Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-312 Ivosidenib

Stand: Januar 2026

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Ivosidenib
[neu diagnostizierte AML mit IDH1-R132-Mutation, Standard-Induktionschemotherapie nicht geeignet]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	II. Zugelassene Arzneimittel im Anwendungsgebiet
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach §35a SGB V: - Decitabin/Cedazuridin (Beschluss vom 15. August 2024) - Ivosidenib (Beschluss vom 18. Januar 2024) - Venetoclax (Beschluss vom 02. Dezember 2021) - Glasdegib (Beschluss vom 18. Februar 2021) - Decitabin (Beschluss vom 02. Mai 2013) Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie (Stand: 10. August 2024) Arzneimittel, die in nicht zugelassenen Anwendungsgebieten (Off-Label-Use) verordnungsfähig sind Hydroxycarbamid bei chronischer myelomonozytärer Leukämie (CMML).
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Ivosidenib L01XX62 Tibsovo	Zugelassenes Anwendungsgebiet: Tibsovo in Kombination mit Azacitidin wird angewendet zur Behandlung von erwachsenen Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitratdehydrogenase-1 (IDH1)-R132-Mutation, die für eine Standard-Induktionschemotherapie nicht geeignet sind.
Chemotherapien	
Azacitidin L01BC07 (Vidaza)	Vidaza ist angezeigt zur Behandlung von erwachsenen Patienten, die für eine Transplantation hämatopoetischer Stammzellen (HSZT) nicht geeignet sind und eines der folgenden Krankheitsbilder aufweisen: […] - akute myeloische Leukämie (AML) mit 20-30 % Blasten und Mehrlinien-Dysplasie gemäß Klassifikation der World Health Organisation (WHO) - AML mit > 30 % Knochenmarkblasten gemäß WHO-Klassifikation.
Cytarabin L01BC01 (Cytarabin Accord)	Zur Induktion der Remission bei akuter myeloischer Leukämie bei Erwachsenen und zur Behandlung anderer akuter Leukämien bei Erwachsenen und Kindern.
Daunorubicin L01DB02 Daunoblastin	<u>Erwachsene</u> Remissionsinduktion bei akuten lymphoblastischen bzw. lymphatischen (ALL) und bei akuten myeloischen Leukämien (AML). Die Anwendung erfolgt in Kombination mit anderen Zytostatika.
Decitabin L01BC08 Dacogen	Dacogen ist indiziert zur Behandlung erwachsener Patienten mit neu diagnostizierter de novo oder sekundärer akuter myeloischer Leukämie (AML) gemäß der Klassifikation der Weltgesundheitsorganisation (WHO), für die eine Standard-Induktionstherapie nicht in Frage kommt.
Decitabin/Cedazuridin	Inaqovi wird angewendet als Monotherapie bei der Behandlung von erwachsenen Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML), für die eine Standard-Induktionschemotherapie nicht in Frage kommt.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01BC58 Inaqovi	
Doxorubicin L01DB01 Ribodoxo	[…] Remissionsinduktion bei akuter myeloischer Leukämie […]
Idarubicin L01DB06 Zavedos	Erwachsene: Zavedos ist in Kombination mit anderen Zytostatika (z. B. Cytarabin) zur Remissionsinduktion und Konsolidierung bei unvorbehandelten Patienten mit akuten myeloischen Leukämien (AML, ANLL) im Erwachsenenalter angezeigt.
Etoposid L01CB01 Etopophos	<u>Entscheidung der Europäischen Komission zur Harmonisierung der Fachinformation von Etopophos:</u> Etopophos ist angezeigt in Kombination mit anderen antineoplastisch wirksamen Präparaten zur Behandlung der akuten myeloischen Leukämie bei Erwachsenen und Kindern. (Stand Juni 2017; EMEA/H/A-30/1417; Entscheidung (2017)4521 of 26/06/2017)
Histamindihydro-chlorid L03AX14 Ceplene	Die Ceplene-Erhaltungstherapie ist indiziert für erwachsene Patienten mit akuter myeloischer Leukämie (AML) in erster Remission, die gleichzeitig mit Interleukin-2 (IL-2) behandelt werden. Die Wirksamkeit von Ceplene wurde bei Patienten über 60 Jahren nicht völlig nachgewiesen.
Tioguanin L01BB03 Tioguanin-Aspen	Induktions- und Konsolidierungsphase der Behandlung der akuten myeloischen Leukämie (AML).
Mitoxantron L01DB07 Ralenova	Mitoxantron ist indiziert zur Behandlung der akuten myeloischen Leukämie (AML) bei Erwachsenen.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
weitere Zytostatika	
Glasdegib L01XJ03 Daurismo	Daurismo wird angewendet in Kombination mit niedrig dosiertem Cytarabin (LDAC, low-dose cytarabine) für die Behandlung von neu diagnostizierter de novo oder sekundärer akuter myeloischer Leukämie (AML) bei erwachsenen Patienten, die nicht für eine Standard-Induktionschemotherapie infrage kommen.
Venetoclax L01XX52 Venclyxto	Venclyxto in Kombination mit einer hypomethylierenden Substanz wird angewendet zur Behandlung erwachsener Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML), die nicht für eine intensive Chemotherapie geeignet sind.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-312 (Ivosidenib)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	18. Dezember 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse event
AML	Acute myeloid leukemia
ASCT	Autologous stem cell transplant
AZA	Azacitidine
BSC	Best Supportive Care
CR	Complete Remission
Cri	CR with incomplete hematologic recovery
DEC	Decitabine
DFS	Disease-free survival
DIC	Disseminated intravascular coagulation
EFS	Event-free survival
ELN	European LeukemiaNet
G-BA	Gemeinsamer Bundesausschuss
GO	Gemtuzumab Ozogamicin
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIDAC	High-Dose Cytarabine
HR	Hazard Ratio
IC	Induction chemotherapy
LDAC	Cytarabin, low-dose
LoE	Level of Evidence
MLFS	Morphologic leukemia-free state
NMA	Network Meta-Analysis
NOS	Newcastle-Ottawa Scale
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PR	Partial response
RCT	randomized controlled trial
RFS	relapse-free survival
RR	Relatives Risiko
SAE	severe adverse even
VEN	Venetoclax
WHO	World Health Organization

1 Indikation

Behandlung von Erwachsenen mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, die für eine Standard- Induktionschemotherapie nicht geeignet sind.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *akute myeloische Leukämie (AML)* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.startpage.com*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 09.07.2025 abgeschlossen. Am 25.11.2025 erfolgte eine Überprüfung der iterativen Handsuche. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 672 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Basierend darauf, wurden insgesamt acht Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten CR identifiziert.

