed

*Conditional reimbursement for 1L CLL
Abbreviations: 1L, first-line; CLL, chronic lymphocytic leukaemia; R/R, relapse/refractory.
Sources: [1-4][103-106];[5,6][107, 108];[7,8][109,110];[9,10][111, 112]; [11][118]; [12][119]; [13][120];[14][121]; [15][122]

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5 INVESTMENTS AND TOOLS REQUIRED

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

- Venetoclax is an oral medication and is not expected to require any specialised equipment, or to necessitate additional resources to store, prepare, or administer the treatment [47].
- No further investments or tools are required for HMAs (azacitidine and decitabine) as these are already established as SoC in clinical practice.
- Monitoring during the initial dose-titration phase does not require any additional investments or tools as protocols and training will already be in place for patients with CLL treated with venetoclax [11, 47].
- Treatment with venetoclax is likely to reduce overall healthcare resource use by reducing the frequency of transfusions required by patients with AML [8, 80].

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6 REQUIREMENTS TO USE THE TECHNOLOGY

Venetoclax is a prescription-only medicine and it is recommended that venetoclax should only be prescribed under the supervision of a physician with experience in the use of anticancer medicinal products, and in the management of their associated adverse events [47].

Venetoclax can be administered at home or during hospital outpatient or inpatient visits. Venetoclax is given in the form of immediate-release tablets for oral administration and patients are instructed to swallow the tablets whole, with water, at approximately the same time each day. The tablets should be taken with a meal to avoid the risk of lack of efficacy and the tablets should not be chewed, crushed, or broken before swallowing [47].

Azacitidine must be administered by a doctor or trained nurse via subcutaneous injection, as per the label [48].

Venetoclax requires a daily dose-titration of 3 days when combined with azacitidine or decitabine. The recommended venetoclax dosing schedule (including dose titration) is shown in Table 6.1.

Table 6.1 Dosing schedule for titration phase in patients with AML

Day of ramp-up phase	Venetoclax daily dose
1	100 mg
2	200 mg
3 and beyond	400 mg

Abbreviations: AML, acute myeloid leukaemia.
Source: [47]

An HMA should be initiated on Cycle 1, Day 1. Azacitidine should be administered at 75 mg/m^2 either intravenously or subcutaneously on Days 1–7 of each 28-day cycle, beginning on Cycle 1, Day 1. Decitabine should be administered at 20 mg/m^2 intravenously on Days 1–5 of each 28-day cycle, beginning on Cycle 1, Day 1. Venetoclax dosing may be interrupted as needed for management of hematologic toxicities and blood count recovery. Venetoclax, in combination with an HMA, should be continued until disease progression or unacceptable toxicity [47].

Venetoclax can cause a rapid reduction in tumour cells, and thus poses a risk for tumour lysis syndrome in the initial 5 week dose titration phase. The following prophylactic measures should be followed [47]:

- All patients should have a white blood cell count <25 × 10^9/L prior to initiation of venetoclax; cytoreduction prior to treatment may be required.
- All patients should be adequately hydrated and receive anti-hyperuricemic agents prior to initiation of the first dose of venetoclax and during the dose titration phase.
- Assess blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) and correct pre-existing abnormalities prior to initiation of treatment with venetoclax.
- Monitor blood chemistries for tumour lysis syndrome at pre-dose, 6–8 hours after each new dose during titration, and 24 hours after the final dose.
- For patients with risk factors for tumour lysis syndrome (e.g., circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment lactate dehydrogenase levels, or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose.

6.1 Additional equipment

No additional equipment is required.

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6.2 Supplies required to use the technology

The following supplies will be needed for each associated aspect of venetoclax treatment.

Azacitidine subcutaneous administration (when venetoclax is given in combination with azacitidine only) [48]:

- Vials of water for reconstitution of powder
- Non-sterile surgical gloves
- Alcohol wipes
- 5 mL injection syringes with needles (recommended 25 gauge)

Decitabine intravenous administration (when venetoclax is given in combination with decitabine only) [52]:

- Protective gloves
- Intravenous access line
- Vials of water to perform reconstitution
- Cold infusion fluids to dilute reconstituted solution (sodium chloride [0.9%] or glucose solution [5%])

Supplies needed to perform blood chemistry monitoring test:

- Several blood chemistry analyses will be conducted as part of the prophylaxis management and tumour lysis syndrome and adverse events monitoring before and throughout the venetoclax treatment cycle. These include measuring potassium, uric acid, phosphorus, calcium, creatine, platelet count, and lactate dehydrogenase level. The analyses are reasonably routine, and any hospital should be equipped with the general supplies and equipment necessary to perform these analyses.

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7 CLINICAL EFFECTIVENESS AND SAFETY

7.1 Summary of clinical effectiveness

- Venetoclax in combination with azacitidine significantly improves median OS in patients with newly diagnosed AML who are ineligible for intensive chemotherapy, achieving a survival benefit of >5 months compared with azacitidine alone. Venetoclax in combination with azacitidine maintains OS benefit across the majority of prognostic subgroups in this patient population [8, 38]. Venetoclax in combination with azacitidine also doubles the survival rate at 2 years (36.5% versus 18.3%, p<0.001) compared with azacitidine monotherapy in patients with AML ineligible for intensive chemotherapy [38].
- Venetoclax in combination with azacitidine results in rapid, durable remissions: venetoclax plus azacitidine doubles the CR + CRi rate compared with azacitidine alone (66% versus 28%, p<0.001) at a median follow-up of 20.5 months [8, 38].
- Similar effectiveness of HMA combinations (azacitidine and decitabine) with venetoclax was demonstrated in the Phase 1b study M14-358 [6]. Long-term follow-up data confirmed that venetoclax in combination with azacitidine or decitabine both demonstrate comparable high, durable response rates [37].
- Venetoclax in combination with azacitidine increases rates of RBC or platelet transfusion independence by ≥19% compared with azacitidine alone, thereby potentially reducing the length of stay in hospital and the associated healthcare costs [8]
- Venetoclax in combination with azacitidine demonstrates longer time to deterioration (TTD) in quality of life by >7 months compared with azacitidine, as measured by the EORTC QLQ-C30 scale (venetoclax in combination with azacitidine: 16.5 months versus 9.3 months, p=0.066) [46].
- Indirect treatment comparisons suggest that, compared with LDAC, venetoclax in combination with azacitidine significantly prolongs OS and EFS, and results in significantly higher rates of CR + CRi [42].

7.2 Summary of safety

- Venetoclax in combination with HMAs (azacitidine or decitabine) has a well-characterised and manageable safety profile that is consistent across trials [6, 8].
- Venetoclax in combination with HMAs (azacitidine or decitabine) has similar 30-day mortality rates to HMAs alone [6, 8, 31].

7.3 Identification and selection of relevant studies

7.3.1 Databases and trial registries

A systematic literature search was conducted in a number of databases, conference proceedings, and websites [123].

The following databases were searched via Ovid platform:

- MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Cochrane Database of Systematic Reviews (CDSR)
- Database of Abstracts of Reviews of Effects (DARE)

The following conference proceedings were searched for abstracts published from Year 2017 via Ovid Northern Light Life Sciences Conference Abstracts

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(http://www.ovid.com/site/catalog/databases/13207.jsp) or via the conference website if the latest conference abstracts were not indexed in Northern Light database:

- European Hematology Association (EHA): https://ehaweb.org/
- American Society of Clinical Oncology (ASCO): https://www.asco.org/
- British Society for Haematology (BSH): https://b-s-h.org.uk/
- European Society for Medical Oncology (ESMO): https://www.esmo.org/
- American Society of Hematology (ASH): https://www.hematology.org/

ClinicalTrials.gov is considered an important data source and was searched via web link (https://clinicaltrials.gov/) to identify clinical trials that reported trial results related to the population of interest. The purpose of this search was to identify clinical trial results that were available on the registry website but not published in a manuscript.

NICE (https://www.nice.org.uk/) and the Scottish Medicines Consortium (https://www.scottishmedicines.org.uk/) websites were searched for HTA reports or manufacturer submissions related to AML. Key clinical studies identified in these reports were cross-checked against those included in this systematic literature review (SLR) [123].

7.3.2 Search dates and limits placed on the searches

The initial searches were conducted in January 2019 and further updated October 2020. Appendix section 8.1.1 presents the October 2020 search strategy (including search date) for all sources searched.

The searches were not restricted by publication date however were restricted to English language publications in human studies [123].

7.3.3 Inclusion and exclusion criteria

The eligibility criteria for the initial, global SLR were defined according to PICO criteria that were as broad as possible, encompassing all possible comparators and outcomes which may be relevant globally (Table 7.1).

The population of interest was defined as treatment-naive adult patients (aged ≥18 years) with AML who are ineligible for intensive chemotherapy. During the study eligibility assessment, 'treatment-naive' was considered interchangeable with 'previously untreated' or 'newly diagnosed'. Patients were considered ineligible for intensive chemotherapy if a study defined patients as being old/elderly, unfit for intensive chemotherapy, unfit for standard chemotherapy, or unfit for high-dose chemotherapy. This allowed studies using many different definitions of 'ineligible' to be identified. To align with the inclusion criteria for VIALE-A and VIALE-C, patients with secondary AML with or without prior treatment with HMAs for MDS were included. To avoid possible heterogeneity, studies specifically designed to recruit patients with HIV, HBV, or HCV infection were excluded. Studies that did not actively exclude patients with HIV, HBV, or HCV were included.

For the purposes of the EUnetHTA REA, additional eligibility criteria were applied to the global SLR to the extent possible after full text review to reflect the EUnetHTA-specific PICO criteria. The revised selection criteria are presented in Table 7.2. The global PICO was modified to identify studies of direct comparisons of venetoclax in combination with HMAs versus the relevant comparators as well as studies of comparator technologies that may enable indirect comparisons. Specifically, studies that compared the following interventions were included: venetoclax plus azacitidine, venetoclax plus decitabine, azacitidine, LDAC, decitabine, glasdegib plus LDAC, and best supportive care. Further, only randomised clinical trials were included and single-arm trials, observational studies, or studies with only one arm of interest were excluded. These additional criteria were designed to identify high-quality comparative data that could enable indirect comparisons and a connected network of venetoclax against all relevant treatments. Because the branches in the network consist of the relative contrast (e.g., odds ratio, hazard ratio) of two treatments, a trial must include a treatment contrast between two or more treatments within the scope of the PICO in order to contribute meaningfully to the evidence network [123].

The selection of relevant studies is described in Appendix section 8.1.2.

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Table 7.1 Inclusion and exclusion criteria: SLR according to broad (global) PICO

Criteria	Inclusion	Exclusion
Population	Treatment-naive adult patients (age ≥18 years) with AML who are ineligible for intensive chemotherapy • 'Treatment-naive' was defined as patients who had not received any prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment ○ Prior treatment for MDS was allowed except for use of cytarabine • 'Treatment-naive' is considered interchangeable with 'previously untreated' or 'newly diagnosed' • 'Ineligible for intensive chemotherapy' included patients described as old/elderly, unfit for intensive chemotherapy, unfit for standard chemotherapy, or unfit for high-dose chemotherapy • Patients with secondary AML with or without prior treatment with HMAs for MDS were included Studies specifically designed to recruit patients with HIV, HBV, or HCV infection were excluded; studies that did not actively exclude patients with HIV, HBV, or HCV were included	• Not adult • Not human • Not treatment-naive AML • Patients with HIV, HBV, or HCV infection • Acute promyelocytic leukaemia
Intervention/ comparator	Studies with at least one of the following regimens: • Venetoclax + azacitidine • Venetoclax + LDAC • Venetoclax + decitabine • Azacitidine • LDAC • Decitabine • Glasdegib + LDAC • Gemtuzumab ozogamicin • CAG (Cytarabine, aclarubicin, G-CSF) • Clofarabine • Gilteritinib • Ivosidenib • Best supportive care including blood transfusion, etoposide, mercaptopurine, or hydroxyurea	Studies without any of the regimens listed in the inclusion criteria
Outcomes	Studies reporting at least one of the following outcomes: • Overall survival • Event-free survival • Progression-free survival • Relapse-free survival • Complete remission • Complete remission with incomplete blood count recovery • Composite complete remission • Complete remission with partial hematologic recovery • Objective response • Partial remission • Duration of remission • Minimal/measurable residual disease • Grade 3 or 4 adverse events • Discontinuation due to adverse events	Studies not reporting any of the outcomes listed in the inclusion criteria

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Study design	• Randomised controlled trials • Non-randomised trials	• Editorials, letters, comments, case reports of individual patients, erratum and notes • Observational studies • SLRs and meta-analyses or review articles
Settings	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 restrictions	English language articles	Non-English language articles
Others considerations	• Inclusion was restricted to studies with ≥20 patients per arm • Studies with mixed myelodysplastic syndromes and AML populations were excluded unless outcomes were reported for the AML subgroup • The bibliographies of SLRs and meta-analyses identified from the search were cross-checked before being excluded	

Abbreviations: AML, acute myeloid leukaemia; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human Immunodeficiency virus; G-CSF, granulocyte-colony stimulating factor; LDAC, low-dose cytarabine; SLR, systematic literature review.
Source: [123]

Table 7.2 Inclusion and exclusion criteria: SLR according to EUnetHTA-specific PICO

Criteria	Inclusion	Exclusion
Population	Treatment-naive adult patients (age ≥18 years) with AML who are ineligible for intensive chemotherapy • 'Treatment-naive' was defined as patients who had not received any prior treatment for AML with the exception of hydroxyurea, allowed through the first cycle of study treatment ○ Prior treatment for MDS was allowed except for use of cytarabine • 'Treatment-naive' is considered interchangeable with 'previously untreated' or 'newly diagnosed' • 'Ineligible for intensive chemotherapy' included patients described as old/elderly, unfit for intensive chemotherapy, unfit for standard chemotherapy, or unfit for high-dose chemotherapy • Patients with secondary AML with or without prior treatment with HMAs for MDS were included Studies specifically designed to recruit patients with HIV, HBV, or HCV infection were excluded; studies that did not actively exclude patients with HIV, HBV, or HCV were included	• Not adult • Not human • Not treatment-naive AML • Patients with HIV, HBV, or HCV infection • Acute promyelocytic leukaemia
Intervention/ comparator	Studies with at least one of the following regimens: • Venetoclax + azacitidine • Venetoclax + decitabine • Azacitidine • LDAC • Decitabine • Glasdegib + LDAC • Best supportive care (varies by country, may include: hydroxyurea, 6-mercaptopurine, 6-thyoguanine, low-dose melphalan, transfusion support, anti-infective therapies, etc.)	Studies without any of the regimens listed in the inclusion criteria

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Outcomes	Studies reporting at least one of the following outcomes: • Overall survival • Complete remission • Complete remission with incomplete blood count recovery • Composite complete remission • Complete remission with partial hematologic recovery • Duration of remission • Event-free survival • Minimal/measurable residual disease • Grade 3 or 4 adverse events • Discontinuation due to adverse events	Studies not reporting any of the outcomes listed in the inclusion criteria
Study design	• Randomised controlled trials	• Editorials, letters, comments, case reports of individual patients, erratum and notes • Observational studies • SLRs and meta-analyses or review articles
Settings	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 restrictions	English language articles	Non-English language articles
Others considerations	• Inclusion was restricted to studies with ≥20 patients per arm • Studies with mixed myelodysplastic syndromes (MDS) and AML populations were excluded unless outcomes were reported for the AML subgroup • The bibliographies of SLRs and meta-analyses identified from the search were cross-checked before being excluded	

Abbreviations: AML, acute myeloid leukaemia; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; G-CSF, granulocyte-colony stimulating factor; LDAC, low-dose cytarabine; SLR, systematic literature review.
Source: [123]

7.3.4 PRISMA flow diagram

The literature search was conducted in January 2019 and updated in October 2020. A total of 10,197 records were identified from the October 2020 search. After removing 2,878 duplicates, a total of 7,319 records were assessed for eligibility (Figure 7.1). A comprehensive overview of the number of records retrieved by each search by date and database is provided in appendix section 8.1.3.

A total of 18 documents corresponding to six unique RCTs met the eligibility criteria for this EUnetHTA REA and were extracted. Of these, one study was selected that directly compared the safety and efficacy of venetoclax in combination with an HMA versus a relevant comparator (azacitidine and LDAC): VIALE-A. The other five studies were selected as potential sources for indirect comparisons of venetoclax in combination with an HMA versus comparators not addressed in VIALE-A (e.g., LDAC, glasdegib in combination with LDAC or BSC) [123].

Summaries of the publications included and excluded during the full-text review, are available in appendix sections 8.1.4 and 8.1.5.

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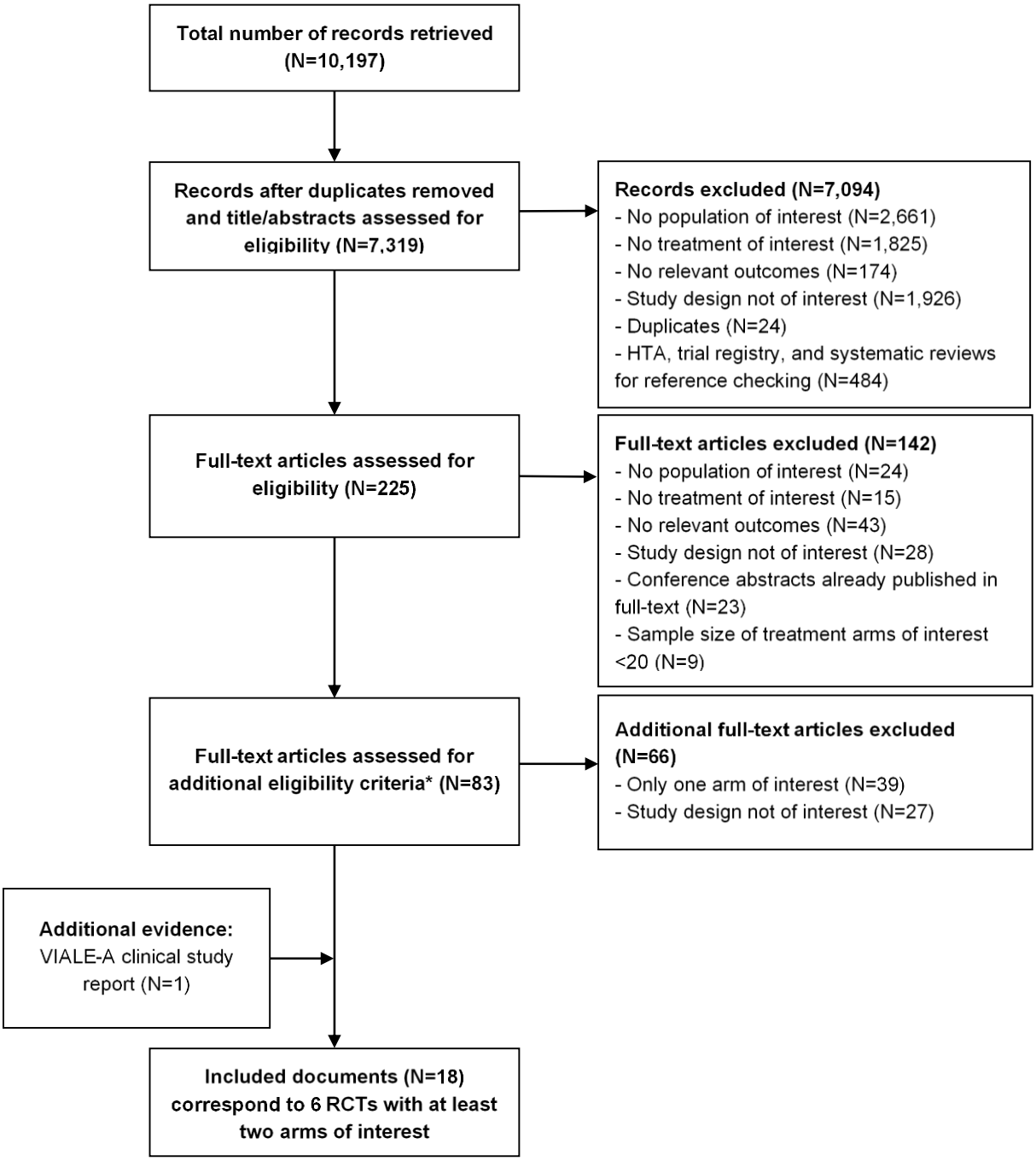
Figure 7.1 PRISMA flow chart



*Additional eligibility criteria were applied according to EUnetHTA-specific PICO:

- Study design of interest: Non-randomised clinical trials removed to correspond with the EUnetHTA-specific PICO for efficacy outcomes
- Updated treatment of interest: venetoclax + azacitidine, venetoclax + decitabine, azacitidine, LDAC, decitabine, glasdegib + LDAC, and BSC

Source: [123]

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7.4 Relevant studies

A total of six studies were considered relevant for this assessment according to the EUnetHTA-specific PICO [123]. In addition, although they were not identified based on the search criteria, the venetoclax Phase 1b study M14-358 and Phase 3 study VIALE-C, provide supportive evidence to VIALE-A as part of the same development program. M14-358 is a Phase 1b open-label non-randomised study of venetoclax in combination with HMAs, azacitidine or decitabine [6]. VIALE-C is another large double-blinded Phase 3 randomised controlled trial of venetoclax in comparison with LDAC alone [9]. Both trials provide further clinical and safety data regarding venetoclax in combination with SoC in patients with newly diagnosed AML. Therefore, they are included in this dossier to provide further evidence for venetoclax, but they were not considered for inclusion in the network of studies for indirect treatment comparison (ITC) (Table 7.3).

The Phase 3, double-blind, multicentre RCT, VIALE-A, from the venetoclax development program was included based on the predefined inclusion/exclusion criteria and was considered the primary source of evidence for this assessment. This trial evaluated efficacy and safety of venetoclax in combination with azacitidine versus azacitidine only in adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy [8].

Six studies were considered for ITCs assessing venetoclax in combination with an HMA versus HMAs, LDAC, glasdegib in combination with LDAC or BSC [8, 30, 31, 101, 102, 124].

Study design, endpoints, treatment, and baseline patient characteristics from the relevant studies are summarized in the following sections.

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Table 7.3 List of all relevant studies for this assessment

Study reference/ID	Available documentation	Status (ongoing/ completed)
Randomised controlled trials (identified by SLR)		
VIALE-A (NCT02993523)	DiNardo C, Jonas B, Pullarkat V, et al. A Randomised, Double-Blind, Placebo-Controlled Study Of Venetoclax With Azacitidine Vs Azacitidine In Treatmentnaive Patients With Acute Myeloid Leukemia Ineligible For Intensive Therapy-VIALE-A. European Hematology Association. 2020:LB2601. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. N Engl J Med 2020;383:617-29 doi: 10.1056/NEJMoa2012971 Clinical study report from AbbVie 22 23	Ongoing Est. completion May 2021
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 Seymour J, Doehner H, Kumar R, et al. Overall survival (OS) and clinical outcomes in older patients with acute myeloid leukemia (AML) treated with azacitidine (AZA) or low-dose cytarabine (LDAC) in the AZA-AML-001 study. Paper presented at: HAEMATOLOGICA2015. Seymour JF, Buckstein R, Santini V, et al. Efficacy and Safety of Azacitidine (AZA) Versus Conventional Care Regimens (CCR) in Patients Aged ≥75 Years with Acute Myeloid Leukemia (AML) in the Phase 3 AZA-AML-001 Study. Blood. 2016;128(22):2818-2818. Seymour JF, Döhner H, Minden MD, et al. Incidence rates of treatment-emergent adverse events and related hospitalization are reduced with azacitidine compared with conventional care regimens in older patients with acute myeloid leukemia. Leuk Lymphom a. 2017;58(6):1412-1423.	Completed
AZA-001 (NCT00071799)	Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28(4):562-569.	Completed
DACO-016 (NCT00260832 2005-004503-11)	Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomised, open-label, Phase 3 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 Mayer J, Arthur C, Delaunay J, et al. Multivariate and subgroup analyses of a randomised, multinational, Phase 3 trial of decitabine vs. treatment choice of supportive care or cytarabine in older patients with newly diagnosed acute myeloid leukemia and poor- or intermediate-risk cytogenetics. BMC Cancer. 2014;14:69.	Completed
Short et al., 2019 (NCT01786343)	Short NJ, Kantarjian HM, Loghavi S, et al. Treatment with a 5 day versus a 10 day schedule of decitabine in older patients with newly diagnosed acute myeloid leukaemia: a randomised Phase 2 trial. Lancet Haematol. 2019;6(1):e29-e37.	Completed
BRIGHT-AML 1003 (NCT01546038	Cortes JE, Heidel FH, Hellmann A, Fiedler W, Smith BD, Robak T, et al. Randomised 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	Completed

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2012-000684-24)	Heuser M, Fiedler W, Sekeres M, et al. Clinical benefit of glasdegib plus low-dose cytarabine in patients with de novo and secondary acute myeloid leukemia: long-term analysis of Phase 2 randomised trial: PS1029. HemaSphere. 2019;3:464-465. Kwon Y, Bell TJ, Solem C, et al. Quality-Adjusted Survival for Low-Dose Cytarabine (LDAC) Versus Glasdegib+ LDAC Among Newly Diagnosed Acute Myeloid Leukemia Patients Who Are Not Candidates for Intensive Chemotherapy: A Q-TWiST Analysis. In: American Society of Hematology Washington, DC; 2019. Smith BD, Papayannidis C, Heuser M, et al. Low-dose cytarabine with or without glasdegib in newly diagnosed patients with acute myeloid leukemia: Long-term analysis of a Phase 2 randomised trial. In: American Society of Clinical Oncology; 2019. Zeidan AM, Schuster MW, Krauter J, et al. Clinical Benefit of Glasdegib in Combination with Azacitidine or Low-Dose Cytarabine in Patients with Acute Myeloid Leukemia. In: American Society of Hematology Washington, DC; 2019. Heuser M, Robak T, Montesinos P, et al. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and four-year overall survival (OS) follow-up. In: American Society of Clinical Oncology; 2020. Heuser M, Robak T, Montesinos P, et al. Glasdegib (GLAS) plus low-dose cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 final report and 4 year overall survival (OS) follow-up. In: European Hematology Association; 2020.	
Randomised and non-randomised controlled trials (supportive of VIALE-A)		
VIALE-C (NCT03069352)	Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a Phase 3 randomised placebo-controlled trial. Blood 2020;135:2137-45 doi: 10.1182/blood.2020004856. Wei AH, Montesinos P, Ivanov V, et al. A Phase 3 study of venetoclax plus low-dose cytarabine in previously untreated older patients with acute myeloid leukemia (VIALE-C): A six-month update. In: American Society of Clinical Oncology; 2020. Clinical study report from AbbVie	Ongoing Est. completion July 2022
M14-358 (NCT02203773)	Pollyea D.A., Pratz K., Letai A., Jonas B.A., Wei A.H., Pullarkat V., Konopleva M., Thirman M.J., Arellano M., Becker P.S., Chyla B., Hong W.-J., Jiang Q., Potluri J., DiNardo C.D. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a Phase 1b study. [Article in Press] American journal of hematology 2020. DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, Frankfurt O, Konopleva M, Wei AH, Kantarjian HM, Xu T, Hong WJ, Chyla B, Potluri J, Pollyea DA, Letai A. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019 Jan 3;133(1):7-17. doi: 10.1182/blood-2018-08-868752. Epub 2018 Oct 25.	Ongoing Est. completion: 27 September 2021

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7.5 Main characteristics of studies

Table 7.4 summarizes the characteristics of the studies VIALE-A, as well as supportive studies (VIALE-C and M14-358) and the studies of relevant comparator technologies.

7.5.1 VIALE-A

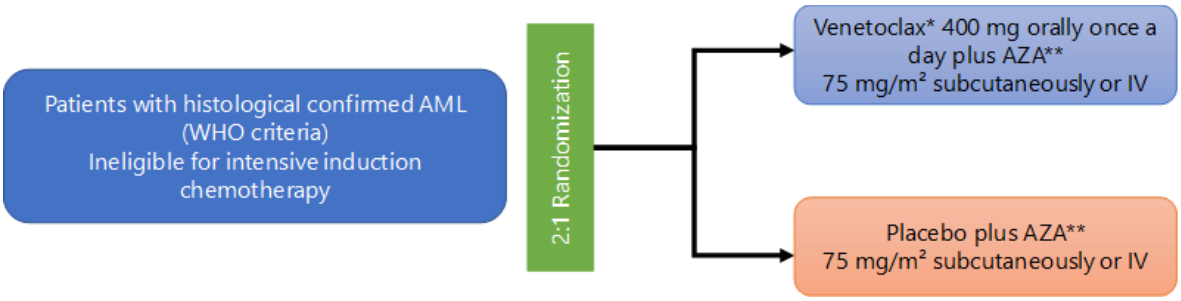
VIALE-A (NCT02993523) was a Phase 3, randomised, double-blind, placebo-controlled, multicentre trial designed to compare the efficacy and safety of venetoclax in combination with azacitidine to a control regimen of placebo plus azacitidine in previously untreated patients with AML who were ineligible for intensive chemotherapy [8]. Eligible patients were randomised in a 2:1 ratio to receive either venetoclax plus azacitidine or placebo plus azacitidine, stratified by age (18 to <75, ≥75), cytogenetics (intermediate risk, poor risk) and region (US, Europe, China, Japan, Rest of world). The study design is illustrated in Figure 7.2. The cut-off date for clinical data was 4 January 2020.

Venetoclax was administered orally, once daily. Venetoclax dose titration began at 100 mg on Day 1 in Cycle 1 and was increased to 200 mg on Day 2, and then to the target dose of 400 mg on Day 3. Dosing was continued at 400 mg until Day 28, and then in all subsequent 28-day cycles. Patients in the control group received an oral venetoclax placebo following the same schedule. All patients received azacitidine 75 mg/m^2, subcutaneously or intravenously, on Days 1–7 of every 28-day cycle.

The intent-to-treat population included all 431 patients who underwent randomization. For US and countries using the US as the reference country, the VIALE-A included a single primary endpoint of OS. For Japan, EU and countries using EU as reference countries, the study included dual-primary endpoints of OS and CR + CRi rate. For OS, it was estimated that 360 deaths among 400 patients would provide 86.7% power to detect a HR of 0.70 with the use of a log-rank test at a two-sided significance level of 0.04.

Patients continued to receive treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other protocol criteria for discontinuation were met [8].

Figure 7.2 VIALE-A study design



Abbreviations: AML; acute myeloid leukaemia; AZA, azacitidine; IV, intravenous; SC, subcutaneous; WHO, World Health Organization.
*Venetoclax (oral) daily ramp-up in Cycle 1; 100 mg D1, 200 mg D2, 400 mg D3 until D 28; subsequent 28-day cycles at 400 mg. **Azacitidine; 75 mg/m^2 IV or SC on days 1-7 for each 28-day cycle.
Source: [8]

7.5.2 VIALE-C (supportive of VIALE-A)

VIALE-C (NCT03069352) was a Phase 3, randomised, double-blind, placebo-controlled, multicentre trial designed to compare the efficacy and safety of venetoclax in combination with low-dose cytarabine (LDAC) to a control regimen of placebo plus LDAC in previously untreated patients with AML who were ineligible for intensive chemotherapy [40]. Eligible patients were randomised in a 2:1 ratio to receive either venetoclax plus LDAC or placebo plus LDAC, stratified AML status (secondary, de novo), age (18 to <75, ≥75) and region (US, Europe, China, Japan, Rest of world)

Venetoclax was administered orally, once daily. Venetoclax dose titration began at 100 mg on Day 1 and was increased over 4 days to reach the target dose of 600 mg (100 mg, 200 mg, 400 mg, 600 mg).

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Dosing continued at 600 mg from Day 4 until Day 28 and then in all subsequent 28-day cycles. Patients in the control group received an oral venetoclax placebo following the same schedule. All patients received LDAC 20 mg/m² subcutaneously on Days 1 to 10 of each 28-day cycle.

The planned sample size was 210 patients; 133 events were required to be observed at the time of analysis. The study was designed to detect a 45.5% reduction in mortality with 90% power and a significance level with 2-sided α of 0.05.

Patients continued treatment until disease progression, unacceptable toxicity, withdrawal of consent, or other protocol criteria for discontinuation were met [40].

7.5.3 M14-358 (supportive of VIALE-A)

M14-358 was a Phase 1b, open-label, non-randomised, multicentre study to evaluate the safety and pharmacokinetics of orally administered venetoclax combined with decitabine or azacitidine and the preliminary efficacy of these combinations. Patients (N = 145) were at least 65 years old with treatment-naive AML and were ineligible for intensive chemotherapy [6].

The study consisted of two phases: dose escalation, in order define recommended dose of venetoclax combined with an HMA, and dose expansion. During dose escalation, oral venetoclax was administered at 400, 800, or 1,200 mg daily in combination with either decitabine (20 mg/m^2, days 1–5, intravenously) or azacitidine (75 mg/m^2, days 1-7, intravenously or subcutaneously). Based on the preliminary safety and efficacy data, two venetoclax dosing schedules (400 mg and 800 mg) were evaluated separately in the expansion stage, in combination with either decitabine or azacitidine.

The number of patients required for the dose-escalation phase was dependent on the toxicities observed as the trial progressed, with 45 patients enrolled. The expansion stage consisted of 100 additional patients, with 25 patients in each dose level of 400 and 800 mg venetoclax, treated with each HMA combination. Safety and efficacy analyses were performed per protocol on all patients who received at least one dose of venetoclax.

7.5.4 AZA-AML-001 (Dombret et al., 2015)

AZA-AML-001 was a Phase 3, randomised, open-label, multicentre trial that evaluated azacitidine efficacy and safety versus conventional care regimens (CCRs) in 488 patients age ≥65 years with newly diagnosed AML with >30% bone marrow blasts. Eligible patients were not considered eligible for hematopoietic stem cell transplantation [30].

CCR consisted of standard intensive chemotherapy, LDAC, and BSC. Before randomization, a CCR was preselected for each patient based on age, ECOG performance status, comorbidities, and regional guidelines and/or institutional practice. Patients were then randomised 1:1 to azacitidine (n = 241) or CCR (n = 247), stratified by preselected CCR (BSC, LDAC, or IC), ECOG performance status (0-1 or 2), and cytogenetic risk (intermediate or poor). Patients assigned to CCR received their preselected treatment [30].

Azacitidine was administered subcutaneously 75 mg/m^2 per day for 7 consecutive days per 28-day treatment cycle for at least six cycles. CCRs were as follows: BSC only (blood product transfusions and antibiotics, with granulocyte colony-stimulating factor for neutropenic infection); subcutaneous LDAC (20 mg twice per day for 10 days per 28-day treatment cycle for at least 4 cycles); or standard induction chemotherapy (cytarabine 100–200 mg/m^2 per day by continuous intravenous infusion for 7 days, plus 3 days of either daunorubicin 45-60 mg/m^2 per day or idarubicin 9-12 mg/m^2 per day) for 1 cycle, followed by up to two consolidation cycles (i.e., the same anthracycline regimen as used at induction and the same cytarabine dose used for induction but administered for 3 to 7 days) for those achieving CR or PR. Reinduction was not allowed. Reduction or delay in azacitidine and LDAC dosing was permitted to allow blood count recovery. All study participants could receive BSC, including transient use of hydroxyurea (hydroxyurea was not allowed within 72 hours before or after azacitidine administration) [30].

The planned sample size (480 patients) assumed a median OS of 10.5 months in the azacitidine arm and 7.5 months in the CCR arm (40% improvement), with a 1% dropout rate from each treatment arm. To demonstrate a statistically significant OS difference at a 1-sided significance level of 0.025 with at

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least 90% power to detect a constant HR of 0.71 the design required 374 deaths. Efficacy analyses were performed for the intent-to-treat population. Comparison of azacitidine versus individual CCRs within treatment preselection groups (intensive chemotherapy, LDAC, or BSC) were exploratory analyses and were not powered to detect statistical differences between treatments. The results should be interpreted with caution [30].

7.5.5 AZA-001 (Fenaux et al., 2010)

AZA-001 was a Phase 3, randomised, open-label, parallel-group, multicentre trial in patients with higher-risk myelodysplastic syndromes. A sub-analysis of this primary trial including only patients with AML with 20–30% bone marrow or peripheral blasts based on central bone marrow review (i.e., with French–American–British-defined, RAEB-t and WHO-defined AML) compared the effects of azacitidine versus CCR on OS. The data cut-off date was 24 July 2007 [101].

One of three CCRs (BSC, LDAC, or intensive chemotherapy) was selected for patients by investigators based on age, ECOG performance status, and comorbidities and institutional, regional, or national guidelines. Preselection was based on the individual choice of the investigator. Patients were then randomly assigned to receive azacitidine or the preselected CCR. No crossover was permitted and use of erythropoietin or darbepoetin was not allowed [101].

Administration of azacitidine was subcutaneous (75 mg/m^2/day) for 7 days of every 28-day cycle, for at least six cycles. BSC included blood product transfusions and antibiotics with granulocyte colony-stimulating factor for neutropenic infection. LDAC was administered subcutaneously (20 mg/m^2/day) for 14 days of every 28-day cycle, for at least four cycles. Intensive chemotherapy consisted of induction with cytarabine (100 to 200 mg/m^2/day by continuous infusion) for 7 days plus daunorubicin (45 to 60 mg/m^2/day), idarubicin (9 to 12 mg/m^2/day), or mitoxantrone (8 to 12 mg/m^2/day) for 3 days. Consolidation therapy was administered to patients with CR or PR. This consisted of one or two courses of the patient's induction therapy but at a reduced dose, followed by BSC. To allow for blood count recovery treatment with azacitidine or LDAC could be delayed as appropriate. All patients could receive BSC, and all treatment regimens were administered until study end or patient discontinuation because of disease progression, unacceptable toxicity, or bone marrow blasts more than 30% with a 50% increase from the pre-treatment blast count [101].

Efficacy analyses included all randomly assigned patients with WHO-defined AML (≥20% bone marrow blasts) [101].

7.5.6 DACO-016 (Kantarjian et al., 2012)

DACO-016 was a Phase 3, randomised, open-label, multicentre trial that compared the efficacy and safety of decitabine with treatment choice in patients aged ≥65 years with newly diagnosed AML and poor- or intermediate-risk cytogenetics [31].

Patients indicated, with physician advice, their preferred treatment choice, either BSC or LDAC. Patients (N = 485) were randomly assigned 1:1 to receive decitabine or treatment choice, stratified by age, cytogenetic risk, and ECOG performance status. Decitabine was administered as 1-hour intravenous infusions, 20 mg/m^2 once per day for five consecutive days every 4 weeks. LDAC was administered as a subcutaneous injection, 20 mg/m^2 per day for 10 consecutive days every 4 weeks. Treatment continued until relapse or progressive disease (PD), death, unacceptable toxicity, lack of clinical benefit, intercurrent illness preventing treatment, or patient/physician request. Patients were allowed hydroxyurea until cycle 1 on day 15 [31].

The planned sample size (480 patients) assumed that median survival was 8 months for decitabine and 6 months for treatment choice. The study was designed to detect a 25% reduction in mortality risk with ≥80% power and a significance level of 0.05 (two-sided). Observation of ≥385 events was required at the time of analysis [31].

7.5.7 Short et al., 2019

Short et al., 2019 was a Phase 2, randomised, open-label, single-centre trial to assess the efficacy of decitabine given in either 5-day or 10-day schedules. This study was conducted at a single academic centre (The University of Texas MD Anderson Cancer Center) [124].

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Eligible patients were adults ≥60 years of age with newly diagnosed AML (by WHO criteria, i.e., ≥20 % blasts, excluding acute promyelocytic leukaemia) who were deemed unsuitable for intensive anthracycline plus cytarabine-based chemotherapy. Criteria for ineligibility for intensive chemotherapy included age, performance status, comorbidities and karyotype. Patients <60 years of age could also be enrolled if deemed not to be a candidate for intensive anthracycline plus cytarabine-based chemotherapy. Randomization took place between 28 February 2013 and 12 April 2018; the data cut-off for this analysis was 15 May 2018 [125].

Patients were randomised to receive decitabine 20 mg/m^2 intravenously as induction for either 5 consecutive days or 10 consecutive days. Initially 40 patients were allocated equally to the two treatment arms using block randomization. After the completion of the equal randomization, the response-adaptive randomization algorithm was employed to unbalance the randomization probabilities in favour of the arm with a superior response rate. Responding patients received decitabine on a 5-day schedule as consolidation for up to 24 cycles. Courses were repeated every 4–8 weeks, depending on toxicity and the recovery of neutrophil and platelet counts.

The planned sample size (100 patients) assumed a composite response rate of about 30% in both arms. If at any time the probability that one of the schedules was better is higher than 0.95, then it would be declared as superior [124].

7.5.8 BRIGHT-AML 1003 (Cortes et al., 2020)

The Phase 2 BRIGHT-AML 1003 trial was a subgroup of the larger randomised, open-label, multicentre B1371003 trial, which enrolled patients with either previously untreated AML or high-risk MDS considered not eligible for intensive chemotherapy. Analyses of the AML patient subgroup were not pre-planned and randomization was stratified by cytogenetic risk (but not formally stratified by AML or MDS). B1371003 was conducted in Europe and North America and started in June 2012; the primary completion date was January 2017 [102].

Patients (N = 132) (stratified by cytogenetic risk: good/intermediate or poor) were randomised at a 2:1 ratio to receive glasdegib in combination with LDAC or LDAC alone. Administration of glasdegib was 100 mg once daily orally in 28-day cycles on a continuous basis. Subcutaneous administration of LDAC (20 mg) was twice daily for 10 days every 28 days. Patients remained on treatment until disease progression, unacceptable toxicity, or patient refusal [102].

The planned sample size (132 patients, including AML and MDS patients) assumed a median OS of approximately 5 months in the LDAC arm and 8 months in the glasdegib in combination with LDAC arm, resulting in an expected HR of 0.625 (i.e., 60% improvement in OS). Observation of 92 OS events would provide 80% power to detect the 60% improvement in OS at one-sided significance level of 0.10. The interim analysis would occur when 46 OS events were observed [102].

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Table 7.4 Key characteristics of the relevant, and supportive, studies for this assessment

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
VIALE-A M15-656 (NCT02993523)	To compare the efficacy and safety of venetoclax plus AZA to placebo + AZA in previously untreated AML patients ineligible for intensive chemotherapy due to medical comorbidities and/or were ≥75 years old	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Key inclusion criteria: Patients aged ≥18 years with previously untreated AML confirmed by WHO criteria. Patients must be considered ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities as defined by the following: • ≥75 years of age; **or** • ≥18 to 74 years of age with at least one of the following comorbidities: – ECOG PS 2 or 3 – Cardiac history of CHF requiring treatment or ejection fraction ≤50% or chronic stable angina – DLCO ≤65% or FEV1 ≤65% – Creatinine clearance ≥30 mL/min to <45 ml/min – Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN – Any other comorbidity that was physician judged to be incompatible with intensive chemotherapy. Patients must have a projected life expectancy of at least 12 weeks. Patients must have an ECOG PS: • 0 to 2 for patients ≥75 years; **or**	• Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3 until Day 28; subsequent 28-day cycles at 400 mg plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle (N = 286) versus • Placebo QD plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle (N = 145)	Dual primary endpoint: OS (months) All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study. Composite CR rate (CR + CR with incomplete hematologic recovery; CR + CRi) Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International	• CR rate • CR + CRh rate • Proportion of patients achieving composite CR by initiation of cycle 2 • Rates of RBC and platelet transfusion independence • CR rates and OS in molecular and cytogenetic subgroups • EFS • MRD response rate • HRQL • Safety Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or CRi. Disease assessments were performed with the use of the modified International Working Group response criteria for AML. Patients were followed for safety and tolerability from the first

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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
			• 0 to 3 for patients ≥18 to 74 years. Patients must have adequate renal function as demonstrated by a creatinine clearance ≥30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-h urine collection. Patients must have adequate liver function as demonstrated by: • AST ≤3.0 × ULN* • ALT ≤3.0 × ULN* • bilirubin ≤1.5 × ULN* *Unless considered due to leukemic organ involvement. • Patients who are <75 years may have a bilirubin of ≤3.0 × ULN. Key exclusion criteria: Prior receipt of any hypomethylating agent, venetoclax, or chemotherapy for myelodysplastic syndrome. Patients with favourable cytogenetic risk as per the AML NCCN Guidelines.		Working Group response criteria for AML.	dose of study drug until 30 days after the last dose of study drug. PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.
VIALE-C M16-043 (NCT03069352) (supportive of VIALE-A)	To compare the efficacy and safety of venetoclax + LDAC to placebo + LDAC in previously untreated AML patients ineligible for intensive chemotherapy due to medical	Phase 3, randomised, double-blind, placebo-controlled, multicentre	Key inclusion criteria: Patients aged ≥18 years with previously untreated AML confirmed by WHO criteria. Patients must be considered ineligible for treatment with a standard cytarabine and anthracycline induction regimen due age or comorbidities as defined by the following: • ≥75 years of age; **or**	• Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, 600 mg Day 4 until D28; subsequent 28-day cycles at 600 mg plus • LDAC 20 mg/m^2 SC on days 1–10 in	OS (months) All patients were followed for survival information (date/cause of death) every 2 months after the last study visit or as needed until the end of the study.	• CR rate • CR + CRi rate • CR + CRh rate • Proportion of patients with CR/CRi and CR/CRh by the initiation of therapy cycle 2 • Rate of transfusion independence

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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
	comorbidities and/or were ≥75 years old		• ≥18 to 74 years of age with at least one of the following comorbidities: – ECOG PS 2 or 3 – Cardiac history of CHF requiring treatment or ejection fraction ≤50% or chronic stable angina – DLCO ≤65% or FEV1 ≤65% – Creatinine clearance ≥30 mL/min to <45 ml/min – Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 × ULN – Any other comorbidity that was physician judged to be incompatible with intensive chemotherapy. Patients must have a projected life expectancy of at least 12 weeks. Patients must have an ECOG PS: • 0 to 2 for patients ≥75 years; **or** • 0 to 3 for patients ≥18 to 74 years. Patients must have adequate renal function as demonstrated by a creatinine clearance ≥30 mL/min; calculated by the Cockcroft Gault formula or measured by 24-h urine collection. Patients must have adequate liver function as demonstrated by: • AST ≤3.0 × ULN* • ALT ≤3.0 × ULN* • bilirubin ≤1.5 × ULN*	every 28-day cycle (N = 143) versus • Placebo QD plus • LDAC 20 mg/m^2 SC on days 1–10 in every 28-day cycle (N = 68)		• EFS • MRD response rate • CR rates and OS in molecular and cytogenetic subgroups • HRQL • Safety Disease assessments were performed at end of Cycle 1 (±3 days) and every 3 cycles starting on Cycle 4 Day 1 and continuing until disease progression as defined per ELN criteria or withdrawn consent. Patients were followed for safety and tolerability from the first dose of study drug until 30 days after the last dose of study drug. PRO assessments were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including the Final Visit.

