Medicinrådet

Bilag til Medicinrådets vurdering af decitabin + cedazuridin i kombination med venetoclax til behandling af akut myeloid leukæmi (AML)

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. decitabin + cedazuridin + venetoclax til AML
2. Forhandlingsnotat fra Amgros vedr. decitabin + cedazuridin + venetoclax til AML
3. Ansøgers endelige ansøgning vedr. decitabin + cedazuridin + venetoclax til AML

Otsuka comments to DMC draft assessment report concerning Inaqovi

The Danish Medicines Council (DMC) has assessed INAQOVI in combination with venetoclax (VEN) for patients with newly diagnosed AML who are not eligible for intensive chemotherapy. The assessment concludes that INAQOVI + VEN and azacitidine (AZA) + VEN are broadly comparable in terms of efficacy and safety, while recognizing the practical differences associated with a fully oral versus injectable hypomethylating agent (HMA) treatment.

We acknowledge the uncertainties highlighted by DMC, including those related to the indirect clinical comparison, treatment duration, relative dose intensity, administration costs and assumptions regarding azacitidine self-administration. These uncertainties may influence the estimated cost difference in either direction and should therefore be considered alongside uncertainties relating to the current AZA price and its use in Danish clinical practice.

Current azacitidine net prices

For the current tender period ending 2027-03-31, Amgros has contracts with several suppliers for AZA and the net prices ranges from [redacted] to [redacted] DKK per vial. Importantly, the current net prices apply only to the current tender period. Prices, suppliers and tender contractors may change thereafter, whereas we believe an INAQOVI price assessment should reflect the expected treatment horizon beyond the current tender period.

Azacitidine home administration

DMC assumes that all AZA injections are administered in hospital during cycle 1 and that 60% self-administer from cycle 2 onwards. Our base-case assumption of 20% home administration draws on the previous DMC assessment of venetoclax + HMA. One Danish KOL informally estimates that approximately 50% of patients self-administer AZA, particularly those who live far from the hospital, are relatively fit and live with another person. However, this estimate is subject to uncertainty and may not reflect the broader eligible population or sustained self-administration throughout treatment. While it suggests greater use than in our base case, it does not establish that 50% as a population wide rate or validate DMC's 60% assumption. A lower proportion therefore remains plausible and should be explored through scenario analysis.

The feasibility of home administration depends on both local service arrangements and individual circumstances. Training, preparation, delivery, monitoring and follow-up may vary across regions. In this older, often frail population, limited mobility, functional impairment, comorbidities and insufficient support may also restrict home administration, while disease progression or changing support needs may affect patients' ability to continue over time.

Home administration can reduce hospital visits but retains the logistical and handling requirements of injectable treatment. Danish hospital guidance describes patient training and assessment, refrigerated transport and storage, expiry checks, injection preparation and sharps disposal, requiring an organized delivery pathway and consistent management by patients or carers. The AZA SmPC specifies chemical and physical in-use stability of up to 22 hours at 2–8°C under the stated preparation conditions. Preparing syringes together for use over five days therefore entails storage and use beyond the authorised conditions for doses administered after that period. This off-label arrangement requires supporting extended-stability evidence and appropriate preparation, cold-chain

management and quality assurance. Chemical and physical stability alone do not establish microbiological safety, which is particularly relevant in an immunocompromised patient population.

Oral INAQOVI removes these injection-specific tasks and the refrigerated supply chain associated with reconstituted AZA, offering a simpler and less resource-intensive pathway for patients and healthcare services - not merely alternative means of receiving treatment at home.

Given the uncertainty around sustained self-administration in routine practice, we consider scenario analysis more informative than relying on the 60% assumption alone. Estimated AZA administration costs increase from approximately DKK 4,564 per patient per cycle at 60% self-administration to DKK 8,568 at 20%, a difference of DKK 4,004 per patient per cycle.

Patient population and budget impact

We acknowledge that DMC estimates approximately 95 Danish patients per year to be eligible for INAQOVI + VEN. This is slightly more than our estimated eligible patient population of 75 patients in year 5.

Based on our model, INAQOVI and AZA are approximately cost-comparable at up to [redacted] AZA home administration. Above this level, the estimated incremental cost of INAQOVI increases from approximately DKK [redacted] per cycle at [redacted] to DKK [redacted] at [redacted].

The absolute national budget impact is constrained by the small eligible population and gradual uptake. This limited budget exposure should be considered alongside the practical benefits of the fully oral regimen and avoided AZA administration burden.

Oral administration

DMC recognizes practical benefits of the fully oral regimen of INAQOVI + VEN, including fewer hospital visits, less transport, reduced burden for patients and caregivers, and avoidance of local injection-site reactions. INAQOVI removes the need for repeated subcutaneous AZA injections and can therefore avoid injection-site reactions and procedure-related injection complications. This may be particularly relevant in AML, where patients frequently experience neutropenia and impaired immune function. Where injections are self-administered at home, appropriate injection techniques, hand hygiene and safe handling are important safe-guards to minimise the risk of local or systemic infection and accidental needlestick injury. These additional requirements are avoided with a fully oral regimen.

Conclusion

Building on efforts such as home administration of subcutaneous AZA, INAQOVI + VEN supports clinicians' goal of reducing hospital visits by offering a fully oral regimen that patients can take conveniently at home.

We acknowledge the clinical and economic uncertainties identified by the DMC. However, these uncertainties affect the comparison in both directions, particularly regarding future AZA net prices, supply availability and the proportion of patients who can self-administer AZA in routine clinical practice. Considering the comparable clinical outcomes, the benefits of a fully oral treatment pathway, and the avoidance of repeated AZA injections, INAQOVI represents a relevant and suitable treatment option for eligible patients in the Danish market.

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

30.10.2026

LSC/MBA

Forhandlingsnotat

Dato for vurdering i Medicinrådet	25.11.2026
Leverandør	Otsuka
Lægemiddel	Inaqovi (decitabin + cedazuridin)
Ansøgt indikation	Voksne patienter med nylig diagnosticeret akut myeloid leukæmi (AML), som ikke er kandidater til behandling med standard induktionskemoterapi.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Inaqovi:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Nuværende SAIP (DKK)	Nuværende rabat ift. AIP	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Inaqovi	35+100 mg (5 stk.)	28.032,72	[redacted]	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Inaqovi, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

Amgros har en eksisterende aftale på Inaqovi. Aftalen gælder til den 30.09.2027 med mulighed for at forlænge i 6 måneder. Der er inkluderet mulighed for prisregulering i aftalen.

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Den nuværende førstelinjebehandling i Danmark til patienter med nyligt diagnosticeret AML, som ikke er egnede til intensiv kemoterapi, er azacitidin (AZA) i kombination med venetoclax (VEN). Inaqovi i kombination med VEN vurderes klinisk ligestillet med AZA + VEN.

Tabel 2 viser de årlige lægemiddeludgifter ved behandling med Inaqovi og AZA. Udgifter til VEN er ikke medtaget i tabel 2, da disse forventes at være ens i begge behandlingsalternativer.

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Inaqovi	35+100 mg (5 stk.)	35+100 mg på dag 1-5, hver 4. uge, oralt	[redacted]	[redacted]
Azacitidin	25 mg/ml (4 ml)	100 mg/m^2* på dag 1-5, hver 4. uge, s.c.	126,47	16.441**

*Overfladeareal 1,83, jf. Medicinrådets vurdering af decitabin + cedazuridin i kombination med venetoclax til behandling af akut myeloid leukæmi (AML)
**Med udgangspunkt i en gennemsnitlig kropsoverflade (BSA) på 1,83 m² estimeres den gennemsnitlige dosis til 183 mg pr. administration. Denne beregning tager udgangspunkt i at der forbruges 2 hætteglas pr. administration.

Status fra andre lande

Tabel 3: Status fra andre lande

Land	Status	Link
Norge	Anbefalet	Link til vurdering
Sverige	Anbefalet	Link til vurdering
England	Under vurdering	Link til status

Opsummering

Amgros har en eksisterende aftale på Inaqovi. Anbefales Inaqovi til AML vil en ny pris træde i kraft den [redacted].

Version log

Version	Date	Revision
2.0	February 20, 2026	New English version approved and published.
1.0	September 1, 2023	The application form is posted on the Danish Medicines Council's website.

©The Danish Medicines Council, 2026
The publication may be freely cited
with clear source attribution.

Language: Danish
Format: PDF
Published by the Danish Medicines Council February 20 2026

Application for assessment of INAQOVI in combination with venetoclax for the treatment of adult patients with newly diagnosed acute myeloid leukaemia who are ineligible for standard induction chemotherapy

Contact information

Contact information	
Business	**Otsuka Pharma Scandinavia AB**
Name	Anna Lindgren
Title	Market Access Manager
Telephone number (incl. country code)	+46 761 150 433
Email	anna.lindgren@otsuka.se
External representation	**N/A**
Title	N/A
Telephone number (incl. country code)	N/A
Email	

Table of Contents

Version log **1**

Contact information **2**

Tables and figures **6**

Abbreviations **1**

1. Information about the drug **5**

2. Summary table **6**

3. Patient population, intervention, choice of comparator(s) and outcome(s) **8**

3.1 Patient population 8

3.1.1 The disease 8

3.1.2 Selected patient population 10

3.2 Intervention 11

3.2.1 The intervention in the context of Danish clinical practice 18

3.2.2 ATMP 20

3.3 Selection of comparator(s) 20

3.4 Subsequent treatment 23

3.5 Relevant outcomes 23

3.5.1 Definition of outcomes 23

3.5.2 Relevance of outcomes 24

3.5.3 The validity of outcomes 24

4. Health economic analysis **24**

4.1 Basic assumptions 24

4.2 Model type and model structure 26

5. Literature overview **27**

5.1 Literature used to assess clinical efficacy and safety 28

5.2 Literature used to assess health-related quality of life 29

5.3 Literature used for input into the health economic model 29

6. Clinical studies **31**

6.1 INAQOVI + VEN compared to AZA + VEN for adult patients with newly diagnosed AML who are ineligible for SIC 31

6.1.1 Relevant studies 31

6.1.2 Comparability of studies 36

6.1.2.1 Comparability of patients across studies 37

6.1.3 Comparability of study population(s) with Danish patients eligible for treatment ... 41
6.1.4 Analysis method ... 41
6.1.5 Effect – results per ASCERTAIN-V study ... 41
6.1.6 Effect – results per VIALE-A study ... 44

7. Comparative analyses ... 46
7.1 Method of analysis ... 46
7.2 Results from the comparative analysis ... 47
7.3 Effect – results per response outcomes ... 48
7.4 Effect – results per OS ... 49

8. Safety ... 50

9. Extrapolation of patient transitions ... 54
9.1 Clinical data for extrapolation of patient transitions ... 54
9.2 Extrapolation using parametric extrapolation models ... 55
9.2.1 Extrapolation of time to treatment discontinuation (TTD) ... 55
9.2.2 Extrapolation of [clinical endpoint 2] ... 58
9.3 Extrapolation using transition probabilities ... 58
9.4 Summary and validity of extrapolated patient transitions ... 59

10. Health-related quality of life ... 60
10.1 Overview ... 60
10.2 Instruments ... 61
10.2.1 [“Instrument 1”] ... 61
10.2.1.1 Study design and instrument [“instrument 1”] ... 61
10.2.1.2 Data collection [“instrument 1”] ... 61
10.2.1.3 Results [“instrument 1”] ... 62
10.2.2 [“Instrument 2”] ... 63
10.2.2.1 Study design and instrument [“instrument 2”] ... 63
10.2.2.2 Data collection [“instrument 2”] ... 63
10.2.2.3 Results [“instrument 2”] ... 63
10.2.3 Summary when reporting multiple instruments ... 63
10.3 Utility values ... 63
10.3.1 Dataset(s) ... 63
10.3.2 Calculation of utility values ... 63
10.3.3 Adverse events, comorbidity and other state-specific adjustments to the utility values ... 63
10.3.4 Results for utility values ... 63

11. Cost calculations ... 64
11.1 Drug costs ... 64
11.1.1 Drug costs for intervention and comparator ... 64
11.1.2 Drug costs for subsequent treatment ... 65

11.2 Hospital costs 65
11.2.1 Administration 65
11.2.2 Disease management 65
11.2.3 Treatment monitoring 66
11.2.4 Management of adverse events 66
11.2.5 Other hospital costs 67
11.3 Patient costs 67
11.4 Other costs 68

12. Results 68
12.1 Sensitivity analyses 70
12.1.1 Deterministic sensitivity analyses 70
12.1.2 Probabilistic sensitivity analyses (PSA) 72

13. Budget impact analysis 74

14. List of experts 74

15. References 75

Appendix A. Study characteristics 79

Appendix B. Results regarding effectiveness per study 84

Appendix C. Subsequent treatment 89

Appendix D. Comparative analyses 90
D.1 Data sources 90
D.2 Analysis Sets for ITC Analyses 90
D.3 Baseline characteristics 91
D.4 MAIC Weighting 93
D.5 Analyses Conducted 94
D.6 MAIC results 95
D.7 Cytogenetic Risk Sensitivity Analysis 96

Appendix E. Extrapolation of patient transitions 98
E.1 Parametric extrapolation models 98
E.1.1 Extrapolation of TTD 98
E.1.1.1 Log-cumulative hazard plots and residual plots 98
E.1.1.2 Internal validity 98
E.1.1.2.1 Assessment of statistical and visual fit (AIC and BIC) 98
E.1.1.2.2 Assessment of smoothed hazard functions 98
E.1.1.3 External validity 98
E.1.1.4 Other assumptions 99
E.1.2 Extrapolations of [clinical endpoint 2] 99
E.2 Transition probabilities 99

E.2.1 Internal validity 99
E.2.2 External validity 99
E.2.3 Other assumptions 99

Appendix F. Serious adverse events 99

Appendix G. Health-related quality of life 101
G.1 Data collection – overview of responses 101
G.2 Reporting of domains 101
G.3 Mapping 102
G.4 Calculation of utility values 102

Appendix H. Literature searches for the clinical assessment 102
H.1 Effect and safety of intervention and comparators 102
H.2 Systematic selection of studies and references 112

Appendix I. Literature searches for health-related quality of life 142
I.1 Systematic search 142
I.2 Focused search 142

Appendix J. Literature searches for supplementary input to the health economic model 142
J.1 Systematic search 142
J.2 Focused search 143

Appendix K. Reasons for confidential information 143

Tables and figures

Table 1. Expected number of patients and patient uptake when implementing the intervention 11
Table 2. Overview of the intervention 11
Table 3. The intervention in the study and the health economic model 12
Table 4. Study Treatment Extent of Exposure - Phase 1 (All Treated Population) 14
Table 5. Study Treatment Extent of Exposure - Phase 2 Part B (All Treated Population) 15
Table 6. Study Treatment Extent of Exposure for INAQOVI and Venetoclax – Phase 1 and Phase 2 Combined (All Treated Population) 17
Table 7. Comparator overview 20
Table 8. Comparator in the study and the health economic model 21
Table 9. Assumptions regarding subsequent treatment in the health economic analysis 23
Table 10. Outcomes 23
Table 11. Basic assumptions in the health economic analysis 24

Table 12. Choice of health economic analysis, model and model structure 26
Table 13. Relevant literature included in the assessment of efficacy and safety 28
Table 14. Relevant literature included in the assessment of health-related quality of life 29
Table 15. Relevant literature used in the health economic model 30
Table 16. Overview of study characteristics for all studies included in the comparison 34
Table 17. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety 37
Table 18. Characteristics of the relevant Danish population and input parameters in the health economic model 41
Table 19. Results from the comparative analysis of INAQOVI + VEN vs. AZA + VEN for adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with VEN + HMA 47
Table 20. Overview of adverse events in ASCERTAIN-V and VIALE-A studies 51
Table 21. Proportion of patients with adverse events in ASCERTAIN-V and VIALE-A studies 52
Table 22. Overview of assumptions regarding extrapolation of TTD 57
Table 23. Transition probabilities in the health economic model 58
Table 24. Transition matrix for [intervention/comparator] 59
Table 25. Modeled averages in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality 59
Table 26. Overview of included instruments for health-related quality of life 60
Table 27. Basis for estimating utility values 61
Table 28. Overview of responses [create a table for both intervention and comparator] 61
Table 29. Overview of responses by health state [create a table for both intervention and comparator] 62
Table 30. Results for [instrument 1] 62
Table 31. Utility values used in the health economic model 63
Table 32. Assumptions regarding administrative costs 65
Table 33. Assumptions regarding costs for disease management 66
Table 34. Assumptions regarding costs for treatment monitoring 66
Table 35. Assumptions regarding costs for management of adverse events 66
Table 36. Assumptions regarding patient time 67
Table 37. Results, discounted estimates, half-cycle corrected (where relevant) and adjusted for background mortality 69
Table 38. Results per drug of the two combination treatments 70
Table 39. Results of deterministic sensitivity analyses 72
Table 40. Budget impact (non-discounted estimates), DKK 74
Table 41. Main characteristics of included studies 79
Table 42. Results per study 84
Table 43 Analysis sets for ASCERTAIN-V and VIALE-A 91
Table 44 ESS and baseline characteristics pre- and post-matching for the variables included in the MAIC weights calculation for the primary analysis 92
Table 45 Summary of analysis steps 94

Table 46. Comparative analysis of studies comparing INAQOVI + VEN with AZA + VEN for adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with VEN + HMA 95
Table 47 SAEs reported by preferred term in ≥1% of patients in Phase I, Phase II Part A and Phase II Part B (safety population) of ASCERTAIN-V 99
Table 48 Serious adverse events that were reported in at least 5% of patients in either treatment group in VIALE-A 101
Table 49 Bibliographic databases 102
Table 50 Conference and Clinical Trial Registry Searches 103
Table 51 Search terms for use in MEDLINE, Embase, CDSR and CENTRAL (searched simultaneously via the Ovid EMBR platform) 103
Table 52 Search strategies for hand-searching of relevant congresses 106
Table 53 Search terms for use in ClinicalTrials.gov 111
Table 54. Inclusion and exclusion criteria for the original SLR and SLR update 112
Table 55. Studies/references included in the Danish assessment 117
Table 56. Excluded studies/references 117
Table 57. Justifications regarding confidential information 143

Figure 1 Pathogenesis of AML 9
Figure 2 Patient funnel estimates 10
Figure 3 Proposed positioning of INAQOVI + VEN in the treatment pathway of adult patients with newly diagnosed AML 19
Figure 4 ASCERTAIN-V study design 32
Figure 5 Forest plot of CR rate by subgroup in Phase II Part B (all treated population, N=101) 42
Figure 6 KM estimate of DOR for CR by investigator assessment in Phase II Part B 43
Figure 7 KM estimate of OS in Phase II Part B (all treated population, N=101) 44
Figure 8 KM estimate of OS in the VIALE-A trial 45
Figure 9 Forest plot of MAIC-weighted results for response outcomes at data cutoff 48
Figure 10 KM curves for OS using MAIC weights from primary analysis 49
Figure 11 Absolute difference in RMST between INAQOVI+VEN and AZA+VEN by timepoint for OS for the primary analysis using MAIC weights 50
Figure 12 Forest plot of MAIC-weighted results for SAE 54
Figure 13 - Extrapolated data for all examined models and KM (INAQOVI + VEN) 55
Figure 14 - Extrapolated data for all examined models (exponential) and KM (AZA + VEN) 56
Figure 15 - Extrapolated data for the selected models comparing INAQOVI + VEN (lognormal) and AZA + VEN (exponential) 56
Figure 16 Incremental costs INAQOVI+VEN minus AZA+VEN by AZA price scenarios (DKK) 70
Figure 17 Incremental costs INAQOVI+VEN minus AZA+VEN by AZA price and dosing scenarios (DKK) 71
Figure 18 PSA results - Distribution of the incremental total costs 73
Figure 19 Histogram of MAIC weights for primary analysis using the primary (imputed) analysis set. 93

Figure 20 Absolute difference in RMST between INAQOVI+VEN and AZA+VEN by timepoint for OS when restricting to intermediate and adverse cytogenetic risk..... 97
Figure 21 PRISMA diagram for the original SLR (February 2025)..... 114
Figure 22 PRISMA diagram for the SLR and update 116

Abbreviations

Abbreviation	Definition
ABL1	ABL proto-oncogene 1
ADaM	Analysis Data Model
AE	Adverse event
AgD	Aggregate data
AIP	Apotekets Inkøbspris
AML	Acute myeloid leukaemia
ANOVA	Analysis of variance
ASCO	American Society of Clinical Oncology
ASH	American Society of Haematology
AUC	Area under the curve
AUC0-24	Area under the curve from time zero to 24 hours post-dose
AUC0-8	Area under the curve from time zero to 8 hours post-dose
AUC0-inf	Area under the curve from time zero to time infinity
AZA	Azacitidine
AZA + VEN	Azacitidine in combination with venetoclax
BM	Bone marrow
BSA	Body surface area
BSC	Best supportive care
CDA	Cytidine deaminase
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CMA	Cost-minimization analysis
Cmax	Maximum observed concentration
Cmin	Lowest concentration of drug in the blood
CMML	Chronic myelomonocytic leukaemia
CR	Complete response
CRh	Complete response with partial haematologic recovery

Cri	Complete response with incomplete haematological recovery
CRp	Complete response with incomplete platelet recovery
CTCAE	Common terminology criteria for adverse events
CYP3A	Cytochrome P450 family 3A
DCO	Data cut-off
DDX	DEAD-box helicase
DEC	decitabine
DEC-C	Decitabine combined with cedazuridine
DKK	Danish krone
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EHA	European Hematology Association
ELN	European LeukemiaNet
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
ESMO	European Society of Medical Oncology
ESS	Effective sample size
F	Female
FA	Feasibility assessment
FLT	Fms-like tyrosine kinase
FLT3-ITD	Internal tandem duplication in the FLT3 gene
HIV	Human immunodeficiency virus
HMA	Hypomethylating agent
HR	Hazard ratio
HRQoL	Health-related quality of life
HSCT	Haematopoietic stem cell transplantation
HTA	Health technology assessment
ICER	Incremental Cost-Effectiveness Ratio
IDH	Isocitrate dehydrogenase

INAQOVI + VEN	INAQOVI in combination with venetoclax
IPD	Individual patient data
IQR	Interquartile range
ITC	Indirect treatment comparison
ITT	The intention-to-treat population
IV	Intravenous
JNHB	Joint Nordic Assessment
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDAC	Low-dose cytarabine
LSM	Least squares mean
M	Male
MAIC	Matching-adjusted indirect comparison
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
MRC	Myelodysplasia-related change
N	Number
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NE	Not evaluable/not estimable
NMP1	Nucleophosmin-1
NORDCAN	Association of the Nordic Cancer Registries
NPM	Nucleophosmin
NR	Not reached
NRAS	Neuroblastoma rat sarcoma viral oncogene homolog
OR	Odds ratio
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PH	Proportional hazards
PK	Pharmacokinetics

PO	Oral administration
PR	Partial response
PS	Performance status
PSA	Probabilistic sensitivity analyses
PV	Prognostic variable
QALY	Quality-Adjusted Life Year
QD	Once daily
RCT	Randomised clinical trial
RMST	Restricted mean survival time
RNA	Ribonucleic acid
SAE	Serious adverse event
SC	Subcutaneous
SIC	Standard induction chemotherapy
SLR	Systematic literature review
SmPC	Summary of product characteristics
SoC	Standard of care
SOHO	Society of Hematologic Oncology
T1/2	Half-life of a drug
TEAE	Treatment-emergent adverse event
TEM	Treatment effect modifier
Tmax	Time taken for a drug to reach the C_{max} after administration
ToT	Time on treatment
TP	Tumour protein
TRAE	Treatment-related adverse event
TTD	Time to treatment discontinuation
TTE	Time-to-event
ULN	Upper limit of normal
USA	United States of America
VEN	Venetoclax
WBC	White blood cell
WHO	World Health Organisation

1. Information about the drug

Drug information	
Trade name	INAQOVI®
Generic name	Decitabine (35 mg) and cedazuridine (100 mg)
Indication as formulated by the European Medicines Agency (EMA)	INAQOVI in combination with venetoclax (VEN) is indicated for the treatment of adult patients with newly diagnosed acute myeloid leukaemia (AML) who are ineligible for standard induction chemotherapy (SIC).
Marketing Authorization Holder in Denmark	Otsuka Pharmaceutical Netherlands B.V.
ATC code	L01BC58
Combination therapy and/or concurrent treatment	Yes, INAQOVI in combination with venetoclax (INAQOVI + VEN).
Expected date of EU approval (marketing authorisation)	The indication extension was granted EMA approval on June 19, 2026
Has the drug received a conditional marketing authorisation?	No.
Has the drug been in 'accelerated' assessment' at EMA?	No.
Does the drug have orphan drug designation?	No.
Other indications approved by the EMA	INAQOVI is indicated as monotherapy for the treatment of adult patients with newly diagnosed AML who are ineligible for standard induction chemotherapy (SIC).
Other indications that have been evaluated by the Danish Medicines Council	No. INAQOVI indicated as monotherapy submission was withdrawn in 2024, therefore there are no other prior assessments in place.
Joint Nordic Assessment (JNHB): **Is current treatment practice comparable across the Nordic countries (DK, FI, IS, NO, SE)?**	INAQOVI + VEN is an outpatient drug that is expected to be assessed through a cost-minimization analysis and is already reimbursed for monotherapy in Sweden, Norway and Finland. Hence it does not match the criteria set out by JNHB's for products suitable for JNHB assessment (1).
Joint Nordic Assessment (JNHB):	No, as described above.

Is the drug suitable for a joint Nordic assessment?	
Has a joint European assessment (JCA) been carried out via the EU HTA Regulation?	No.
Delivery	BEGR
Packaging – types, sizes/number of units and concentrations	35 mg/100 mg film-coated tablets. Double aluminium foil blisters containing 5 tablets.

2. Summary table

Overview	
Indication relevant to the assessment	INAQOVI in combination with venetoclax (VEN) is indicated for the treatment of adult patients with newly diagnosed acute AML who are ineligible for standard induction chemotherapy (SIC). There are no deviations from the European Medicines Agency (EMA) indication.
Dosage regimen and administration route	Intervention: INAQOVI 35 mg/100 mg (oral) + VEN 400 mg (oral) The recommended dose of INAQOVI: 1 tablet once daily on Days 1 through 5 of each 28 day cycle. The recommended dose of VEN: ramp up Days 1–3 (100 → 200 → 400 mg), then 400 mg daily Days 4–28. Cycles are to be repeated every 28 days. Treatment is recommended to be continued for a minimum of 4 cycles until disease progression or unacceptable toxicity. In some patients a complete or partial response may take longer than 4 cycles.
Comparator selection	Comparator: azacitidine (AZA) 100 mg/m^2 (subcutaneous [SC]) + venetoclax 400 mg (oral) (AZA + VEN) The recommended dose of AZA: every day for five days (clinical dosing confirmed by a Danish clinical expert) (2), followed by a 3-week rest period. The recommended dose of VEN: ramp up Days 1–3 (100 → 200 → 400 mg), then 400 mg daily Days 4–28. This treatment cycle will be repeated every 4 weeks for at least 6 treatment cycles.

Prognosis with current standard treatment (comparator(s))	Prognosis for patients with newly diagnosed AML who are not eligible for standard induction chemotherapy remains poor, and long-term survival is limited. For this patient population, AZA+VEN has become the standard first-line therapy in Denmark (3). In the phase III VIALE-A trial, which forms the basis for Danish use, median overall survival (OS) was 14.7 months with AZA+VEN compared with 9.6 months with AZA alone. In patients with achieved response (Complete Response + Complete Response with incomplete haematological recovery), the 2-year survival was 73.6% for AZA+VEN and 63.6% for AZA+placebo, respectively (4).
Type of documentation for the clinical evaluation	Indirect treatment comparison (ITC) study.
Main outcomes including at least one outcome for health-related quality of life (difference/improvement compared to comparator(s))	ASCERTAIN-V phase I/II trial: Primary endpoints: Phase I: VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2; Phase II Part A: CR rate and VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2; Phase II Part B: CR rate. Secondary endpoints: Phase I: CR, CR+CRh, CR+CRi rates, time to and duration of CR or CRh, OS. Phase II Part A & B: CR, CR+CRh, CR+CRi rates, time to and duration of CR or CRh, OS.
Serious adverse events for the intervention and comparator	N/A
Type of health economic analysis	Cost-minimization analysis (CMA)
Health economic model	CMA
Outcomes and sources for extrapolating patient transitions	N/A
Instrument and sources for health-related quality of life	ASCERTAIN-V: Health-related quality of life (HRQoL) data was not collected. VIALE-A: EQ-5D-5L, EORTC QLQ-C30, PROMIS Cancer Fatigue SF 7a. No HRQoL comparison could be performed between the VIALE-A and ASCERTAIN-V studies.
Life years gained (discounted, corrected for half-cycle and background mortality)	N/A

QALYs gained (discounted, corrected for half-cycle and background mortality)	N/A
ICER (DKK/QALY) (discounted, corrected for half-cycle and background mortality)	As the two treatment combinations are assumed to have equivalent clinical effectiveness and safety, a CMA has been conducted. Therefore, an ICER expressed as DKK/QALY is not applicable, as there is no difference in QALYs between the comparators. The analysis therefore focuses solely on the comparison of total costs per treatment duration (6 cycles). Incremental costs for 6 cycles (intervention – comparator): 110,510 DKK only considering the drug acquisition costs, and 70,537 considering all costs.
Company's assessment of uncertainty	Parameter uncertainty was assessed through probabilistic sensitivity analysis (PSA).

3. Patient population, intervention, choice of comparator(s) and outcome(s)

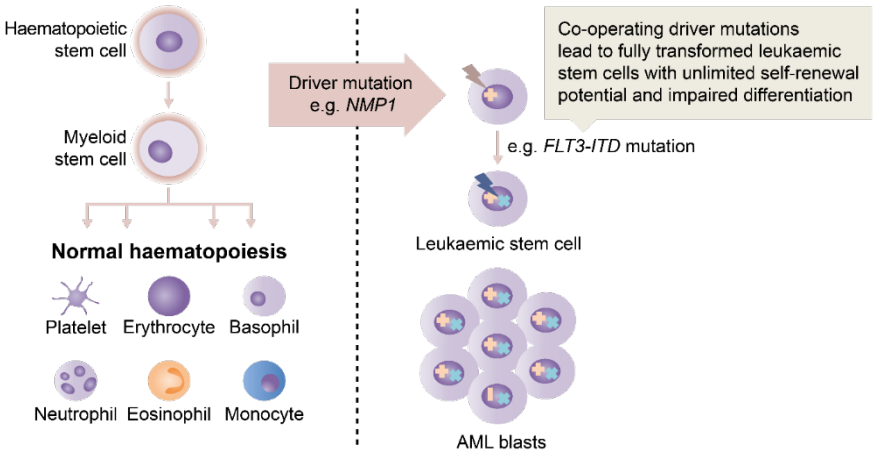
3.1 Patient population

3.1.1 The disease

Acute myeloid leukaemia (AML) is an aggressive, rapidly progressing haematological cancer that is characterised by the overproduction and accumulation of abnormal myeloblasts in the bone marrow (BM) and peripheral blood of affected patients (5, 6). AML is a clinically heterogeneous disease which is characterised by a range of chromosomal abnormalities and genetic mutations that can disrupt almost all aspects of cell transformation (7). As AML results in impaired differentiation of haematopoietic stem cells and abnormal, uncontrolled proliferation of immature myeloid precursor cells (myoblasts), patients are left with insufficient erythrocytes, platelets and neutrophils, as shown in Figure 1 (5, 8, 9).

AML generally presents with signs and symptoms that are characteristics of the proliferation of malignant cells and the loss of normal, functioning blood cells (10). Specifically, anaemia results in fatigue and weakness; neutropenia leads to increased risk of infection; and thrombocytopenia increases the risk of bleeding complications and often leads to bruising (11). AML also has the worst survival outcomes of any leukaemia, with an estimated five-year survival rate of 17% in Europe (12), though NORDCAN reports a relatively 5-year survival of 32.7% and 34% for men and women respectively in Denmark (13).

Figure 1 Pathogenesis of AML



Abbreviations: AML: acute myeloid leukaemia; FLT3-ITD: internal tandem duplication in the FLT3 gene; NMP1: nucleophosmin-1.

Source: Adapted from Siveen et al. (2017) and The Lecturio Medical Concepts Library (2022).(8, 9)

Whilst the cause of the genetic mutations in patients with AML is unclear, a number of factors have been identified which increase a patient's risk of developing AML. Key risk factors for AML include older age, male sex, prior chemotherapy or radiation therapy, high radiation exposure, contact with carcinogenic chemicals such as benzene, smoking, pre-existing blood disorders, and certain genetic conditions such as Down syndrome (14).

AML is diagnosed primarily based on morphological inspection revealing a myeloid blast cell count of ≥20% (in a count of 500 cells) (15). Morphological inspection is also important to differentiate AML from other conditions, such as promyelocytic leukaemia (15).

Patients with AML who are ineligible for standard induction chemotherapy (SIC) face substantial unmet needs, including poorer health related quality of life (HRQoL) outcomes compared to the broader AML population, primarily due to older age, comorbidities, and a poor prognosis (16).

In patients with AML who are ineligible for SIC, the direct costs associated with venetoclax (VEN) + parenteral hypomethylating agents (HMAs) results in a considerable burden on healthcare resources due to the necessity for patients to frequently attend hospital in order to receive treatment. These costs are in addition to the high medical costs associated with the management of emergency complications and symptoms associated with AML (17). The frequent hospital appointments required for treatment with VEN + parenteral HMAs negatively impacts patients' HRQoL due to travel burden, extended hospital stays, and increased risk of infection (16, 18, 19). These treatment-related burdens also impact families and/or caregivers of patients with AML, as they often assist with frequent hospital visits (20).

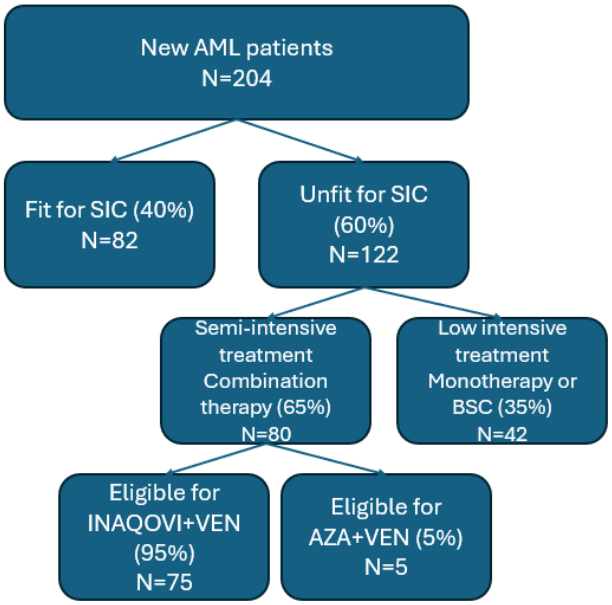
A population based registry study in Sweden estimated that the expected 5-year cost per patient with AML treated with a parenteral HMA was €80,010, the majority of which was

for non-drug costs including €12,395 for outpatient visits (2018 EUR) (21). Therefore, an unmet need exists for an additional, all oral treatment option which could improve outcomes and reduce the economic burden (17, 22, 23).

3.1.2 Selected patient population

Denmark's total population was approximately 6,03 million in 2024, of which around 4,75 million were aged ≥20, according to Statistikbanken (24). The incidence rate of AML in this age group, for both sexes combined, was 4.3 per 100,000 in 2024, based on the latest available data from NORDCAN (25). This will translate in 204 new patients ≥20 years diagnosed with AML every year. 60% of the new diagnosed AML patients (N=122 patients) are estimated to be unfit for SIC, based on the input from a Danish clinician with experience in treating patients with AML in Denmark (2). Furthermore, the Danish clinician provided an estimate of approximately 65% out of the unfit for SIC group (N=122 patients), meaning around 80 patients would undergo a semi-intensive treatment with a combination therapy (HMA + VEN) (2). According to Danish clinician insights, the majority of these patients, 95% (N=75 patients), are estimated to be eligible for INAQOVI + VEN therapy. Figure 2 summarizes the patient funnel estimates.

Figure 2 Patient funnel estimates



Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; N, number; SIC, standard induction chemotherapy; VEN, venetoclax.

Source: Otsuka based on the guidelines from Dansk Akut Leukaemi Gruppe (3), Statistikbanken (24), NORDCAN (25) and Danish clinician interview (2).

In addition, Table 1 shows the expected number of patients in line with EMA indication, which translates into the number of newly diagnosticated AML patients who are unfit for SIC. Regarding the patient uptake, considering a slower uptake in the first year, there was assumed that only 55 patients will start treatment with INAQOVI + VEN in year 1, and 75 new patients will be on treatment from year 2 onwards.

Table 1. Expected number of patients and patient uptake when implementing the intervention

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Expected number of patients*	122	122	122	122	122
Patient uptake**	*55 (45%)*	*75 (61%)*	*75 (61%)*	*75 (61%)*	*75 (61%)*

*Number of patients who are unfit for SIC
** Number of new patients in Denmark who are eligible for treatment with INAQOVI + VEN in the coming years

3.2 Intervention

Given that VEN has an identical posology when used in combination with INAQOVI or azacitidine (AZA), it has not been considered separately in Sections 3.1.2 and 3.3 . The intervention assessed is INAQOVI + VEN, while the comparator is AZA + VEN.