3.2 Systematische Reviews

Zhu J et al., 2024 [8].

Venetoclax combined chemotherapy versus chemotherapy alone for acute myeloid leukemia: a systematic review and meta-analysis

Fragestellung

To compare the efficacy and safety of venetoclax (VEN) in combination with chemotherapy (chemo) versus chemo alone in the treatment of acute myeloid leukemia (AML).

Methodik

Population:

- adult patients with AML

Intervention/Komparator:

- VEN + chemo vs. chemo

Endpunkte:

- CR, CRi, MLFS, ORR, EFS, OS

Recherche/Suchzeitraum:

- -06.2023
- PubMed, Embase, Web of Science, Cochrane Library

Qualitätsbewertung der Studien:

- Cohort Studies: Newcastle-Ottawa Scale (NOS)
- RCTs: Cochrane Risk of Bias Assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 articles
- 3124 patients

Qualität der Studien:

- Siehe Table 1

Charakteristika der Population/Studien:

TABLE 1 Baseline characteristics of include studies and methodological assessment.

Authors	Study period	Country	Study design	Types of AML	Patients (n)	Median age(years)	Male(n)	Median follow-up	Combination chemother-apy regimen	Chemotherapy alone	Quality score
					Venetoclax +chemo/ Chemo	Venetoclax +chemo/ Chemo	Venetoclax +chemo/ Chemo				
Cherry (8)	2007-2020	USA	Cohort	Newly diagnosed AML	143/149	68.35/52.47	72/78	4.65years	The simultaneous combination of ven and aza at any dose or schedule, and 149 received IC, defined as a multiday cytarabine-containing regimen at $100 mg/m^2 per day	Intensive chemotherapy	7
DiNardo (10)	2017-2019	USA	RCT	Previously untreated patients with confirmed AML who were ineligible for standard induction therapy	286/145	75.67/75.91	172/87	20.5 months	Venetoclax (Venetoclax was administered orally, once daily, with food. For mitigation of the tumor lysis syndrome during cycle 1, the dose of venetoclax was 100 mg on day 1 and 200 mg on day 2; on day 3, the target dose of 400 mg was reached and continued until day 28) + azacitidine (5 mg per square meter of body-surface area, subcutaneously or intravenously, on days 1 through 7 every 28-day cycle)	Placebo + azacitidine (5 mg per square meter of body-surface area, subcutaneously or intravenously, on days 1 through 7 every 28-day cycle)	NA
Gershon (12)	2014-2021	USA	Cohort	Newly diagnosed AML	619/480	74.80/75.80	383/295	6.3 months	Venetoclax + HMAs (Aza ± hydroxyurea, or Dec ± hydroxyurea)	HMA monotherapy (Aza ± hydroxyurea, or Dec ± hydroxyurea)	6
Kwag (13)	2013-2021	Korea	Cohort	Newly diagnosed AML	74/74	71.35/72.71	32/37	8.5 months	The DEC+VEN group received the same daily dose of DEC for five days combined with 28 days of VEN (400 mg daily) per cycle.	DEC monotherapy consisted of administering 20 mg/m2 intravenous DEC daily for five days.	8
Lachowiez (14)	2010-2021	USA	Cohort	Newly diagnosed AML	85/194	46.06/49.60	44/87	30 months	Venetoclax + IC (FLAG-IDA or CLIA)	IC (FIA, CLIA, or CIA)	8
Maiti (5)	2005-2020	USA	Cohort	Relapsed or refractory AML	65/130	62.14/57.20	39/72	49.3 months	Decitabine 20 mg/m2 daily for 10 days every 4 to 6 weeks with venetoclax 400 mg daily or equivalent (with concomitant azole antifungals) for induction.	IC (salvage therapy with idarubicin with cytarabine (IA), with or without cladribine (CLIA), clofarabine (CIA), or fludarabine (FIA or FLAG- IDA)–based regimens)	9
Maiti (15)	2000-2019	USA	Cohort	Newly diagnosed AML	85/85	73.06/71.94	45/48	81.2 months	The regimen comprised of daily venetoclax with decitabine 20 mg/m2 IV for 10 days for "induction", followed by decitabine for 5-days as consolidation.	Intensive chemotherapy containing at least moderate dose of cytarabine 1 g/m2/d	8

TABLE 1 Continued

Authors	Study period	Country	Study design	Types of AML	Patients (n)	Median age(years)	Male(n)	Median follow-up	Combination chemotherapy regimen	Chemotherapy alone	Quality score
					Venetoclax +chemo/ Chemo	Venetoclax +chemo/ Chemo	Venetoclax +chemo/ Chemo				
									Venetoclax dose was 400 mg daily or equivalent with concomitant azoles.		
Park (16)	2018-2021	Korea	Cohort	Relapsed or refractory AML	54/89	49.41/48.58	24/52	22.5 months	VEN with HMA (VEN/HMA) or with LDAC (VEN/LDAC) was administered in 28-day cycles.	IC (MEC, FLANG, or FLAG-IDA)	8
Wei (9)	2017-2019	Multicenter	RCT	AML who had not received prior AML treatment and were ineligible for intensive chemotherapy	142/68	74.99/74.34	78/39	17.5 months	Venetoclax (100 mg venetoclax orally on day 1, 200 mg on day 2, 400 mg on day 3, and 600 mg daily on days 4–28 of cycle 1 and daily in all subsequent 28-day cycles) + LDAC (20 mg/m2 subcutaneously on days 1–10 of each 28-day cycle)	Placebo + LDAC (20 mg/m2 subcutaneously on days 1–10 of each 28-day cycle)	NA

AML, acute myeloid leukemia.