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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
			*Unless considered due to leukemic organ involvement. • Patients who are <75 years may have a bilirubin of ≤3.0 × ULN. Key exclusion criteria: • Prior receipt of treatment for AML, except hydroxyurea (allowed through the first cycle of study treatment). • Prior treatment for myelodysplastic syndrome is allowed except for use of cytarabine. • Had an antecedent MPN including myelofibrosis, essential thrombocytosis, polycythaemia vera, or CML with or without BCR-ABL 1 translocation and AML with BCR-ABL 1 translocation. • Have acute promyelocytic leukaemia • Has known CNS involvement with AML • Has received strong or moderate cytochrome P450 3A4 inducers 7 days prior to the initiation of study treatment. • Patients with cardiovascular disability, chronic respiratory disease or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, history of other malignancies, any other			

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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
			medical condition or known hypersensitivity to any of the study medications including excipients of LDAC. • Previous treatment with venetoclax and/or current participation in any other research study with investigational products.			
M14-358 (NCT02203773) (supportive of VIALE-A)	To evaluate the safety and pharmacokinetics of orally administered venetoclax combined with DEC or AZA and the preliminary efficacy of these combinations	Phase 1b, open-label, non-randomised, multicentre study	Key inclusion criteria: • Confirmed AML by WHO criteria • Ineligible for treatment with a standard cytarabine and anthracycline induction regimen due to comorbidity or other factors • Received no prior treatment for AML with the exception of hydroxyurea • ECOG PS of 2 for subjects ≥75 years of age, or 0 to 3 for subjects ≥60 to 74 years of age • Adequate kidney and liver function as described in the protocol Key exclusion criteria: • Received treatment with an HMA and/or chemotherapeutic agent for an antecedent hematologic disorder • History of Myeloproliferative Neoplasm • Favourable risk cytogenetics as categorized by the NCCN Guidelines Version 2, 2014 for AML	Dose escalation: • Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, until maximum dose is reached (400, 800, or 1,200 mg); max dose until D28; subsequent 28-day cycles at 400 mg or 800 mg or 1,200 mg plus • AZA (75 mg/m^2, days 1–7, IV or subcutaneously) or • DEC (20 mg/m^2, days 1–5, IV) Expansion: • Venetoclax QD, ramp-up in Cycle 1; 100 mg Day 1, 200 mg Day 2, 400 mg Day 3, (600 mg Day 4, 800 mg Day 5) until	Response: • CR • CRi • ORR (CR + CRi + PR) Determined by the number of subjects who achieve a CR/CRi. Reponses were evaluated per the International Working Group criteria for AML. Time frame: Measured up to 1 year after the last subject last dose. Pharmacokinetics: • AUC from 0 to the time of the last measurable concentration	• Percent of subjects who move on to stem cell transplant. • Duration of Response defined as the number of days from the date of first response per the IWG criteria for AML to the earliest recurrence or PD. • EFS defined as the number of days from the date of first dose to the date of earliest evidence of relapse, subsequent treatment other than stem cell transplant while in composite complete response (CR + CRi), or death. Time frame: Measured up to 1 year after the last subject last dose

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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
			• t(8;21), inv(16), t(16;16) or t(15;17) karyotype abnormalities • Acute promyelocytic leukaemia. • Active CNS involvement with AML • Received a strong and/or moderate CYP3A inducer within 7 days prior to the initiation of study treatment	Day 28; subsequent 28-day cycles at 400 mg or 800 mg plus • AZA 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle or • DEC (20 mg/m^2, days 1–5, IV) All treated patients (N = 145) • Venetoclax 400 mg (N = 60; 29 with AZA, 31 with • DEC) • Venetoclax 800 mg (N = 74; 37 each AZA or DEC) • Venetoclax 1,200 mg (N = 11; 6 AZA, 5 DEC)	• AUC from 0 to the time of the last measurable concentration. • Half-life • Cmax • Maximum observed concentration, occurring at Tmax. • Clearance defined as the rate at which drug is cleared from the blood. • AUC over a 24-hour dose interval. • Time to Cmax • AUC from 0 to infinity Time frame: For approximately 5 days following a single dose of venetoclax OS: Defined as the number of days from the date of enrolment to the date of death.	

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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
					Time frame: Measured up to 1 year after the last subject last dose	
AZA-AML-001 (NCT01074047)	To evaluate the efficacy and safety of AZA compared with conventional care regimens (doctor's choice of BSC only, LDAC, or standard intensive chemotherapy) in patients age ≥65 years with newly diagnosed AML and >30 % BM blasts	Phase 3, open-label, international, multicentre, randomised	Key inclusion criteria: • 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) • ECOG PS ≤2 • WBC count ≤15 × 10^9/L Key exclusion criteria: • 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 hematologic disorders other than MDS (e.g., myeloproliferative neoplasms) • Other malignancies • Uncontrolled systemic infection • Prior DEC, AZA, or cytarabine treatment • Prior AML therapy (except hydroxyurea, which was allowed up to 2 weeks before the	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 intensive chemotherapy: 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.	Secondary outcomes: • 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, WBC count, BM blasts, and prior history of MDS

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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
			screening haematology sample was taken) • Any experimental drug within 4 weeks of starting study treatment			
AZA-001 (NCT00071799)	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 ≥20 % BM blasts or peripheral blasts based on central BM review (i.e., with FAB-defined RAEB-t and WHO-defined AML).	Phase 3, international, multicentre, randomised, controlled, parallel-group, open-label trial	Key inclusion criteria: • Aged ≥18 years • Patients with ≥20% BM or peripheral blasts based on central BM review (i.e., with FAB-defined RAEB-t and WHO-defined AML) • ECOG PS 0–2 • estimated life expectancy of ≥3 months Key exclusion criteria: • Patients with therapy-related myelodysplastic syndrome, previous AZA treatment, or planned allogeneic stem-cell transplantation	Treatment phase: Patients were randomly assigned (1:1) to receive AZA or conventional care regimen. AZA: N = 55 • preselected for BSC: N = 36 • preselected for LDAC: N = 14 • preselected for IC: N = 5 Conventional care regimen: N = 58 • BSC: N = 27 • LDAC: N = 20 • IC: N = 11	OS, analysed by comparison of the AZA and combined conventional care groups. OS was defined as time from random assignment until death from any cause.	Secondary outcomes: • Morphologic CR assessed according to International Working Group AML response criteria • Transfusion independence defined as absence of RBC or platelet transfusions during 56 consecutive days • AEs (assessed using National Cancer Institute Common Toxicity Criteria, version 2.0), rate of fever requiring intravenous antibiotics, and hospitalisation rates and duration
DACO-016 (NCT00260832)	To compare the efficacy and safety of DEC with patient choice, with physician advice (BSC or LDAC) in	Phase 3, open-label, international, multicentre, randomised	Key inclusion criteria: • Aged ≥65 years with newly diagnosed, histologically confirmed de novo or secondary AML (≥20 % blasts) and poor- or intermediate-risk cytogenetics	Treatment phase: Patients were randomly assigned (1:1) to receive DEC or treatment choice. • DEC: N = 242	OS (months), defined as time from randomization to death as result from any cause.	Secondary outcomes: • CR • CRp • Remission (evaluated by using modified 2003 IWG criteria)

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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
	older patients with AML		(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 Key exclusion criteria: • Acute promyelocytic leukaemia • t(8;21) or inv(16) karyotype abnormalities • CNS leukaemia • Active systemic malignancies • Unstable angina or New York Heart Association class 3/4 congestive heart failure • Inaspirable BM, 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 BM or stem-cell transplantation for 12 weeks before randomization • Received radiotherapy for extramedullary disease for 2 weeks pre-randomization	• 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.		• CRi • AEs
Short et al., 2019 (NCT01786343)	To evaluate the relative safety and efficacy of DEC given at a	Phase 2, randomised, open-label, single-centre	Key inclusion criteria: • Adults ≥60 years of age with newly diagnosed, previously	Treatment phase: Patients were randomly assigned to receive DEC	Composite response rate of CR, CRp, and CRi of the 5-day and	Secondary outcomes: • PR was defined according to the

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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
	dose of 20 mg/m^2 IV for either 5 or 10 consecutive days in older patients with AML unfit for intensive chemotherapy		untreated, AML (by WHO criteria, i.e., ≥20 % blasts, excluding acute promyelocytic leukaemia) who were deemed unsuitable for intensive chemotherapy as determined by Kantarjian's score [125] • Patients <60 years of age could also be enrolled if deemed not to be a candidate for intensive anthracycline plus cytarabine-based chemotherapy as determined by Kantarjian's score • ECOG PS of 0–3 • adequate renal and hepatic function, including a creatinine <2.5 mg/dL and total bilirubin <2.0 mg/dL • Patients with antecedent hematologic disorder (e.g., myelodysplastic syndrome or myeloproliferative neoplasm) were eligible, but they may not have received any prior HMAs Key exclusion criteria: • Uncontrolled intercurrent illness including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, active significant other cancers requiring chemotherapy and/or radiation therapy within past 6 months (excluding non-melanoma skin cancer) or psychiatric illness/social situations that would limit	5-day or 10-day schedule: DEC 5-day: N = 28 DEC 10-day: N = 43. The imbalance of the arms was due to the better performance of the 10-day DEC schedule during the initial period of the trial.	10-day DEC schedules assessed at any time during treatment. CR, CRp, and CRi, were defined according to the revised IWG guidelines for response assessment in AML.	revised IWG guidelines for response assessment in AML. • MRD was assessed by multiparameter flow cytometry performed on the BM at the time of remission as previously described. MRD positivity was defined as a cluster of at least 20 cells showing altered expression of ≥2 antigens. The sensitivity of this MRD assay was at least 0.01%. • Remission duration was calculated from the time of CR/CRp/CRi until relapse (censored for death in remission). • RFS was calculated from the time of remission until relapse or death. • OS was calculated from the time of treatment initiation until death.

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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
			compliance with study requirements			• Safety was assessed with the CTCAE version 4.0.
BRIGHT-AML 1003 (NCT01546038)	To evaluate the efficacy and safety of glasdegib plus LDAC versus LDAC in patients with AML or high-risk MDS who were not eligible for intensive chemotherapy	Phase 2, randomised, open-label, multicentre	Key inclusion criteria: • 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 Key exclusion criteria: • Acute promyelocytic leukaemia, • t(9;22) cytogenetic translocation • Active other malignancy • Known active uncontrolled leukaemia of the CNS • Prior treatment with Hedgehog inhibitor or other investigational	Treatment phase: • Glasdegib (100 mg once daily orally in 28-day cycles on a continuous basis) + LDAC (20 mg SC twice daily for 10 days every 28 days) (N = 78) • LDAC (20 mg SC 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.	Secondary outcomes: • CR, defined as those with repeat BM showing ≤5 % myeloblasts, peripheral blood showing neutrophils ≥1,000/all, platelets ≥100,000/µL, 0 % blast and haemoglobin ≥11 g/dL, normal maturation of all cell lines. • Disease specific efficacy endpoints such as CRi, MLFS, PR, PRi, MR, SD, CRc, CRm • Type, incidence, severity (graded by the NCI CTCAE, Version 4.0), timing, seriousness, and relatedness of AEs. Additional outcomes: • Transfusion need: Independence from transfusion is presented in terms of absolute and relative frequencies

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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
			agent for the treatment of an antecedent hematologic disease			

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukaemia; AST, aspartate aminotransferase; AUC, area under the plasma concentration-time curve; AUCt, area under the plasma concentration-time curve from time zero to time t; AZA, azacitidine; BM, bone marrow; BSC, best supportive care; CML, chronic myelogenous leukaemia; CNS, central nervous system; CR, complete response; CRc, cytogenic complete response; CRh, complete response with partial haematological recovery; CRi, complete response with incomplete blood count recovery; CRm, molecular complete response; CRp, complete response with incomplete platelet recovery, CTCAE, Common Terminology Criteria for Adverse Events; CYP3A, Cytochrome P450 family 3 subfamily A; DEC, decitabine; DLCO, diffusing capacity for carbon monoxide; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; ELN, European LeukemiaNet; FAB, French-American-British classification system; FEV1, forced expiratory volume in 1 minute; HIV, human immunodeficiency virus; HMA, hypomethylating agent; HRQL, health-related quality of life; IC, intensive chemotherapy; IV, intravenous; IWG, International Working Group; LDAC, low-dose cytarabine; MDS, Myelodysplastic syndrome; MLFS, morphologic leukaemia-free state; MPN, myeloproliferative neoplasms; MR, minor response; MRD, minimal/measurable residual disease; NCCN, National Comprehensive Cancer Network; NCI, National Cancer Institute; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial remission; PRi, partial remission with incomplete blood count recovery; PRO, patient-reported outcome; QD, once daily; RAEB-t, refractory anaemia with excess blasts in transformation; RBC, red blood cell; RFS, relapse-free survival; SC, subcutaneous; SD, stable disease; ULN, upper limit of normal; WBC, white blood cells; WHO, World Health Organization.
Source: [6, 8, 30, 31, 38, 40, 101, 124, 126-134].

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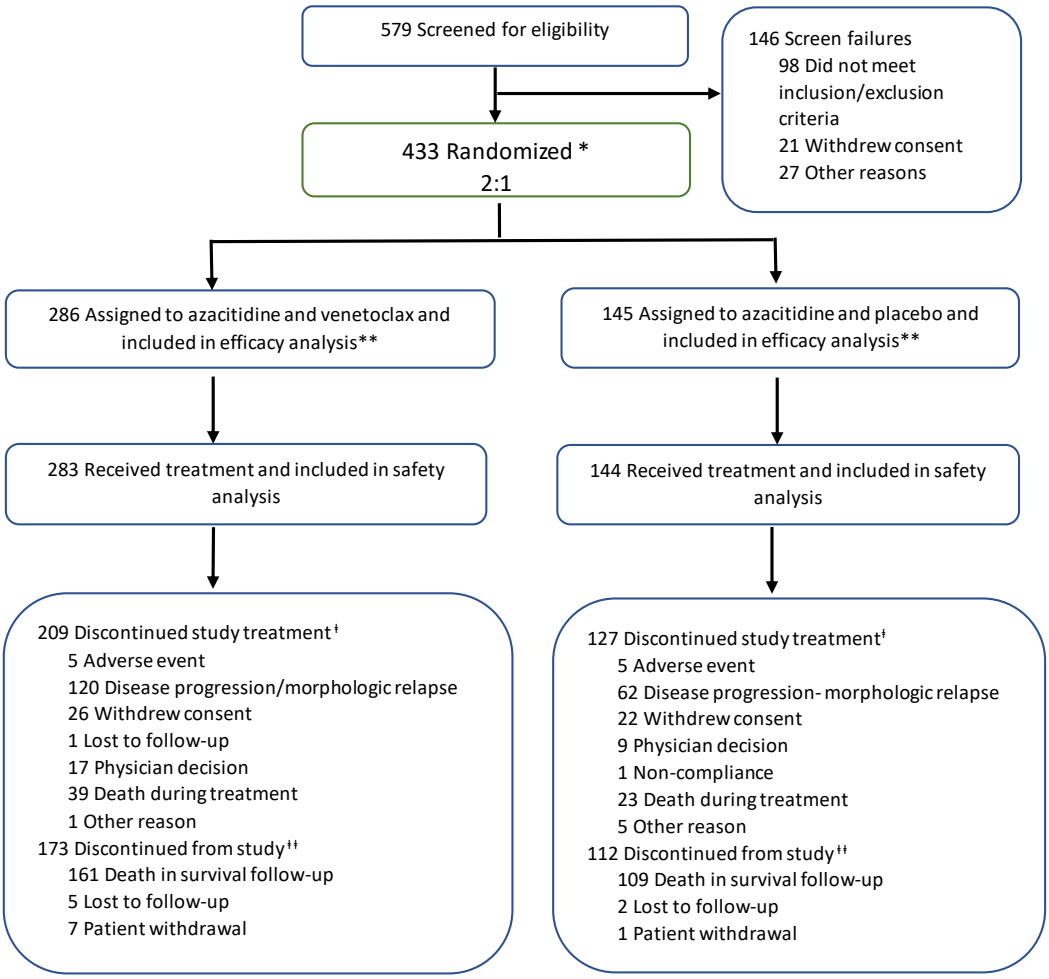
7.5.9 Study flow diagrams

Figure 7.3 through Figure 7.8 present consolidated standards of reporting trials (CONSORT) flow diagrams of 6 studies identified as relevant to this assessment by the SLR.

VIALE-A

Figure 7.3 Patient disposition in VIALE-A study



*Two patients were not stratified by cytogenetic risk. They were excluded from efficacy analysis but included in the safety analysis. Six patients who did not receive treatment were excluded from the safety analysis set.
**Two patients randomised to receive azacitidine + venetoclax and 1 patient randomised to receive azacitidine + placebo did not receive any treatment due to deterioration of pre-existing medical illness.
† Patients who discontinued treatment but were followed for survival.
†† Patients who were no longer observed for survival follow-up.
Two patients in azacitidine + venetoclax arm and 1 patient in the azacitidine + placebo arm underwent transplantation after discontinuing study treatment.
Source: [8]

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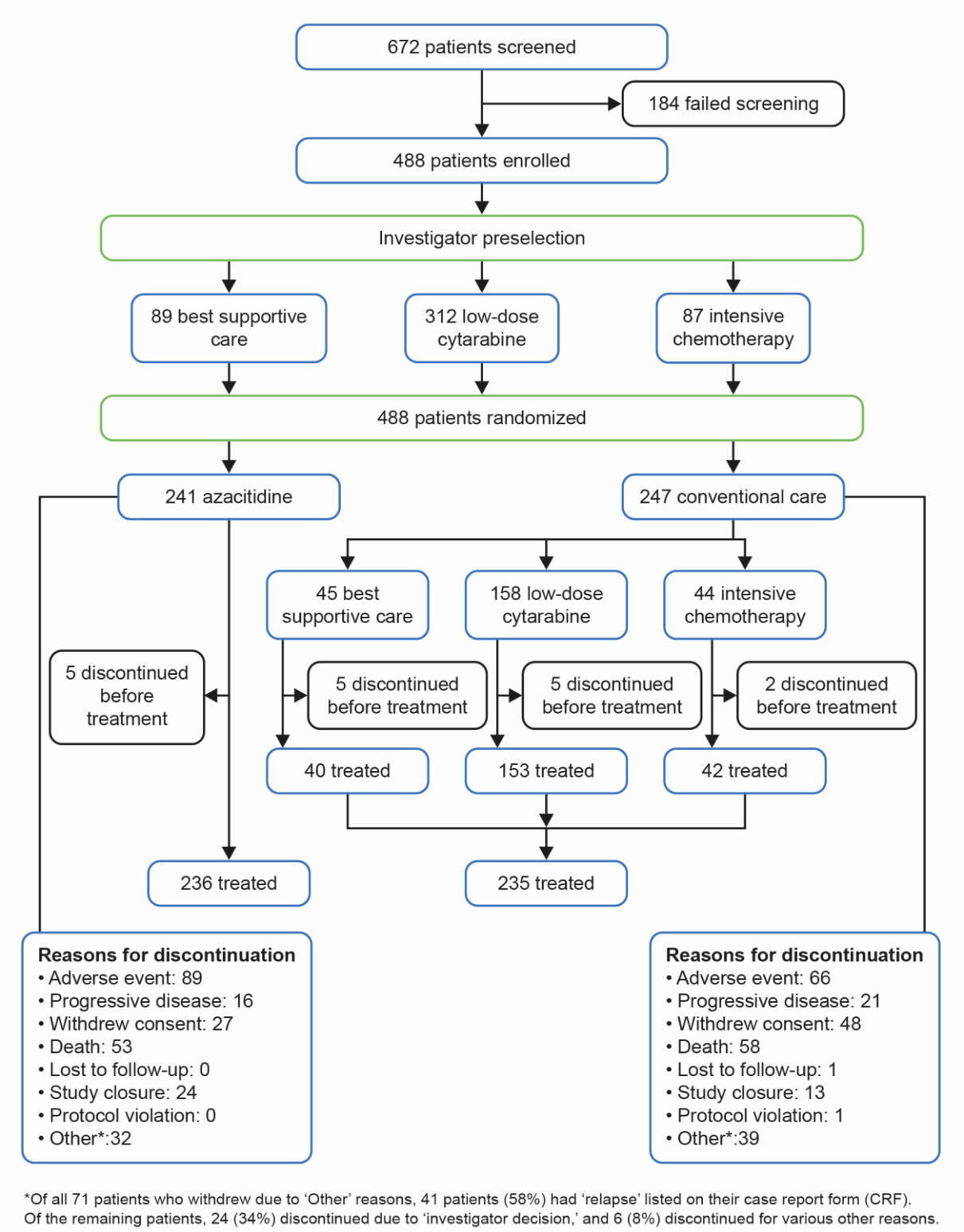
Relevant comparator studies

Figure 7.4 Patient disposition in AZA-AML-001 study



Source: [30]

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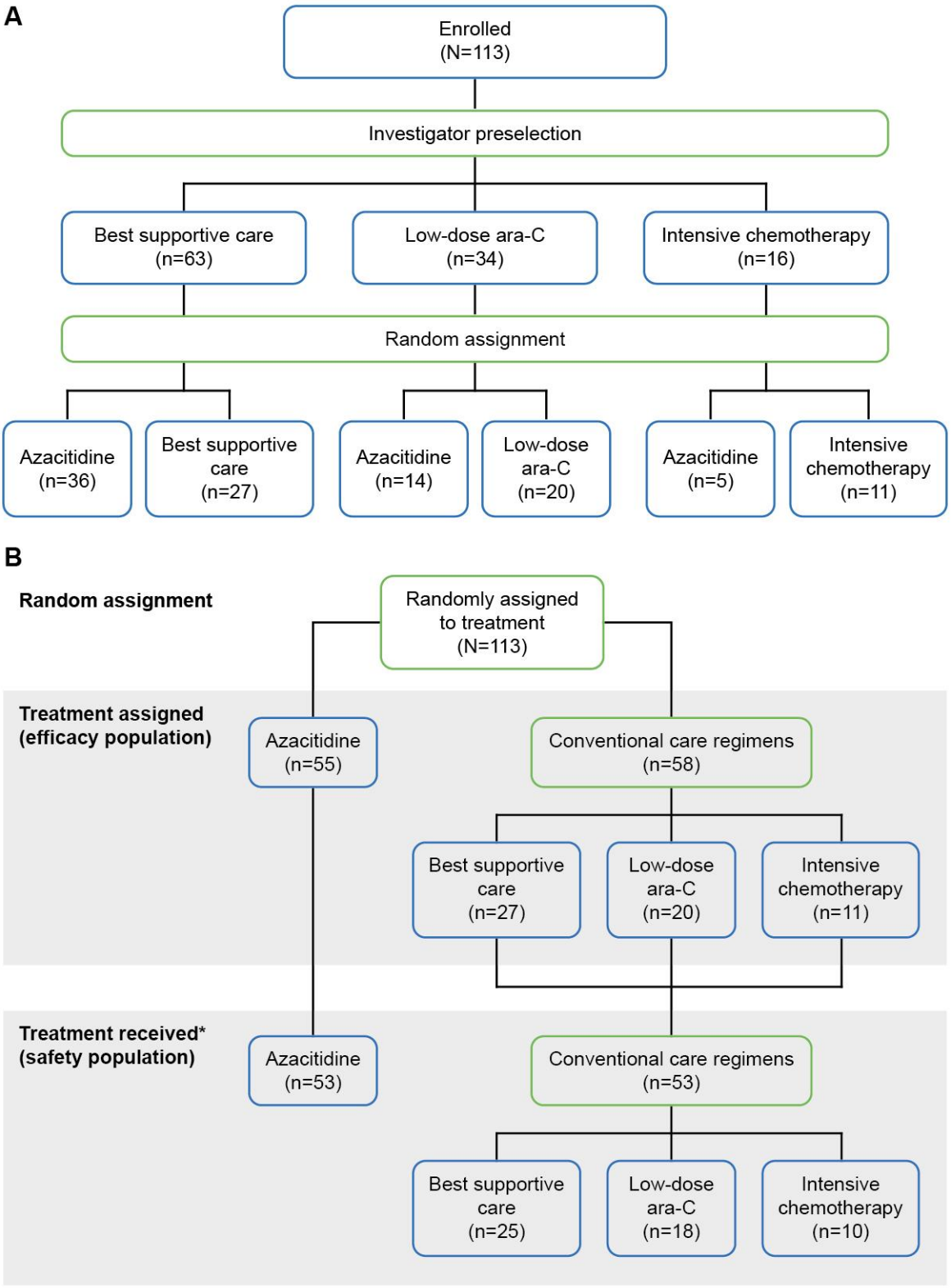
Figure 7.5 Patient disposition in AZA-001 study; (A) patient enrolment and investigator preselection of conventional care regimen and (B) subsequent random assignment to treatment and treatment received



*Seven patients withdrew from the study before receiving treatment and were not included in the safety population; two of the patients were from the azacitidine group, and five were from the conventional care regimen group (best supportive care, N=2; low-dose cytarabine [ara-C], N=2; and intensive chemotherapy, N=1).

Source: [101]

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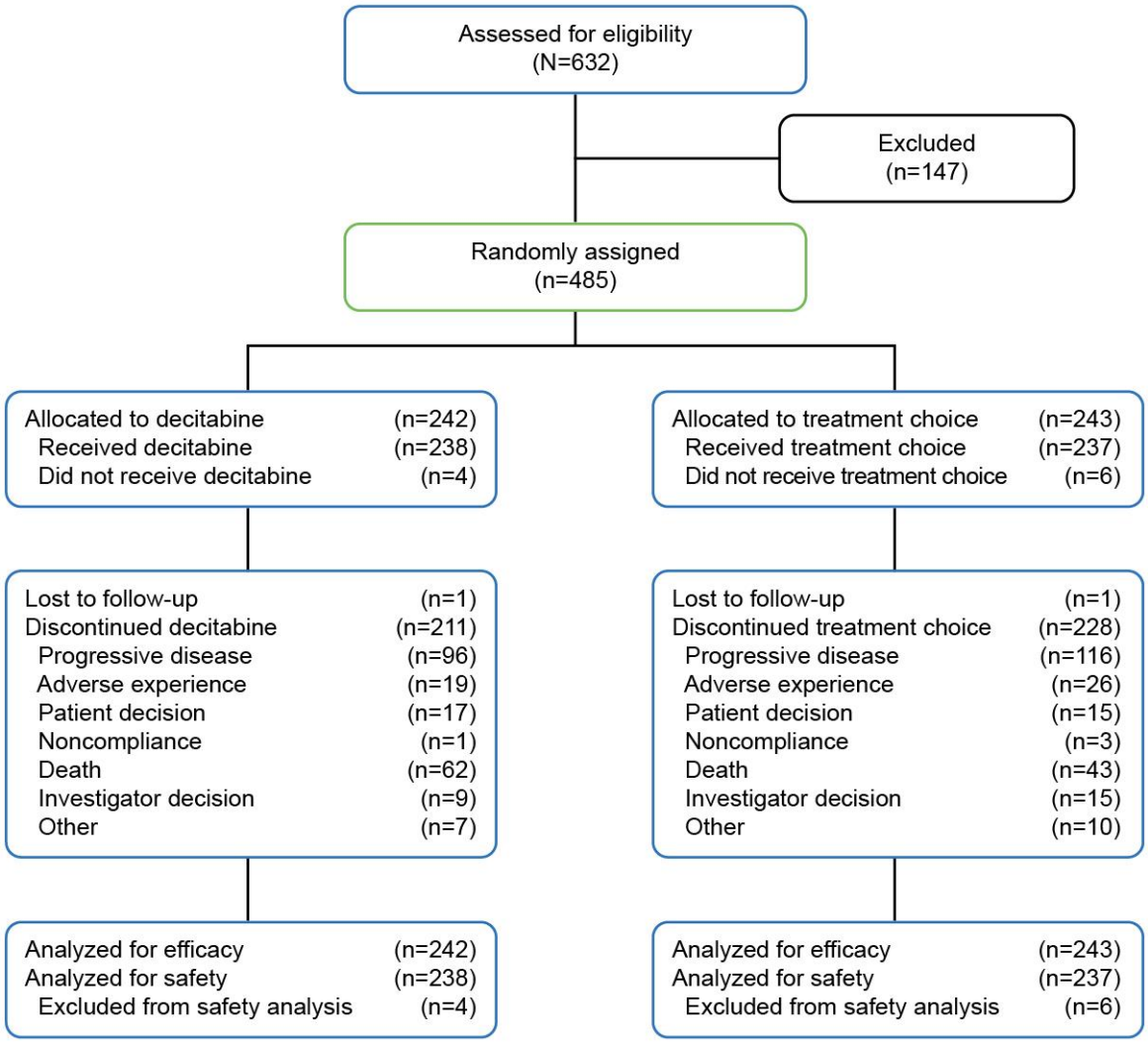
Figure 7.6 Patient disposition in DACO-016 study



Source: [31]

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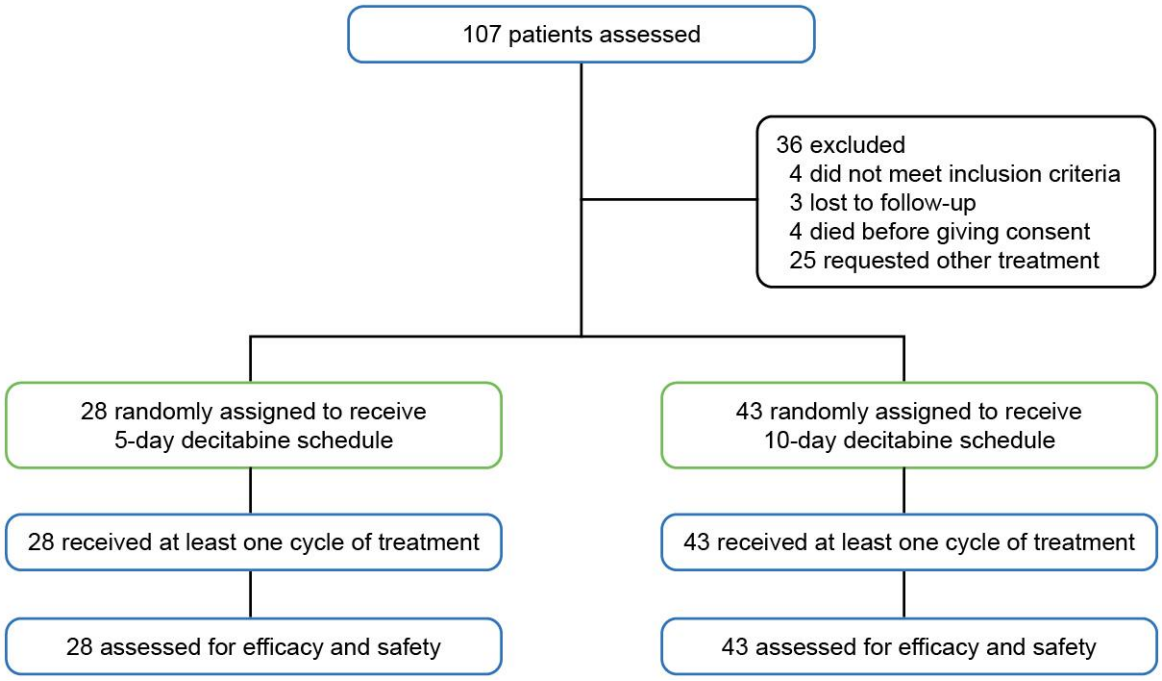
Figure 7.7 Patient disposition in Short et al., 2019 study



Source: [124]

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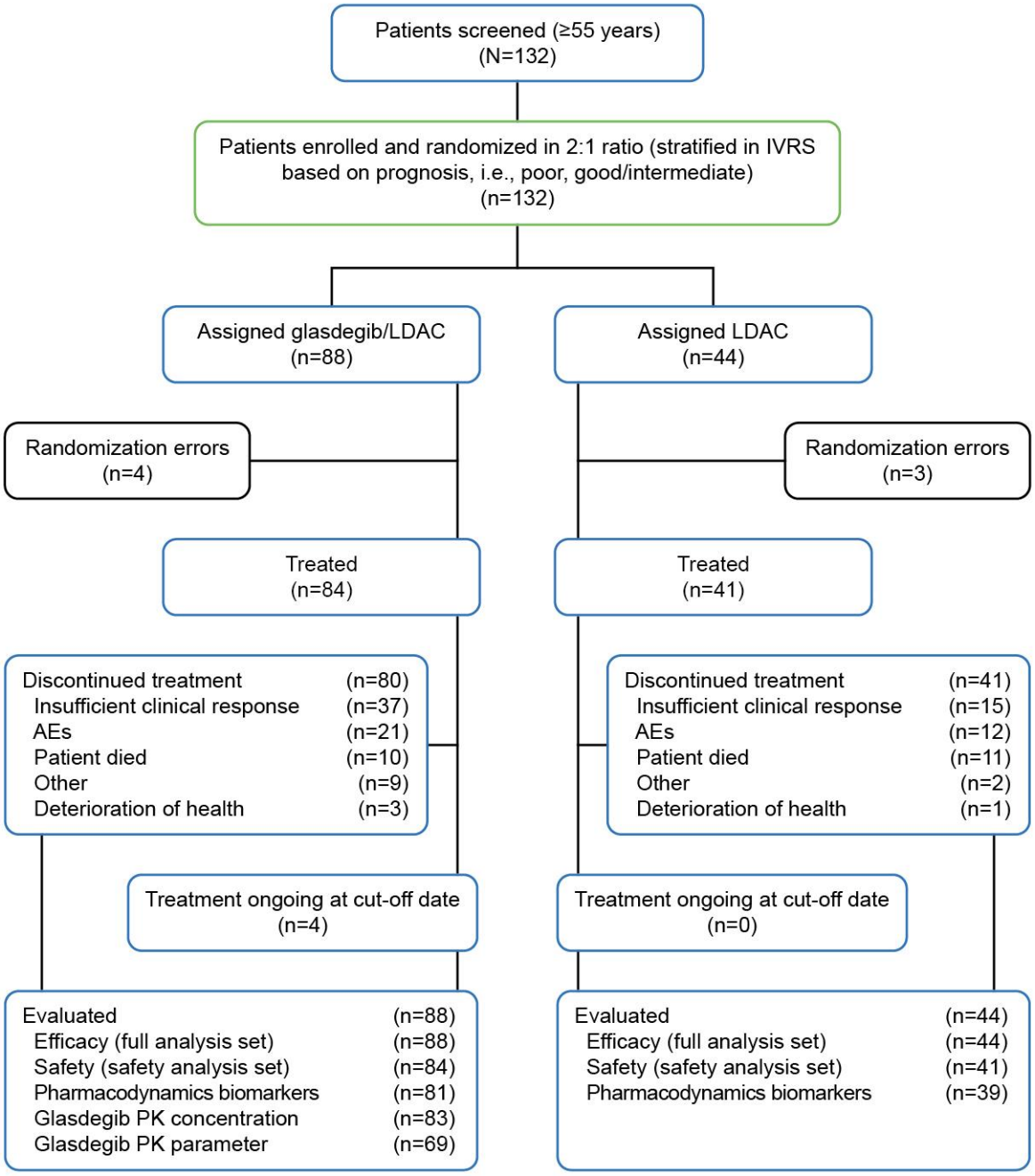
Figure 7.8 Patient disposition in BRIGHT-AML 1003 study



Data-cut 3 January 2017 (primary data-cut). Insufficient clinical response was determined by clinical judgment.
The randomization errors in 7/132 patients (5%) were due to patients withdrawing consent or failing to maintain eligibility requirements. Discontinuations were attributed to the last study treatment received. Treated was defined as patients who received at least one non-zero dose of glasdegib or LDAC.
AE, adverse event; IVRS, interactive voice response system; LDAC, low-dose cytarabine; PK, pharmacokinetic(s).

Source: [102]

7.5.10 Key demographic and baseline characteristics

Key demographic and baseline characteristics for all RCTs identified as relevant to this assessment by the SLR and the studies that support the pivotal trial, VIALE-A, for venetoclax in combination with an HMA for the treatment of adult patients with newly diagnosed AML who are ineligible for intensive chemotherapy are summarized in Table 7.5 and Table 7.6 [123]. A summary of the safety outcomes for all relevant trials is available in section 7.9 and appendix section 8.1.7

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Table 7.5 Summary of baseline patient demographics and clinical characteristics for VIALE-A, supportive studies and relevant comparator studies (part 1)

Study name	Treatment	N of patients randomised	Age (year), median (range)	Sex (male), n (%)	ECOG/WHO PS 0/1, n (%)	ECOG/WHO PS 2, n (%)	Primary/ de novo AML, n (%)	Secondary AML, n (%)
VIALE-A	VEN + AZA	286	76 (49, 91)	172 (60)	157 (55%)	113 (40%)	214 (75%)	72 (25%)
	Placebo + AZA	145	76 (60, 90)	87 (60%)	81 (56%)	59 (41%)	110 (76%)	35 (24%)
VIALE-C (supportive)	VEN + LDAC	143	76 (36, 93)	78 (55%)	74 (52%)	63 (44%)	85 (59%)	58 (41%)
	Placebo + LDAC	68	76 (41, 88)	39 (57%)	34 (50%)	25 (37%)	45 (66%)	23 (34%)
M14-358 (supportive)	VEN + AZA	22	75 (65, 82)	11 (50)	18 (82)	4 (18)	16 (73)	6 (27)
	VEN + DEC	23	74 (68, 85)	9 (39)	19 (86)	4 (17)	20 (87)	3 (13)
AZA-AML-001	AZA, combined	241	75.0 (64, 91)	139 (58%)	186 (77%)	55 (22%)	NR	NR
	CCR, combined	247	75.0 (65, 89)	149 (60%)	189 (77%)	58 (23%)	NR	NR
	AZA, preselected BSC	44	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	45	78.0 (67, 89)	29 (64%)	30 (67%)	15 (33%)	NR	NR
	AZA, preselected LDAC[b]	154	76.0 (64, 90)	NR	NR	NR	NR	NR
	CCR, preselected LDAC	158	75.0 (65, 88)	94 (60%)	123 (78%)	35 (22%)	NR	NR
	AZA, preselected IC	43	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	44	70.5 (65, 81)	26 (59%)	36 (82%)	8 (18%)	NR	NR
AZA-001	AZA, combined	55	70 (52, 80)	37 (67%)	51 (93%)	4 (7%)	NR	NR
	CCR, combined	58	70 (50, 83)	41 (71%)	56 (97%)	0 (0%)	NR	NR
	AZA, preselected BSC	36	70 (52, 80)	21 (58%)	32 (89%)	4 (11%)	NR	NR
	CCR, preselected BSC	27	70 (56, 81)	16 (59%)	26 (96%)	0 (0.0%)	NR	NR
	AZA, preselected LDAC	14	69 (55, 78)	13 (93%)	14 (100%)	0 (0.0%)	NR	NR
	CCR, preselected LDAC	20	71 (56, 83)	15 (75%)	19 (95%)	0 (0.0%)	NR	NR
	AZA, preselected IC	5	63 (53, 78)	3 (60%)	5 (100%)	0 (0.0%)	NR	NR

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Study name	Treatment	N of patients randomised	Age (year), median (range)	Sex (male), n (%)	ECOG/WHO PS 0/1, n (%)	ECOG/WHO PS 2, n (%)	Primary/ de novo AML, n (%)	Secondary AML, n (%)
	CCR, preselected IC	11	65 (50, 76)	10 (91%)	11 (100%)	0 (0.0%)	NR	NR
DACO-016	DEC 5d	242	73 (64, 89)	137 (57%)	184 (76%)	58 (24%)	155 (64%)	87 (36%)
	TC	243	73 (64, 91)	151 (62%)	183 (75%)	60 (25%)	157 (65%)	84 (35%)
	TC, LDAC	215	73 (64, 91)	131 (61%)	164 (76%)	51 (24%)	140 (65%)	73 (34%)
	TC, SC	28	75 (66, 86)	20 (71%)	19 (68%)	9 (32%)	17 (61%)	11 (39%)
Short et al., 2019	DEC 5d	28	77 (70, 80)	NR	18 (64%)	NR	15 (54%)	13 (46%)
	DEC 10d	43	78 (69, 82)	NR	30 (70%)	NR	25 (58%)	18 (42%)
BRIGHT-AML 1003[a]	GLAS + LDAC	77	77 (64, 92)	59 (77%)	35 (46%)	41 (53%)	38 (49%)	39 (51%)
	LDAC	38	76 (58, 83)	23 (61%)	20 (53%)	18 (47%)	18 (47%)	20 (53%)

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; DEC, decitabine; ECOG, Eastern Cooperative Oncology Group; GLAS, glasdegib; IC, intensive chemotherapy; LDAC, low-dose cytarabine; NR, not reported; PS, performance status; SC, supportive care; TC, treatment choice; VEN, venetoclax; WHO, World Health Organization.

[a] Baseline data were reported in the FDA DAURISMO (glasdegib) label.
[b] Baseline data for AZA, preselected LDAC group, were reported in Seymour 2015 (secondary publication).

Source: [123]

Table 7.6 Summary of baseline patient demographics and clinical characteristics for VIALE-A, supportive studies and relevant comparator studies (part 2)

Study name	Treatment	N of patients randomised	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
VIALE-A	VEN + AZA	286	182 (63.6%)	104 (36.4%)	NR	NR	47.0 (4.4, 100.0)	85 (29.7%)	61 (21.3%)	140 (49.0%)
	Placebo + AZA	145	89 (61.4%)	56 (38.6%)	NR	NR	47.0 (11.0, 99.0)	41 (28.3%)	33 (22.8%)	71 (49.0%)
VIALE-C (supportive)	VEN + LDAC	143	91 (63.6%)	47 (32.9%)	NR	NR	NR	42 (29.4%)	36 (25.2%)	65 (45.5%)
	Placebo + LDAC	68	46 (67.6%)	20 (29.4%)	NR	NR	NR	18 (26.5%)	22 (32.4%)	28 (41.2%)
M14-358 (supportive)	VEN + AZA	143	12 (55%)	10 (45%)	NR	NR	NR	6 (27%)	9 (41%)	7 (32%)
	VEN + DEC	68	15 (65%)	8 (35%)	NR	NR	NR	5 (22%)	7 (30%)	11 (48%)

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Study name	Treatment	N of patients randomised	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
AZA-AML-001	AZA, combined	241	155 (64.3%)	85 (35.3%)	3.1 (0.0, 33.0)	52 (3, 585)	70.0 (2.0, 100.0)	NR	NR	173 (71.8%)
	CCR, combined	247	160 (64.8%)	85 (34.4%)	2.3 (0.0, 90.0)	56 (6, 327)	72.0 (2.0, 100.0)	NR	NR	193 (78.1%)
	AZA, preselected BSC	44	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	45	29 (64.4%)	16 (35.6%)	2.3 (1.0, 23.0)	52 (7, 161)	76.0 (9.0, 100.0)	NR	NR	36 (80.0%)
	AZA, preselected LDAC[b]	154	NR	NR	NR	NR	70.0 (2.0, 100.0)	NR	NR	NR
	CCR, preselected LDAC	158	104 (65.8%)	54 (34.2%)	2.3 (0.0, 73.0)	54 (6, 327)	74.0 (4.0, 100.0)	NR	NR	128 (81.0%)
	AZA, preselected IC	43	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	44	27 (61.4%)	15 (34.1%)	2.2 (1.0, 90.0)	62 (9, 273)	70.0 (6.0, 100.0)	NR	NR	29 (65.9%)
AZA-001	AZA, combined	55	38 (69.1%)	14 (25.5%)	NR	NR	23.0 (20.0, 34.0)	NR	NR	NR
	CCR, combined	58	43 (74.1%)	13 (22.4%)	NR	NR	23.1 (13.0, 68.9)	NR	NR	NR
	AZA, preselected BSC	36	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected BSC	27	19 (70.4%)	8 (29.6%)	NR	NR	22.5 (13.0, 29.2)	NR	NR	NR
	AZA, preselected LDAC	14	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected LDAC	20	18 (90.0%)	1 (5.0%)	NR	NR	22.0 (20.0, 28.0)	NR	NR	NR
	AZA, preselected IC	5	NR	NR	NR	NR	NR	NR	NR	NR
	CCR, preselected IC	11	6 (54.5%)	4 (36.4%)	NR	NR	27.0 (21.0, 68.9)	NR	NR	NR
DACO-016	DEC 5d	242	152 (62.8%)	87 (36.0%)	3.1 (0.3, 127.0)	58 (6, 487)	NR	65 (26.9%)	67 (27.7%)	105 (43.4%)
	TC	243	154 (63.4%)	87 (35.8%)	3.7 (0.5, 80.9)	50 (6, 490)	NR	58 (23.9%)	74 (30.5%)	101 (41.6%)

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Study name	Treatment	N of patients randomised	Cytogenetic risk		WBC, 10^9/L, median (range)	Platelets, 10^9/L, median (range)	BM blasts (%), median (range)	BM blasts <30%, n (%)	BM blasts ≥30 to <50%, n (%)	BM blasts ≥50%, n (%)
			Intermediate/ good, n (%)	Poor, n (%)						
	TC, LDAC	215	134 (62.3%)	79 (36.7%)	3.7 (0.5, 80.9)	NR	NR	53 (24.7%)	64 (29.8%)	90 (41.9%)
	TC, SC	28	20 (71.4%)	8 (28.6%)	2.7 (0.7, 26.5)	NR	NR	5 (17.9%)	10 (35.7%)	11 (39.3%)
Short et al., 2019	DEC 5d	28	NR	NR	2.0 (1.5, 3.9)	25 (14, 60)	40.0 (29.0, 68.0)	NR	NR	NR
	DEC 10d	43	NR	NR	3.2 (1.9, 10.6)	37 (24, 83)	46.0 (25.0, 64.0)	NR	NR	NR
BRIGHT-AML 1003[a]	GLAS + LDAC	77	48 (62.3%)	29 (37.7%)	NR	NR	NR	NR	NR	NR
	LDAC	38	21 (55.3%)	17 (44.7%)	NR	NR	NR	NR	NR	NR

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; BM, bone marrow; BSC, best supportive care; CCR, conventional care regimens; DEC, decitabine; GLAS, glasdegib; IC, intensive chemotherapy; LDAC, low-dose cytarabine; NR, not reported; SC, supportive care; TC, treatment choice; VEN, venetoclax; WBC, white blood cell.
[a] Baseline data were reported in the FDA DAURISMO (glasdegib) label.
[b] Baseline data for AZA, preselected LDAC group, were reported in Seymour 2015 (secondary publication).
Source: [123]

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7.6 Indirect treatment comparison: network meta-analysis

As direct evidence was only identified for venetoclax in combination with an HMA versus azacitidine only (VIALE-A), the appropriateness and feasibility of conducting anchored ITCs of venetoclax in combination with an HMA versus other relevant comparators was assessed. This included an appraisal of the bias risk in relevant trials, an evaluation of available outcomes and linkages, a cross-trial heterogeneity assessment, and an evaluation of the proportional hazards assumption for OS.