Table 2. Overview of the intervention

Therapeutic indication relevant to the assessment	INAQOVI + VEN is anticipated to be indicated for the treatment of adult patients with newly diagnosed AML who are ineligible for SIC (26).
Generic name	Decitabine/Cedazuridine
ATC code	L01BC58
Mechanism of action	Decitabine is a nucleoside metabolic inhibitor that is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into deoxyribonucleic acid (DNA) and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation and/or apoptosis. Decitabine induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA (26, 27). Cytidine deaminase (CDA) is an enzyme that is responsible for the degradation of cytidine nucleosides, including the cytidine analog decitabine. High levels of CDA in the gastrointestinal tract and liver rapidly degrade these nucleosides and prohibit or limit their oral bioavailability. Cedazuridine inhibits CDA. Oral administration of cedazuridine with decitabine increases the systemic exposure of decitabine via inhibition of first pass

	metabolism of decitabine in the gut and liver by CDA (26, 27).
Route of administration	Oral
Packaging type, pack sizes, shelf life and strengths	INAQOVI is available as a film-coated tablet containing a fixed-dose combination of decitabine (35 mg) and cedazuridine (100 mg). The medicine is supplied in foil blister packs containing 5 tablets. The shelf life is 5 years (26).
Package size(s)	Each pack contains 5 tablets (26).
If vials: Can these be shared?	N/A
Pre-medication: Is premedication required? If yes, specify which	N/A
Co-administration: Is the drug to be administered with other drugs? If yes, specify which	Yes, INAQOVI should be administered in combination with VEN (26).
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	Complete blood cell counts must be obtained prior to the initiation of treatment, prior to each cycle, and as clinically indicated to monitor response and toxicity, as per INAQOVI + VEN SmPC (26).

Abbreviations: AML, acute myeloid leukaemia; CDA, Cytidine deaminase; DNA, Deoxyribonucleic acid; N/A, not applicable; SIC, standard induction chemotherapy, VEN, venetoclax.

Table 3. The intervention in the study and the health economic model

	Study (28)	Health economic model
Dosage and frequency	Phase I, Phase II Part A and B had the same dosing schedule. Cycle 1, INAQOVI (35 mg decitabine and 100 mg cedazuridine) was given in combination with VEN on Days 1–5. VEN was dosed as a ramp-up on Day 1 (100 mg) and Day 2 (200 mg), followed by 400 mg daily on Days 3–28. During Cycle 2 and beyond, patients receive INAQOVI + VEN 400 mg daily in combination on Days 1–5, and VEN 400 mg daily alone on Days 6–28.	The same dosing schedule as used in the clinical study is applied.

	Study (28)	Health economic model
Average dose	INAQOVI was administered as a fixed-dose tablet containing 35 mg decitabine and 100 mg cedazuridine per administration. An average administered dose was not reported. Dose modifications were implemented through changes in the number of dosing days rather than tablet strength.	The model applies 35 mg decitabine/100 mg cedazuridine per administration (the same dosing schedule as used in the clinical study), with treatment exposure determined by the number of dosing days. Therefore, an average dose is not applied as a separate model input.
Criteria for treatment discontinuation	Patients received study treatment until disease progression, unacceptable toxicity, withdrawal from the study, or death.	Not applicable as a separate model input. Explicit treatment discontinuation criteria are not modelled, as treatment duration is captured through the number of treatment cycles, with 6 cycles applied for both treatments in the base case.
Treatment duration	Median treatment cycles: Phase I: 4.0 months Phase II A: 5.0 months Phase II B: 4.0 months	6 cycles of 28 days each, based on ASCERTAIN-V and VIALE-A studies.
Dose adjustment: Specify whether/how dose adjustments are applied*	The mean number of dosing days for both VEN and DEC-C (INAQOVI) decreased¥ from phase I to phase 2B (28): • Cycle 1 mean days: - Phase I: VEN, 27.3; DEC-C, 5 - Phase II B: VEN, 23.9; DEC-C, 5 • Cycle 3 mean days (28): - Phase I: VEN, 18.8; DEC-C, 4.9 - Phase II B: VEN, 17.5; DEC-C, 4.4	As ASCERTAIN-V is a Phase I/II study, dose adjustments were permitted and observed across study parts, but these adjustments were not incorporated into the CMA due to the fact that the CMA presents costs per treatment duration (6 cycles) rather than modelling individual dose modifications.
Treatment interruption: Specify whether/how treatment interruptions (pause) are applied*	Treatment interruptions for INAQOVI and VEN may occur due to toxicity (primarily myelosuppression) and are managed by delaying the next	Toxicity-related treatment interruptions were not modelled separately, as the model assumes comparable safety between arms.

	Study (28)	Health economic model
	cycle until haematologic recovery.	

¥ During the ASCERTAIN-V study, the protocol change implemented for Phase II Part B aimed to mitigate treatment-related myelosuppression by conducting early BM assessments to identify leukemic blast clearance prior to completion of a full cycle of venetoclax.(29)

Abbreviations: DEC-C, Decitabine combined with cedazuridine; N/A, not applicable; VEN, venetoclax.

Exposure and Treatment Compliance

Extent of Exposure

Phase 1

All patients in Phase 1 (N=30) received at least one dose of INAQOVI and at least one dose of venetoclax. The median (min, max) total dose (mg) of INAQOVI and venetoclax received by patients in Phase 1 was 2565.0 mg (675, 19035 mg) and 29160.0 mg (6300, 124170 mg), respectively. The median (min, max) duration of treatment was 3.5 months (0.2, 39.1 months) with INAQOVI and 3.8 months (0.6, 39.1 months) with venetoclax, both for a median of 4.0 cycles (1, 33 cycles).

One (3.3%) patient had a dose reduction of both INAQOVI and venetoclax due to adverse events (AE), no patients had a dose reduction of INAQOVI only due to AEs, and 6 (20.0%) patients had a dose reduction of venetoclax only due to AEs. Eleven (36.7%) patients had a dose interruption/delay of both INAQOVI and venetoclax due to AEs, no patients had a dose interruption/delay of INAQOVI only due to AEs, and 4 (13.3%) patients had a dose interruption/delay of venetoclax only due to AEs.

Table 4. Study Treatment Extent of Exposure - Phase 1 (All Treated Population)

	Inaqovi (N=30)	Venetoclax (N=30)
Duration of treatment (months)		
Mean (SD)	7.41 (9.541)	7.75 (9.370)
Median	3.52	3.76
Min, Max	0.2, 39.1	0.6, 39.1
Number of patients with treatment duration, n (%)		
<3 months	12 (40.0)	12 (40.0)
3 – 6 months	8 (26.7)	8 (26.7)
6 – 9 months	1 (3.3)	1 (3.3)
9 – 12 months	2 (6.7)	2 (6.7)
>12 months	7 (23.3)	7 (23.3)
Total dose received (mg)		
Mean (SD)	3645.0 (4018.38)	36102.3 (28450.48)

Median	2565.0	29160.0
Min, Max	675, 19035	6300, 124170
Relative dose intensity (%)		
Mean (SD)	93.61 (11.900)	79.66 (25.157)
Median	100.00	91.37
Min, Max	53.0, 100.0	25.0, 101.1
Summary of no. of cycles treated		
Mean (SD)	6.6 (7.92)	6.6 (7.92)
Median	4.0	4.0
Min, Max	1, 33	1, 33

Abbreviations: max=maximum; min=minimum; n=number of patients in specific subgroup; N=total number of patients;

SD=standard deviation

Relative dose intensity was calculated as dose intensity divided by planned dose intensity, expressed as a percentage, where dose intensity was defined as cumulative dose received divided by the planned number of treatment days.

Source: ASTX727-07 Clinical Study Report

Phase 2 Part B

All patients in Phase 2 Part B (N=101) received at least one dose of INAQOVI and at least one dose of venetoclax. The median (min, max) total dose (mg) of INAQOVI and venetoclax received by patients during Phase 2 Part B was 2700.0 mg (675, 8775 mg) and 27410.0 mg (1200, 112300 mg) respectively. The median (min, max) duration of treatment with INAQOVI was 5.5 months (0.2, 17.2 months), and 5.5 months (0.2, 17.2 months) with venetoclax, both for a median of 4.0 cycles (1,15 cycles).

One (1.0%) patient had a dose reduction of both INAQOVI and venetoclax due to an AE, 4 (4.0%) patients had a dose reduction of INAQOVI only due to an AE, and 9 (8.9%) patients had a dose reduction of venetoclax only due to an AE. 53 (52.5%) patients had a dose interruption/delay of both INAQOVI and venetoclax due to an AE, 7 (6.9%) patients had a dose interruption/delay of INAQOVI only due to an AE, and 35 (34.7%) patients had a dose interruption/delay of venetoclax only due to an AE.

Table 5. Study Treatment Extent of Exposure - Phase 2 Part B (All Treated Population)

	Inaqovi (N=101)	Venetoclax (N=101)
Duration of treatment (months)		
Mean (SD)	5.783 (4.7305)	6.027 (4.5565)
Median	5.454	5.520

Min, Max	0.16, 17.18	0.20, 17.18
Number of patients with treatment duration, n (%)		
<3 months	38 (37.6)	35 (34.7)
3–6 months	19 (18.8)	19 (18.8)
6–9 months	14 (13.9)	18 (17.8)
9–12 months	16 (15.8)	15 (14.9)
>12 months	14 (13.9)	14 (13.9)
Total dose received (mg)		
Mean (SD)	3043.5 (2077.20)	30760.2 (22551.08)
Median	2700.0	27410.0
Min, Max	675, 8775	1200, 112300
Relative dose intensity (%)		
Mean (SD)	92.88 (11.344)	71.94 (25.915)
Median	100.00	75.06
Min, Max	54.8, 100.0	17.6, 105.5
Summary of no. of cycles treated		
Mean (SD)	5.3 (3.72)	5.2 (3.69)
Median	4.0	4.0
Min, Max	1, 15	1, 15

Abbreviations: max=maximum; min=minimum; n=number of patients in specific subgroup; N=total number of patients;

SD=standard deviation

Relative dose intensity was calculated as dose intensity divided by planned dose intensity, expressed as a percentage, where dose intensity was defined as cumulative dose received divided by the planned number of treatment days.

Source: ASTX727-07 Clinical Study Report

Phase 1 and Phase 2 Combined

All patients in Phase 1 and Phase 2 (N=189) received at least one dose of INAQOVI and at least one dose of venetoclax. The median (min, max) cumulative dose per cycle (mg) for Phase 1 and Phase 2 combined was 675.0 mg (341.1, 675.0 mg) for INAQOVI and 7005.0 mg (1200.0, 11550.0 mg) for venetoclax. The median (min, max) duration of treatment with INAQOVI was 4.9 months (0.2, 39.1 months) and 5.2 months (0.2, 39.1 months) with venetoclax, both for a median of 4.0 cycles (1, 33 cycles). 80 (42.3%) and 85 (45.0%) patients were exposed to INAQOVI and venetoclax, respectively, for 6 months or longer. 39 (20.6%) patients were exposed to both INAQOVI and venetoclax for ≥12 months.

Two (1.1%) patients had a dose reduction of both INAQOVI and venetoclax due to AEs, 8 (4.2%) patients had a dose reduction of INAQOVI only due to AEs, and 17 (9.0%) patients had a dose reduction of venetoclax only due to AEs. 96 (50.8%) patients had a dose interruption/delay of both INAQOVI and venetoclax due to AEs, 9 (4.8%) patients had a dose interruption/delay of INAQOVI only due to AEs, and 55 (29.1%) patients had a dose interruption/delay of venetoclax only due to AEs. 13 (6.9%) patients had both INAQOVI and venetoclax withdrawn due to AEs, 1 (0.5%) patient had INAQOVI withdrawn due to AEs, and 1(0.5%) patient had venetoclax withdrawn due to AEs.

Table 6. Study Treatment Extent of Exposure for INAQOVI and Venetoclax – Phase 1 and Phase 2 Combined (All Treated Population)

	Phase 1 and 2	
	Inaqovi (N=189) n (%)	**Venetoclax (N=189) n (%)**
Duration of Treatment (months)		
Mean (SD)	6.965 (7.1589)	7.265 (7.0349)
Median	4.90	5.22
Min, Max	0.16, 39.10	0.20, 39.13
Number of Patients with Treatment Duration, n (%)		
<3 months	71 (37.6)	68 (36.0)
3-6 months	38 (20.1)	36 (19.0)
≥6 months	80 (42.3)	85 (45.0)
6-9 months	20 (10.6)	26 (13.8)
9-12 months	21 (11.1)	20 (10.6)
>12 months	39 (20.6)	39 (20.6)
Cumulative Dose per Cycle (Subject Level) (mg)		
Mean (SD)	602.58 (94.973)	6892.61 (2493.053)
Median	675.00	7005.00

Min, Max	341.1, 675.0	1200.0, 11550.0
Relative Dose Intensity (%)		
Mean (SD)	91.61 (12.818)	74.30 (25.445)
Median	100.00	80.0
Min, Max	52.2, 100.0	17.6, 105.5
Summary of No. of Cycles Treated		
Mean (SD)	6.1 (5.72)	6.1 (5.72)
Median	4.0	4.0
Min, Max	1, 33	1, 33

Abbreviations: FDC=fixed-dose combination; max=maximum; min=minimum; n=number of patients in a specific subgroup; N=total number of patients; no=numbers; SD=standard deviation

Relative dose intensity was calculated as dose intensity divided by planned dose intensity, expressed as a percentage, where dose intensity was defined as cumulative dose received divided by the planned number of treatment days.

Source: ASTX727-07 Clinical Study Report

3.2.1 The intervention in the context of Danish clinical practice

Amongst patients diagnosed with AML, treatment with SIC consisting of (3+10) treatment with high-dose cytarabine and daunorubicin followed by consolidation therapy is the preferred method of treatment due to its capability to induce and maintain long-lasting remission (23). SIC regimens are associated with considerable toxicity which renders them unsuitable for use in a proportion of the AML patient population (15, 23). This is because patient age or other comorbidities lead to a higher risk of treatment-related mortality, and as such, assessment for SIC eligibility is a critical step prior to initiating treatment for patients with AML (15, 23). Recently, the treatment landscape for patients with AML who are ineligible for SIC has moved towards combination and triplet therapies, with HMA being a key backbone therapy for both emerging standard of care (SoC; VEN + HMA) and current pipeline treatments.

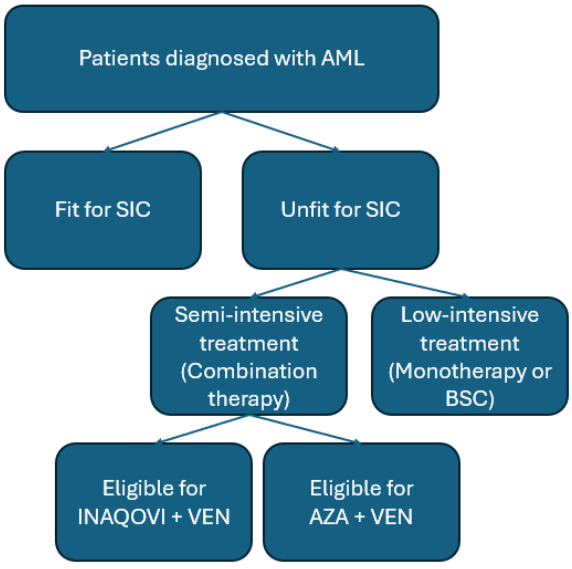
In current clinical practice, it is estimated that 50-60% of AML patients are ineligible for treatment with SIC, and as such receive non-intensive treatments (30, 31). For patients with AML who are ineligible for SIC, VEN + HMA therapy is considered the current SoC (15, 23, 32). However, within the population of AML patients who are ineligible for SIC, there exists a further sub-population of patients for whom VEN and HMA is also unsuitable due to treatment side effects or inability to meet the treatment requirements, such as ECOG PS (33). For patients unsuitable for VEN + HMA, low-intensive treatment such as HMA monotherapy or BSC are available options.

There is a proportion of patients who are ineligible for SIC who may have problems with mobility or be particularly frail, and as such may have difficulty accessing treatment to HMAs (both in combination or as monotherapy) due to the frequent hospital visits (5–7 consecutive days every month) required for intravenous (IV) or SC administration (18).

In the current (from 2024) guidelines from Dansk Akut Leukaemi Gruppe, treatment has been divided into intensive treatment (SIC), semi-intensive treatment (VEN and HMA [e.g. AZA] combination therapy), and low-intensive treatment which can consists of low-dose cytarabine (LDAC) or HMA monotherapy (either SC AZA or IV decitabine are described). The semi-intensive treatment group aligns with the described patient population for this application (3). For these patients, INAQOVI + VEN offers a more convenient, orally administered treatment option that can be taken at home (26). A literature review examining the decreased efficacy of HMAs in real-world studies associated the suboptimal outcomes with underutilization and low adherence to HMA therapies. An oral HMA formulation is speculated to improve persistence and therefore also clinical outcomes (34). Another literature review alongside a patient preference study comparing patient preferences for oral versus IV administered oncologic treatments/parenteral HMA treatments concluded that patients prefer oral treatments over IV treatments. Convenience, perception of efficacy, safety and past experience were factors impacting this patient preference of oral agents (35, 36).

VEN in combination with HMA (e.g. AZA) was approved by the Danish Medicine Council as treatment for patients with newly diagnosed AML who are ineligible for SIC (37). As previously mentioned, INAQOVI + VEN may offer advantages due to its fully oral administration route, potentially reducing healthcare resource use and alleviating patient burden associated with SC administrations. The proposed positioning of INAQOVI + VEN in the AML treatment pathway is presented in Figure 3.

Figure 3 Proposed positioning of INAQOVI + VEN in the treatment pathway of adult patients with newly diagnosed AML



Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; BSC, best supportive care; SIC, standard induction chemotherapy; VEN, venetoclax.

Source: Otsuka based on the guidelines from Dansk Akut Leukaemi Gruppe (3)

3.2.2 ATMP

N/A

3.3 Selection of comparator(s)

The current standard treatment for this indication is VEN in combination with an HMA. According to the AML national care program approved Jan 2024 by Dansk Akut Leukæmi Gruppe, AZA+VEN is mentioned in the semi-intensive treatment category as a first-line treatment option for AML patients who, based on patient- and disease-related factors, are not suitable for intensive chemotherapy (3). Moreover, based on the precedent of the DMC assessment of VEN combination therapy in AML, SC AZA is likewise chosen as comparator. Though there is no head-to-head comparison of AZA + VEN and INAQOVI + VEN, there is indirect evidence that demonstrates the clinical equivalence of INAQOVI + VEN and AZA + VEN (38). As shown by the indirect treatment comparison (ITC) report, across OS and response outcomes, results suggested that INAQOVI + VEN is overall comparable to AZA + VEN for patients with newly diagnosed AML who are ineligible for SIC (38).

Table 7. Comparator overview

Therapeutic indication relevant to the assessment	AZA 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.(39)
Generic name	Azacitidine
ATC code	L01BC07
Mechanism of action	AZA exerts its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of AZA may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to AZA. Incorporation of AZA into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer

	suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of AZA to clinical outcomes has not been established (39) .
Administration method	Subcutaneous (SC)
Packaging type, pack sizes, shelf life and strengths	Strength: AZA 25 mg/mL powder for suspension for injection. Clear glass vial (type I) sealed with bromobutyl rubber stopper and flip-off-seal, containing 100 mg of AZA. Pack size: 1 vial Unopened powder vial: 3 years. After preparation: reconstituted AZA is stable for 45 minutes at 25°C or 8 hours at 2–8°C with unrefrigerated water, and up to 22 hours at 2–8°C with refrigerated water (39).
Package size(s)	Pack size: 1 vial
If vials: Can these be shared?	No
Pre-medication: Should pre-medication be administered? Which one?	No
Co-administration: Should the drug be administered with other drugs? Which ones?	Yes, AZA should be administered in combination with VEN (39).
Need for diagnostics, monitoring or other tests (e.g., *companion diagnostics*)	Complete blood cell counts must be obtained prior to the initiation of treatment, prior to each cycle, and as clinically indicated to monitor response and toxicity, as per SmPC (39).

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; DNA, deoxyribonucleic acid; HSCT, haematopoietic stem cell transplantation; RNA, Ribonucleic acid; SmpC, summary of product characteristics VEN, venetoclax; WHO, World Health Organisation.

Table 8. Comparator in the study and the health economic model

	Study	Health economic model
Dosage and frequency	75 mg per meter2 of body surface area subcutaneously or intravenously on days 1 through 7 every 28-day cycle (4).	100 mg/m2 body surface area (BSA). Five days QD, followed by a rest period of 21 days (28-day treatment cycle) (37, 40, 41). This was accepted by the DMC in the VEN combination therapy assessment (37). SmPC of AZA states 75 mg/m2 BSA QD for seven days (39) and it was

	Study	Health economic model
		incorporated in the model for illustrative purposes only; however 100 mg/m2 BSA during five days achieves similar results and was previously accepted by the DMC (37). This dosing is used in the base case in line with the clinical praxis and it was confirmed by a Danish clinician with experience in treating patients with AML in Denmark (2).
Average dose	N/A	N/A
Criteria for treatment discontinuation	Patients continued to receive treatment until they had disease progression or unacceptable toxic effects, until they withdrew consent, or until they met any protocol-defined criteria (4).	N/A
Treatment duration	It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression. (39)	6 cycles of 28 days each, based on ASCERTAIN-V and VIALE-A studies. The model accounts for treatment discontinuation using multiple parametric extrapolation models.
Dose adjustment: Specify whether/how dose adjustments are applied*	No routine dose reductions of AZA were mandated upfront; adjustments were reactive and based on safety findings during treatment (4).	In the health economic model, it is possible to choose either dosage according to SmPC or according to clinical practice. However, no dose adjustments within the selected number of treatment cycles are possible.
Treatment interruption (pause): Specify whether/how treatment interruptions are applied*	Treatment cannot be paused.	Pausing is not included in the calculation.

Abbreviations: AZA, azacitidine; BSA, body surface area; DMC, Danish Medicines Council; N/A, not applicable; QD, quaque die (once daily); SmPC, Summary of Product Characteristics.

3.4 Subsequent treatment

Danish guidelines position VEN + HMA–based regimens as first-line treatment for AML patients ineligible for intensive chemotherapy, with no routine subsequent active treatment defined after this setting (3). In the previous DMC assessment of VEN + AZA, some subsequent active treatments were reported; however, DMC considered subsequent treatment patterns to be similar between treatment arms and therefore excluded subsequent-treatment costs from the base-case analysis. As no clinically meaningful differences in subsequent treatment are expected between DEC-C + VEN and AZA + VEN, subsequent active treatment is likewise not included in the current health economic analysis, and patients are assumed to receive BSC/palliative care following discontinuation of VEN + HMA.

Table 9. Assumptions regarding subsequent treatment in the health economic analysis

Subsequent treatment	[Intervention] %	[Comparator] %	Average treatment duration including source	Dosage (Dose, frequency and form of administration including source)	Any assumptions regarding dose adjustment and pause including source
N/A					

3.5 Relevant outcomes

3.5.1 Definition of outcomes

Table 10 summarizes the efficacy outcomes included in the comparative analysis (OS, CR, CR+CRh and CR+CRi). The safety outcomes included in the comparative analysis are described in Section 8 with further details provided in Appendix F.

Table 10. Outcomes

Outcome	Follow-up time	Definition
OS	ASCERTAIN-V: median follow up of 11.2 months VIALE-A: median follow up of 20.5 months	ASCERTAIN-V: The time from the date of first dose until death due to any cause. VIALE-A: Time from randomisation until death due to any cause.
CR		

Outcome	Follow-up time	Definition
CR+CRh		Rate of CR, CR + CRh, and CR + CRi will be defined as the number of subjects whose best response is CR, CR or CRh, and CR or CRi divided by the total number of subjects in the All Treated Population (Primary analysis).
CR+CRi		
Safety outcomes		Safety outcomes included in the comparative analysis are described in Section 8 and Appendix F.

3.5.2 Relevance of outcomes

The key outcomes summarised in Table 10 are part of the ITC analysis described in Section 7. Information on the outcomes validity is provided below in Section 3.5.3.

3.5.3 The validity of outcomes

The validity of the selected outcomes is supported by EMA guidance for anticancer and haematological malignancy trials, which recognizes survival, disease response, time-to-event endpoints, and patient-reported outcomes as relevant measures for evaluating treatment efficacy and clinical benefit (42).

4. Health economic analysis

4.1 Basic assumptions

This section describes the model settings. The cost-minimization analysis (CMA) considers costs over a treatment duration of six cycles for both the intervention and the comparator. For the comparator (AZA +VEN) it is assumed that 80% of patients receive SC AZA administration at the hospital, while 20% receive administration at home for three out of five days (37). Further details are presented in Section 11. The overall structure and rationale of the model is further described in Section 4.2.

Table 11. Basic assumptions in the health economic analysis

Assumption regarding	Assumption	Justification
Patient population	Adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with VEN + HMA.	This reflects the patient population for which reimbursement is requested.
Intervention	Orally administrated INAQOVI 35 mg/100 mg, QD day 1 through 5 in 28-day cycles, for	In line with treatment regimen in SmPC and in ASCERTAIN-V trial (26, 28).

Assumption regarding	Assumption	Justification
	at least four cycles + VEN: ramp up Days 1–3 (100 → 200 → 400 mg), then 400 mg daily Days 4–28.	
Comparator(s)	Parenterally administered 100 mg/m2 BSA AZA, QD day 1 through 5 in 28-day cycles, for at least six cycles + VEN: ramp up Days 1–3 (100 → 200 → 400 mg), then 400 mg daily Days 4–28.	100 mg/m2 BSA during five days achieves similar results versus SmPC of AZA 75 mg/m2 BSA QD for seven days (39) and was previously accepted by the DMC (37). This dosing is used in the base case in line with the clinical praxis and it was confirmed by a Danish clinician with experience in treating patients with AML in Denmark (2).
Clinical outcomes	The outcome in the CMA is costs.	Effects (i.e. life-years, quality-adjusted life-years) are not studied as clinical effects are assumed equal.
Analysis type	CMA	Based on the ITC results (38), no clinically relevant differences in efficacy were identified between treatments; therefore, a CMA was deemed appropriate.
Model type	CMA	The ITC results (38), indicate comparable clinical efficacy between treatments; therefore, a CMA was conducted.
Average age at entry into the model	N/A	CMA analysis shows the difference in costs per treatment duration (6 cycles) and does not model patient characteristics.
Time horizon	0.4 years (equals to 6 cycles)	The CMA considers costs per treatment duration (6 cycles), but there is an option to extend the time horizon up to 30 years.
Cycle length	28-day cycle	Reflects treatment cycles of intervention and comparator (26).

Assumption regarding	Assumption	Justification
Half-cycle correction	N/A	The CMA does not include half-cycle correction.

Abbreviations: AML, acute myeloid leukaemia; CMA, Cost-minimization analysis; N/A, not applicable; QD, quaque die (once daily); SmPC, Summary of Product Characteristics; VEN, venetoclax.

4.2 Model type and model structure

A CMA was applied to compare costs for INAQOVI + VEN versus AZA + VEN for the treatment of patients with AML in Denmark. The CMA was developed in Microsoft® Excel®. CMA was considered appropriate as the efficacy of INAQOVI + VEN and AZA + VEN is assumed to be comparable, as described in Section 7. Consequently, the analysis focuses on differences in treatment administration, monitoring, patient time, transportation, and other treatment-related costs.

VEN has the same recommended posology when used in combination with AZA or INAQOVI; however, calculated VEN-related costs differ slightly between the treatment arms due to differences in treatment exposure, including treatment interruptions and dose modifications, as reflected in the model. The health economic model, submitted together with this dossier, presents costs over a treatment duration of six cycles for both the intervention and comparator.

The CMA uses simple traces to follow the proportion of patients on treatment in the intervention and comparator arms. More advanced state transitions, like Markov trace, was not implemented in the model considering the equivalent efficacy and safety profiles of INAQOVI + VEN and AZA + VEN.

The first two sheets in the model are the standard DMC sheets. The “Cover” sheet summarises the key assumptions and the medications used in the CMA, and a colour code defining the user-editable, calculated, and results cells. The “Calculations & Results” sheet presents the drug acquisition costs, total costs and difference between the intervention and the comparator per treatment duration. The “Model inputs” sheet discusses the dosing regimen, the relevant drug administration costs, disease management costs and patient time and transportation costs. Lastly, the “References” sheet presents the links to the sources of information used in the model.

A 3.5% discount rate was applied to the costs. However, the base-case treatment duration was set to 6 cycles of 28-days. Therefore, the base-case model outcomes did not have to be discounted.

Table 12. Choice of health economic analysis, model and model structure

Health economic analysis	Model type	Model structure	Assumptions
CMA	CMA	The difference in costs per treatment	The clinical effects of the intervention and

Health economic analysis	Model type	Model structure	Assumptions
		duration 0.4 year (6 cycles).	comparator are equivalent, according to the ITC results (38).

5. Literature overview

A clinical systematic literature review (SLR) was conducted in February 2025 and updated in January 2026. The full details are provided in Appendix H. The aim of the SLR was to identify clinical efficacy, effectiveness, safety and HRQoL data for INAQOVI, AZA or other HMAs in combination with VEN for the treatment of AML patients ineligible for SIC. The original SLR and subsequent update identified a total of 73 publications reporting on 42 unique studies. The clinical evidence gathered from this SLR as well as update was used to inform an ITC of VEN with INAQOVI against AZA + VEN, VIALE-A representing the most robust source of evidence for AZA + VEN to include in the ITC given its randomised clinical trial (RCT) design, multicentre setting and sufficient reporting of adjustment variables to allow for an unanchored ITC (38). A full-text publication for ASCERTAIN-V was not available at the time searches were conducted, as the manuscript was planned for publication in 2026. Therefore, ASCERTAIN-V was not included in the SLR, and data on file was used to determine comparability of other HMA+VEN trials with ASCERTAIN-V.

5.1 Literature used to assess clinical efficacy and safety

The references used in the assessment of clinical efficacy and safety are included in Table 13.

Table 13. Relevant literature included in the assessment of efficacy and safety

Reference	Study name	NCT number	Study dates (Start date and expected end date, data cut-off and expected data cut-offs)	Used when comparing*
Roboz GJ, Zeidan AM, Mannis GN, Montesinos P, Arnan M, Savona MR, Odenike O, McCloskey JK, Amin HV, Fathi AT, Bernal del Castillo T. All-Oral Treatment of Newly Diagnosed Acute Myeloid Leukemia. New England Journal of Medicine. 2026 Jun 4;394(21):2107-16.(43) (28)	ASCERTAIN-V	NCT04657081	Start: 09/02/21 End:31/12/26 Data cut-off: 30/09/24 (primary analysis)	OS, response outcomes (CR, CR + CRh, CR + CRi) and safety for INAQOVI +VEN vs. AZA + VEN for adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with HMA + VEN.
DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. New England journal of medicine. 2020 Aug 13;383(7):617-29. (4)	VIALE-A	NCT02993523	Start: 02/02/17 End: 01/12/21 Data cut-off: 04/01/20 (primary analysis)	Same as above.

Abbreviations: AML: acute myeloid leukaemia; AZA, azacitidine; CR: complete response; CRh: complete response with partial haematologic recovery; CRi: complete response with incomplete haematological recovery; OS, overall survival; VEN, venetoclax.

5.2 Literature used to assess health-related quality of life

Health-related quality of life (HRQoL) was not collected in ASCERTAIN-V trial. The SLR has identified VIALE-A trial as the only relevant study reporting HRQoL data, and it was included in Table 14.

Table 14. Relevant literature included in the assessment of health-related quality of life

Reference	Instrument and purpose	Identification method (documented in appendix)	Used in paragraph
DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. New England journal of medicine. 2020 Aug 13;383(7):617-29. (4)	EQ-5D-5L for estimating utility values, EORTC QLQ-C30 for assessing cancer-specific HRQoL, and PROMIS Fatigue SF-7a for evaluating fatigue burden.	Systematic literature review (clinical SLR updated in January 2026)	Section 10.

Notes: EQ-5D-5L is a standardized generic HRQoL instrument developed by the EuroQol Group, used to estimate health utility values across five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each assessed on five severity levels. The EORTC QLQ-C30 is a validated cancer-specific HRQoL questionnaire developed by the European Organisation for Research and Treatment of Cancer, comprising functional scales, symptom scales, and a global health status/quality of life scale. PROMIS Fatigue Short Form 7a (PROMIS Fatigue SF-7a) is a patient-reported outcome measure developed by the NIH PROMIS initiative to evaluate the severity and impact of fatigue on daily functioning over the past 7 days.

5.3 Literature used for input into the health economic model

To support assumption used in the model referring to AZA + VEN home administration, a targeted literature review was conducted (Table 15).

Table 15. Relevant literature used in the health economic model

Reference (Full citation including reference number)	Input/estimate	Identification method (documented in appendix)	Used in paragraph
DMC. Venetoclax (Venclyxto) in combination with a hypomethylating agent (37)		Targeted literature review	Section 11.

6. Clinical studies

6.1 INAQOVI + VEN compared to AZA + VEN for adult patients with newly diagnosed AML who are ineligible for SIC

6.1.1 Relevant studies

Decitabine combined with cedazuridine (DEC-C), the oral formulation used in INAQOVI has previously been studied in randomized crossover trials comparing oral DEC-C with intravenous decitabine in patients with myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML). In the ASCERTAIN program, oral DEC-C demonstrated equivalent systemic exposure (AUC) to IV decitabine and a similar safety profile, forming the basis for its monotherapy approval (44). Similarly, the AML registrational cohort of the ASCERTAIN program showed that oral DEC-C achieved comparable systemic exposure to intravenous decitabine with a consistent safety profile, supporting its use as an oral alternative to IV administration in AML patients (45). This proof of concept for the oral formulation established the foundation for using DEC-C as a backbone in combination regimens such as the ASCERTAIN-V trial.

The pharmacokinetics (PK), efficacy and safety of INAQOVI + VEN for the treatment of AML was evaluated in a Phase I/II, single-arm, open-label, multicentre, non-randomised interventional study (ASCERTAIN-V) (28). ASCERTAIN-V was composed of Phase I and Phase II, including Phase II A and Phase II B (Figure 4). The study enrolled adult patients with newly diagnosed AML aged 75 years or older, or who had comorbidities that made them ineligible for SIC (28). The intention-to-treat (ITT) population is in focus for this submission.

Figure 4 ASCERTAIN-V study design



Abbreviations: PK: pharmacokinetic.
Sources: Otsuka Data on File (INAQOVI in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia Clinical Study Report; Figure 2) 2025 (43).

The data cut-off date (DCO) for Phase I was 17th July 2024 (43). The data cut-off date for Phase II Part A and Phase II Part B was 30th September 2024 (28). At the time of the respective data-cuts, a total of 50 patients were still receiving treatment: one (3.3%) patient in Phase I, nine (15.5%) patients in Phase II Part A, and 40 (39.6%) patients in Phase II Part B (28). No further data cut is currently planned.

Treatment was discontinued for 29 (96.7%) patients in Phase I, 49 (84.5%) patients in Phase II Part A, and 61 (60.4%) patients in Phase II Part B (28). For all three parts of the trial, the primary reason for treatment discontinuation was disease progression, which was observed in 14 (46.7%) patients in Phase I, 22 (37.9%) patients in Phase II Part A, and 18 (17.8%) patients in Phase II Part B (28).

At the time of the current analysis (Phase I DCO: 17th July 2024; Phase II Part A and Phase II Part B DCO: 30th September 2024), median follow-up times were as follows: Phase I 34.3 months, Phase II Part A 26.0 months, Phase II Part B 11.2 months.

All enrolled patients in Phase I (n=30), Phase IIA (n=58), Phase IIB (n=101) received at least one dose of study treatment, and thus represent both the enrolled, and treated populations. As all treated patients were included in the analysis of efficacy and safety outcomes, the primary efficacy population is equivalent to the safety population.

In terms of the internal and external validity of the study, Phase I sample size was determined using an equivalence test of means using two one-sided tests (46). It was calculated that a total sample size of ~24 evaluable patients would achieve 75%–89%

power. In Phase II Part A, a sample size of approximately 98–100 subjects was planned offering over 99% power at a 5% significance level for the PK endpoint (46). Phase II Part B sample size was determined using the same methods as Phase II Part A. Moreover, the study has been performed in 50 study centres across North America and Europe, including Canada, USA and Spain, with predefined study endpoints and key inclusion and exclusion criteria (please see Appendix A).

Since the key source of evidence for INAQOVI + VEN is from a single arm trial (ASCERTAIN-V), the comparative efficacy and safety of INAQOVI + VEN versus AZA + VEN has been explored using ITCs. The results are presented below in Table 16 and throughout Section 6 and Section 7.

Table 16. Overview of study characteristics for all studies included in the comparison

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
ASCERTAIN-V (NCT04657081) (28, 43)	Phase I/II single-arm, open-label, non-randomised interventional study	The study included a 21-day screening phase, followed by 28-day treatment cycles, and a 30-day follow-up period. Patients continued treatment until disease progression, unacceptable toxicity, or withdrawal from the study. The median duration of follow-up was 11.2 months.	Adults with newly diagnosed AML who are aged 75 years or older, or who have comorbidities that preclude the use of SIC.	Orally administered INAQOVI (35mg decitabine, 100 mg cedazuridine) on Days 1–5 of every 28-day cycle in combination with VEN (400 mg QD)	AZA (75 mg/m2 per day on day 1–7 of every 28-day cycle in combination with VEN (400 mg QD)	Primary: In Phase I, the primary endpoints were VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2. In Phase II Part A and B, the treatment dosing schedule remained the same as Phase I. However, in Phase II Part A the co-primary endpoints were CR rate and VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2; in Phase II Part B, the pivotal portion of the ASCERTAIN-V trial, the primary endpoint was CR rate. Secondary: Phase I (Decitabine and cedazuridine AUC0–24 and Cmax on Day 5 with VEN; cedazuridine AUC0-8 on Day 5 with VEN in Cycle 2, Incidence and severity of AEs, CR rate, CR+CRh rate, CR+CRi rate, Time to CR or CRh, Duration of CR or CRh, OS, 5-day cumulative decitabine AUC in Cycle 2, Decitabine AUC0–24 and Cmax on Days 1 and 2 in Cycle 2, Cedazuridine AUC0-8 on Days 1, 2, and 5 in Cycle 2; AUC0–24, AUC0-inf and Cmax on Days 1, 2, and 5 in Cycle 2, Cmax, Cmin, Tmax, T1/2), Phase II Part A (Decitabine and cedazuridine AUC0–24, Cmax, AUC0-8, and AUC0-inf on Day 5 with VEN in Cycle 2, Incidence and severity of AEs, CR+CRh rate, CR+CRi rate, Time to CR or CRh, Duration of CR or CRh, OS, Cmax, Cmin, Tmax, T1/2), Phase II Part B (Decitabine and cedazuridine AUC0–24, Cmax, AUC0-8, and AUC0-inf on Day 5 with venetoclax in Cycle 1, Incidence and severity of AEs, CR+CRh rate, CR+CRi rate, Time to CR or CRh, Duration of CR or CRh, OS, Cmax, Cmin, Tmax, T1/2).