TABLE 2 Subgroup analysis.

Subgroup	CR				CRi				MLFS				Overall response				OS				EFS			
	Study	OR [95%CI]	*P* value	I^2	Study	OR [95%CI]	*P* value	I^2	Study	OR [95%CI]	*P* value	I^2	Study	OR [95%CI]	*P* value	I^2	Study	HR [95% CI]	*P* value	I^2	Study	HR [95% CI]	*P* value	I^2
Total	7	1.74 [1.12-2.69]	0.01	65%	6	2.88 [1.99-4.18]	<0.00001	35%	5	3.49 [1.80-6.74]	0.0002	0%	5	3.05 [1.58-5.86]	0.0009	77%	8	0.68 [0.61-0.76]	<0.00001	2%	4	0.53 [0.43-0.64]	<0.00001	0%
Study design																								
RCT	1	4.94 [1.85-13.18]	0.001	NA													2	0.67 [0.55-0.82]	<0.00001	0%	1	0.61 [0.44-0.85]	0.003	NA
Cohort	6	1.51 [1.02-2.25]	0.04	55%													6	0.68 [0.60-0.77]	<0.00001	29%	3	0.49 [0.38-0.62]	<0.00001	0%
Combining scheme																								
Venetoclax +azacitidine	1	0.91 [0.57-1.46]	0.7	NA	1	3.63 [1.15-11.40]	0.03	NA	1	1.71 [0.54-5.35]	0.36	NA	1	1.40 [0.83-2.36]	0.21	NA	1	0.66 [0.52-0.84]	0.0006	NA				
Venetoclax +decitabine	3	2.23 [1.34-3.69]	0.002	32%	3	3.79 [2.36-6.08]	<0.00001	0%	2	3.61 [1.37-9.49]	0.009	0%	2	5.45 [2.13-13.94]	0.0004	73%	3	0.55 [0.43-0.71]	<0.00001	0%	2	0.47 [0.35-0.61]	<0.00001	0%
Venetoclax +IC	1	1.16 [0.61-2.20]	0.66	NA	1	0.69 [0.22-2.17]	0.52	NA	1	21.48 [1.14-403.52]	0.04	NA					1	0.63 [0.35-1.13]	0.12	NA	1	0.57 [0.34-0.96]	0.03	NA
Venetoclax +cytarabine	1	4.94 [1.85-13.18]	0.001	NA													1	0.70 [0.50-0.98]	0.04	NA	1	0.61 [0.44-0.85]	0.003	NA
Region																								
Asia	2	2.18 [0.73-6.49]	0.16	75%	2	3.11 [1.52-6.34]	0.002	0%	2	4.75 [0.98-23.14]	0.05	0%	2	4.26 [1.00-18.22]	0.05	88%	2	0.77 [0.56-1.05]	0.09	71%				
America	4	1.31 [0.88-1.93]	0.18	39%	4	2.80 [1.81-4.33]	<0.00001	58%	3	3.23 [1.56-6.70]	0.002	31%	3	2.39 [1.21-4.68]	0.01	64%	5	0.67 [0.59-0.75]	<0.00001	0%				
Types of AML																								
Newly diagnosed	5	1.97 [1.06-3.66]	0.03	76%	4	0.35 [0.13-0.96]	0.04	0%	3	2.91 [1.17-7.23]	0.02	24%	3	3.44 [0.99-11.94]	0.05	88%	6	0.67 [0.60-0.75]	<0.00001	0%	3	0.55 [0.44-0.68]	<0.00001	0%
Relapsed or refractory	2	1.37 [0.83-2.27]	0.22	0%	2	2.89 [1.88-4.43]	<0.00001	59%	2	4.32 [1.67-11.17]	0.003	0%	2	2.71 [1.63-4.52]	0.0001	18%	2	0.74 [0.54-1.02]	0.06	76%	1	0.46 [0.30-0.71]	0.0004	NA

AML, Acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete hematologic recovery; MLFS, morphologic leukemia-free state; EFS, Event-Free Survival; OS, overall survival; OR, odds ratio; CI, confidence intervals; HR, hazard ratio; IC, intensive chemotherapy.

Studienergebnisse:

- Event-free survival and OS
  - (1) EFS: Seven studies reported the EFS of the patients. The results showed that the VEN+chemo group had a longer EFS compared to the chemo alone group, and the combined effect was statistically significant (HR=0.53, 95%CI: 0.43-0.64). There was no significant heterogeneity in the study results (I^2 = 0%, P=0.65), as depicted in Figure 2E. The funnel plot (Figure 3E), and Egger's test (P=0.781) found no obvious publication bias;
  - (2) OS: Eight studies used OS as the evaluation measure. The results showed that the VEN+chemo group had a longer OS compared to the chemo alone group, and the combined effect was statistically significant (HR=0.68, 95%CI: 0.61-0.76). There was no significant heterogeneity in the study results (I^2 = 2%, P=0.42), as depicted in Figure 2F. The funnel plot (Figure 3F), and Egger's test (P=0.551) exhibited no significant publication bias.
- Safety
  - We found that almost all patients experienced at least one AE (99%). The most prevalent AEs observed in both study groups included neutropenia, thrombocytopenia, nausea, and infection. Although the SAEs incidence in VEN+chemo group was higher than chemo alone group, but the difference was not statistically significant(P>0.05) in AEs and SAEs. Early 30-day mortality, of VEN+chemo group was superior to the chemo alone group (OR=0.23, 95%CI=0.12-0.48, P<0.0001).