7.6.1 Risk of bias in relevant trials

For relevant studies, critical appraisal of the quality of each trial was conducted following the Centre for Reviews and Dissemination (CRD) risk of bias assessment checklist for RCTs recommended by NICE (Table 7.7) [123, 135]. A high risk of bias was identified for BRIGHT-AML 1003, AZA-AML-001, AZA-001, DACO-016, and Short et al., 2019 due to the open-label trial design which could potentially increase performance bias and detection bias. Further high risk of bias was identified for AZA-001 due to unexplained imbalances in drop-outs between each arm and a lack of transparency in outcome reporting. Overall, including these studies in the ITC may introduce bias into the ITC results. A detailed assessment of the risk of bias in relevant studies is provided in the appendix, Table 8.11.

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Table 7.7 Summary of risk of bias assessment for relevant studies

Study name	Was randomization carried out appropriately?	Was the concealment of treatment allocation prior to enrolment and assignment adequate?	Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Is there any evidence to suggest that the authors measured more outcomes than they reported?	Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
BRIGHT-AML 1003	Low	Low	Unclear	High	Low	Unclear	Unclear
DACO-016	Low	Unclear	Low	High	Low	Unclear	Unclear
Short et al., 2019	Low	Low	Low	High	Unclear	Unclear	Unclear
AZA-001	Low	Low	Low	High	High	High	Unclear
AZA-AML-001	Low	Low	Low	High	Low	Unclear	Unclear
VIALE-A	Low	Low	Low	Low	Low	Low	Low

Risk of bias: Low, High, Unclear
Source: [123]

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7.6.2 Feasibility assessment 1: outcomes and available linkages

The feasibility of an anchored ITC (e.g., a network meta-analysis [NMA]) was assessed in terms of available linkages (common trial arms) and comparable outcomes. OS and CR + CRi were the only outcomes for which a network across comparators of interest could be constructed (Table 7.8). Data for HRQL and EFS was not reported across trials. Composite CR (CR + CRi) was chosen as the most relevant evaluation of response over CR and CRi alone. The feasibility of an NMA depended on the azacitidine–LDAC link, which was crucial in providing a connected network, formed through the AZA-AML-001 and AZA-001 trials (Figure 7.9 and Figure 7.10).

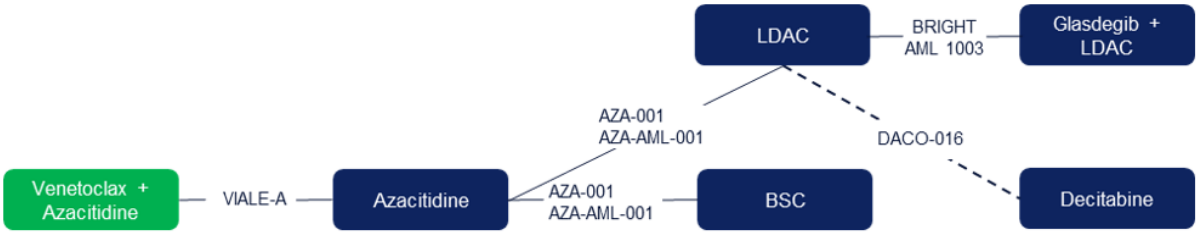
For decitabine, two trials (DACO-016 and Short et al., 2019) of the EMA-approved dose of 20 mg/m^2 once per day for 5 consecutive days every 4 weeks were identified [52]. The Short et al. (2019) trial only provided a contrast between the "on-label" 5-day schedule of decitabine versus the "off-label" 10-day schedule of decitabine and therefore could not be included in the potential ITC network [124]. In addition, OS was reported for treatment choice and not reported separately for LDAC and BSC in DACO-016. As 215/243 (88.5%) of patients randomised to treatment choice received LDAC in DACO-16, the HR for decitabine versus treatment choice would need to serve as a surrogate for the HR of decitabine versus LDAC in order for decitabine to be included in the network for OS.

Table 7.8 Available outcomes of relevant studies for ITC

Trial ID	Intervention versus comparator	HR of OS	KM curve of OS	HR of EFS	KM curve of EFS	CR	CRi	CR + CRi
AZA-AML-001	Azacitidine versus BSC	√	√	--	--	√	√	√
	Azacitidine versus LDAC	√	√	--	--	√	√	√
BRIGHT-AML 1003	Glasdegib + LDAC versus LDAC	√	√	--	--	√	√	√
AZA-001	Azacitidine versus BSC	√	--	--	--	√	--	--
	Azacitidine versus LDAC	√	--	--	--	√	--	--
DACO-016	Decitabine versus Treatment choice (BSC or LDAC)	√	√	--	--	√	√	√
VIALE-A	Venetoclax + azacitidine versus Azacitidine	√	√	√	√	√	√	√

Abbreviations: BSC, best supportive care; CR, complete remission; CRi, complete remission with incomplete blood count recovery; EFS, event-free survival; KM, Kaplan-Meier; LDAC, low-dose cytarabine; OS, overall survival
Source: [42]

Figure 7.9 Evidence network diagram for OS



Abbreviations: BSC, best supportive care, LDAC, low-dose cytarabine; OS, overall survival.
Dotted lines for DACO-016 indicates that while patients were not randomised to LDAC, OS is reported separately for LDAC.
Source: [42]

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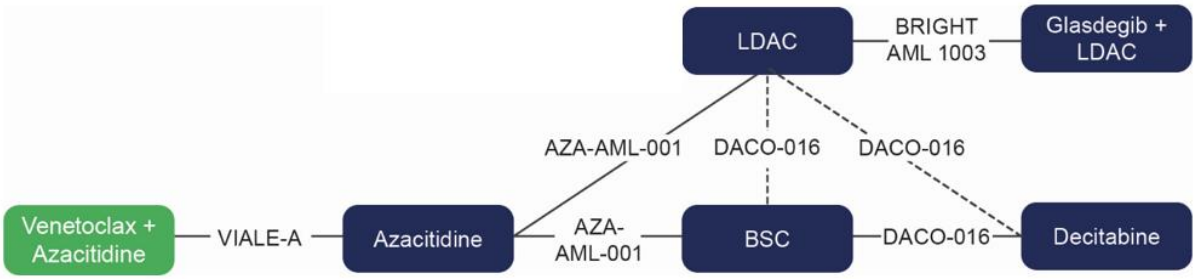
Figure 7.10 Evidence network diagram for CR + CRi



Abbreviations: BSC, best supportive care; CR + CRi, composite complete remission (complete remission or complete remission with incomplete hematologic recovery); LDAC, low-dose cytarabine.
Dotted lines for DACO-016 indicates that while patients were not randomised to LDAC or BSC, CR/CRi is reported separately for LDAC and BSC.
Source: [42]

7.6.3 Feasibility assessment 2: heterogeneity

Based on the trials identified in the SLR and identified for inclusion in the ITC network, the study design, including patient population and baseline characteristics, were assessed across trials to evaluate overall comparability. Heterogeneity in the study design and baseline characteristics across the trials included in a network may mean the required ITC assumptions cannot be met and the estimates of comparative efficacy would be misleading.

Baseline characteristics
Important differences in the baseline characteristics of the trial populations relevant to this assessment were identified during the feasibility assessment (Table 7.5 and Table 7.6) [42].

- All trials enrolled more males than females, with the sex distribution ranging from ~55% to ~70%; however, the sex distribution of BRIGHT-AML 1003 was significantly different.
- The median age of patients in AZA-001 (70 years) was younger compared with other relevant studies: VIALE-A (76 years), AZA-AML-001 (75 years), and BRIGHT-AML 1003 (77 years).
- Over 90% of patients in the AZA-001 trial had an ECOG performance status of 0 or 1, which was higher than in VIALE-A (~55%) and AZA-AML-001 (~75%). A higher proportion of patients in BRIGHT-AML 1003 had ECOG status of 2 (~50%) than in VIALE-A (~40%).
- The VIALE-A, AZA-001, and AZA-AML-001 trials excluded patients with prior HMA treatment, while BRIGHT-AML 1003 included 18.2% of patients with prior HMA treatment.
- In addition, the number of patients with primary AML versus secondary AML was much higher in VIALE-A in comparison with BRIGHT-AML 1003.
- A higher proportion of patients in the azacitidine arm of VIALE-A had poor cytogenic risk compared with the azacitidine arm of AZA-001 at 39% and 26%, respectively.
- Patients in VIALE-A had a median bone marrow blast count of 47%, whereas those AZA-AML-001 and AZA-001 had a median blast count of ~71% and ~23%, respectively. These extreme differences are not surprising considering the BM blast restrictions in AZA-AML-001 and AZA-001 trials.

Based on prior research regarding AML prognostic factors, the above baseline characteristics are potentially relevant confounders and effect modifiers meaning that the treatment effects across trials may not be comparable and that the transitivity assumption required for an NMA is likely violated [42]. The multivariate analysis of OS in VIALE-C indicated that AML status (*de novo* versus secondary), cytogenetic risk (intermediate versus poor), ECOG performance status (<2 versus ≥2), and age (<75 versus ≥75 years) significantly correlated with OS, thereby identifying them as baseline prognostic factors (see Table 8.12 in appendix section 8.3 for more information). This is consistent with EUnetHTA's previous assessment of glasdegib in combination with LDAC, which states: "subgroup analyses from BRIGHT AML 1003 descriptively show larger effects in patients with ECOG PS 2 and secondary AML, supporting the effect modifying potential of these factors" [32].

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Furthermore, other potentially relevant effect modifiers could not be controlled for because of unavailable information from trials identified as relevant for an ITC (e.g., history of severe cardiac disease, serum creatinine >1.3 mg/dL) [32].

Taken together, the above assessment suggests there are considerable differences between trials in potentially effect modifying patient characteristics (e.g., type of AML, ECOG performance status, in particular due to different trial-specific inclusion criteria). Hence, the central similarity assumption for valid ITCs is ultimately violated. This has already been identified by EUnetHTA in the glasdegib report in the same indication. Specifically, BRIGHT-AML 1003, AZA-AML-001 and DACO-016 were deemed too heterogeneous to produce meaningful ITC results, even via a simulated treatment comparison [32].

Patient population: definition of ineligibility

Inclusion criteria for VIALE-A objectively define patient ineligibility to receive intensive chemotherapy. From the inclusion criteria for AZA-AML-001, AZA-001, and DACO-016, it is unclear whether the patients recruited were exclusively ineligible to receive intensive chemotherapy (Table 7.9) [30, 31, 101]. Therefore, because it is possible that these three studies include patients not in the population of interest, an ITC may not be relevant for decision-making, as previously reported by EUnetHTA [32]. The definition of ineligibility used for BRIGHT-AML 1003 differs from that in VIALE-A, particularly with regard to minimum age (Table 7.9) [102]. The heterogeneity between the populations of interest may mean an ITC versus glasdegib in combination with LDAC would not be informative for decision-making. The baseline characteristics of the relevant studies are presented in Table 7.5 and Table 7.6.

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Table 7.9 Comparability of study design and patient population of relevant studies for ITC

	VIALE-A	AZA-AML-001	AZA-001	DAC0-016	BRIGHT-AML 1003
Intervention versus comparator	Venetoclax + azacitidine (N = 286) versus Azacitidine (N = 145)	Azacitidine (N = 241) versus CCR • LDAC (N = 158) • BSC (N = 45) • IC (N = 44)	Azacitidine (N = 55) versus CCR • LDAC (n = 20) • BSC (N = 27) • IC (N = 11)	Decitabine (N = 242) versus Treatment choice • LDAC (N = 215) • BSC (N = 28)	Glasdegib + LDAC (N = 78) versus LDAC (N = 38)
Dosage/definition of common comparators	Azacitidine: 75 mg/m^2, SC or IV, on days 1–7 every 28-day cycle	• Azacitidine: 75 mg/m^2, SC, on days 1–7 every 28-day cycle • LDAC: 20 mg twice a day (irrespective of body surface area) for 10 days per 28-day treatment cycle • BSC: blood product transfusions and antibiotics	• Azacitidine: 75 mg/m^2, SC, on days 1–7 every 28-day cycle • LDAC: 20 mg/m^2 once a day for 14 days per 28-day treatment cycle • BSC: blood product transfusions and antibiotics	• LDAC: 20 mg/m^2 once a day for 10 days per 28-day treatment cycle • BSC: regimen unclear	LDAC: 20 mg twice a day (irrespective of body surface area) for 10 days per 28-day treatment cycle
Treatment allocation	Double-blinded treatment allocation	Open-label treatment of patients within the control group was pre-selected by the investigator	Open-label treatment of patients within the control group was pre-selected by the investigator	Open-label LDAC versus BSC was by patient choice with physician advice and thus was not a random allotment	Open-label treatment allocation
Trial population: Definition of 'ineligibility'	Objectively defined criteria for ineligibility for IC Aged ≥18 years plus ≥1 of the following criteria:* • ≥75 years of age • ECOG PS 2 or 3 • creatinine clearance ≥30 mL/min to <45 mL/min • severe cardiac disease • DLCO ≤65% or FEV1 ≤65% • moderate hepatic impairment	No definition provided. Unclear whether the patient population exclusively included individuals not eligible for IC	No definition provided. Unclear whether the patient population exclusively included individuals not eligible for IC	No definition provided. Unclear whether the patient population exclusively included individuals not eligible for IC	Clearly defined criteria for ineligibility for IC Aged ≥55 years plus ≥1 of the following criteria: • age ≥75 years • ECOG PS = 2 • serum creatinine >1.3 mg/dL, • severe cardiac disease

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Trial population: disease	• Newly diagnosed AML • No BM blast restriction	• Newly diagnosed AML • BM blasts >30%	• Not exclusively AML, sub-analyses for AML only • BM blasts 20-30%	• Newly diagnosed AML • No BM blast restriction	• Not exclusively AML, post hoc subgroup analyses for AML only • No BM blast restriction

Abbreviations: AML, acute myeloid leukaemia; BM, bone marrow; BSC, best supportive care; CCR, conventional care regimen; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG PS, Eastern Cooperative Oncology Group performance status; FEV, forced expiratory volume; LDAC, low-dose cytarabine; IC, intensive chemotherapy; IV, intravenous; SC, subcutaneous
*Plus any other comorbidity that the physician judges to be incompatible with IC.
Source: [8, 30, 31, 101, 102]

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Patient population: treatment allocation

The AZA-AML-001, AZA-001, and DACO-016 trials are key to including BSC in the network, but treatment allocation in these trials was based on preselection criteria (Table 7.9). In AZA-AML-001 and AZA-001, azacitidine was compared against LDAC in a patient population preselected for LDAC, and azacitidine was compared against BSC in a patient population preselected for BSC [30, 101]. Due to the non-transparent nature of the treatment pre-selection criteria, populations enrolled in the LDAC and BSC arms may not be comparable with VIALE-A. Within the control arm of DACO-016, patients were not randomised to LDAC or BSC, instead treatment was based on patient choice with physician advice [31]. Again, this limits the ability to make inferences from an ITC that uses data from these trials.

Interventions and comparators

A comparability assessment indicated that there are important differences in the common comparator arms of the trials in the network (Table 7.9).

- The AZA-AML-001, AZA-001 and DACO-016 trials are key to including BSC in the network, but the information regarding BSC in the trials is very limited due to the small sample sizes of the BSC groups (Table 7.9) [30, 31, 101].

- The difference in LDAC dosing among the trials introduces unquantifiable bias in OS and response baseline risk, which limits the ability to utilize LDAC as a common comparator arm to connect these trials [8, 30, 31, 101, 102].

- In DACO-016, the inclusion of patients receiving BSC in the LDAC control group will likely underestimate the efficacy of LDAC in this control arm (and overestimate the relative efficacy of decitabine versus LDAC) [31].

Adjusting for heterogeneity: methodological limitations

The small number of trials, relative to number of contrasts, may make adjustment techniques such as meta-regression infeasible as there would not be enough free-parameters to estimate the meta-regression coefficients [42].

7.6.4 Feasibility assessment 3: proportional hazards assumptions

The proportional hazards assumption for OS was evaluated for the identified trials in which Kaplan-Meier curves are available using log-log cumulative hazard plots (appendix 8.2.1, Figure 8.2-Figure 8.5) [42].

The log-log plots for OS in the VIALE-A trial (Figure 8.2), and in the BRIGHT-AML 1003 trial (Figure 8.5) suggest a low risk of violation of the proportional hazards assumption because the two curves in each plot are largely parallel. The log-log plot for OS in DACO-016 (Figure 8.4) suggests a moderate risk of violation of the proportional hazards assumptions because the two curves are largely overlapping with occasional crossing. The log-log plot for OS in the AZA-AML-001 trial (Figure 8.3) suggests a moderate risk of violation of the proportional hazards assumption because both arms cross at month 20 and the small and insignificant HR of 0.90 (95% CI: 0.70, 1.16; p=0.43) is not consistent with the substantial difference in median survival time of 4.8 months (azacitidine: 11.2 [95% CI: 8.8, 13.4] months; LDAC: 6.4 [95% CI: 4.8, 9.1] months). Survival curves were not reported in the investigator preselected treatment groups in the AZA-001 trial, so the proportional hazards assumption could not be evaluated [42].

7.6.5 Feasibility assessment: conclusion

Formal feasibility assessment of the similarity of trials is crucial to a high quality and robust ITC as this ensures that the underlying assumptions are systematically explored and that the risks of indirectly comparing treatment effects from RCTs for a particular research question are transparent. The validity of an anchored ITC like an NMA relies on limited systematic differences among the studies included in the network across treatment comparisons, particularly patient or disease characteristics that are treatment effect modifiers. The results of these feasibility analyses demonstrate that the systematic differences are of a magnitude that would risk producing biased results that are misleading and difficult to interpret.

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Initial feasibility assessments found that a network could be constructed for two outcomes, OS and CR + CRi, with AZA-AML-001 providing the critical linkage in the network. However, a heterogeneity assessment exposed significant differences between the trials in the network due in part to differences in the inclusion/exclusion criteria of the trials (Table 7.9).

- ITC versus BSC: The potential for an ITC versus BSC is limited by the design of the trials that are key to including BSC in the network: AZA-AML-001, AZA-001, and DACO-016. Each of these trials did not definitively include only patients who were ineligible for intensive chemotherapy as there is no clear definition of ineligibility to intensive chemotherapy provided in the trial. AZA-AML-001 and AZA-001 were conducted in patient populations with restricted bone marrow blast counts, whereas there was no restriction of blast counts in VIALE-A [8, 30, 31, 101]. Patients were not completely randomised but were allocated to BSC either by preselection using non-transparent criteria or by patient choice with physician advice [30, 31, 101]. Furthermore, only a small number of patients in each trial were allocated to BSC. Therefore, the limited data for BSC from trials that may not be completely in the population of interest and which also have a high degree of uncertainty, mean an ITC versus BSC would not be feasible or informative for decision-making.
- ITC versus glasdegib in combination with LDAC: The potential for an ITC of venetoclax in combination with azacitidine versus glasdegib in combination with LDAC lies with the inclusion of BRIGHT-AML 1003 in the network. Regarding baseline characteristics, differences exist in potential effect modifiers such as ECOG status, type of AML (*de novo* versus secondary) and cytogenic risk between the studies, indicating that the treatment effects across trials may not be comparable [8, 40, 134]. These differences are driven by the fact that the eligibility criteria for BRIGHT-AML 1003 and VIALE-A are not aligned. These factors support why an ITC using BRIGHT-AML 1003 is not feasible.
- ITC versus decitabine: DACO-016 is the only available trial that could provide an ITC of venetoclax combinations versus decitabine. The patient population in DACO-016 may also not be the population of interest as there is no clear definition of ineligibility to intensive chemotherapy provided in the trial [31]. Unfortunately, the control arm in the DACO-016 trial does not fully correspond to the common comparator treatment (LDAC) in AZA-AML-001, AZA-001 or BRIGHT-AML 1003 due to the inclusion of patients allocated to BSC. Furthermore, patients were not randomised to LDAC or BSC, instead treatment was based on patient choice with physician advice. Consequently, an ITC based on evidence from DACO-016 is not feasible and the results would not be informative for decision-making.

All the potential ITCs are limited by the fact that individual patient data are not available for the relevant comparator studies, meaning that all potential effect modifiers cannot be controlled for in the analysis.

In summary, there is a substantial risk that these fundamental differences in trial design, including lack of transparent randomization, lack of clear ineligibility criteria, conflicting common comparator arm dosing, and substantial differences in baseline characteristics (potential effect modifiers), may introduce bias, threatening the overall validity of ITCs versus LDAC, BSC, glasdegib in combination with LDAC, and decitabine. Therefore, these ITCs are considered not feasible or informative for decision-making.

Due to the limitations of the relevant evidence available, comparisons (direct or indirect) are lacking for venetoclax in combination with azacitidine versus certain comparators of interest (e.g., BSC and glasdegib in combination with LDAC) and can be considered an evidence gap. However, VIALE-A provides robust evidence (a head-to-head, double-blind, Phase 3 trial) versus the comparator that is considered to be most appropriate by ESMO guidelines [25].

7.7 Indirect treatment comparison: propensity score weighting analysis using individual patient data

7.7.1 Comparison

Due to the availability of individual patient data (IPD) from the two Phase 3, double-blind randomised trials included in the venetoclax clinical development programme, VIALE-A and VIALE-C, as well as the feasibility challenges of conducting an anchored ITC like an NMA, propensity score analyses were conducted to compare the efficacy outcomes of the venetoclax plus azacitidine arm in VIALE-A versus the LDAC arm in VIALE-C [8, 40, 42]. This comparison is relevant in markets where azacitidine is restricted, as clinicians may want to replace their use of LDAC with venetoclax in combination with azacitidine (see section 3). The outcomes considered in the propensity score analyses were OS, EFS and composite CR (CR + CRi).

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It should be noted that VIALE-A and VIALE-C do not share a common comparator arm, and thus the comparison of venetoclax plus azacitidine versus LDAC is technically unanchored. However, VIALE-A and VIALE-C have very similar trial designs and inclusion/exclusion criteria (Table 7.4). The baseline characteristics of the venetoclax in combination with azacitidine arm in VIALE-A and the LDAC arm of VIALE-C are comparable in terms of main characteristics e.g., age, ECOG, type of AML, and bone marrow blast count (Table 7.5 and Table 7.6). This means the central similarity assumption between these trials is strong, even before propensity score weighting. The propensity score weighting takes into account all observed effect modifiers and prognostic variables which further limits the risk of bias from an unanchored comparison.

The key difference between VIALE-A and VIALE-C is the inclusion of patients with prior HMA use and favourable cytogenetic risk in the LDAC arm in VIALE-C who were not enrolled in VIALE-A per protocol. However, even the percentage of these patients was not very high (25%). This analysis excluded such patients to produce more meaningful results from the comparison [8, 40].

Additional unanchored approaches to compare venetoclax in combination with azacitidine versus other relevant comparators (e.g., BSC and glasdegib in combination with LDAC) were considered. However, for the same reasons discussed throughout section 7.6, these comparisons were deemed not appropriate following an appropriateness and feasibility assessment. Relevant rationale included high risk of bias in the BRIGHT-AML 1003, AZA-AML-001, AZA-001, and DACO-016 trials and significant differences across trial design (e.g., definition of patient populations [ineligibility for intensive chemotherapy], treatment allocation, treatment regimen/dosages, baseline characteristic including [bone marrow blast count] and potential violations in the proportional hazards assumptions) that could not be corrected for even by using venetoclax IPD. The advantage of an ITC approach including only VIALE-A and VIALE-C is the availability of IPD for all the trials included in the analysis. This reduces the limitations associated with a typical unanchored analysis using literature-based data i.e., the assumption that all effect modifiers and prognostic factors are accounted for.

7.7.2 Analytic approach

The propensity score weighting method was applied to evaluate the relative efficacy of treatments using IPD data from compatible studies. Propensity score weighting reduces observed baseline differences between two comparison cohorts by increasing or decreasing the relative contributions of individual patients in the two cohorts so that, after weighting, the two cohorts would have similar average baseline characteristics on a population level [136]. Specifically, a propensity score (i.e., the probability of treatment assignment) was assigned to each patient and the subsequent analyses were evaluated using data weighted by the inverse of the propensity score. The propensity score for each patient was estimated using a logistic regression model with the enrolment of the venetoclax plus azacitidine arm versus the LDAC arm as the outcome and a set of observed baseline characteristics as covariates. The baseline covariates were selected based on prior research regarding AML prognostic factors and potential confounders. These variables include age, race, sex, AML status, AML with myelodysplasia-related changes, history of MDS status, ECOG score, cytogenetic risk category and bone marrow blasts [42].

Overall, propensity score analysis allows for further relevant comparisons without the heterogeneity concerns of an NMA, using individual patient level data from two high-quality similarly designed clinical trials, reducing bias and improving the robustness of the comparative efficacy measure. Adjustment for a broad set of confounders and effect modifiers results in a balanced, homogeneous comparison [42].

For further information on the methodology of the propensity score weighting approach see appendix sections 8.2.2 and 8.2.3.

7.7.3 Main and sensitivity analyses

Given the high similarities between the study populations, study designs, and baseline characteristics of the VIALE-A and VIALE-C trials (Table 7.4, Table 7.5 and Table 7.6), propensity score analysis was deemed appropriate. The main analyses excluded patients with prior HMA use and favourable cytogenetic risk in VIALE-C because patients with these characteristics were not included in VIALE-A per protocol. Subgroup analyses was also conducted to compare the efficacy of venetoclax in combination with azacitidine versus LDAC in patients with >30% bone marrow blasts due to the

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relevance of this subgroup in certain markets. Selected baseline characteristics were included as independent variables in the propensity score model [8, 40, 42].

Main analyses: venetoclax plus azacitidine versus LDAC

All 286 patients treated with venetoclax plus azacitidine in VIALE-A and all 51 patients treated with LDAC without prior HMA use or favourable cytogenetic risk in VIALE-C were included in the propensity score analysis in the overall population [42].

All 206 patients treated with venetoclax plus azacitidine in VIALE-A and all 37 patients treated with LDAC without prior HMA use or favourable cytogenetic risk in VIALE-C were included in the propensity score analysis in the subgroup of patients with bone marrow blasts greater than 30% [42].

Sensitivity analyses*: *venetoclax plus azacitidine versus LDAC

Sensitivity analyses were conducted to evaluate the robustness of results by including patients with prior HMA use or favourable cytogenetic risk in the LDAC arm in VIALE-C in the analytical sample [42].

All 286 patients treated with venetoclax plus azacitidine in VIALE-A and all 68 patients treated with LDAC in VIALE-C were included in the propensity score analysis in the overall population [42].

All 206 patients treated with venetoclax plus azacitidine in VIALE-A and all 52 patients treated with LDAC in VIALE-were included in the propensity score analysis in the subgroup of patients with bone marrow blasts greater than 30% [42].

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7.8 Individual study results (clinical outcomes)

A summary of the methods of collection and analyses of efficacy endpoints for the VIALE-A trial, and supporting trials VIALE-C and M14-358, are presented in Table 7.10.

Table 7.10 Methods of data collection and analysis of efficacy

Study reference/ID	Endpoint definition	Method of analysis
VIALE-A VIALE-C M14-358	OS The number of days from randomization to the date of death.	Data for each patient were censored at the date of the last visit or the date on which the patient was last known to be alive. The distributions were estimated for each treatment arm using Kaplan-Meier methodology and compared using the log-rank test stratified by age (18-<75, ≥75 years), cytogenetic risk (intermediate risk, poor risk). The HR between treatment arms was estimated using the Cox proportional hazards model with the same stratification factors used in the log-rank test, with a significance level of 0.04 (two-sided) for VIALE-A and 0.05 (two-sided) for VIALE-C. **M14-358:** Analysed by Kaplan-Meier methodology using data from all enrolled subjects. Median time survival were estimated and 95% CI for the median time survival will be presented.
VIALE-A VIALE-C M14-358	Composite CR rate (CR or CR with incomplete hematologic recovery [CR + CRi]) Calculated based on current IWG criteria for AML. CR defined as absolute neutrophil count >10^3/µL, platelets >10^5/µL, red cell transfusion independence, and bone marrow with <5% blasts. Incomplete hematologic recovery was defined as all of the criteria for CR, except for neutropenia ≤10^3/µL or thrombocytopenia ≤10^5/µL.	Bone marrow assessments were performed at screening, at the end of cycle 1, and every three cycles thereafter until two consecutive samples confirmed a CR or a CR with incomplete hematologic recovery. Disease assessments were performed with the use of the modified IWG response criteria for AML. Composite CR was compared between the treatment groups with the use of the Cochran–Mantel–Haenszel test with the same age and cytogenetic risk factors as OS. **VIALE-A:** The primary analysis for CR + CRi was to occur 6 months after the first 225 subjects were randomised. A significance level of 0.01 out of 0.05 (two-sided) was allocated for this analysis.
VIALE-A VIALE-C M14-358	CR with or without partial hematologic recovery (CR + CRh) Defined as all the criteria for CR, except that both the neutrophil and platelet counts were lower than the threshold designated for complete recovery (for neutropenia >0.5 x 10^3/µL and a platelet count of >0.5 x 10^5/µL).	Analysed as per composite CR rates.
VIALE-A VIALE-C M14-358	Rates of RBC and platelet transfusion independence Defined as ≥56 days during treatment with no RBC or platelet transfusion.	Calculated as the proportion of patients who achieved RBC transfusion independence post baseline. Rates were compared between the treatment groups with the use of the Cochran–Mantel–Haenszel test.

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VIALE-A VIALE-C	Composite CR and OS in molecular and cytogenetic subgroups Cytogenetic risk was evaluated by investigators per NCCN guidelines for AML.	Calculated as per OS in the ITT population and composite CR rates.
VIALE-A VIALE-C	EFS The number of days from randomization to disease progression, treatment failure (failure to achieve complete remission or <5% bone marrow blasts after ≥6 cycles of treatment), confirmed relapse, or death.	Analysed using the same statistical method as the OS endpoint.
VIALE-A	MRD response in patients attaining composite CR The number of patients who achieved either a CR or CRi, and a best MRD value $<10^{-3}$ of residual blasts per leukocytes as measured centrally in bone marrow.	Evaluated in bone marrow aspirates collected from all patients using a centralised, validated multicolour flow cytometry assay, the recognized gold standard. Rates were compared between the treatment groups with the use of the Cochran–Mantel–Haenszel test.
VIALE-A VIALE-C	HRQL EORTC QLQ-C30, PROMIS Cancer Fatigue SF 7a, and the EQ-5D-5L, were included to assess patients HRQL, functioning, and symptoms.	The EORTC QLQ-C30, PROMIS Cancer Fatigue SF 7a, and EQ-5D-5L questionnaires were collected on or within 3 days prior to Cycle 1 Day 1 and then on Day 1 of every other cycle throughout the trial, including Final Visit. For all instruments, TTD was calculated and summarized as the quartiles, median, and 95% CI for each treatment arm. Stratified Kaplan-Meier curves are presented and the unadjusted log-rank p value for the difference between treatment arms. TTD was defined as worsening from baseline in PRO-specific meaningful change thresholds of ≥10 points for the EORTC QLQ-C30.

Abbreviations: AML, acute myeloid leukaemia; CR, complete response; CRi, complete response with incomplete blood count recovery; EFS, event-free survival; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; EQ-5D-5L, EuroQol 5 dimension 5-level questionnaire; HRQL, health-related quality of life; ITT, intent-to-treat population; IWG, international working group; MRD, minimal/measurable residual disease; NCCN, National Comprehensive Cancer Network; OS, overall survival; PROMIS, patient-reported outcomes measurement information system; RBC, red blood cell; TTD, time to deterioration.
Sources:[6, 8, 38, 40, 41, 46]

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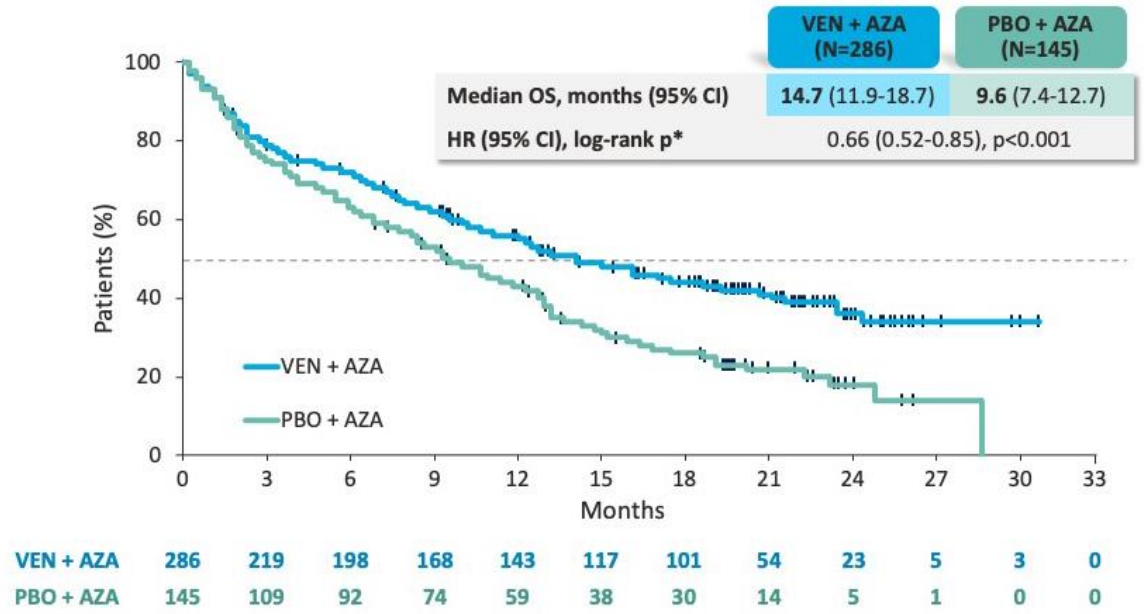
7.8.1 Overall survival

With a median follow-up of 20.5 months, survival of patients receiving venetoclax plus azacitidine was significantly improved by 34% compared with the azacitidine arm (HR: 0.66 [95% CI: 0.52, 0.85], p<0.001) (Figure 7.11). Median OS was 14.7 months (95% CI: 11.9, 18.7) among patients treated with venetoclax plus azacitidine compared with 9.6 months (95% CI: 7.4, 12.7) in the azacitidine arm [8]. The OS rate at 1 year was 55.8% (95% CI: 49.7, 61.5) for venetoclax plus azacitidine compared with 43.8% (95% CI: 35.5, 51.8) in the azacitidine arm. At 2 years, the OS rates were 36.5% (95% CI: 29.7, 43.4) and 18.3% (95% CI: 11.1, 27.0), respectively [38]. At the time of analysis, 77 (27%) and 18 (12%) patients remained on treatment in the venetoclax plus azacitidine and azacitidine arms, respectively [8].

The median OS data from VIALE-A is supported by the Phase 1b study, M14-358, that assessed efficacy and safety of venetoclax in combination with an HMA (azacitidine or decitabine). At a median duration of follow-up of 29 months, median OS for venetoclax in combination with azacitidine was 16.4 months (95% CI: 11.3, 24.5). For patients treated with venetoclax in combination with decitabine the median OS was 16.2 months (95% CI: 9.1, 27.8) at a median duration of follow-up of 40 months. Median OS for venetoclax in combination with azacitidine and venetoclax in combination with decitabine are consistent with each other in M14-358 and both are consistent with the median OS reported for venetoclax plus azacitidine arm of VIALE-A [8, 37].

The improvement in survival from VIALE-A is also supported by the Phase 3 trial, VIALE-C, which assessed the efficacy and safety of venetoclax in combination with LDAC versus LDAC only. Among patients receiving venetoclax plus LDAC, survival was improved by 30% compared with LDAC only (HR: 0.70 [95% CI: 0.50, 0.99]; p=0.04) after a median duration of 17.5 months follow-up [9].

Figure 7.11 Kaplan–Meier estimates of OS: venetoclax plus azacitidine versus azacitidine plus placebo



Abbreviations: Aza, azacitidine; CI, confidence interval; OS, overall survival; Pbo, placebo; Ven, venetoclax.
*Log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk).
Source: [8]

7.8.2 Remission rates

Remission rates in the VIALE-A trial were significantly higher in patients treated with venetoclax plus azacitidine compared with azacitidine only (Table 7.11). In addition, responses were achieved in a shorter duration in the venetoclax plus azacitidine arm compared with those in the azacitidine arm – that is, prior to initiation of cycle 2 [8].

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The median duration of CR in the venetoclax plus azacitidine arm was 17.5 months (95% CI: 13.6, NR) compared with 13.4 months (95% CI: 5.8, 15.5) in the azacitidine arm. Median time to first response (either CR or CRi) was 1.3 months (range: 0.6, 9.9) in the venetoclax plus azacitidine arm compared with 2.8 months (range: 0.8, 13.2) in the azacitidine arm. The median duration of composite CR was 17.5 months (95% CI: 13.6, NR) in the venetoclax plus azacitidine arm compared with 13.4 months (95% CI: 5.8, 15.5) in the azacitidine arm [8].

For patients who achieved a CR or CRh, the median time to first response and response duration were 1.0 (range: 0.6, 14.3) versus 2.6 months (range: 0.8, 13.2), and 17.8 months (95% CI: 15.3, NR) versus 13.9 months (95% CI: 10.4, 15.7) in the venetoclax plus azacitidine versus azacitidine arms, respectively [8].

Table 7.11 Remission rates in the VIALE-A trial

Remission rates % patients, (95% CI)	Venetoclax + azacitidine (n = 143)	Placebo + azacitidine (n = 68)	P value
CR	36.7 (31.1, 42.6)	17.9 (12.1, 25.2)	<0.001
Composite CR (CR + CRi)	66.4 (60.6, 71.9)	28.3 (21.1, 36.3)	<0.001
CR + CRh	64.7 (58.8, 70.2)	22.8 (16.2, 30.5)	<0.001

Abbreviations: CI, confidence interval; CR, complete response; CRh, complete response with partial haematological recovery; CRi, complete response with incomplete blood count recovery.
Source: [8, 38].

Both the high rate and duration of composite CR in VIALE-A are supported by M14-358. Rates of composite CR were consistent between the venetoclax plus azacitidine and venetoclax plus decitabine arms (Table 7.12) [37].

Table 7.12 Composite CR rates and DOR from the M14-358 trial

Cohort	Composite CR (CR + CRi), n (%)	DOR*, months (95% CI)
Venetoclax (400 mg) + azacitidine (n = 84)	60 (71)	21.9 (15.1, 30.2)
Venetoclax (400 mg) + decitabine (n = 31)	23 (74)	15.0 (7.2, 30.0)

Abbreviations: CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; DOR, duration of response.
*Only for those patients who achieved a best response of CR or CRi.
Source: [37]

VIALE-A was supported by the remission rates in the VIALE-C trial, which were higher in patients treated with venetoclax plus LDAC compared with LDAC only (Table 7.13). Again, similar to VIALE-A, responses were achieved in a shorter duration in the venetoclax plus LDAC arm compared with those in the LDAC arm – that is, prior to initiation of cycle 2 [40].

Table 7.13 Remission rates in the VIALE-C trial at 6-month follow-up

Remission rates % patients	Venetoclax + LDAC (n = 143)	Placebo + LDAC (n = 68)
CR + CRi	48	13
CR + CRh	48	15

Abbreviations: CI, confidence interval; CR, complete response; CRh, complete response with partial haematological recovery; CRi, complete response with incomplete blood count recovery; LDAC, low-dose cytarabine.
Source: [9]

7.8.3 Transfusion independence

AML disrupts normal haematopoiesis and so transfusion independence is an indicator of clinical benefit for patients receiving treatment for AML [137, 138]. Rates of post-baseline transfusion independence were statistically significantly improved in patients treated with venetoclax plus azacitidine compared with the azacitidine arm in the VIALE-A trial (Table 7.14) [8].

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Table 7.14 Rates of transfusion independence in the VIALE-A trial

Endpoint	Venetoclax + azacitidine (n = 286)	Placebo + azacitidine (n = 145)	P value
Transfusion independence %, (95% CI)			
RBCs	60 (54, 66)	35 (27, 44)	<0.001
Platelets	69 (63, 74)	50 (41, 58)	<0.001

Abbreviations: CI, confidence interval; RBC, red blood cells.
Source: [8]

At long-term follow-up, rate of transfusion independence for RBC or platelets during the M14-358 treatment period was comparable among subjects who received either venetoclax in combination with azacitidine or decitabine at 64% and 70% and 61% and 87%, respectively, and similar to the 60% and 69% seen in the intervention arm of VIALE-A. The median duration of transfusion independence (RBC and platelet) in M14-358 was 145.0 days and 110.0 days for venetoclax plus azacitidine and venetoclax plus decitabine, respectively [37].

In the VIALE-C trial, higher rates of transfusion independence were consistently reported in the venetoclax plus LDAC treatment arm compared with LDAC alone at 6-month follow-up (Table 7.15) [9]. The percentage increase in transfusion independence for RBCs and platelets was a similar magnitude in VIALE-A and VIALE-C.

Table 7.15 Rates of transfusion independence in the VIALE-C trial at 6-month follow-up

Endpoint	Venetoclax + LDAC (n = 143)	Placebo + LDAC (n = 68)
Transfusion independence %		
RBCs	43	19
Platelets	49	32

Abbreviations: CI, confidence interval; LDAC, low-dose cytarabine; RBC, red blood cells.
Source: [9]

7.8.4 Minimal/measurable residual disease

MRD is a marker for the depth of response to AML therapy, a prognostic indicator for OS and response, and a source of cells that may drive relapse. Therefore, MRD response was considered a relevant metric to evaluate the quality of the remission (CR, CRi, or CRh) in response to venetoclax combinations [39].

In VIALE-A, MRD response was defined as having $<10^{-3}$ of residual blasts per leukocytes as measured in the bone marrow, per ELN recommendations [8, 26].

Among patients who achieved a remission of CR + CRi (composite CR), MRD negativity was achieved in 23.4% (95% CI: 18.6, 28.8) of those receiving venetoclax plus azacitidine compared with 7.6% (95% CI: 3.8, 13.2) in the azacitidine arm [8].

7.8.5 Event-free survival

Venetoclax in combination with azacitidine significantly improved EFS compared with placebo plus azacitidine (HR: 0.63 [95% CI: 0.50, 0.80]; p<0.001) (Figure 7.12). Median EFS was 9.8 months (95% CI: 8.4, 11.8) versus 7.0 months (95% CI: 5.6, 9.5), respectively [8].

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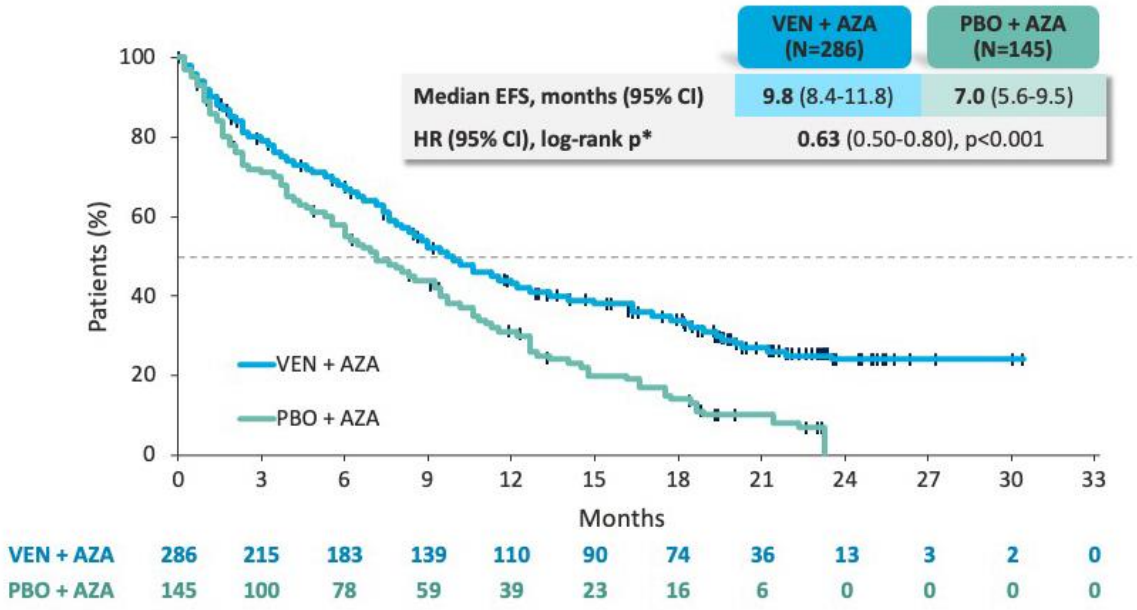
Figure 7.12 Kaplan–Meier estimates of EFS in the VIALE-A trial



Abbreviations: Aza, azacitidine; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; Pbo, placebo; Ven, venetoclax.
* Log-rank test stratified by age (18-<75, ≥75 years) and cytogenetic risk (intermediate risk, poor risk).
Tick marks indicate censored data.
Source:[8]

The improvement in median EFS in VIALE-A was similar to that achieved in VIALE-C. At the time of the 6-month follow-up data cut-off, the addition of venetoclax to LDAC demonstrated an improved median EFS compared with LDAC alone (4.9 months versus 2.1 months; HR: 0.61 [95% CI: 0.44, 0.84]; p=0.003) [9]. Venetoclax plus LDAC in VIALE-C and venetoclax plus azacitidine in VIALE-A both achieved a 2.8 month increase in median EFS versus the control arms.

7.8.6 Efficacy among different subgroups

To evaluate the impact of demographic and baseline characteristics, including molecular marker, on efficacy, subgroup analyses were performed for response rates and OS [40]. Subgroup analyses were not pre-specified for any other outcomes and further *post hoc* analysis were not performed due to concerns of inflated family-wise false positive rate and lack of statistical power. The only subgroup analyses presented that was not pre-specified is bone marrow blast count.

OS by subgroup analysis is shown in Figure 7.13. In most subgroups, OS was consistently improved for patients in the venetoclax plus azacitidine arm compared with the azacitidine only arm. In all subgroups, the combination of venetoclax plus azacitidine was associated with a consistently higher rate of composite CR than the azacitidine arm (Table 7.16). Specifically, in molecular subgroups, rate of composite CR was significantly higher for the combination of venetoclax plus azacitidine versus the azacitidine (Table 7.16) [8].