Study name, NCT number (reference)	Studio design	Duration of study	Patient population	Intervention	Comparator	Outcomes and follow-up time
VIALE-A (NCT02993523) (4)	Randomised, double-blind, placebo-controlled Phase III study	The median duration of follow-up was 43.2 months.	AML patients ≥18 years old not previously treated for AML ineligible for SIC or cytarabine therapies.	VEN (400 mg QD) in combination with AZA (75 mg/m2 per day for days 1–7 of each four-week cycle	Placebo in combination with AZA (75 mg/m2 per day for days 1–7 of each four-week cycle)	Primary: OS and percentage of participants with CR + CRi - up to ~4.8 years (from study start to death or last follow-up; DCO: 1 December 2021). Secondary: CR rate, EFS, CR+CRh - up to 2 years after last participant randomized; EORTC QLQ-C30 - up to 2 years after last subject last visit; fatigue (PROMIS Cancer Fatigue SF-7a) - up to 3 years after last subject last visit;

Abbreviations: AE: adverse event; AML: acute myeloid leukaemia; AUC: area under the curve; AZA, azacitidine; Cmax: highest concentration of drug in the blood; Cmin: lowest concentration of drug in the blood; CR: complete response; CRh: complete response with partial haematologic recovery; CRi: complete response with incomplete haematological recovery; DCO: data cut-off; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; OS: overall survival; QD: once daily; SIC: standard induction chemotherapy; T1/2: time taken to decrease concentration of drug in the blood by 50%; Tmax: time taken to reach maximum concentration of drug in the blood; VEN, venetoclax.

6.1.2 Comparability of studies

A heterogeneity assessment and outcome availability were conducted to evaluate the comparability of the ASCERTAIN-V trial with the AZA + VEN arm of the VIALE-A trial(38). Variation (or heterogeneity) between studies was assessed across study characteristics, intervention definitions, dose modification approaches and patient baseline characteristics. While both studies evaluated newly diagnosed AML in clinical trial settings, ASCERTAIN-V was a single-arm Phase IIb trial whereas VIALE-A was a Phase III RCT. As a result, any comparison using ASCERTAIN-V individual patient data (IPD) would need to be unanchored and limited to the AZA + VEN arm of VIALE-A. ASCERTAIN-V took place primarily in US study sites (64.4% of patients in US sites) with smaller proportions of patients treated in Canada (3%) and Spain (32.3%). VIALE-A took place across a larger number of countries in different regions, overlapping with ASCERTAIN-V in the US, Canada and Spain. During clinical validation with expert KOLs, geographic region was not considered to be an important determinant of AML outcomes. Regarding baseline characteristics, they are presented below in Section 6.1.2.1.

Additionally, differences in VEN dose-modification strategies for haematologic toxicity and CYP3A inhibitor use were identified and considered during clinical validation with KOLs.

As for the outcomes availability, two measures of composite response, CR+CRi and CR+CRh, were available in both ASCERTAIN-V and VIALE-A, reported as the proportion of patients that had reached CR+CRi or CR+CRh at DCO. Also CR (not as a composite with CRi or CRh) was available in both ASCERTAIN-V and VIALE-A at DCO. For the comparison at DCO, although follow up time at DCO differed between the two trials (median of 11.2 months for ASCERTAIN-V; median of 20.5 months for VIALE-A), both trials continued follow up for sufficiently long to capture first response for all participants that would have achieved a response with HMA+VEN.

For OS, time-to-event data were available in the form of IPD for ASCERTAIN-V and digitizable KM curves for VIALE-A up to both initial (median follow up of 20.5 months) and final DCO (median follow up of 43.2 months). Given the relatively shorter follow-up time for ASCERTAIN-V, it was considered more suitable to use the OS KM curve at the initial DCO from VIALE-A for comparison. For duration of response (DOR), it was not possible to tailor the MAIC weighting approach to this specific analysis set, therefore DOR analyses are not considered to be as reliable as those for OS.

6.1.2.1 Comparability of patients across studies

For most baseline characteristics, ASCERTAIN-V and VIALE-A used comparable or standard definitions, however, the studies differed on how they defined cytogenetic risk. ASCERTAIN-V used the European LeukemiaNet (ELN) 2017 criteria,(47) and VIALE-A used the National Comprehensive Cancer Network (NCCN) v2.2016 criteria (48). Based on clinical validation from global clinical experts, the ELN 2017 and NCCN v2.2016 cytogenetic risk criteria were deemed comparable, with minimal implications from considering NCCN v2.2016 categories to be equivalent to ELN 2017 categories. A summary of baseline characteristics for ASCERTAIN-V and the AZA+VEN arm of VIALE-A is included in Table 17.

Table 17. Baseline characteristics of patients in included studies for the comparative analysis of efficacy and safety

		ASCERTAIN-V	VIALE-A
		Phase II Part B (n=101)[f]	AZA+VEN Arm (n=286)[b]
Age (years)	Mean (SD)	77.8 (5.0)	75.6 (6.1)
	Median (IQR)	78 (6)	76 (NR)
	Less than 75 years	18.8	NR
	75 years or older	81.2	61
Sex	Female	39.6	40
	Male	60.4	60
Race	Asian	6.9	23

		ASCERTAIN-V	VIALE-A
		Phase II Part B (n=101)[f]	AZA+VEN Arm (n=286)[b]
	Black or African American	3.0	1
	White	80.2	76
	Other, unknown or NR	9.9	0
Ethnicity	Hispanic or Latino	7.9	NR
	Not Hispanic or Latino	77.2	NR
	Unknown, NR or missing	14.8	NR
MRC	Positive MRC status	56.4	32
Cytogenetic Risk	Adverse	29.7	36
	Intermediate	33.7	64
	Favorable	31.7	0
	Test failed or missing	5.0	NR
ECOG score	0-1	78.2	55

		ASCERTAIN-V	VIALE-A
		Phase II Part B (n=101)[f]	AZA+VEN Arm (n=286)[b]
	2-3	20.8	45
	Missing	1.0	NR
Genetic mutations	IDH1/IDH2	25.7	25c
	TP53	22.8	23d
	NPM1	14.8	17d
	FLT3-ITD	12.9	NR
	FLT3-TKD	4.0	NR
	FLT3-ITD/FLT3-TKD	14.8	14e
	KRAS	12.9	NR
	NRAS	16.8	NR
	KRAS/NRAS	23.8	NR
	DDX41	3.0	NR

		ASCERTAIN-V	VIALE-A
		Phase II Part B (n=101)[f]	AZA+VEN Arm (n=286)[b]
Bone marrow blasts	Mean (SD) percentage of total cells	45.3 (23.3)[a]	NR
	Bone marrow blasts <30%	34.6	30
	Bone marrow blasts 30% or more	64.4	70
	Missing	1.0	NR
Concomitant CYP3A inhibitor therapy	Strong CYP3A inhibitor	72.3	7.7
	Moderate CYP3A inhibitor	6.9	14.3
	Any CYP3A inhibitor	74.3	22.0

Footnotes: [a]1 missing, denominator is 100; [b] For AZA+VEN, percentages are included from several different data sources for VIALE-A, therefore, percentages are rounded based on how they were reported in the original publications;(4, 49, 50) [c] Denominator 245; [d] Denominator 163; [e] Denominator 206; [f]ASCERTAIN-V baseline characteristics were obtained from the ASCERTAIN-V Clinical Study Report (Phase 2b all-treated population, N=101; data cut-off September 2024) (43). Any differences between these values and those reported in Roboz et al. (2026) (28) arise from post hoc reclassification of cytogenetic risk, updated mutation assessment methods, and alternative definitions of transfusion dependence used in the publication.

Abbreviations: CYP3A, cytochrome P450 family 3A; DDX, DEAD-box helicase; ECOG, Eastern Cooperative Oncology Group; F, female; FLT, fms-like tyrosine kinase; IDH, isocitrate dehydrogenase; KRAS, kirsten rat sarcoma viral oncogene homolog; M, male; MRC, myelodysplastic-related changes; NPM, nucleophosmin; NRAS, neuroblastoma rat sarcoma viral oncogene homolog; TP, tumour protein.

6.1.3 Comparability of study population(s) with Danish patients eligible for treatment

According to a Danish clinical expert, the study population in ASCERTAIN-V is considered representative of AML patients treated in Danish clinical practice (2).

The input used in the CMA is mean BSA as presented below. This parameter is essential as the dosing of AZA is based on the patient's BSA. Other specific patient characteristics were not considered to have a material impact on the model results and were therefore not included in the CMA.

Table 18. Characteristics of the relevant Danish population and input parameters in the health economic model

	Danish population	Study population (43)	Health economic model (43)
Mean BSA	Not found	1.83	1.83

6.1.4 Analysis method

Analyses were primarily descriptive due to the single-arm design of the ASCERTAIN-V study. Pharmacokinetic endpoints (e.g., AUC0-24 and Cmax) were summarised using standard pharmacokinetic exposure metrics. Clinical efficacy endpoints, including complete remission (CR) according to ELN 2017 criteria, were summarised using proportions with corresponding 95% confidence intervals. Time-to-event outcomes such as OS and duration of response were analysed using Kaplan–Meier methods (29, 51).

No comparative modelling (e.g., hazard ratio estimation) was performed due to the absence of a control arm. Analyses were conducted in the treated population of enrolled patients receiving study treatment (29, 51).

Please note that Section 6.1.5 presents the key efficacy results from Phase II Part B (median follow-up: 11.2 months), which represents the pivotal efficacy population of the ASCERTAIN-V trial.

6.1.5 Effect – results per ASCERTAIN-V study

In the ASCERTAIN-V study, primary objective in Phase I was to assess VEN pharmacokinetic exposures (AUC0–24 and Cmax) when given with oral DEC-C (INAQOVI) versus when given without oral DEC-C (28). PK analyses demonstrated that co-administration of VEN with oral DEC-C did not result in a clinically significant drug-drug interaction (28). The geometric mean ratio for VEN AUC0–24 in the presence vs absence of DEC-C was approximately 102%, indicating equivalent exposure (28).

In the pivotal Phase II B cohort (n ≈ 101), oral DEC-C plus VEN was associated with favourable remission rates and durable clinical benefit. Detailed results for CR, composite response rates, duration of response, and overall survival are presented

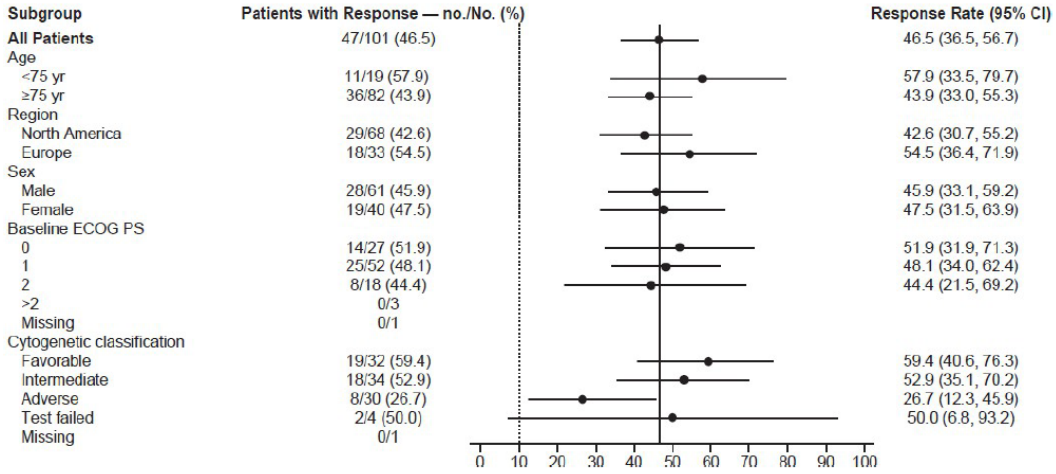
below. Outcomes for Phase II included pharmacokinetic parameters (AUC0–24 and Cmax), and efficacy endpoints including CR + CRi, duration of response, time to response, and overall survival (28).

Primary endpoint: complete response (Phase II Part B)

After a median follow-up of 11.2 months, the primary endpoint of CR rate as determined by investigator assessment was 46.5% (95% CI: 36.5, 56.7), with CR achieved by 47 patients (28, 43). The efficacy results from Phase II Part A and Phase I support these results, indicating the Phase II Part B efficacy results are robust.

A subgroup analysis of CR rates based on age, gender, baseline Eastern Cooperative Oncology Group (ECOG) performance status (PS), region and cytogenetic classification, demonstrated that CR rates were generally consistent across these subgroups, relative to the overall cohort (28). Full subgroup analysis results are presented in Figure 5. (28).

Figure 5 Forest plot of CR rate by subgroup in Phase II Part B (all treated population, N=101)



Abbreviations: CI: confidence interval; CR: complete response; ECOG: Eastern Cooperative Oncology Group.
Source: Supplementary Appendix to Roboz et al. (2026), All-oral treatment of newly diagnosed acute myeloid leukemia (Figure S3) (28).

Secondary endpoint: composite response rates

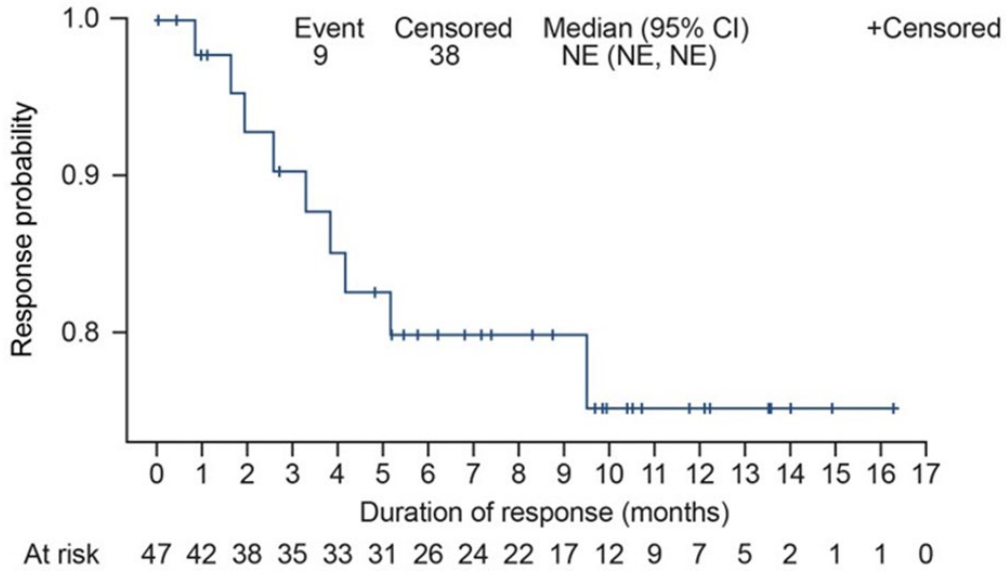
CR+CRh was achieved by 52 (51.5%) patients (95% CI: 41.3, 61.6), and CR+CRi was achieved by 64 (63.4%) patients (95% CI: 53.2, 72.7) (28).

Secondary endpoints: duration of response and time to response

At the time of DCO (30th September 2024), median DOR for both CR and CR or CRh was not reached (28). The CR responders remaining in response at 3 and 6 months were 90.4% and 80.0% of all responders, respectively; CR or CRh responders remaining in response at 3 and 6 months were 88.1% and 77.8% of all responders, respectively. KM estimate of DOR for CR is presented in Figure 6. The median times to CR, and CR or CRh

measured by investigator assessment were 2.4 months and 2.1 months, respectively (28).

Figure 6 KM estimate of DOR for CR by investigator assessment in Phase II Part B (all responders, CR N=47; CR or CRh N=52)

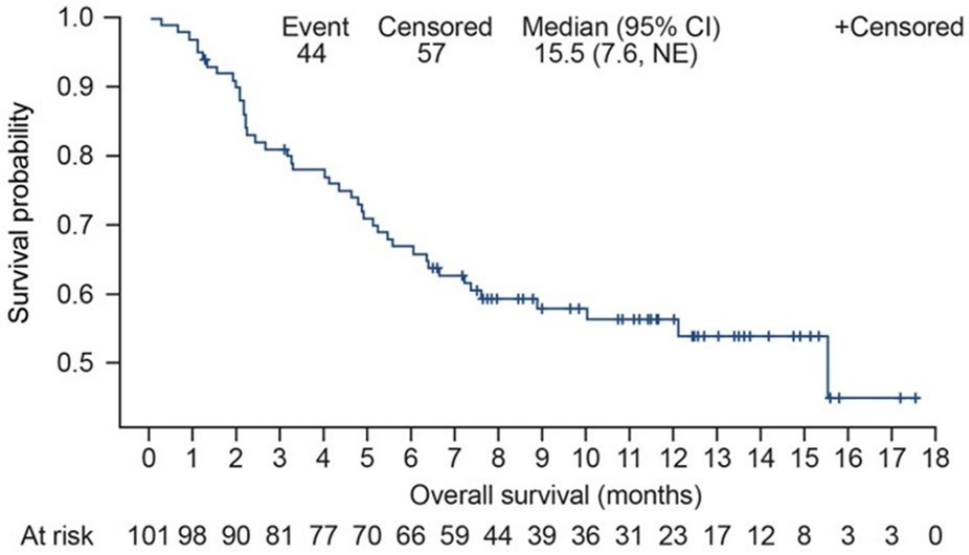


Abbreviations: CI: confidence interval; CR: complete response; CRh: complete response with partial haematologic recovery; DOR: duration of response; KM: Kaplan-Meier; NE: Not evaluable.
Source: Otsuka Data on File (INAQOVI in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia Clinical Study Report; Figure 7) 2025 (43).

Secondary endpoint: overall survival

At the time of the DCO, OS data were mature. These data demonstrated that the median OS for patients treated with INAQOVI + VEN was 15.5 months (95% CI: 7.6, NE) and the estimated OS at 6 months was 66.9% (95% CI: 56.7, 75.2) in Phase II Part B, as shown in Figure 7 (28, 43).

Figure 7 KM estimate of OS in Phase II Part B (all treated population, N=101)



Footnotes: At DCO (30th September 2024), OS data were mature.

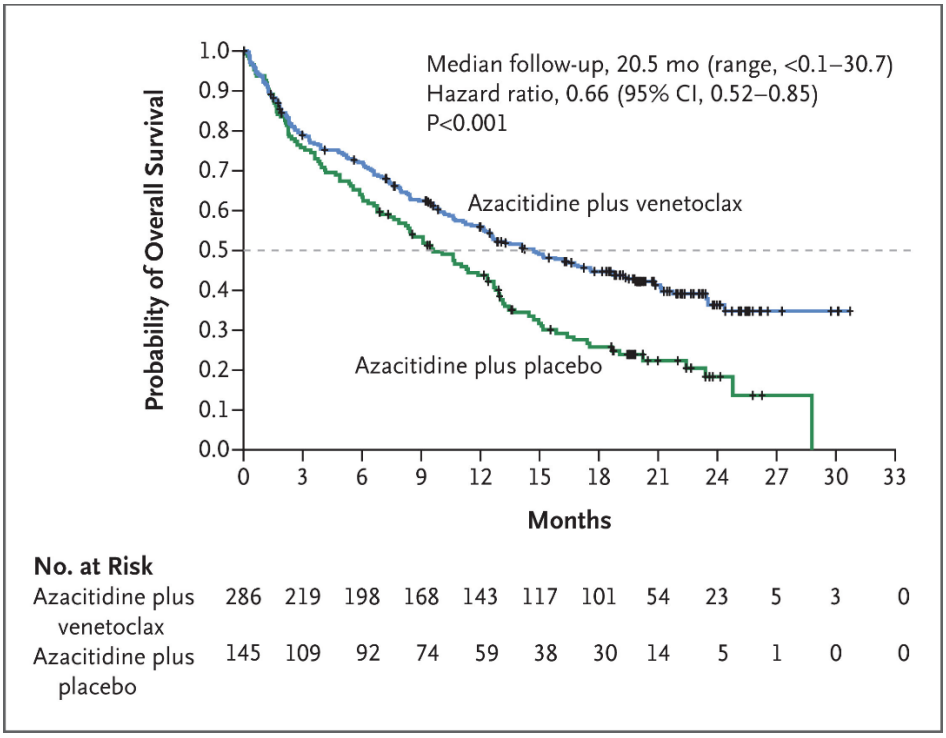
Abbreviations: CI: confidence interval; KM: Kaplan-Meier; NE: Not evaluable; OS: overall survival.
Source: Otsuka Data on File (INAQOVI in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia Clinical Study Report; Figure 8) 2025 (43).

6.1.6 Effect – results per VIALE-A study

Primary endpoint: overall survival

The median duration of follow-up was 20.5 months (range, <0.1 to 30.7). The median OS was 14.7 months (95% confidence interval [CI], 11.9 to 18.7) in the AZA + VEN group and 9.6 months (95% CI, 7.4 to 12.7) in the control group (hazard ratio for death, 0.66; 95% CI, 0.52 to 0.85; P<0.001), as shown in Figure 8 (4).

Figure 8 KM estimate of OS in the VIALE-A trial



Abbreviations: CI: confidence interval; KM: Kaplan-Meier; OS: overall survival.

Source: (4)

Secondary endpoint: response outcomes (CR + CRi; CR; CR+CRh) and duration of response (DOR)

Composite complete remission (CR + CRi) was achieved in 66.4% (95% CI, 60.6 to 71.9) of the patients in the AZA + VEN group and 28.3% (95% CI, 21.1 to 36.3) of the patients in the control group (P<0.001). The median duration of CR + CRi was 17.5 months (95% CI, 13.6 to not reached [NR]) in the AZA + VEN group and 13.4 months (95% CI, 5.8 to 15.5) in the control group. Complete remission (CR) was achieved in 36.7% and 17.9% of the patients, respectively (P<0.001), and the duration of CR was 17.5 months (95% CI, 15.3 to NR) and 13.3 months (95% CI, 8.5 to 17.6) (4).

Similarly, complete remission plus complete remission with partial hematologic recovery (CR+CRh) was achieved in 64.7% (95% CI, 58.8 to 70.2) of the patients in the AZA + VEN group and in 22.8% (95% CI, 16.2 to 30.5) of those in the control group (P<0.001)(4). The duration of response was 17.8 months (95% CI, 15.3 to NR) and 13.9 months (95% CI, 10.4 to 15.7), respectively.

7. Comparative analyses

7.1 Method of analysis

Given its established use in ITCs submitted to HTA bodies, unanchored MAIC was used as the primary population-adjusted ITC approach and applied to all outcomes analyzed (38).

The matching-adjusted indirect comparison MAIC approach is a form of population adjusted indirect comparison designed to mitigate between-study differences in eligibility criteria and adjust for between-study differences in baseline characteristics, resulting in a fairer comparison between interventions. In practice, MAIC re-weighs individual patient data (IPD) from one trial (ASCERTAIN-V) to the published baseline summary statistics of another trial (VIALE-A) (38).

In an unanchored comparison, the absence of a common comparator means that no adjustment is made by default for between-trial differences in PVs, which is protected by randomization in a simple anchored Bucher ITC of RCT evidence (52). Consequently, the compared study populations must be balanced not only in distributions of all treatment effect modifiers (TEMs), as would be the case for any ITC, but also prognostic variables (PVs)(52). TEMs and PVs were identified as part of the preliminary evidence synthesis assessment through targeted review of published literature and subsequently validated by global clinician experts in the treatment of AML, as part of the feasibility assessment (FA).

Based on the feasibility assessment, the primary MAIC analysis adjusted for age, adverse cytogenetic risk, ECOG performance score, MRC status and gender, as defined below.

- *Age:* defined as ≥75 years or <75 years
- *ECOG:* defined as ≤2 or >2 (up to 2 and greater than 2)
- *Cytogenetic risk:* defined using ELN 2017 criteria for ASCERTAIN-V and NCCN v2.2016 criteria for VIALE-A, dichotomising into adverse/poor cytogenetic risk vs other (inclusive of favourable and intermediate risk categories); poor cytogenetic risk under NCCN v2.2016 criteria were considered to be equivalent to adverse cytogenetic risk under ELN 2017. Further individual genetic mutations were assessed for heterogeneity, and it was concluded that adjustment for these in addition to adverse cytogenetic risk as defined by ELN 2017/NCCN v.2.2016 criteria was not required
- *Gender:* defined as male or female
- *MRC status:* defined as whether MRC is present

A sensitivity analysis additionally adjusting for concomitant CYP3A inhibitor therapy use, defined as no CYP3A inhibitors, moderate CYP3A or P-gp inhibitors, or strong CYP3A inhibitors was recommended and further details are provided in Appendix D.

Sample size and baseline characteristics

The full ITT sample size was 101 for ASCERTAIN-V, the sample without cytogenetic risk imputation (complete case analysis) was 95 patients, and the primary analysis dataset after imputation of cytogenetic risk was 98 patients.

The reported sample size for the AZA+VEN arm in VIALE-A was 286. Since VIALE-A was considered to have similar eligibility criteria to ASCERTAIN-V, no population restriction was performed, except in a sensitivity analysis specified to further explore differences in cytogenetic risk (more details in Appendix D). Baseline characteristics before and after weighting are presented in Appendix D.

MAIC Weighting

Following population adjustment, baseline characteristics in ASCERTAIN-V were successfully matched to the AZA + VEN arm of VIALE-A.(38) After weighting, the effective sample size for the ASCERTAIN-V population was approx. 56 patients, representing a ~43% reduction from the original sample size (38). Further details and the weights used are presented in Figure 19 in Appendix D.

7.2 Results from the comparative analysis

Absolute and relative results from the comparative analysis of INAQOVI + VEN vs. AZA + VEN are summarized in Table 19. MAIC-weighted difference in RMST was selected as the primary ITC method for OS. For response outcomes, an unanchored MAIC approach to compare absolute odds of each binary outcome (CR, CR+CRh, CR+CRi) was applied. There was no statistical difference between INAQOVI+VEN and AZA+VEN across outcomes (OS and response outcomes).

Table 19. Results from the comparative analysis of INAQOVI + VEN vs. AZA + VEN for adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with VEN + HMA

Outcome	INAQOVI + VEN (N=101)	AZA + VEN (N=286)	Result (MAIC comparison)
OS	Median: 15.5 months (95% CI: 7.4, NR)	Median: 14.7 months (95% CI: 11.9, 18.7)	RMST model (17.5 months): 0.697 (95% CI: -1.073, 2.466)
CR	46.5% (95% CI: 36.5, 56.7)	36.7% (95% CI: NR, NR)	Unanchored ITC using MAIC (DCO): 1.721 (95% CI: 0.952, 3.108)
CR+CRh	51.5% (95% CI: 41.3, 61.6)	64.7% (95% CI: 58.8, 70.2)	Unanchored ITC using MAIC (DCO): 0.636 (95% CI: 0.352, 1.147)

Outcome	INAQOVI + VEN (N=101)	AZA + VEN (N=286)	Result (MAIC comparison)
CR+CRi	63.4 % (95% CI: 53.2, 72.7)	66.4% (95% CI: 60.6, 71.9)	Unanchored ITC using MAIC (DCO): 1.209 (95% CI: 0.659, 2.221)

Footnotes: The primary analysis results were based on unanchored ITC using MAIC to adjust for population-level covariates. Response outcomes were assessed at the data cut-off (DCO) corresponding to the initial VIALE-A DCO, as most patients treated with HMA + VEN achieve first response within the first four cycles, several months before DCO in both trials. OS was assessed using RMST at 17.5 months, representing the latest evaluable time point with stable comparative estimates between treatments.

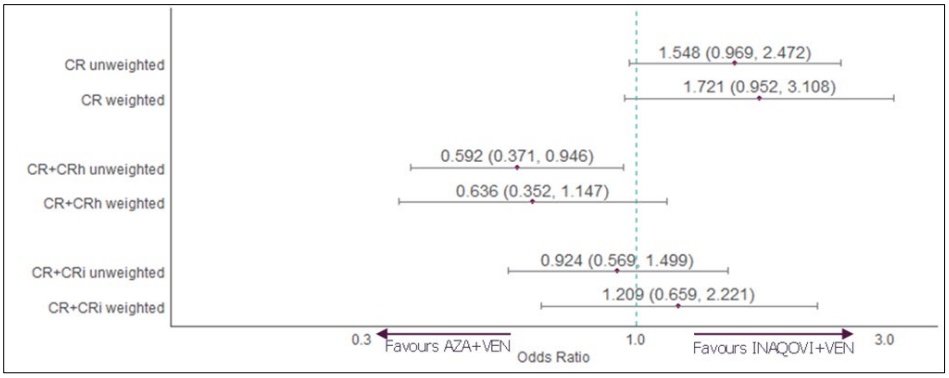
Abbreviations: AML: acute myeloid leukaemia; AZA, azacitidine; CI, confidence interval; CR: complete response; CRh: complete response with partial haematologic recovery; CRi: complete response with incomplete haematological recovery; DCO: data cut-off; HMA, hypomethylating agents; OS: overall survival; MAIC, matching-adjusted indirect treatment comparison; NR, not reported; Restricted mean survival time; VEN, venetoclax.

7.3 Effect – results per response outcomes

For response outcomes estimated using MAIC, there was no statistical difference between INAQOVI + VEN and AZA + VEN across outcomes (38). Population adjustment via the MAIC led to improved results for INAQOVI + VEN compared to unweighted results.

Odds ratios obtained from the MAIC at DCO suggest that INAQOVI + VEN was numerically favoured with respect to CR and comparable to AZA + VEN with respect to CR+CRi, with CR+CRh results numerically favouring AZA + VEN (Figure 9) (38).

Figure 9 Forest plot of MAIC-weighted results for response outcomes at data cutoff



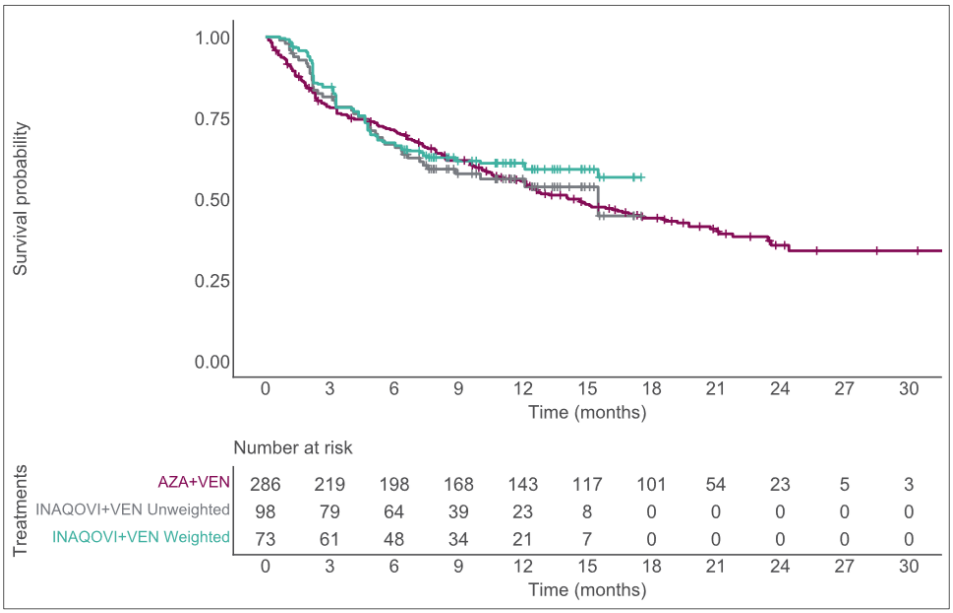
Abbreviations: AZA+VEN: azacitidine in combination with venetoclax; CR: Complete response; CR+CRi: complete response or complete response with incomplete hematologic recovery; CR+CRh: complete response or complete response with partial hematologic recovery; INAQOVI+VEN: INAQOVI in combination with venetoclax; MAIC: matching-adjusted indirect treatment comparison.

Source: Otsuka Data on File (Unanchored Indirect Comparisons —Technical Report) (38).

7.4 Effect – results per OS

OS was assessed using time-to-event data from ASCERTAIN-V and reconstructed Kaplan-Meier data from VIALE-A. Median OS prior to population adjustment was 15.5 months for INAQOVI + VEN and 14.7 months for AZA + VEN (38). Following MAIC weighting, median OS for INAQOVI + VEN in the population matched to VIALE-A was not reached, indicating that data may be immature when weighting is applied (Figure 10) (38).

Figure 10 KM curves for OS using MAIC weights from primary analysis



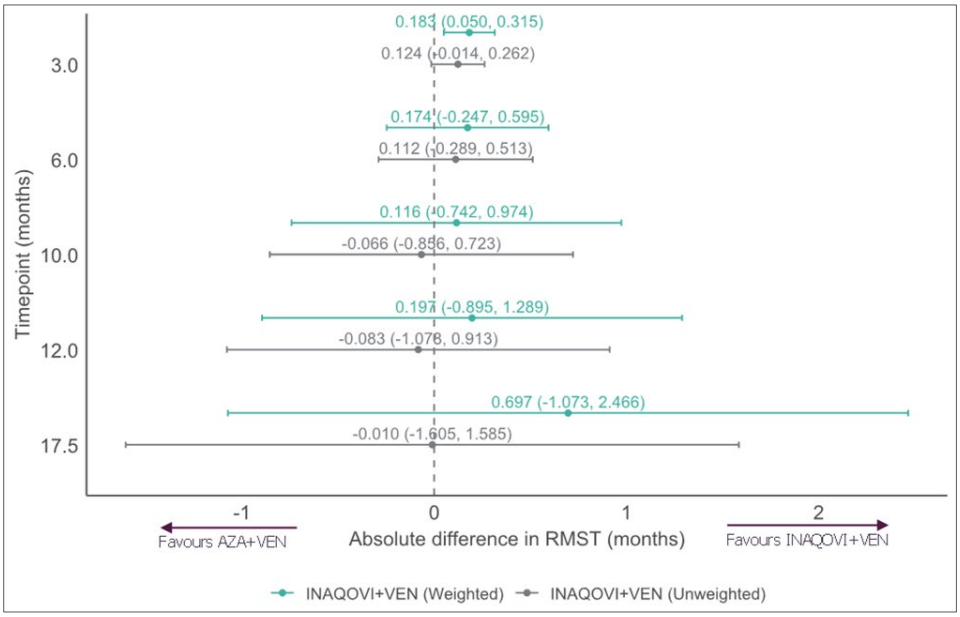
Abbreviations: AZA+VEN: azacitidine in combination with venetoclax; INAQOVI+VEN; INAQOVI in combination with venetoclax; KM: Kaplan-Meier; OS: overall survival.

Source: Otsuka Data on File (Unanchored Indirect Comparisons —Technical Report) (38).

The PH assumption was evaluated using both a log-log survival plot and Schoenfeld residual plot. The PH assumption was considered to be violated based on the log-log plots (38). Additionally, three separate cut-off points were attempted for a piecewise Cox model based on inspection of the log-log plot. Consequently, hazard ratios calculated from piecewise Cox models would not adequately account for non-proportional hazards (38).

Restricted mean survival time (RMST) does not rely on the PH assumption and was therefore considered a robust alternative to hazards ratios calculated from the Cox PH model in the presence of non-proportional hazards. MAIC-weighted RMST for OS was statistically significantly greater for INAQOVI + VEN compared with AZA + VEN at three months, indicating longer OS before three months (Figure 11) (38). For all subsequent timepoints, OS was not statistically significant between treatments. Uncertainty was higher at later timepoints due to instability in RMST uncertainty estimates close to the end of the time horizon for the KM curve.

Figure 11 Absolute difference in RMST between INAQOVI+VEN and AZA+VEN by timepoint for OS for the primary analysis using MAIC weights



Abbreviations: AZA+VEN: azacitidine in combination with venetoclax; INAQOVI+VEN: INAQOVI in combination with venetoclax; OS: overall survival; RMST: restricted mean survival time.

Source: Otsuka Data on File (Unanchored Indirect Comparisons —Technical Report) (38).

Using the unweighted curve for INAQOVI + VEN, difference in RMST was not statistically significantly different between INAQOVI + VEN vs. AZA + VEN at any timepoint. Population adjustment via the MAIC led to improved results for INAQOVI + VEN compared to unweighted results, however, statistically significant differences were only observed at the three-month timepoint (38). During clinical validation, KOLs confirmed that they did not expect OS results to meaningfully differ between INAQOVI + VEN and AZA + VEN (38).

8. Safety

For ASCERTAIN-V, safety analyses were performed independently for Phase I (N=30), Phase II Part A (N=58), and Phase II Part B (N=101) on the safety population, which included all patients who were enrolled in the study who received any amount of study treatment (28). At the time of the current analysis (Phase I DCO: 17th July 2024; Phase II Part A and Phase II Part B DCO: 30th September 2024), median follow-up times were as follows: Phase I 34.3 months, Phase II Part A 26.0 months, Phase II Part B 11.2 months.