Anmerkung/Fazit der Autoren

VEN-based combination therapy demonstrates significant efficacy and a favorable safety profile in patients with AML, potentially providing a more appropriate treatment option. Nevertheless, due to the limited available literature and the presence of heterogeneity and potential publication bias, it is imperative to undertake further prospective studies in the future. These studies are essential for providing more accurate and convincing evidence to guide therapeutic decisions in patients.

Kommentare zum Review

Review kombiniert RCTs und Kohortenstudien.

Es ist unklar, wie viele Personen in den eingeschlossenen Studien des Reviews neu diagnostizierte akute myeloische Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, haben.

Li X et al., 2023 [5].

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

Fragestellung

This NMA aimed to compare the relative efficacy of VEN-based combinations (VEN + AZA and VEN + LDAC) with AZA, LDAC, and DEC monotherapies and BSC alone, in adult patients with untreated AML deemed ineligible for intensive chemotherapy.

Methodik

Population:

- Treatment-naive adult patients (age ≥ 18 years) with AML
- ineligible for intensive chemotherapy

Intervention/Komparator:

- VEN-based combinations (VEN + AZA and VEN + LDAC) vs. AZA, LDAC, and DEC monotherapies and BSC alone

Endpunkte:

- CR, Cri, OS

Recherche/Suchzeitraum:

- -10.2020
- MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Database of Abstracts of Reviews of Effects

Qualitätsbewertung der Studien:

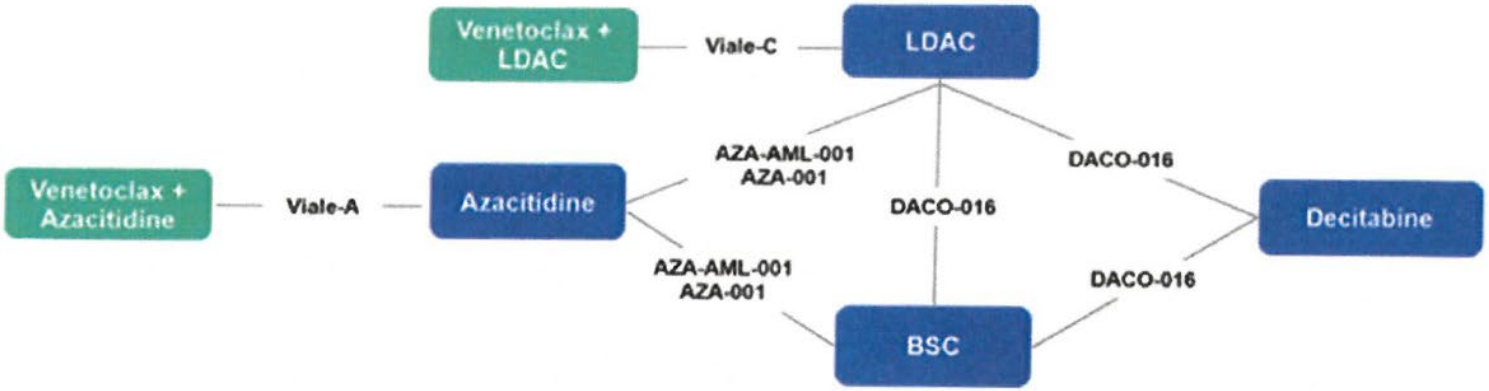
- Centre for Reviews and Dissemination risk of bias assessment checklist for RCTs

Ergebnisse

Anzahl eingeschlossener Studien:

- 5

Figure 2. Network diagram for the NMA of CR + CRi and OS.



Notes: CR + CRi was not available for AZA-001. The HR for OS reported for DACO-016 was used for DEC versus LDAC because 88% patients in the treatment choice arm received LDAC. AZA indicates azacitidine; BSC, best supportive care; CR + CRi, complete remission + complete remission with incomplete blood count recovery; DEC, decitabine; HR, hazard ratio; LDAC, low-dose cytarabine; NMA, network meta-analysis; OS, overall survival; VEN, venetoclax.

Charakteristika der Population/Studien:

Table S4. Summary of study characteristics for trials included in the NMA

Trial	Trial Registration Number	Blinding	Study Population	Treatment Arm	Sample Size
AZA-AML-001 (Dombret et al., 2015)[1,2]	NCT01074047	Open-label	Patients age ≥ 65 years with newly diagnosed AML and >30% bone marrow blasts	CCR - combined	247
				AZA - combined	241
				CCR - preselected BSC	45
				AZA - preselected BSC	44
				CCR - preselected LDAC	158
				AZA - preselected LDAC	154
				CCR - preselected IC	44
				AZA - preselected IC	43
AZA-001 (Fenaux et al., 2009)[3,4]	NCT00071799	Open-label	AML patients with ≥20% bone marrow or peripheral blasts based on central bone marrow review (i.e., with FAB-defined RAEB-t and WHO-defined AML)	CCR - combined	58
				AZA - combined	55
				CCR - preselected BSC	27
				AZA - preselected BSC	36
				CCR - preselected LDAC	20
				AZA - preselected LDAC	14
				CCR - preselected IC	11
				AZA - preselected IC	5
DACO-016 (Kantarjian et al., 2012)	NCT00260832	Open-label	≥ 65 years old with newly diagnosed, histologically confirmed de novo or secondary AML (≥20% blasts) and poor- or intermediate-risk cytogenetics (Southwest Oncology Group categorization), ECOG PS of 0 to 2, WBC count ≤40,000/mm, bilirubin ≤1.5 × the ULN, AST or ALT ≤2.5 × the ULN, creatinine clearance ≥40 mL/min, and life expectancy ≥12 weeks	DEC	242
				LDAC	215
				BSC	28
Viale-A (Dinardo et al., 2020)	NCT02993523	Double-blind	Treatment-naïve patients with AML ineligible for intensive therapy	AZA	145
				Venetoclax + AZA	286
Viale-C (Wei et al., 2020)	NCT03069352	Double-blind	Treatment-naïve patients with AML who are considered ineligible for anthracycline-containing intensive induction chemotherapy	LDAC	68
				Venetoclax + LDAC	143