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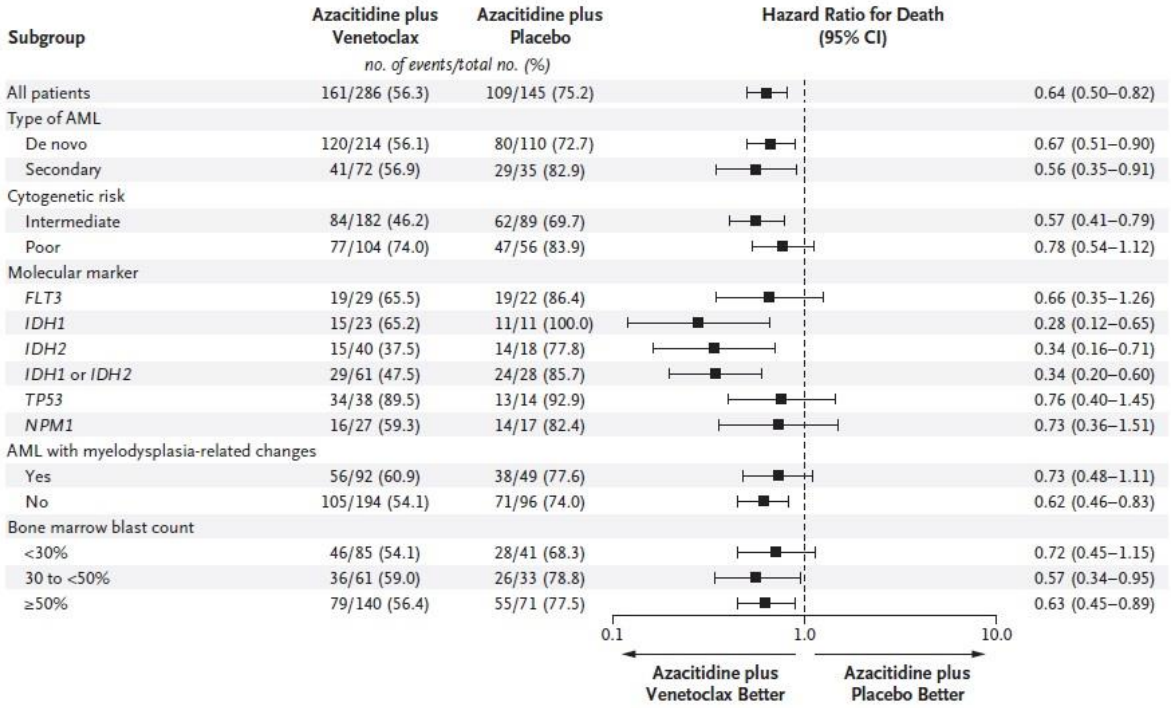
Figure 7.13 Subgroup analysis of OS



Abbreviations: AML, acute myeloid leukaemia; CI, confidence intervals.
Source: [8]

Table 7.16 Composite CR rates by subgroups in the VIALE-A trial

Subgroup	Venetoclax + azacitidine (n = 286)	Placebo + azacitidine (n = 145)
Composite CR, n/N (%)		
Mutation subgroup		
IDH1/2	46/61 (75.4)	3/28 (10.7)
FLT3	21/29 (72.4)	8/22 (36.4)
NPM1	18/27 (66.7)	4/17 (23.5)
TP53	21/38 (55.3)	0/14 (0)
Type of AML		
De novo	142/214 (66.4)	33/110 (30.0)
Secondary	48/72 (66.7)	8/35 (22.9)
Cytogenic risk		
Intermediate	135/182 (74.2)	28/89 (31.5)
Poor	55/104 (52.9)	13/56 (23.2)
AML with MRC		
Yes	56/92 (60.9)	11/49 (22.4)
No	134/194 (69.1)	30/96 (31.3)
Bone marrow blast count		
<30%	65 /85 (76.5)	16/41 (39.0)
30–50%	35/61 (57.4)	9/33 (27.3)
≥50%	90/140 (64.3)	16/71 (22.5)

Abbreviations: AML, acute myeloid leukaemia; CR, complete response; MRC, myelodysplasia-related changes.
Complete response as per investigator assessment.
Source: [8].

The results of the subgroup analyses for VIALE-A are consistent with those for VIALE-C. Across all patient subgroups in VIALE-C, patients treated with venetoclax plus LDAC had increased rates of

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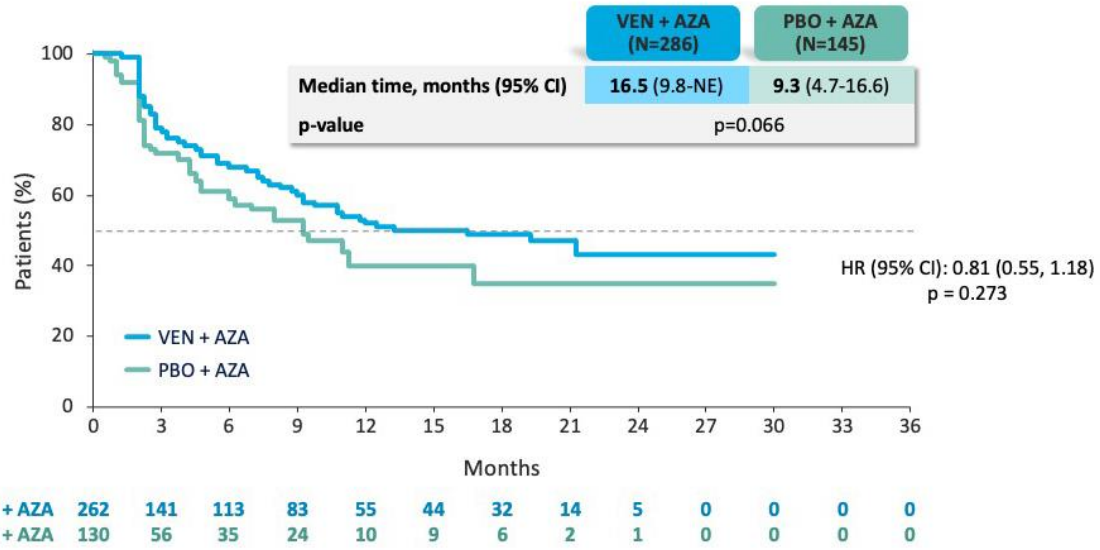
remission (CR, CRi, CRh) compared with those treated with placebo plus LDAC. Similarly, patient survival showed a trend toward longer median OS in patients treated with venetoclax compared with placebo across most patient subgroups, except those with mutant FLT3 [40].

7.8.7 HRQL: EORTC QLQ-C30 GHS/QoL

The EORTC QLQ-C30 GHS/QoL scale is comprised of two items that measure patient's general health status and quality of life in the past week. The items are scored on a seven-point numeric rating scale, where 1 indicates 'very poor health/QoL' and 7 indicates 'excellent health/QoL'. TTD was assessed to quantify differences between treatment groups [46].

In VIALE-A, treatment with venetoclax plus azacitidine had a longer TTD by 7.2 months more than azacitidine alone, although the difference was not statistically significant (median TTD: 16.5 months versus 9.3 months; p=0.066) (Figure 7.14). The adjusted HR was 0.81 (95% CI: 0.55, 1.18). This result was observed for all subgroup analyses; patients in the venetoclax plus azacitidine arm experienced consistently longer TTD than those in the azacitidine only arm, although these differences also did not reach statistical significance [38, 46].

Figure 7.14 TTD on the EORTC QLQ-C30 by treatment group in the VIALE-A trial



Abbreviations: AZA, azacitidine; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; PBO, placebo; NE, not estimated; TTD, time to deterioration; VEN, venetoclax.
Source: [46]

Consistent with VIALE-A, VIALE-C indicated that treatment with venetoclax plus LDAC showed a longer TTD by 8.7 months more than LDAC alone, (median TTD: 11.3 months versus 2.6 months; p=0.011). The adjusted HR was 0.37 (95% CI: 0.21, 0.64; p<0.001) [46].

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7.8.8 Summary efficacy tables

The tables below (Table 7.17-Table 7.19) detail the key efficacy outcomes for the pivotal trial, VIALE-A, and each supporting trial, VIALE-C and M14-358.

Table 7.17 VIALE-A: key efficacy outcomes

Outcome	Venetoclax + AZA n = 286	Placebo + AZA n = 145	VEN + AZA vs AZA HR (95% CI)	P value
Median OS (95% CI)	14.7 months (11.9, 18.7)	9.6 months (7.4, 12.7)	0.66 (0.52, 0.85)	<0.001
OS rate (95% CI) 1 year 2 year	 55.8% (49.7, 61.5%) 36.5% (29.7, 43.4%)	 43.8% (35.5, 51.8%) 18.3% (11.1, 27.0)	NA	NA
CR, % patients (95% CI)	36.7 (31.1, 42.6)	17.9 (12.1, 25.2)	NA	<0.001
Composite CR (CR + CRi), % patients (95% CI)	66.4 (60.6, 71.9)	28.3 (21.1, 36.3)	NA	<0.001
CR + CRh, % patients (95% CI)	64.7 (58.8, 70.2)	22.8 (16.2, 30.5)	NA	<0.001
Transfusion independence % patients (95% CI) RBC Platelets	 59.8 (53.9, 65.5) 68.5 (62.8, 73.9)	 35.2 (27.4, 43.5) 49.7 (41.3, 58.1)	 NA NA	 <0.001 <0.001
MRD response, % patients of those who achieved composite CR (95% CI)	23.4 (18.6, 28.8)	7.6 (3.8, 13.2)	NA	<0.001
Median EFS (95% CI)	9.8 months (8.4, 11.8)	7.0 months (5.6, 9.5),	0.63 (0.50, 0.80)	<0.001

Abbreviations: AZA, azacitidine; CI, confidence interval; CR, complete response; CRh, complete response with partial haematological recovery; CRi, complete response with incomplete blood count recovery; EFS, event-free survival; HR, hazard ratio; MRD, minimal/measurable residual disease; NA, not applicable; OS, overall survival; RBC, red blood cells; VEN, venetoclax.
Source: [8, 38]

Table 7.18 VIALE-C: key efficacy outcomes

Outcome*	Venetoclax + LDAC n = 143	Placebo + LDAC n = 68	VEN + LDAC vs LDAC HR (95% CI)	P value
Median OS (95% CI)	8.4 months (5.9, 10.1)	4.1 months (3.1, 8.1)	0.70 (0.50, 0.99)	0.041
Composite CR (CR + CRi), % patients	48	13	NA	NA
CR + CRh, % patients	48	15	NA	NA
Transfusion independence % patients RBC Platelets	 43 49	 19 32	 NA NA	NA
Median EFS	4.9 months	2.1 months	0.61 (0.44, 0.84)	0.003

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Abbreviations: CI, confidence interval; CR, complete response; CRh, complete response with partial haematological recovery; CRi, complete response with incomplete blood count recovery; EFS, event-free survival; HR, hazard ratio; LDAC, low-dose cytarabine; NA, not applicable; OS, overall survival.
*Data from 6-month follow-up..
Source: [9, 40].

Table 7.19 M14-358: key efficacy outcomes

Outcome	Venetoclax + azacitidine n = 84	Venetoclax + decitabine n = 31
Median OS (95% CI)	16.4 (11.3, 24.5)	16.2 (9.1, 27.8)
CR, % patients	44	55
Composite CR (CR + CRi), % patients	71	74
Transfusion independence % patients		
RBC	64	61
Platelets	70	87

Abbreviations: CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; OS, overall survival; RBC, red blood cells.
Source: [37]

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7.9 Individual study results (safety outcomes)

A summary of the methods of collection and analysis of safety endpoints for the pivotal VIALE-A trial and supporting VIALE-C and M14-358 trials is presented in Table 7.20.

Table 7.20. Methods of data collection and analysis of safety

Study reference/ID	Endpoint definition	Method of analysis
VIALE-A VIALE-C M14-358	Safety Evaluated via study drug exposure, incidence of AEs, serious AEs, deaths, and changes in laboratory values or vital signs.	AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03 VIALE-A and VIALE-C; version 4.0 M14-358). Treatment-emergent AEs were defined as those that occurred between the first dose of study drug until 30 days after the last dose of study drug.

Abbreviations: AE, adverse event.
Source: [6, 8, 40]

A summary of AEs reported in ≥20% of patients in either treatment arm is presented in Table 7.21. Overall, 427 patients were included in the safety analysis (venetoclax plus azacitidine, n = 283; azacitidine arm n = 144). Patients received a median of 7.0 treatment cycles (range: 1.0, 30.0) in the venetoclax plus azacitidine arm compared with 4.5 (range: 1.0, 26.0) in the azacitidine arm. All patients experienced at least one AE; 235 (83%) and 105 (73%) patients on venetoclax plus azacitidine and azacitidine arms experienced a serious AE, respectively [8].

The most frequently reported grade ≥3 haematological AEs (in the venetoclax plus azacitidine and the azacitidine arm, respectively) included thrombocytopenia (45%/38%), neutropenia (42%/28%), febrile neutropenia (42%/19%), anaemia (26%/20%), and leukopenia (21%/12%). Notable serious AEs (grade ≥3) in the venetoclax plus azacitidine and the azacitidine arm, respectively, were febrile neutropenia (30%/10%) and pneumonia (16%/22%). TLS was reported during venetoclax dose ramp-up in three (1%) patients in the venetoclax plus azacitidine arm and none in the azacitidine arm; all were transient biochemical changes that resolved with uricosuric agents and calcium supplements without treatment interruption [8].

The incidence of grade ≥3 venetoclax/placebo-related AEs was 76.3% in the venetoclax plus azacitidine arm and 49.3% in the placebo plus azacitidine arm. The most common venetoclax/placebo-related AEs (occurring in ≥20% of subjects) in the venetoclax plus azacitidine arm and the placebo plus azacitidine arm were neutropenia (35.7% versus 21.5%), thrombocytopenia (33.6% versus 20.1%), and febrile neutropenia (27.9% versus 7.6%). Overall, the incidence of AEs with a reasonable possibility of being due to azacitidine was 86.9% in the venetoclax plus azacitidine arm and 75.0% in the placebo plus azacitidine arm [38].

The proportion of patients with dose discontinuation due to AEs was similar between the arms (24% venetoclax plus azacitidine versus 20% azacitidine). Venetoclax or placebo dose interruption between cycles and azacitidine dose reduction due to AEs (venetoclax plus azacitidine/azacitidine) occurred in 72%/57% and 3%/4% patients respectively, and were primarily due to neutropenia (19%/10%), febrile neutropenia (20%/4%), and thrombocytopenia (10%/4%). Dose interruptions including delay between treatment cycles and duration reduction to 21 of 28 days per cycle for count recovery after marrow leukaemia clearance occurred in 53% and 28% in venetoclax plus azacitidine and azacitidine arms, respectively; 15%/2% patients had ≥2 interruptions for count recovery in the venetoclax plus azacitidine and azacitidine arms, respectively [8].

Overall, a similar percentage of patients in both arms had AEs leading to death (64 patients [23%] and 29 patients [20%] in the venetoclax in combination with azacitidine arm and azacitidine arm, respectively). The number of patients with a reasonable possibility as assessed by the investigator that venetoclax/placebo-related AEs led to death was 11 (3.9%) in the venetoclax plus azacitidine arm and 2 (1.4%) in the placebo plus azacitidine arm. Azacitidine-related AEs may have led to death in 12 (4.2%) patients in the venetoclax plus azacitidine arm and 2 (1.4%) patients in the placebo plus azacitidine arm [38].

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The 30-day mortality rate was similar in the venetoclax plus azacitidine and azacitidine arms: 7% (n = 21) and 6% (n = 9), respectively [8].

For a summary of VIALE-A safety outcomes with absolute difference and relative risk, see appendix section 8.5.

Table 7.21 Most common AEs in the VIALE-A trial (≥20%)

AEs	No. patients (%)			
	Venetoclax plus azacitidine n = 283		Placebo plus azacitidine n = 144	
	All grade* n = 283	Grade 3 or 4** n = 279	All grade* n = 144	Grade 3 or 4** n = 139
All AEs	283 (100)	279 (99)	144 (100)	139 (97)
Haematologic AEs	236 (83)	233 (82)	100 (69)	98 (68)
Thrombocytopenia	130 (46)	126 (45)	58 (40)	55 (38)
Neutropenia	119 (42)	119 (42)	42 (29)	41 (28)
Febrile neutropenia	118 (42)	118 (42)	27 (19)	27 (19)
Anaemia	78 (28)	74 (26)	30 (21)	29 (20)
Leukopenia	58 (21)	58 (21)	20 (14)	17 (12)
Non-haematologic AEs	-	-	-	-
Nausea	124 (44)	5 (2)	50 (35)	1 (1)
Constipation	121 (43)	2 (1)	56 (39)	2 (1)
Diarrhoea	117 (41)	13 (5)	48 (33)	4 (3)
Vomiting	84 (30)	6 (2)	33 (23)	1 (1)
Hypokalaemia	81 (29)	30 (11)	41 (28)	15 (10)
Peripheral oedema	69 (24)	1 (<1)	26 (18)	0
Pyrexia	66 (23)	5 (2)	32 (22)	2 (1)
Fatigue	59 (21)	8 (3)	24 (17)	2 (1)
Decreased appetite	72 (25)	12 (4)	25 (17)	1 (1)
Infections	239 (84)	180 (64)	97 (67)	74 (51)
Pneumonia	65 (23)	56 (20)	39 (27)	36 (25)
Serious AEs* **	235 (83)	232 (82)	105 (73)	102 (71)
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anaemia	14 (5)	14 (5)	6 (4)	6 (4)
Neutropenia	13 (5)	13 (5)	3 (2)	3 (2)
Atrial fibrillation	13 (5)	10 (4)	2 (1)	2 (1)
Pneumonia	47 (17)	46 (16)	32 (22)	31 (22)
Sepsis	16 (6)	16 (6)	12 (8)	12 (8)

Abbreviation: AE, adverse event.
Includes all patients who received at least one dose of either of the treatment. *AEs shown were reported in ≥20% of patients in either treatment arms. **Grade 3 or 4 AEs ≥10% occurrence. ***Serious AEs ≥5% occurrence
Source: [8]

Results from VIALE-C and M14-358 are supportive of those from VIALE-A and together these studies indicate that the safety profile of venetoclax combinations is well-characterised and manageable. The most common AEs (≥25% of patients) reported in VIALE-C (venetoclax plus LDAC) and M14-358 (venetoclax plus decitabine) are consistent with VIALE-A (venetoclax plus azacitidine): nausea, constipation, vomiting, hypokalaemia, anaemia, febrile neutropenia, neutropenia, thrombocytopenia, diarrhoea, decreased white blood cell count, and fatigue. Similarly to VIALE-A, the most common grade ≥3 AEs (≥20% of patients) in patients treated with venetoclax in combination with decitabine in M14-358 and patient treated with venetoclax in combination with LDAC in VIALE-C were febrile neutropenia, anaemia, thrombocytopenia, pneumonia, and neutropenia. The rate of discontinuation due to AEs was similar to VIALE-A for patients treated with venetoclax in combination with azacitidine in M14-358, at 25%. The rate of discontinuation due to AEs for patients treated with venetoclax in combination with decitabine in M14-358 was 26% and for patients treated with venetoclax in combination with LDAC in VIALE-C was 25% [9, 37, 40].

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For a summary of VIALE-C safety outcomes with absolute difference and relative risk, see appendix section 8.5.

Overall, venetoclax in combination with azacitidine has a well-characterised and manageable safety profile with similar discontinuation rates to HMAs and LDAC alone. AEs are consistent with what would be expected in an AML population, particularly haematologic AEs including anaemia, neutropenia, febrile neutropenia, and thrombocytopenia. These AEs have also been reported in patients with AML receiving an HMA or LDAC monotherapy. Early mortality was not increased with the addition of venetoclax to azacitidine; 30-day and 60-day mortality rates with this combination therapy compared with the backbone therapies alone suggest tolerability of this regimen. Importantly, TLS risk can be mitigated with prophylaxis and daily ramp-up dosing of venetoclax and with a controlled white blood cell count <25 k/µL prior to initiation of therapy [6, 8, 9, 40, 47].

These conclusions are based on data relevant to the intended patient population collected from ongoing, double-blind, placebo-controlled randomised studies of venetoclax or placebo in combination with azacitidine or LDAC and are supported by ongoing, non-randomised studies of venetoclax in combination with azacitidine, decitabine, or LDAC [8, 40].

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7.10 Indirect treatment comparison: results of propensity score weighting analysis (PSW)

7.10.1 Venetoclax plus azacitidine versus LDAC: overall population

Given that patients with prior HMA use and favourable cytogenetic risk in the LDAC arm were not enrolled in VIALE-A per protocol, this analysis excluded patients with prior HMA use or favourable cytogenetic risk in VIALE-C as well. After weighting, all baseline characteristics included in the propensity score model were balanced between the two treatment arms (Table 7.22) [42].

Table 7.22 Overall population – baseline characteristics for LDAC and venetoclax + azacitidine before and after weighting

Baseline characteristics	Before weighting				After weighting			
	LDAC N = 50	VEN + AZA N = 285	Standardized mean difference	P value	LDAC N = 50	VEN + AZA N = 285	Standardized mean difference	P value
Age <75	40.00%	38.95%	0.022	1.000	38.67%	39.10%	0.009	0.955
Female	44.00%	40.00%	0.081	0.708	42.05%	40.62%	0.029	0.853
Race: white	68.00%	75.79%	0.174	0.322	74.52%	74.62%	0.002	0.987
Secondary AML	18.00%	25.26%	0.177	0.354	24.97%	24.19%	0.018	0.917
AML with MRC	28.00%	32.28%	0.093	0.663	33.71%	31.68%	0.043	0.792
Antecedent haematological history of MDS	12.00%	17.19%	0.147	0.479	18.47%	16.46%	0.053	0.765
ECOG PS <2	46.00%	55.09%	0.183	0.301	53.97%	53.73%	0.005	0.976
IVRS cytogenetic risk: poor	32.00%	34.74%	0.058	0.830	33.51%	34.29%	0.017	0.918
Bone marrow blast count	54.13 ± 24.21	52.04 ± 24.26	0.086	0.573	53.49 ± 24.33	52.39 ± 24.32	0.045	0.773

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; ECOG PS, Eastern Cooperative Oncology Group performance status; IVRS, interactive voice recognition system; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; VEN, venetoclax.
[a]A total of 2 patients were excluded from the analysis due to missingness. Among them, 1 patient has missing data in cytogenetic risk in the LDAC arm and 1 patient has missing data in bone marrow blast count in the VEN + AZA arm.
[b]Categorical outcomes were compared using a chi-squared test, and continuous outcomes with an ANOVA.
Source: [42]

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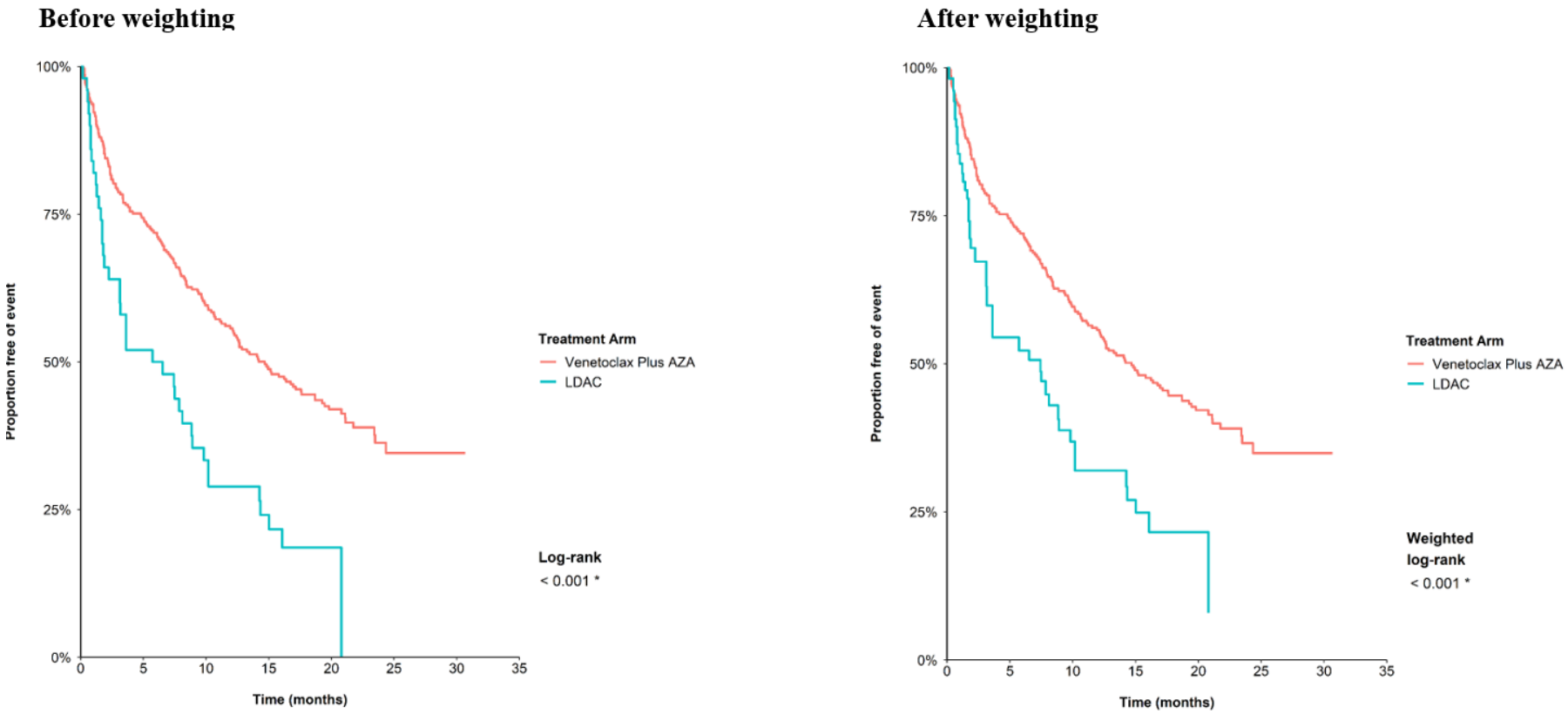
PSW results: overall population – OS

Before weighting, OS was significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.69 months [95% CI: 11.53, 18.69]) compared with patients treated with LDAC (median OS: 6.13 months [95% CI: 2.23, 8.90]; log-rank p<0.001; HR: 0.47 [95% CI: 0.33, 0.67]; Figure 7.15, Table 7.23). After weighting, OS was still significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.69 months [95% CI: 12.12, 19.25]) compared with patients treated with LDAC (median OS: 7.43 months [95% CI: 3.15, 10.18]; log-rank p<0.001; HR: 0.50 [95% CI: 0.35, 0.73]; Figure 7.15, Table 7.23) [42].

Figure 7.15 Overall population – OS before and after weighting



Abbreviations: AZA, azacitidine; LDAC, low-dose cytarabine; OS, overall survival
Source: [42]

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Table 7.23 Overall population – summary statistics of OS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value
LDAC	50	40	6.13 (2.23, 8.90)	Reference	-	7.43 (3.15, 10.18)	Reference	-
Venetoclax + azacitidine	285	161	14.69 (11.53, 18.69)	0.47 (0.33, 0.67)	<0.001*	14.69 (12.12, 19.25)	0.50 (0.35, 0.73)	<0.001*

Abbreviations: CI, confidence interval; HR, hazard ratio; LDAC, low-dose cytarabine; OS, overall survival.
*Denotes statistical significance at the level of 0.05.
Source: [42]

PSW results: overall population – EFS

Before weighting, venetoclax plus azacitidine was associated with a significantly lower risk of experiencing disease progression, relapse, treatment failure, or death (median time to event: 9.66 months [95% CI: 8.41, 11.53]) compared with LDAC (median time to event: 3.02 months [95% CI: 1.45, 5.72]; log-rank p<0.001; HR: 0.40 [95% CI: 0.28, 0.56]; Figure 7.16, Table 7.24). After weighting, venetoclax plus azacitidine was still associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.79 months [95% CI: 8.41, 11.99]) compared with LDAC (median time to event: 3.06 months [95% CI: 1.71, 5.82]; log-rank p<0.001; HR: 0.40 [95% CI: 0.28, 0.58] Figure 7.16, Table 7.24) [42].

Table 7.24 Overall population – summary statistics of EFS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value
LDAC	50	43	3.02 (1.45, 5.72)	Reference	-	3.06 (1.71, 5.82)	Reference	-
Venetoclax + azacitidine	285	190	9.66 (8.41, 11.53)	0.40 (0.28, 0.56)	<0.001*	9.79 (8.41, 11.99)	0.40 (0.28, 0.58)	<0.001*

Abbreviations: CI, confidence interval; HR, hazard ratio; LDAC, low-dose cytarabine; OS, overall survival.
*Denotes statistical significance at the level of 0.05.
Source: [42]

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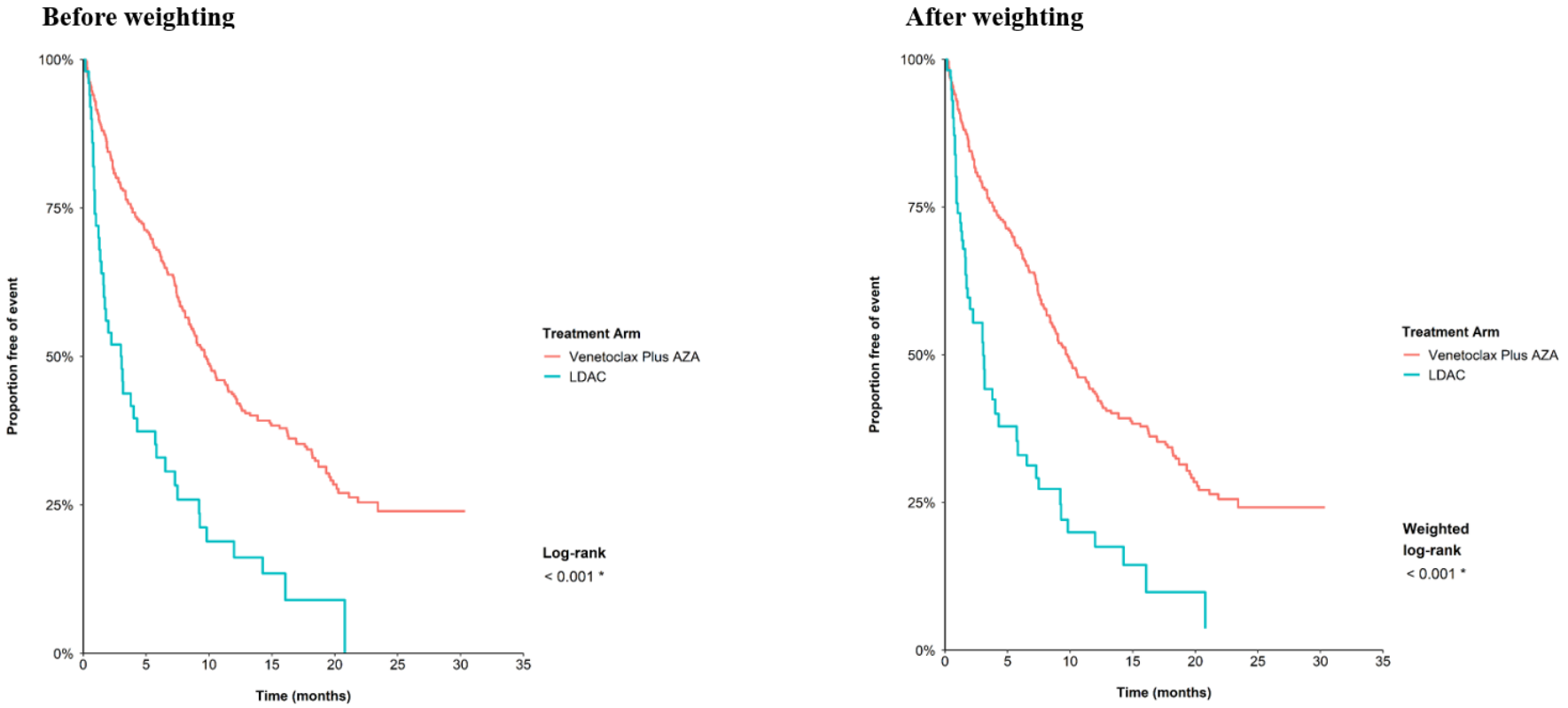
Figure 7.16 Overall population – EFS before and after weighting



Abbreviations: AZA, azacitidine; EFS, event-free survival; LDAC, low-dose cytarabine.
Source: [42]

PSW results: overall population – CR + CRi

Compared with patients treated with LDAC, patients treated with venetoclax plus azacitidine were more likely to achieve CR (OR: 5.79 [95% CI: 1.72, 19.51]), CRi (OR: 6.66 [95% CI: 1.55, 28.63]), and CR + CRi (OR: 10.39 [95% CI: 3.88, 27.84]) before weighting (Table 7.25). After weighting, patients treated with venetoclax plus azacitidine were still more likely to achieve CR (OR: 5.75 [95% CI: 1.62, 20.48]), CRi (OR: 7.49 [95% CI: 1.73, 32.52]), and CR + CRi (OR: 10.80 [95% CI: 3.89, 29.94]) compared with patients treated with LDAC (Table 7.25) [42].

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Table 7.25 Overall population – comparison of CR, CRi, and CR + CRi for venetoclax + azacitidine versus LDAC before and after weighting

	Before weighting				After weighting			
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA versus LDAC	P value	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA versus LDAC	P value
CR	0.37 (0.31, 0.43)	0.10 (0.04, 0.22)	5.25 (2.02, 13.64)	<0.001 *	0.37 (0.31, 0.43)	0.10 (0.04, 0.22)	5.17 (1.97, 13.56)	<0.001 *
CRi	0.29 (0.24, 0.35)	0.06 (0.02, 0.17)	6.55 (1.98, 21.62)	<0.01 *	0.29 (0.24, 0.35)	0.06 (0.02, 0.17)	6.46 (1.94, 21.52)	<0.01 *
CR + CRi	0.66 (0.61, 0.72)	0.16 (0.08, 0.29)	10.34 (4.67, 22.89)	<0.001 *	0.66 (0.61, 0.72)	0.16 (0.08, 0.29)	10.17 (4.55, 22.73)	<0.001 *

Abbreviations: AZA, azacitidine; CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; LDAC, low-dose cytarabine; OR, odds ratio; VEN, venetoclax.
*Denotes statistical significance at the level of 0.05.
Source: [42]

7.10.2 AML patients with >30% bone marrow blasts

This analysis also excluded patients with prior HMA use or favourable cytogenetic risk in VIALE-C and was restricted to patients with bone marrow blast count greater than 30%. After weighting, all baseline characteristics included in the propensity score model were balanced between the two treatment arms (Table 7.26) [42].

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Table 7.26 AML patients with >30% bone marrow blasts – baseline characteristics for LDAC and venetoclax + azacitidine before and after weighting

Baseline Characteristics	Before weighting				After weighting			
	LDAC N = 36	VEN + AZA N = 206	Standardized mean difference	P value	LDAC N = 36	VEN + AZA N = 206	Standardized mean difference	P value
Age <75	47.22%	37.86%	0.190	0.381	41.50%	39.33%	0.044	0.813
Female	36.11%	39.32%	0.066	0.858	40.06%	38.88%	0.024	0.900
Race: White	63.89%	74.27%	0.226	0.277	72.40%	72.71%	0.007	0.968
Secondary AML	16.67%	23.79%	0.178	0.468	22.76%	22.72%	0.001	0.996
AML with MRC	25.00%	26.70%	0.039	0.993	28.65%	26.47%	0.049	0.805
Antecedent haematological history of MDS	11.11%	16.99%	0.170	0.468	17.23%	16.16%	0.029	0.892
ECOG performance status <2	41.67%	55.34%	0.276	0.182	49.83%	53.23%	0.068	0.721
IVRS cytogenetic risk: poor	38.89%	32.04%	0.144	0.539	32.60%	32.97%	0.008	0.967
Bone marrow blast count	65.75 ± 17.90	62.78 ± 19.75	0.157	0.400	64.91 ± 16.67	63.24 ± 19.77	0.091	0.580

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; IVRS, interactive voice recognition system; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; VEN, venetoclax.
[a]One patient was removed from the analysis due to missingness in cytogenetic risk.
[b]Categorical outcomes were compared using a chi-squared test, and continuous outcomes with an ANOVA.
Source: [42]

PSW results: AML patients with >30% bone marrow blasts – OS

Before weighting, OS was significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.06 months [95% CI: 10.41, 16.95]) compared with patients treated with LDAC (median OS: 3.61 months [95% CI: 1.87, 7.85]; log-rank p<0.001; HR: 0.47 [95% CI: 0.31, 0.70]; Figure 7.17, Table 7.27). After weighting, OS was still significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.06 months [95% CI: 10.61, 17.15]) compared with patients treated with LDAC (median OS: 3.61 months [95% CI: 3.12, 10.18]; log-rank p<0.001; HR: 0.47 [95% CI: 0.32, 0.69]; Figure 7.17, Table 7.27) [42].

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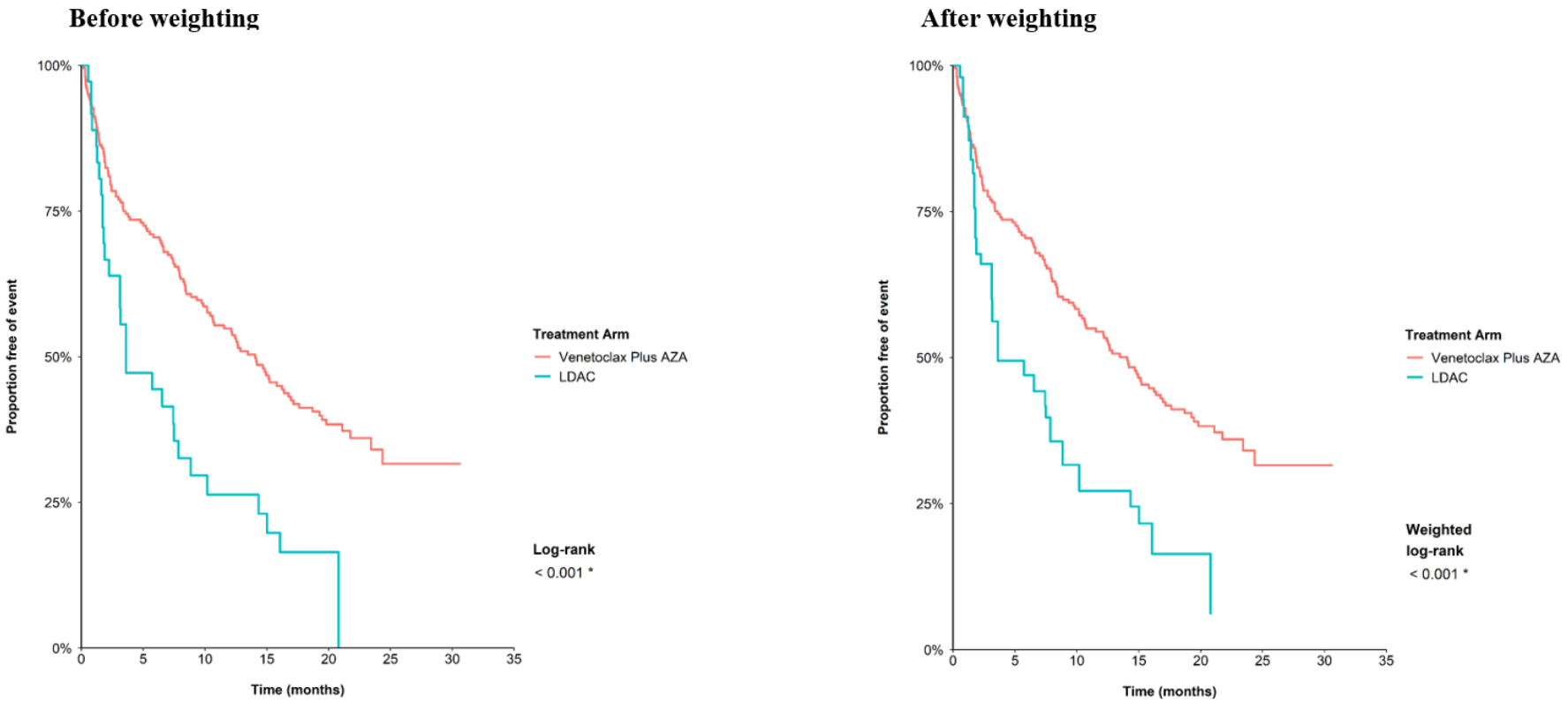
Figure 7.17 AML patients with >30% bone marrow blasts – OS before and after weighting



Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; LDAC, low-dose cytarabine; OS, overall survival.
Source: [42]

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Table 7.27 AML patients with >30% bone marrow blasts – summary statistics of OS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value
LDAC	36	30	3.61 (1.87, 7.85)	Reference	-	3.61 (3.12, 10.18)	Reference	-
Venetoclax + azacitidine	206	121	14.06 (10.41, 16.95)	0.47 (0.31, 0.70)	<0.001*	14.06 (10.61, 17.15)	0.47 (0.32, 0.69)	<0.001*

Abbreviations: AML, acute myeloid leukaemia; CI, confidence interval; HR, hazard ratio; LDAC, low-dose cytarabine; OS, overall survival.
*Denotes statistical significance at the level of 0.05.
Source: [42]

PSW results: AML patients with >30% bone marrow blasts – EFS

Before weighting, venetoclax plus azacitidine was associated with a significantly lower risk of experiencing disease progression, relapse, treatment failure, or death (median time to event: 9.00 months [95% CI: 7.59, 11.50]) compared with LDAC (median time to event: 3.02 months [95% CI: 1.61, 5.82]; log-rank p<0.001; HR: 0.41 [95% CI: 0.28, 0.61]; Figure 7.18, Table 7.28). After weighting, venetoclax combined with azacitidine was still associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.00 months, 95% CI: 7.69, 11.53) compared with LDAC (median time to event: 3.06 months, 95% CI: 1.71, 6.54; log-rank p<0.001; HR: 0.42, 95% CI: 0.28, 0.61; Figure 7.18, Table 7.28) [42].

Table 7.28 AML patients with >30% bone marrow blasts – Summary statistics of EFS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median EFS (95% CI)	HR (95% CI)	P value	Median EFS (95% CI)	HR (95% CI)	P value
LDAC	36	32	3.02 (1.61, 5.82)	Reference	-	3.06 (1.71, 6.54)	Reference	-
Venetoclax + azacitidine	206	136	9.00 (7.59, 11.50)	0.41 (0.28, 0.61)	<0.001*	9.00 (7.69, 11.53)	0.42 (0.28, 0.61)	<0.001*

Abbreviations: AML, acute myeloid leukaemia; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; LDAC, low-dose cytarabine.
*Denotes statistical significance at the level of 0.05.
Source: [42]

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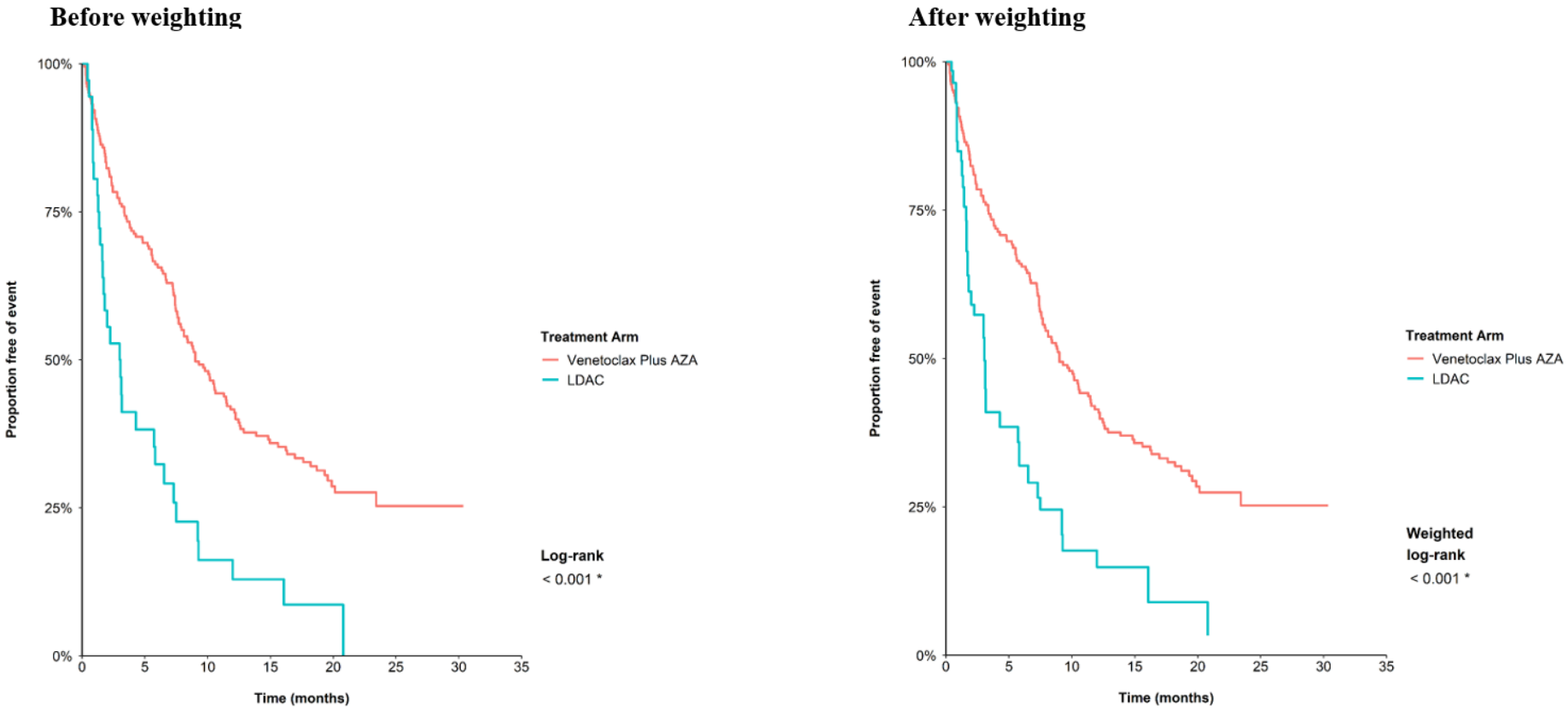
Figure 7.18 AML patients with >30% bone marrow blasts – EFS before and after weighting



Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; EFS, event-free survival; LDAC, low-dose cytarabine.
Source: [42]

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PSW results: AML patients with >30% bone marrow blasts – CR + CRi

Compared with patients treated with LDAC, those treated with venetoclax plus azacitidine were more likely to achieve CR (OR: 5.79 [95% CI: 1.72, 19.51]), CRi (OR: 6.66 [95% CI: 1.55, 28.63]), and CR + CRi (OR: 10.39 [95% CI: 3.88, 27.84]) before weighting (Table 7.29). After weighting, patients treated with venetoclax plus azacitidine were still more likely to achieve CR (OR: 5.75 [95% CI: 1.62, 20.48]), CRi (OR: 7.49 [95% CI: 1.73, 32.52]), and CR + CRi (OR: 10.80 [95% CI: 3.89, 29.94]) compared with patients treated with LDAC (Table 7.29) [42].