In the VIALE-A study, 427 patients were included in the safety analysis (283 in the AZA + VEN group and 144 in the control group). The median duration of follow-up was 20.5 months. An overview of AEs events in ASCERTAIN-V and VIALE-A is provided in Table 20.

Table 20. Overview of adverse events in ASCERTAIN-V and VIALE-A studies

	ASCERTAIN-V (28)			VIALE-A (4)	
	Phase I (N=30) n (%)	Phase II A (N=58) n (%)	Phase II B (N=101) n (%)	AZA + VEN (N=283) n (%)	AZA + Placebo (N=144) n (%)
All adverse events (AE), n (%)	30 (100.00)	58 (100.0)	100 (99.0)	283 (100)	144 (100)
Serious AE (SAE), n (%) [1]	19 (63.3)	45 (77.6)	85 (84.2)	235 (83)	105 (73)
AE grade ≥ 3, n (%) [2]	26 (86.7)	53 (91.4)	99 (98.0)	279 (99)	139 (97)
Dose reduction due to AE, n (%)	7 (23.3)	5 (8.6)	14 (13.9)	NR (3)	NR (4)
Treatment discontinuation due to AE, n (%)	0	6 (10.3)	9 (8.9)	NR (24)	NR (20)

Footnotes: MedDRA Version 27.0; Treatment-emergent adverse events are defined as events that first occur or worsen on or after the date of the first study treatment (C1D1) until 30 days after the last dose of study treatment. The median duration of follow-up was 34.3 months for ASCERTAIN-V Phase I, 26.0 months for ASCERTAIN-V Phase II A, 11.2 months for ASCERTAIN-V Phase II B and 20.5 months for VIALE-A study.

Abbreviations: AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; N: number of patients; NR, not reported; SAE: serious adverse event.
Source: Roboz et al. (2026), All-oral treatment of newly diagnosed acute myeloid leukemia (Table 3)(28)

Table 21 shows the number and proportion of patients with adverse events in ASCERTAIN-V and VIALE-A studies. For ASCERTAIN-V, all treatment-related adverse event reported in at least 20% within Phase I, Phase II Part A or Phase II Part B are summarized. Likewise, for VIALE-A study, adverse events reported in at least 20% of patients in either treatment group are listed.

Table 21. Proportion of patients with adverse events in ASCERTAIN-V and VIALE-A studies

	ASCERTAIN-V (28)						VIALE-A (4)			
	Phase I (N=30) n (%)		Phase II A (N=58) n (%)		Phase II B (N=101) n (%)		AZA + VEN (N=283) n (%)		AZA + Placebo (N=144) n (%)	
	All	Grade ≥ 3	All	Grade ≥ 3	All	Grade ≥ 3	All †	Grade ≥ 3 ‡	All †	Grade ≥ 3 ‡
Febrile Neutropenia	0	0	14 (24)	14 (24)	25 (25)	25 (25)	118 (42)	118 (42)	27 (19)	27 (19)
Diarrhoea	NR	NR	NR	NR	NR	NR	117 (41)	13 (5)	48 (33)	4 (3)
Anaemia	6 (20)	6 (20)	15 (26)	13 (22)	33 (33)	30 (30)	78 (28)	74 (26)	30 (21)	29 (20)
Constipation	10 (30)	1 (3)	6 (10)	0	8 (8)	0	121 (43)	2 (1)	56 (39)	2 (1)
Hypokalaemia	NR	NR	NR	NR	NR	NR	81 (29)	30 (11)	41 (28)	15 (10)
Neutrophil Count Decreased	16 (53)	16 (53)	16 (28)	16 (28)	21 (21)	20 (20)	NR	NR	NR	NR
Nausea	6 (20)	0	10 (17)	0	20 (20)	0	124 (44)	5 (2)	50 (35)	1 (1)
Platelet Count Decreased	11 (37)	11 (37)	17 (29)	17 (29)	27 (27)	25 (25)	NR	NR	NR	NR
Decreased Appetite	NR	NR	NR	NR	NR	NR	72 (25)	12 (4)	25 (17)	1 (1)

	ASCERTAIN-V (28)						VIALE-A (4)			
	Phase I (N=30) n (%)		Phase II A (N=58) n (%)		Phase II B (N=101) n (%)		AZA + VEN (N=283) n (%)		AZA + Placebo (N=144) n (%)	
Neutropenia	1 (3)	1 (3)	13 (22)	13 (22)	26 (26)	26 (26)	119 (42)	119 (42)	42 (29)	41 (28)
Fatigue	NR	NR	NR	NR	NR	NR	59 (21)	8 (3)	24 (17)	2 (1)
Oedema Peripheral	NR	NR	NR	NR	NR	NR	69 (24)	1 (<1)	26 (18)	0
White Blood Cell Count Decreased	5 (17)	5 (17)	17 (29)	17 (29)	15 (15)	15 (15)	58 (21)	58 (21)	20 (14)	17 (12)
Thrombocytopenia	2 (7)	2 (7)	6 (10)	5 (9)	22 (22)	20 (20)	130 (46)	126 (45)	58 (40)	55 (38)

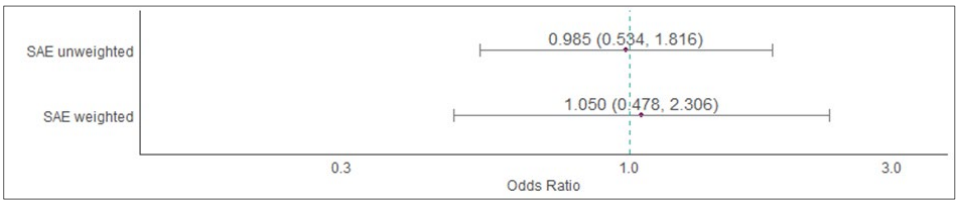
Note: The relatedness of adverse events to treatment was determined by the investigator. Shown are events that occurred in at least 20% of the patients in any group.
Abbreviations: AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients in a specific subgroup; TEAE: treatment-emergent adverse event; SAE: serious adverse event.

Source: Roboz et al. (2026), All-oral treatment of newly diagnosed acute myeloid leukemia (Table 3). (28) and (4)

During the ITC (previously described in Section 7), SAEs were evaluated to compare the safety profiles of INAQOVI + VEN and AZA + VEN (38).

Across both the unweighted ITC and MAIC for SAEs, odds ratios were close to one suggesting that patients receiving AZA + VEN had similar odds of experiencing SAEs compared to INAQOVI + VEN (Figure 12). Population adjustment via the MAIC did not lead to meaningfully different results compared to the unweighted comparison. The expected similarity in the safety profile between the intervention and the comparator was also confirmed by a Danish clinician with experience in treating patients with AML in Denmark (2).

Figure 12 Forest plot of MAIC-weighted results for SAE



Abbreviations: AZA+VEN: azacitidine in combination with venetoclax; INAQOVI+VEN: INAQOVI in combination with venetoclax; MAIC: matching-adjusted indirect treatment comparison; SAE: serious adverse events.

Source: Otsuka Data on File (Unanchored Indirect Comparisons —Technical Report).(38)

9. Extrapolation of patient transitions

9.1 Clinical data for extrapolation of patient transitions

The analysis considers only the transition from on treatment to treatment discontinued. Time to treatment discontinuation (TTD) is modelled independently for INAQOVI + VEN and AZA + VEN. The extrapolated TTD curves determine the proportion of patients continuing to receive treatment and therefore the duration of treatment-related drug and administration costs.

The TTD includes progression, unacceptable toxicity, death, withdrawal or another protocol-defined reason. The extrapolation for INAQOVI + VEN was based on patients remaining on treatment in the ASCERTAIN-V study. A fully parametric TTD curve was fitted to the available patient-level data investigating Exponential, Weibull, Gompertz, lognormal, log-logistic and generalized gamma distributions. The lognormal distribution was selected for the base case because it had the best BIC (rank 1), and a near-best AIC (rank 2).

For AZA + VEN, patient-level TTD data from VIALE-A were not available. Therefore, time on treatment (ToT) was approximated based on the reported median ToT of 7.4 months. An exponential distribution was calibrated to the reported median, corresponding to a

log-rate of -2.3680. The model therefore assumes a constant discontinuation hazard beyond the reported median.

Separate treatment duration curves are used because ASCERTAIN-V was a single-arm study and VIALE-A was a separate randomized trial, and the available data differed between the studies. The ASCERTAIN-V TTD extrapolation was based on patient-level data, whereas the VIALE-A ToT was approximated from the reported median. Consequently, differences between the curves may reflect differences in study populations, follow-up, treatment management and discontinuation practices, as well as differences in the underlying data and modelling approaches.

9.2 Extrapolation using parametric extrapolation models

9.2.1 Extrapolation of time to treatment discontinuation (TTD)

Extrapolated data for all examined models

Figure 13 - Extrapolated data for all examined models and KM (INAQOVI + VEN)

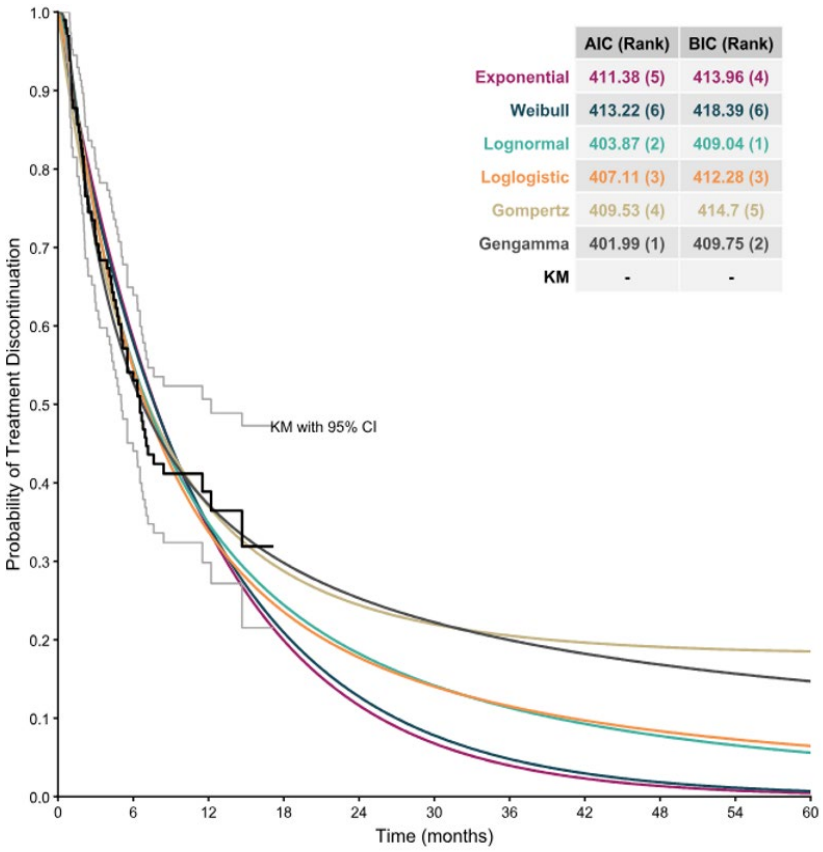
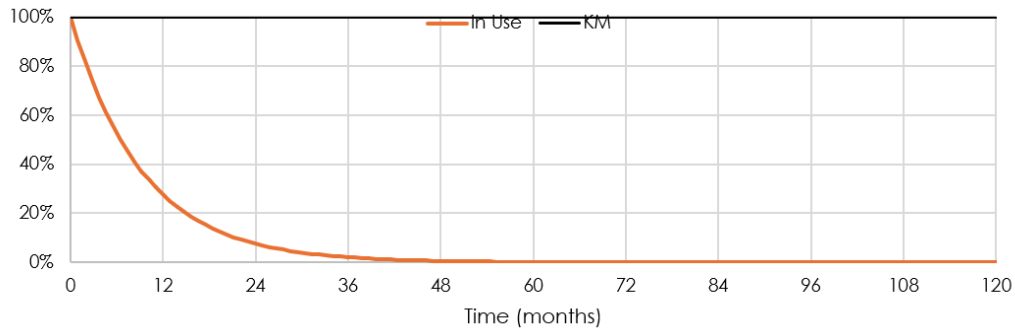


Figure 14 - Extrapolated data for all examined models (exponential) and KM (AZA + VEN)



Extrapolated data for the selected models comparing INAQOVI + VEN and AZA + VEN

Figure 15 - Extrapolated data for the selected models comparing INAQOVI + VEN (lognormal) and AZA + VEN (exponential)

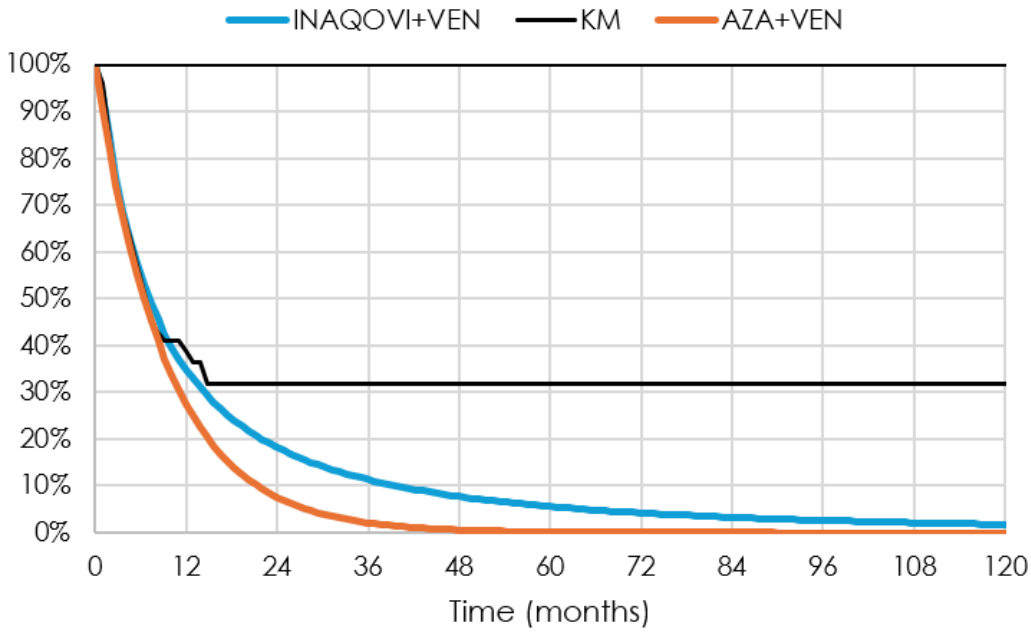


Table 22. Overview of assumptions regarding extrapolation of TTD

Method/approach	Description/assumption
Data	Intervention: INAQOVI+ Venetoclax, informed by ASCERTAIN-V. Comparator: azacitidine + Venetoclax, informed by VIALE-A.
Selected distribution	Intervention: lognormal. It ranked first by BIC and second by AIC. Comparator: exponential, calibrated to the VIALE-A median treatment exposure because a comparator patient-level TTD curve was unavailable for the present analysis. Comparator log-rate: −2.22895 per month; assumed variance: 0.0167 (same as for INAQOVI + Venetoclax)
Models investigated	Intervention: exponential, Weibull, Gompertz, log-normal, log-logistic and generalized gamma models were investigated. Comparator: a median-calibrated exponential model was used. Alternative comparator distributions could not be robustly estimated from the published VIALE-A median alone. The model allows for selecting the between the remaining exponential models, but these are based on the same analysis as for the intervention.
Assumptions	
Proportional hazards between intervention and comparator	No
Flexible parametric models	No
Cure point and/or share	No
Treatment waning	No
Any other assumptions	No
Internal validity	
Distribution with best AIC fit	Intervention: generalized gamma, AIC rank 1. Comparator: not assessable, as only one extrapolation model (exponential) was considered based on published aggregate data
Distribution with best BIC fit	Intervention: lognormal, BIC rank 1.

Method/approach	Description/assumption
	Comparator: not assessable from published aggregate data.
Distribution(s) with best visual fit on probability scale (e.g., Kaplan-Meier data)	Intervention: Gengamma Comparator: not applicable
Distribution(s) with best visual fit according to evaluation of smoothed hazards	Intervention: Not assessed. Comparator: Not assessed.
External validity	
References for validating external validity	Intervention: None; Not assessed based on the available evidence. Comparator: None; external validity was not assessed based on the available evidence.
Distribution with highest external validity	Intervention: Not assessable, as external validity was not evaluated. Comparator: Not assessable, as external validity was not evaluated.

9.2.2 Extrapolation of [clinical endpoint 2]

N/A

9.3 Extrapolation using transition probabilities

N/A

Table 23. Transition probabilities in the health economic model

From health state	To health state	Transition probability, including calculation	Assumption	Reference
A	*A*	*E.g., S(t+Δt)/S(t)*	*E.g., time-dependent, and different between arms as …*	*[study name]*
	B	*E.g., 1− S(t+Δt)/S(t)*	*…*	

From health state	To health state	Transition probability, including calculation	Assumption	Reference
	C	*…*		
B	*B*	*E.g., 0.05* $1 - e^{-\lambda t}$*, where* λ *is the hazard rate and* t *is the cycle length*	*E.g., constant over time and the same in both arms*	
	…	*…*		

Table 24. Transition matrix for [intervention/comparator]

Off/On	State A	State B	State C	…
State A	*S(t+Δt)/S(t)*	*1− S(t+Δt)/S(t)*	*…*	
State B	*…*	*0.05*	*…*	
State C				
…				

9.4 Summary and validity of extrapolated patient transitions

N/A

Table 25. Modeled averages in years, undiscounted estimates, half-cycle corrected and adjusted for background mortality

	[Intervention]	[Comparator]	Difference
Total life years			
Life years in [health state A]			
Life years in [health state B]			

	[Intervention]	[Comparator]	Difference
Duration of treatment [Drug A]			
Duration of treatment [Drug B]			
...			

10. Health-related quality of life

10.1 Overview

HRQoL data were not collected in ASCERTAIN-V trial. However, oral-based treatment regimens could address a crucial, unmet medical need and improve the HRQoL of patients with AML, as suggested by the patient preference study and confirmed by a Danish clinician with experience in treating patients with AML in Denmark (2, 35). It should be noted that no HRQoL benefit is claimed for the CMA presented in this submission, but potential differences are captured through resource use, and patient time/transportation assumptions. The claim for non-inferiority is supported the totality of clinical evidence, including efficacy and safety.

As the SLR (Appendix I) has identified VIALE-A trial as the only relevant study reporting HRQoL data, Table 26 includes an overview of the patient reported outcomes instruments from the VIALE-A study. The primary VIALE-A publication did not report formal HRQoL or patient-reported outcome analyses (4), therefore, no further information was included in Section 10.2. As a result of the above-mentioned factors, no HRQoL comparison could be performed between the VIALE-A and ASCERTAIN-V studies.

Table 26. Overview of included instruments for health-related quality of life

Instrument	Median follow-up time and data cut	Application	Source	Reference to description
EQ-5D-5L	Median follow-up: 20.5 months (4 January 2021)	Utility values and HRQoL assessment	VIALE-A	NR
EORTC QLQ-C30	Median follow-up: 20.5 months (4 January 2021)	HRQoL and symptom assessment	VIALE-A	NR

Instrument	Median follow-up time and data cut	Application	Source	Reference to description
PROMIS Cancer Fatigue SF 7a	Median follow-up: 20.5 months (4 January 2021)	Assessment of fatigue-related HRQoL and patient-reported symptoms	VIALE-A	NR

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol 5-Dimension 5-Level questionnaire; HRQoL, health-related quality of life; NR, not reported; PROMIS Cancer Fatigue SF 7a, Patient-Reported Outcomes Measurement Information System Cancer Fatigue Short Form 7a.

Table 27. Basis for estimating utility values

Instrument	Preference weights	Source	Short description
N/A			

10.2 Instruments

N/A

10.2.1 ["Instrument 1"]

10.2.1.1 Study design and instrument ["instrument 1"]

N/A

10.2.1.2 Data collection ["instrument 1"]

N/A

Table 28. Overview of responses [create a table for both intervention and comparator]

Time	Number of patients "at risk "* at time t (expected number of responses) N	Number of responses at time t N	Proportion of responses out of the number of patients "at risk " at time t** %	Proportion of responses out of the number of patients at randomisation*** %
N/A				

* Number of patients "at risk": Patients who have not died or been censored before time *t*, and who are therefore expected to complete the questionnaire. Patients who have discontinued treatment must be counted.

**Proportion of responses out of patients "at risk" at time *t* = number of responses at time *t*/number of patients "at risk" at time *t*.

***Proportion of responses since randomization = number of responses at time *t*/number of patients at randomisation.

Table 29. Overview of responses by health state [create a table for both intervention and comparator]

Health state	Number of responses in health state N	Number of patients who have provided at least one response in the health state N
N/A		

10.2.1.3 Results ["instrument 1"]

N/A

Example of a figure showing average change over time in a given measure of health-related quality of life:

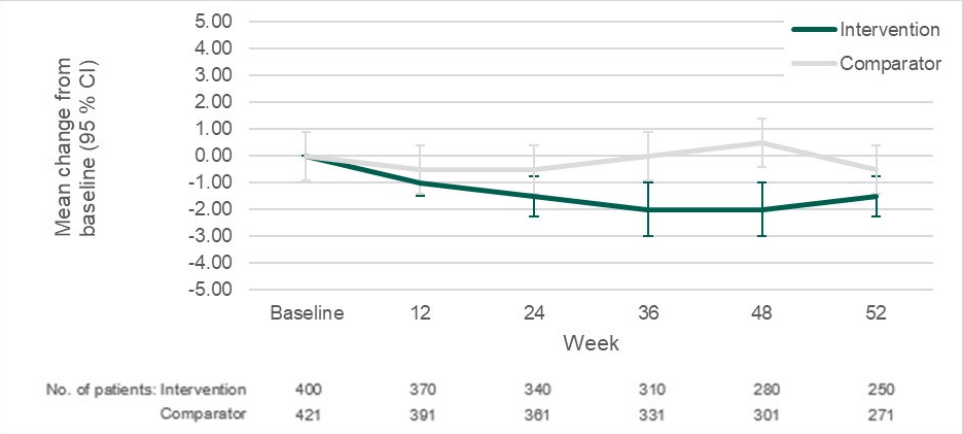


Table 30. Results for [instrument 1]

Time	Intervention	Comparator	Difference
	Average (SE)	Average (SE)	Difference (95%CI)
N/A			

10.2.2 ["Instrument 2"]

10.2.2.1 Study design and instrument ["instrument 2"]

N/A

10.2.2.2 Data collection ["instrument 2"]

N/A

10.2.2.3 Results ["instrument 2"]

N/A

10.2.3 Summary when reporting multiple instruments

N/A

10.3 Utility values

10.3.1 Dataset(s)

N/A

10.3.2 Calculation of utility values

N/A

10.3.3 Adverse events, comorbidity and other state-specific adjustments to the utility values

N/A

10.3.4 Results for utility values

N/A

Table 31. Utility values used in the health economic model

	Utility value [95% CI]	Instrument, preference weight	Source and reference
Main analysis			

	Utility value [95% CI]	Instrument, preference weight	Source and reference
State A	0.761 [0.700-0.810]	EQ-5D-5L, UK	Study 1, Section 10.3.2
State B			
...			
Decrease in health-related quality of life			
...			
State A			
...			

11. Cost calculations

This CMA includes drug acquisition costs, administration costs, disease management and patient costs as described in the following sections. Costs related to disease progression were not included, as compared treatments were assumed to have similar disease progression profile.

All costs were adjusted in each cycle respectively based on the selected TTD curves of the intervention and comparator.

11.1 Drug costs

11.1.1 Drug costs for intervention and comparator

The packaging of INAQOVI is adapted to the treatment regimen, including five tablets for each day of the treatment cycle. No drug wastage was assumed for this treatment arm. No vial sharing for AZA is assumed in the estimation of medicine costs.

The Apotekets Inkøbspris (AIP) for INAQOVI is 28,032.72 DKK for a package of 5 tablets with 35 mg decitabine and 100 mg cedazuridine. The AIP for AZA is 498.00 DKK for a package of 4 mL of 25 mg/mL.

11.1.2 Drug costs for subsequent treatment

Danish guidelines position VEN + HMA–based regimens as first-line treatment for AML patients ineligible for intensive chemotherapy, with no routine subsequent active treatment defined after this setting (3). Therefore, no differential subsequent treatment costs were included in the CMA.

11.2 Hospital costs

11.2.1 Administration

The HMA is administered via IV or SC, though as AZA is considered as comparator and is mostly administered via SC, IV administration is not considered. It is assumed that 20% of patients can administer AZA + VEN at home for three out of the five days of administration and therefore do not incur administration costs for these administrations, based on clinical practice reported in the DMC report of VEN and HMA combination therapy submission (37). For these patients, administration costs for AZA administered at home are not applied; instead, the analysis includes a hospital preparation fee for AZA and the cost of delivery of the prepared medication to the patient's home per treatment cycle that are further described in Section 11.4. For the remaining two out of five administration days, and for the remaining 80% of patients attending the hospital daily for 5 days per cycle for SC administration of AZA, the cost shown in Table 32 has been applied. The duration of each SC hospital administration is assumed to be 1.25 hour. No administration costs are included for oral therapies.

Table 32. Assumptions regarding administrative costs

Route of administration	Diagnosis and procedure codes*	DRG group	Unit cost, DKK
SC	MDC17 1-dagsgruppe, pat. mindst 7 år	17MA98	2,114.00 DKK

11.2.2 Disease management

Disease management requirements associated with VEN initiation during the first treatment cycle were considered equal between treatment arms and were therefore not included in the CMA, in line with the cost-minimisation approach focusing on differential costs only. The analysis accounts for differences in disease management between patients treated with INAQOVI + VEN and AZA + VEN. It is assumed that 20% of patients self-administer AZA at home and are monitored through one specialist consultation per treatment cycle. For the remaining patients receiving hospital-based SC administration of AZA, no separate disease management costs are applied, as monitoring is assumed to occur during administration visits. For INAQOVI + VEN, it was assumed one specialist consultation per treatment cycle in accordance with monitoring recommendations from SmPC. The duration of each SC hospital visit is assumed to be 1.25 hours.

Table 33. Assumptions regarding costs for disease management

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
Specialist visit consultation (hematology)	Once per cycle (28 days)	1.25 h	MDC17 1-dagsgruppe, pat. mindst 7 år	17MA98	2,114.00 DKK

11.2.3 Treatment monitoring

Treatment monitoring is assumed to take place during the specialist consultation visit in each treatment cycle for INAQOVI + VEN, as well as for home administration of AZA +VEN. For hospital-administered AZA +VEN, treatment monitoring is assumed to occur during the SC administration visit at the hospital. For more details, please see Section 11.2.1 and Section 11.2.2 above. As mentioned, the CMA accounts for routine disease and treatment monitoring in line with clinical practice. However, no companion diagnostics or specific predictive diagnostic tests are required for the intervention.

Table 34. Assumptions regarding costs for treatment monitoring

Activity/Pathway	Frequency	Duration	Diagnosis and procedure codes*	DRG group	Unit cost
N/A					

*Include other patient information if relevant to the selection of DRG group; A = action diagnosis; P = procedure.

11.2.4 Management of adverse events

As shown by the ITC results and confirmed by a Danish clinician with experience in treating patients with AML in Denmark, the two therapies are overall comparable in terms of safety (2, 38). Therefore, it is assumed that AEs are similar and will be managed in the same way regardless of the patient is treated with INAQOVI + VEN or AZA + VEN. Therefore, all costs associated with management of adverse events are excluded and are hence not relevant in this CMA.

Table 35. Assumptions regarding costs for management of adverse events

Adverse event	Proportion		Diagnosis codes*	DRG group	Unit cost
	[Intervention]	[comparator]			
N/A					

*Include relevant procedure codes and other patient information if relevant for the selection of DRG group; A = action diagnosis; B = secondary diagnosis.

11.2.5 Other hospital costs

Azacitidine is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing AZA suspensions (39). Procedures for proper handling and disposal of anticancer medicinal products should be applied (39). Therefore, it is assumed that AZA is prepared by healthcare professionals. Regardless of where the injection is administered (hospital or home setting), the suspensions need to be prepared. Consequently, for home-administered AZA (three out of five days for 20% of patients), a single preparation fee per cycle was applied (~DKK 411, 20% of DRG 49PR06 "Hjælpeprocedure, ukompliceret" [DKK 2,053]), based on the assumption that AZA is bulk-prepared for self-administration as per Danish KOL input (2). Furthermore, delivery costs are assumed equal to patient transport costs (150 DKK per one delivery per cycle), with hospital-prepared AZA delivered once per cycle to self-administering patients' homes as per Danish KOL input (2). Other hospital costs were not included, as these were assumed to be equal between treatment arms and therefore not relevant for this CMA.

11.3 Patient costs

Patient costs differ between treatment arms due to differences in the frequency of hospital visits for SC administration and monitoring. These costs include both patient time and transportation.

For INAQOVI + VEN, patient costs are associated with one specialist visit per treatment cycle for disease management and monitoring.

For AZA + VEN, patient costs are linked to two components:

- SC administration visits at the hospital, where 80% of patients are assumed to attend the hospital for all administrations, while 20% are assumed to attend only two out of five administration days.
- Disease management visits, where 20% of patients are assumed to have one specialist visit per treatment cycle.

Table 36. Assumptions regarding patient time

Activity	Frequency of activity	Time spent on activity	Transport time	Note
Specialist consultation visit for INAQOVI + VEN	One visit per treatment cycle	1.25 hours 200 DKK per hour	1 hour 150 DKK per visit per DMC guidelines (53)	Includes disease management and monitoring.

Activity	Frequency of activity	Time spent on activity	Transport time	Note
SC administration visit for AZA + VEN (80% of patients)	Five days according to the clinical practice per cycle (28-days)	1.25 hours 200 DKK per hour	1 hour 150 DKK per visit per DMC guidelines (53)	Applies to 80% of patients receiving hospital-administered SC AZA.
SC administration visit for AZA + VEN (20% of patients)	Hospital visit on 2 out of 5 administration days	1.25 hours 200 DKK per hour	1 hour 150 DKK per visit per DMC guidelines (53)	Applies to 20% of patients with reduced hospital administration visits.
Specialist consultation visit for AZA + VEN (20% of patients)	One visit per treatment cycle	1.25 hours 200 DKK per hour	1 hour 150 DKK per visit per DMC guidelines (53)	Includes disease management and monitoring for 20% of patients.

11.4 Other costs

N/A

12. Results

The results of the CMA are presented below in Table 37. Incremental costs were calculated as INAQOVI + VEN minus AZA + VEN; therefore, negative values indicate cost savings for INAQOVI + VEN and positive values indicate cost savings for AZA + VEN. The difference in costs between INAQOVI + VEN and AZA + VEN is 110,510 DKK only considering the drug acquisition costs, and 70,537 considering all costs, when following dosing according to clinical practice (AZA + VEN) for 6 cycles. [redacted] A full per oral administration treatment alternative is assumed to increase adherence to the treatment. Furthermore, elderly patients may suffer from injection reactions and side effects after treatment with subcutaneous AZA. These injection reactions may come with an additional cost, which are excluded in this CMA.

Since HMA + VEN combinations are mainly life prolonging treatment and not curatively intended, quality of life and less time spend in hospitals have high priority when choosing treatment alternatives.

Table 37. Results, discounted estimates, half-cycle corrected (where relevant) and adjusted for background mortality

	INAQOVI + VEN	AZA + VEN	Difference
Drug costs	303,278 DKK	192,768 DKK	110,510 DKK
Drug costs for subsequent treatment	N/A	N/A	N/A
Administration	0	41,895 DKK	-41,895 DKK
Disease management	10,262 DKK	2,067 DKK	8,195 DKK
Treatment monitoring	N/A	N/A	N/A
Management of adverse events	N/A	N/A	N/A
Patient costs	1,942 DKK	8,215 DKK	-6,273 DKK
Other costs, e.g., co-medication	N/A	N/A	N/A
Total costs	**315,483 DKK**	**244,946 DKK**	**70,537 DKK**
Life years in health state A	N/A	N/A	N/A
Life years in health state B	N/A	N/A	N/A
Total life years	**N/A**	**N/A**	**N/A**
QALYs in health state A	N/A	N/A	N/A
QALYs in health state B	N/A	N/A	N/A
Total QALYs	**N/A**	**N/A**	**N/A**
Incremental costs per life year gained	**N/A**		
Incremental costs per QALY gained (ICER)	**N/A**		

Table 38 shows the drug costs for each drug part of the two combination therapies, INAQOVI + VEN and AZA + VEN. The small difference in VEN costs between the treatment arms (1,224 DKK) is driven by differences in the modelled treatment duration and resulting VEN exposure. As described above, treatment duration for INAQOVI + VEN is based on the ASCERTAIN-V TTD extrapolation using patient-level data, whereas treatment duration for AZA + VEN is approximated based on the median ToT reported in VIALE-A.

Table 38. Results per drug of the two combination treatments

	Drug costs
Intervention: INAQOVI	136,084 DKK
Intervention: Venetoclax	167,194 DKK
Comparator: Azacitidine	24,351 DKK
Comparator: Venetoclax	168,418 DKK

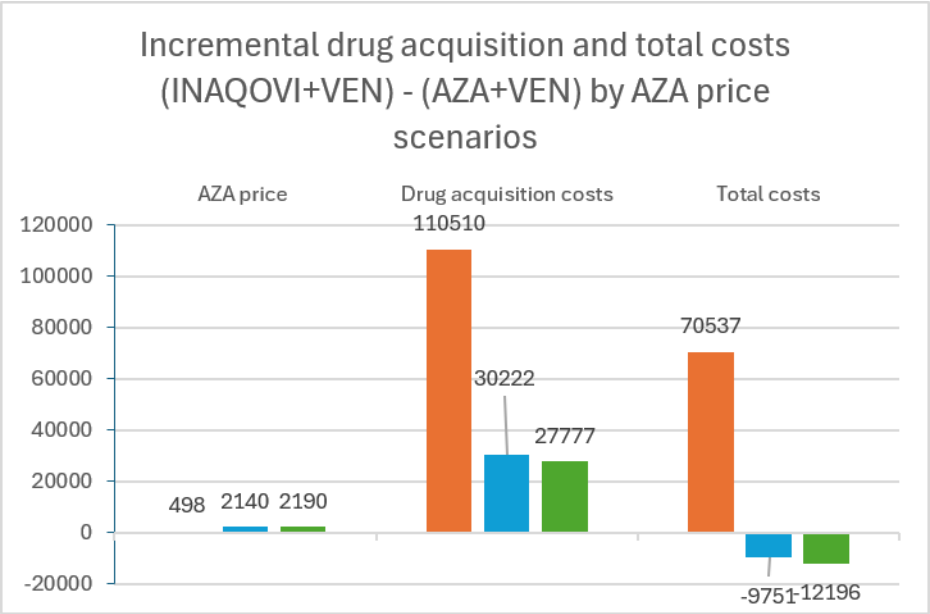
12.1 Sensitivity analyses

Given the cost-minimization framework of the model, sensitivity analyses are presented in Section 12.1.1 to illustrate the impact on incremental costs. As parameter distributions were not available, uncertainty in comparator costs was explored through scenario analyses using three alternative comparator price assumptions, incorporating differences in observed comparator prices and dosing assumptions derived from SmPC dosing versus clinical practice dosing. Moreover, additional parameters were varied to further explore uncertainty, with the resulting scenarios presented in Table 39.

12.1.1 Deterministic sensitivity analyses

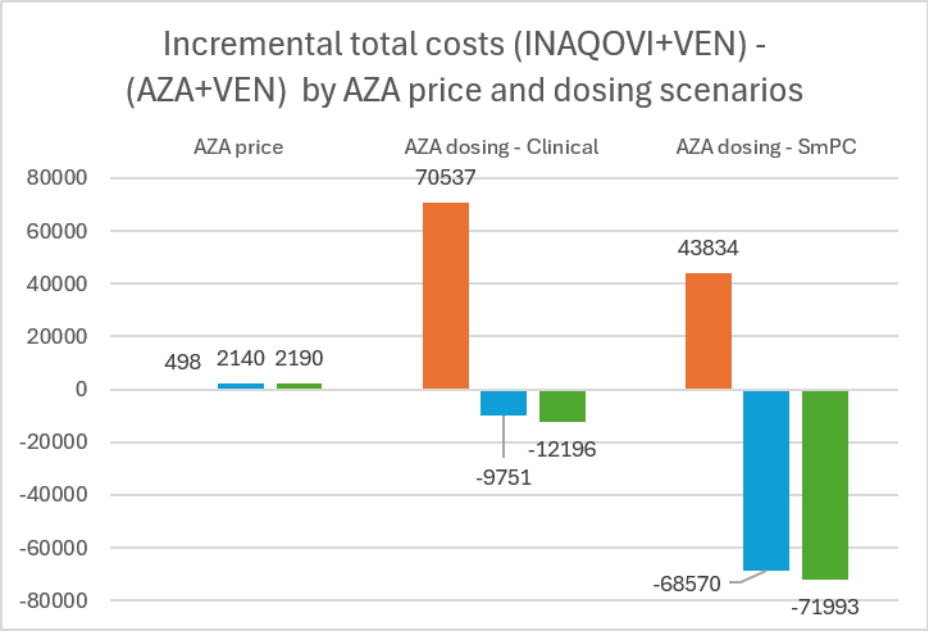
Incremental costs were explored by varying the price of AZA (Figure 16) and by varying the price of AZA together with the dosing scenario: AZA administered according to clinical practice vs. administered according to SmPC, given the fact that both dosing regimens are recognized as appropriate treatment options in the 2024 clinical guidelines (Figure 17). Incremental costs were calculated as INAQOVI + VEN minus AZA + VEN; therefore, negative values indicate cost savings for INAQOVI + VEN and positive values indicate cost savings for AZA + VEN. The AZA price scenarios are included solely for sensitivity analysis purposes and should not be interpreted as a comparison of AZA products or market prices in Denmark. As only one AZA product is currently sold in Denmark, the scenarios are intended to illustrate the impact of alternative acquisition cost assumptions on the results. Additional scenario analyses were conducted to explore the uncertainty and they are summarized in Table 39 below.