Abbreviations: AZA: Azacitidine; AML: Acute Myeloid Leukemia; ALT: Alanine Transaminase; AST: Aspartate Transaminase; BSC: Best Supportive Care;

Abbreviations: AZA: Azacitidine; AML: Acute Myeloid Leukemia; ALT: Alanine Transaminase; AST: Aspartate Transaminase; BSC: Best Supportive Care; CR+CRi: Complete Remission + Complete Remission with Incomplete Blood Count Recovery; CCR: Conventional Care Regimens; DEC: Decitabine; ECOG: Eastem Cooperative Oncology Group; FAB: French-American-British Classification; IC: Intensive chemotherapy; LDAC: Low-dose Cytarabine; NMA: Network Meta-analysis; RAEB-t: Refractory Anemia with Excess Blasts in Transformation; ULN: Upper Limit of Normal; VEN: Venetoclax; WBC: White Blood Cell; WHO: World Health Organization.

Notes:

[l] AZA-AML-001 included patients >30% bone marrow blasts. Patients were randomly assigned on the basis of local pathology assessment of baseline bone marrow blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review.

[2] In AZA-AML-001, randomization was stratified by preselected CCR (BSC, LDAC, or IC). Patients assigned to CCR received their preselected treatment.

[3] AZA-001 included patients with 20-30% bone marrow blasts. One patient in the BSC group had a bone marrow blast count of 13% but was included based on a peripheral blast count of 20%. In addition, one patient in the LDAC arm had blast count of34%.

[4] In AZA-001, patients were randomly assigned to receive AZA or their preselected CCR (LDAC, BSC, or IC).

Table S6. Summary of OS for trials included in the NMA

Trial	Treatment Arm	N	OS	
			Hazard Ratio	95% CI
AZA-AML-001 (Dombret et al., 2015)[1]	BSC	45	Reference	
	AZA	44	0.60	[0.38, 0.95]
AZA-AML-001 (Dombret et al., 2015)[1]	LDAC	158	Reference	
	AZA	154	0.90	[0.70, 1.16]
AZA-001 (Fenaux et al., 2009)[2]	BSC	27	Reference	
	AZA	36	0.48	[0.24, 0.94]
AZA-001 (Fenaux et al., 2009)[2]	LDAC	20	Reference	
	AZA	14	0.37	[0.12, 1.13]
DACO-016 (Kantarjian et al., 2012)[3]	LDAC	243	Reference	
	DEC	242	0.82	[0.68, 0.99]
Viale-A (Dinardo et al., 2020)	AZA	145	Reference	
	VEN + AZA	286	0.66	[0.52, 0.85]
Viale-C (Wei et al., 2020)	LDAC	68	Reference	
	VEN + LDAC	143	0.70	[0.50, 0.99]

Abbreviations: AZA: Azacitidine; BSC: Best Supportive Care; CI: Confidence Interval; DEC: Decitabine; HR: Hazard Ratio; LDAC: Low-dose Cytarabine; NMA: Network Meta-analysis; OS: Overall Survival; TC: Treatment Choice; VEN: Venetoclax.

[l] AZA-AML-001 included patients >30% bone marrow blasts. Patients were randomly assigned because of local pathology assessment of baseline bone marrow blast count, which was subsequently reviewed by the central pathologist; in a small number of cases, baseline blast count was <30% upon central review.

[2] AZA-001 included patients with 20-30% bone marrow blasts. One patient in the BSC group had a bone marrow blast count of 13% but was included based on a peripheral blast count of20%. In addition, one patient in the LDAC arm had blast count of34%.

[3] In DACO-016, the HR of OS was reported for DEC vs. treatment choice (TC) (LDAC or BSC), not specifically for DEC vs. LDAC or DEC vs. BSC. Given that most patients in the TC arm (88%) received LDAC, the HR for DEC.

Qualität der Studien:

Table S7. Risk of bias assessment

Study name	*Q1. Was randomization carried out appropriately?*	*Q2. Was the concealment of treatment allocation adequate?*	*Q3. Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?*	*Q4. Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?*	*Q5. Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?*	*Q6. Is there any evidence to suggest that the authors measured more outcomes than they reported?*	*Q7. Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?*
	Risk of bias (High/Low/Unclear)	*Risk of bias (High/Low/Unclear)*	*Risk of bias (High/Low/Unclear)*	*Risk of bias (High/Low/Unclear)*	*Risk of bias (High/Low/Unclear)*	*Risk of bias (High/Low/Unclear)*	*Risk of bias (High/Low/Unclear)*
AZA-AML-001 (Dombret et al., 2015[1])	Low	Low	Low	High	Low	Unclear	Unclear
AZA-001 (Fenaux et al., 2009[2])	Low	Low	Low	High	High	High	Unclear
DACO-016 (Kantarjian et al., 2012[5])	Low	Unclear	Low	High	Low	Unclear	Unclear
VIALE-A (Dinardo et al., 2020[6])	Low	Low	Low	Low	Low	Unclear	Unclear
VIALE-C (Wei et al., 2020[7])	Low	Low	Low	Low	Low	Unclear	Unclear

AML: Acute myeloid leukemia; AZA: Azacitidine.

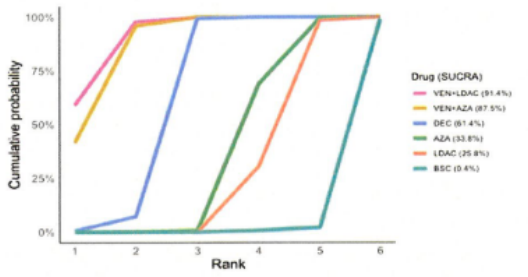
Studienergebnisse:

Table 2. Pairwise treatment comparisons of OS.