Table 7.29 AML patients with >30% bone marrow blasts – Comparison of CR, CRi, and CR + CRi for venetoclax + azacitidine versus LDAC before and after weighting

	Before weighting				After weighting			
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA versus LDAC	P value	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR for VEN + AZA versus LDAC	P value
CR	0.34 (0.28, 0.41)	0.08 (0.03, 0.23)	5.79 (1.72, 19.51)	<0.01 *	0.34 (0.28, 0.41)	0.08 (0.03, 0.24)	5.75 (1.62, 20.48)	<0.01 *
CRi	0.28 (0.22, 0.35)	0.06 (0.01, 0.20)	6.66 (1.55, 28.63)	<0.05 *	0.28 (0.22, 0.35)	0.05 (0.01, 0.18)	7.49 (1.73, 32.52)	<0.01 *
CR + CRi	0.63 (0.56, 0.69)	0.14 (0.06, 0.29)	10.39 (3.88, 27.84)	<0.001 *	0.62 (0.55, 0.69)	0.13 (0.05, 0.29)	10.80 (3.89, 29.94)	<0.001 *

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; LDAC, low-dose cytarabine; OR, odds ratio; VEN, venetoclax.
*Denotes statistical significance at the level of 0.05.
Source: [42]

For venetoclax plus azacitidine versus LDAC PSW sensitivity analyses, see appendix section 8.6.

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7.11 Conclusions

7.11.1 Efficacy of venetoclax in patients with AML ineligible for intensive therapy

The VIALE-A trial has demonstrated that the addition of venetoclax to azacitidine is more effective than azacitidine alone in patients with AML who are ineligible for intensive therapy, overall and in the majority of subpopulations [8, 38]. Venetoclax in combination with azacitidine resulted in longer OS, rapid responses with clinically meaningful improvements in response rates, greater transfusion independence rates, longer EFS, and increased TTD in EORTC QLQ-C30 GHS/QoL compared with azacitidine monotherapy in patients who were ineligible for intensive therapy [8, 46].

Data from the Phase 3 trial VIALE-C and Phase 1b trial M14-358 both confirm and support the results of VIALE-A. Specifically, M14-358 demonstrates that venetoclax in combination with an HMA is similarly effective, irrespective of whether the HMA is azacitidine or decitabine [6, 37].

In the VIALE-A trial, venetoclax in combination with azacitidine led to a statistically significant and clinically meaningful reduction in the risk of death in newly diagnosed patients with AML who were ineligible to receive intensive chemotherapy compared with patients randomised to receive azacitidine alone (14.7 months versus 9.6 months; HR: 0.66 [95% CI: 0.52, 0.85]; p<0.001) [8].

In VIALE-A, venetoclax in combination with azacitidine resulted in increases in remission rates (CR + CRi, CR, and CR + CRh) compared with azacitidine alone. CR + CRi, CR, and CR + CRh were rapidly achieved, as measured by the response rates by the initiation of Cycle 2. Responses were also durable: patients sustained long-term benefit with ongoing treatment [8, 38].

Additional efficacy endpoints of transfusion independence (RBC or platelets) and EFS in VIALE-A were improved with venetoclax in combination with azacitidine over azacitidine alone [8]. For HRQL as measured by EORTC QLQ-C30 GHS/QoL, venetoclax in combination with azacitidine resulted in a clinically meaningful increase in median TTD compared with azacitidine alone [46].

In addition to the direct clinical evidence, IPD from the VIALE-A and VIALE-C trials were used to indirectly compare venetoclax plus azacitidine with LDAC using a propensity score weighting technique due to the relevance of this comparison in markets where azacitidine is restricted. The propensity score analyses demonstrated that venetoclax plus azacitidine is associated with statistically significantly prolonged OS and EFS, and significantly higher rates of achieving CR + CRi compared with LDAC. The results were similar in a subpopulation of patients with >30% bone-marrow blasts. Sensitivity analyses confirmed that the results of the propensity score analyses were robust. Other ITC comparisons (e.g. versus glasdegib in combination with LDAC and BSC) were assessed but were deemed not informative for decision-making following feasibility assessment due to excessive heterogeneity between the trials and considerable uncertainty in the data due to non-transparent trial designs and the unblinded nature of some of the studies as well as the use of *post-hoc* analyses [42]. Therefore, this should be acknowledged as an evidence gap. However, the most relevant comparisons have been investigated through VIALE-A and the indirect comparison of venetoclax in combination with azacitidine versus LDAC. European guidelines recommend HMAs as first-choice treatment for newly diagnosed patients with AML ineligible for intensive chemotherapy, with LDAC as a suitable alternative [25, 68]. VIALE-A provides robust evidence as a large double-blinded Phase 3 randomised controlled trial that demonstrates the comparative effectiveness of venetoclax in combination with azacitidine versus the most clinically relevant comparator [8, 40]. A comparison of venetoclax in combination with azacitidine versus LDAC was performed as this comparison is relevant to a small number of markets where the use of azacitidine is restricted [35, 36].

Overall, venetoclax in combination with an HMA is a highly effective treatment in patients with AML who are ineligible for intensive therapy as measured by OS, remission rates (CR + CRi, CR, and CR + CRh), duration of response, transfusion independence, EFS, and HRQL [6, 8, 46].

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7.11.2 Safety of venetoclax in patients ineligible for intensive chemotherapy

Results from the Phase 3 VIALE-A study demonstrate that the safety profile of venetoclax in combination with azacitidine is well-characterised and manageable in the newly diagnosed AML patient population ineligible for intensive chemotherapy. No new risks were identified with venetoclax at the proposed dosing in combination with azacitidine among patients with AML, and venetoclax can be combined with HMAs without adding clinically significant toxicity. In the VIALE-A trial, the rate of discontinuation of venetoclax combination therapy at the proposed doses for events unrelated to disease progression was unremarkable compared with the monotherapy treatment arm [8].

Safety data from the Phase 3 trial VIALE-C and Phase 1b trial M14-358 support the conclusion that the safety profile of venetoclax combinations is well-characterised and manageable in this population. Specifically, results from M14-358 indicated that the safety profiles of venetoclax in combination with azacitidine and in combination with decitabine are comparable and consistent [6, 37].

The safety profile of venetoclax in combination with azacitidine is consistent with the natural history of AML and is as expected given its mode of action and on-target effect. The most common AEs occurring in ≥30% of patients treated with venetoclax in combination with azacitidine in the VIALE-A study were febrile neutropenia, neutropenia, thrombocytopenia, constipation, vomiting, diarrhoea, and nausea. Overall rates of AEs and SAEs reported in VIALE-A were similar between treatment arms, with the exception of febrile neutropenia and neutropenia in VIALE-A which were somewhat higher among patients who received venetoclax in combination with azacitidine compared with azacitidine alone. Febrile neutropenia, neutropenia, thrombocytopenia, and anaemia were the most common grade ≥3 AEs among patients treated at the target doses of venetoclax. The most common SAEs across all treatment arms were febrile neutropenia and pneumonia, which are consistent with expectations in an AML treatment setting. The majority of patients did not require discontinuation of venetoclax therapy despite AEs or SAEs. Overall, safety events were manageable using routine oncology practices [8, 38].

Although TLS is a known risk with venetoclax as a result of on-target effects and rapid reduction of tumour volume, it did not appear to be a significant risk among patients with AML treated with venetoclax in combination with azacitidine. In the VIALE-A trial, the rate of TLS was low in patients treated with venetoclax in combination with azacitidine (3 patients). TLS risk can be mitigated with prophylaxis and ramp-up dosing of venetoclax, and with a controlled white blood cell count <25 k/µL prior to initiation of therapy [6, 8, 47].

Early mortality was not increased with the addition of venetoclax to azacitidine. AEs leading to death were not substantially different between patients treated with venetoclax in combination with azacitidine, and patients treated with placebo in combination with azacitidine (22.6% and 20.1%, respectively) [6, 8].

In summary, venetoclax in combination with an HMA provides a valuable treatment option with a well-characterised and manageable safety profile for patients with newly diagnosed AML who are ineligible for intensive chemotherapy [6, 8].

7.12 Strengths and limitations

7.12.1 Internal validity

The internal validity of VIALE-A was assessed using the Cochrane Collaboration framework to assess the risk of bias in RCTs, as referred to in the EUnetHTA guideline for the internal validity of randomised controlled trials [139, 140]. Five major types of bias were considered: selection, performance, detection, attrition, and reporting. Other sources of bias were also considered.

Selection bias
Interactive Response Technology (IRT) was used to generate the random allocation sequence and conceal the allocation before inclusion of patients in a trial. The IRT was used to randomise subjects into the two treatment arms in a 2:1 ratio (VIALE-A: venetoclax + azacitidine or placebo + azacitidine). A bottle (kit) number randomization schedule and a subject randomization schedule was generated by the Clinical

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Statistics Department at AbbVie prior to the start of the study. A copy of all randomization schedules was kept by the Clinical Statistics Department at AbbVie and a copy was forwarded to the IRT vendor. Subject randomization in VIALE-A was stratified by age (18 to <75, ≥75), cytogenetics (intermediate risk, poor risk), and region (US, EU, China, Japan, rest of world) [8].

Subjects who met all the inclusion criteria and none of the exclusion criteria after screening proceeded to randomization. The site contacted the IRT vendor/system to complete the randomization process and obtain study drug assignment. Subjects received a separate unique 6-digit randomization number that was automatically recorded in the electronic case report form through the IRT system. This randomization number was used only by AbbVie for loading the treatment schedule into the database [8].

Performance and detection bias

For VIALE-A, the Investigator, study site personnel, AbbVie personnel with direct oversight conduct and management of the trial, and the subject were blinded to each subject's treatment with venetoclax or placebo throughout the course of the study. All subjects were treated with open-label azacitidine. If the blind was broken for a subject currently on study treatment by the investigator, that subject was discontinued from study treatment and post-treatment or survival follow-up commenced [8].

All response- or progression-related endpoints (e.g., CR/CRi and EFS) were based on the investigator assessment. In addition to being reviewed by the investigator and local haematopathologists, all disease assessment information was sent to an Independent Review Committee (IRC) to provide response assessment. Interpretations from the IRC were not shared with sites [8].

Attrition bias

For VIALE-A (data cut-off 4 January 2020), none of the protocol deviations, including (but not limited to) inclusion/exclusion criteria violation, receipt of wrong treatment or incorrect dose of study drug and withdrawals, were considered to have affected the study outcome or interpretation of the study results or conclusions [38].

Subjects who had no disease assessment were considered as non-responders in the estimation of response rates. Subjects who had not experienced disease progression or death were censored at last disease assessment dates (bone marrow or haematology lab) for analyses of DOR and EFS. Subjects who were still alive were censored at the last known alive dates. Subjects who did not take any study drug were considered transfusion dependent in the analysis of transfusion independence rates [8].

Reporting bias

AbbVie provided the study protocols, clinical study reports, and several publications for the venetoclax studies relevant to this assessment; thus, the possibility of selective outcome reporting is regarded as low.

Validity of endpoints

All outcomes were clearly defined in the trial protocol and outcome reporting was objective. All outcomes were analysed and reported in accordance with a priori protocols. Furthermore, established and patient-relevant outcomes for AML were used for benefit and risk assessment. The primary analysis of all response or progression related endpoints (e.g., CR/CRi) were based on the investigator assessment. Sensitivity analyses were performed based on the IRC's assessment [8].

For VIALE-A, efficacy analyses were performed on the Efficacy Analysis Set (called Full Analysis Set in the Statistical Analysis Plan), defined as all randomised subjects in Group 2. This group consisted of subjects randomised under Protocol Amendment 1 and later versions (Group 1 consisted of only 2 subjects). The safety analyses were performed on the Safety Analysis Set, defined as all subjects who received at least 1 dose of study drug (venetoclax or placebo, in combination with azacitidine) [8].

All subjects had response assessments according to the revised IWG criteria for AML; these were slightly modified by evaluating progressive disease per ELN recommendations [8].

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Transfusion independence was defined by IWG criteria as a period of at least 56 days with no transfusion between the first dose of study drug and the last dose of study drug + 30 days.

PRO instruments, such as the EORTC QLQ-C30, were self-administered by subjects using electronic tablets supplied by AbbVie; site personnel did not provide interpretation or assistance to subjects other than encouragement to complete the tasks. The EORTC QLQ-C30 was developed and validated for use in a cancer patient population, and its reliability and validity are highly consistent across different language-cultural groups [8].

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. In addition, the investigator was required to assess causality. The safety analysis was performed using MedDRA (version 19.1) in accordance with good clinical practice. The classification of severity and relationship to study drug was performed according to NCI CTCAE Version 4.03 [8]. The presentation according to standardized MedDRA terminology complies with international standards and is therefore considered valid.

Other sources of bias
The findings from evaluated subgroups, most notably among patients with either de novo or secondary AML, intermediate cytogenetic risk, and IDH1 or IDH2 mutations, should be interpreted with caution due the small number of patients in each of these subgroups. In addition, subgroup analysis of blast count (<30% versus >30%) was conducted post hoc [8].

No other aspects which could potentially increase the risk of bias were identified. Therefore, based on the randomised, double-blind, controlled design of VIALE-A, the risk of bias on study level is considered low.

Consistency of the results
Venetoclax in combination with azacitidine, decitabine or LDAC achieved consistent improvements across Phase 3 and Phase 1b/2 trials. Venetoclax combinations resulted in longer OS, rapid responses with clinically meaningful improvements in response rates, greater transfusion independence rates, and longer EFS compared with placebo in combination with azacitidine or LDAC and currently available monotherapies for subjects who were ineligible for intensive therapy. Specifically, clinical outcomes for venetoclax in combination with azacitidine were similar to those seen for venetoclax in combination with decitabine [7, 8, 37, 40]. Venetoclax in combination with azacitidine or LDAC was an effective treatment in subjects with AML who were ineligible for intensive therapy, both overall and in the majority of subpopulations. Across both randomised studies (VIALE-A and VIALE-C), venetoclax in combination with azacitidine or LDAC demonstrated similar trends survival benefit, with HRs of 0.66 (95% CI: 0.52, 0.85) and 0.75 (95% CI: 0.52, 1.07), respectively.

The overall safety profile observed in the VIALE-A study was consistent with the results of the VIALE-C and the Phase 1b/2 studies (M14-358 and M14-387) in subjects treated with venetoclax at the proposed doses in combination with either azacitidine, decitabine, or LDAC. Across studies, venetoclax had a manageable safety profile that is considered to be acceptable in the AML patient population evaluated. Overall, the risks associated with the combination of venetoclax with azacitidine are consistent with the established safety profiles of the agents and natural history of AML. These events were generally manageable using standard medical practices [7, 8, 37, 40].

7.12.2 Relevance of the evidence base

The study population included adult patients newly diagnosed with AML who were ineligible for intensive chemotherapy. This corresponds to the target population of venetoclax according to the proposed label indication and is transferable to the European healthcare context with regard to both general patient characteristics and disease-specific criteria. All subjects in VIALE-A met the objective criteria for ineligibility for intensive chemotherapy. VIALE-A recruited patients from multiple sites across Europe, with European patients constituting approximately 40% of the final study cohort. The baseline characteristics including age

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and sex distribution correspond to that reported by European guidelines and epidemiology studies [8, 25, 141, 142].

VIALE-A is a Phase 3 randomised controlled trial that demonstrates the clinical effectiveness and safety of venetoclax in combination with an HMA (azacitidine). The comparative clinical effectiveness and safety of venetoclax in combination with azacitidine was compared with azacitidine alone, which represents the SoC according to European clinical practice guidelines. In such guidelines, HMAs are considered first-choice treatment for newly diagnosed patients ineligible for intensive chemotherapy, followed by LDAC [25, 26]. A comparison of venetoclax in combination with azacitidine versus LDAC was performed as this comparison is relevant to a small number of markets where the use of azacitidine is restricted. There is no direct or indirect comparative effectiveness evidence available comparing venetoclax in combination with azacitidine versus other comparators identified in the PICO, including glasdegib in combination with LDAC or BSC. Although ITCs were considered, comparability and feasibility assessments indicated that such analyses would be non-informative due to excessive heterogeneity between the trials and considerable uncertainty in the data due to non-transparent trial designs. Therefore, this should be acknowledged as an evidence gap.

All endpoints used for the presentation of efficacy and safety in this assessment are patient-relevant and reflect those proposed in the ELN guidelines. Specifically, clinical observation suggests that patients who achieve CR may have improved HRQL, for example, due to receipt of fewer transfusions and spending less time in medical facilities than patients who do not achieve CR, even if survival is not improved; the same may apply to CRi [26]. The endpoints were collected using valid instruments and analysed using adequate methods.

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8 APPENDICES

8.1 Systematic literature review supplemental information

8.1.1 Search strategy

Embase (OvidSP)
Embase 1974 to 2020 Week 41 (Search date: 13 October 2020)

#	Searches	Results
1	exp acute myeloid leukemia/	42220
2	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or granulocytic)).tw.	73125
3	(ANLL or AML).tw.	65705
4	or/1-3	113146
5	exp venetoclax/ or (venetoclax or venclexta or venclyxto or ABT-199 or ABT199 or ABT-0199 or GDC-0199 or RG7601).tw.	3932
6	exp azacitidine/ or (azacitidine or 5-azacytidine or azacytidine or vidaza or U-18496).tw.	14975
7	exp cytarabine/ or (cytarabine or Alexan or Arabine or ARA-cell or Aracytin or Aracytine or Cytarbel or Cytosar or Erpalfa or Starasid or Udicil or CHX-3311 or U 19920 or U-29920A HCl or WR-28453).tw.	62218
8	exp decitabine/ or (decitabine or dacogen).tw.	6962
9	exp glasdegib/ or (glasdegib or daurismo or PF-04449913).tw.	352
10	exp gemtuzumab ozogamicin/ or exp gemtuzumab/ or (gemtuzumab or mylotarg or CDP-771 or CMA-676 or WAY-CMA-676).tw.	3852
11	exp clofarabine/ or (clofarabine or Clolar or Evoltra).tw.	2537
12	exp granulocyte colony stimulating factor/ or (granulocyte colony stimulating factor or G-CSF or filgrastim or lenograstim or Granix or Neupogen or Zarxio or Grasin or Nivestim or Tevagrastim).tw.	57167
13	exp aclarubicin/ or (aclarubicin or aclacinomycin or Aclacin or Aclacinomycine or Aclacinon or Aclaplastin or Jaclacin or MA144-A1).tw.	2294
14	(CAG or (Cytarabine adj3 aclarubicin adj3 G-CSF)).tw.	16291
15	exp gilteritinib/ or (gilteritinib or XOSPATA or ASP2215 or ASP-2215).tw.	430
16	exp ivosidenib/ or (ivosidenib or Tibsovo or AG-120 or AG120).tw.	441
17	exp palliative therapy/ or (palliative therapy or palliative care or palliative treatment or palliation or supportive therapy or supportive care or BSC).tw.	163426
18	exp hydroxyurea/ or (hydroxycarbamide or hydroxyurea or Droxia or Hydrea or SQ 1089 or WR 83799).tw.	27998
19	exp mercaptopurine/ or (mercaptopurine or Purinethol or Purixan or Alti-Mercaptopurine or Flocofil or Ismipur or Leukerin or Mercaleukim or Mercaptina or Purinethiol or Puri-Nethol or Xaluprine or BW 57-323H or U-4748 or WR-2785).tw.	25919
20	exp etoposide/ or (etoposide or Lastet or VP-16 or VP-16-213).tw.	91252
21	or/5-20	418108
22	Clinical Trial/ or Randomised Controlled Trial/ or controlled clinical trial/ or multicenter study/ or Phase 3 clinical trial/ or Phase 4 clinical trial/ or exp RANDOMIZATION/ or Single Blind Procedure/ or Double Blind Procedure/ or Crossover Procedure/ or PLACEBO/ or Prospective Study/	2211052
23	(randomi?ed controlled trial$ or rct or (random$ adj2 allocat$) or single blind$ or double blind$ or ((treble or triple) adj blind$) or placebo$).tw.	644780
24	Phase 1 clinical trial/ or Phase 2 clinical trial/ or (phase i$ or phase ii$ or phase iii$ or phase iv$ or phase 1$ or phase 2$ or phase 3$ or phase 4$).tw.	401252

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25	Non Randomised Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	36181
26	(single arm or open label).tw.	93410
27	Case Study/ or case report.tw. or abstract report/ or letter/ or Conference proceeding.pt. or Conference abstract.pt. or Editorial.pt. or Letter.pt. or Note.pt.	6960472
28	(or/22-26) not 27	1954574
29	exp animal/ or nonhuman/ or (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.	28129094
30	exp Human/ or Human Experiment.tw.	21450788
31	29 not (29 and 30)	6678315
32	(4 and 21 and 28) not 31	4056
33	limit 32 to english language	3823

Source: [123]

Medline (OvidSP)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) 1946 to October 12, 2020 (Search date: 13 October 2020)

#	**Searches**	**Results**
1	exp Leukemia, Myeloid, Acute/	55854
2	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or granulocytic)).tw.	49725
3	(ANLL or AML).tw.	35782
4	or/1-3	84030
5	(venetoclax or venclexta or venclyxto or ABT-199 or ABT199 or ABT-0199 or GDC-0199 or RG7601).tw.	1191
6	exp azacitidine/ or (azacitidine or 5-azacytidine or azacytidine or vidaza or U-18496).tw.	8969
7	exp cytarabine/ or (cytarabine or Alexan or Arabine or ARA-cell or Aracytin or Aracytine or Cytarbel or Cytosar or Erpalfa or Starasid or Udicil or CHX-3311 or U 19920 or U-29920A HCl or WR-28453).tw.	17939
8	(decitabine or dacogen).tw.	1859
9	(glasdegib or daurismo or PF-04449913).tw.	71
10	(gemtuzumab or mylotarg or CDP-771 or CMA-676 or WAY-CMA-676).tw.	711
11	(clofarabine or Clolar or Evoltra).tw.	517
12	exp granulocyte colony stimulating factor/ or (granulocyte colony stimulating factor or G-CSF or filgrastim or lenograstim or Granix or Neupogen or Zarxio or Grasin or Nivestim or Tevagrastim).tw.	25389
13	exp ACLARUBICIN/ or (aclarubicin or aclacinomycin or Aclacin or Aclacinomycine or Aclacinon or Aclaplastin or Jaclacin or MA144-A1).tw.	1095
14	(CAG or (Cytarabine adj3 aclarubicin adj3 G-CSF)).tw.	10891
15	(gilteritinib or XOSPATA or ASP2215 or ASP-2215).tw.	117
16	(ivosidenib or Tibsovo or AG-120 or AG120).tw.	113
17	exp Palliative Care/ or (palliative therapy or palliative care or palliative treatment or palliation or supportive therapy or supportive care or BSC).tw.	100730
18	exp HYDROXYUREA/ or (hydroxycarbamide or hydroxyurea or Droxia or Hydrea or SQ 1089 or WR 83799).tw.	12646
19	exp MERCAPTOPURINE/ or (mercaptopurine or Purinethol or Purixan or Alti-Mercaptopurine or Flocofil or Ismipur or Leukerin or Mercaleukim or Mercaptina or Purinethiol or Puri-Nethol or Xaluprine or BW 57-323H or U-4748 or WR-2785).tw.	21408
20	exp ETOPOSIDE/ or (etoposide or Lastet or VP-16 or VP-16-213).tw.	27010

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21	or/5-20	219407
22	Randomised Controlled Trials as Topic/ or randomised controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or exp Clinical Trials as topic/ or PLACEBOS/	1191374
23	(clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or controlled clinical trial or randomised controlled trial or multicenter study or clinical trial).pt.	1029212
24	((clinical adj trial$) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)) or placebo$ or randomly allocated or (allocated adj2 random$)).tw.	673319
25	(phase i$ or phase ii$ or phase iii$ or phase iv$ or phase 1$ or phase 2$ or phase 3$ or phase 4$).tw.	248083
26	Non Randomised Controlled Trials as Topic/ or (Non randomi?ed adj3 trial?).tw. or (Nonrandomi?ed adj3 trial?).tw. or "Quasi Experimental".tw.	22359
27	(single arm or open label).tw.	52293
28	case report.tw. or letter/ or historical article/	1811466
29	(or/22-27) not 28	1822233
30	exp animal/ or (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).tw.	23986129
31	exp Human/ or Human Experiment.tw.	18761295
32	30 not (30 and 31)	5224846
33	(4 and 21 and 29) not 32	3409
34	limit 33 to english language	3181

Source: [123]

CENTRAL (OvidSP)

EBM Reviews – Cochrane Central Register of Controlled Trials September 2020 (Search date: 13 October 2020)

#	**Searches**	**Results**
1	exp Leukemia, Myeloid, Acute/	1554
2	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or granulocytic)).ti,ab,kw.	4618
3	(ANLL or AML).ti,ab,kw.	4295
4	or/1-3	6216
5	(venetoclax or venclexta or venclyxto or ABT-199 or ABT199 or ABT-0199 or GDC-0199 or RG7601).ti,ab,kw.	265
6	exp azacitidine/ or (azacitidine or 5-azacytidine or azacytidine or vidaza or U-18496).ti,ab,kw.	806
7	exp cytarabine/ or (cytarabine or Alexan or Arabine or ARA-cell or Aracytin or Aracytine or Cytarbel or Cytosar or Erpalfa or Starasid or Udicil or CHX-3311 or U 19920 or U-29920A HCl or WR-28453).ti,ab,kw.	2827
8	(decitabine or dacogen).ti,ab,kw.	438
9	(glasdegib or daurismo or PF-04449913).ti,ab,kw.	59
10	(gemtuzumab or mylotarg or CDP-771 or CMA-676 or WAY-CMA-676).ti,ab,kw.	200
11	(clofarabine or Clolar or Evoltra).ti,ab,kw.	145
12	exp granulocyte colony stimulating factor/ or (granulocyte colony stimulating factor or G-CSF or filgrastim or lenograstim or Granix or Neupogen or Zarxio or Grasin or Nivestim or Tevagrastim).ti,ab,kw.	4659
13	exp ACLARUBICIN/ or (aclarubicin or aclacinomycin or Aclacin or Aclacinomycine or Aclacinon or Aclaplastin or Jaclacin or MA144-A1).ti,ab,kw.	68
14	(CAG or (Cytarabine adj3 aclarubicin adj3 G-CSF)).ti,ab,kw.	584
15	(gilteritinib or XOSPATA or ASP2215 or ASP-2215).ti,ab,kw.	54

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16	(ivosidenib or Tibsovo or AG-120 or AG120).ti,ab,kw.	40
17	exp Palliative Care/ or (palliative therapy or palliative care or palliative treatment or palliation or supportive therapy or supportive care or BSC).ti,ab,kw.	10413
18	exp HYDROXYUREA/ or (hydroxycarbamide or hydroxyurea or Droxia or Hydrea or SQ 1089 or WR 83799).ti,ab,kw.	1269
19	exp MERCAPTOPURINE/ or (mercaptopurine or Purinethol or Purixan or Alti-Mercaptopurine or Flocofil or Ismipur or Leukerin or Mercaleukim or Mercaptina or Purinethiol or Puri-Nethol or Xaluprine or BW 57-323H or U-4748 or WR-2785).ti,ab,kw.	1852
20	exp ETOPOSIDE/ or (etoposide or Lastet or VP-16 or VP-16-213).ti,ab,kw.	4055
21	or/5-20	24827
22	4 and 21	2745
23	limit 22 to english language	1799

Source: [123]

CDSR (OvidSP)

EBM Reviews – Cochrane Database of Systematic Reviews 2005 to October 7, 2020 (Search date: 13 October 2020)

#	**Searches**	**Results**
1	Leukemia, Myeloid, Acute.kw.	7
2	Leukemia, Basophilic, Acute.kw.	0
3	Leukemia, Eosinophilic, Acute.kw.	0
4	Leukemia, Erythroblastic, Acute.kw.	0
5	Leukemia, Mast-Cell.kw.	0
6	Leukemia, Megakaryoblastic, Acute.kw.	0
7	Leukemia, Monocytic, Acute.kw.	0
8	Leukemia, Promyelocytic, Acute.kw.	1
9	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non?lymphoblastic or nonlymphocytic or non?lymphocytic or granulocytic)).ti,ab,kw.	18
10	(ANLL or AML).ti,ab,kw.	10
11	or/1-10	19

Source: [123]

DARE (OvidSP)

EBM Reviews – Database of Abstracts of Reviews of Effects 1st Quarter 2016 (Search date: 13 October 2020)

#	**Searches**	**Results**
1	Leukemia, Myeloid, Acute.kw.	29
2	Leukemia, Basophilic, Acute.kw.	0
3	Leukemia, Eosinophilic, Acute.kw.	0
4	Leukemia, Erythroblastic, Acute.kw.	0
5	Leukemia, Mast-Cell.kw.	0
6	Leukemia, Megakaryoblastic, Acute.kw.	0
7	Leukemia, Monocytic, Acute.kw.	0
8	Leukemia, Promyelocytic, Acute.kw.	7
9	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non?lymphoblastic or nonlymphocytic or non?lymphocytic or granulocytic)).tw.	43
10	(ANLL or AML).tw.	10
11	or/1-10	51

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Source: [123]

Northern Light (OvidSP)

Northern Light Life Sciences Conference Abstracts 2010 – 2020 Week 39 (Search date: 13 October 2020)

#	Searches	Results
1	(Acute adj2 leuk?emia$ adj2 (myeloid or myelogenous or myeloblastic or myelocytic or nonlymphoblastic or non-lymphoblastic or nonlymphocytic or non-lymphocytic or granulocytic)).ti,ab.	8752
2	(ANLL or AML).ti,ab.	13211
3	or/1-2	15000
4	(venetoclax or venclexta or venclyxto or ABT-199 or ABT199 or ABT-0199 or GDC-0199 or RG7601).ti,ab.	844
5	(azacitidine or 5-azacytidine or azacytidine or vidaza or U-18496).ti,ab.	1385
6	(cytarabine or Alexan or Arabine or ARA-cell or Aracytin or Aracytine or Cytarbel or Cytosar or Erpalfa or Starasid or Udicil or CHX-3311 or U 19920 or U-29920AHCl or WR-28453).ti,ab.	1240
7	(decitabine or dacogen).ti,ab.	611
8	(glasdegib or daurismo or PF-04449913).ti,ab.	57
9	(gemtuzumab or mylotarg or CDP-771 or CMA-676 or WAY-CMA-676).ti,ab.	154
10	(clofarabine or Clolar or Evoltra).ti,ab.	275
11	(granulocyte colony stimulating factor or G-CSF or filgrastim or lenograstim or Granix or Neupogen or Zarxio or Grasin or Nivestim or Tevagrastim).ti,ab.	2676
12	(aclarubicin or aclacinomycin or Aclacin or Aclacinomycine or Aclacinon or Aclaplastin or Jaclacin or MA144-A1).ti,ab.	21
13	(CAG or (Cytarabine adj3 aclarubicin adj3 G-CSF)).ti,ab.	1060
14	(gilteritinib or XOSPATA or ASP2215 or ASP-2215).ti,ab.	54
15	(ivosidenib or Tibsovo or AG-120 or AG120).ti,ab.	59
16	(palliative therapy or palliative care or palliative treatment or palliation or supportive therapy or supportive care or BSC).ti,ab.	9328
17	(hydroxycarbamide or hydroxyurea or Droxia or Hydrea or SQ 1089 or WR 83799).ti,ab.	857
18	(mercaptopurine or Purinethol or Purixan or Alti-Mercaptopurine or Flocofil or Ismipur or Leukerin or Mercaleukim or Mercaptina or Purinethiol or Puri-Nethol or Xaluprine or BW 57-323H or U-4748 or WR-2785).ti,ab.	224
19	(etoposide or Lastet or VP-16 or VP-16-213).ti,ab.	1350
20	or/4-19	19328
21	("American Society of Hematology" or "ASH").cf.	50853
22	("American Society of Clinical Oncology" or "ASCO").cf.	59353
23	("European Hematology Association" or "EHA").cf.	21167
24	("European Society for Medical Oncology" or "ESMO").cf.	15406
25	("British Society for Haematology" or "BSH").cf.	3360
26	or/21-25	150139
27	3 and 20 and 26	1946
28	limit 27 to yr="2017 -Current"	694

Source: [123]

ClinicalTrials.gov

The ClinicalTrials.gov was searched via web link (www.clinicaltrials.gov). The search was conducted by searching 'Acute Myeloid Leukemia' in disease and apply filters 'With Results' and 'Interventional'. A total of 474 records were retrieved on 13 October 2020 [123].

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NICE website
Acute myeloid leukaemia was searched via web link (https://www.nice.org.uk/search) on 13 October 2020. Five technology appraisal guidance (TA218, TA399, TA523, TA545, and TA552) relevant to the population of interest were retrieved [123].

SMC website
Acute myeloid leukaemia was searched via web link (https://www.scottishmedicines.org.uk/medicines-advice/) on 13 October 2020. Five published submissions (SMC2130, SMC2089, 1330/18, 589/09 full submission, and 589/09 resubmission) relevant to the population of interest were retrieved [123].

EHA 2020 Virtual Congress
As of 13 October 2020, the Ovid Northern Light database did not index abstracts from the EHA 2020 virtual congress. The 25th EHA Virtual Congress 2020 abstracts were accessed on 13 October 2020 via the EHA Learning Centre [123]
https://library.ehaweb.org/eha/#!*menu=6*browseby=3*sortby=2*ce_id=1766*featured=16775

Abstract titles were searched for key words: venetoclax, azacitidine, cytarabine, decitabine, glasdegib, gemtuzumab, clofarabine, granulocyte colony stimulating factor, aclarubicin, CAG, gilteritinib, ivosidenib, palliative therapy, hydroxyurea, mercaptopurine, or etoposide [123].

A total of 39 records judged relevant to the SLR were retrieved for screening [123].

ASCO 2020 Annual Meeting
As of 13 October 2020, the Ovid Northern Light database did not index abstracts from the ASCO 2020 Annual Meeting. Manual search was conducted on 13 October 2020 via URL [123].

https://meetinglibrary.asco.org/results;page=0?filters=JTVCJTdCJTIyZmllbGQlMjIlM0ElMjJNZWRpYVR5cGVzJTIyJTJDJTIydmFsdWUlMjIlM0ElMjBYnN0cmFjdHMlMjIlMkMlMjJxdWVyeVZhbHVlJTIyJTNBJTIyQWJzdHJhY3RzJTIyJTJDJTIyY2hpbGRyZW4lMjIlM0ElNUIlNUQlN0QlNUQ%3D&meetingView=2020%20ASCO%20Virtual%20Scientific%20Program

Abstract titles were searched for by restricting the topic to "cancers – hematologic malignancies – leukemia". A total of 107 records judged relevant to the SLR were retrieved for screening" [123].

8.1.2 Selection of relevant studies

Study selection was undertaken in three steps, including two levels of article screening and data extraction (Figure 8.1). The detailed inclusion/exclusion criteria provided in Table 7.2 were used as a guideline for the study selection to ensure that all decisions regarding the inclusion and exclusion of studies were consistent [123].

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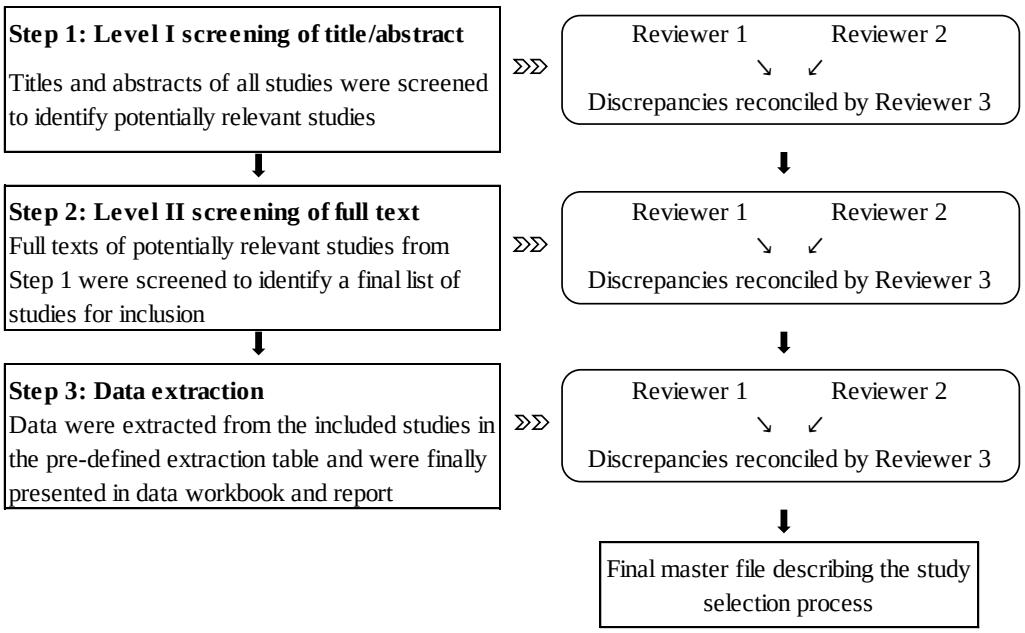
Figure 8.1 Study selection and data extraction process



Source: [123]

Level I screening based on title and abstract

Citations from multiple database searches were imported from Ovid to a literature review management software DistillerSR. Title and abstracts were screened by two independent reviewers after removing duplicates. Any discrepancies in the inclusion/exclusion decisions between the reviewers were reconciled by a third reviewer. Citations that did not match the eligibility criteria were excluded at Level I. During instances when decisions could be made to include or exclude citations based on title and abstract, full-text copies were obtained and assessed at Level II [123].

Level II screening based on full text publication

Full text publications for citations included in the Level I screening were reviewed by two independent reviewers against the inclusion/exclusion criteria. Any discrepancies in the inclusion/exclusion decisions between reviewers were reconciled by a third reviewer. The studies retained after this stage were included for data extraction [123].

Records identified from the ClinicalTrials.gov website were also reviewed against the inclusion/exclusion criteria. Clinical trials with study results that fulfilled the inclusion criteria but were not published elsewhere were included. SLR, meta-analysis and HTA reports were reviewed to identify additional studies [123].

Finally, a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram was produced to describe the study selection process, reasons for exclusion per level of screening, and the list of articles selected for data extraction [123].

Data extraction

A data extraction template was developed to extract clinical study details, baseline characteristics, efficacy, and safety data. A separate quality check was conducted following the data extraction. For full publications included in the review, journal websites were cross-checked for the availability of supplementary materials.

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Mean, median, standard deviation, standard error, and range were extracted for continuous variables where possible. For categorical variables, frequency and percentage were extracted. For survival outcomes, median, HR, CI, p value, and availability of Kaplan-Meier curves were extracted. The following data were collected as part of the extraction [123].

Publication details

- Author, year, publication type, trial registry number, trial name

Study details

- Study phase, randomization design, study population, inclusion/exclusion criteria, subgroups

Treatment details

- Treatment names, dosing schedule, treatment duration, number of cycles, concomitant medication, treatment information after disease progression

Baseline characteristics

- Age, sex, weight, body mass index, body surface area
- Disease duration, ECOG performance status, AML classification, primary/secondary AML, cytogenetic risk status, white blood cell counts, neutrophil count, platelets, bone marrow blasts, prior MDS treatment details, mutation specific characteristics, prior hypomethylating agent treatments, prior hematopoietic stem cell transplantation information

Efficacy outcomes (main population and subgroup)

- OS, PFS, EFS, RFS
- CR, CRi, composite CR, CRh, objective response, partial remission
- Stable disease, progressive disease, resistant disease, MRD
- Time to first response, time to first relapse, time to progression, time to CR, time to CRi, time to treatment failure, duration of remission

Safety outcomes

- Any AE, grade 3 or 4 AEs
  Discontinuation due to death, discontinuation due to progressive disease, discontinuation due to any AE, discontinuation due to withdrawn consent, discontinuation due to alternative therapy

Critical appraisal of evidence

For included studies, critical appraisal of evidence was conducted following the CRD risk of bias assessment checklist for RCTs [143]. The following questions were used to critically appraise the quality of each trial [123].

- Was the method used to generate random allocations adequate?
- Was the concealment of treatment allocation adequate?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Were there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

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8.1.3 Records retrieved

The literature search was first conducted in January 2019 and updated in October 2020 (Table 8.1). A total of 10,197 records were identified from the October 2020 search. After removing 2,878 duplicates, a total of 7,319 records were assessed for eligibility [123].