Figure 16 Incremental costs INAQOVI+VEN minus AZA+VEN by AZA price scenarios (DKK)



Note: Colours correspond to the different comparator acquisition prices (AIPs) presented in the first set of bars and are applied consistently across all outcomes in the figure. Orange represents the comparator with an AIP of DKK 498, blue represents the comparator with an AIP of DKK 2,140, and green represents the comparator with an AIP of DKK 2,190.

Figure 17 Incremental costs INAQOVI+VEN minus AZA+VEN by AZA price and dosing scenarios (DKK)



Note: Colours correspond to the different comparator acquisition prices (AIPs) presented in the first set of bars and are applied consistently across all outcomes in the figure. Orange represents the comparator with an AIP of DKK 498, blue represents the comparator with an AIP of DKK 2,140, and green represents the comparator with an AIP of DKK 2,190.

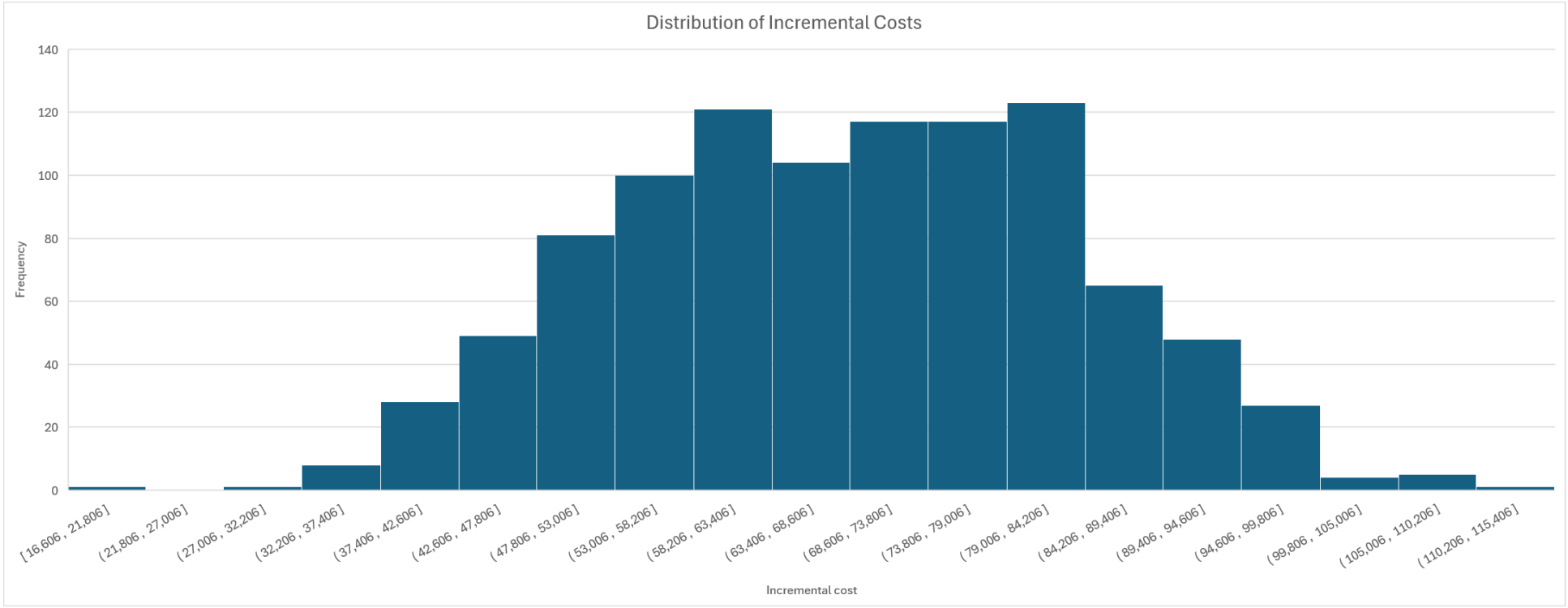
Table 39. Results of deterministic sensitivity analyses

Deterministic sensitivity analysis	Incremental costs	Incremental QALYs	ICER
Base case	Drug acquisition costs: 110,510 DKK Total costs: 70,537 DKK	N/A	N/A
Time for a hospital visit: 2 h	Drug acquisition costs: 110,510 DKK Total costs: 68,185 DKK	N/A	N/A
Number of specialist visit consultation per cycle per patient: 2 visits for INAQOVI+VEN and also for AZA+VEN (home admin)	Drug acquisition costs: 110,510 DKK Total costs: 78,732 DKK	N/A	N/A
Gengamma extrapolation for INAQOVI + VEN TTD	Drug acquisition costs: 103,973 DKK Total costs: 63,738 DKK	N/A	N/A
		N/A	N/A

12.1.2 Probabilistic sensitivity analyses (PSA)

A histogram was prepared visualising the total incremental costs between INAQOVI + VEN and AZA + VEN based on 1000 iterations of a PSA. The incremental costs are presented in Figure 18.

Figure 18 PSA results - Distribution of the incremental total costs



13. Budget impact analysis

Not applicable, in accordance with the DMC guidelines and the communication provided during the DMC pre-meeting indicating that a budget impact analysis was not required.

Table 40. Budget impact (non-discounted estimates), DKK

	Year 1	Year 2	Year 3	Year 4	Year 5
Regional costs of recommendation					
Drug costs	[x]	[x]	[x]	[x]	[x]
Other regional hospital costs	[x]	[x]	[x]	[x]	[x]
Total by recommendation	[x]	[x]	[x]	[x]	[x]
Regional costs of non-recommendation					
Drug costs	[x]	[x]	[x]	[x]	[x]
Other regional hospital costs	[x]	[x]	[x]	[x]	[x]
Total for non-recommendation	[x]	[x]	[x]	[x]	[x]
Total budget impact	[x]	[x]	[x]	[x]	[x]

14. List of experts

[redacted]

15. References

1. Joint Nordic HTAB. Products suitable for joint HTA through JNHB. 2025.

[redacted]

3. Dansk Akut Leukæmi Gruppe. Behandling af patienter med akut myeloid leukæmi (AML). 2024.
4. DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-29.
5. De Kouchkovsky I, Abdul-Hay M. Acute myeloid leukemia: a comprehensive review and 2016 update. Blood Cancer J. 2016;6(7):e441.
6. Kumar CC. Genetic abnormalities and challenges in the treatment of acute myeloid leukemia. Genes Cancer. 2011;2(2):95-107.
7. Licht JD, Sternberg DW. The molecular pathology of acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2005(1):137-42.
8. Siveen KS, Uddin S, Mohammad RM. Targeting acute myeloid leukemia stem cell signaling by natural products. Mol Cancer. 2017;16(1):13.
9. The Lecturio Medical Concept Library. Acute Myeloid leukaemia - Classfication and survival rate. Available at: https://www.lecturio.com/concepts/acute-myeloid-leukemia/. Last accessed: March 2025 2022 [
10. National Cancer Institute. Acute myeloid leukemia treatment (PDQ®) – patient version. Available at: https://www.cancer.gov/types/leukemia/patient/adult-aml-treatment-pdq. Last accessed: March 2025 [
11. American Cancer Society. Cancer facts & figures. 2022. Available at: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf. Last accessed: March 2025.
12. De Angelis R, Minicozzi P, Sant M, Dal Maso L, Brewster DH, Osca-Gelis G, et al. Survival variations by country and age for lymphoid and myeloid malignancies in Europe 2000–2007: Results of EUROCARE-5 population-based study. European Journal of Cancer. 2015;51(15):2254-68.
13. Association of Nordic Cancer R, International Agency for Research on C. NORDCAN: Acute myeloid leukemia (AML), both sexes, survival data (Denmark), 2019–2023. 2026.
14. Mayo Clinic. Acute myelogenous leukemia. 2024. [Available from: https://www.mayoclinic.org/diseases-conditions/acute-myelogenous-leukemia/symptoms-causes/syc-20369109.
15. Heuser M, Ofran Y, Boissel N, Mauri SB, Craddock C, Janssen J, et al. Acute myeloid leukaemia in adult patients: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(6):697-712.
16. Otsuka Data on File. Clinical Validation Meeting Minutes. December 2022.
17. Ito T, Sanford D, Tomuleasa C, Hsiao HH, Olivera LJE, Enjeti AK, et al. Healthcare resource utilization trends in patients with acute myeloid leukemia ineligible for intensive chemotherapy receiving first-line systemic treatment or best supportive care: A multicenter international study. Eur J Haematol. 2022;109(1):58-68.
18. Fujimaki K, Miyashita K, Kawasaki R, Tomita N, Ishigatsubo Y. Efficacy and safety of a 5-day regimen of azacitidine for patients with high-risk myelodysplastic syndromes. Blood. 2014;124(21):1929-.
19. Crawford R, Sully K, Conroy R, Johnson C, Doward L, Bell T, et al. Patient-Centered Insights on Treatment Decision Making and Living with Acute Myeloid Leukemia and Other Hematologic Cancers. Patient. 2020;13(1):83-102.

20. Grover S, Rina K, Malhotra P, Khadwal A. Correlates of Positive Aspects of Caregiving Among Family Caregivers of Patients with Acute Myeloblastic Leukaemia. Indian J Hematol Blood Transfus. 2018;34(4):612-7.
21. Hernlund E, Redig J, Paulsson B, Rangert Derolf Å, Höglund M, Vertuani S, et al. Socioeconomic cost of AML in Sweden-A population-based study using multiple nation-wide registers. EJHaem. 2021;2(3):385-93.
22. Zeidan AM, Mahmoud D, Kucmin-Bemelmans IT, Alleman CJM, Hensen M, Skikne B, et al. Economic burden associated with acute myeloid leukemia treatment. Expert Rev Hematol. 2016;9(1):79-89.
23. Döhner H, Wei AH, Appelbaum FR, Craddock C, DiNardo CD, Dombret H, et al. Diagnosis and management of AML in adults: 2022 ELN recommendations from an international expert panel. Blood. 2022.
24. Statistics D. Statistikbanken table 20021. Copenhagen, Denmark: Statistics Denmark; 2026.
25. International Agency for Research on C. NORDCAN 2.0 (ANCR/IARC), AML trends, both sexes, ages 20+, 2018–2024. Version 9.4 ed2024.
26. European Medicines Agency. INAQOVI - Summary of Product Characteristics. 2026.
27. Patel AA, Cahill K, Saygin C, Odenike O. Cedazuridine/decitabine: from preclinical to clinical development in myeloid malignancies. Blood Adv. 2021;5(8):2264-71.
28. Roboz GJ, Zeidan AM, Mannis GN, Montesinos P, Arnan M, Savona MR, et al. All-Oral Treatment of Newly Diagnosed Acute Myeloid Leukemia. New England Journal of Medicine. 2026;394(21):2107-16.
29. Roboz G. All-oral decitabine/cedazuridine (DEC-C) + venetoclax (VEN). European Hematology Association; 2025.
30. Griffiths EA, Carraway HE, Chandhok NS, Prebet T. Advances in non-intensive chemotherapy treatment options for adults diagnosed with acute myeloid leukemia. Leuk Res. 2020;91:106339.
31. Cortes JE, Mehta P. Determination of fitness and therapeutic options in older patients with acute myeloid leukemia. Am J Hematol. 2021;96(4):493-507.
32. Bérard E, Röllig C, Bertoli S, Pigneux A, Tavitian S, Kramer M, et al. A scoring system for AML patients aged 70 years or older, eligible for intensive chemotherapy: a study based on a large European data set using the DATAML, SAL, and PETHEMA registries. Blood Cancer J. 2022;12(7):107.
33. DiNardo CD, Pratz, K., Pullarkat, V., Jonas, B. A., Arellano, M., Becker, P. S., Frankfurt, O., Konopleva, M., Wei, A. H., Kantarjian, H. M., Xu, T., Hong, W. J., Chyla, B., Potluri, J., Pollyea, D. A. and Letai, A. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood. 2019;133(1):7–17.
34. Zeidan AM, Salimi T, Epstein RS. Real-world use and outcomes of hypomethylating agent therapy in higher-risk myelodysplastic syndromes: why are we not achieving the promise of clinical trials? Future Oncol. 2021;17(36):5163-75.
35. Delmas A, Batchelder L, Arora I, Bayet S, Bruhn D, Eberhardt A, et al. Exploring preferences of different modes of administration of hypomethylating agent treatments among patients with acute myeloid leukemia. Front Oncol. 2023;13:1160966.
36. Eek D, Krohe M, Mazar I, Horsfield A, Pompilus F, Friebe R, et al. Patient-reported preferences for oral versus intravenous administration for the treatment of cancer: a review of the literature. Patient Prefer Adherence. 2016;10:1609-21.
37. Danish Medicine Council. Medicinrådets anbefaling vedrørende venetoclax i kombination med azacitidin til behandling af akut myeloid leukæmi (AML). 2022.
38. Otsuka Data on File. INAQOVI in Combination with Venetoclax for AML: Unanchored Indirect Comparisons - Technical Report. 2026.

39. Medical Products A. Azacitidine SUN 25 mg/ml powder for suspension for injection: Summary of Product Characteristics (SmPC). 2024.
40. Park S, Park SY, Lee JH, Choi EJ, Lee KH, Yoon SS, et al. Five-day versus 7-day treatment regimen with azacitidine in lower risk myelodysplastic syndrome: A phase 2, multicenter, randomized trial. Cancer. 2022;128(23):4095-108.
41. Sadashiv SK, Hilton C, Khan C, Rossetti JM, Benjamin HL, Fazal S, et al. Efficacy and tolerability of treatment with azacitidine for 5 days in elderly patients with acute myeloid leukemia. Cancer Med. 2014;3(6):1570-8.
42. European Medicines A, Committee for Medicinal Products for Human U. Guideline on the clinical evaluation of anticancer medicinal products. Guideline. Amsterdam, Netherlands: European Medicines Agency; 2024.
43. Otsuka Data on File. ASTX727 in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia. Clinical Study Report. 2025.
44. Garcia-Manero G, McCloskey J, Griffiths EA, Yee KWL, Zeidan AM, Al-Kali A, et al. Oral decitabine-cedazuridine versus intravenous decitabine for myelodysplastic syndromes and chronic myelomonocytic leukaemia (ASCERTAIN): a registrational, randomised, crossover, pharmacokinetics, phase 3 study. The Lancet Haematology. 2024;11(1):e15-e26.
45. Geissler K, Koristek Z, Del Castillo TB, Novák J, Rodríguez-Macías G, Metzelder SK, et al. Oral decitabine/cedazuridine versus intravenous decitabine for acute myeloid leukaemia: A randomised, crossover, registration, pharmacokinetics study. Br J Haematol. 2024;205(5):1734-45.
46. Otsuka Data on File. ASTX727 in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia. Clinical Study Protocol. 2024.
47. Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129(4):424-47.
48. Network NCC. NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia, Version 2.2016. 2016 [Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1411.
49. Jonas BA, DiNardo C, Fracchiolla N, Pristupa A, Ishizawa K, Jin J, et al. Use of CYP3Ai and impact on outcomes in patients with acute myeloid leukemia treated with venetoclax plus azacitidine in the VIALE-A study. Am J Hematol. 2022;97(11):E422-E5.
50. Pratz KW, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Dohner H, et al. Long-term follow-up of VIALE-A: Venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. Am J Hematol. 2024;99(4):615-24.
51. ClinicalTrials.gov. Pharmacokinetics, Safety, and Efficacy of ASTX727 in Combination With Venetoclax in Acute Myeloid Leukemia. 2021.
52. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE. Sheffield, UK: NICE Decision Support Unit; 2016.
53. Medicinraadet. Opgørelse af omkostninger 2026.
54. Pratz KW, Jonas BA, Pullarkat V, Recher C, Schuh AC, Thirman MJ, et al. Measurable Residual Disease Response and Prognosis in Treatment-Naive Acute Myeloid Leukemia With Venetoclax and Azacitidine. J Clin Oncol. 2022;40(8):855-65.
55. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021). Cochrane, 2021. Available at: www.training.cochrane.org/handbook. [Last accessed: 22 April 2025].
56. Daver N, Vyas P, Huls G, Döhner H, Maury S, Novak J, et al. The ENHANCE-3 study: venetoclax and azacitidine plus magrolimab or placebo for untreated AML unfit for intensive therapy. Blood. 2025;146(5):601-11.

57. Willekens C, Bazinet A, Chraibi S, Bataller A, Decroocq J, Arani N, et al. Reduced venetoclax exposure to 7 days vs standard exposure with hypomethylating agents in newly diagnosed AML patients. Blood Cancer Journal. 2025;15(1) (no pagination).
58. Manda S, Anz, B. M., Benton, C., Broun, E. R., Yimer, H. A., Renshaw, J. S., Geils, G., Berdeja, J., Cruz, J., Melear, J. M., Fanning, S., Fletcher, L., Li, Y., Duan, Y., Werner, M. E., Potluri, J., Pai, M. V. and Donnellan, W. B. A phase 3b study of venetoclax and azacitidine or decitabine in an outpatient setting in patients with acute myeloid leukemia. Hematological Oncology. 2024;42(3):e3274.

Appendix A. Study characteristics

Table 41. Main characteristics of included studies

ASCERTAIN-V	NCT number: NCT04657081
Purpose	ASCERTAIN-V aimed to evaluate the PK, efficacy and safety of INAQOVI + VEN for the treatment of AML.
Publications – title, author, journal, year	Roboz GJ, Zeidan AM, Mannis GN, Montesinos P, Arnan M, Savona MR, Odenike O, McCloskey JK, Amin HV, Fathi AT, Bernal del Castillo T. All-Oral Treatment of Newly Diagnosed Acute Myeloid Leukemia. New England Journal of Medicine. 2026 Jun 4;394(21):2107-16.
Study type and design	ASCERTAIN-V was a Phase I/II, single-arm, open-label, multicentre, non-randomised interventional study. The study enrolled adult patients with newly diagnosed AML aged 75 years or older, or who had comorbidities that made them ineligible for SIC. Crossover was not applicable, due to lack of a comparator arm.
Number of trial participants (N)	Phase I: 30; Phase II Part A: 58; Phase II Part B: 101

Primary inclusion criteria	Patients were required to fulfil all the following criteria:
	• Age ≥18 years old
	• Histological confirmation of newly diagnosed AML by WHO 2016 criteria
	• Projected life expectancy of at least three months
	• Ineligible for SIC as defined by:
	  ○ Age ≥75 years old, or
	  ○ Age 18–74 and at least one of the following comorbidities:
	  ▪ Severe cardiac disorder (e.g., congestive heart failure requiring treatment, ejection fraction ≤50%, or chronic stable angina)
	  ▪ Severe pulmonary disorder (e.g., DLCO ≤65% or FEV_1 ≤65%)
	  ▪ Creatinine clearance ≥30 mL/min to <45 mL/min
	  ▪ Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0 times upper limit of normal
	  ▪ Phase I: ECOG PS 2 (subjects with ECOG PS ≥3 are not eligible)
	  ▪ Phase II Part A and Phase II Part B: ECOG PS 2 or 3 (subjects with ECOG PS 4 are not eligible)
	• ECOG PS:
	
	Phase I: ECOG PS 0–2; Phase II Part A and Phase II Part B: ECOG PS 0–3

Primary exclusion criteria	Patients meeting any of the following criteria were excluded from the study:

- Medical conditions including:
  - History of myeloproliferative neoplasm including myelofibrosis, essential thrombocythemia, polycythaemia vera, chronic myeloid leukaemia with or without BCR-ABL1 translocation and AML with BCR-ABL1 translocation
  - The following karyotype abnormalities: t(8;21), inv(16) or t(15;17), or other acute promyelocytic leukaemia variants that remain sensitive to all-trans retinoic acid therapy
  - Known active CNS involvement from AML
  - Known HIV infection
  - Known active hepatitis B or C infection (detectable viral load)
  - Severe hepatic impairment defined as: bilirubin >1.5 times the upper limit of normal (ULN) for subjects ≥75 years or >3 times the ULN for subjects <75 years; or aspartate aminotransferase/serum glutamic oxaloacetic transaminase or alanine aminotransferase/ serum glutamic pyruvic transaminase >3 times the ULN
  - Severe renal impairment defined as: calculated creatinine clearance or glomerular filtration rate <30 mL/min
  - Cardiovascular disability status of New York Heart Association Class >2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity results in fatigue, palpitations, dyspnoea or anginal pain
  - Malabsorption syndrome or other condition that precludes enteral route of administration
  - Significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular or pulmonary disease, any other medical condition or known hypersensitivity to any of the study medications that in the opinion of the investigator would adversely affect participation in the study
  - Clinically significant uncontrolled systemic infection requiring therapy (viral, bacterial, or fungal)
  - History of other malignancies prior to study entry (excluding adequately treated in situ carcinoma of the breast or cervix uteri, localised basal cell carcinoma or squamous cell carcinoma of the skin, previous malignancy adequately treated and controlled, and any early stage malignancy for which no definitive therapy is required)
  - White blood cell (WBC) count >25,000/µL[a]
- Prior or concomitant therapy including:
  - HMAs (azacitidine or decitabine) or VEN including prior treatment for MDS
  - CAR-T cell therapy
  - Investigational therapies for AML or MDS
  - Participants who cannot discontinue concomitant prophylactic antifungal therapy with CYP3A inhibitor activity or other concomitant medications with moderate or strong cytochrome P450 3A inhibitor activity ≥7 days or

ASCERTAIN-V	NCT number: NCT04657081
	5 half-lives, whichever is greater, prior to the first day of study treatment ○ Participants who cannot discontinue concomitant drugs that are strong CYP3A or P-glycoprotein inhibitors ≥7 days or 5 half-lives, whichever is greater, prior to the first day of study treatment Participants who cannot avoid concomitant drugs known as moderate or strong CYP3A inducers
Intervention	Orally administered INAQOVI (35mg decitabine, 100 mg cedazuridine) on Days 1–5 of every 28 day cycle in combination with VEN (400 mg QD), received by 189 participants (Phases I/II).
Comparator(s)	Not applicable as ASCERTAIN-V was designed as a single-arm trial.
Follow-up time	Median follow-up for Phase I, Phase II Part A and Phase II Part B was 34.3, 26.0 and 11.2 months, respectively.
Is the study used in the health economic model?	No, this study supports the assumed clinical equivalence.
Primary, secondary and exploratory endpoints	Primary endpoints: Phase I: VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2; Phase II Part A: CR rate and VEN AUC0–24 and Cmax on Day 5 with INAQOVI and Day 15 without INAQOVI in Cycle 2; Phase II Part B: CR rate. Secondary endpoints: Phase I: DEC-C AUC0–24 and Cmax on Day 5 with VEN; cedazuridine AUC0-8 on Day 5 with VEN in Cycle 2, AEs, CR, CR+CRh, CR+CRi rates, time to and duration of CR or CRh, OS, 5-day cumulative decitabine AUC in Cycle 2, Decitabine AUC0–24 and Cmax on Days 1 and 2 in Cycle 2, Cedazuridine AUC0-8 on Days 1, 2, and 5 in Cycle 2; AUC0–24, AUC0-inf and Cmax on Days 1, 2, and 5 in Cycle 2, Cmax, Cmin, Tmax, T1/2. Phase II Part A & B: DEC-C AUC0–24, Cmax, AUC0-8, and AUC0-inf on Day 5 with VEN in Cycle 2 (Phase II Part A) and in Cycle 1 (Phase II Part A). AEs, CR, CR+CRh, CR+CRi rates, time to and duration of CR or CRh, OS, Cmax, Cmin, Tmax, T1/2. Exploratory endpoints: Minimal residual disease (MRD) status and biomarker- or risk-based subgroup analyses, including analyses according to ELN risk stratification.
Analysis method	PK endpoints were summarised using standard exposure metrics, and clinical endpoints were reported descriptively. Handling of missing data

ASCERTAIN-V	NCT number: NCT04657081
	followed standard clinical trial practice; no formal imputation or hazard ratio modelling was required for the primary analyses.
Subgroup analyses	Subgroup analyses were conducted in the Phase II Part B efficacy population and evaluated CR rates across prespecified subgroups defined by baseline demographic and clinical characteristics (age, sex, race/ethnicity, region, ECOG performance status, prior systemic therapy and cytogenetic classification). Complete remission (CR) rates were summarized descriptively within each subgroup. The analyses assessed the consistency of treatment response across baseline demographic and disease-related characteristics within the single-arm study population. No comparative modelling between treatment arms was performed due to the single-arm study design. Subgroup analyses were pre-specified for the Phase II Part B efficacy population and evaluated CR rates across the predefined baseline demographic and clinical subgroups. The subgroup analyses were descriptive and exploratory. The study was not statistically powered to detect differences between subgroups, and therefore the analyses were intended to assess consistency of treatment effects rather than to formally test subgroup-specific hypotheses.
Other relevant information	N/A

VIALE-A	NCT number: NCT02993523
Purpose	To compare the efficacy and safety of venetoclax plus azacitidine versus azacitidine alone in previously untreated AML patients who were ineligible for intensive induction chemotherapy.
Publications – title, author, journal, year	DiNardo CD, Jonas BA, Pullarkat V, Thirman MJ, Garcia JS, Wei AH, Konopleva M, Döhner H, Letai A, Fenaux P, Koller E. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. New England journal of medicine. 2020 Aug 13;383(7):617-29.
Study type and design	Randomised, double-blind, placebo-controlled Phase III study. No planned treatment crossover between randomized arms. Patients remained on assigned treatment until discontinuation/progression or other protocol-defined criteria.
Number of trial participants (N)	AML patients ≥18 years old not previously treated for AML ineligible for SIC; N=431 patients

VIALE-A	NCT number: NCT02993523
Primary inclusion criteria	Patients with a confirmed diagnosis of previously untreated AML according to WHO criteria.
Primary exclusion criteria	• Previous receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome • Patients with favourable cytogenetic risk according to the AML National Comprehensive Cancer Network (NCCN) guidelines.
Intervention	Venetoclax 400 mg orally once daily (following a Cycle 1 ramp-up of 100 mg Day 1, 200 mg Day 2, and 400 mg from Day 3) on Days 1–28 + azacitidine 75 mg/m² SC or IV on Days 1–7 of each 28-day cycle (n=286).
Comparator(s)	Matching oral placebo once daily on Days 1–28 + azacitidine 75 mg/m² SC or IV on Days 1–7 of each 28-day cycle (n=145)
Follow-up time	Median follow-up time: 20.5 months.
Is the study used in the health economic model?	No, this study supports the assumed clinical equivalence.
Primary, secondary and exploratory endpoints	Primary endpoints: Overall Survival (OS); Percentage of Participants with Complete Remission (CR) and Complete Remission with Incomplete Marrow Recovery (CRi). Secondary endpoints: Event-Free Survival (EFS); Global Health Status/Quality of Life (GHS/QoL); Composite Complete Remission (CR+CRi); Complete Remission and Complete Remission with Partial Hematologic Recovery (CR+CRh); Post-Baseline Transfusion Independence Rate; Complete Remission (CR) Rate; Fatigue/Quality of Life assessed using PROMIS Cancer Fatigue Short Form 7a.
Analysis method	Time-to-event endpoints (OS and EFS) were analyzed using Kaplan-Meier methods, stratified log-rank tests, and stratified Cox proportional hazards models to estimate HRs and 95% CIs. Binary response endpoints (e.g., CR+CRi, CR+CRh, CR and transfusion independence) were analyzed using Cochran-Mantel-Haenszel tests accounting for randomization stratification factors. Patient-reported QoL outcomes were assessed using EORTC QLQ-C30 and PROMIS Cancer Fatigue SF 7a.
Subgroup analyses	Overall survival was evaluated across prespecified subgroups, including age, sex, AML type, cytogenetic risk, and molecular mutation status (e.g., IDH1/2, FLT3, NPM1 and TP53).
Other relevant information	N/A

Appendix B. Results regarding effectiveness per study

Table 42. Results per study

Results of ASCERTAIN-V (NCT04657081)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
CR rate Follow up: 11.2 months	INAQOVI + VEN	47	46.5% (36.5-56.7)	N/A	N/A	N/A	N/A	N/A	N/A	All primary efficacy analyses were performed based on the ITT population using the Investigator's assessment. Confidence Intervals (CI) for binomial proportions were estimated using the Clopper–Pearson method.	(28)
	N/A	N/A	N/A								
Composite response rate: CR+CRh	INAQOVI + VEN	52	51.5% (41.3-61.6)	N/A	N/A	N/A	N/A	N/A	N/A	Rates at fixed time-points were derived from the KM estimate and the corresponding CI was derived based on the Greenwood formula for	(28)
	N/A	N/A	N/A								

Results of ASCERTAIN-V (NCT04657081)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
Follow up: 11.2 months										variance derivation and on log-log transformation applied on the survivor function, S(t).	
Composite response rate: CR+Cri Follow up: 11.2 months	INAQOVI + VEN	64	63.4% (53.2-72.7)	N/A	N/A	N/A	N/A	N/A	N/A	Rates at fixed time-points were derived from the KM estimate and the corresponding CI was derived based on the Greenwood formula for variance derivation and on log-log transformation applied on the survivor function, S(t).	(28)
	N/A	N/A	N/A								
Duration of response: CR and CR or CRh	INAQOVI + VEN	CR: 47 CRh: 52	Median DOR for both CR and CR or CRh was not reached.	N/A	N/A	N/A	N/A	N/A	N/A	Time to event endpoints (ie, DOR, OS) were estimated using Kaplan-Meier techniques. Median survival time along with	(28)

Results of ASCERTAIN-V (NCT04657081)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
Follow up: 11.2 months	N/A	N/A	N/A							95% CIs were constructed based on a log-log transformed CI for the survivor function, S(t).	
OS	INAQOVI + VEN	101	15.5 (7.6-Not evaluable) months	N/A	N/A	N/A	N/A	N/A	N/A	Same as above.	(28)
AUC0-24	INAQOVI + VEN	55	26,310	102% Ratio of Geo LSM	90% CI:87.3-119.3		N/A	N/A	N/A	The VEN AUC0–24 and Cmax values on Cycle 2 Day 5 when given with INAQOVI was compared descriptively and evaluated for similarity to the AUC0–24 and Cmax values on Cycle 2 Day 15 (when given alone) by calculating the ratio of the geometric mean AUC0–24	(28)
	VEN	49	25,780								

Results of ASCERTAIN-V (NCT04657081)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P*- value	Difference	95% CI	*P*- value		
										and Cmax (intra-subject). The 90% CIs for the ratios of VEN AUC0–24 and Cmax when given with INAQOVI relative to when given alone (intra-subject) was calculated using ln-transformed data. Ln-transformed results was back-transformed to the original scale by exponentiation to obtain geometric mean ratios. Drug-drug interactions between INAQOVI and VEN were assessed through an Analysis of Variance (ANOVA) and the ratio of geometric least square mean (LSM). Drug-drug interactions between	

Results of ASCERTAIN-V (NCT04657081)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Analysis methods	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P*- value**	**Difference**	**95% CI**	***P*- value**		
										INAQOVI and VEN were assessed through an ANOVA test of the primary endpoints (AUC0–24 and Cmax) for INAQOVI + VEN compared to VEN only.	
Cmax	INAQOVI + VEN	55	1,879	97.3% Ratio of Geo LSM	90% CI:85.3-111.0		N/A	N/A	N/A	Same as above.	(28)
	VEN	49	1,931								

Appendix C. Subsequent treatment

N/A

Appendix D. Comparative analyses

Following the results of the feasibility assessment (FA), unanchored ITCs using aggregate data for AZA+VEN from VIALE-A and IPD from ASCERTAIN-V were recommended for all endpoints.

D.1 Data sources

IPD from ASCERTAIN-V has been shared by Taiho, via Otsuka, as Analysis Data Model (ADaM) datasets which were used to form analysis data for the MAICs. In terms of outcome data for AZA+VEN, OS and DOR data were available from KM curves in VIALE-A, and all binary outcome data were reported as proportion of patients with the outcome (n and %) by VIALE-A. Analysis of OS and DOR made use of time-to-event data from ASCERTAIN-V and pseudo-IPD from a digitisation of the OS and DOR KM curves from VIALE-A. The response outcomes used response rates (given as an n and %) from VIALE-A. A further source of information was published KM curves from VIALE-A publications,(4, 50, 54) where time-to-event IPD for AZA+VEN were reconstructed for OS and DOR from VIALE-A. Pseudo-IPD for OS was generated by digitising KM figures in the primary VIALE-A studies, DiNardo 2020 and Pratz 2024 and pseudo-IPD for DOR used KM figures in Pratz 2022, a follow on study focusing on results grouped by MRD status (4, 50, 54). Based on the way that DOR was reported in Pratz 2022, the full dataset used for other outcomes is not used for DOR.

D.2 Analysis Sets for ITC Analyses

In the ASCERTAIN-V analysis dataset (Table 43), six INAQOVI+VEN patients had missing data for adjustment variables (TEMs and PVs). Where possible, missing data were imputed using available supplemental data in the primary analysis. As such, among five patients with missing cytogenetic risk data, three had abnormal karyotypes and were automatically classified as adverse risk. For the other two patients with missing data for cytogenetic risk, sufficient data to infer cytogenetic risk category were unavailable, and therefore these patients were excluded in the primary analysis. One patient had missing ECOG data and was excluded. To ensure comparability, unweighted analyses, despite not requiring data for TEMs and PVs for adjustment, used the same analysis sets as the primary analysis.

Table 43 Analysis sets for ASCERTAIN-V and VIALE-A

Study	Full ITT	Complete case[a]	Primary analysis: Imputed[b]
ASCERTAIN-V	101	95	98
VIALE-A	286	286	286

Footnotes: [a] Without imputation of cytogenetic risk data as adjustment variable. [b] With imputation of cytogenetic risk data as adjustment variable.

Abbreviations: ITT, intent-to-treat.

D.3 Baseline characteristics

Baseline characteristics before and after weighting, and the weighting matching for the variables included in the MAIC weights calculation are presented in Table 44.

Table 44 ESS and baseline characteristics pre- and post-matching for the variables included in the MAIC weights calculation for the primary analysis

	VIALE-A Baseline Characteristics (aggregate data)	ASCERTAIN-V Analysis Dataset Baseline Characteristics (IPD Pre-Matching)	Matched data
Positive MRC Status	32%	56.1%	32.0%
Age ≥75	61%	80.6%	61.0%
ECOG PS ≥2	45%	21.4%	45.0%
Cytogenetic Risk Category: Adverse	36%	32.7%	36.0%
Gender: Male	60%	61.2%	60.0%
ESS		98.000[a]	55.898

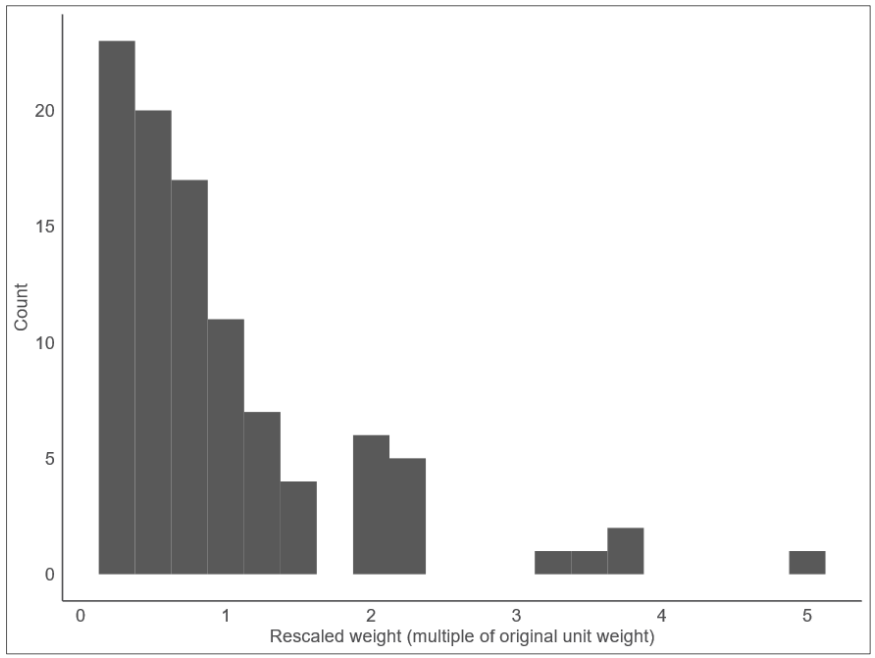
Note: Data was matched based on MRC Status, Age ≥75, ECOG PS ≥2, Cytogenetic Risk Category, Gender.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ESS, effective sample size; IPD, individual patient data; MRC, myelodysplasia-related changes; PS, performance status.

D.4 MAIC Weighting

Weighting for all TEMs and PVs of interest led to a moderate proportion of zero weights and limited skew (Figure 19). These diagnostics are considered acceptable for valid interpretation of MAIC results.(38)

Figure 19 Histogram of MAIC weights for primary analysis using the primary (imputed) analysis set.



Abbreviations: MAIC, matching-adjusted indirect treatment comparison.

D.5 Analyses Conducted

The primary and sensitivity conducted based on the recommendations of the FA and the analysis approach are provided in Table 45.