Treatment comparison for OS, HR (95% credible interval)					
VEN + AZA	VEN + LDAC	AZA	LDAC	DEC	BSC
0.81 (0.50, 1.32)					
0.66* (0.52-0.85)	0.81 (0.54-1.24)				
0.57* (0.41-0.81)	0.70* (0.50-0.99)	0.86 (0.67-1.10)			
0.70 (0.47-1.03)	0.86 (0.58-1.26)	1.05 (0.77-1.43)	1.22* (1.01-1.47)		
0.37* (0.24-0.59)	0.46* (0.26-0.80)	0.56* (0.38-0.82)	0.65 (0.41-1.01)	0.53* (0.33-0.86)	

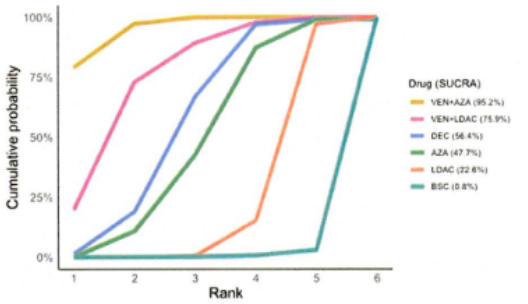
Note. Comparisons between treatments should be read as the hazard ratio for the column-defining treatment versus the row-defining treatment. A hazard ratio below one favors the column-defining treatment.
AZA indicates azacitidine; BSC, best supportive care; DEC, decitabine; HR, hazard ratio; LDAC, low-dose cytarabine; OS, overall survival; VEN, venetoclax.
*Significant results: the 95% credible interval does not contain one.

Figure 3. SUCRA plots for CR + CRi.



Note: The SUCRA value represents the probability that a treatment is among the most effective options. The higher the SUCRA value and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks among all evaluated treatments. SUCRA(i) can be interpreted as the average proportion of treatments with a probability of being less effective than i. AZA indicates azacitidine; BSC, best supportive care; CR + CRi, complete remission + complete remission with incomplete blood count recovery; DEC, decitabine; LDAC, low-dose cytarabine; SUCRA, surface under the cumulative ranking curve; VEN, venetoclax.

Figure 4. SUCRA plots for OS.



Note: The SUCRA value represents the probability that a treatment is among the most effective options. The higher the SUCRA value and the closer to 100%, the higher the likelihood that a therapy is in the top rank or one of the top ranks among all evaluated treatments. SUCRA(i) can be interpreted as the average proportion of treatments with a probability of being less effective than i. AZA indicates azacitidine; BSC, best supportive care; DEC, decitabine; LDAC, low-dose cytarabine; OS, overall survival; SUCRA, surface under the cumulative ranking curve; VEN, venetoclax.

Anmerkung/Fazit der Autoren

[…] head-to-head clinical trials directly comparing VEN-based combination therapies with alternative therapies remain scarce. To address this knowledge gap, the present NMA study indirectly compared VEN + AZA and VEN + LDAC with conventional care regimens and found significant improvements in OS and remission rates relative to AZA. LDAC, and BSC alone. The demonstration of improved outcomes with VEN-based combination therapies among treatment-naive patients with AML who are ineligible for intensive chemotherapy in turn reinforces clinical guideline recommendations directing their use toward this patient population. Future indirect comparisons of VEN-based combination therapies and alternative therapies are warranted once more clinical trial results become available to strengthen and broaden the network.

Kommentare zum Review

Die systematischen Reviews von [7] und [3] beschäftigten sich ebenfalls mit weniger intensiven und/oder Venetoclax-basierten Therapien für Personen, die für eine Standard-Induktionschemotherapie ungeeignet sind. Da alle verglichenen Therapien in dieser NMA enthalten sind, werden sie nicht einzeln dargestellt.

Es ist unklar, wie viele Personen in den eingeschlossenen Studien des Reviews neu diagnostizierte akute myeloische Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, haben. Im Diskussionsteil des Reviews wird ausgeführt, dass Klinische Studien außerdem gezeigt haben, dass VEN + AZA und VEN + LDAC bei allen Mutationssubtypen der AML wirksam sind, wobei neu diagnostizierte Patienten mit IDH1/2- und NPMl-mutierter AML tendenziell sogar noch besser auf die Therapie ansprechen als die Gesamtpopulation.

24. DiNardo CD, Jenas BA. Pullarkat V. et ai. Azaciddine and venetodax in previously untreated acute myeloid leukemia. N EnglJ Med. 2020;383(7):617-629.
25. Wei AH. Montesinos P, Ivanov V, et ai. Venetoclax plus LDAC for newly diagnosed AML inetigible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Bfood. 2020;135(24):2137-2145.

Heuser M et al., 2023 [4].

Therapies for acute myeloid leukemia in patients ineligible for standard induction chemotherapy: a systematic review

Fragestellung

The objective of this systematic literature review (SLR) was to identify and qualitatively assess the clinical efficacy and safety evidence for current and emerging treatments for patients with newly diagnosed AML who are ineligible for first-line IC.

Methodik

Population:

- Adult patients with newly diagnosed AML who are ineligible for first-line IC.

Intervention/Komparator:

- chemotherapy (decitabine, azacitidine, FLUGA [fludarabine, cytarabine and filgrastim], sapacitabine, ATRA [all-trans retinoic acid], LDAC, GRASPA [L-asparaginase encapsulated in red blood cells, eryaspase] and guadecitabine), immunotherapy (lenalidomide, durvalumab, talacotuzumab, lintuzumab and gemtuzumab ozogamicin), targeted therapy (venetoclax, enasidenib, gilteritinib, ivosidenib, volasertib, glasdegib, barasertib [AZD1152] and tipifarnib), and BSC.