Table 8.1 Number of records retrieved by the searches

Data source	Number of records identified in October 2020 update search
MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (Ovid SP)	3,181
Embase (Ovid SP)	3,823
Cochrane Central Register of Controlled Trials (CENTRAL) (Ovid SP)	1,799
Cochrane Database of Systematic Reviews (CDSR) (Ovid SP)	19
Database of Abstracts of Reviews of Effects (DARE) (Ovid SP)	51
Northern Light Life Sciences Conference Abstracts (Ovid SP) European Hematology Association (EHA) American Society of Clinical Oncology (ASCO) British Society for Haematology (BSH) American Society of Hematology (ASH) European Society for Medical Oncology (ESMO)	694
ClinicalTrial.gov	474
National Institute for Health and Care Excellence (NICE) website	5
Scottish Medicines Consortium (SMC) website	5
European Hematology Association (EHA) 2020 Virtual Congress: https://ehaweb.org/	39
American Society of Clinical Oncology (ASCO) 2020 Annual Meeting: https://www.asco.org/	107
Total number of records retrieved	**10,197**
Duplicates	**2,878**
Total number of unique records assessed for eligibility	**7,319**

Source: [123]

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8.1.4 Full-text articles excluded

Table 8.2 Full-text articles excluded (N=142)

First author's last name	Publication year	Reason for exclusion	Title
Amadori	2010	Outcomes	Randomised trial of two schedules of low-dose gemtuzumab ozogamicin as induction monotherapy for newly diagnosed acute myeloid leukaemia in older patients not considered candidates for intensive chemotherapy. A phase II study of the EORTC and GIMEMA leukaemia groups (AML-19)
Dohner	2018	Outcomes	Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care
Savona	2018	Population	Extended dosing with CC-486 (oral azacitidine) in patients with myeloid malignancies
Chen	2018	Population	Thalidomide in Combination with Chemotherapy in Treating Elderly Patients with Acute Myeloid Leukemia
Seymour	2017	Outcomes	Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens
Craddock	2017	Population	Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature
Arthur	2015	Outcomes	Post hoc analysis of the relationship between baseline white blood cell count and survival outcome in a randomised phase iii trial of decitabine in older patients with newly diagnosed acute myeloid leukemia
Grishina	2015	Outcomes	DECIDER: Prospective randomised multicenter phase II trial of low-dose decitabine (DAC) administered alone or in combination with the histone deacetylase inhibitor valproic acid (VPA) and all-trans retinoic acid (ATRA) in patients >60 years with acute myeloid leukemia who are ineligible for induction chemotherapy
Savona	2018	Intervention/Comparator	Phase ib study of glasdegib, a hedgehog pathway inhibitor, in combination with standard chemotherapy in patients with AML or high-risk MDS
Montalban-Bravo	2017	Outcomes	A clinical trial for patients with acute myeloid leukemia or myelodysplastic syndromes not eligible for standard clinical trials
Burnett	2017	Population	A comparison of clofarabine with ara-C, each in combination with daunorubicin as induction treatment in older patients with acute myeloid leukaemia
Burnett	2015	Outcomes	A randomised comparison of the novel nucleoside analogue sapacitabine with low-dose cytarabine in older patients with acute myeloid leukaemia
Pleyer	2017	Study design	Azacitidine for front-line therapy of patients with AML: Reproducible efficacy established by direct comparison of international phase 3 trial data with registry data from the austrian azacitidine registry of the AGMT study group
Lowenberg	2017	Population	Therapeutic value of clofarabine in younger and middle-aged (18-65 years) adults with newly diagnosed AML
Takahashi	2016	Study design	Clofarabine Plus Low-Dose Cytarabine Is as Effective as and Less Toxic Than Intensive Chemotherapy in Elderly AML Patients
El-Jawahri	2016	Outcomes	Phase II Trial of Reduced-Intensity Busulfan/Clofarabine Conditioning with Allogeneic Hematopoietic Stem Cell Transplantation for Patients with Acute Myeloid Leukemia, Myelodysplastic Syndromes, and Acute Lymphoid Leukemia
Prebet	2016	Outcomes	Azacitidine with or without Entinostat for the treatment of therapy-related myeloid neoplasm: Further results of the E1905 North American Leukemia Intergroup study

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First author's last name	Publication year	Reason for exclusion	Title
Kadia	2015	Intervention/Comparator	Final results of a phase 2 trial of clofarabine and low-dose cytarabine alternating with decitabine in older patients with newly diagnosed acute myeloid leukemia
Jacob	2015	Study design	Decitabine Compared with Low-Dose Cytarabine for the Treatment of Older Patients with Newly Diagnosed Acute Myeloid Leukemia: A Pilot Study of Safety, Efficacy, and Cost-Effectiveness
He	2015	Outcomes	Decitabine reduces transfusion dependence in older patients with acute myeloid leukemia: Results from a post hoc analysis of a randomised phase III study
Tomeczkowski	2015	Study design	Converging or Crossing Curves: Untie the Gordian Knot or Cut it? Appropriate Statistics for Non-Proportional Hazards in Decitabine DACO-016 Study (AML)
Thepot	2014	Study design	Azacitidine in untreated acute myeloid leukemia: A report on 149 patients
Martinez-Cuadron	2014	Sample size < 20 per arm	Phase II trial to assess the safety and efficacy of clofarabine in combination with low-dose cytarabine in elderly patients with acute myeloid leukemia
Willemze	2014	Population	Clofarabine in combination with a standard remission induction regimen (cytosine arabinoside and idarubicin) in patients with previously untreated intermediate and bad-risk acute myelogenous leukemia (AML) or high-risk myelodysplastic syndrome (HR-MDS): Phase I results of an ongoing phase I/II study of the leukemia groups of EORTC and GIMEMA (EORTC GIMEMA 06061/AML-14A trial)
Thomas	2014	Outcomes	A post hoc sensitivity analysis of survival probabilities in a multinational phase III trial of decitabine in older patients with newly diagnosed acute myeloid leukemia
Sadashiv	2014	Sample size < 20 per arm	Efficacy and tolerability of treatment with azacitidine for 5 days in elderly patients with acute myeloid leukemia
Vigil	2013	Intervention/Comparator	Phase II trial of clofarabine and daunorubicin as induction therapy for acute myeloid leukemia patients greater than or equal to 60 years of age
Suzuki	2013	Sample size < 20 per arm	Phase I study of clofarabine in adult patients with acute myeloid leukemia in Japan
Cross	2013	Study design	Pretreatment long interspersed element (LINE)-1 methylation levels, not early hypomethylation under treatment, predict hematological response to azacitidine in elderly patients with acute myeloid leukemia
Faderl	2012	Intervention/Comparator	Clofarabine plus low-dose cytarabine followed by clofarabine plus low-dose cytarabine alternating with decitabine in acute myeloid leukemia frontline therapy for older patients
Lubbert	2012	Intervention/Comparator	A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy
Magenau	2011	Population	Clofarabine and busulfan conditioning facilitates engraftment and provides significant antitumor activity in nonremission hematologic malignancies
Garcia-Manero	2011	Sample size < 20 per arm	Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia
Lubbert	2011	Population	Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomised phase III study of the european organisation for research and treatment of cancer leukemia group and the German MDS study group
Silverman	2011	Population	Continued azacitidine therapy beyond time of first response improves quality of response in patients with higher-risk myelodysplastic syndromes

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Szotkowski	2010	Study design	Prognostic factors and treatment outcome in 1,516 adult patients with de novo and secondary acute myeloid leukemia in 1999-2009 in 5 hematology intensive care centers in the Czech Republic
Fenaux	2010	Population	Prolonged survival with improved tolerability in higher-risk myelodysplastic syndromes: Azacitidine compared with low dose ara-C: Research paper
Blum	2007	Population	Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia
Silverman	2006	Study design	Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B
Faderl	2006	Intervention/Comparator	Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older
Nabhan	2005	Sample size < 20 per arm	Phase II pilot trial of gemtuzumab ozogamicin (GO) as first line therapy in acute myeloid leukemia patients age 65 or older
Estey	2002	Population	Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: Comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside
Kenealy	2018	Population	Azacitidine with or without lenalidomide in higher risk myelodysplastic syndrome & low blast acute myeloid leukemia
Heiblig	2016	Study design	Treatment with Low-Dose Cytarabine in Elderly Patients (Age 70 Years or Older) with Acute Myeloid Leukemia: A Single Institution Experience
Fenaux	2008	Full publication included	Azacitidine prolongs overall survival and reduces infections and hospitalizations in patients with WHO-defined acute myeloid leukaemia compared with conventional care regimens: an update
Ramos	2015	Study design	Azacitidine frontline therapy for unfit acute myeloid leukemia patients: clinical use and outcome prediction
Maurillo	2012	Study design	Azacitidine for the treatment of patients with acute myeloid leukemia: report of 82 patients enrolled in an Italian Compassionate Program
Burnett	2007	Intervention/Comparator	A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment
Siddiqui	1994	Intervention/Comparator	Comparison of survival. Chemotherapeutically treated and untreated older patient with acute myeloid leukemia
Ruiz-Arguelles	1992	Population	Long-term treatment results for acute megakaryoblastic leukaemia patients: a multicentre study
Tilly	1990	Population	Low-dose cytarabine versus intensive chemotherapy in the treatment of acute nonlymphocytic leukemia in the elderly
Hellstrom	1990	Population	Treatment of myelodysplastic syndromes with retinoic acid and 1 alpha-hydroxy-vitamin D3 in combination with low-dose ara-C is not superior to ara-C alone. Results from a randomised study. The Scandinavian Myelodysplasia Group (SMG)
Perri	1985	Population	Low-dose ARA-C fails to enhance differentiation of leukaemic cells
Short	2017	Full publication included	A randomised phase II trial of 5-day versus 10-day schedules of decitabine for older patients with previously untreated acute myeloid leukemia
Schuh	2015	Outcomes	Overall survival (OS) without complete remission (CR) in older patients with acute myeloid leukemia (AML): azacitidine (AZA) vs conventional care regimens (CCR) in the AZAAML-001 study
Potluri	2017	Study design	Phase 3, randomised, double-blind, placebo-controlled study of venetoclax combined with azacitidine versus azacitidine in treatment-naive patients with acute myeloid leukemia

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Borlenghi	2017	Study design	Efficacy and safety of decitabine in elderly AML patients: a real life multicenter experience of the network rete ematologica lombarda
Pratz	2017	Full publication included	Safety and efficacy of venetoclax (VEN) in combination with decitabine or azacitidine in treatment-naive, elderly patients (≥65 years) with acute myeloid leukemia (AML)
Schuh	2017	Outcomes	Stable disease with hematologic improvement is clinically meaningful for older patients with acute myeloid leukemia treated with azacitidine
Jaekel	2016	Outcomes	Response-adapted sequential azacitidine and induction chemotherapy in patients >60 years old with newly diagnosed AML eligible for chemotherapy (RAS-AZIC): interim analysis of the DRKS00004519 study
Pollyea	2016	Outcomes	Results of a phase 1B study of venetoclax plus decitabine or azacitidine in untreated acute myeloid leukemia patients >65 years ineligible for standard induction therapy
Seymour	2016	Outcomes	Hospitalization for treatment-emergent adverse events (TEAE) in older (>65 years) patients with acute myeloid leukemia (AML) with >30% marrow blasts in the phase 3 AZA-AML-001 study
Lin	2016	Sample size < 20 per arm	Phase 1B/2 study of venetoclax with low-dose cytarabine in treatment-naive patients aged >65 years with acute myelogenous leukemia
Seymour	2016	Outcomes	Azacitidine (AZA) vs conventional care regimens (CCR) in patients with acute myeloid leukemia (AML) with myelodysplasia-related changes (MRC) in AZA-AML-001 per central review
Feng	2016	Intervention/Comparator	Efficacy and safety of etoposide in combination with G-CSF, low-dose cytarabine and aclarubicin in newly diagnosed elderly patients with acute myeloid leukemia
Borate	2016	Intervention/Comparator	Phase 1B study of glasdegib (pf-04449913) in combination with azacitidine in patients with higher risk myelodysplastic syndrome, oligoblastic acute myeloid leukemia, or chronic myelomonocytic leukemia
Montalban-Bravo	2016	Outcomes	A phase II clinical trial of azacitidine and vorinostat for patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) with poor performance status, comorbidities, other active malignancies or organ dysfunction not eligible for conventional clinical trials
Khan	2016	Full publication included	Randomised phase II trial of two schedules of decitabine as frontline therapy in elderly patients with acute myeloid leukemia ineligible for standard cytotoxic induction regimens
Dennis	2016	Outcomes	A randomised assessment of ganetespib combined with low dose Ara-C versus low dose ara-C in older patients with acute myeloid leukaemia: results of the LI-1 trial
Dohner	2016	Outcomes	Azacitidine (AZA) prolongs overall survival in older patients with acute myeloid leukemia (AML) with poor prognostic karyotypes compared with conventional care regimens (CCR)
Craddock	2016	Outcomes	Vorinostat does not improve outcome in patients with acute myeloid leukemia and high risk myelodysplasia treated with azacitidine: results of the UK trials acceleration programme ravva trial
Cortes	2016	Full publication included	A phase 2 randomised study of low dose ara-C with or without glasdegib (PF-04449913) in untreated patients with acute myeloid leukemia or high-risk myelodysplastic syndrome
Garcia-Manero	2017	Outcomes	Panobinostat plus azacitidine in adult patients with MDS, CMML, or AML: Results of a phase 2B study
Dohner	2015	Outcomes	Overall survival (OS) and clinical outcomes in older patients with acute myeloid leukemia (AML) treated with azacitidine (AZA) or intensive chemotherapy (IC) in the AZAAML-001 study
Seymour	2015	Outcomes	Azacitidine versus Conventional Care Regimens (CCR) in older patients with newly diagnosed AML (>30% marrow blasts) with myelodysplasia-related changes: Subgroup analysis of the AZA-AML-001 study

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First author's last name	Publication year	Reason for exclusion	Title
Dohner	2015	Outcomes	Overall survival in older patients with newly diagnosed AML with >30% bone marrow blasts and poor-risk cytogenetics treated with azacitidine: Subanalysis of the AZA-AML-001 study
Kenealy	2015	Outcomes	The addition of lenalidomide to azacitidine achieves higher responses but no improvement in twelve month clinical benefit or PFS; main analysis australian ALLG MDS4 trial
Kenealy	2013	Outcomes	The combination of azacitidine and lenalidomide is deliverable without unexpected toxicity; Interim safety results of the ALLG MDS4 randomised trial
Zeidan	2013	Study design	Application of the French Prognostic Score to assess overall survival in a US-based cohort of patients treated with azacitidine
Dombret	2014	Full publication included	Results of a phase 3, multicenter, randomised, open-label study of azacitidine (AZA) vs conventional care regimens (CCR) in older patients with newly diagnosed acute myeloid leukemia (AML)
Kenealy	2014	Population	The addition of lenalidomide to azacitidine in higher risk MDS is deliverable with higher response rates; first analysis of the ALLG MDS4 randomised phase ii study
Mayer	2014	Full publication included	Multivariate and subgroup analyses of a multinational phase III trial of decitabine in older patients with newly diagnosed acute myeloid leukemia
Thomas	2014	Full publication included	A post hoc landmark analysis of survival probabilities in a multinational phase III trial of decitabine in older patients with newly diagnosed acute myeloid leukemia
Burnett	2013	Full publication included	The addition of gemtuzumab ozogamicin to low dose ARA-C improves remission rates but not survival: Results of the UK LRF AML14 and NCRI AML16 "pick a winner" comparison
Thomas	2011	Full publication included	Results from a randomised phase III trial of decitabine versus supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed AML
Nicholas	2018	Full publication included	Five-Day Versus Ten-Day Schedules of Decitabine In Older Patients With Newly Diagnosed Acute Myeloid Leukemia: Results of a Randomised Phase II Study
Daniel	2018	Full publication included	Venetoclax In Combination With Hypomethylating Agents Induces Rapid, Deep, And Durable Responses In Patients With AML Ineligible For Intensive Therapy
Vidhya	2018	Population	Azacitidine Improves Outcome In Patients With MDS And AML With High Risk Cytogenetics - a Single Center Experience
Jordi	2018	Sample size < 20 per arm	Multicenter, Open-Label, 3-Arm Study of Gilteritinib, Gilteritinib Plus Azacitidine, Or Azacitidine Alone In Newly Diagnosed FLT3 Mutated (FLT3mut+) Acute Myeloid Leukemia (AML) Patients Ineligible For Intensive Induction Chemotherapy: Findings From the Safety Cohort
X. Thomas	2018	Outcomes	A Phase 2b of Eryaspase in Combination with Low-Dose Cytarabine as First-Line Therapy in Elderly Patients with Acute Myeloid Leukemia (Enforce - Nct01810705)
Courtney Denton	2018	Full publication included	Durable Response With Venetoclax In Combination With Decitabine Or Azacitadine In Elderly Patients With Acute Myeloid Leukemia (AML)
Courtney	2017	Sample size < 20 per arm	Mutant Isocitrate Dehydrogenase (MIDH) Inhibitors, Enasidenib Or Ivosidenib, In Combination With Azacitidine (AZA): Preliminary Results of a Phase 1b/2 Study In Patients With Newly Diagnosed Acute Myeloid Leukemia (AML)
Courtney	2017	Full publication included	Updated Safety And Efficacy of Venetoclax With Decitabine Or Azacitidine In Treatment-Naive, Elderly Patients With Acute Myeloid Leukemia

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First author's last name	Publication year	Reason for exclusion	Title
Daniel	2017	Study design	Venetoclax (Ven) With Azacitidine (Aza) For Untreated Elderly Acute Myeloid Leukemia (AML) Patients (Pts) Unfit For Induction Chemotherapy: Single Center Clinical Experience And Mechanistic Insights From Correlative Studies
Krakow	2020	Population	Phase I/II multisite trial of optimally dosed clofarabine and low-dose TBI for hematopoietic cell transplantation in acute myeloid leukemia
Cortes	2019	Outcomes	Glasdegib plus intensive/nonintensive chemotherapy in untreated acute myeloid leukemia: BRIGHT AML 1019 Phase III trials
Tsirogianni	2019	Outcomes	Natural killer cell cytotoxicity is a predictor of outcome for patients with high risk myelodysplastic syndrome and oligoblastic acute myeloid leukemia treated with azacytidine
Tremblay	2019	Study design	Overall survival of glasdegib in combination with low-dose cytarabine, azacitidine, and decitabine among adult patients with previously untreated AML: Comparative effectiveness using simulated treatment comparisons
Anonymous	2019	Study design	Gilteritinib Likely New Standard Care for AML
Othus	2019	Intervention/Comparator	Relative survival following response to 7 + 3 versus azacytidine is similar in acute myeloid leukemia and high-risk myelodysplastic syndromes: an analysis of four SWOG studies
Agarwa	2019	Outcomes	Optimizing venetoclax dose in combination with low intensive therapies in elderly patients with newly diagnosed acute myeloid leukemia: An exposure-response analysis
Richard-Carpentie	2019	Study design	Venetoclax for the treatment of newly diagnosed acute myeloid leukemia in patients who are ineligible for intensive chemotherapy
Ho	2019	Outcomes	Prior Gemtuzumab Ozogamicin Exposure in Adults with Acute Myeloid Leukemia Does Not Increase Hepatic Veno-Occlusive Disease Risk after Allogeneic Hematopoietic Cell Transplantation: a Center for International Blood and Marrow Transplant Research Analysis
Wei	2019	Population	The QUAZAR AML-001 maintenance trial: results of a phase III international, randomised, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission
Fernandez	2019	Outcomes	AGILE: a phase 3, multicenter, double-blind, randomised, placebo-controlled study of ivosidenib in combination with azacitidine in adult patients with previously untreated acute myeloid leukemia with an IDH1 mutation
Luger	2019	Intervention/Comparator	Phase II randomised trial of gilteritinib vs midostaurin in newly diagnosed FLT3 mutated acute myeloid leukemia (AML)
Van Beekhuizen	2019	Study design	Overall survival of glasdegib in combination with low-dose cytarabine and azacitidine by bone marrow blasts among adult patients with previously untreated acute myeloid leukemia: comparative effectiveness using indirect treatment comparisons
Hay	2019	Study design	Accrual barriers and detection of early toxicity signal in older less-fit patients treated with azacitidine and nivolumab for newly diagnosed acute myeloid leukemia (AML) or high-risk myelodysplastic syndrome (MDS) in the SWOG 1612 platform randomised phase II/III clinical trial
Roboz	2019	Outcomes	Results from a global randomised phase 3 study of guadecitabine (G) Vs treatment choice (TC) in 815 patients with treatment naA[spacing macron]ve (TN) AML unfit for intensive chemotherapy (IC) ASTRAL-1 Study: analysis by number of cycles
Papayannidis	2019	Duplicates	Low-dose cytarabine with or without glasdegib in newly diagnosed patients with acute myeloid leukemia: long-term analysis of a phase 2 randomised trial

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First author's last name	Publication year	Reason for exclusion	Title
Merchant	2019	Outcomes	Biomarkers correlating with overall survival (OS) and response to glasdegib and intensive or nonintensive chemotherapy in patients with acute myeloid leukemia (AML)
Cortes	2018	Population	Glasdegib improved overall survival in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who achieved complete remission (CR) and those who did not achieve CR
Garcia-Manero	2018	Outcomes	A phase 3, randomised study of pracinostat (PRAN) in combination with azacitidine (AZA) versus placebo in patients ≥18 years with newly diagnosed acute myeloid leukemia (AML) unfit for standard induction chemotherapy (IC)
Stein	2018	Outcomes	AGILE: a phase 3, multicenter, randomised, placebo-controlled study of ivosidenib in combination with azacitidine in adult patients with previously untreated acute myeloid leukemia with an IDH1 mutation
Lubbert	2017	Duplicates	Results of the decider trial (AMLSG 14-09) comparing decitabine (DAC) with or without valproic acid (VPA) and with or without ATRA in newly diagnosed elderly non-fit AML patients
Chyla	2019	Study design	Response To Venetoclax In Combination With Low Intensity Therapy (LDAC Or HMA) In Untreated Patients With Acute Myeloid Leukemia Patients With IDH, FLT3 And Other Mutations And Correlations With BCL2 Family Expression
Platzbecke	2019	Population	Azacitidine For Pre-Emptive Treatment of Measurable-Residual Disease In MDS/AML Patients At High Risk of Hematological Relapse: Results of the Second Cohort of the RELAZA2 Trial
Luger	2019	Duplicates	Phase II Randomised Trial of Gilteritinib Vs Midostaurin In Newly Diagnosed FLT3 Mutated Acute Myeloid Leukemia (AML)
Amany	2019	Study design	Hypomethylating Agent Maintenance Therapy After Allogeneic Stem Cell Transplant Improves Transplant Outcome In High Risk Acute Myelogenous Leukemia
Thota	2019	Intervention/Comparator	Outcomes of AML Patients Treated With Gemtuzumab-Ozogamicin Based Therapies: A Cue To Optimal Chemotherapy Backbone
Tiong	2019	Sample size < 20 per arm	Rapid Elimination of NPM1 Mutant Measurable Residual Disease (MRD) Using Low Intensity Venetoclax-Based Combinations In Acute Myeloid Leukemia (AML)
DiNardo	2019	Duplicates	Enasidenib Plus Azacitidine Significantly Improves Complete Remission And Overall Response Compared With Azacitidine Alone In Patients With Newly Diagnosed Acute Myeloid Leukemia (AML) With Isocitrate Dehydrogenase 2 (IDH2) Mutations: Interim Phase II Results From an Ongoing, Randomised Study
Fernandez	2019	Duplicates	AGILE: A Phase 3, Multicenter, Double-Blind, Randomised, Placebo-Controlled Study of Ivosidenib In Combination With Azacitidine In Adult Patients With Previously Untreated Acute Myeloid Leukemia With an IDH1 Mutation
Zeidan	2019	Duplicates	Efficacy And Safety of Azacitidine (AZA) In Combination With the Anti-PD-L1 Durvalumab (Durva) For the Front-Line Treatment of Older Patients (Pts) With Acute Myeloid Leukemia (AML) Who Are Unfit For Intensive Chemotherapy (IC) And Pts With Higher-Risk Myelodysplastic Syndromes (HR-MDS): Results From a Large, International, Randomised Phase 2 Study
Pratz	2019	Intervention/Comparator	Outcomes After Stem Cell Transplant In Older Patients With Acute Myeloid Leukemia Treated With Venetoclax-Based Therapies
Kadia	2019	Intervention/Comparator	Venetoclax Combined With Cladribine + Low Dose AraC (LDAC) Alternating With 5-Azacytidine Produces High Rates of Minimal Residual Disease (MRD) Negative Complete Remissions (CR) In Older Patients With Newly Diagnosed Acute Myeloid Leukemia (AML)

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First author's last name	Publication year	Reason for exclusion	Title
Kwon	2019	Duplicates	Quality-Adjusted Survival For Low-Dose Cytarabine (LDAC) Versus Glasdegib+LDAC Among Newly Diagnosed Acute Myeloid Leukemia Patients Who Are Not Candidates For Intensive Chemotherapy: A Q-TWiST Analysis
Asghari	2019	Study design	Hypomethylating Agent And Venetoclax Combination Yields Comparable Outcomes To CPX-351 In Newly Diagnosed Acute Myeloid Leukemia
Zeidan	2019	Duplicates	Clinical Benefit of Glasdegib In Combination With Azacitidine Or Low-Dose Cytarabine In Patients With Acute Myeloid Leukemia
DiNardo	2019	Duplicates	Cytogenetic And Molecular Drivers of Outcome With Venetoclax-Based Combination Therapies In Treatment-NaiVe Elderly Patients With Acute Myeloid Leukaemia
Shoukier	2019	Study design	Activity of Venetoclax-Based Therapy In TP53-Mutated Acute Myeloid Leukemia
Rasmussen	2018	Population	A Randomised Phase Ii Study of Standard Dose Azacitidine Alone or in Combination with Lenalidomide in High-Risk Mds with a Karyotype Including Del(5q)
Imbergamo	2018	Study design	Azacitidine or Decitabine Frontline Therapy for Acute Myeloid Leukemia in Elderly Patients?
Boss	2020	Outcomes	Epigenetic and immunomodulatory effects of azacitidine (AZA) in combination with the anti-PD-L1 durvalumab (DURVA) in AML and MDS: results from a large, international, randomised phase 2 study
Lin	2020	Outcomes	An evaluation of overall survival in patients with newly diagnosed acute myeloid leukemia and the relationship with glasdegib treatment and exposure
Solem	2020	Outcomes	A quality-adjusted survival time without symptoms or toxicities analysis of glasdegib plus low-dose cytarabine versus low-dose cytarabine as initial therapy for acute myeloid leukemia in patients who are not considered candidates for intensive chemotherapy
Cortes	2020	Outcomes	Survival outcomes and clinical benefit in patients with acute myeloid leukemia treated with glasdegib and low-dose cytarabine according to response to therapy
Lowenberg	2020	Study design	The long road: improving outcome in elderly unfit AML?
Huls	2020	Outcomes	Ibrutinib added to 10-day decitabine for older patients with AML and higher risk MDS
Wang	2020	Outcomes	Effect of Early Blood Counts On Overall Survival (OS) Following Glasdegib + LDAC In Newly Diagnosed AML: BRIGHT AML 1003 Post Hoc Analysis
Beekhuizen	2020	Study design	The Comparative Effectiveness of Glasdegib In Combination With Low-Dose Cytarabine Versus Azacitidine By Bone Marrow Blasts Counts Among Patients With Newly-Diagnosed Acute Myeloid Leukemia Who Are Ineligible For Intensive Chemotherapy
Jonas	2020	Study design	Timing of Response To Venetoclax Combination Treatment In Older Patients With Acute Myeloid Leukemia

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Table 8.3 Additional full-text articles excluded based on additional criteria for EUnetHTA (N=66)

First author's last name	Publication year	Reason for exclusion	Title
Roboz	2018	Intervention/Comparator	Randomised trial of 10 days of decitabine 6 bortezomib in untreated older patients with AML: CALGB 11002 (Alliance)
Medeiros	2018	Intervention/Comparator	Randomised study of continuous high-dose Lenalidomide, sequential Azacitidine and Lenalidomide, or azacitidine in persons 65 years and over with newly-diagnosed acute myeloid leukemia
Amadori	2005	Study design	Gemtuzumab ozogamicin (Mylotarg) as single-agent treatment for frail patients 61 years of age and older with acute myeloid leukemia: Final results of AML-15B, a phase 2 study of the European Organisation for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell'Adulto Leukemia Groups
Issa	2015	Intervention/Comparator	Results of phase 2 randomised study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia
Dennis	2015	Intervention/Comparator	Vosaroxin and vosaroxin plus low-dose Ara-C (LDAC) vs low-dose Ara-C alone in older patients with acute myeloid leukemia
Dohner	2014	Intervention/Comparator	Randomised, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy
Prebet	2014	Intervention/Comparator	Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: Results of the US Leukemia intergroup trial E1905
Passweg	2014	Study design	Azacytidine for acute myeloid leukemia in elderly or frail patients: A phase II trial (SAKK 30/07)
Burnett	2013	Intervention/Comparator	The addition of gemtuzumab ozogamicin to low-dose Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: Results from the LRF AML14 and NCRI AML16 pick-a-winner comparison
Sekeres	2013	Intervention/Comparator	Randomised, phase IIb study of low-dose cytarabine and lintuzumab versus low-dose cytarabine and placebo in older adults with untreated acute myeloid leukemia
Kantarjian	2013	Intervention/Comparator	Stage i of a phase 2 study assessing the efficacy, safety, and tolerability of barasertib (AZD1152) versus low-dose cytosine arabinoside in elderly patients with acute myeloid leukemia
Al-Ali	2012	Study design	Azacitidine in patients with acute myeloid leukemia medically unfit for or resistant to chemotherapy: A multicenter phase I/II study
Claxton	2012	Study design	Outpatient consolidation treatment with clofarabine in a phase 2 study of older adult patients with previously untreated acute myelogenous leukemia
Burnett	2011	Intervention/Comparator	The addition of arsenic trioxide to low-dose Ara-C in older patients with AML does not improve outcome
Cashen	2010	Study design	Multicenter, phase II study of decitabine for the first-line treatment of older patients with Acute Myeloid Leukemia
Kantarjian	2010	Study design	Phase II study of clofarabine monotherapy in previously untreated older adults with acute myeloid leukemia and unfavorable prognostic factors
Burnett	2010	Study design	European development of clofarabine as treatment for older patients with acute myeloid leukemia considered unsuitable for intensive chemotherapy
Harousseau	2009	Intervention/Comparator	A randomised phase 3 study of tipifarnib compared with best supportive care, including hydroxyurea, in the treatment of newly diagnosed acute myeloid leukemia in patients 70 years or older

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First author's last name	Publication year	Reason for exclusion	Title
Blum	2010	Study design	Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine
Suzushima	2010	Study design	Low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor for elderly patients with previously untreated acute myeloid leukemia
Faderl	2008	Intervention/Comparator	A randomised study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome
Qian	2007	Study design	Effect of low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor priming (CAG regimen) on the outcome of elderly patients with acute myeloid leukemia
Powell	1989	Study design	Low-dose ara-C therapy for acute myelogenous leukemia in elderly patients
Kantarjian	2017	Intervention/Comparator	Results of a phase 3 study of elderly patients with newly diagnosed AML treated with sapacitabine and decitabine administered in alternating cycles
Wei	2017	Study design	Updated safety and efficacy results of phase 1/2 study of venetoclax plus low-dose cytarabine in treatment-naive acute myeloid leukemia patients aged ≥65 years and unfit for standard induction therapy
Dohner	2016	Intervention/Comparator	Phase III randomised trial of volasertib plus low-dose cytarabine (LDAC) versus placebo plus LDAC in patients aged >65 years with previously untreated AML, ineligible for intensive therapy
DiNardo	2019	Intervention/Comparator	Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia
Montesinos	2016	Intervention/Comparator	Preliminary results of the flugaza trial: a phase III randomised, open label study comparing azacytidine versus fludarabine and cytarabine (FLUGA Scheme) in elderly patients with newly diagnosed acute myeloid leukemia
Lubbert	2016	Study design	Results of the randomised phase II study decider (AMLSG 14-09) comparing decitabine (DAC) with or without valproic acid (VPA) and with or without all-trans retinoic acid (ATRA) add-on in newly diagnosed elderly non-fit AML patients
Wei	2016	Study design	Safety and efficacy of venetoclax plus low-dose cytarabine in treatment-naive patients aged >65 years with acute myeloid leukemia
Xu	2013	Intervention/Comparator	Comparative efficacy of homoharringtonine plus cytarabine and decitabine in patients with MDS/AML
DiNardo	2018	Intervention/Comparator	Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study
Abu-Taleb	2013	Intervention/Comparator	Low dose cytarabine with or without anthracycline in the induction treatment of elderly patients with acute myeloid leukemia
Martinelli	2012	Intervention/Comparator	Stage I findings of a two-stage phase II study to assess the efficacy, safety, and tolerability of barasertib (AZD1152) compared with low-dose cytosine arabinoside (LDAC) in elderly patients (pts) with acute myeloid leukemia (AML)
Lancet	2011	Intervention/Comparator	Lintuzumab and low-dose cytarabine compared with placebo and low-dose cytarabine in patients with untreated acute myeloid leukemia (AML) 60 years and older: Results of a randomised, double-blinded phase 2b study
Gail	2018	Study design	Ivosidenib (AG-120) Induced Durable Remissions And Transfusion Independence In Patients With IDH1-Mutant Untreated AML: Results From a Phase 1 Dose Escalation And Expansion Study
Abhishek	2018	Study design	Interim Analysis of Phase II Study of Venetoclax With 10-Day Decitabine (DEC10-VEN) In Acute Myeloid Leukemia And Myelodysplastic Syndrome
Andrew	2018	Study design	Venetoclax With Low-Dose Cytarabine Induces Rapid, Deep, And Durable Responses In Previously Untreated Older Adults With AML Ineligible For Intensive Chemotherapy

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First author's last name	Publication year	Reason for exclusion	Title
Jorge	2018	Intervention/Comparator	Glasdegib In Addition To Intensive Or Non-Intensive Chemotherapy In Patients With Acute Myeloid Leukemia: Safety Analysis of Glasdegib 'On Target' Adverse Events
Andrew	2017	Study design	Phase 1/2 Study of Venetoclax With Low-Dose Cytarabine In Treatment-Naive, Elderly Patients With Acute Myeloid Leukemia Unfit For Intensive Chemotherapy: 1-Year Outcomes
Montesinos	2020	Intervention/Comparator	Safety and efficacy of talacotuzumab plus decitabine or decitabine alone in patients with acute myeloid leukemia not eligible for chemotherapy: results from a multicenter, randomised, phase 2/3 study
Roboz	2020	Study design	Ivosidenib induces deep durable remissions in patients with newly diagnosed IDH1-mutant acute myeloid leukemia
Pongudom	2020	Intervention/Comparator	Efficacy and Safety of Metronomic Chemotherapy Versus Palliative Hydroxyurea in Unfit Acute Myeloid Leukemia Patients: A Multicenter, Open-Label Randomised Controlled Trial
Zhao	2020	Intervention/Comparator	Decitabine combined with CAG regimen in the treatment of elderly patients with acute myeloid leukemia
Wei	2019	Study design	Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: Results from a phase Ib/II study
Zeidan	2019	Intervention/Comparator	Efficacy and safety of azacitidine (AZA) in combination with the anti-PD-L1 durvalumab (durva) for the front-line treatment of older patients (pts) with acute myeloid leukemia (AML) who are unfit for intensive chemotherapy (IC) and pts with higher-risk myelodysplasic syndromes (HR-MDS): results from a large, international, randomised phase 2 study
DiNardo	2019	Intervention/Comparator	Enasidenib plus azacitidine significantly improves complete remission and overall response compared with azacitidine alone in patients with newly diagnosed acute myeloid leukemia (AML) with isocitrate dehydrogenase 2 (IDH2) mutations: interim phase II results from an ongoing, randomised study
Winters	2019	Study design	Venetoclax And Azacitidine For Older Newly Diagnosed Patients With Acute Myeloid Leukemia: A Single-Institution Pilot Study Using Measurable Residual Disease To Guide Therapy
Maiti	2019	Study design	Ten-Day Decitabine With Venetoclax (DEC10-VEN) In Acute Myeloid Leukemia: Updated Results of a Phase II Trial
Roboz	2019	Study design	Ivosidenib (IVO; AG-120) In IDH1-Mutant Newly-Diagnosed Acute Myeloid Leukemia (ND AML): Updated Results From a Phase 1 Study
Strickland	2018	Study design	Cytogenetic and Molecular Drivers of Outcome with Venetoclax-Based Combination Therapies in Treatment-Naive Elderly Patients with Aml
Polo	2020	Intervention/Comparator	Flugaza Trial: A Phase Iii Randomised, Open Label Study Comparing Azacitidine Versus Fludarabine And Cytarabine (Fluga Scheme) In Elderly Patients With Newly Diagnosed Acute Myeloid Leukemia
Wei	2020	Study design	Long-Term Follow-Up Of A Phase 1/2 Study Of Venetoclax Plus Low-Dose Cytarabine In Previously Untreated Older Adults With Acute Myeloid Leukemia
Dennis	2020	Intervention/Comparator	A Randomised Evaluation Of Low-Dose Ara-C Plus Ac220 (Quizartinib) Versus Low Dose Ara-C In Older Patients With Acute Myeloid Leukaemia: Results From The Li-1 Trial
Zeidan	2020	Intervention/Comparator	Comparative Results Of Azacitidine And Decitabine From A Large Prospective Phase 3 Study In Treatment Naïve Acute Myeloid Leukemia (Tn-Aml) Not Eligible For Intensive Chemotherapy
DiNardo	2020	Intervention/Comparator	Effect of enasidenib (ENA) plus azacitidine (AZA) on complete remission and overall response versus AZA monotherapy in mutant/-IDH2/ (/mIDH2/) newly diagnosed acute myeloid leukemia (ND-AML).

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First author's last name	Publication year	Reason for exclusion	Title
Amadori	2016	Intervention/Comparator	Gemtuzumab Ozogamicin Versus Best Supportive Care in Older Patients With Newly Diagnosed Acute Myeloid Leukemia Unsuitable for Intensive Chemotherapy: Results of the Randomised Phase III EORTC GIMEMA AML-19 Trial
Burnett	2013	Intervention/Comparator	Clofarabine doubles the response rate in older patients with acute myeloid leukemia but does not improve survival
DiNardo	2020	Intervention/Comparator	Enasidenib plus azacitidine significantly improves complete remission and overall response rates versus azacitidine monotherapy in mutant-idh2 newly diagnosed acute myeloid leukemia (ND-AML)
Hupfer	2020	Intervention/Comparator	Role of functional parameters in elderly AML patients deemed unfit for induction chemotherapy: results from the decider trial
Lubbert	2020	Intervention/Comparator	All-trans retinoic acid improves survival in elderly aml patients by delaying decitabine resistance development: results of a randomised trial (decider study)
DiNardo	2020	Study design	10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: a single-centre, phase 2 trial
Abhishek	2020	Study design	Ten-Day Decitabine With Venetoclax (DEC10-VEN) In AML And High-Risk (HR) MDS
DiNardo	2020	Intervention/Comparator	Effect of Enasidenib (ENA) Plus Azacitidine (AZA) On Complete Remission And Overall Response Versus AZA Monotherapy In Mutant-IDH2 (MIDH2) Newly Diagnosed Acute Myeloid Leukemia (ND-AML)
Wei	2020	Intervention/Comparator	A Phase 3 Study Of Venetoclax Plus Low-Dose Cytarabine In Previously Untreated Older Patients With Acute Myeloid Leukemia (VIALE-C): A 6-Month Update
Wei	2020	Intervention/Comparator	Venetoclax plus LDAC for patients with untreated AML ineligible for intensive chemotherapy: phase 3 randomised placebo-controlled trial

Source: [123].

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8.1.5 Included documents

Table 8.4 Included documents (N=18)

First author's last name	Publication year	Study name	Trial registration number	Title
Cortes	2018	BRIGHT AML 1003	NCT01546038	Randomised comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome
Zeidan	2019	BRIGHT AML 1003	NCT01546038	Clinical Benefit of Glasdegib in Combination with Azacitidine or Low-Dose Cytarabine in Patients with Acute Myeloid Leukemia
Kwon	2019	BRIGHT AML 1003	NCT01546038	Quality-Adjusted Survival for Low-Dose Cytarabine (LDAC) Versus Glasdegib+LDAC Among Newly Diagnosed Acute Myeloid Leukemia Patients Who Are Not Candidates for Intensive Chemotherapy: A Q-TWiST Analysis
Heuser	2019	BRIGHT AML 1003	NCT01546038	Clinical Benefit of Glasdegib Plus Low-Dose Cytarabine in Patients with De Novo and Secondary Acute Myeloid Leukemia: Long-Term Analysis of a Phase 2 Randomised Trial
Smith	2019	BRIGHT AML 1003	NCT01546038	Low-dose cytarabine with or without glasdegib in newly diagnosed patients with acute myeloid leukemia: Long-term analysis of a phase 2 randomised trial.
Heuser	2020	BRIGHT AML 1003	NCT01546038	Glasdegib (GLAS) Plus Low-Dose Cytarabine (LDAC) in AML or MDS: BRIGHT AML 1003 Final Report And 4-Year Overall Survival (OS) Follow-Up.
Kantarijian	2012	Kantarjian 2012	NCT00260832	Multicenter, randomised, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia
Mayer	2014	Mayer 2014	NCT00260832	Multivariate and subgroup analyses of a randomised, multinational, phase 3 trial of decitabine vs treatment choice of supportive care or cytarabine in older patients with newly diagnosed acute myeloid leukemia and poor- or intermediate-risk cytogenetics
Short	2019	Short et al., 2019	NCT01786343	Treatment with a 5-day versus a 10-day schedule of decitabine in older patients with newly diagnosed acute myeloid leukaemia: a randomised phase 2 trial
Fenaux	2010	AZA-001	NCT00071799	Azacitidine Prolongs Overall Survival Compared With Conventional Care Regimens in Elderly Patients With Low Bone Marrow Blast Count Acute Myeloid Leukemia
Dombret	2015	AZA-AML-001	NCT01074047	International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts
Seymour	2016	AZA-AML-001	NCT01074047	Efficacy and safety of azacitidine (AZA) versus conventional care regimens (CCR) in patients aged >75 years with acute myeloid leukemia (AML) in the Phase 3 AZA-AML-001 Study
Seymour	2015	AZA-AML-001	NCT01074047	Overall survival (OS) and clinical outcomes in older patients with acute myeloid leukemia (AML) treated with azacitidine (AZA) or low-dose cytarabine (LDAC) in the AZA-AML-001 study
Seymour	2016	AZA-AML-001	NCT01074047	Incidence rates of treatment-emergent adverse events and related hospitalization are reduced with azacitidine compared with conventional care regimens in older patients with acute myeloid leukemia
DiNardo	2020	VIALE-A	NCT02993523	A Randomised, Double-Blind, Placebo-Controlled Study Of Venetoclax With Azacitidine VS Azacitidine In Treatment-Naïve Patients With Acute Myeloid Leukemia Ineligible For Intensive Therapy-VIALE-A

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First author's last name	Publication year	Study name	Trial registration number	Title
AbbVie data on file		VIALE-A	NCT02993523	A Randomised, Double-Blind, Placebo Controlled Phase 3 Study of Venetoclax in Combination with Azacitidine Versus Azacitidine in Treatment Naïve Subjects with Acute Myeloid Leukemia Who Are Ineligible for Standard Induction Therapy
DiNardo	2020	VIALE-A	NCT02993523	Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia
Heuser	2020	BRIGHT AML 1003	NCT01546038	Glasdegib Plus Low-Dose Cytarabine in AML or MDS: BRIGHT AML 1003 Final Report and 4-Year Overall Survival Follow-Up

Source: [123].

8.1.6 Efficacy outcomes of relevant comparator studies

OS: all patients with AML

Table 8.5 Overall survival for all AML patients from relevant comparator studies

Study name	Treatment	Sample size	Overall Survival (OS)		
			Median, months (95% CI)	Hazard ratio (95% CI)	Landmark rates
BRIGHT AML 1003[a1-6]	GLAS + LDAC	78	8.3 (4.7, 12.2)	0.53 (0.35, 0.80)	59.7%; 6 months 28.2%; 20 months
	LDAC	38	4.3 (1.9, 5.7)	NA	33.4%; 6 months; 7.9%; 20 months
Kantarjian 2012[7,8]	DEC 5d	242	7.7 (6.2, 9.2)	0.82 (0.68, 0.99)	NR
	TC	243	5.0 (4.3, 6.3)	NA	NR
Short 2019[9]	DEC 5d	28	5.5 (NR, NR)	0.82 (0.49, 1.39)	25.0%; 1-year
	DEC 10d	43	6.0 (NR, NR)	NA	25.0%; 1-year
AZA-001[10]	AZA - combined	55	24.5 (14.6, NR)	0.47 (0.28, 0.79)	50.2%; 2-year
	CCR - combined	58	16.0 (11.5, 17.5)	NA	15.9%; 2-year
	AZA - preselected BSC	36	19.1 (11.2, NR)	0.48 (0.24, 0.94)	46.3%; 2-year
	CCR - BSC	27	13.4 (5.2, 17.5)	NA	0.0%; 2-year
	AZA - preselected LDAC	14	24.5 (18.4, NR)	0.37 (0.12, 1.13)	56.3%; 2-year
	CCR - LDAC	20	17.0 (14.5, 25.8)	NA	31.8%, 2-year
	AZA - preselected IC	5	NR (2.7, NR)	0.97 (0.19, 5.10)	60.0%; 2-year
	CCR - IC	11	14.2 (10.8, 24.1)	NA	25.0%; 2-year
AZA-AML-001[11-14]	AZA - combined	241	10.4 (8.0, 12.7)	0.85 (0.69, 1.03)[b]	46.5%; 1-year
	CCR - combined	247	6.5 (5.0, 8.6)	NA	34.2%; 1-year
	AZA - preselected BSC	44	5.8 (3.6, 9.7)	0.60 (0.38, 0.95)	30.3%; 1-year
	CCR - preselected BSC	45	3.7 (2.8, 5.7)	NA	18.6%; 1-year
	AZA - preselected LDAC	154	11.2 (8.8, 13.4)	0.90 (0.70, 1.16)	48.5%; 1-year
	CCR - preselected LDAC	158	6.4 (4.8, 9.1)	NA	34.0%; 1-year
	AZA - preselected IC	43	13.3 (7.2, 19.9)	0.85 (0.52, 1.38)	55.8%; 1-year
	CCR - preselected IC	44	12.2 (7.5, 15.1)	NA	50.9%; 1-year

[a]Median OS was reported in Heuser 2020a (data cut: March 2019). 6-month OS was reported in Zeidan 2019 (data cut: October 11, 2018) and 20-month OS was reported in Kwon 2019 (data cut: January, 2017).

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[b]When adjusted for use of subsequent AML therapy as a time-dependent variable, AZA improved OS compared with CCRs (HR, 0.75; 95% CI, 0.59-0.94; P= .0130).
Source: [1-6][102, 144-149],[7][31], [8][150], [9][124], [10][101], [11-14][30, 151-153].

OS: AML subgroups

Table 8.6 Overall survival for patients in AML subgroups from relevant comparator studies

Study name	Treatment	Sample size	Subgroups	Overall Survival (OS)		
				Median, months (95% CI)	Hazard ratio (95% CI)	Landmark rates
BRIGHT AML 1003[a1-6]	GLAS + LDAC	38	De novo AML	6.6 (3.7, 12.4)	0.75 (0.41, 1.36)	NR
	LDAC	18	De novo AML	4.3 (1.3, 10.7)	NA	NR
	GLAS + LDAC	40	Secondary AML	9.1 (4.4, 16.5)	0.29 (0.15, 0.55)	NR
	LDAC	20	Secondary AML	4.1 (1.5, 6.4)	NA	NR
Kantarjian 2012[7,8]	DEC 5d	71	Age< 70	9.1 (NR, NR)	1.01 (0.70, 1.45)	NR
	TC	70	Age< 70	4.9 (NR, NR)	NA	NR
	DEC 5d	76	Age70-74	8.0 (NR, NR)	0.79 (0.56, 1.11)	NR
	TC	74	Age70-74	5.7 (NR, NR)	NA	NR
	DEC 5d	95	Age>=75	6.3 (NR, NR)	0.72 (0.57, 0.91)	NR
	TC	99	Age>=75	4.5 (NR, NR)	NA	NR
	DEC 5d	155	De novo AML	8.2 (NR, NR)	0.71 (0.56, 0.91)	NR
	TC	157	De novo AML	5.2 (NR, NR)	NA	NR
	DEC 5d	87	Secondary AML	7.1 (NR, NR)	0.92 (0.66, 1.29)	NR
	TC	84	Secondary AML	4.9 (NR, NR)	NA	NR
	DEC 5d	65	Marrow blasts 20%-30%	8.0 (NR, NR)	1.12 (0.76, 1.66)	NR
	TC	58	Marrow blasts 20%-30%	6.1 (NR, NR)	NA	NR
	DEC 5d	172	Marrow blasts >30%	7.1 (NR, NR)	0.72 (0.57, 0.91)	NR
	TC	175	Marrow blasts >30%	4.3 (NR, NR)	NA	NR
Short 2019[9]	DEC 5d	15	De novo AML	7.3 (NR, NR)	NA	NR
	DEC 10d	25	De novo AML	7.1 (NR, NR)	NA	NR
	DEC 5d	13	Secondary AML	4.4 (NR, NR)	NA	NR
	DEC 10d	18	Secondary AML	5.4 (NR, NR)	NA	NR
AZA-AML-001[10-13]	AZA - combined	103	Age <75	14.2 (NR, NR)	0.73 (0.54, 0.99)	86.3%; 3 months 77.5%; 6 months 66.7%; 9 months 57.8%; 12 months
	CCR - combined	120	Age <75	9.6 (NR, NR)	NA	73.9%; 3 months 59.5%; 6 months 51.8%; 9 months 42.2%; 12 months
	AZA - combined	138	Age ≥75	7.0 (NR, NR)	0.91 (0.69, 1.20)	71.4%; 3 months 51.5%; 6 months 44.1%; 9 months 38.1%; 12 months

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Study name	Treatment	Sample size	Subgroups	Overall Survival (OS)		
				Median, months (95% CI)	Hazard ratio (95% CI)	Landmark rates
	CCR - combined	127	Age ≥75	4.0 (NR, NR)	NA	64.7%; 3 months 46.5%; 6 months 34.0%; 9 months 26.6%; 12 months

[a] OS was reported in Heuser 2020a (data cut: March 2019).
Source: [1-6][102, 144-149],[7][31], [8][150], [9][124], [10-13][30, 151-153].

EFS: all patients with AML from relevant comparator studies

EFS was reported in only one of the comparator trials. In the AZA-AML-001 trial, median EFS for AZA-combined arm and CCR-combined arm was 6.7 months (95% CI: 5.0-8.8) and 4.8 months (95% CI: 3.8-6.0), respectively.

Treatment response: all patients with AML

Table 8.7 Treatment response of all patients with AML from relevant comparator studies

Study name	Treatment	Sample size	CR, n (%)	CRi, n (%)	CR + CRi, n (%)	CR +CRh, n (%)	CR + CRp + CRi, n (%)	Partial remission, n (%)	Stable disease, n (%)	Progressive disease, n (%)	Resistant disease, n (%)
BRIGHT AML-1003[a1-6]	GLAS + LDAC	78	15 (19.2%)	4 (5.1%)	19 (24.4%)	NR	NR	5 (6.4%)	14 (17.9%)	NR	NR
	LDAC	38	1 (2.6%)	1 (2.6%)	2 (5.3%)	NR	NR	0 (0.0%)	9 (23.7%)	NR	NR
Kantarjian 2012[b7,8]	DEC 5d	242	38 (15.7%)	24 (9.9%)	62 (25.6%)	NR	NR	6 (2.5%)	67 (27.7%)	50 (20.7%)	NR
	TC	243	18 (7.4%)	7 (2.9%)	25 (10.3%)	NR	NR	9 (3.7%)	55 (22.6%)	79 (32.5%)	NR
	TC - LDAC	215	17 (7.9%)	6 (2.8%)	23 (10.7%)	NR	NR	8 (3.7%)	52 (24.2%)	69 (32.1%)	NR
	TC - SC	28	1 (3.6%)	1 (3.6%)	2 (7.1%)	NR	NR	1 (3.6%)	3 (10.7%)	10 (35.7%)	NR
Short 2019[9]	DEC 5d	28	8 (28.6%)	1 (3.6%)	NR	NR	12 (42.9%)	0 (0.0%)	NR	NR	NR
	DEC 10d	43	13 (30.2%)	2 (4.7%)	NR	NR	17 (39.5%)	1 (2.3%)	NR	NR	NR
AZA-001[10]	AZA - combined	55	10 (18.2%)	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - combined	58	9 (15.5%)	NR	NR	NR	NR	NR	NR	NR	NR
	AZA - preselected BSC	36	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - preselected BSC	27	0 (0.0%)	NR	NR	NR	NR	NR	NR	NR	NR
	AZA - preselected LDAC	14	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - preselected LDAC	20	3 (15.0%)	NR	NR	NR	NR	NR	NR	NR	NR
	AZA - preselected IC	5	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - preselected IC	11	6 (54.5%)	NR	NR	NR	NR	NR	NR	NR	NR

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AZA-AML-001[11-14]	AZA - combined	241	47 (19.5%)	20 (8.3%)	67 (27.8%)	NR	NR	3 (1.2%)	71 (29.5%)	20 (8.3%)	NR
	CCR - combined	247	54 (21.9%)	8 (3.2%)	62 (25.1%)	NR	NR	3 (1.2%)	59 (23.9%)	20 (8.1%)	NR
	AZA - preselected BSC	44	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - preselected BSC	45	NR	NR	0 (0.0%)	NR	NR	NR	NR	NR	NR
	AZA - preselected LDAC	154	NR	NR	42 (27.0%)	NR	NR	NR	NR	NR	NR
	CCR - preselected LDAC	158	NR	NR	41 (25.9%)	NR	NR	NR	NR	NR	NR
	AZA - preselected IC	43	NR	NR	NR	NR	NR	NR	NR	NR	NR
	CCR - preselected IC	44	NR	NR	21 (47.7%)	NR	NR	NR	NR	NR	NR

[a] Responses were reported in Heuser 2020b (data cut: March 2019).
[b] Data cut: October 28, 2009.
Source: [1-6][102, 144-149],[7][31], [8][150], [9][124], [10][101], [11-14][30, 151-153].