Table 45 Summary of analysis steps

Analysis	Step 1: Adjustment	Step 2: Diagnostics	Step 3: Uncertainty Estimation	Step 4: Comparing Outcomes
MAIC with binary outcomes	Compute weights for IPD population to match covariate distribution of AgD	For MAIC weights: ESS, histograms of weights	Apply sandwich estimators to estimate uncertainty	Apply unanchored MAIC approach to compare absolute odds of each binary outcome (CR, CR+CRh, CR+CRi, SAE) using VIALE-A as the comparator trial
MAIC with TTE outcomes		For MAIC weights: ESS, histograms of weights For PH assumption: Schoenfeld residuals plots, log-log plots (KM curve)		Fit a Cox regression model using IPD and AgD for TTE outcomes (OS, DOR) in comparison between ASCERTAIN-V and VIALE-A If the PH assumption is violated, consider piecewise models or estimating difference in RMST using the weighted survival curves for ASCERTAIN-V and VIALE-A

Abbreviations: AgD, aggregate data; CR, complete response; CR+CRi, complete response or complete response with incomplete hematologic recovery; CR+CRh, complete response or complete response with partial hematologic recovery; DOR, duration of response; ESS, effective sample size; IPD, individual patient data; KM, Kaplan-Meier; MAIC, matching-adjusted indirect treatment comparison; OS, overall survival; PH, proportional hazards; SAE, serious adverse events; TTE, time-to-event.

D.6 MAIC results

This section provides the results of the primary analysis using the primary analysis set with imputed data for cytogenetic risk (i.e. n=98 from ASCERTAIN-V and the ITT population from VIALE-A).

Table 46. Comparative analysis of studies comparing INAQOVI + VEN with AZA + VEN for adult, newly diagnosed patients with AML who are eligible for semi-intensive treatment with VEN + HMA

Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
Median OS	ASCERTAIN-V (28) VIALE-A (4)	0.697	-1.073, 2.466	≥ 0.05	NR	NR	NR	An unanchored ITC using MAIC was conducted to adjust for population-level covariates, with treatment differences in RMST estimated using bootstrapping to account for uncertainty associated with the MAIC weighting.	Yes, to indicate comparable clinical efficacy between treatments; therefore, a CMA was conducted.
CR	ASCERTAIN-V (28) VIALE-A (4)	NR	NR	NR	Odd ratio: 1.721	0.952, 3.108	≥ 0.05	Unanchored ITC using MAIC to adjust for population level covariates.	Same as above.

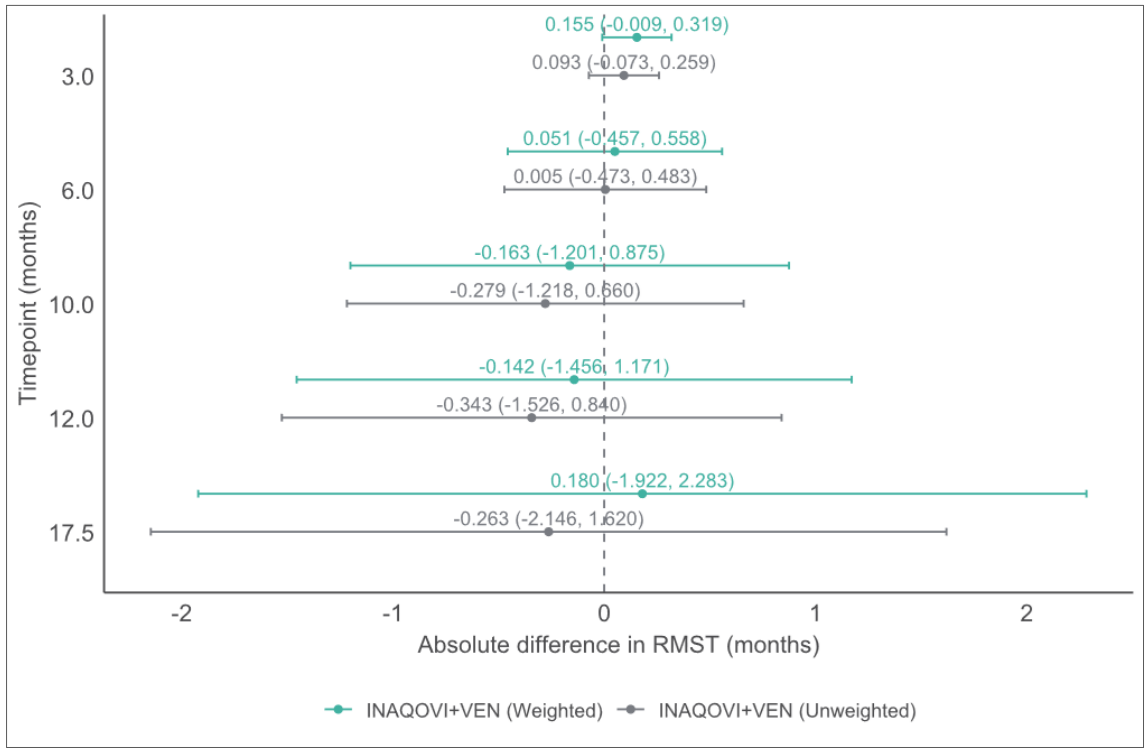
Outcome		Absolute difference			Relative difference			Analysis method	Are results used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P-value	Difference	CI	P-value		
CR+CRh	ASCERTAIN-V (28) VIALE-A (4)	NR	NR	NR	Odd ratio: 0.636	0.352, 1.147	≥ 0.05	Unanchored ITC using MAIC to adjust for population level covariates.	Same as above.
CR+CRi	ASCERTAIN-V (28) VIALE-A (4)	NR	NR	NR	Odd ratio: 1.209	0.659, 2.221	≥ 0.05	Unanchored ITC using MAIC to adjust for population level covariates.	Same as above.

Abbreviations: CR, complete response; CR+CRi, complete response or complete response with incomplete hematologic recovery; CR+CRh, complete response or complete response with partial hematologic recovery; MAIC, matching-adjusted indirect treatment comparison; NR, not reported; OS, overall survival.

D.7 Cytogenetic Risk Sensitivity Analysis

For all timepoints, difference in RMST for OS was not statistically significant between INAQOVI+VEN and AZA+VEN, suggesting there was no meaningful difference between INAQOVI+VEN and AZA+VEN after restricting to intermediate and adverse cytogenetic risk, consistent with the primary analysis results (Figure 20).

Figure 20 Absolute difference in RMST between INAQOVI+VEN and AZA+VEN by timepoint for OS when restricting to intermediate and adverse cytogenetic risk



Abbreviations: AZA+VEN, azacitidine in combination with venetoclax; INAQOVI+VEN, INAQOVI in combination with venetoclax; OS, overall survival; RMST, restricted mean survival time.

Appendix E. Extrapolation of patient transitions

E.1 Parametric extrapolation models

E.1.1 Extrapolation of TTD

E.1.1.1 Log-cumulative hazard plots and residual plots

N/A - the necessary data were not available for this assessment.

E.1.1.2 Internal validity

E.1.1.2.1 Assessment of statistical and visual fit (AIC and BIC)

Extrapolation model	AIC (Rank)	BIC (RANK)
Exponential	411.38 (5)	413.96 (4)
Weibull	413.22 (6)	418.39 (6)
Lognormal	403.87 (2)	409.04 (1)
Loglogistic	407.11 (3)	412.28 (3)
Gompertz	409.53 (4)	414.7 (5)
Gengamma	401.99 (1)	409.75 (2)

The generalized gamma distribution provided the best statistical fit according to AIC, with an AIC of 401.99. The log-normal distribution ranked second, with an AIC of 403.87. The difference in AIC between these models was 1.88, indicating that both distributions had substantial statistical support and that the improvement associated with the generalized gamma model was relatively small.

The gengamma distribution was selected as the best visual fit to the TTD KM after comparing the curves.

E.1.1.2.2 Assessment of smoothed hazard functions

N/A - the necessary data were not available for this assessment.

E.1.1.3 External validity

N/A - the necessary data were not available for this assessment.

E.1.1.4 Other assumptions

N/A

E.1.2 Extrapolations of [clinical endpoint 2]

N/A

E.2 Transition probabilities

E.2.1 Internal validity

N/A

E.2.2 External validity

N/A

E.2.3 Other assumptions

N/A

Appendix F. Serious adverse events

A summary of treatment-emergent SAEs in ≥1% of patients in ASCERTAIN-V is presented in Table 47. Giving the availability of published data, serious adverse events that were reported in VIALE-A in at least 5% of patients in either treatment group are listed in Table 48.

Table 47 SAEs reported by preferred term in ≥1% of patients in Phase I, Phase II Part A and Phase II Part B (safety population) of ASCERTAIN-V

Preferred Term	Phase I (N=30) n (%)	Phase II Part A (N=58) n (%)	Phase II Part B (N=101) n (%)
	Any Grade	Any Grade	Any Grade
Patients with at least 1 SAE	19 (63.3)	45 (77.6)	85 (84.2)
Sepsis	5 (16.7)	8 (13.8)	11 (10.9)
Febrile Neutropenia	3 (10.0)	17 (29.3)	33 (32.7)
Pneumonia	3 (10.0)	8 (13.8)	8 (7.9)
Bronchopulmonary Aspergillosis	2 (6.7)	-	-

Preferred Term	Phase I (N=30) n (%)	Phase II Part A (N=58) n (%)	Phase II Part B (N=101) n (%)
	Any Grade	Any Grade	Any Grade
Cellulitis	2 (6.7)	-	3 (3.0)
Confusional Stage	2 (6.7)	-	-
Fatigue	-	4 (6.9)	-
Hypotension	-	4 (6.9)	-
Asthenia	-	3 (5.2)	-
Respiratory Failure	-	3 (5.2)	-
Abdominal Infection	-	2 (3.4)	-
Acute Kidney Injury	-	2 (3.4)	-
Anorectal Infection	-	2 (3.4)	-
Bacteraemia	-	2 (3.4)	4 (4.0)
Cerebrovascular Accident	-	2 (3.4)	-
Diarrhoea	-	2 (3.4)	-
Hypoxia	-	2 (3.4)	-
Syncope	-	2 (3.4)	-
Thrombocytopenia	-	2 (3.4)	-
Urinary Tract Infection	-	2 (3.4)	-
Anaemia	-	-	5 (5.0)
Escherichia Bacteraemia	-	-	4 (4.0)
Pneumonia Fungal	-	-	4 (4.0)
Septic Shock	-	-	4 (4.0)
Cardiac Arrest	-	-	3 (3.0)
Haemorrhage Intracranial	-	-	3 (3.0)
Muscular Weakness	-	-	3 (3.0)
Cholecystitis	-	-	2 (2.0)
Covid-19	-	-	2 (2.0)
Diverticulitis	-	-	2 (2.0)
Platelet Count decreased	-	-	2 (2.0)
Pleural Effusion	-	-	2 (2.0)
Respiratory Failure	-	-	2 (2.0)

Preferred Term	Phase I (N=30) n (%)	Phase II Part A (N=58) n (%)	Phase II Part B (N=101) n (%)
	Any Grade	Any Grade	Any Grade
Skin infection	-	-	2 (2.0)
Streptococcal Bacteraemia	-	-	2 (2.0)
Subdural Haematoma	-	-	2 (2.0)
Upper Respiratory Tract Infection	-	-	2 (2.0)
Abdominal Injury	-	-	1 (1.0)

Footnotes: AEs were evaluated on CTCAE v5.0; MedDRA v27.0; Includes events reported between the first dose and 30 days after the last dose of the study treatment.
Abbreviations: CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event.
Source: Otsuka Data on File (INAQOVI in Combination with Venetoclax in Adult Patients with Acute Myeloid Leukemia Clinical Study Report; Table 64, Table 65 and Table 66) 2025 (43).

Table 48 Serious adverse events that were reported in at least 5% of patients in either treatment group in VIALE-A

Event	AZA + VEN (N=283) n (%)		AZA + Placebo (N=144) n (%)	
	All	Grade ≥ 3	All	Grade ≥ 3
Serious adverse events	**235 (83)**	**232 (82)**	**105 (73)**	**102 (71)**
Febrile neutropenia	84 (30)	84 (30)	15 (10)	15 (10)
Anemia	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)

Appendix G. Health-related quality of life

G.1 Data collection – overview of responses

N/A

G.2 Reporting of domains

N/A

G.3 Mapping

N/A

G.4 Calculation of utility values

N/A

Appendix H. Literature searches for the clinical assessment

H.1 Effect and safety of intervention and comparators

An SLR was conducted in February 2025 and subsequently updated in January 2026 to identify efficacy, effectiveness, safety and HRQoL outcomes of VEN with INAQOVI and its relevant comparators for the treatment of AML patients ineligible for SIC.

The following databases (Table 49) were searched in the original SLR from their inception dates to 18th February 2025, and from 1st January 2025 to 12th January 2026 for the update, using the search terms presented in Table 51.

Table 49 Bibliographic databases

Database	Platform/Website	Date of search
Medline	Searched simultaneously via the Ovid EMBR platform.	Original 18.02.2025 and updated 13.01.2026
Embase		
CDSR		
CENTRAL		

Additionally, conference proceedings for the last three years (i.e., 2023–2025) from the following five congresses were hand searched to identify any relevant abstracts (searched 5th March 2025 for the original SLR; 23rd January 2026 for the SLR update). ClinicalTrials.gov was searched using the Advanced search function. For the update, the same search terms as the original SLR were used to find relevant clinical trials published since the original SLR was conducted (searched 11th March 2025 for the original SLR; 21st January 2026 for the SLR update). Full details of the search strategies for hand-

searching of relevant congresses and for clinical trials are presented in Table 52 and Table 53, respectively.

Table 50 Conference and Clinical Trial Registry Searches

Source	Website	Search strategy/ keywords used	Date of search
American Society of Clinical Oncology (ASCO)	https://www.asco.org/	Please see Table 52 and Table 53 below.	Original 05.03.2025 and updated 23.01.2026
European Society of Medical Oncology (ESMO)	http://www.esmo.org/		
American Society of Hematology (ASH)	http://www.hematology.org/		
European Hematology Association (EHA)	https://ehaweb.org/		
Society of Hematologic Oncology (SOHO)	https://sohoonline.org/SOHO/SOHO/Home.aspx		
ClinicalTrials.gov	https://clinicaltrials.gov/		Original 11.03.2025 and updated 21.01.2026

Table 51 Search terms for use in MEDLINE, Embase, CDSR and CENTRAL (searched simultaneously via the Ovid EMBR platform)

Term Group	#	Searches	Original SLR Results 18.02.2025	SLR Update Results 13.06.2026
Disease Area: AML	1	Leukemia, Myeloid, Acute/ or acute myeloid leukemia/	177596	193082
	2	(AML or acute myeloid leuk?emia or acute granulocytic leuk?emia or acute myeloblastic leuk?emia or acute myelocytic leukaemia or	201523	218993

Term Group	#	Searches	Original SLR Results 18.02.2025	SLR Update Results 13.06.2026
		acute myelogenous leuk?emia or acute nonlymphoblastic leuk?emia or acute nonlymphocytic leuk?emia).ti,ab,kf,kw.		
	3	1 or 2	252378	271671
Intervention: Venetoclax	4	Venetoclax/	13230	16833
	5	(venetoclax or venclexta or venclyxto or a 11954250 or a11954250 or abt 199 or abt199 or "gdc 0199" or gdc0199 or rg 7601 or rg7601 or ro 5537382 or ro5537382).ti,ab,kf,kw.	14035	18032
	6	4 or 5	18344	22980
Study Design: RCTs	7	Randomized Controlled Trials as Topic/ or "randomized controlled trial (topic)"/	515429	550649
	8	Randomized Controlled Trial/	1496823	1789712
	9	Random Allocation/ or randomization/	234394	236275
	10	Double-Blind Method/ or double blind procedure/	584487	674975
	11	Single-Blind Method/ or single blind procedure/	120839	149114
	12	Cross-Over Studies/ or crossover procedure/	188576	216680
	13	Placebos.mp. or placebo/ [mp=ti, ot, ab, fx, sh, hw, kw, tx, ct, tn, dm, mf, dv, kf, dq, bt, nm, ox, px, rx, ui, sy, ux, mx]	491480	581426
	14	exp Clinical Trials as Topic/ or exp "clinical trial (topic)"/	979287	1024311
	15	Clinical Trial/	1628279	2204188
	16	Clinical Trial, Phase II/ or phase 2 clinical trial/ or Clinical Trial, Phase III/ or phase 3 clinical trial/ or Clinical Trial, Phase IV/ or phase 4 clinical trial/	264892	371710
	17	Controlled Clinical Trial/ or Adaptive Clinical Trial/ or multicenter study/	1252099	1410985
	18	randomized controlled trial.pt.	632037	654809
	19	clinical trial.pt.	541060	1091236
	20	(clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv).pt.	67923	72378
	21	(controlled clinical trial or multicenter study).pt.	456127	480631
	22	(clinical adj trial$).ti,ab,kf,kw.	1848628	2048661
	23	((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).ti,ab,kf,kw.	897034	1001811
	24	placebo$.ti,ab,kf,kw.	1049156	1164469
	25	(allocat$ adj2 random$).ti,ab,kf,kw.	171369	187918
	26	(Randomi?ed adj2 trial$).ti,ab,kf,kw.	1948776	2159134
	27	rct.ti,ab,kf,kw.	148590	174668
	28	(single arm adj3 (trial$ or stud$)).ti,ab,kf,kw.	39468	56226
	29	(open label adj (trial$ or stud$)).ti,ab,kf,kw.	54845	70476
	30	(non blinded adj (trial$ or stud$)).ti,ab,kf,kw.	930	1141
	31	(pragmatic trial$ or pragmatic stud$).ti,ab,kf,kw. or Pragmatic Clinical Trial/ or pragmatic trial/	15552	18488
	32	or/7-31	6713944	7620603
Study Design: Observational Studies	33	Epidemiologic Studies/	299062	358397
	34	Observational Study/	586692	703884
	35	Cohort Studies/ or cohort analysis/	1655248	1913776

Term Group	#	Searches	Original SLR Results 18.02.2025	SLR Update Results 13.06.2026
	36	exp Case-Control Studies/ or exp case control study/	1854578	1966501
	37	Cross-Sectional Studies/ or cross-sectional study/	1240818	1383348
	38	Clinical Study/	174292	176962
	39	Follow-Up Studies/ or follow up/	3100518	3398956
	40	Longitudinal Studies/ or longitudinal study/	421408	471624
	41	Retrospective Studies/ or retrospective study/	3041801	3356466
	42	(Prospective Studies/ not Randomized Controlled Trials as Topic/) or (prospective study/ not "randomized controlled trial (topic)"/)	1787299	1883539
	43	(observational adj (study or studies)).ti,ab,kf,kw.	514727	597653
	44	(cohort adj (study or studies)).ti,ab,kf,kw.	964458	1099401
	45	cohort analy$.ti,ab,kf,kw.	68794	76398
	46	case control.ti,ab,kf,kw.	403567	429540
	47	cross sectional.ti,ab,kf,kw.	1422067	1585047
	48	(follow up adj (study or studies)).ti,ab,kf,kw.	151032	160403
	49	longitudinal.ti,ab,kf,kw.	901164	997594
	50	retrospective.ti,ab,kf,kw.	2355906	2630025
	51	(chart adj3 review$).ti,ab,kf,kw.	191989	207820
	52	exp Registries/ or exp disease registry/	335118	353732
	53	(registry or registries).ti,ab,kf,kw.	572712	633499
	54	(prospective adj (study or studies)).ti,ab,kf,kw.	673078	724559
	55	(epidemiologic$ adj (study or studies)).ti,ab,kf,kw.	238432	249442
	56	(evaluation adj (study or studies)).ti,ab,kf,kw.	23735	25609
	57	(medical record$ or real world or population based or survey$ or questionnaire$ or medicare or medicaid or marketscan).ti,ab,kf,kw.	4925692	5401054
	58	or/33-57	14845494	16188257
Exclusion Terms	59	conference$.pt.	6412895	6897197
	60	limit 59 to yr="1974-2022"	5809778	5865473
	61	exp animals/ not exp humans/	10991068	11319882
	62	(comment or editorial or case reports or historical article or preprint).pt.	5383219	5621635
	63	editorial/ or case report/	4574244	4781993
	64	(case stud$ or case report$).ti.	959341	1035859
	65	or/60-64	24422353	25181388
Combination	66	(3 and 6) not 65	4912	7155
	67	66 use cctr	191	263
	68	66 use coch	0	0
	69	(3 and 6 and (32 or 58)) not 65	2790	4487
	70	or/67-69	2853	4565
	71	remove duplicates from 70	**2215**	3730
	72	limit 71 to yr="2025"	-	**841**

Database(s): EBM Reviews – Cochrane Central Register of Controlled Trials (December 2024 [original SLR]; December 2025 [SLR update]), EBM Reviews – Cochrane Database of Systematic Reviews (2005 to February 12, 2025 [original SLR]; 2005 to January 7, 2026 [SLR update]), Embase (1974 to February 18, 2025 [original SLR]; 1974 to January 9, 2026 [SLR update]), and Ovid MEDLINE(R) (including Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily; 1946 to February 18, 2025 [original SLR] and 1946 to January 12, 2026 [SLR update]).

Table 52 Search strategies for hand-searching of relevant congresses

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
American Society of Clinical Oncology (ASCO)	♦ 2023 ♦ 2024 ♦ 2025	♦ Filtered by year: 2023/2024/2025 ♦ Filtered by meeting: ASCO Annual Meeting ♦ Filtered by media: Abstracts, Posters, Slides ♦ Typed the following search terms in one by one into the search bar: 1. Venetoclax 2. Venclexta 3. Venclyxto 4. abt 199 5. abt199 6. gdc 0199 7. gdc0199 Screened titles and abstracts for relevance against the eligibility criteria	**Total: 43** 2023: 24 1. 24 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0 2024: 19 1. 19 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0	**2025: 52** 1. 42 2. 0 3. 0 4. 10 5. 0 6. 0 7. 0	**Total: 1** 2023: 0 2024: 0 2025: 1
European Society of Medical Oncology (ESMO)	♦ 2023 ♦ 2024 ♦ 2025	♦ Filtered by format: Abstracts, ePosters, Slides ♦ Typed the following search terms in one by one into the search bar: 1. Venetoclax 2. Venclexta 3. Venclyxto 4. abt 199 5. abt199 6. gdc 0199 7. gdc0199 Screened titles and abstracts for relevance against the eligibility criteria	**Total: 8** 2023: 3 1. 3 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0 2024: 5 1. 5 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0	**2025: 24** 1. 3 2. 0 3. 0 4. 21 5. 0 6. 0 7. 0	**Total: 0** 2023: 0 2024: 0 2025: 0
American Society of	♦ 2023	**2023**	**Total: 234**	**2025: ~390**	**Total: 21** 2023: 0 2024: 4

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
Hematology (ASH)	♦ 2024 ♦ 2025	♦ Filtered by Abstract Category using Ctrl to select multiple: 613. Acute Myeloid Leukemias: Clinical and Epidemiological 615. Acute Myeloid Leukemias: Commercially Available Therapies, Excluding Transplantation and Cellular Immunotherapies 616. Acute Myeloid Leukemias: Investigational Therapies, Excluding Transplantation and Cellular Immunotherapies 617. Acute Myeloid Leukemias: Biomarkers, Molecular Markers and Minimal Residual Disease in Diaganosis and Prognosis **2024** ♦ Filtered by Abstract Category using Ctrl to select multiple: 615. Acute Myeloid Leukemias: Clinical and Epidemiological 616. Acute Myeloid Leukemias: Investigational Drug and Cellular Therapies 617. Acute Myeloid Leukemias: Commercially Available Therapies 618. Acute Myeloid Leukemias: Biomarkers and Molecular Markers in Diuganosis and Prognosis 619. Acute Myeloid Leukemias: Disease Burden and Minial Residual Disease in Prognosis and Treatment ♦ Filtered by Hematology Disease Topics & Pathways: Diseases – Myeloid Malignancies	2023: 99 1. 99 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0 2024: 135 1. 135 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0		2025: 17

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
		– Acute Myeloid Malignancies – AML ♦ Typed the following search terms in one by one into the search bar: 1. Venetoclax 2. Venclexta 3. Venclyxto 4. abt 199 5. abt199 6. gdc 0199 7. gdc0199 Screened titles and abstracts for relevance against the eligibility criteria **2025** *Search I* ♦ Under Results, selected "Sessions" and filtered by Topic "Hematologic Malignancy" ♦ For sub-topics, selected all of the below categories at once: 615. Acute Myeloid Leukemias: Clinical and Epidemiological 616. Acute Myeloid Leukemias: Investigational Drug and Cellular Therapies 617. Acute Myeloid Leukemias: Commercially Available Therapies 618. Acute Myeloid Leukemias: Biomarkers and Molecular Markers in Diuganosis and Prognosis 619. Acute Myeloid Leukemias: Disease Burden and Minial Residual			

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
		Disease in Prognosis and Treatment ♦ Filtered by Keywords: Acute Myeloid Malignancies; AML *Search II* ♦ Selected “Abstracts” under Results. Went to Filters>Category>Select all categories as above i.e. 615 to 619 ♦ In the search box, searched for Venetoclax Screened the titles of all listed abstracts/presentations for eligibility			
European Hematology Association (EHA)	♦ 2023 ♦ 2024 ♦ 2025 Abstract Book PDF Online materials: Link	♦ In Adobe, used Ctrl+F keyboard to access search function ♦ Opened ‘Full Acrobat Search’ ♦ Clicked 'Show More Options' and ticked 'Stemming' ♦ Under 'Return results containing', selected 'Match exact word or phrase’ ♦ Typed in the following search terms in one line and clicked search: 1. VENETOCLAX 2. VENCLEXTA 3. VENCLYXTO 4. ABT 199 5. ABT199 6. GDC 0199 7. GDC0199 ♦ Selected ‘Case-Sensitive’ Clicked through and highlighted the title for	**Total: 228** 2023: 93 1. 93 2. 0 3. 0 4. 3 5. 0 6. 0 7. 0 2024: 135 1. 135 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0	**2025: 129** Publications only: 67 Oral: 7 Poster: 55	**Total: 15** 2023: 7 2024: 7 2025: 1 (Oral)

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
		each abstract that came up within the section Screened titles and abstracts for relevance against the eligibility criteria **<u>2025</u>** Relevant sections searched in PDF: Acute myeloid leukemia – Clinical Acute myeloid leukemia - Biology & translational research			
Society of Hematologic Oncology (SOHO)	♦ 2023 ♦ 2024 ♦ 2025 Abstract Book PDF Posters: link	♦ In Adobe, used Ctrl+F keyboard to access search function ♦ Opened 'Full Acrobat Search' ♦ Clicked 'Show More Options' and ticked 'Stemming' ♦ Under 'Return results containing', selected 'Match exact word or phrase' ♦ Typed the following search terms in one by one into the search bar: 1. Venetoclax 2. Venclexta 3. Venclyxto 4. abt 199 5. abt199 6. gdc 0199 7. gdc0199 ♦ Went to the 'Acute Myeloid Leukemia' section	**Total: 67** 2023: 42 1. 42 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0 2024: 25 1. 25 2. 0 3. 0 4. 0 5. 0 6. 0 7. 0	**2025: ~240** Abstract book PDFs: 61 Posters: ~180	**Total: 6** 2023: 2 2024: 1 2025: 3 (Posters)

Conference	Link	Search Strategy	Original SLR Hits (05.03.2025)	SLR Update Hits (23.01.2026)	Included
		Clicked through and highlighted the title for each abstract that came up within the section For highlighted articles, screened titles and abstracts for relevance against the eligibility criteria **2025** Accessed posters link and screened the listed records to identify any relevant posters			
Total hits:			580	**835**	**21 (original SLR)** **22 (SLR update)**
				Prioritised for data extraction:	**12**

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; EHA, European Hematology Association; ESMO, European Society of Medical Oncology; SOHO, Society of Hematologic Oncology; promotes advancement in hematologic malignancies.

Table 53 Search terms for use in ClinicalTrials.gov

Condition	Intervention	Study results	Age	Original Hits (11.03.2025)	SLR Update Hits (21.01.2026)	Included
Acute myeloid leukemia OR acute myeloid leukaemia OR AML	venetoclax OR venclexta OR venclyxto OR a 11954250 OR a11954250 OR abt 199 OR abt199 OR "gdc 0199" OR gdc0199 OR rg 7601 OR rg7601 OR ro 5537382 OR ro5537382	With results	Adult (18-64) OR Older adult (65+)	23	30	**10 (original SLR)** **5 (SLR update)**
					Total included:	**15**
					Prioritised for data extraction:	**13**

Abbreviations: AML, Acute Myeloid Leukaemia.

H.2 Systematic selection of studies and references

The inclusion and exclusion criteria used to assess the relevance of the titles, abstracts and full texts are presented in Table 54.

Table 54. Inclusion and exclusion criteria for the original SLR and SLR update

Domain	Inclusion Criteria	Exclusion Criteria
Patient population	♦ Adult patients (≥18 years) with AML, who are ineligible for SIC[a]	♦ Individuals without AML ♦ Patients who are eligible for intensive induction chemotherapy ♦ Patients aged <18 years
Intervention	♦ Any hypomethylating agent (AZA, DEC or INAQOVI) in combination with VEN ♦ Low-dose cytarabine (also referred to as LDC/LDAC) in combination with VEN[b]	♦ Studies not investigating a hypomethylating agent or low-dose cytarabine in combination with VEN
Comparator	♦ Any or none	♦ N/A
Outcomes	Outcomes, including but not limited to: **Clinical outcomes:** ♦ Survival (e.g., OS, PFS [INV PFS; BIRC PFS; PFS rate to be extracted if median PFS unavailable]) ♦ Overall response rate (including CR and PR) ♦ Duration of response ♦ Disease progression ♦ Haematological improvements ♦ Clinical benefit rate ♦ Disease Control Rate **Safety outcomes:** ♦ AEs (including TRAEs and serious AEs) ♦ Discontinuations due to AEs ♦ Mortality **HRQoL outcomes** ascertained via generic or disease-specific questionnaires, including: ♦ QoL-E ♦ EORTC QLQ-C30 ♦ EORTC QLQ-Leu ♦ FACIT ♦ FACT-Leu ♦ EQ-5D ♦ SF-36 **Prognostic factors and treatment-effect modifiers:**[c]	♦ Studies reporting any other outcomes, e.g., pharmacokinetics, epidemiology, economic outcomes ♦ Studies reporting a relevant outcome but in a mixed population where results for the eligible population are not reported separately

Domain	Inclusion Criteria	Exclusion Criteria
	♦ Patient characteristics that influence clinical outcomes and/or modify the effect of treatment, including but not limited to: ♦ Demographic (e.g., age, sex, ethnicity) ♦ Behavioural (e.g., alcohol consumption, smoking, physical activity, treatment adherence) ♦ Disease-specific (e.g., stage, disease severity, symptoms, disease markers, genetic mutations) ♦ Co-morbid (e.g., other conditions accompanying the disease)	
Study design	♦ Interventional randomised controlled trials (RCTs) and non-RCTs ♦ Observational studies (case series, prospective/retrospective cohorts, cross sectional studies, case control studies)	♦ Any other study design
	Relevant SLRs and (N)MAs were identified at the title/abstract review stage and hand-searched for relevant studies. They were excluded at the full text review stage unless they presented primary research.	
Publication type	♦ Primary research articles ♦ Letters, if they report primary research ♦ Conference abstracts (published in or after 2023 for the original SLR; since February 2025 for the SLR update *[new evidence published since the original searches were conducted])*	♦ Non-primary research publications, including narrative reviews, editorials, guidelines, commentaries, opinion pieces, case reports/studies ♦ Conference abstracts published before 2023 for the original SLR, and prior to February 2025 for the SLR update
Language	♦ Studies with an abstract or full text published in the English language	♦ Publications without an abstract or full-text in the English language
Other	♦ Any location ♦ Human subjects	♦ In vitro or animal studies

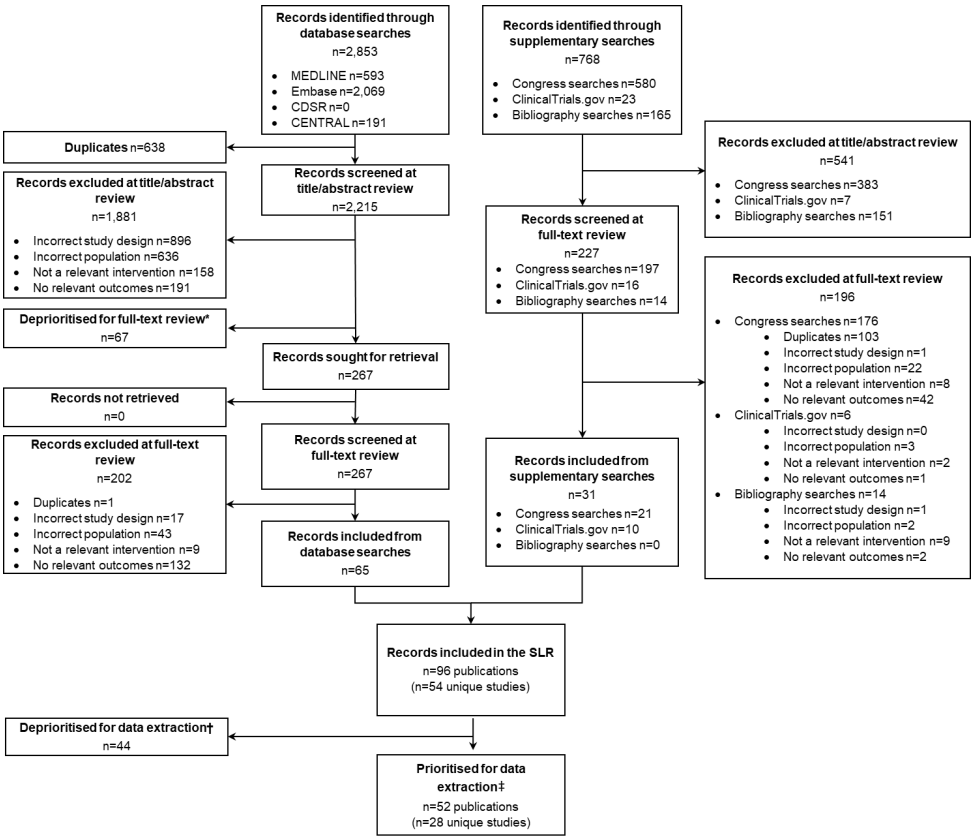
Footnotes: [a]A patient may be ineligible for SIC due to being aged 75 years or older, or the presence of certain comorbidities, including (but not limited to) severe cardiac disorder, severe pulmonary disorder, creatinine clearance ≥30 mL/min to <45 mL/min and moderate hepatic impairment. [b]Approved for use in US but not approved in Europe; included as a potential intervention of interest to explore at a later stage if needed. These studies were logged under the current SLR but not extracted. [c]Studies reporting any prognostic factors and treatment-effect modifiers were identified and logged appropriately. However, these were not extracted under the current SLR and will only be used to inform any follow-on analyses and discussions with clinicians.
Abbreviations: AE, adverse events; AML, Acute Myeloid Leukaemia; AZA, azacitidine; BIRC, Blinded Independent Review Committee; CR, complete response; DEC, decitabine; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; FACIT, Functional Assessment of Chronic Illness Therapy – Fatigue; INV, Investigator-Assessed; (N)MA, (network) meta-analysis; OS, overall survival; PFS, progression-free survival; PR, partial response; QoL-E, 29-item Quality of Life E; RCT, randomised clinical trial; SF-36, 36-item Short Form Survey; SIC, standard induction chemotherapy; SLR, systematic literature review; TRAE, treatment-related adverse event; VEN, venetoclax.

The most stringent record screening process as recommended by the Cochrane Collaboration was followed at each review stage for the SLR and SLR update: (55)

- Each title and abstract were reviewed against the eligibility criteria by two independent reviewers. Where the applicability of the inclusion criteria was unclear, the article was included at this stage in order to ensure that all potentially relevant studies were captured. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision.
- Full text publications of records included at abstract stage were then reviewed against the eligibility criteria by two independent reviewers. In cases where the publication did not give enough information to be sure it met the eligibility criteria; the publication was excluded to ensure that only relevant publications were ultimately included in the SLR. The results of the two reviewers were compared and any disagreements resolved by discussion until a consensus was met. If necessary, a third independent reviewer arbitrated the final decision.

A PRISMA diagram from the original SLR showing the flow of records through each stage of the review process is presented in Figure 21.