Endpunkte:

- OS, event-free survival [EFS], relapse-free survival [RFS], disease-free survival [DFS], complete response [CR], partial response [PR] and adverse events [AEs]

Recherche/Suchzeitraum:

- -10.2021
- Embase, MEDLINE, Cochrane

Qualitätsbewertung der Studien:

- Cochrane ROB2

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 unique studies
- reported in 60 publication

Charakteristika der Population/Studien:

Table S6. Summary of key characteristics of included studies

Study	Secondary publications	Trial phase	Patient population	Treatment arms	Sample size	Primary outcomes	Secondary outcomes	Follow-up, median (mo)
HMAs								
HMAs vs chemotherapy								
PETHEMA-FLUGAZA (NCT02319135) [53]	[18]	III	Previously untreated patients ineligible for standard IC	FLUGA	283	OS	2- and 3-year OS, EFS, DFS, RFS; cumulative incidence of relapse; CR according to % of MRD in bone marrow as assessed by flow cytometry; ORR (CR plus CR with incomplete haematological recovery); early mortality at 30 and 60 days	32.90
				Azacitidine				29.10
SEAMLESS (NCT01303796) [44]	NA	III	Newly diagnosed patients ineligible for IC	Sapacitabine + decitabine	482	OS	CR, CRp, PR, HI, and stable disease with corresponding durations, transfusion requirements, duration of hospitalizations, 1-year survival	NR
				Decitabine				
DECIDER (NCT00867672, EudraCT: 2009-009916-33, DRKS00000733) [46]	[62, 70]	II	Primary or secondary AML (≥20% blasts in the peripheral blood or bone marrow who are treatment-naïve patients ineligible for standard remission-IC	Decitabine	204	ORR	OS, EFS, PFS, overall best response (CR, CRi, PR, antileukemic effect), HRQoL, AEs	25.1[a]
				Valproate + decitabine				
				ATRA + decitabine				
				Valproate + ATRA + decitabine				
HMAs vs immunotherapy								
NCT01358734 [47]		II	Newly diagnosed patients ineligible to receive a transplant	Lenalidomide	88	OS	CR, CRi, remission duration	NR
				Azacitidine + lenalidomide				
				Azacitidine				
NCT02775903 [56]	NA	II	Previously untreated patients ineligible for IC	Durvalumab + azacitidine	129	ORR, CR, CRi	OS, PFS, safety	NR

				Azacitidine				
NCT02472145 [50]	[90]	II/III	Patients with untreated AML who are ineligible for intense IC or HSCT	Talacotuzumab + decitabine Decitabine	316	EFS	CR rate, OS, CR+CRi rate, ORR, HRQoL, safety	NR
HMAs vs targeted therapy								
VIALE-A (NCT02993523) [38]	[73, 87]	III	Previously untreated, sAML, ineligible for IC	Venetoclax + azacitidine Azacitidine + placebo	433	OS	CRc (CR or CRi), CRh, CR by the initiation of cycle 2, RBC and PLT TI, OS in molecular and cytogenetic subgroups, EFS, MRD by flow cytometry, QoL	20.5
AG221-AML-005 (NCT02677922) [39]	[63]	II	Newly diagnosed, mutant-*IDH2* AML ineligible for IC	Enasidenib + azacitidine Azacitidine	101	Safety, tolerability, recommended combination dose of enasidenib	ORR, CRh	NR
NCT02752035 [54]	NA	III	Newly diagnosed m*FLT3* AML patients ineligible for IC	Gilteritinib + azacitidine Azacitidine	123	OS	EFS, response rates, safety/tolerability, PK	9.76 17.97
AGILE (NCT03173248) [49]	NA	III	Previously untreated patients with *IDH1* mutation and ineligible for IC	Ivosidenib + azacitidine Azacitidine + placebo	146	EFS	OS, CR rate, CR+CRh rate, ORR, HRQoL, safety	12.4
LDAC								
LDAC vs chemotherapy								
AML-16 (ISRCTN 11036523; NCT00454480) [35]	NA	II/III	Previously untreated patients ineligible for IC	LDAC Clofarabine	406	OR, CRi, ORR	Resistant disease, induction death, mortality, OS, RFS, survival from CR, survival from non-CR, survival from relapse	25.0
ISRCTN40571019; ISRCTN11036523 [34]	NA	II/III	Untreated AML patients ineligible for IC	LDAC Sapacitabine	143	ORR	OS, RFS	NR

LDAC vs immunotherapy								
NCT00528333 [52]	NA	IIb	Untreated AML patients	Lintuzumab + LDAC LDAC + placebo	211	OS	PLT and RBC transfusion requirements, infections/fevers requiring hospitalisation or IV antibiotics, and serial peripheral blood counts, HRQoL	NR
LI-1 [36]	NA	II	AML patients unsuitable for IC	Lenalidomide + LDAC LDAC	202	OS, complete remission (CR + CRi) achievement, reasons for failure, duration of response (CR/CRi), relapse rates and deaths in first CR	Toxicity, supportive care requirements, QoL assessments (measured using EORTC QLQ-30, EQ5D and HADS tools)	NR
LDAC vs targeted therapy								
BI 1230.4 (NCT00804856) [40]	NA	II	Previously untreated AML patients ineligible for IC	Volasertib + LDAC LDAC	87	ORR	EFS, RFS, OS, and incidence and intensity of AEs, PK	28.3
VIALE-C (NCT03069352) [55]	[81, 82, 84]	III	Previously untreated AML ineligible for IC	Venetoclax + LDAC LDAC + placebo	211	OS	Response rate, TI, EFS	12.0
BRIGHT AML 1003 (NCT01546038) [37]	[66, 67, 69, 72, 75, 76, 79, 80, 86, 89]	II	Newly diagnosed AML patients ineligible for IC	Glasdegib + LDAC LDAC	132	OS	Clinical efficacy endpoints, safety and tolerability, PK, PD, effect on QTc interval	21.7[a]
	NA	III		Volasertib + LDAC	666	ORR	OS, safety	NR