Treatment response: patients in AML subgroups

Table 8.8 Treatment response of patient in AML subgroups from relevant comparator studies

Study name	Treatment	Sample size	Subgroup	CR + CRi, n (%)	CR + CRp, n (%)	CR +CRh, n (%)	CR + CRp + CRi, n (%)
Kantarjian 2012[a1,2]	DEC 5d	71	Age< 70	NR	12 (16.9%)	NR	NR
	TC	70	Age< 70	NR	9 (12.9%)	NR	NR
	DEC 5d	76	Age70-74	NR	12 (15.8%)	NR	NR
	TC	74	Age70-74	NR	6 (8.1%)	NR	NR
	DEC 5d	95	Age ≥75	NR	19 (20.0%)	NR	NR
	TC	99	Age ≥75	NR	4 (4.0%)	NR	NR
	DEC 5d	65	Marrow blasts 20%-30%	NR	15 (23.1%)	NR	NR
	TC	58	Marrow blasts 20%-30%	NR	4 (6.9%)	NR	NR
	DEC 5d	172	Marrow blasts >30%	NR	28 (16.3%)	NR	NR
	TC	175	Marrow blasts >30%	NR	15 (8.6%)	NR	NR
	DEC 5d	155	De novo AML	NR	30 (19.4%)	NR	NR
	TC	157	De novo AML	NR	16 (10.2%)	NR	NR
	DEC 5d	87	Secondary AML	NR	13 (14.9%)	NR	NR
	TC	84	Secondary AML	NR	3 (3.6%)	NR	NR
Short 2019[3]	DEC 5d	15	De novo AML	NR	NR	NR	7 (46.7%)
	DEC 10d	25	De novo AML	NR	NR	NR	9 (36.0%)
	DEC 5d	13	Secondary AML	NR	NR	NR	5 (38.5%)
	DEC 10d	18	Secondary AML	NR	NR	NR	8 (44.4%)
AZA-AML-001[4-7]	AZA - combined	103	Age <75	33 (32.0%)	NR	NR	NR
	CCR - combined	120	Age <75	36 (30.0%)	NR	NR	NR

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Study name	Treatment	Sample size	Subgroup	CR + CRi, n (%)	CR + CRp, n (%)	CR +CRh, n (%)	CR + CRp + CRi, n (%)
	AZA - combined	138	Age ≥75	35 (25.4%)	NR	NR	NR
	CCR - combined	127	Age ≥75	27 (21.3%)	NR	NR	NR

[a] CR + CRp for subgroups was reported in Mayer 2014 (data cut: October 29, 2010).
Source:[1][31], [2][150], [3][124], [4-7][30, 151-153].

Transfusion independence: all patients from relevant comparator studies
Publications for AZA-001, AZA-AML-001, and BRIGHT AML-1003 reported transfusion independence data; DACO-016 and Short et al., 2019, did not report data for this outcome. This was expected according to the study designs.

Among patients with RBC or platelet transfusion dependence at baseline in AZA-001, a significantly higher proportion achieved transfusion independence with azacitidine compared with CCR for RBC (41% versus 18%, respectively; p=0.04) but not for platelets (53% v 40%, respectively; p=0.69). When patients preselected for intensive chemotherapy were removed from the analysis, the rates for RBC transfusion independence were 44% for patients receiving azacitidine versus 15% for those receiving CCR (p=0.01), and for platelet transfusion independence were 50% versus 40%, respectively (p=0.70) [101].

In AZA-AML-001, a higher proportion of patients who were transfusion dependent at baseline in the azacitidine treatment arm attained RBC transfusion independence (38.5% versus 27.6% in the CCR arm) or platelet transfusion independence (40.6% versus 29.3%). Total numbers of patients in the azacitidine and CCR groups who remained RBC transfusion independent, or became RBC transfusion independent on treatment, were 105 (43.6%; 95% CI: 37.2%, 50.1%) and 76 (30.8%; 95% CI: 25.1%, 36.9%), respectively, and who remained or became platelet transfusion independent were 142 (58.9%; 95% CI: 52.4%, 65.2%) and 106 (42.9%; 95%CI: 36.7%, 49.3%), respectively [30].

Lastly in the BRIGHT AML-1003 trial, among patients who did not achieve CR, transfusion independence was achieved by 9/60 patients (15.0%) receiving glasdegib + LDAC and 1/35 patients (2.9%) receiving LDAC alone. For patients who did achieve a CR, 13/15 patients who received glasdegib + LDAC were transfusion independent (86.6%) and in the LDAC-only arm 1/1 patients achieved a CR and was transfusion independent at the time of analysis (100%) [134].

HRQL outcomes of relevant comparator studies
HRQL outcome results were reported for AZA-AML-001 only. HRQL data were not expected for BRIGHT AML-1003, DACO-016, AZA-001 or Short et al., 2019, according to the study designs.

<u>EORTC QLQ-C30 (AZA-AML-001)</u>
The population in the AZA-AML-001 trial that was evaluable for HRQL initially comprised 291 patients (azacitidine, 157; CCR, 134). This patient subset decreased over time in both groups, but at a faster rate in the CCR arm after cycle 3. Change from baseline scores for primary and secondary domains of the QLQ-C30 generally improved over 9 treatment cycles in both arms. No HRQL detriment was seen with azacitidine or CCR at the group level during treatment. Only a few changes met the minimally important difference threshold. In the CCR group, Fatigue (cycles 7 and 9) decreased by the minimally important difference (indicative of HRQL reduction), while Global Health Status/QoL (cycle 9) increased by the minimally important difference (indicative of HRQL improvement). No changes in the azacitidine group met the minimally important difference threshold [30].

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8.1.7 Safety outcomes of comparator relevant studies

AEs, SAEs, and discontinuation

Table 8.9 Summary of AEs

Study name	Treatment	Sample size	Any AE, n (%)	Grade 3 or 4 AEs, n (%)	Any SAEs, n (%)	Deaths due to AEs, n (%)
BRIGHT-AML 1003[a1-6]	GLAS + LDAC	NR	NR (83.7%)	NR (51.2%)	NR (83.7%)[h]	NR
	LDAC	NR	NR	NR	NR (51.2%)[h]	NR
DACO-016[7,8]	DEC 5d	238	NR	221 (92.9%)[b]	190 (80.0%)	58 (24.4%)[c]
	TC	237	NR	204 (86.1%)[b]	162 (68.0%)	NR
	TC – LDAC	208	NR	188 (90.4%)[b]	150 (72.0%)	39 (18.8%)[c]
	TC – SC	29	NR	16 (55.2%)[c]	12 (41.0%)	NR
Short et al., 2019[d9]	DEC 5d	28	NR	NR	NR	NR
	DEC 10d	43	NR	NR	NR	NR
AZA-001[e10]	AZA – combined	53	NR	NR	NR	NR
	CCR – combined	53	NR	NR	NR	NR
	AZA – preselected BSC	NR	NR	NR	NR	NR
	CCR – preselected BSC	25	NR	NR	NR	NR
	AZA – preselected LDAC	NR	NR	NR	NR	NR
	CCR – preselected LDAC	18	NR	NR	NR	NR
	AZA – preselected IC	NR	NR	NR	NR	NR
	CCR – preselected IC	10	NR	NR	NR	NR
AZA-AML-001[f 11-14]	AZA – combined	236[g]	234 (99.2%)	NR	NR	NR
	CCR – combined	235[g]	235 (100.0%)	NR	NR	NR
	AZA – preselected BSC	NR	NR	NR	NR	NR
	CCR – preselected BSC	40	NR	NR	NR	NR
	AZA – preselected LDAC	NR	NR	NR	NR	NR
	CCR – preselected LDAC	153	NR	NR	NR	NR
	AZA – preselected IC	NR	NR	NR	NR	NR
	CCR – preselected IC	42	NR	NR	NR	NR

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Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; DEC, decitabine; GLAS, glasdegib; IC, intensive chemotherapy; LDAC, low-dose cytarabine; NR, not reported; SAE, serious adverse event; TC, treatment choice; VEN, venetoclax.
[a] Any AEs and serious AEs were reported for AML patients in Smith 2019 (data cut: 11 October 2018).
[b] Treatment-emergent AEs of grades 3 or 4 in ≥10% of patients.
[c] Deaths during treatment or ≤30 days after the last study drug dose.
[d] Specific grade 1–5 AEs were reported but not extracted
[e] Grade 3 or 4 thrombocytopenia, neutropenia, anaemia were reported for each treatment but not extracted.
[f] Treatment-emergent AEs defined as new or worsening AEs between the time of first dose (or randomization for BSC only) to the end of the safety follow-up period.
[g] Safety population comprised 471 patients (AZA 236; CCR 235); 5 patients randomly assigned to AZA and 7 patients randomly assigned to CCR did not receive study treatment, and 5 patients in the CCR arm had no post-dose safety assessment.
[h] After the first 90 days of treatment.
Source: [1-6][102, 144-149],[7][31], [8][150], [9][124], [10][101], [11-14][30, 151-153].

Table 8.10 Summary of treatment discontinuations

Study name	Treatment	Sample Size	Discontinuation due to death, n (%)	Discontinuation due to progressive disease, n (%)	Discontinuation due to any AE, n (%)	Discontinuation due to withdrawn consent, n (%)
BRIGHT-AML 1003[a1-6]	GLAS + LDAC	NR	NR	NR	NR	NR
	LDAC	NR	NR	NR	NR	NR
Kantarjian, 2012[b7,8]	DEC 5d	238	62 (26.1%)	96 (40.3%)	19 (8.0%)	NR
	TC	237	43 (18.1%)	116 (48.9%)	26 (11.0%)	NR
	TC – LDAC	208	NR	NR	NR	NR
	TC – SC	29	NR	NR	NR	NR
Short et al., 2019[9]	DEC 5d	28	NR	NR	NR	NR
	DEC 10d	43	NR	NR	NR	NR
AZA-001[10]	AZA – combined	53	NR	NR	4 (7.5%)	NR
	CCR – combined	53	NR	NR	3 (5.7%)	NR
	AZA – preselected BSC	NR	NR	NR	NR	NR
	CCR – preselected BSC	25	NR	NR	NR	NR
	AZA – preselected LDAC	NR	NR	NR	NR	NR
	CCR – preselected LDAC	18	NR	NR	NR	NR
	AZA – preselected IC	NR	NR	NR	NR	NR
	CCR – preselected IC	10	NR	NR	NR	NR
AZA-AML-001[c11-14]	AZA – combined	236	53 (22.5%)	16 (6.8%)	89 (37.7%)	27 (11.4%)
	CCR – combined	235	58 (24.7%)	21 (8.9%)	66 (28.1%)	48 (20.4%)
	AZA – preselected BSC	NR	NR	NR	NR	NR
	CCR – preselected BSC	40	NR	NR	NR	NR
	AZA – preselected LDAC	NR	NR	NR	NR	NR

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	CCR – preselected LDAC	153	NR	NR	NR	NR
	AZA – preselected IC	NR	NR	NR	NR	NR
	CCR – preselected IC	42	NR	NR	NR	NR

AE, adverse event; AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; CCR, conventional care regimens; DEC, decitabine; GLAS, glasdegib; IC, intensive chemotherapy; LDAC, low-dose cytarabine; NR, not reported; SC, supportive care; TC, treatment choice; VEN, venetoclax.
[a] Discontinuation outcomes were reported for mixed MDS and AML patients but not extracted.
[b] Data cut: 2009.
[c] Safety population comprised 471 patients (AZA 236; CCR 235); 5 patients randomly assigned to AZA and 7 patients randomly assigned to CCR did not receive study treatment, and 5 patients in the CCR arm had no post-dose safety assessment.
Source: [1-6][102, 144-149],[7][31], [8][150], [9][124], [10][101], [11-14][30, 151-153].

Treatment-related AEs

In BRIGHT AML-1003 the rates of treatment-related AEs were 81.0% in the glasdegib plus LDAC arm and 58.5% in the LDAC arm [102].

Treatment-related AEs of any grade occurred in 175 (74%) patients treated with decitabine and 152 (73%) patients treated with LDAC in DACO-016 [31].

The pivotal trial paper for DACO-016 also reported that TRAEs of any grade occurred in 175 (74%) patients treated with decitabine and 152 (73%) patients treated with LDAC [31].

AZA-001, AZA-AML-001, and Short et al., 2019, did not report TRAE data.

Dose reductions

In AZA-AML-001, AEs leading to dose reductions occurred for 3.4%, 1.3%, and 4.8% of patients in the azacitidine, LDAC, and intensive chemotherapy arms, respectively [30].

BRIGHT AML-1003, DACO-016, AZA-001 and Short et al., 2019, did not report dose-reduction data.

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8.1.8 Detailed risk of bias assessment

Table 8.11 Detailed risk of bias assessment for relevant studies

Study name	Was randomization carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
BRIGHT AML 1003	Patient randomization was obtained by the investigator or the designee from the interactive voice response system.	Low	Patient randomization was obtained by the investigator or the designee from the interactive voice response system.	Low	Baseline characteristics were presented but the balance between two arms were not discussed	Un-clear	Due to the open-label setting, participants were aware of the treatment allocation. This would potentially increase performance bias and detection bias.	High	Discontinuation rate was similar in both groups.	Low	Unclear	Un-clear	Efficacy analysis included all patients randomised (ITT population); did not mention how missing data were handled.	Un-clear
DACO-016	Patients were randomly assigned 1:1 to receive decitabine or TC by using a stratified permuted block method.	Low	No mention of method of allocation concealment.	Un-clear	Patient demographics and baseline clinical characteristics were balanced.	Low	Due to the open-label setting, participants were aware of the treatment allocation. This would potentially increase performance bias and detection bias.	High	No. Drop-out rates were similar between two groups.	Low	Unclear	Un-clear	Yes, the analysis was done in ITT population. Did not mention how they handled missing data.	Un-clear
Short et al., 2019	Randomization was determined by a Bayesian response-adaptive randomization algorithm at enrolment.	Low	Randomization was determined by a Bayesian response-adaptive randomization algorithm at enrolment.	Low	The study groups were imbalanced because of superior performance with the 10-day schedule of decitabine during the initial enrolment period. Baseline characteristics	Low	Due to the open-label setting, participants were aware of the treatment allocation. This would potentially increase performance bias and detection bias.	High	NR	Un-clear	Unclear	Un-clear	Yes, the analysis was done in ITT population. Did not mention how they handled missing data.	Un-clear

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Study name	Was randomization carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
					were well balanced across treatment groups randomly assigned to groups.									
AZA-001	Randomization was done centrally, with allocation by telephone. The randomization sequence was computer generated independently by Pharmaceutical Product Development.	Low	Randomization was done centrally, with allocation by telephone. The randomization sequence was computer generated independently by Pharmaceutical Product Development.	Low	Table 1 reports several prognostic factors for each group.	Low	No. This is an open label study.	High	Numbers of patients who discontinued treatment are reported for each group. Appears that more patients dropped out of the conventional care arm than the AZA arm.	High	Overall adverse event rates do not seem to be reported. Authors only report rates for selected events.	High	Yes. Efficacy analysis included all randomised patients (intention to treat population). The study did not report how missing data were handled.	Un-clear
AZA-AML-001	A central, stratified, and permuted block randomization method and interactive voice response system were used to randomly assign patients 1:1 to receive azacitidine or CCR.	Low	A central, stratified, and permuted block randomization method and interactive voice response system were used to randomly assign patients 1:1 to receive azacitidine or CCR.	Low	Baseline demographic and disease characteristics were generally balanced between treatment arms.	Low	Due to the open-label setting, participants were aware of the treatment allocation. This would potentially increase performance bias and detection bias.	High	No. Drop-out rates were similar between two groups.	Low	Unclear	Un-clear	Efficacy analysis were performed on ITT population. Patients with a missing value for any covariate in the final model (n 5 10 [2.0%]) were excluded from analysis.	Un-clear
VIALE-A	Patients were randomised to venetoclax plus azacitidine, and placebo plus azacitidine arm, stratified by age	Low	Patients were randomised to venetoclax plus azacitidine, and placebo plus azacitidine arm, stratified by age	Low	Baseline demographic and disease characteristics were generally balanced between treatment arms.	Low	Due to the double-blind setting, participants were not aware of the treatment allocation.	Low	Discontinuation rate was similar in both groups.	Low	Protocol specified outcomes reported	Low	Yes, the methods are appropriate. All efficacy analyses were performed on all randomised patients. All safety analyses were	Low

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Study name	Was randomization carried out appropriately?		Was the concealment of treatment allocation adequate?		Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?		Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?		Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?		Is there any evidence to suggest that the authors measured more outcomes than they reported?		Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	
	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias	How is the question addressed in the study?	Risk of bias
	(18 to <75, ≥75), cytogenetics (intermediate risk, poor risk) and region (US, EU, Japan, Rest of world).		(18 to <75, ≥75), cytogenetics (intermediate risk, poor risk) and region (US, EU, Japan, Rest of world).										performed on all patients who took at least 1 dose of study drug.	

AML, acute myeloid leukaemia; AZA, azacitidine; CCR, conventional care regimens; LDAC, low-dose cytarabine; ITT, intention to treat; NR, not reported; TC, treatment choice.
Source: [123].

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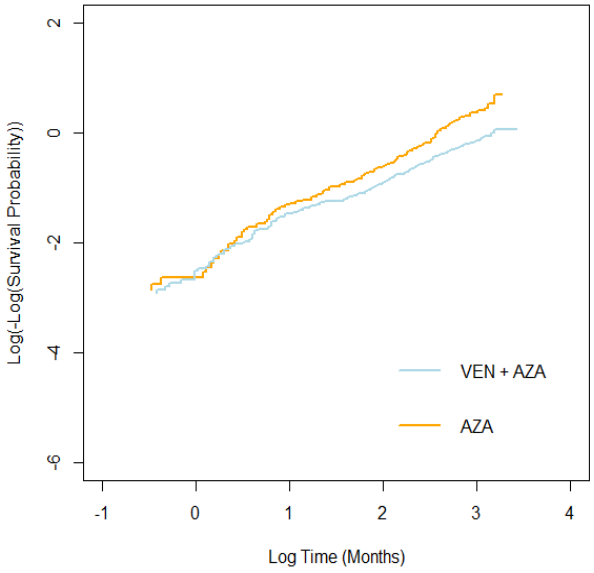
8.2 Indirect treatment comparisons supplemental information

8.2.1 ITC feasibility assessment: proportional hazards assumptions

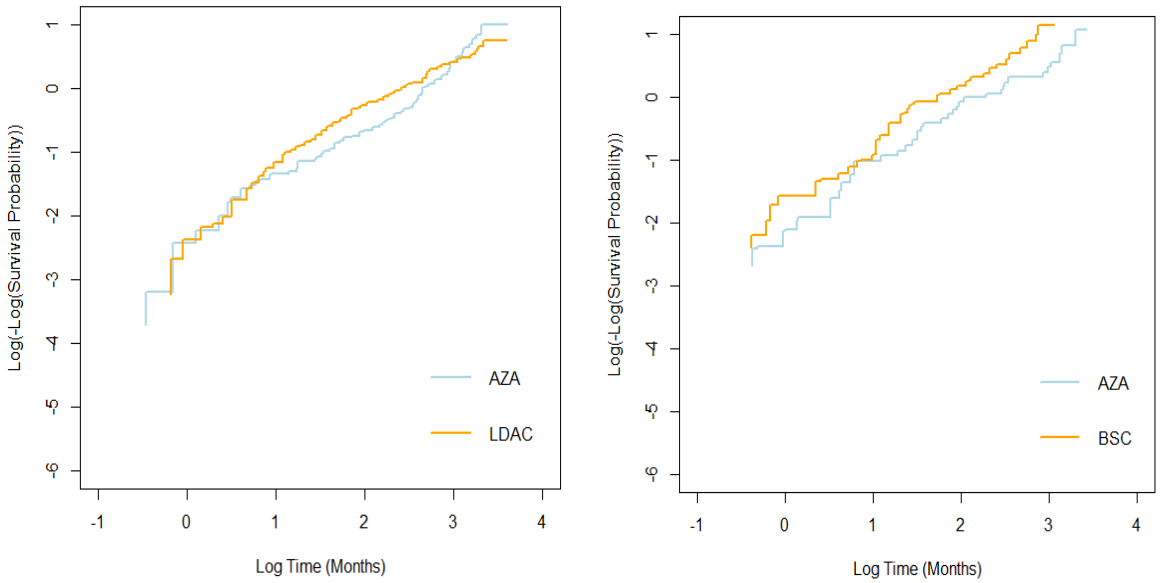
The proportional hazards assumption for OS was evaluated for the identified trials in which Kaplan-Meier curves are available using log-log cumulative hazard plots (Figure 8.2-Figure 8.5) [42].

Figure 8.2 Log-log plot of OS for venetoclax + azacitidine versus azacitidine in VIALE-A



Abbreviations: AZA, azacitidine; OS, overall survival; VEN, venetoclax.
Source: [42]

Figure 8.3 Log-log plot of OS for azacitidine versus LDAC in AZA-AML-001 (left panel); Log-log plot of OS for azacitidine versus BSC in AZA-AML-001 (right panel)



Abbreviations: AZA, azacitidine; BSC, best supportive care; LDAC, low-dose cytarabine; OS, overall survival.
Source: [42]

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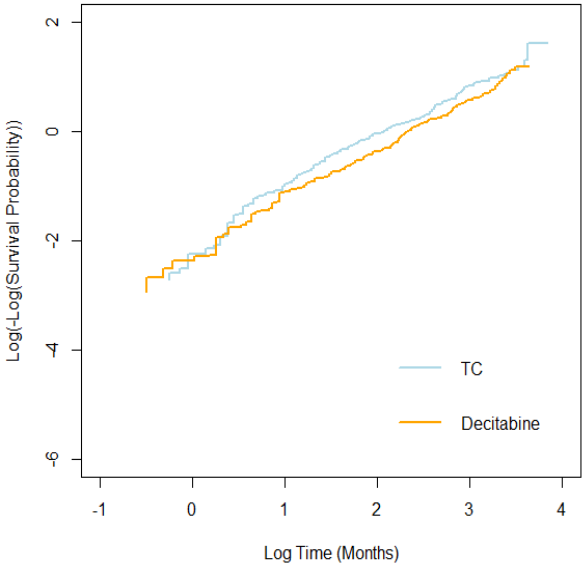
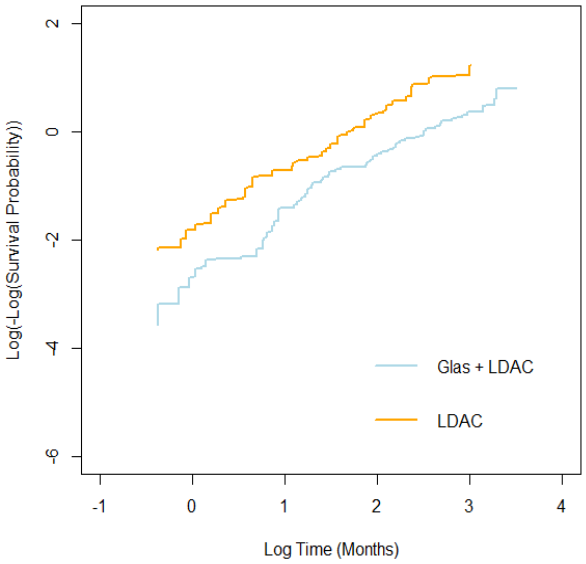
Figure 8.4 Log-log plot of OS for decitabine versus treatment choice in DACO-016



Abbreviations: OS, overall survival; TC, treatment choice.
Source: [42]

Figure 8.5 Log-log plot of OS for glasdegib + LDAC versus LDAC in BRIGHT-AML 1003



Abbreviations: Glas, glasdegib; LDAC, low-dose cytarabine; OS, overall survival.
Source: [42]

8.2.2 Propensity score weighting analysis: methodology

The propensity score weighting method was applied to evaluate the relative efficacy of treatments using IPD data from compatible studies.

Comparison of interest
Propensity score weighting analyses were performed to compare the efficacy outcomes of the venetoclax + azacitidine arm in VIALE-A versus the LDAC arm in VIALE-C in the overall population and in the subgroup of patients with >30% bone marrow blasts [42].

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Data sources

This analyses used anonymized individual patient level data from the Phase 3 randomised clinical trials of venetoclax combination therapies, including VIALE-A (NCT02993523; data cut-off date: 4 January 2020) and VIALE-C (NCT03069352; data cut-off date: 15 August 2019) [42].

Feasibility of Propensity Score Analysis

A feasibility assessment was conducted to review the study population, study design, baseline characteristics and outcomes of venetoclax + azacitidine arm in VIALE-A and the LDAC arm in VIALE-C in order to evaluate the comparability across the two cohorts [154].

In particular, the following information was compared across the two trials [154]:

- Inclusion/exclusion criteria
- Study design (e.g., trial duration, outcome assessment schedule)
- Availability and comparability of key baseline characteristics across trials

Both VIALE-A and VIALE-C trials were randomised, double-blind, placebo controlled, Phase 3 studies and enrolled treatment-naive patients with AML who are ineligible for intensive chemotherapy. The median age of patients in both trials were 76 years. Both trials included more males than females with the sex distribution ranging from ~55% to ~60%. 50% of patients in VIALE-C had ECOG status of 0 or 1, which was slightly lower than in VIALE-A (~55%). Both trials included around 70% of patients with greater than 30% bone marrow blast counts. The VIALE-A trial excluded patients with prior HMA treatment, while the VIALE-C trial allowed patients with prior HMA treatment. Given the high similarities between the study populations, study designs, and baseline characteristics of the VIALE-A and VIALE-C trials, propensity score analysis was deemed feasible [8, 40].

Inclusion and Exclusion Criteria

All inclusion and exclusion criteria of the two Phase 3 randomised clinical trials of venetoclax combination therapies were applied in this study.

Outcomes and covariates

<u>Outcomes</u>

The following efficacy outcomes were considered in the propensity score weighting analysis [154]:

- OS
- EFS
- Composite CR (CR + CRi)

<u>Covariates</u>

Based on prior research regarding AML prognostic factors and potential confounders, the following baseline characteristics were considered as independent variables in the propensity score model [154]:

- Demographic characteristics
  - Age
  - Sex
  - Race
- Clinical characteristics
  - AML type (primary or secondary)
  - AML with myelodysplasia related changes (MRC)
  - Prior MDS
  - Bone marrow blasts
  - Cytogenetic risk (poor, intermediate, favourable)
  - ECOG performance status

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Analytic approach

A propensity score weighting method was applied to compare the efficacy outcomes of the venetoclax + azacitidine arm in VIALE-A and the LDAC arm in VIALE-C in the overall AML population and in the subgroup of patients with >30% bone marrow blasts. Propensity score weighting can reduce selection bias by adjusting for the observed baseline differences between the two cohorts (i.e., patients from the venetoclax + azacitidine arm in VIALE-A and those from the LDAC arm in VIALE-C) by increasing or decreasing the relative contributions of individual patients in the two cohorts so that, after weighting, the two cohorts would have on average similar baseline characteristics. Specifically, a propensity score (i.e., the probability of treatment assignment) was assigned to each patient and the subsequent analyses was evaluated using data weighted by the inverse of the propensity score. The propensity score for each patient is estimated using a logistic regression model with the enrolment of the venetoclax + azacitidine arm versus the LDAC arm as the outcome and a set of observed baseline characteristics as covariates [42].

This analysis excluded patients with prior HMA use and favourable cytogenetic risk in the LDAC arm in VIALE-C because patients with these characteristics were not enrolled in VIALE-A per protocol. This analysis estimated the propensity score for each patient via a logistic regression model with the enrolment in the venetoclax + azacitidine arm versus the LDAC arm as the outcome and a set of observed baseline characteristics as covariates. The baseline covariates were selected based on prior research on AML prognostic factors and potential confounders. These variables include age, race, sex, AML status, AML with MRC, history of MDS status, ECOG score, cytogenetic risk category and bone marrow blasts. Patients with missing values for any of these selected baseline characteristics were excluded from the analysis [42].

The statistical tests for the comparison of the two balanced cohorts were based on weighted t-tests for continuous variables and weighted Chi-squared tests for categorical variables. Time-to-event outcomes were compared using weighted Cox models. The standard errors, 95% CIs, and p values for the comparisons between the two balanced cohorts were based on robust estimates of the variances that account for variability in the propensity score weights. All statistical analyses were conducted using R software [42].

Sensitivity analyses

Sensitivity analyses were conducted to evaluate the robustness of results by including patients with prior HMA use or favourable cytogenetic risk in the LDAC arm in VIALE-C in the analytical sample [42].

Subgroup analyses

The propensity score weighting analysis was also conducted to compare the efficacy of venetoclax + azacitidine versus LDAC in the subgroup of patients with >30% bone marrow blasts [42].

8.2.3 Propensity score weighting analysis: code

```
rm(list = ls())



library(data.table)

library(tidyverse)

library(stats)



# Read in data-set

directory <- "[Insert data directory path]"
```


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```
D <- readRDS(directory) %>%

setDT()



######################## Calculate propensity scores ####################


# Set up the formula

thisFormula <- as.formula(paste("treatment_var ~ age_cat + sex + race + secamlfl + amlmrcfl + ahhmdsfl + ecogbl_cat + cyt + bmbl"))


# treatment_var: variable for treatment levels (for example: Venetoclax + AZA [1] vs LDAC [0])

# age_cat: categorical flag for age (≥75 years vs <75 years)

# sex: categorical flag for sex (Male vs Female)

# race: categorical flag for race (White vs Non-white)

# secamlfl: categorical flag for secondary acute myeloid leukemia (Yes vs No)

# amlmrcfl: categorical flag for acute myeloid leukemia with myelodysplasia related changes (Yes vs No)

# ahhmdsfl: categorical flag for antecedent hematological history of myelodysplastic syndrome (Yes vs No)

# ecogbl_cat: categorical flag for eastern cooperative oncology group (ECOG) score (≥2 vs <2)

# cyt: categorical flag for cytogenetic risk category (for example: poor vs favorable or intermediate)

# bmbl: continuous variable for bone-marrow blast count during baseline period


# compute logistic regression model to estimate propensity scores

regObj <- stats::glm(thisFormula, data = D, family = binomial(), na.action = na.omit)


estimated_propensity_scores <- predict(regObj, type = "response")


D[ , propensity_score := estimated_propensity_scores]


######################## Calculate weights ####################
```


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```
D[, stabilized_numerator := predict.glm(glm(treatment_var~1, family = binomial(), na.action = na.omit), type = "response")]

D[, stabilized_propensity_weight := ifelse(treatment_var == 1, stabilized_numerator/propensity_score, (1-stabilized_numerator)/(1 - propensity_score))]


########################## Output weights ####################


write.csv(D,"[insert file-path]")
```

8.3 VIALE-C post-hoc multivariate analysis of OS (exploratory)

A *post hoc* stepwise multivariate Cox proportional hazard model was used to assess baseline prognostic factors that may have influenced OS. The results at primary analysis indicated that AML status (*de novo* versus secondary), cytogenetic risk (intermediate versus poor), ECOG performance status (<2 versus ≥2), and age (>75 years versus ≥75 years) were significantly correlated with OS (Table 8.12). After adjusting for these factors, the adjusted HR comparing OS in patients receiving venetoclax plus LDAC with patients receiving LDAC alone was significant (HR: 0.67 [95% CI: 0.47, 0.96]; p=0.03) [40]. This indicates that treatment with venetoclax plus LDAC results in a 33% reduction in the risk of death compared with LDAC alone.

Table 8.12 Post-hoc multivariable analysis of OS data at primary analysis

Covariates	HR (95% CI)	P value
Treatment arm (venetoclax + LDAC versus control)	0.67 (0.47, 0.96)	0.03
Age (<75 versus ≥75)	0.56 (0.37, 0.84)	0.005
AML status (*de novo* versus secondary)	0.59 (0.41, 0.85)	0.004
ECOG performance status (<2 versus ≥2)	0.48 (0.33, 0.70)	<0.001
Cytogenetic risk (intermediate versus poor)	0.57 (0.40, 0.82)	0.003

Abbreviations: AML, acute myeloid leukaemia; ECOG, Eastern Cooperative Oncology Group: HR, hazard ratio; LDAC, low -dose cytarabine: OS, overall survival.
Source: [40]

8.4 VIALE-C safety summary

At 6-month follow-up, a total of 141 patients (99.3%) in the venetoclax plus LDAC arm and 67 patients (98.5%) in the placebo plus LDAC arm experienced at least one AE [40]. As observed in previous studies of AML, the most frequently reported grade 3 or 4 AEs were haematologic in nature and included (venetoclax plus LDAC versus placebo plus LDAC, respectively): febrile neutropenia (32% versus 29%), neutropenia (49% versus 18%) and thrombocytopenia (45% versus 38%) [9]. Serious AEs (any grade) included febrile neutropenia (17% versus 18%) and pneumonia (14% versus 10%); all other SAEs occurred in <10% of patients [9]. TLS occurred in 8 (5.6%) patients in the venetoclax arm and no patients in the placebo arm [40].

Table 8.13 presents a summary of treatment-emergent AEs at primary analysis. Serious AEs (any grade) were reported in 66% and 62% of patients in the venetoclax and placebo arms, respectively [40].

Overall, a similar percentage of patients in both arms had AEs leading to death (33 patients [23%] and 14 patients [21%], respectively) [40].

The 30-day mortality rates were 13% (n = 18) and 16% (n = 11) in the venetoclax plus LDAC and LDAC plus placebo arms, respectively [40].

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At primary analysis, 36 patients (25%) treated with venetoclax plus LDAC and 16 (24%) treated with placebo plus LDAC had AEs leading to treatment discontinuation. Sixty-three percent and 53% of patients in the venetoclax and placebo arms, respectively, had dose interruptions because of AEs; dose reductions because of AEs occurred in 9% and 6% of patients, respectively. The most common AEs (>5% of patients) leading to dose interruption or reduction were (venetoclax plus LDAC vs placebo plus LDAC): neutropenia (18% vs 7%), thrombocytopenia (15% vs 9%), febrile neutropenia (6% vs 7%), and pneumonia (6% vs 7%) [40].[40].

Table 8.13 Summary of treatment emergent AEs across all patients in the VIALE-C trial at primary analysis

AE	No. patients (%)	
	Venetoclax + LDAC n = 142	Placebo + LDAC n = 68
Hematologic AEs (grade ≥3)*		
Thrombocytopenia	64 (45)	25 (37)
Neutropenia	66 (46)	11 (16)
Febrile neutropenia	45 (32)	20 (29)
Anaemia	36 (25)	15 (22)
Non-hematologic AEs (any grade)*		
Nausea	60 (42)	21 (31)
Hypokalaemia	40 (28)	15 (22)
Diarrhoea	40 (28)	11 (16)
Constipation	26 (18)	21 (31)
Vomiting	36 (25)	9 (13)
Pneumonia	29 (20)	11 (16)
Oedema peripheral	19 (13)	14 (21)
Selected key AML serious AEs		
Febrile neutropenia	23 (16)	12 (18)
Pneumonia	18 (13)	7 (10)
Sepsis	8 (6)	4 (6)
Thrombocytopenia	7 (5)	2 (3)
Anaemia	4 (3)	0
Neutropenia	4 (3)	0

Abbreviations: AE, adverse event; AML, acute myeloid leukaemia; LDAC, low-dose cytarabine. *AEs shown were reported in ≥20% of patients in either treatment arm
Source: [40]

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8.5 VIALE-A safety outcomes: absolute difference and relative risk

8.5.1 Additional safety outcomes

The following tables show the AE data yielded from the VIALE-A trial including AE, SAEs, AEs leading to death or discontinuation for venetoclax in combination with azacitidine and azacitidine plus placebo, separated by system organ class where appropriate. Relative risk and risk difference ratios are provided to allow for statistical comparison of the AE rates experienced in each treatment arm.

Table 8.14 Overview of safety in the VIALE-A trial

Patients with:	No. patients (%)		VEN + AZA versus PBO + AZA	
	VEN + AZA (N = 283)	PBO + AZA (N = 144)	Relative risk (95% CI)*	Risk difference (95% CI)*
Any AE	283 (100)	144 (100)		
Any serious AE	235 (83.0)	105 (72.9)	1.14 (1.02, 1.27)	10.12 (1.65, 18.60)
Any AE leading to VEN/PBO or AZA interruption or discontinuation	231 (81.6)	92 (63.9)	1.28 (1.12, 1.46)	17.74 (8.69, 26.79)
Fatal AE (AE leading to death)	64 (22.6)	29 (20.1)	1.12 (0.76, 1.66)	2.48 (-5.69, 10.64)

Abbreviations: AE, adverse event; AZA, azacitidine; CI, confidence interval; PBO, placebo; VEN, venetoclax.
Data are subject to a cut-off date of 4 January 2020.
*Wald confidence limits.
Source: [38]

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Table 8.15 Analysis of most frequent treatment-emergent AEs by system organ class (in ≥5% of patients overall)

MedDRA 21.0 System Organ Class Preferred Term	No. patients (%)		VEN + AZA versus PBO + AZA	
	VEN + AZA (N = 283)	PBO + AZA (N = 144)	Relative risk (95% CI)*	Risk difference (95% CI)*
Any AE	283 (100)	144 (100)		
Blood and lymphatic system disorders	236 (83.4)	100 (69.4)	1.20 (1.06, 1.35)	13.95 (5.26, 22.63)
Thrombocytopenia	130 (45.9)	58 (40.3)	1.14 (0.90, 1.44)	5.66 (-4.23, 15.55)
Neutropenia	119 (42.0)	42 (29.2)	1.44 (1.08, 1.92)	12.88 (3.49, 22.27)
Febrile neutropenia	118 (41.7)	27 (18.8)	2.22 (1.54, 3.21)	22.95 (14.36, 31.53)
Anaemia	78 (27.6)	30 (20.8)	1.32 (0.91, 1.92)	6.73 (-1.70, 15.16)
Leukopenia	58 (20.5)	20 (13.9)	1.48 (0.93, 2.35)	6.61 (-0.74, 13.96)
Cardiac disorders	88 (31.1)	37 (25.7)	1.21 (0.87, 1.68)	5.40 (-3.54, 14.35)
Atrial fibrillation	33 (11.7)	15 (10.4)	1.12 (0.63, 1.99)	1.24 (-4.99, 7.48)
Cardiac failure	15 (5.3)	5 (3.5)	1.53 (0.57, 4.12)	1.83 (-2.14, 5.80)
Tachycardia	9 (3.2)	5 (3.5)	0.92 (0.31, 2.68)	-0.29 (-3.91, 3.33)
Ear and labyrinth disorders	25 (8.8)	5 (3.5)	2.54 (0.99, 6.51)	5.36 (0.90, 9.82)
Vertigo	14 (4.9)	1 (0.7)	7.12 (0.95, 53.64)	4.25 (1.39, 7.12)
Eye disorders	29 (10.2)	15 (10.4)	0.98 (0.55, 1.77)	-0.17 (-6.28, 5.94)
Conjunctival haemorrhage	8 (2.8)	5 (3.5)	0.81 (0.27, 2.44)	-0.65 (-4.20, 2.91)
Gastrointestinal disorders	241 (85.2)	112 (77.8)	1.09 (0.99, 1.21)	7.38 (-0.57, 15.34)
Nausea	124 (43.8)	50 (34.7)	1.26 (0.97, 1.64)	9.09 (-0.60, 18.78)
Constipation	121 (42.8)	56 (38.9)	1.10 (0.86, 1.40)	3.87 (-5.96, 13.70)
Diarrhoea	117 (41.3)	48 (33.3)	1.24 (0.95, 1.62)	8.01 (-1.59, 17.61)
Vomiting	84 (29.7)	33 (22.9)	1.30 (0.91, 1.84)	6.77 (-1.92, 15.45)
Stomatitis	33 (11.7)	8 (5.6)	2.10 (1.00, 4.43)	6.11 (0.82, 11.39)
Abdominal pain	31 (11.0)	12 (8.3)	1.31 (0.70, 2.48)	2.62 (-3.18, 8.42)
Haemorrhoids	28 (9.9)	7 (4.9)	2.04 (0.91, 4.55)	5.03 (0.09, 9.98)
Dyspepsia	19 (6.7)	8 (5.6)	1.21 (0.54, 2.69)	1.16 (-3.59, 5.90)
Abdominal pain upper	16 (5.7)	4 (2.8)	2.04 (0.69, 5.98)	2.88 (-0.92, 6.68)
Mouth ulceration	11 (3.9)	6 (4.2)	0.93 (0.35, 2.47)	-0.28 (-4.24, 3.69)
Abdominal distension	8 (2.8)	6 (4.2)	0.68 (0.24, 1.92)	-1.34 (-5.13, 2.45)
Proctalgia	8 (2.8)	4 (2.8)	1.02 (0.31, 3.32)	0.05 (-3.26, 3.36)
Mouth haemorrhage	5 (1.8)	5 (3.5)	0.51 (0.15, 1.73)	-1.71 (-5.07, 1.66)

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General disorders and administration site conditions	195 (68.9)	95 (66.0)	1.04 (0.91, 1.20)	2.93 (-6.50, 12.36)
Oedema peripheral	69 (24.4)	26 (18.1)	1.35 (0.90, 2.02)	6.33 (-1.70, 14.36)
Pyrexia	66 (23.3)	32 (22.2)	1.05 (0.72, 1.52)	1.10 (-7.29, 9.49)
Fatigue	59 (20.8)	24 (16.7)	1.25 (0.81, 1.92)	4.18 (-3.53, 11.89)
Asthenia	44 (15.5)	12 (8.3)	1.87 (1.02, 3.42)	7.21 (1.03, 13.40)
Injection site erythema	17 (6.0)	10 (6.9)	0.87 (0.41, 1.84)	-0.94 (-5.93, 4.05)
Pain	16 (5.7)	4 (2.8)	2.04 (0.69, 5.98)	2.88 (-0.92, 6.68)
Malaise	15 (5.3)	2 (1.4)	3.82 (0.88, 16.46)	3.91 (0.68, 7.15)
Injection site reaction	13 (4.6)	10 (6.9)	0.66 (0.30, 1.47)	-2.35 (-7.17, 2.46)
Chills	11 (3.9)	2 (1.4)	2.80 (0.63, 12.46)	2.50 (-0.46, 5.45)
Non-cardiac chest pain	11 (3.9)	2 (1.4)	2.80 (0.63, 12.46)	2.50 (-0.46, 5.45)
Chest discomfort	8 (2.8)	2 (1.4)	2.04 (0.44, 9.46)	1.44 (-1.28, 4.16)
Chest pain	8 (2.8)	4 (2.8)	1.02 (0.31, 3.32)	0.05 (-3.26, 3.36)
Injection site pain	8 (2.8)	4 (2.8)	1.02 (0.31, 3.32)	0.05 (-3.26, 3.36)
Hepatobiliary disorders	35 (12.4)	6 (4.2)	2.97 (1.28, 6.89)	8.20 (3.16, 13.24)
Hyperbilirubinaemia	9 (3.2)	3 (2.1)	1.53 (0.42, 5.55)	1.10 (-2.00, 4.20)
Infections and infestations	239 (84.5)	97 (67.4)	1.25 (1.11, 1.42)	17.09 (8.35, 25.84)
Pneumonia	65 (23.0)	39 (27.1)	0.85 (0.60, 1.19)	-4.12 (-12.87, 4.64)
Upper respiratory tract infection	26 (9.2)	13 (9.0)	1.02 (0.54, 1.92)	0.16 (-5.61, 5.92)
Urinary tract infection	26 (9.2)	11 (7.6)	1.20 (0.61, 2.36)	1.55 (-3.94, 7.04)
Lung infection	19 (6.7)	4 (2.8)	2.42 (0.84, 6.97)	3.94 (-0.03, 7.90)
Sepsis	18 (6.4)	13 (9.0)	0.70 (0.36, 1.40)	-2.67 (-8.14, 2.81)
Oral herpes	17 (6.0)	6 (4.2)	1.44 (0.58, 3.58)	1.84 (-2.44, 6.12)
Cellulitis	16 (5.7)	8 (5.6)	1.02 (0.45, 2.32)	0.10 (-4.51, 4.71)
Oral candidiasis	16 (5.7)	5 (3.5)	1.63 (0.61, 4.36)	2.18 (-1.84, 6.20)
Bronchitis	15 (5.3)	4 (2.8)	1.91 (0.65, 5.64)	2.52 (-1.22, 6.27)
Influenza	13 (4.6)	6 (4.2)	1.10 (0.43, 2.84)	0.43 (-3.65, 4.50)
Injury, poisoning and procedural complications	83 (29.3)	42 (29.2)	1.01 (0.74, 1.37)	0.16 (-8.96, 9.29)
Fall	28 (9.9)	10 (6.9)	1.42 (0.71, 2.85)	2.95 (-2.47, 8.37)
Transfusion reaction	13 (4.6)	6 (4.2)	1.10 (0.43, 2.84)	0.43 (-3.65, 4.50)
Contusion	10 (3.5)	12 (8.3)	0.42 (0.19, 0.96)	-4.80 (-9.80, 0.20)
Procedural pain	5 (1.8)	5 (3.5)	0.51 (0.15, 1.73)	-1.71 (-5.07, 1.66)
Investigations	136 (48.1)	56 (38.9)	1.24 (0.97, 1.57)	9.17 (-0.70, 19.03)
Weight decreased	37 (13.1)	14 (9.7)	1.34 (0.75, 2.41)	3.35 (-2.88, 9.58)
Alanine aminotransferase increased	21 (7.4)	12 (8.3)	0.89 (0.45, 1.76)	-0.91 (-6.36, 4.54)