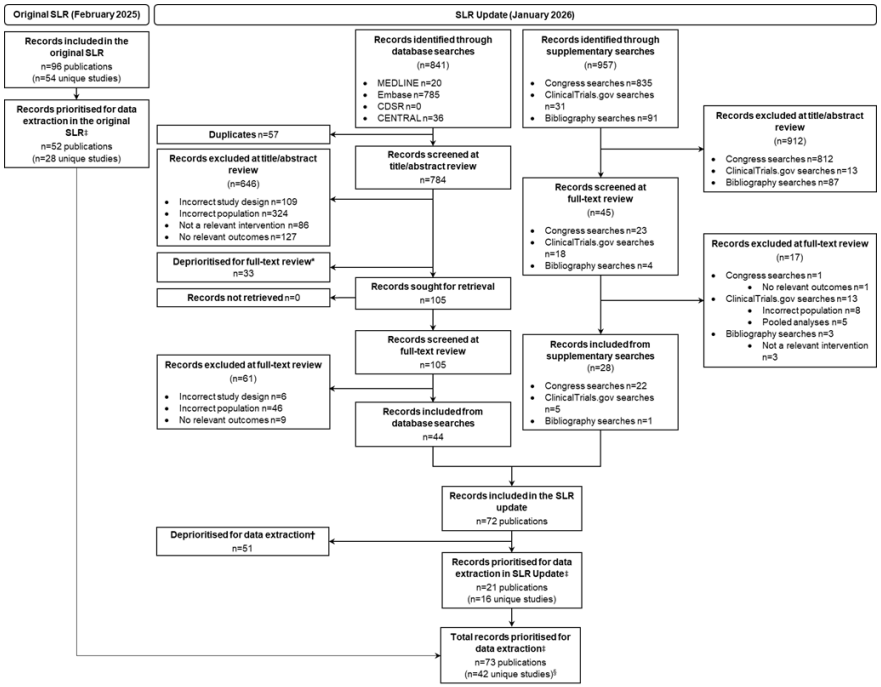
Figure 21 PRISMA diagram for the original SLR (February 2025)



Footnotes: *Articles that included interventions other than HMA+VEN or a triple regimen were deprioritised for full-text review. †To supplement the subsequent FA/ITC, articles were deprioritised for data extraction if

they reported a) on patients treated with AZA, DEC or INAQOVI in combination with VEN without stratified outcomes for each HMA, b) a lack of baseline data for newly diagnosed AML patients ineligible for SIC, c) on patients treated with VEN + unspecified HMAs, d) on patients treated with triple therapy or e) pooled analyses of existing trials. ‡Articles were prioritised for extraction if they reported on patients treated with AZA, DEC or INAQOVI in combination with VEN (with stratified outcomes for each HMA) and also included baseline data for newly diagnosed AML patients ineligible for SIC. Abbreviations, AML, acute myeloid leukaemia; AZA, azacitidine; CDSR, Cochrane Database of Systematic Reviews; CENTRAL, Cochrane Central Register of Controlled Trials; DEC, decitabine; HMA, hypomethylating agent; SIC, standard induction chemotherapy; SLR, systematic literature review; VEN, venetoclax.

Figure 22 PRISMA diagram for the SLR and update



Footnotes: *Articles that included interventions other than HMA+VEN or a triple regimen were deprioritised for full-text review. †To supplement the subsequent FA/ITC, articles were deprioritised for data extraction if they reported a) on patients treated with AZA, DEC or INAQOVI in combination with VEN without stratified outcomes for each HMA, b) a lack of baseline data for newly diagnosed AML patients ineligible for SIC, c) on patients treated with VEN + unspecified HMAs, d) on patients treated with triple therapy or e) pooled analyses of existing trials. ‡Articles were prioritised for extraction if they included patients undergoing treatment with VEN in combination with AZA, DEC and CED. §Two studies identified in the 2026 update had already been captured in the original 2025 SLR. However, the 2026 publications were designated as primary sources, and the previously designated primaries were reclassified as secondary publications.(56, 57). Abbreviations: AML: acute myeloid leukaemia; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CED: cedazuridine; DEC: decitabine; HMA: hypomethylating agent; ITC: intensive chemotherapy; SIC: standard intensive chemotherapy; SLR: systematic literature review; VEN: venetoclax

A high volume of records were identified following initial SLR searches, leading to the need for a prioritisation strategy to focus on studies most relevant for the FA. The following studies were subsequently prioritised:

- Studies assessing patients treated with azacitidine, decitabine or INAQOVI + venetoclax, with any combined outcomes stratified by HMA (no pooled analyses)
- Studies reporting baseline data for newly diagnosed AML patients who are ineligible for SIC

The original SLR and subsequent update identified a total of 73 publications reporting on 42 unique studies.

Based on the SLR results, of the three studies deemed eligible for the ITC, a Phase Ib trial investigating azacitidine + venetoclax, which preceded the pivotal Phase III VIALE-A trial, was deprioritised in favour of VIALE-A.(33, 38) Manda 2024, a Phase IIIb trial of azacitidine + venetoclax was also deprioritised because it was conducted in an outpatient setting where HMA + venetoclax dosing is substantially more flexible than clinical trial settings, which could have introduced bias when compared to the trial setting of ASCERTAIN-V (28, 38, 58). VIALE-A (Table 55) represented the most robust source of evidence for azacitidine + venetoclax to include in the ITC given its RCT design, multicentre setting and sufficient reporting of TEMs and PVs to allow for an unanchored ITC.(38)

Table 55. Studies/references included in the Danish assessment

Study	Reference(s)
VIALE-A (NCT02993523)	DiNardo, CD; Jonas, BA; Pullarkat, V et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. New England Journal of Medicine. 2020;383(7):617-629.

Table 56. Excluded studies/references

Study	Reference(s)
Original SLR (February 2025)	
1	Abbas, HA; Ayoub, E; Sun, H et al. Clinical and molecular profiling of AML patients with chromosome 7 or 7q deletions in the context of TP53 alterations and venetoclax treatment. Leukemia and Lymphoma. 2022;63(13):3105-3116.

Study	Reference(s)
2	Abbott, D; Cherry, E; Amaya, M et al. The propriety of upgrading responses to venetoclax + azacitidine in newly diagnosed patients with acute myeloid leukemia. Leukemia and Lymphoma. 2021;62(6):1466-1473.
3	Abernathy, KM; Perciavalle, MA; Gatwood, KS et al. Real-world analysis of tumor lysis syndrome in patients started on venetoclax combination for acute myeloid leukemia. Journal of Oncology Pharmacy Practice. 2023;29(6):1326-1333.
4	Acar, IH; Aslaner Ak, M; Akyol, G et al. Multicentral Retrospective Analysis of Venetoclax-Based Treatments in AML and MDS: A Real-World Study by the Turkish Hematology Network Group. Medicina. 2024;60(10).
5	Agarwal, S; Gopalakrishnan, S; Mensing, S et al. Optimizing venetoclax dose in combination with low intensive therapies in elderly patients with newly diagnosed acute myeloid leukemia: An exposure-response analysis. Hematological Oncology. 2019;37(4):464-473.
6	Agarwal, SK; DiNardo, CD; Potluri, J et al. Management of Venetoclax-Posaconazole Interaction in Acute Myeloid Leukemia Patients: Evaluation of Dose Adjustments. Clinical Therapeutics. 2017;39(2):359-367.
7	Alber, D; Rummelt, C; Strussmann, T et al. Single-Center Experience of Decitabine/Venetoclax in Newly Diagnosed Older AML Patients with Non-Favorable Genetics: Bridging to Allo-HCT or Treatment Continuation. Blood. 2023;142(Supplement 1):7091.
8	Aldoss, I; Zhang, J; Mei, M et al. Venetoclax and hypomethylating agents in FLT3-mutated acute myeloid leukemia. American Journal of Hematology. 2020;95(10):1193-1199.
9	Aldoss, I; Zhang, J; Pillai, R et al. Venetoclax and hypomethylating agents in TP53-mutated acute myeloid leukaemia. British Journal of Haematology. 2019;187(2):e45-e48.
10	Amador-Medina, LF; Crespo-Solis, E; Turrubiates-Hernandez, FJ et al. Venetoclax with low-dose cytarabine, a forgotten combination in patients with acute myeloid leukemia ineligible for intensive chemotherapy: a systematic review. Hematology, Transfusion and Cell Therapy. 2024;46(Supplement 6):S322-S331.
11	Arora, S; Zainaldin, C; Bathini, S et al. Tumor lysis syndrome and infectious complications during treatment with venetoclax combined with azacitidine or decitabine in patients with acute myeloid leukemia. Leukemia Research. 2022;117(no pagination).
12	Arribas, I; Pomares, H; Quinones, T et al. Venetoclax Exposure Reduction in Venetoclax-Hypomethylating Agents Combination Is Feasible and Has the Same Efficacy in Patients with Acute Myeloblastic Leukemia. Experience of a Single Center. Blood. 2023;142(Supplement 1):5930.

Study	Reference(s)
13	Arslan, S; Zhang, J; Dhakal, P et al. Outcomes of therapy with venetoclax combined with a hypomethylating agent in favorable-risk acute myeloid leukemia. American Journal of Hematology. 2021;96(3):E59-E63.
14	Ashraf, B; Jeon-Slaughter, H; Nguyen, H et al. AML-522 Outcomes of Patients Treated With Venetoclax-Based Combination Therapy in Acute Myeloid Leukemia and High-Grade Myeloid Neoplasms; Real World Data from a Single Center Cohort. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(Supplement 2):S259.
15	Baba, Y; Hida, N; Sambe, T et al. Efficacy of Venetoclax and Azacitidine in Acute Myeloid Leukemia Compared to Azacitidine Monotherapy: Real-World Experience. Anticancer Research. 2024;44(5):2003-2007.
16	Badar, T; Atallah, EL; Shallis, RM et al. Comparable Survival of Treatment Naive TP53 Mutated Acute Myeloid Leukemia Treated with Hypomethylating Agent Compared to Hypomethylating Agent Plus Venetoclax Based Therapy. Blood. 2023;142(Supplement 1):592.
17	Badar, T; Knutson, K; Foran, JM et al. T-Cells Immune Cluster Analysis Using Cytof Identifies Unique Patient Subgroups with TP53 Mutation and Predicts Complete Remission (CR) in Patients with Acute Myeloid Leukemia (AML) Receiving Venetoclax Plus Hypomethylating Agent Therapy. Blood. 2023;142(Supplement 1):1563.
18	Badar, T; Nanaa, A; Atallah, E et al. Comparing venetoclax in combination with hypomethylating agents to hypomethylating agent-based therapies for treatment naive TP53-mutated acute myeloid leukemia: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND). Blood Cancer Journal. 2024;14(1) (no pagination).
19	Baden, D; Wolgast, N; Pohlmann, A et al. Does time to treatment matter with venetoclax as first-line treatment for AML? Oncology Research and Treatment. 2023;46(Supplement 5):139.
20	Baden, D; Zukunft, S; Hernandez, G et al. Time from diagnosis to treatment has no impact on survival in newly diagnosed acute myeloid leukemia treated with venetoclax-based regimens. Haematologica. 2024;109(8):2469-2477.
21	Bang, SY; Park, S; Kwag, D et al. A Successful Bridge Therapy Combining Hypomethylating Agents with Venetoclax for Adult Patients with Newly Diagnosed or Relapsed/Refractory Acute Myeloid Leukemia. Cancers. 2023;15(6) (no pagination).
22	Bataller, A; Bazinet, A; DiNardo, CD et al. Prognostic risk signature in patients with acute myeloid leukemia treated with hypomethylating agents and venetoclax. Blood Advances. 2024;8(4):927-935.

Study	Reference(s)
23	Bataller, A; Bazinet, A; DiNardo, CD et al. Validation of the Prognostic Risk Signatures for Older Patients with Acute Myeloid Leukemia Treated with Hypomethylating Agents and Venetoclax. Blood. 2023;142(Supplement 1):4228.
24	Bataller, A; Loghavi, S; Gerstein, Y et al. Characteristics and clinical outcomes of patients with myeloid malignancies and DDX41 variants. American Journal of Hematology. 2023;98(11):1780-1790.
25	Bataller, A; Loghavi, S; Gerstein, Y et al. Characteristics and Outcomes of Patients With Acute Myeloid Leukemia and DDX41 Mutation. Clinical Lymphoma, Myeloma and Leukemia. 2023;23(Supplement 1):S277.
26	Bawek, S; Patel, P; Wang, K et al. Optimal Therapeutic Strategies in Relapsed/Refractory AML with Prior Exposure to Venetoclax Based Therapy. Blood. 2023;142(Supplement 1):4271.
27	Begna, KH; Gangat, N; Al-Kali, A et al. Acute myeloid leukemia after age 70 years: A retrospective comparison of survival following treatment with intensive versus HMA +/- venetoclax chemotherapy. American Journal of Hematology. 2021;96(4):E108-E111.
28	Berton, G; Sedaki, B; Collomb, E et al. Poor prognosis of SRSF2 gene mutations in patients treated with VEN-AZA for newly diagnosed acute myeloid leukemia. Leukemia Research. 2024;141(no pagination).
29	Berton, G; Sedaki, B; Collomb, E et al. Poor Prognosis of SRSF2 Gene Mutations in Patients Treated with Venetoclax-Azacitidine (VEN-AZA) for Newly Diagnosed Acute Myeloid Leukemia. a Multicentric Real-Life Study of 117 Patients. Blood. 2023;142(Supplement 1):2848.
30	Bewersdorf, JP; Shimony, S; Shallis, RM et al. Combination therapy with hypomethylating agents and venetoclax versus intensive induction chemotherapy in IDH1- or IDH2-mutant newly diagnosed acute myeloid leukemia-A multicenter cohort study. American Journal of Hematology. 2024;99(8):1640-1643.
31	Bewersdorf, JP; Shimony, S; Shallis, RM et al. Intensive Induction Chemotherapy (IC) Vs Hypomethylating Agents + Venetoclax (HMA/VEN) in IDH1- or IDH2-Mutant Newly Diagnosed Acute Myeloid Leukemia (AML) - a Multicenter Cohort Study. Blood. 2023;142(Supplement 1):1589.
32	Bewersdorf, JP; Shimony, S; Shallis, RM et al. Intensive Induction Chemotherapy Vs Hypomethylating Agents + Venetoclax (HMA/VEN) in NPM1-Mutant Newly Diagnosed Acute Myeloid Leukemia (AML) - a Multicenter Cohort Study. Blood. 2023;142(Supplement 1):2964.
33	Bewersdorf, JP; Shimony, S; Shallis, RM et al. Intensive induction chemotherapy vs hypomethylating agents in combination with venetoclax in NPM1-mutant AML. Blood Advances. 2024;8(18):4845-4855.

Study	Reference(s)
34	Bi, X; Begun, Z; Grosso, DA et al. Characteristics and Clinical Outcomes of Patients with Acute Myeloid Leukemia with TP53 Mutations - a Single Center Experience. Blood. 2023;142(Supplement 1):2847.
35	Boddu, PC; Kantarjian, HM; Ravandi, F et al. Characteristics and outcomes of older patients with secondary acute myeloid leukemia according to treatment approach. Cancer. 2017;123(16):3050-3060.
36	Boisclair, S; Naing, PT; Zhou, E et al. Outcomes and Hospital Resource Utilization Associated with Decreased Ven Exposure in Acute Myeloid Leukemia Patients: A Real-World Retrospective Review. Blood. 2023;142(Supplement 1):4268.
37	Boisclair, S; Naing, PT; Zhou, E et al. Survival Outcomes Associated with Molecular and Cytogenetic Alterations in AML Patients Treated with Hypomethylating Agent and Venetoclax. Blood. 2023;142(Supplement 1):2904.
38	Boisclair, S; Zhou, E; Naing, P et al. Less is more: An analysis of venetoclax and hypomethylating agent post-induction treatment modifications in AML. Leukemia Research. 2024;143(no pagination).
39	Borate, UM; Huang, Y; Welkie, RL et al. Influence of Pre-Treatment Features and Therapy Choice By Physicians on Overall Survival in Older Adults with Acute Myeloid Leukemia: A Report from the Beat AML Master Trial. Blood. 2023;142(Supplement 1):4332.
40	Bouligny, IM; Murray, G; Doyel, M et al. Venetoclax with decitabine or azacitidine in the first-line treatment of acute myeloid leukemia. eJHaem. 2023;4(2):381-392.
41	Bouligny, IM; Murray, G; Ho, T et al. Abbreviated venetoclax with decitabine or azacitidine in acute myeloid leukemia. Leukemia Research. 2023;134(no pagination).
42	Brackman, D; Eckert, D; Menon, R et al. Venetoclax exposure-efficacy and exposure-safety relationships in patients with treatment-naive acute myeloid leukemia who are ineligible for intensive chemotherapy. Hematological Oncology. 2022;40(2):269-279.
43	Burke, M; Sallman, DA; Denson, A et al. Antifungal Prophylaxis in Newly Diagnosed Acute Myeloid Leukemia Treated with a Hypomethylating Agent and Venetoclax: A Real-World Experience in Pharmacovigilance. Blood. 2023;142(Supplement 1):2899.
44	Chen, EC; Liu, Y; Harris, CE et al. Outcomes of antifungal prophylaxis for newly diagnosed AML patients treated with a hypomethylating agent and venetoclax. Leukemia and Lymphoma. 2022;63(8):1934-1941.
45	Chen, TT; Lin, CC; Lo, WJ et al. Venetoclax Plus Azacitidine as a Bridge Treatment to Allogeneic Stem Cell Transplantation in Unfit Patients with Acute Myeloid Leukemia. Cancers. 2024;16(6) (no pagination).

Study	Reference(s)
46	Chen, Y; Zheng, J; Weng, Y et al. Myelodysplasia-related gene mutations are associated with favorable prognosis in patients with TP53-mutant acute myeloid leukemia. Annals of Hematology. 2024;103(4):1211-1220.
47	Chin, KK; Derkach, A; Famulare, C et al. Despite High Rates of Remission, Treatment of IDH-Mutant AML with Hypomethylating Agents and Venetoclax Is Associated with Frequent Treatment Delays, Modifications, and Transfusions. Blood. 2023;142(Supplement 1):1519.
48	Chin, KK; Derkach, A; Famulare, C et al. HMA/VEN treatment modifications and associated outcomes in IDH-mutant AML. Leukemia and Lymphoma. 2025;66(2):270-278.
49	Chojecki, AL; Arnall, J; Boselli, D et al. Outcomes and hospitalization patterns of patients with acute myelogenous leukemia treated with frontline CPX-351 or HMA/venetoclax. Leukemia Research. 2022;119(no pagination).
50	Colunga-Lozano, LE; Nampo, FK; Agarwal, A et al. Less intensive antileukemic therapies (monotherapy and/or combination) for older adults with acute myeloid leukemia who are not candidates for intensive antileukemic therapy: A systematic review and metaanalysis. PLoS ONE. 2022;17(2 February) (no pagination).
51	Cordella, S; Giusti, D; De Bellis, E et al. Secondary acute myeloid leukemia and early infection are independent predictors of poor survival in acute myeloid leukemia treated with hypomethylating agents and venetoclax. Hematological Oncology. 2024;42(5) (no pagination).
52	Cui, J; Chen, X; Li, C et al. Reduced duration and dosage of venetoclax is efficient in newly diagnosed patients with acute myeloid leukemia. Hematology (United Kingdom). 2023;29(1) (no pagination).
53	Daver, NG; Iqbal, S; Huang, J et al. Clinical characteristics and overall survival among acute myeloid leukemia patients with TP53 gene mutation or chromosome 17p deletion. American Journal of Hematology. 2023;98(8):1176-1184.
54	Daver, NG; Iqbal, S; Renard, C et al. Treatment outcomes for newly diagnosed, treatment-naive TP53-mutated acute myeloid leukemia: a systematic review and meta-analysis. Journal of Hematology and Oncology. 2023;16(1) (no pagination).
55	Desai, P; Garcia, JS; Zeidner, JF et al. Comparative Analysis of Clinical Outcomes and Healthcare Resource Utilization (HRU) in Patients (Pts) with Newly Diagnosed (ND) Acute Myeloid Leukemia (AML) Unfit for High-Intensity Chemotherapy Treated with Venetoclax (VEN) Vs Other Therapies: Results from the AML Real World Evidence (ARC) Initiative. Blood. 2023;142(Supplement 1):5173.
56	Dohner, H; Pratz, KW; DiNardo, CD et al. Genetic risk stratification and outcomes among treatment-naive patients with AML treated with venetoclax and azacitidine. Blood. 2024.

Study	Reference(s)
57	Du, Y; Li, C; Yan, J. The efficacy and safety of venetoclax and azacytidine combination treatment in patients with acute myeloid leukemia and myelodysplastic syndrome: systematic review and meta-analysis. Hematology (United Kingdom). 2023;28(1) (no pagination).
58	Feld, J; Tremblay, D; Dougherty, M et al. Safety and Efficacy: Clinical Experience of Venetoclax in Combination with Hypomethylating Agents in Both Newly Diagnosed and Relapsed/Refractory Advanced Myeloid Malignancies. HemaSphere. 2021;5(4) (no pagination).
59	Feng, J; Yuan, RF; Tang, HL et al. Efficacy and Safety of Venetoclax-Based Induction Therapy in Acute Myeloid Leukemia. [Chinese]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2023;31(4):960-966.
60	Fleischmann, M; Eisele, F; Kraus, S et al. Assessment of Reduced Duration of Venetoclax in Combination with Azacytidine in Patients with Acute Myeloid Leukemia. Oncology Research and Treatment. 2024;47(Supplement 2):305.
61	Fleischmann, M; Jentzsch, M; Brioli, A et al. Azacitidine in combination with shortened venetoclax treatment cycles in patients with acute myeloid leukemia. Annals of Hematology. 2024.
62	Freeman, T; Williams, K; Puto, M et al. Real-World Experience of Adults With Acute Myeloid Leukemia on Hypomethylating Agents With or Without Venetoclax at a Comprehensive Cancer Center. World Journal of Oncology. 2023;14(1):40-50.
63	Gando, Y; Yasu, T. Real-world treatment patterns of venetoclax and azacytidine therapy in Japanese patients with acute myeloid leukemia. Annals of Hematology. 2023;102(5):1283-1285.
64	Gangat, N; Johnson, I; McCullough, K et al. Molecular predictors of response to venetoclax plus hypomethylating agent in treatment-naive acute myeloid leukemia. Haematologica. 2022;107(10):2501-2505.
65	Garciaz, S; Bertoli, S; Sallman, DA et al. Acute Myeloid Leukemia Patients Who Stopped Venetoclax or/and Azacytidine for Other Reasons Than Progression Have a Prolonged Treatment Free Remission and Overall Survival. a Filo Study. Blood. 2023;142(Supplement 1):161.
66	Garciaz, S; Dumas, PY; Bertoli, S et al. Outcomes of acute myeloid leukemia patients who responded to venetoclax and azacitidine and stopped treatment. American Journal of Hematology. 2024;99(10):1870-1876.
67	Garciaz, S; Hospital, MA; Alary, AS et al. Azacitidine plus Venetoclax for the Treatment of Relapsed and Newly Diagnosed Acute Myeloid Leukemia Patients. Cancers. 2022;14(8) (no pagination).

Study	Reference(s)
68	Giudice, V; Serio, B; Ferrara, I et al. Clinical efficacy of azacytidine and venetoclax and prognostic impact of Tim-3 and galectin-9 in acute myeloid leukemia and high-risk myelodysplastic syndromes: A single-center real-life experience. Frontiers in Pharmacology. 2022;13(no pagination).
69	Gor, J; Bouligny, I; Ho, T et al. Impact of COVID-19 Pandemic on Overall Survival in Acute Myeloid Leukemia: A Comprehensive Cancer Center Experience of 627 Patients. Blood. 2023;142(Supplement 1):7437.
70	Guinter, MA; Kerr, BT; Calip, GS et al. Low Socioeconomic Status Confers Poorer Real-World Overall Survival for Patients with Acute Myeloid Leukemia Treated in the Modern Era. Blood. 2023;142(Supplement 1):2437.
71	Gutman, JA; Winters, A; Kent, A et al. Higher-dose venetoclax with measurable residual diseaseguided azacitidine discontinuation in newly diagnosed acute myeloid leukemia. Haematologica. 2023;108(10):2616-2625.
72	Hadjis, AD; White, GW; Catania, C et al. Frail and Pre-Frail Older Adults with Acute Myeloid Leukemia Have Inferior Survival Due to Higher Rates of Disease-Related Deaths. Blood. 2023;142(Supplement 1):376.
73	Halim, NAA; Chan, TW; Wong, GC et al. Topic: AS08-Treatment/AS08a-Current treatment options - Higher risk MDS: Single-Center Experience Of Azacitidine-Venetoclax In Secondary Acute Myeloid Leukemia (Aml), Arising From Myelodysplastic Syndrome (Mds), Myeloproliferative Neoplasm (Mpn) Or Mds/Mpn Overlap. Leukemia Research. 2023;Conference: The 17th International Congress on Myelodysplastic Syndromes. Marseille France. 128(Supplement) (no pagination).
74	Hammond, D; Loghavi, S; Wang, SA et al. Response patterns and impact of MRD in patients with IDH1/2-mutated AML treated with venetoclax and hypomethylating agents. Blood Cancer Journal. 2023;13(1) (no pagination).
75	Hara, R; Machida, S; Hashimoto, N et al. Impact of previous anthracycline therapy in patients with acute myeloid leukemia receiving venetoclax. International Journal of Hematology. 2023;118(6):711-717.
76	He, H; Wen, X; Zheng, H. Efficacy and safety of venetoclax-based combination therapy for previously untreated acute myeloid leukemia: a meta-analysis. Hematology (United Kingdom). 2024;29(1) (no pagination).
77	Heiblig, M; Tavernier, E; Requena, GA et al. Real-World Use of Azacitidine (AZA) and Venetoclax (VEN) in Acute Myeloid Leukemia (AML) in Frontline and Relapse/Refractory (R/R) Settings: Multicenter Study From French AURAML Group. Clinical Lymphoma, Myeloma and Leukemia. 2023;23(Supplement 1):S303.
78	Heuser, M; Fernandez, C; Hauch, O et al. Therapies for acute myeloid leukemia in patients ineligible for standard induction chemotherapy: a systematic review. Future Oncology. 2023;19(11):789-810.

Study	Reference(s)
79	Ho, T; Murray, G; Gor, J et al. Recent Advancements in Acute Myeloid Leukemia Have Led to Incremental Improvement in Overall Survival. Blood. 2023;142(Supplement 1):5187.
80	Huang, R; He, H; Xu, X et al. Venetoclax plus a hypomethylating agent versus cytarabine, aclarubicin, and granulocyte colony-stimulating factor chemotherapy as a first-line therapy for newly diagnosed acute myeloid leukemia: A propensity score-matched analysis. Cancer. 2024;130(14):2472-2481.
81	Hubner, SE; de Camargo Magalhaes, ES; Hoff, FW et al. DNA Damage Response-Related Proteins Are Prognostic for Outcome in Both Adult and Pediatric Acute Myelogenous Leukemia Patients: Samples from Adults and from Children Enrolled in a Children's Oncology Group Study. International Journal of Molecular Sciences. 2023;24(6) (no pagination).
82	Huntington, SF; Ingham, MP; Okonkwo, L et al. Treatment patterns, economic burden, and overall survival in US Medicare Advantage beneficiaries newly diagnosed with acute myeloid leukemia (AML) in 2015-2020. Leukemia and Lymphoma. 2022;63(5):1180-1190.
83	Iqbal, A; Dubey, M; Randhawa, AS et al. Improved Treatment Outcomes With Modified Induction Therapy in Acute Myeloid Leukemia (AML): A Retrospective Observational Study From a Regional Cancer Center. Cureus. 2024;16(1):e53303.
84	Islam, N; Reuben, JS; Dale, J et al. Predictive Models for Long Term Survival of AML Patients Treated with Venetoclax and Azacitidine or 7+3 Based on Post Treatment Events and Responses: Retrospective Cohort Study. JMIR Cancer. 2024;10(no pagination).
85	Jain, AG; Volpe, VO; Wang, C et al. Outcomes by best response with hypomethylating agent plus venetoclax in adults with previously untreated acute myeloid leukemia. Annals of Hematology. 2024.
86	Jain, J; Byrd, KP; Male, HJ et al. Characteristics and Outcomes of Patients with DDX41-Mutated Acute Myeloid Leukemia: A Single-Center Experience. Blood. 2023;142(Supplement 1):4227.
87	Jensen, CE; Deal, AM; Wardell, AC et al. Home time among older adults with acute myeloid leukemia by therapy intensity. Haematologica. 2024;109(5):1588-1592.
88	Jimenez-Vicente, C; Guardia-Torrelles, A; Perez-Valencia, AI et al. Clinical management of patients diagnosed with acute myeloid leukemia treated with venetoclax in combination with hypomethylating agents after achieving a response: a real-life study. Annals of Hematology. 2024;103(10):4033-4043.
89	Jin, D; Chen, H; He, J et al. Impact of AML1/ETO Fusion on the Efficacy of Venetoclax Plus Hypomethylating Agents in Newly Diagnosed Acute Myeloid Leukemia. Targeted Oncology. 2024;19(2):237-249.

Study	Reference(s)
90	Jin, D; He, J; Chen, H et al. Impact of monocytic differentiation on acute myeloid leukemia patients treated with venetoclax and hypomethylating agents. Cancer Medicine. 2024;13(14) (no pagination).
91	Kaddam, I; Crosland, H; Hodson, J et al. Induction mortality rate in elderly AML patients treated with venetoclax/azacitidine compared to standard induction chemotherapy. British Journal of Haematology. 2023;201(Supplement 1):121.
92	Kadia, TM; Reville, PK; Wang, X et al. Phase II Study of Venetoclax Added to Cladribine Plus Low-Dose Cytarabine Alternating With 5-Azacitidine in Older Patients With Newly Diagnosed Acute Myeloid Leukemia. Journal of Clinical Oncology. 2022;374(no pagination).
93	Kapoor, P; Gupta, R; Kaushal, SA et al. Prevalence of IDH1/IDH2 Mutations in Adult Indian Acute Myeloid Leukaemia Patients and Their Impact on Outcome. Indian Journal of Hematology and Blood Transfusion. 2024.
94	Karrar, O; Abdelmagid, M; Rana, M et al. Venetoclax duration (14 vs. 21 vs. 28 days) in combination with hypomethylating agent in newly diagnosed acute myeloid leukemia: Comparative analysis of response, toxicity, and survival. American Journal of Hematology. 2024;99(2):E63-E66.
95	Karrar, O; Iftikhar, M; McCullough, K et al. Survival and Prognosis Among 301 Patients with Newly-Diagnosed Acute Myeloid Leukemia Following Venetoclax Plus Hypomethylating Agent Therapy. Blood. 2023;142(Supplement 1):591.
96	Khouderchah, CJ; Benitez, LL; Marini, BL et al. Tumor lysis syndrome in patients with acute myeloid leukemia treated with venetoclax and hypomethylating agents with or without dose ramp-up. Leukemia and Lymphoma. 2024;65(2):228-234.
97	Kim, K; Maiti, A; Loghavi, S et al. Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax. Cancer. 2021;127(20):3772-3781.
98	Kobayashi, T; Sato, H; Miura, M et al. Overexposure to venetoclax is associated with prolonged-duration of neutropenia during venetoclax and azacitidine therapy in Japanese patients with acute myeloid leukemia. Cancer Chemotherapy and Pharmacology. 2024;94(2):285-296.
99	Konopleva, M; DiNardo, C; Sun, Y et al. Findings From an Analysis of Patients With Monocytic and Monocytic-Like Acute Myeloid Leukemia (AML), Including AML-M4 and AML-M5, Treated With Venetoclax (Ven) Plus Azacitidine (Aza). Clinical Lymphoma, Myeloma and Leukemia. 2023;23(Supplement 1):S266-S267.
100	Konopleva, M; Thirman, MJ; Pratz, KW et al. Impact of FLT3 Mutation on Outcomes after Venetoclax and Azacitidine for Patients with Treatment-Naive Acute Myeloid Leukemia. Clinical Cancer Research. 2022;28(13):2744-2752.

Study	Reference(s)
101	Kwag, D; Cho, BS; Bang, SY et al. Venetoclax with decitabine versus decitabine monotherapy in elderly acute myeloid leukemia: a propensity score-matched analysis. Blood Cancer Journal. 2022;12(12) (no pagination).
102	Lachowiez, CA; Loghavi, S; Furudate, K et al. Impact of splicing mutations in acute myeloid leukemia treated with hypomethylating agents combined with venetoclax. Blood Advances. 2021;5(8):2173-2183.
103	Lachowiez, CA; Loghavi, S; Kadia, TM et al. Outcomes of older patients with NPM1-mutated AML: Current treatments and the promise of venetoclax-based regimens. Blood Advances. 2020;4(7):1311-1320.
104	Lantz, J; Pham, N; Jones, C et al. Treatment Outcomes with Hypomethylating Agents and Venetoclax for AML in the Community Compared to an Academic Setting. Blood. 2023;142(Supplement 1):7436.
105	Levitz, D; Fedorov, K; Goldfinger, M. A Metabolically Optimized, Non-Cytotoxic Low-Dose Weekly Decitabine/Venetoclax Regimen in MDS and AML. Clinical Lymphoma, Myeloma and Leukemia. 2023;23(Supplement 1):S282-S283.
106	Levitz, D; Sauntharajah, Y; Fedorov, K et al. A Metabolically Optimized, Noncytotoxic Low-Dose Weekly Decitabine/Venetoclax in MDS and AML. Clinical Cancer Research. 2023;29(15):2774-2780.
107	Li, X; Suh, HS; Lachaine, J et al. Comparative Efficacy of Venetoclax-Based Combination Therapies and Other Therapies in Treatment-Naive Patients With Acute Myeloid Leukemia Ineligible for Intensive Chemotherapy: A Network Meta-Analysis. Value in Health. 2023;26(12):1689-1696.
108	Lian, Y; Ti, J; Ma, L et al. Analysis and clinical characteristics of acute myeloid leukemia developing with prior or concurrent tumors in non cyto- or radiotherapy exposure patients in a single center. Hematology (United Kingdom). 2023;28(1) (no pagination).
109	Lin, X; Zhang, Y; Zhao, Y et al. Venetoclax Combined with HMA Versus CAG Based Chemotherapy in Acute Myeloid Leukemia: A Propensity Score Matched Analysis. Blood. 2023;142(Supplement 1):2901.
110	Liu, B; Guo, Y; Deng, L et al. The efficacy and adverse events of venetoclax in combination with hypomethylating agents treatment for patients with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. Hematology (United Kingdom). 2020;25(1):414-423.
111	Lloret-Madrid, P; Boluda, B; Martinez-Lopez, J et al. Treatment patterns and outcomes in secondary acute myeloid leukemia arising after hypomethylating agents: PETHEMA registry study. Cancer. 2025;131(1) (no pagination).

Study	Reference(s)
112	Lou, D; Liu, L; Qin, W. Clinical analysis of venetoclax combined with azacitidine in elderly patients with newly diagnosed acute myeloid leukemia. [Chinese]. Chinese Journal of Clinical Oncology. 2022;49(15):775-780.
113	Ma, X; Liu, Y; Yang, M et al. A Real-World Single-Institution Experience with Vitamin C Supplementation for Hypomethylated Drugs Combined with Venetoclax Versus "7+3" in Elderly AML Patients. Blood. 2023;142(Supplement 1):5917.
114	Marshalek, JP; Epistola, R; Tomassetti, S. Real-world treatment outcomes from a retrospective cohort of patients with acute myeloid leukemia from an urban safety net hospital. Journal of Oncology Pharmacy Practice. 2024.
115	Martinez-Cuadron, D; Boluda, B; Algarra, JL et al. Treatment Outcomes in Unfit Patients with Newly Acute Myeloid Leukemia According to IDH1 Mutational Status: Real World Evidence from the Pethema Epidemiologic Registry. Blood. 2023;142(Supplement 1):4223.
116	Matthews, AH; Perl, AE; Luger, SM et al. Real-world effectiveness of CPX-351 vs venetoclax and azacitidine in acute myeloid leukemia. Blood Advances. 2022;6(13):3997-4005.
117	Mims, A; Xie, Z; Vasconcelos, A et al. Intensive Chemotherapy (IC) Followed By Oral Azacitidine (AZA) Maintenance Versus Venetoclax (VEN) Plus AZA for Patients (pts) with Acute Myeloid Leukemia (AML): Retrospective Analysis of an Electronic Medical Record (EMR) Database in the United States. Blood. 2023;142(Supplement 1):550.
118	Miyashita, N; Onozawa, M; Matsukawa, T et al. Novel stratification for newly diagnosed acute myeloid leukaemia treated with venetoclax-based therapy in the real world: Hokkaido Leukemia Net Study. British Journal of Haematology. 2024;204(4):1549-1553.
119	Montalban-Bravo, G; Kanagal-Shamanna, R; Li, Z et al. Phenotypic subtypes of leukaemic transformation in chronic myelomonocytic leukaemia. British Journal of Haematology. 2023;203(4):581-592.
120	Morsia, E; McCullough, K; Joshi, M et al. Venetoclax and hypomethylating agents in acute myeloid leukemia: Mayo Clinic series on 86 patients. American Journal of Hematology. 2020;95(12):1511-1521.
121	Mustafa Ali, MK; Corley, EM; Alharthy, H et al. Outcomes of Newly Diagnosed Acute Myeloid Leukemia Patients Treated With Hypomethylating Agents With or Without Venetoclax: A Propensity Score-Adjusted Cohort Study. Frontiers in Oncology. 2022;12(no pagination).
122	Mustafa Ali, MK; Williams, MT; Corley, EM et al. Impact of KRAS and NRAS mutations on outcomes in acute myeloid leukemia. Leukemia and Lymphoma. 2023;64(5):962-971.