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Aspartate aminotransferase increased	21 (7.4)	13 (9.0)	0.82 (0.42, 1.59)	-1.61 (-7.20, 3.98)
Blood bilirubin increased	21 (7.4)	5 (3.5)	2.14 (0.82, 5.55)	3.95 (-0.33, 8.22)
C-reactive protein increased	17 (6.0)	5 (3.5)	1.73 (0.65, 4.59)	2.53 (-1.54, 6.61)
Blood alkaline phosphatase increased	14 (4.9)	4 (2.8)	1.78 (0.60, 5.31)	2.17 (-1.52, 5.86)
Blood creatinine increased	14 (4.9)	8 (5.6)	0.89 (0.38, 2.07)	-0.61 (-5.12, 3.91)
Platelet count decreased	13 (4.6)	1 (0.7)	6.61 (0.87, 50.07)	3.90 (1.11, 6.69)
White blood cell count decreased	11 (3.9)	2 (1.4)	2.80 (0.63, 12.46)	2.50 (-0.46, 5.45)
Metabolism and nutrition disorders	175 (61.8)	79 (54.9)	1.13 (0.95, 1.34)	6.98 (-2.93, 16.88)
Hypokalaemia	81 (28.6)	41 (28.5)	1.01 (0.73, 1.38)	0.15 (-8.91, 9.21)
Decreased appetite	72 (25.4)	25 (17.4)	1.47 (0.97, 2.20)	8.08 (0.08, 16.08)
Hypophosphataemia	35 (12.4)	17 (11.8)	1.05 (0.61, 1.80)	0.56 (-5.96, 7.08)
Hypoalbuminaemia	22 (7.8)	13 (9.0)	0.86 (0.45, 1.66)	-1.25 (-6.88, 4.37)
Hypomagnesaemia	21 (7.4)	5 (3.5)	2.14 (0.82, 5.55)	3.95 (-0.33, 8.22)
Hypocalcaemia	17 (6.0)	8 (5.6)	1.08 (0.48, 2.45)	0.45 (-4.20, 5.11)
Hyponatraemia	16 (5.7)	7 (4.9)	1.16 (0.49, 2.76)	0.79 (-3.63, 5.22)
Hyperkalaemia	13 (4.6)	4 (2.8)	1.65 (0.55, 4.98)	1.82 (-1.81, 5.44)
Hyperglycaemia	11 (3.9)	6 (4.2)	0.93 (0.35, 2.47)	-0.28 (-4.24, 3.69)
Hyperuricaemia	9 (3.2)	5 (3.5)	0.92 (0.31, 2.68)	-0.29 (-3.91, 3.33)
Fluid overload	7 (2.5)	4 (2.8)	0.89 (0.27, 2.99)	-0.30 (-3.54, 2.93)
Musculoskeletal and connective tissue disorders	110 (38.9)	50 (34.7)	1.12 (0.86, 1.46)	4.15 (-5.48, 13.78)
Arthralgia	33 (11.7)	7 (4.9)	2.40 (1.09, 5.29)	6.80 (1.67, 11.93)
Back pain	24 (8.5)	13 (9.0)	0.94 (0.49, 1.79)	-0.55 (-6.24, 5.15)
Pain in extremity	22 (7.8)	14 (9.7)	0.80 (0.42, 1.52)	-1.95 (-7.71, 3.81)
Musculoskeletal pain	18 (6.4)	5 (3.5)	1.83 (0.69, 4.83)	2.89 (-1.24, 7.01)
Muscular weakness	12 (4.2)	3 (2.1)	2.04 (0.58, 7.10)	2.16 (-1.15, 5.47)
Myalgia	12 (4.2)	2 (1.4)	3.05 (0.69, 13.46)	2.85 (-0.18, 5.88)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	18 (6.4)	9 (6.3)	1.02 (0.47, 2.21)	0.11 (-4.76, 4.98)
Malignant neoplasm progression	4 (1.4)	6 (4.2)	0.34 (0.10, 1.18)	-2.75 (-6.29, 0.79)
Nervous system disorders	107 (37.8)	39 (27.1)	1.40 (1.03, 1.90)	10.73 (1.53, 19.92)
Dizziness	37 (13.1)	10 (6.9)	1.88 (0.96, 3.68)	6.13 (0.41, 11.85)
Headache	30 (10.6)	10 (6.9)	1.53 (0.77, 3.03)	3.66 (-1.83, 9.14)
Dysgeusia	11 (3.9)	3 (2.1)	1.87 (0.53, 6.58)	1.80 (-1.44, 5.05)
Psychiatric disorders	71 (25.1)	37 (25.7)	0.98 (0.69, 1.38)	-0.61 (-9.35, 8.14)
Insomnia	35 (12.4)	15 (10.4)	1.19 (0.67, 2.10)	1.95 (-4.34, 8.24)

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Confusional state	15 (5.3)	5 (3.5)	1.53 (0.57, 4.12)	1.83 (-2.14, 5.80)
Anxiety	13 (4.6)	3 (2.1)	2.20 (0.64, 7.61)	2.51 (-0.86, 5.89)
Delirium	9 (3.2)	3 (2.1)	1.53 (0.42, 5.55)	1.10 (-2.00, 4.20)
Renal and urinary disorders	71 (25.1)	33 (22.9)	1.09 (0.76, 1.57)	2.17 (-6.35, 10.69)
Acute kidney injury	25 (8.8)	13 (9.0)	0.98 (0.52, 1.85)	-0.19 (-5.92, 5.54)
Urinary retention	11 (3.9)	1 (0.7)	5.60 (0.73, 42.93)	3.19 (0.56, 5.82)
Haematuria	10 (3.5)	5 (3.5)	1.02 (0.35, 2.92)	0.06 (-3.62, 3.74)
Pollakiuria	9 (3.2)	5 (3.5)	0.92 (0.31, 2.68)	-0.29 (-3.91, 3.33)
Reproductive system and breast disorders	17 (6.0)	4 (2.8)	2.16 (0.74, 6.31)	3.23 (-0.63, 7.09)
Respiratory, thoracic and mediastinal disorders	138 (48.8)	60 (41.7)	1.17 (0.93, 1.47)	7.10 (-2.84, 17.03)
Dyspnoea	37 (13.1)	11 (7.6)	1.71 (0.90, 3.25)	5.44 (-0.42, 11.29)
Cough	35 (12.4)	20 (13.9)	0.89 (0.53, 1.49)	-1.52 (-8.35, 5.31)
Pleural effusion	28 (9.9)	8 (5.6)	1.78 (0.83, 3.81)	4.34 (-0.77, 9.45)
Epistaxis	26 (9.2)	12 (8.3)	1.10 (0.57, 2.12)	0.85 (-4.78, 6.48)
Oropharyngeal pain	25 (8.8)	6 (4.2)	2.12 (0.89, 5.05)	4.67 (0.02, 9.31)
Dyspnoea exertional	12 (4.2)	2 (1.4)	3.05 (0.69, 13.46)	2.85 (-0.18, 5.88)
Haemoptysis	8 (2.8)	4 (2.8)	1.02 (0.31, 3.32)	0.05 (-3.26, 3.36)
Skin and subcutaneous tissue disorders	137 (48.4)	51 (35.4)	1.37 (1.06, 1.76)	12.99 (3.25, 22.74)
Pruritus	28 (9.9)	6 (4.2)	2.37 (1.01, 5.60)	5.73 (0.96, 10.50)
Rash	26 (9.2)	9 (6.3)	1.47 (0.71, 3.05)	2.94 (-2.25, 8.13)
Rash maculo-papular	23 (8.1)	4 (2.8)	2.93 (1.03, 8.30)	5.35 (1.19, 9.51)
Petechiae	17 (6.0)	8 (5.6)	1.08 (0.48, 2.45)	0.45 (-4.20, 5.11)
Dry skin	16 (5.7)	3 (2.1)	2.71 (0.80, 9.16)	3.57 (0.01, 7.13)
Erythema	15 (5.3)	5 (3.5)	1.53 (0.57, 4.12)	1.83 (-2.14, 5.80)
Pruritus generalised	4 (1.4)	6 (4.2)	0.34 (0.10, 1.18)	-2.75 (-6.29, 0.79)
Vascular disorders	85 (30.0)	37 (25.7)	1.17 (0.84, 1.63)	4.34 (-4.57, 13.25)
Hypotension	28 (9.9)	9 (6.3)	1.58 (0.77, 3.26)	3.64 (-1.62, 8.91)
Hypertension	26 (9.2)	12 (8.3)	1.10 (0.57, 2.12)	0.85 (-4.78, 6.48)
Haematoma	16 (5.7)	8 (5.6)	1.02 (0.45, 2.32)	0.10 (-4.51, 4.71)

Abbreviations: AE, adverse event; AZA, azacitidine; CI, confidence interval; PBO, placebo; VEN, venetoclax.
Data are subject to a cut-off date of 4 January 2020.
*Wald confidence limits.
Source: [38]

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Table 8.16 VIALE-A: Analysis of most frequent treatment-emergent serious AEs by system organ class (in ≥3% of patients overall)

MedDRA 21.0 System Organ Class Preferred term	No. patients, (%)		VEN + AZA versus PBO + AZA	
	VEN + AZA (N = 283)	PBO + AZA (N = 144)	Relative risk (95% CI)*	Risk difference (95% CI)*
Any AE	235 (83.0)	105 (72.9)	1.14 (1.02, 1.27)	10.12 (1.65, 18.60)
Blood and lymphatic system disorders	113 (39.9)	24 (16.7)	2.40 (1.62, 3.55)	23.26 (14.92, 31.61)
Febrile neutropenia	84 (29.7)	15 (10.4)	2.85 (1.71, 4.75)	19.27 (11.97, 26.56)
Anaemia	14 (4.9)	6 (4.2)	1.19 (0.47, 3.02)	0.78 (-3.35, 4.91)
Neutropenia	13 (4.6)	3 (2.1)	2.20 (0.64, 7.61)	2.51 (-0.86, 5.89)
Thrombocytopenia	12 (4.2)	2 (1.4)	3.05 (0.69, 13.46)	2.85 (-0.18, 5.88)
Cardiac disorders	38 (13.4)	14 (9.7)	1.38 (0.77, 2.46)	3.71 (-2.56, 9.97)
Atrial fibrillation	13 (4.6)	2 (1.4)	3.31 (0.76, 14.46)	3.20 (0.11, 6.30)
Cardiac failure	6 (2.1)	3 (2.1)	1.02 (0.26, 4.01)	0.04 (-2.84, 2.91)
Gastrointestinal disorders	32 (11.3)	14 (9.7)	1.16 (0.64, 2.11)	1.59 (-4.50, 7.67)
Diarrhoea	6 (2.1)	2 (1.4)	1.53 (0.31, 7.47)	0.73 (-1.81, 3.27)
General disorders and administration site conditions	31 (11.0)	17 (11.8)	0.93 (0.53, 1.62)	-0.85 (-7.26, 5.55)
Pyrexia	7 (2.5)	3 (2.1)	1.19 (0.31, 4.52)	0.39 (-2.56, 3.34)
Death	4 (1.4)	2 (1.4)	1.02 (0.19, 5.49)	0.02 (-2.33, 2.38)
General physical health deterioration	3 (1.1)	4 (2.8)	0.38 (0.09, 1.68)	-1.72 (-4.66, 1.22)
Infections and infestations	162 (57.2)	63 (43.8)	1.31 (1.06, 1.62)	13.49 (3.55, 23.44)
Pneumonia	47 (16.6)	32 (22.2)	0.75 (0.50, 1.12)	-5.61 (-13.67, 2.44)
Sepsis	16 (5.7)	12 (8.3)	0.68 (0.33, 1.40)	-2.68 (-7.93, 2.58)
Escherichia sepsis	8 (2.8)	2 (1.4)	2.04 (0.44, 9.46)	1.44 (-1.28, 4.16)
Influenza	8 (2.8)	2 (1.4)	2.04 (0.44, 9.46)	1.44 (-1.28, 4.16)
Lung infection	8 (2.8)	3 (2.1)	1.36 (0.37, 5.04)	0.74 (-2.28, 3.77)
Septic shock	7 (2.5)	1 (0.7)	3.56 (0.44, 28.67)	1.78 (-0.48, 4.04)
Urinary tract infection	7 (2.5)	3 (2.1)	1.19 (0.31, 4.52)	0.39 (-2.56, 3.34)
Injury, poisoning and procedural complications	8 (2.8)	8 (5.6)	0.51 (0.19, 1.33)	-2.73 (-6.94, 1.48)
Investigations	10 (3.5)	4 (2.8)	1.27 (0.41, 3.99)	0.76 (-2.68, 4.20)
Metabolism and nutrition disorders	9 (3.2)	6 (4.2)	0.76 (0.28, 2.10)	-0.99 (-4.84, 2.86)
Musculoskeletal and connective tissue disorders	5 (1.8)	1 (0.7)	2.54 (0.30, 21.57)	1.07 (-0.98, 3.12)
Neoplasms benign, malignant and unspecified (inc. cysts and polyps)	6 (2.1)	7 (4.9)	0.44 (0.15, 1.27)	-2.74 (-6.63, 1.15)
Malignant neoplasm progression	2 (0.7)	5 (3.5)	0.20 (0.04, 1.04)	-2.77 (-5.91, 0.38)

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Nervous system disorders	21 (7.4)	6 (4.2)	1.78 (0.74, 4.31)	3.25 (-1.22, 7.72)
Psychiatric disorders	6 (2.1)	1 (0.7)	3.05 (0.37, 25.12)	1.43 (-0.73, 3.58)
Renal and urinary disorders	13 (4.6)	8 (5.6)	0.83 (0.35, 1.95)	-0.96 (-5.43, 3.50)
Acute kidney injury	5 (1.8)	5 (3.5)	0.51 (0.15, 1.73)	-1.71 (-5.07, 1.66)
Respiratory, thoracic and mediastinal disorders	23 (8.1)	10 (6.9)	1.17 (0.57, 2.39)	1.18 (-4.05, 6.41)
Vascular disorders	10 (3.5)	5 (3.5)	1.02 (0.35, 2.92)	0.06 (-3.62, 3.74)
Hypotension	5 (1.8)	2 (1.4)	1.27 (0.25, 6.48)	0.38 (-2.07, 2.83)

Abbreviations: AE, adverse event; AZA, azacitidine; CI, confidence interval; PBO, placebo; VEN, venetoclax.
Data are subject to a cut-off date of 4 January 2020.
*Wald confidence limits.
Source: [38]

Table 8.17 VIALE-A: Analysis of treatment-emergent AEs leading to death by system organ class and preferred term

MedDRA 21.0 System Organ Class Preferred Term	No. patients (%)		VEN + AZA versus PBO + AZA	
	VEN + AZA (N = 283)	PBO + AZA (N = 144)	Relative risk (95% CI)*	Risk difference (95% CI)*
Any AE	64 (22.6)	29 (20.1)	1.12 (0.76, 1.66)	2.48 (-5.69, 10.64)
Cardiac disorders	8 (2.8)	6 (4.2)	0.68 (0.24, 1.92)	-1.34 (-5.13, 2.45)
Cardiac arrest	3 (1.1)	2 (1.4)	0.76 (0.13, 4.52)	-0.33 (-2.58, 1.92)
Atrial fibrillation	2 (0.7)	0		0.71 (-0.27, 1.68)
Gastrointestinal disorders	2 (0.7)	0		0.71 (-0.27, 1.68)
General disorders and administration site conditions	9 (3.2)	7 (4.9)	0.65 (0.25, 1.72)	-1.68 (-5.75, 2.38)
Death	4 (1.4)	2 (1.4)	1.02 (0.19, 5.49)	0.02 (-2.33, 2.38)
Multiple organ dysfunction syndrome	2 (0.7)	1 (0.7)	1.02 (0.09, 11.13)	0.01 (-1.66, 1.68)
Systemic inflammatory response syndrome	2 (0.7)	1 (0.7)	1.02 (0.09, 11.13)	0.01 (-1.66, 1.68)
General physical health deterioration	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)
Infections and infestations	26 (9.2)	11 (7.6)	1.20 (0.61, 2.36)	1.55 (-3.94, 7.04)
Pneumonia	11 (3.9)	3 (2.1)	1.87 (0.53, 6.58)	1.80 (-1.44, 5.05)
Sepsis	6 (2.1)	5 (3.5)	0.61 (0.19, 1.97)	-1.35 (-4.78, 2.08)
Septic shock	3 (1.1)	1 (0.7)	1.53 (0.16, 14.54)	0.37 (-1.44, 2.17)
Klebsiella infection	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)
Metabolism and nutrition disorders	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)
Nervous system disorders	10 (3.5)	1 (0.7)	5.09 (0.66, 39.36)	2.84 (0.30, 5.38)
Haemorrhage intracranial	3 (1.1)	0		1.06 (-0.13, 2.25)

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Cerebral haemorrhage	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)
Renal and urinary disorders	2 (0.7)	0		0.71 (-0.27, 1.68)
Renal failure	2 (0.7)	0		0.71 (-0.27, 1.68)
Respiratory, thoracic and mediastinal disorders	5 (1.8)	3 (2.1)	0.85 (0.21, 3.50)	-0.32 (-3.11, 2.48)
Respiratory failure	3 (1.1)	0		1.06 (-0.13, 2.25)
Acute respiratory distress syndrome	1 (0.4)	0		0.35 (-0.34, 1.04)
Acute respiratory failure	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)
Vascular disorders	1 (0.4)	1 (0.7)	0.51 (0.03, 8.08)	-0.34 (-1.86, 1.18)

Abbreviations: AE, adverse event; AZA, azacitidine; CI, confidence interval; PBO, placebo; VEN, venetoclax.
Data are subject to a cut-off date of 4 January 2020.
*Wald confidence limits.
Source: [38]

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8.6 Propensity score matching results for venetoclax plus azacitidine versus LDAC: sensitivity analyses

8.6.1 Sensitivity analysis – overall population

A sensitivity analysis was conducted that included all patients enrolled in the LDAC arm in VIALE-C, regardless of whether they had prior HMA use or favourable cytogenetic risk. After weighting, all baseline characteristics included in the propensity score model were balanced between the two treatment arms (Table 8.18) [42].

Table 8.18 Sensitivity analysis, overall population – Baseline characteristics for LDAC and venetoclax + AZA before and after weighting

Baseline characteristics	Before weighting				After weighting			
	LDAC N = 50	VEN + AZA N = 206	Standardized mean difference	P value	LDAC N = 50	VEN + AZA N = 206	Standardized mean difference	P value
Age <75	40.91%	38.95%	0.040	0.877	37.68%	39.28%	0.033	0.812
Female	40.91%	40.00%	0.019	1.000	39.37%	40.14%	0.016	0.911
Race: white	69.70%	75.79%	0.137	0.385	73.76%	74.55%	0.018	0.893
Secondary AML	33.33%	25.26%	0.178	0.238	25.80%	26.73%	0.021	0.872
AML with MRC	39.39%	32.28%	0.149	0.338	32.54%	33.57%	0.022	0.871
Antecedent hematological history of MDS	24.24%	17.19%	0.175	0.249	18.78%	18.58%	0.005	0.969
ECOG PS <2	50.00%	55.09%	0.102	0.542	52.78%	53.98%	0.024	0.863
IVRS cytogenetic risk: poor	30.30%	34.74%	0.095	0.588	34.06%	33.87%	0.004	0.979
Bone marrow blast count	50.99 ± 23.09	52.04 ± 24.26	0.044	0.750	53.32 ± 23.91	51.94 ± 24.21	0.057	0.688

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; IVRS, interactive voice recognition system; LDAC, low -dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; VEN, venetoclax.
[a]2 patients were removed from the analysis due to missingness in cytogenetic risk. 1 patient was removed due to missingness in bone marrow blast count.
[b]Categorical outcomes were compared using a chi-squared test, and continuous outcomes with an ANOVA
Source: [42]

Sensitivity analysis results: overall population – OS

Before weighting, OS was significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.69 months [95% CI: 11.53, 18.69]) compared with patients treated with LDAC (median OS: 4.11 months [95% CI: 3.06, 7.85]; p<0.001; HR: 0.44, 95% CI: [0.32, 0.61]; [42].

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Figure 8.6, Table 8.19) [42]. After weighting, OS was still significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.69 months [95% CI: 12.19, 19.25]) compared with patients treated with LDAC (median OS: 5.72 months [95% CI: 3.15, 9.82]; p<0.001; HR: 0.47, 95% CI: [0.34, 0.66];[42].

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Figure 8.6, Table 8.19) [42].

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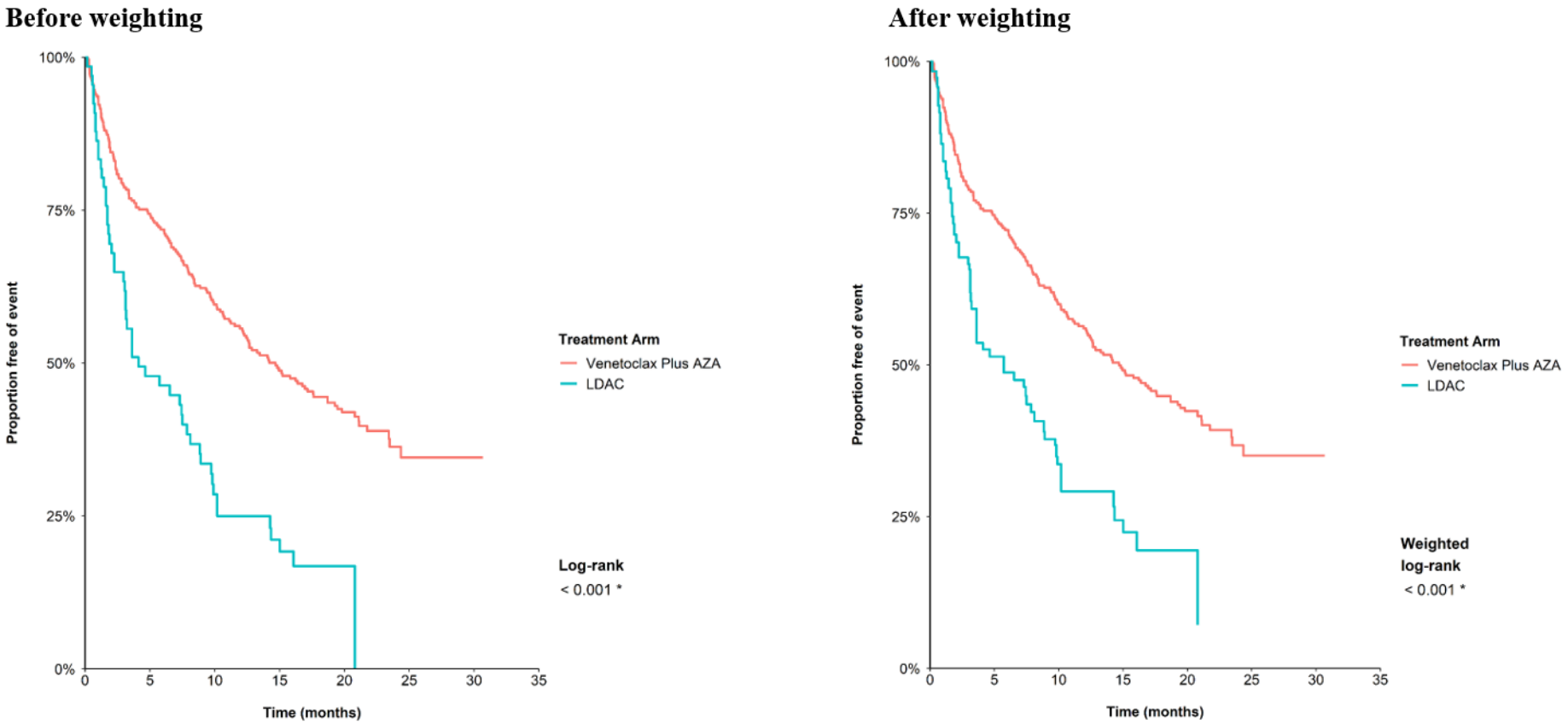
Figure 8.6 Sensitivity analysis, overall population – OS before and after weighting



Abbreviations: AZA, azacitidine; LDAC, low-dose cytarabine; OS, overall survival.
Source: [42]

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Table 8.19 Sensitivity analysis, overall population – summary statistics of OS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value
LDAC	66	53	4.11 (3.06, 7.85)	Reference	-	5.72 (3.15, 9.82)	Reference	-
Venetoclax + azacitidine	285	161	14.69 (11.53, 18.69)	0.44 (0.32, 0.61)	<0.001*	14.69 (12.19, 19.25)	0.47 (0.34, 0.66)	<0.001*

Abbreviations: CI, confidence interval; HR, hazard ratio; LDAC, low -dose cytarabine; OS, overall survival.
*denotes statistical significance at the level of 0.05.
Source: [42]

Sensitivity analysis results: overall population – EFS

Before weighting, venetoclax + AZA was associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.66 months [95% CI: 8.41, 11.53]) compared with LDAC (median time to event: 2.12 months [95% CI:1.54, 3.15]; log-rank p<0.001; HR: 0.37, 95% CI: [0.27, 0.50]; Figure 8.7,Table 8.20). After weighting, venetoclax plus azacitidine was still associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.89 months [95% CI: 8.54, 12.12]) compared with LDAC (median time to event: 2.23 months [95% CI: 1.61, 5.72]; p<0.001; HR: 0.38 [95% CI: 0.28, 0.53]; Figure 8.7, Table 8.20) [42].

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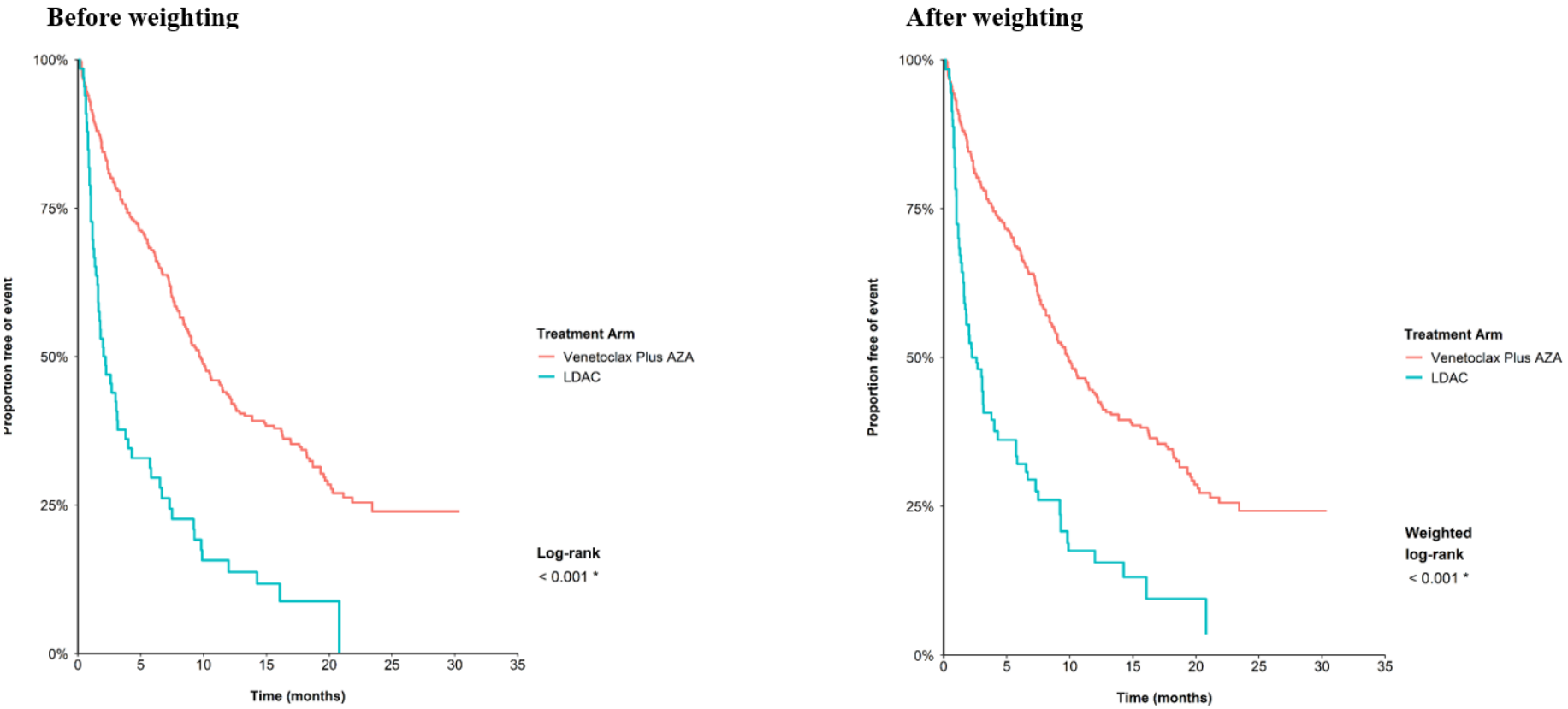
Figure 8.7 Sensitivity analysis, overall population – EFS before and after weighting



Abbreviations: AZA, azacitidine; EFS, event-free survival; LDAC, low-dose cytarabine.
Source: [42]

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Table 8.20 Sensitivity analysis, overall population – summary statistics of EFS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median EFS (95% CI)	HR (95% CI)	P value	Median EFS (95% CI)	HR (95% CI)	P value
LDAC	66	58	2.12 (1.54, 3.15)	Reference	-	2.23 (1.61, 5.72)	Reference	-
Venetoclax + azacitidine	285	190	9.66 (8.41, 11.53)	0.37 (0.27, 0.50)	<0.001*	9.89 (8.54, 12.12)	0.38 (0.28, 0.53)	<0.001*

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; LDAC, low-dose cytarabine.
*Denotes statistical significance at the level of 0.05.
Source: [42]

Sensitivity analysis results: overall population – CR + CRi

Compared with patients treated with LDAC, those treated with venetoclax plus azacitidine were more likely to achieve CR (OR: 7.12 [95% CI: 2.77, 18.27]), CRi (OR: 6.48 [95% CI: 2.28, 18.38]), and CR + CRi (OR: 12.47 [95% CI: 5.92, 26.26]) before weighting (Table 8.21). After weighting, patients treated with venetoclax plus azacitidine were still more likely to achieve CR (OR: 6.02 [95% CI: 2.32, 15.60]), CRi (OR: 5.62 [95% CI: 1.89, 16.73]), and CR + CRi (OR: 10.52 [95% CI: 4.90, 22.58]) than those treated with LDAC (Table 8.21) [42].

Table 8.21 Sensitivity analysis, overall population – comparison of CR, CRi, and CR + CRi for venetoclax + azacitidine versus LDAC before and after weighting

	Before weighting				After weighting			
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR VEN + AZA versus LDAC	P value	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR VEN + AZA versus LDAC	P value
CR	0.37 (0.31, 0.43)	0.08 (0.03, 0.17)	7.12 (2.77, 18.27)	<0.001*	0.37 (0.31, 0.43)	0.09 (0.04, 0.20)	6.02 (2.32, 15.60)	<0.001*
CRi	0.29 (0.24, 0.35)	0.06 (0.02, 0.15)	6.48 (2.28, 18.38)	<0.001*	0.29 (0.24, 0.35)	0.07 (0.03, 0.18)	5.62 (1.89, 16.73)	<0.01*
CR + CRi	0.66 (0.61, 0.72)	0.14 (0.07, 0.24)	12.47 (5.92, 26.26)	<0.001*	0.66 (0.61, 0.72)	0.16 (0.08, 0.28)	10.52 (4.90, 22.58)	<0.001*

Abbreviations: AZA, azacitidine, CI, confidence interval; CR, complete response; CRi, complete response with incomplete blood count recovery; LDAC, low-dose cytarabine; OR, odds ratio; VEN, venetoclax.
*Denotes statistical significance at the level of 0.05.
Source: [42]

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8.6.2 Sensitivity analysis – AML patients with >30% bone marrow blasts

As a sensitivity analysis, all patients with bone marrow blast count greater than 30% enrolled in the LDAC arm in VIALE-C (regardless of whether they had prior HMA use or favourable cytogenetic risk) were included in the analysis. After weighting, all baseline characteristics included in the propensity score model were balanced between the two treatment arms (Table 8.22) [42].

Table 8.22 Sensitivity analysis, patients with >30% bone marrow blasts – baseline characteristics for LDAC and venetoclax + azacitidine before and after weighting

Baseline characteristics	Before weighting				After weighting			
	LDAC N = 50	VEN + AZA N = 206	Standardized mean difference	P value	LDAC N = 50	VEN + AZA N = 206	Standardized mean difference	P value
Age <75	44.00%	37.86%	0.125	0.525	35.92%	38.91%	0.062	0.700
Female	36.00%	39.32%	0.069	0.787	36.49%	38.51%	0.042	0.804
Race: White	68.00%	74.27%	0.139	0.472	72.79%	72.92%	0.003	0.985
Secondary AML	34.00%	23.79%	0.227	0.193	24.04%	25.63%	0.037	0.808
AML with MRC	38.00%	26.70%	0.243	0.159	27.92%	28.87%	0.021	0.891
Antecedent hematological history of MDS	24.00%	16.99%	0.174	0.345	18.10%	18.41%	0.008	0.958
ECOG performance status <2	48.00%	55.34%	0.147	0.438	53.60%	53.79%	0.004	0.982
IVRS cytogenetic risk: poor	32.00%	32.04%	0.001	1.000	32.88%	32.09%	0.017	0.920
Bone marrow blast count	59.84 ± 19.25	62.78 ± 19.75	0.151	0.344	63.61 ± 18.91	62.31 ± 19.71	0.067	0.675

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; ECOG, Eastern Cooperative Oncology Group; IVRS, interactive voice recognition system; LDAC, low-dose cytarabine; MDS, myelodysplastic syndrome; MRC, myelodysplasia related changes; VEN, venetoclax.
[a]2 patients were removed from the analysis due to missingness in cytogenetic risk.
[b]Categorical outcomes were compared using a chi-squared test, and continuous outcomes with an ANOVA.
Source: [42]

Sensitivity analysis results: AML patients with >30% bone marrow blasts – OS

Before weighting, OS was significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.06 months [95% CI: 10.41, 16.95]) compared with patients treated with LDAC (median OS: 3.61 months [95% CI: 2.23, 7.29]; p<0.001; HR: 0.42 [95% CI: 0.29, 0.60]; Figure 8.8, Table 8.23). After weighting, OS was still significantly prolonged for patients treated with venetoclax plus azacitidine (median OS: 14.06 months [95% CI: 10.64, 17.15]) compared with patients treated with LDAC (median OS: 4.11 months [95% CI: 3.12, 10.18]; p<0.001; HR: 0.48 [95% CI: 0.33, 0.70]; Figure 8.8, Table 8.23) [42].

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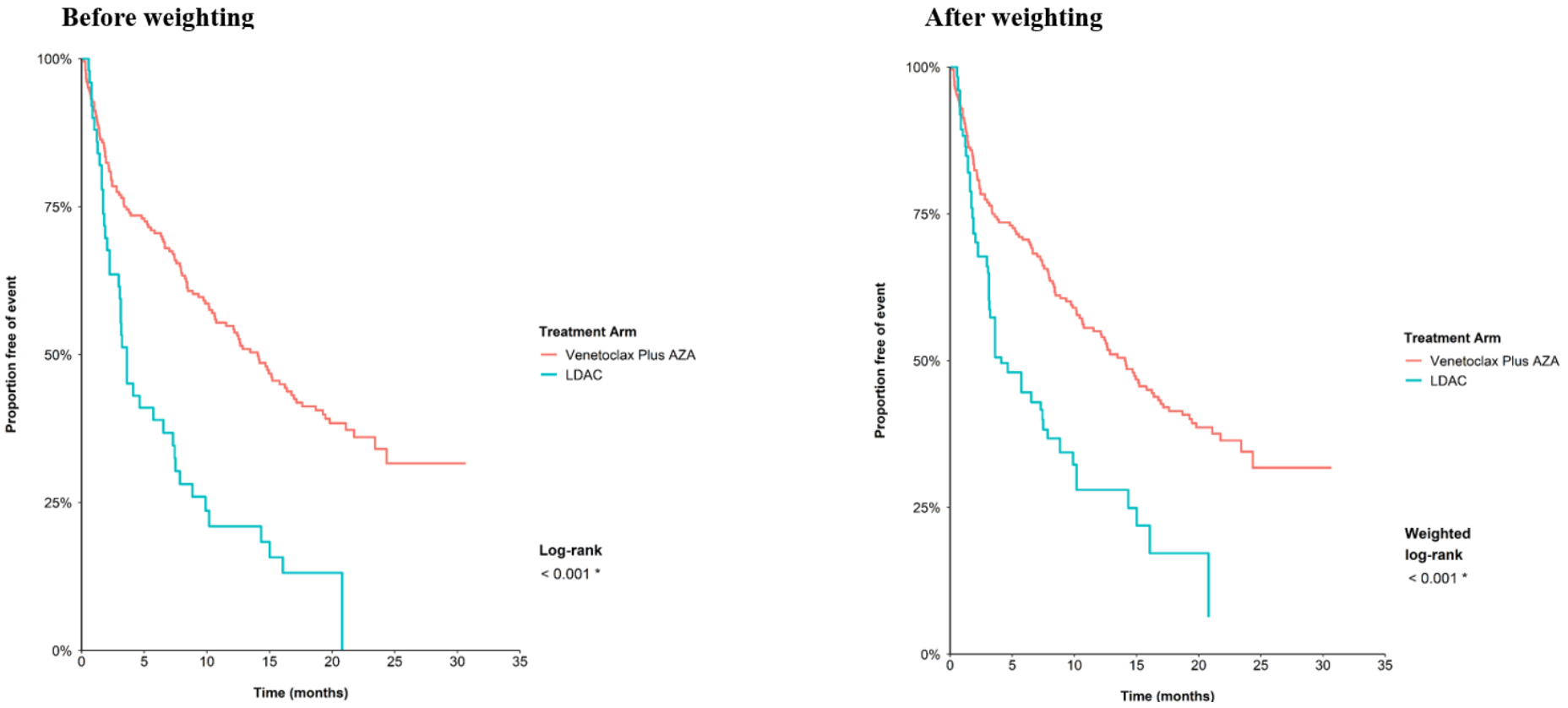
Figure 8.8 Sensitivity analysis, patients with >30% bone marrow blasts – OS before and after weighting



Abbreviations: AZA, azacitidine; LDAC, low-dose cytarabine; OS, overall survival.
Source: [42]

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Table 8.23 Sensitivity analysis, patients with >30% bone marrow blasts – summary statistics of OS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median OS (95% CI)	HR (95% CI)	P value	Median OS (95% CI)	HR (95% CI)	P value
LDAC	50	42	3.61 (2.23, 7.29)	Reference	-	4.11 (3.12, 10.18)	Reference	-
Venetoclax + azacitidine	206	121	14.06 (10.41, 16.95)	0.42 (0.29, 0.60)	<0.001*	14.06 (10.64, 17.15)	0.48 (0.33, 0.70)	<0.001*

Abbreviations: CI, confidence intervals; HR, hazard ratio; LDAC, low -dose cytarabine; OS, overall survival.
*Denotes statistical significance at the level of 0.05.
Source: [42]

Sensitivity analysis results: AML patients with >30% bone marrow blasts – EFS

Before weighting, venetoclax plus azacitidine was associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.00 months [95% CI: 7.59, 11.50]) compared with LDAC (median time to event: 2.12 months [95% CI: 1.54, 3.12]; p<0.001; HR: 0.35 [95% CI: 0.25, 0.50]; Figure 8.9,Table 8.24). After weighting, venetoclax plus azacitidine was still associated with a significantly lower risk of disease progression, relapse, treatment failure, or death (median time to event: 9.30 months [95% CI: 7.69, 11.83]) compared with LDAC (median time to event: 2.60 months [95% CI: 1.61, 5.82]; p<0.001; HR: 0.39 [95% CI: 0.27, 0.55]; Figure 8.9,Table 8.24) [42].

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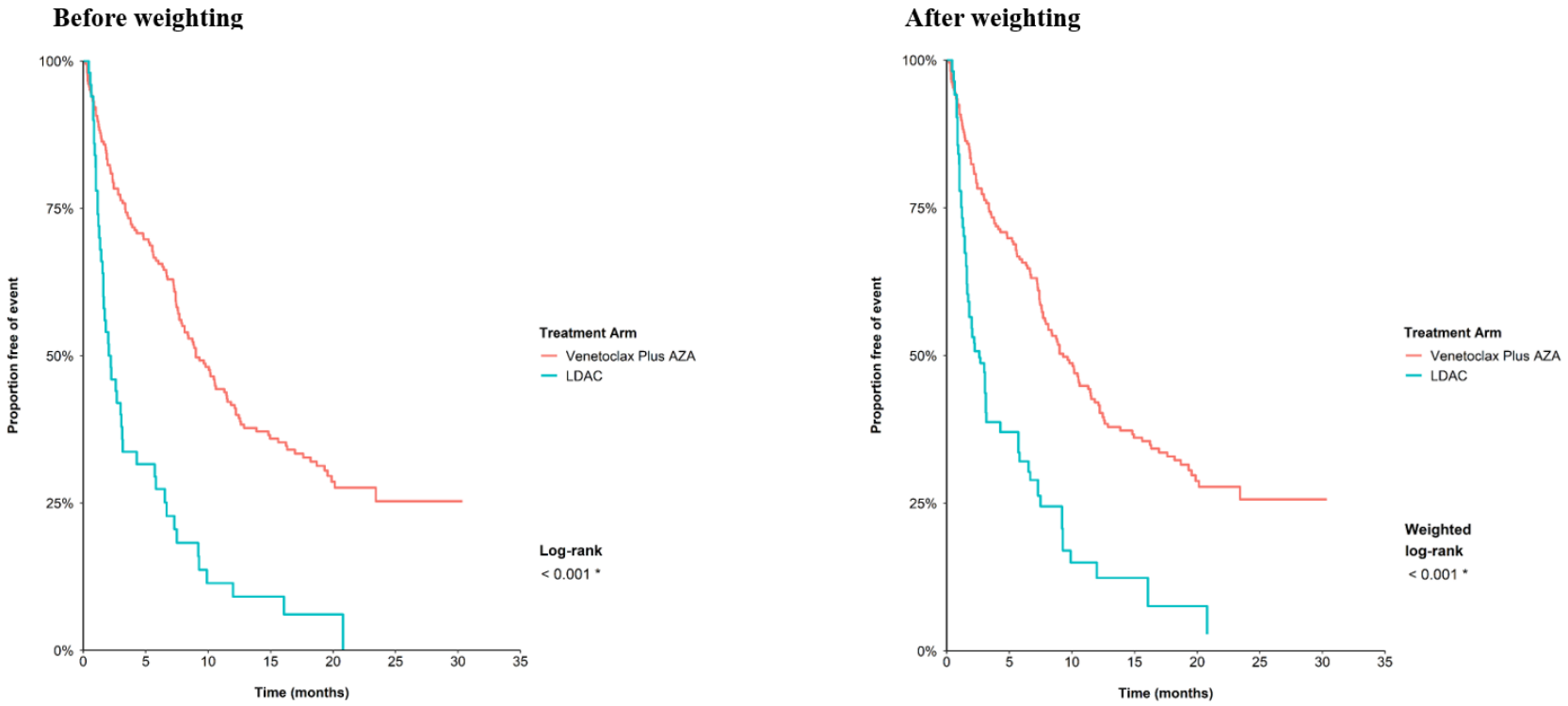
Figure 8.9 Sensitivity analysis, patients with >30% bone marrow blasts – EFS before and after weighting



Abbreviations: AZA, azacitidine; EFS, event-free survival; LDAC, low-dose cytarabine.
Source: [42]

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Table 8.24 Sensitivity analysis, patients with >30% bone marrow blasts – summary statistics of EFS before and after weighting

Treatment	N	Events	Before weighting			After weighting		
			Median EFS (95% CI)	HR (95% CI)	P value	Median EFS (95% CI)	HR (95% CI)	P value
LDAC	50	46	2.12 (1.54, 3.12)	Reference		2.60 (1.61, 5.82)	Reference	
Venetoclax + azacitidine	206	136	9.00 (7.59, 11.50)	0.35 (0.25, 0.50)	<0.001*	9.30 (7.69, 11.83)	0.39 (0.27, 0.55)	<0.001*

Abbreviations: CI, confidence interval; EFS, event-free survival; HR, hazard ratio; LDAC, low-dose cytarabine.
*Denotes statistical significance at the level of 0.05.
Source: [42]

Sensitivity analysis results: AML patients with >30% bone marrow blasts – CR + CRi

Compared with patients treated with LDAC, those treated with venetoclax plus azacitidine were more likely to achieve CR (OR: 8.24 [95% CI: 2.48, 27.41]), CRi (OR: 6.14 [95% CI: 1.84, 20.51]), and CR + CRi (OR: 12.29 [95% CI: 5.00, 30.17]) before weighting (Table 8.25). After weighting, the ORs only marginally changed for CR (OR: 6.15 [95% CI: 1.79, 21.12]), CRi (OR: 5.75 [95% CI: 1.51, 21.85]), and CR + CRi (OR: 9.99 [95% CI: 3.85, 25.94]) (Table 8.25) [42].

Table 8.25 Sensitivity analysis, patients with >30% bone marrow blasts – comparison of CR, CRi, and CR + CRi for venetoclax + azacitidine versus LDAC before and after weighting

	Before weighting				After weighting			
	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR VEN + AZA versus LDAC	P value	VEN + AZA % (95% CI)	LDAC % (95% CI)	OR VEN + AZA versus LDAC	P value
CR	0.34 (0.28, 0.41)	0.06 (0.02, 0.17)	8.24 (2.48, 27.41)	<0.001 *	0.34 (0.28, 0.41)	0.08 (0.03, 0.22)	6.15 (1.79, 21.12)	<0.01 *
CRi	0.28 (0.22, 0.35)	0.06 (0.02, 0.17)	6.14 (1.84, 20.51)	<0.01 *	0.28 (0.22, 0.34)	0.06 (0.02, 0.20)	5.75 (1.51, 21.85)	<0.05 *
CR + CRi	0.63 (0.56, 0.69)	0.12 (0.05, 0.24)	12.29 (5.00, 30.17)	<0.001 *	0.62 (0.55, 0.69)	0.14 (0.06, 0.29)	9.99 (3.85, 25.94)	<0.001 *

Abbreviations: AZA, azacitidine; CI, confidence interval; CR, complete response; CRi, complete response with incomplete bone marrow recovery; LDAC, low-dose cytarabine; OR, odds ratio; VEN, venetoclax.
*Denotes statistical significance at the level of 0.05.
Source: [42]

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