Study	Reference(s)
123	Naka, R; Kondo, T; Nishikubo, M et al. Venetoclax and azacitidine therapy in acute myeloid leukemia patients with severe renal impairment. American Journal of Hematology. 2023;98(9):E251-E254.
124	Nathan, DI; Hoffman, R; Ahire, D et al. The Presence of Ring Chromosomes in Patients with Myeloid Neoplasms Is Predictive of a Poor Outcome. Blood. 2023;142(Supplement 1):2940.
125	Nurse, DP; Zabor, EC; Cancilla, D et al. Outcomes of blast-phase MPN and JAK2, MPL, and CALRmutated de novo AML: A propensity score-adjusted cohort study. Journal of Clinical Oncology Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2024;42(16 Supplement).
126	Oh, SA; Kim, EY. Efficacy of epigenetic agents for older patients with acute myeloid leukemia and myelodysplastic syndrome in randomized controlled trials: a systematic review and network meta-analysis. Clinical and Experimental Medicine. 2023;23(6):2705-2714.
127	Othman, J; Tiong, IS; O'Nions, J et al. Molecular MRD is strongly prognostic in patients with NPM1-mutated AML receiving venetoclax-based nonintensive therapy. Blood. 2024;143(4):336-341.
128	Othman, TA; Mei, M; Zhang, J et al. Rebound thrombocytosis is associated with response in AML patients treated with venetoclax and hypomethylating agents. American Journal of Hematology. 2021;96(5):E140-E143.
129	Otoukesh, S; Zhang, J; Nakamura, R et al. The efficacy of venetoclax and hypomethylating agents in acute myeloid leukemia with extramedullary involvement. Leukemia and Lymphoma. 2020;61(8):2020-2023.
130	Papadopoulou, V; Schoumans, J; Basset, V et al. Single-center, observational study of AML/MDS-EB with IDH1/2 mutations: genetic profile, immunophenotypes, mutational kinetics and outcomes. Hematology (United Kingdom). 2023;28(1) (no pagination).
131	Papayannidis, C; Nanni, J; Cristiano, G et al. Impact of infectious comorbidity and overall time of hospitalization in total outpatient management of acute myeloid leukemia patients following venetoclax and hypomethylating agents. European Journal of Haematology. 2022;108(6):449-459.
132	Park, S; Kim, TY; Cho, BS et al. Prognostic value of European LeukemiaNet 2022 criteria and genomic clusters using machine learning in older adults with acute myeloid leukemia. Haematologica. 2024;109(4):1095-1106.
133	Patel, SA; Lloyd, MR; Cerny, J et al. Clinico-genomic profiling and clonal dynamic modeling of TP53-aberrant myelodysplastic syndrome and acute myeloid leukemia. Leukemia and Lymphoma. 2021;62(14):3348-3360.

Study	Reference(s)
134	Pelcovits, A; Moore, J; Bakow, B et al. Tumor lysis syndrome risk in outpatient versus inpatient administration of venetoclax and hypomethlators for acute myeloid leukemia. Supportive Care in Cancer. 2021;29(9):5323-5327.
135	Pervitsky, V; Guglielmo, J; Moskoff, B et al. Characterization of a multidisciplinary team's role in hospital discharge for patients receiving hypomethylating agents with venetoclax as induction therapy for acute myeloid leukemia. Supportive Care in Cancer. 2023;31(4) (no pagination).
136	Pham, N; Lantz, J; Jones, C et al. Clinical outcomes of patients receiving venetoclax and hypomethylating agents for AML in academic and academic-community partnerships. Journal of Clinical Oncology Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2024;42(16 Supplement).
137	Pollyea, DA; DiNardo, CD; Arellano, ML et al. Impact of Venetoclax and Azacitidine in Treatment-Naive Patients with Acute Myeloid Leukemia and IDH1/2 Mutations. Clinical Cancer Research. 2022;28(13):2753-2761.
138	Pollyea, DA; Pratz, KW; Wei, AH et al. Outcomes in Patients with Poor-Risk Cytogenetics with or without TP53 Mutations Treated with Venetoclax and Azacitidine. Clinical cancer research : an official journal of the American Association for Cancer Research. 2022;28(24):5272-5279.
139	Pratz, KW; Panayiotidis, P; Recher, C et al. Venetoclax combinations delay the time to deterioration of HRQoL in unfit patients with acute myeloid leukemia. Blood Cancer Journal. 2022;12(4) (no pagination).
140	Qin, Y; Kuang, P; Liu, T. Venetoclax combined with hypomethylating agents or low-dose cytarabine as induction chemotherapy for patients with untreated acute myeloid leukemia ineligible for intensive chemotherapy: a systematic review and meta-analysis. Clinical and Experimental Medicine. 2023;23(2):219-227.
141	Qureshi, Z; Altaf, F; Jamil, A et al. Safety, Efficacy, and Predictive Factors of Venetoclax-Based Regimens in Elderly Acute Myeloid Leukemia Patients: A Meta-Analysis. Clinical Lymphoma, Myeloma and Leukemia. 2024;24(11):e835-e851.
142	Ravindra, A; Acharya, L; Loeffler, B et al. Venetoclax-based therapy in treatment-naive and relapsed/refractory acute myeloid leukemia. Leukemia Research. 2023;135(no pagination).
143	Roman Souza, G; Lucero, KT; Mines, I et al. Clinical Outcomes and Cardiovascular Adverse Events of Patients with Acute Myeloid Leukemia Treated with Venetoclax Plus a Hypomethylating Agent or Low-Dose Cytarabine in the Veterans Health Administration: A National Retrospective Cohort Study. Blood. 2023;142(Supplement 1):4235.

Study	Reference(s)
144	Rowe, M; Babushok, D; Carroll, M et al. Tumor Lysis Syndrome in Acute Myeloid Leukemia Patients Treated With a Venetoclax Based Regimen. European Journal of Haematology. 2024.
145	Rowe, M; Babushok, DV; Carroll, M et al. Comparing Cairo Bishop and Howard Criteria for Identifying Clinically Meaningful Tumor Lysis Syndrome Among Acute Myeloid Leukemia Patients Treated with Venetoclax and Hypomethylating Agents: A Single Center Experience. Blood. 2023;142(Supplement 1):5095.
146	Rummelt, C; Alber, D; Biavasco, F et al. Single-Center Experience of Decitabine and Venetoclax in Newly Diagnosed Older AML Patients with Non-Favorable Genetics: Bridging to Allo-HCT or Treatment Continuation. Oncology Research and Treatment. 2024;47(Supplement 2):264.
147	Russo, D; Polverelli, N; Bernardi, S et al. Venetoclax plus decitabine as a bridge to allogeneic haematopoietic stem-cell transplantation in older patients with acute myeloid leukaemia (VEN-DEC GITMO): final report of a multicentre, single-arm, phase 2 trial. The Lancet Haematology. 2024;11(11):e830-e838.
148	Salhotra, A; Aribi, A; Ngo, D et al. Outcome of secondary acute myeloid leukemia treated with hypomethylating agent plus venetoclax (HMA-Ven) or liposomal daunorubicin-cytarabine (CPX-351). American Journal of Hematology. 2021;96(6):E196-E200.
149	Salhotra, A; Tsai, NC; Zhang, J et al. Venetoclax and hypomethylating agents yield high response rates and favourable transplant outcomes in patients with newly diagnosed acute myeloid leukaemia. British Journal of Haematology. 2022;196(6):e71-e74.
150	Sanka, P; Egan, P; Niroula, R et al. Inpatient Versus Outpatient Administration of Hypomethylating Agents and Venetoclax in Acute Myeloid Leukemia. Blood. 2023;142(Supplement 1):4229.
151	Sasaki, K; Ravandi, F; Kadia, TM et al. Prediction of survival with lower intensity therapy among older patients with acute myeloid leukemia. Cancer. 2023;129(7):1017-1029.
152	Sato, H; Kobayashi, T; Kameoka, Y et al. Prognostic impact of peripheral blood WT1 mRNA dynamics in patients with acute myeloid leukemia treated with venetoclax combination therapy. International Journal of Clinical Oncology. 2024;29(4):481-492.
153	Schulz, F; Roggenbuck, C; Kundgen, A et al. Outcomes in patients with acute myeloid leukemia older than 70 years within the last 30 years, a single center experience. Annals of hematology. 2025;11.
154	Sekiguchi, Y; Tsutsumi, H; Kudo, M et al. Prognostic Factors in Patients with Acute Myeloid Leukemia Treated with the Combination of Venetoclax plus

Study	Reference(s)
	Azacitidine(VEN+AZA). Gan to kagaku ryoho. 2024;Cancer & chemotherapy. 51(11):1143-1152.
155	Senapati, J; Dhawan, R; Aggarwal, M et al. Venetoclax and azacitidine (VenAZA) combination therapy in young unfit patients with AML: a perspective from a developing country. Leukemia and Lymphoma. 2021;62(6):1514-1517.
156	Shaikh, MRMA; Singh, B; Singh, R et al. A Retrospective Comparative Analysis of Intensive Vs. Non-Intensive Chemotherapy in Treatment Naive Acute Myeloid Leukemia (AML) Patients in India. Blood. 2023;142(Supplement 1):5842.
157	Shanker, S; Hasserjian, RP; Madanat, Y et al. Impact of myelodysplasia-related mutations on 2022 European LeukemiaNet genetic risk classification in de novo acute myeloid leukemia with normal karyotype. American Journal of Hematology. 2025;100(1):180-184.
158	Shapiro, L; Mantzaris, I; Shastri, A et al. AML-351 Low-Dose Weekly Decitabine and Venetoclax in TP53-Mutated Myeloid Malignancies. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(Supplement 2):S241.
159	Shimony, S; Bewersdorf, JP; Shallis, RM et al. Hypomethylating agents plus venetoclax compared with intensive induction chemotherapy regimens in molecularly defined secondary AML. Leukemia. 2024;38(4):762-768.
160	Shimony, S; Fell, G; Chen, EC et al. FLT3-ITD does not predict inferior prognosis in acute myeloid leukemia patients aged >=60 years. Blood Advances. 2023;7(18):5354-5358.
161	Shimony, S; Garcia, JS; Keating, J et al. Molecular Ontogeny in AML Is Both Prognostic and Predictive in Patients Treated with Hypomethylating Agents Plus Venetoclax. Blood. 2023;142(Supplement 1):977.
162	Shimony, S; Garcia, JS; Keating, J et al. Molecular ontogeny underlies the benefit of adding venetoclax to hypomethylating agents in newly diagnosed AML patients. Leukemia. 2024;38(7):1494-1500.
163	Shimony, S; Rozental, A; Bewersdorf, JP et al. Investigational venetoclax combination therapy in acute myeloid leukemia - a systematic review and meta-analysis. Haematologica. 2022;107(12):2955-2960.
164	Short, NJ; Montalban-Bravo, G; Hwang, H et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. Blood Advances. 2020;4(22):5681-5689.
165	Short, NJ; Venugopal, S; Qiao, W et al. Impact of frontline treatment approach on outcomes in patients with secondary AML with prior hypomethylating agent exposure. Journal of Hematology and Oncology. 2022;15(1) (no pagination).

Study	Reference(s)
166	Smalinskaite, T; Lukascius, L; Vaitekenaite, V et al. AML-700 Prolonged Cytopenias After First-Line Treatment With Venetoclax and Hypomethylating Agent in Newly Diagnosed AML/MDS-IB. Clinical Lymphoma, Myeloma and Leukemia. 2024;24(Supplement 1):S332.
167	Solana-Altabella, A; Rodriguez-Veiga, R; Martinez-Cuadron, D et al. A systematic review of venetoclax for the treatment of unfit AML patients in real-world: is all that glitters gold? Annals of Hematology. 2024.
168	Sossa-Melo, C; Abello-Polo, V; Salazar, LA et al. Characteristics, outcomes and treatment patterns in acute myeloid leukemia patients 60 years or older in Colombia: a RENEHOC-PETHEMA study. Annals of hematology. 2025;16.
169	Stemler, J; de Jonge, N; Skoetz, N et al. Antifungal prophylaxis in adult patients with acute myeloid leukaemia treated with novel targeted therapies: a systematic review and expert consensus recommendation from the European Hematology Association. The Lancet Haematology. 2022;9(5):e361-e373.
170	Sutter, T; Schittenhelm, M; Volken, T et al. Treatment regimens in patients over 64 years with acute myeloid leukaemia: a retrospective single-institution, multi-site analysis. Hematology (United Kingdom). 2023;28(1) (no pagination).
171	Swain, RN; Wadhera, S; Singh, C et al. Comparable Short Term Outcomes Among Patients with Newly Diagnosed Acute Myeloid Leukemia with or without Myelodysplasia Related Gene Mutations Treated with Azacytidine-Venetoclax: Observations from a Single Center Retrospective Cohort. Indian Journal of Hematology and Blood Transfusion. 2024.
172	Teja, BR; Attili, SVS; Vutukuru, A et al. Retrospective comparison of venetoclax +azacytadine and mini conditioning (5+2) regimen in elderly AML patients: Efficacy and safety analysis. Annals of Oncology. 2024;35(Supplement 4):S1692.
173	Todisco, E; Papayannidis, C; Fracchiolla, N et al. AVALON: The Italian cohort study on real-life efficacy of hypomethylating agents plus venetoclax in newly diagnosed or relapsed/refractory patients with acute myeloid leukemia. Cancer. 2023;129(7):992-1004.
174	Trape, G; De Angelis, G; Morucci, M et al. Treatment in patients with acute myeloid leukemia/high-risk myelodysplastic syndrome with hypomethylating agents: Day-hospital management compared to home care setting. European Journal of Haematology. 2023;111(2):311-317.
175	Tremblay, D; Feld, J; Dougherty, M et al. Venetoclax and hypomethylating agent combination therapy in acute myeloid leukemia secondary to a myeloproliferative neoplasm. Leukemia Research. 2020;98(no pagination).

Study	Reference(s)
176	Ucciero, A; Pagnoni, F; Scotti, L et al. Venetoclax with Hypomethylating Agents in Newly Diagnosed Acute Myeloid Leukemia: A Systematic Review and Meta-Analysis of Survival Data from Real-World Studies. Cancers. 2023;15(18) (no pagination).
177	Urlu, SM; Cengiz Seval, G; Erdogan Yucel, E et al. Acute Myeloid Leukemia in Elderly, Unfit Patients: Analysis of Turkish AML Prospective Registry Database, on Behalf of Acute Leukemia Working Group of Turkish Society of Hematology. Blood. 2023;142(Supplement 1):5931.
178	Vachhani, P; Flahavan, EM; Xu, T et al. Venetoclax and Hypomethylating Agents as First-line Treatment in Newly Diagnosed Patients with AML in a Predominately Community Setting in the US. Oncologist. 2022;27(11):907-918.
179	Velayati, A; Dickerson, J; Graf, K et al. Impact of Discharge Timing for Extended-Course Decitabine and Venetoclax in Acute Myeloid Leukemia (AML). Clinical Lymphoma, Myeloma and Leukemia. 2023;23(Supplement 1):S290.
180	Venditti, A; Hou, JZ; Fenaux, P et al. Outcomes in Chemotherapy-Ineligible Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia Treated with Venetoclax Plus Azacitidine: A Pooled Analysis. Blood. 2023;142(Supplement 1):2886.
181	Venugopal, S; Maiti, A; DiNardo, CD et al. Decitabine and venetoclax for IDH1/2-mutated acute myeloid leukemia. American Journal of Hematology. 2021;96(5):E154-E157.
182	Venugopal, S; Maiti, A; DiNardo, CD et al. Prognostic impact of conventional cytogenetics in acute myeloid leukemia treated with venetoclax and decitabine. Leukemia and Lymphoma. 2021;62(14):3501-3505.
183	Villarreal Hernandez, J; Pomares, H; Sturla, A et al. Clinical Characteristics of Patients with TP53 Multihit MDS and AML. a Single-Center Experience. Blood. 2023;142(Supplement 1):5868.
184	Wan, CL; Huang, YH; Huang, SM et al. Investigations of the prognostic value of RUNX1 mutation in acute myeloid leukemia patients: Data from a real-world study. Leukemia Research. 2024;139(no pagination).
185	Wan, CL; Liu, YQ; Liu, FT et al. Venetoclax with hypomethylating agents versus intensive chemotherapy in newly diagnosed acute myeloid leukemia with myelodysplasia related changes: A propensity score-matched analysis based on International Consensus Classification. Blood Cancer Journal. 2024;14(1) (no pagination).
186	Wang, KY; Fan, BR; Zhang, QW et al. The Efficacy and Safety of Venetoclax Combined with Azacitidine in the Treatment of Adult Patients with Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy. [Chinese]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2024;32(2):342-346.

Study	Reference(s)
187	Wang, M; Cao, HY; Tan, KW et al. Venetoclax plus hypomethylating agents in newly diagnosed acute myeloid leukemia patients with RUNX1::RUNX1T1: a retrospective propensity score matching study. Blood Cancer Journal. 2023;13(1) (no pagination).
188	Wang, ST; Chou, CH; Chen, TT et al. High rate of invasive fungal infections during early cycles of azacitidine for patients with acute myeloid leukemia. Frontiers in Cellular and Infection Microbiology. 2022;12(no pagination).
189	Wei, MY; Yin, J; Liao, Y et al. The efficacy and safety of venetoclax combined with demethylating agents in elderly patients with acute myeloid leukemia: a systematic review and meta-analysis. European Review for Medical and Pharmacological Sciences. 2024;28(5):1837-1846.
190	Weng, G; Huang, J; He, X et al. Hypomethylating agents plus modified priming regimens compared with venetoclax-based regimens based on molecular characteristics for newly diagnosed patients with acute myeloid leukemia: a multi-center cohort study. Annals of Hematology. 2023;102(12):3369-3381.
191	Winters, AC; Gutman, JA; Purev, E et al. Real-world experience of venetoclax with azacitidine for untreated patients with acute myeloid leukemia. Blood Advances. 2019;3(20):2911-2919.
192	Xin, F; Yu, YH; Shen, XL et al. The efficacy of the combination of venetoclax and hypomethylating agents versus HAG agents in patients with acute myeloid leukemia: a retrospective study. Hematology (United Kingdom). 2024;29(1) (no pagination).
193	Xu, Y; Li, D; Wang, N et al. miR-182 promoter hypermethylation predicts the better outcome of AML patients treated with AZA + VEN in a real-world setting. Clinical Epigenetics. 2025;17(1):18.
194	Yamaguchi, Y; Hirano, D; Minami, R et al. Efficacy and safety of venetoclax and azacytidine for acute myeloid leukemia: a retrospective, single-center study. Annals of Oncology. 2024;35(Supplement 3):S1333.
195	Yavuz, S; Malkan, UY. Comparison of regimens targeting complete remission in the first-line treatment of acute myeloid leukemia patients. European Review for Medical and Pharmacological Sciences. 2024;28(21):4493-4506.
196	Yin, Z; Yao, Z; Chen, D et al. Homoharringtonine may help improve the outcomes of venetoclax and azacitidine in AML1-ETO positive acute myeloid leukemia. Journal of Cancer Research and Clinical Oncology. 2024;150(7) (no pagination).
197	Zeidan, AM; Pollyea, DA; Borate, U et al. Venetoclax plus azacitidine compared with intensive chemotherapy as induction for patients with acute myeloid leukemia: retrospective analysis of an electronic medical record database in the United States. Annals of Hematology. 2023;102(4):749-754.

Study	Reference(s)
198	Zhang, F; Liu, Y; Zhu, Y et al. Molecular, clinical, and prognostic implications of RAS pathway alterations in adult acute myeloid leukemia. Leukemia and Lymphoma. 2025.
199	Zhao, D; Zarif, M; Zhou, Q et al. TP53 Mutations in AML Patients Are Associated with Dismal Clinical Outcome Irrespective of Frontline Induction Regimen and Allogeneic Hematopoietic Cell Transplantation. Cancers. 2023;15(12) (no pagination).
200	Zheng, W; Fu, S; Luo, X et al. Ultra-Low-Dose of Decitabine with Venetoclax As Induction and Consolidation Therapy for Elderly or Frail Newly Diagnosed Acute Myeloid Leukemia and High Risk Myelodysplastic Syndrome Patients. Blood. 2023;142(Supplement 1):5934.
201	Zheng, YL; Ding, T; Xiao, XF et al. [Clinical Study of Venetoclax Combined with Azacitidine in the Treatment of Patients with Adult Acute Myeloid Leukemia]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2024;32(4):1046-1050.
202	Zhu, W; Zhu, L; Hu, X et al. Safety and infection risk factors in elderly acute myeloid leukemia patients undergoing induction therapy with venetoclax combined with hypomethylating agents. American Journal of Cancer Research. 2024;14(12):5897-5908.
SLR Update (January 2026)	
1	Alam J, Kumari L, Shaikh U, *et al.* Outcomes of patients with Acute Myeloid Leukemia receiving venetoclax in combination with azacitidine: A single center retrospective study from Pakistan. Journal of Cancer & Allied Specialties 2025;11:1-7.
2	Albliwi M, Zabor EC, Hanna J, *et al.* Comparative Outcomes of Intensive Chemotherapy Versus Venetoclax Plus Hypomethylating Agents in Acute Myeloid Leukemia Patients Aged 60-75 Years: A Propensity Score-Adjusted Cohort Study. Clinical Lymphoma, Myeloma and Leukemia. 2025.
3	Ball S, Jain AG, Al Ali N, *et al.* Hypomethylating Agent and Venetoclax Combination Is a Safe and Effective Alternative to Intensive Chemotherapy in Older (>= 70 Years) Patients With Newly Diagnosed Favorable Risk Acute Myeloid Leukemia. American Journal of Hematology 2025;100(10):1920-1923.
4	Bataller A, Goulart HE, Issa GC, *et al.* Characteristics and outcomes of newly diagnosed acute myeloid Leukemia with KMT2A rearrangements. Leukemia 2025;39(7):1640-1649.
5	Cai Y, Rui J, Ding Z, *et al.* Better Response and Prognosis of Venetoclax Plus Hypomethylating Agents Over Intensive Chemotherapy in Young Adults With Newly Diagnosed ASXL1-Mutated Acute Myeloid Leukemia. Cancer Medicine 2025;14(14) (no pagination).

Study	Reference(s)
6	Chen X, Yan Y, Cheng Q, *et al.* Genotype-guided comparison of VEN/HMA versus intensive chemotherapy in newly diagnosed intermediate-risk AML: a multicenter real-world study. Blood Cancer Journal 2025;15(1) (no pagination).
7	Chen Y, Wang Z, Cai R, *et al.* Significant prognostic improvement in elderly patients with acute myeloid leukemia treated with hypomethylating agents and venetoclax: outcomes from a retrospective real-world analysis. Annals of Medicine 2025;57(1) (no pagination).
8	Cho BS, Kim KY, Kwag D, *et al.* Transplantation Outcomes after Venetoclax-Decitabine Compared to Conventional Chemotherapy As an Induction Therapy: A Propensity Score Matched Cohort Analysis. Transplantation and Cellular Therapy 2025;31(2 Supplement):S127.
9	Cinar OE, Kanat A, Erer K, *et al.* Risk Factors for Infectious Adverse Events in Newly Diagnosed Acute Myeloid Leukemia Patients Treated With Venetoclax Combinations: A Retrospective Single-Centre Real-World Experience. Cancer Reports 2025;8(12) (no pagination).
10	Ciotti G, Atanasio A, Marconi G, *et al.* Real-Life Outcomes in Patients with Acute Myeloid Leukemia Secondary to Myeloproliferative Neoplasia: Results of Multicentric ENEA Study. HemaSphere 2025;9(Supplement 1):311-313.
11	Diekmann B, Van Roon EN, Veeger N, *et al.* Venetoclax for Older Patients with Newly Diagnosed Acute Myeloid Leukemia in the Dutch Real-World: Usage and Outcomes. HemaSphere 2025;9(Supplement 1):383-384.
12	Esplund J, Leidy S, Byrd K, *et al.* AML-828: Prognostic Impact and Clinical Outcomes of IDH1/IDH2 Mutations in Newly Diagnosed Acute Myeloid Leukemia Treated With Hypomethylating Agents and Venetoclax. Clinical Lymphoma, Myeloma and Leukemia 2025;25(Supplement 1):S462.
13	Fang Q, Fung CY, Wang J, *et al.* Hypomethylating agent versus venetoclax combination: an electronic health records-based target trial emulation among Asian elderly patients with newly diagnosed acute myeloid leukaemia in Hong Kong. Therapeutic Advances in Hematology 2025;16(no pagination).
14	Filimon S, Ghamari A, Vakilpour A, *et al.* Cardiovascular Events in Patients with Acute Myeloid Leukemia Treated with Venetoclax: A Multicenter Study. Journal of the American College of Cardiology 2025;85(12 Supplement):2865.
15	Gil-Sierra MD, Mantopoulos T, Barouma I, *et al.* Indirect treatment comparison of ivosidenib and other therapies in patients with newly diagnosed acute myeloid leukemia. Future Oncology 2025;21(17):2225-2235.
16	Granatkin M, Egor V, Ahmetova A, *et al.* Azacitidine and Venetoclax in the Treatment of Elderly Patients with Acute Myeloid Leukemia: A Single-Centre

Study	Reference(s)
	Experience Incorporating the Updated Risk Classification for Low-Intensity Regimens. HemaSphere 2025;9(Supplement 1):474-475.
17	Gurnari C, Fianchi L, Meddi E, *et al.* Clinico-Genomic Features of Therapy-Related Myeloid Neoplasms (T-Mns): A Nationwide Study. HemaSphere 2025;9(Supplement 1):59-61.
18	Huang W, Wang M, Xie J, *et al.* Adult AML with NUP98 rearrangements should be stratified into adverse-risk group. Blood Cancer Journal 2025;15(1) (no pagination).
19	Ikoma Y, Nakamura N, Kaneda Y, *et al.* Impact of myelodysplasia-related gene mutations and residual mutations at remission in venetoclax/azacitidine for AML. Leukemia 2025;39(6):1362-1367.
20	Istomin O, Veremiychyk O, Lysytsia O. Venetoclax/azacitidine vs intensive chemotherapy as a bridge to allogeneic HSCT in AML: Experience from Ukraine. Journal of Clinical Oncology. Conference 2025;43.
21	Jimenez-Vicente C, Cardus A, Castano-Diez S, *et al.* Prognostic value of measurable residual disease (MRD) for venetoclax in combination with hypomethylating agents in patients diagnosed with acute myeloid leukemia: validation of the ELN-2021 MRD recommendations. Blood Cancer Journal 2025;15(1) (no pagination).
22	Kanaya M, Onozawa M, Matsukawa T, *et al.* Comparable outcomes with 14-, 21-, or standard 28-day venetoclax in the first cycle of azacitidine-venetoclax in untreated acute myeloid leukemia: real-world experience from the Hokkaido Leukemia Net. Blood Cancer Journal 2025;15(1) (no pagination).
23	Karakus V, Pinar IE, Iltar U, *et al.* Clinical Characteristics, Treatment Approaches, and Survival Predictors in Adult Acute Myeloid Leukemia: Interim Results from the Turkish Society of Hematology AML Registry +. Journal of Clinical Medicine 2025;14(20) (no pagination).
24	Khan F, Ajenaghughrure G, Qadri H, *et al.* AML-851: Real-World Comparison of Hypomethylating Agent-Venetoclax and Intensive Chemotherapy in Elderly Acute Myeloid Leukemia: Survival and Safety Insights From a Global Matched Cohort. Clinical Lymphoma, Myeloma and Leukemia 2025;25(Supplement 1):S464.
25	Kruger K, Gabdoulline R, Wichmann M, *et al.* Prognostic Role of Kidney Disease in Newly Diagnosed Acute Myeloid Leukemia Under Venetoclax-Based Low-Intensity Therapy. Cancers 2025;17(18) (no pagination).
26	Kwag D, Cho BS, Park S, *et al.* Objectively measured physical function predicts mortality in older adults with acute myeloid leukemia treated by lower-intensity therapy: A prospective cohort study. Journal of Geriatric Oncology 2025;16(8) (no pagination).

Study	Reference(s)
27	Lachowiez CA, Barcellos A, Zettler CM, *et al.* Treatment Patterns and Real-World Outcomes of Molecular Subgroups in Patients With AML Receiving Frontline Venetoclax-Based Therapy. JCO Oncology Practice 2025;(no pagination).
28	Li W, Kang S, Jiao Y, *et al.* Comparative efficacy and safety in low-intensity treatment for acute myeloid leukemia in older patients: a systematic review and network meta-analysis. European Journal of Medical Research 2025;30(1) (no pagination).
29	Li X, Zhu XY, Xiao XB, *et al.* Safety and efficacy of semi-dose venetoclax plus azacitidine in unfit acute myeloid leukemia patients in China: a real-world single-center study. Investigational New Drugs 2025;43(4):915-923.
30	Lian J, Zhuang X, Chen Y, *et al.* Prognostic value of Day 14 measurable residual disease in acute myeloid leukemia treated with venetoclax and azacitidine. Cancer 2025;131(17) (no pagination).
31	Liu Y, Zhang Y, Gao J, *et al.* Venetoclax and hypomethylating agents versus induction chemotherapy for newly diagnosed acute myeloid leukemia patients: a systematic review and meta-analysis. BMC Cancer 2025;25(1) (no pagination).
32	Mao Y, Cai Y, Wu Y, *et al.* The efficacy of varying doses of venetoclax combined with azacitidine for newly diagnosed adult acute myeloid leukemia in real-world settings: a single-center retrospective analysis. Hematology (United Kingdom) 2025;30(1) (no pagination).
33	Mudd TW, Diebold K, Parks K, *et al.* Outcomes with intensive chemotherapy, compared to hypomethylating agent + venetoclax, in patients with intermediate and adverse risk acute myeloid leukemia. Leukemia Research 2025;156(no pagination).
34	Osanno L, Brocque L, Bourguignon L, *et al.* Predicting the toxicity-efficacy ratio of venetoclax in real-world patients. Annals of Hematology. 2025.
35	Petermichl V, Fuchs S, Weber M, *et al.* Prognostic Impact of the AML60+ Score for Elderly Patients with Acute Myeloid Leukemia Treated with Hypomethylating Agents: A Retrospective Multicentric Analysis. Cancers 2025;17(16) (no pagination).
36	Pullarkat, V; Pratz, KW; Dohner, H *et al.* Venetoclax and azacitidine in untreated patients with therapy-related acute myeloid leukemia, antecedent myelodysplastic syndromes or chronic myelomonocytic leukemia. Blood Cancer Journal. 2025;15(1) (no pagination).
37	Rattanathammethee T, Chanswangphuwana C, Silpsamrit P, *et al.* Outcomes of Real-World Investigations on Azacitidine Plus Venetoclax in Acute Myeloid Leukemia: ORION-AML Study. HemaSphere 2025;9(Supplement 1):416-418.

Study	Reference(s)
38	Rattanathammethee T, Chanswangphuwana C, Silpsamrit P, *et al.* Real-world outcomes of azacitidine plus venetoclax in acute myeloid leukemia: a multicenter retrospective cohort study from Thailand. Therapeutic Advances in Hematology 2025;16(no pagination).
39	Rockwell B, Mantzaris I, Shastri A, *et al.* Dosing decitabine and venetoclax for terminal differentiation to improve outcomes in TP53 mutant MDS and AML. Journal of Clinical Oncology. Conference 2025;43.
40	Saiyin T, Christou G, Sabloff M, *et al.* Incidence of Tumour Lysis Syndrome in Patients with Acute Myeloid Leukemia During Initiation of Therapy with Azacitidine and Venetoclax: A Retrospective Chart Review from a Canadian Single-Centre Perspective. Current Oncology 2025;32(4) (no pagination).
41	Sanchez J, Jones MK, Julian K, *et al.* Tolerability and outcomes with serial cycles of 28 days of venetoclax in newly diagnosed patients with AML. Journal of Clinical Oncology. Conference 2025;43.
42	Sanz-Solas A, Saiz-Rodriguez M, Simal SC, *et al.* Comparative efficacy of venetoclax and hypomethylating agents in acute myeloid leukemia treatment: a meta-analysis of clinical trials and Real-World outcomes. Annals of Hematology 2025;104(9):4505-4514.
43	Shimada T, Takahata A, Tanaka K, *et al.* Efficacy and safety of venetoclax-based regimens versus intensive chemotherapy in older adults with newly diagnosed acute myeloid leukemia: a single-center retrospective study. International Journal of Hematology. 2025.
44	Swaminathan M, DiNardo CD, Maiti A, *et al.* VEN in combination with 10-day DEC in newly diagnosed elderly or relapsed/refractory acute myeloid leukemia, and high-risk myelodysplastic syndrome: long term follow-up of a phase 2 trial. Blood Cancer Journal 2025;15(1) (no pagination).
45	Talbot A, Debureaux PE, Lillo-Le Louet A, *et al.* Safety of venetoclax in real-world experience: data from the French national database of pharmacovigilance through all indications in hematological malignancies over 5 years. Therapeutic Advances in Hematology 2025;16(no pagination).
46	Venditti, A; Hou, JZ; Fenaux, P *et al.* Outcomes of patients treated with venetoclax plus azacitidine versus azacitidine alone stratified by advanced age and acute myeloid leukemia composite model. Leukemia. 2025;39(11):2697-2707.
47	Venkatadasari I, Qureshi I, McCarthy N, *et al.* Real-World Experience of Bone Marrow Flow MRD Monitoring in AML Patients Receiving Venetoclax and Azacitidine as First-Line Treatment: Single-Centre Study. HemaSphere 2025;9(Supplement 1):515-516.

Study	Reference(s)
48	Wang LL, Zhang J, Zhang Y, *et al.* Retrospective Analysis of Venetoclax Combined with Azacitidine Compared with "3+7" or Similar Regimens for Newly Diagnosed Patients with Acute Myeloid Leukemia. [Chinese]. Zhongguo shi yan xue ye xue za zhi 2025;33(3):672-681.
49	Wang LY, Gao HT, Fu Q, *et al.* Decoding the molecular drivers of TP53-mutant acute myeloid leukaemia: Clinical implications and prognostic insights. British Journal of Haematology. 2025.
50	Wang T, Huang J, Jia Y, *et al.* The association of FAT1 mutations with therapeutic outcomes in AML, especially in receiving venetoclax combination. Frontiers in Oncology 2025;15(no pagination).
51	Wang Y, Chen Y, Ji D, *et al.* Meta-analysis on the effectiveness and safety of venetoclax-based combination therapy with hypomethylation in acute myeloid leukemia. European Journal of Medical Research 2025;30(1) (no pagination).
52	Wolach O, Desai P, Chen EC, *et al.* Real-world patient management practices in responders to venetoclax for newly diagnosed acute myeloid leukemia. Journal of Clinical Oncology. Conference 2025;43.
53	Wu Z, Chen Y, Wang Z, *et al.* Prognostic impact of methylation-related gene mutations in elderly acute myeloid leukemia: a real-world retrospective analysis. Frontiers in Medicine 2025;12(no pagination).
54	Wurm S, Moritz JM, Petzer V, *et al.* Efficacy assessment following shortened venetoclax exposure in AML patients treated with venetoclax plus hypomethylating agents: a real-world, multicentric study. Blood Cancer Journal 2025;15(1) (no pagination).
55	Yates SJ, Weiss JJ, Sneider A, *et al.* Longer time from diagnosis to initiation of hypomethylating agents plus venetoclax for acute myeloid leukemia does not worsen survival: results from the Consortium on Myeloid Malignancies and Neoplastic Diseases (COMMAND). Haematologica. 2025;24.
56	Yu Z, Li S, Pei R, *et al.* Venetoclax combined with azacitidine in elderly acute myeloid leukemia: A retrospective comparison of 14-day vs 28-day dosing regimens. Medicine (United States) 2025;104(33):e43979.
57	Zale AD, Sandeep Kaduluri VP, Webster JA, *et al.* Intensive chemotherapy vs venetoclax/hypomethylating agents for patients aged 60 to 75 years with favorable, NPM1-mutated AML. Blood Neoplasia 2025;2:100133.
58	Zhao R, Wang Y, Dijkstra M, *et al.* Chart Review Study on the Real-World Cytopenia Management of Patients with Acute Myeloid Leukemia Treated with Venetoclax and Hypomethylating Agents. HemaSphere 2025;9(Supplement 1):304-305.

Study	Reference(s)
59	Zhu M, Yang J, Wu Y. Clinical Case Analysis of 21 Patients with BPDCN and PDC-AML. HemaSphere 2025;9(Supplement 1):334-336.
60	Zimmer M, Jacob B, Spica M, *et al.* Outcomes of acute myeloid leukemia treated with a hypomethylating agent and venetoclax. Cancer Research. Conference: American Association for Cancer Research, AACR 2025;85.
61	Zou J, Yuan G, He J, *et al.* Survival Analysis of Long-Term Treatment with Venetoclax-Azacitidine in Newly Diagnosed Acute Myeloid Leukemia: Multicentre Real-World Outcomes in China. HemaSphere 2025;9(Supplement 1):2558-2559.

Appendix I. Literature searches for health-related quality of life

I.1 Systematic search

The SLR is described in detail in Appendix H. Out of the 42 unique studies prioritised for extraction as mentioned in Appendix H, only VIALE-A included HRQoL reported outcomes.

I.2 Focused search

N/A

Appendix J. Literature searches for supplementary input to the health economic model

J.1 Systematic search

N/A

J.2 Focused search

A targeted literature search was conducted on 15 February 2026 to identify information on AZA administration in Danish clinical practice among AML patients receiving VEN combination therapy. Searches were performed using Google and the Medicinrådet website with keywords including “venetoclax”, “azacitidine”, “AML”, “Denmark”, and “subcutaneous administration”.

The search identified the Medicinrådet recommendation for VEN (Venclyxto) in combination with a HMA in AML, which also provided evidence that approximately one-third of patients self-administer SC AZA for 3 out of 5 treatment days in Danish clinical practice.

Appendix K. Reasons for confidential information

Table 57 includes the justification for confidential information marking of specific sections/parts of the application.

Table 57. Justifications regarding confidential information

Parameter	Justification
Results from Cost Minimising Analysis • Section 12 Results, pages 68	The confidential marked statement contains sensitive information regarding Otsuka's strategy, negotiation position, and assessment of the economic impact of INAQOVI + VEN. Disclosure of pricing strategy may cause commercial harm to Otsuka.
Name and workplace of the interviewed clinical expert • Section 14 List of experts, page 74 • Section 15 References, page 75	The name and workplace of the clinical expert is considered confidential as it contains personal data and identifiable expert opinions provided under confidentiality conditions. Disclosure would risk breaching data protection requirements, violate consent agreements, expose commercially sensitive insights, and potentially impact the expert’s professional position.

Medicinrådet

The Secretariat of the Danish Medicines Council
The Danish Medicines Council, Dampfærgevej 27-29, 3rd floor
2100 Copenhagen Ø

+ 45 70 10 36 00
medicinraadet@medicinraadet.dk

www.medicinraadet.dk