POLO-AML-2 (NCT01721876) [41]			Previously untreated (except for hydroxyurea) AML ineligible for standard IC	LDAC + placebo				
SPARK-AML1 (NCT00952588) [31]	NA	II/III	Newly diagnosed, de-novo, sAML patients ineligible for IC with anthracycline-based combination chemotherapy	Barasertib LDAC	74	CR	DoR, DFS, time to complete response, OS, % of patients with worsened TOI, % of patients with worsened FACT-Leu score	NR
LDAC vs other								
ENFORCE (NCT01810705; EudraCT 2012-002026-78) [32]	NA	IIb	Newly diagnosed patients, ineligible for IC	LDAC + GRASPA LDAC	123	OS	CR, Cri, PR, PFS, QoL, RFS, safety, hospitalisations, transfusion dependence, PK, PD, immunogenicity, biomarker cytogenetic testing	24
BSC								
BSC vs immunotherapy								
AML-19 (NCT00091234) [33]	[59]	III	Previously untreated, de-novo, sAML patients ineligible for IC	Gemtuzumab ozogamicin BSC	237	OS	Safety	NR
BSC vs targeted therapy								
FIGHT-AML-301 (NCT00093990) [43]	[88]	III	Newly diagnosed de-novo or sAML patients ineligible for IC	Tipifarnib BSC	457	OS	PFS, CR, CR duration, rate of morphologic leukaemia-free state, 1-year survival	18.7[b]
Others								
DACO-016 (NCT00260832) [45]	[60, 65, 71, 77, 78, 83]	III	Newly diagnosed, de-novo or sAML patients	Decitabine Treatment choice (supportive care or LDAC)	485	OS	CR, safety	NR
Mohammed et al. [48]	NA	NR		LDAC	60	OS		NR

			Newly diagnosed patients ineligible for standard of care	BSC			Comparison of the QoL regarding the length of hospital stays, mode and frequency of hospital admission in the two groups	
AZA-AML-001 (NCT01074047) [42]	[64, 74]	III	Newly diagnosed, de-novo or sAML not considered eligible for HSCT	Azacitidine CCR	488	OS	OS and OS in patient subgroup, CR, CRi, PR, stable disease, EFS, RFS, RBC and PLT TI	24.4
ASTRAL-1 (NCT02348489) [51]	[57, 58, 68, 85]	III	Untreated AML patients ineligible for IC	Guadecitabine Treatment choice (azacitidine, decitabine, or LDAC)	815	CR, OS	PFS, EFS	25.5

[a] Median follow-up for OS

[b] Median days converted to median months

AEs, adverse events; AML, acute myeloid leukaemia; ATRA, all-trans retinoic acid; BSC, best supportive care; CCR, conventional care regimen; CR, complete response/complete remission; CRc, composite complete remission; CRh, complete remission with partial haematological recovery; CRi, complete remission with incomplete blood count recovery; CRp, complete remission with incomplete platelet recovery; DFS, disease free survival; DoR, duration of response; DRKS, Deutsches Register Klinischer Studien (German Clinical Trials Register); EFS, event-free survival; EORTC QLQ-30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire – Core Questionnaire; EQ5D, EuroQoL five-dimension scale; EudraCT, European Union Drug Regulating Authorities Clinical Trials; FACT-Leu, Functional Assessment of Cancer Therapy - Leukaemia ; FLT3, FMS-like tyrosine kinase 3; FLUGA, fludarabine, cytarabine, and filgrastim; GRASPA, L-asparaginase encapsulated in red blood cells, eryaspase; HADS, Hospital Anxiety and Depression Scale; HI, haematologic improvement; HMA, hypomethylating agents; HRQoL, health-related quality of life; HSTC, hematopoietic stem cell transplantation; IC, induction chemotherapy; IDH, isocitrate dehydrogenase; ISRCTN, International Standard Randomised Controlled Trial Number; LDAC, low dose cytarabine; mo, months; MRD, measurable residual disease; NA, not available; NCT, national clinical trial; NR, not reported; ORR, overall objective response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression- free survival; PK, pharmacokinetics; PLT, platelet; PR, partial response; QoL, quality of life; QTc, corrected QT; RBC, red blood cell; RFS, relapse-free survival; sAML, secondary acute myeloid leukaemia; TI, transfusion independence; TOI, trial outcome index.

Qualität der Studien:

Study ID	D1	D2	D3	D4	D5	Overall
VIALE-C [55]	+	+	+	+	+	+
VIALE-A [38]	+	+	+	+	+	+
BI 1230.4 [40]	!	!	+	+	!	!
NCT00528333 [52]	+	+	+	+	+	+
BRIGHT AML 1003 [37]	!	!	+	!	+	!
POLO-AML-2 [41]	+	+	+	+	+	+
ISRCTN40571019/ISRCTN11036523 [34]	!	+	+	+	+	!
NCT01358734 [47]	+	+	+	+	!	!
FIGHT-AML-301 [43]	+	+	+	+	+	+
NCT02775903 [56]	!	-	+	+	!	-
AML-19 [33]	+	+	+	+	+	+
Mohammed et al. 2021 [48]	!	!	+	+	!	!
AML-16 [35]	!	+	+	+	+	!
PETHEMA-FLUGAZA [53]	!	+	+	+	+	!
SEAMLESS [44]	+	!	+	+	+	!
AG221-AML-005 [39]	+	!	+	+	+	!
DECIDER [46]	+	+	+	+	+	+
DACO-016 [45]	+	+	+	+	+	+
ASTRAL-1 [51]	!	!	+	!	+	!
AZA-AML-001 [42]	+	+	+	+	+	+
LI-1 [36]	!	-	+	-	!	-
NCT02752035 [54]	!	-	+	-	+	-
AGILE [49]	+	+	+	+	+	+
NCT02472145 [50]	+	+	+	+	+	+
SPARK-AML1 [31]	!	!	+	-	+	-
ENFORCE [32]	+	!	+	-	+	-

+ Low risk
! Some concerns
- High risk

D1 Randomisation process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 6. Risk of bias.

Studienergebnisse:

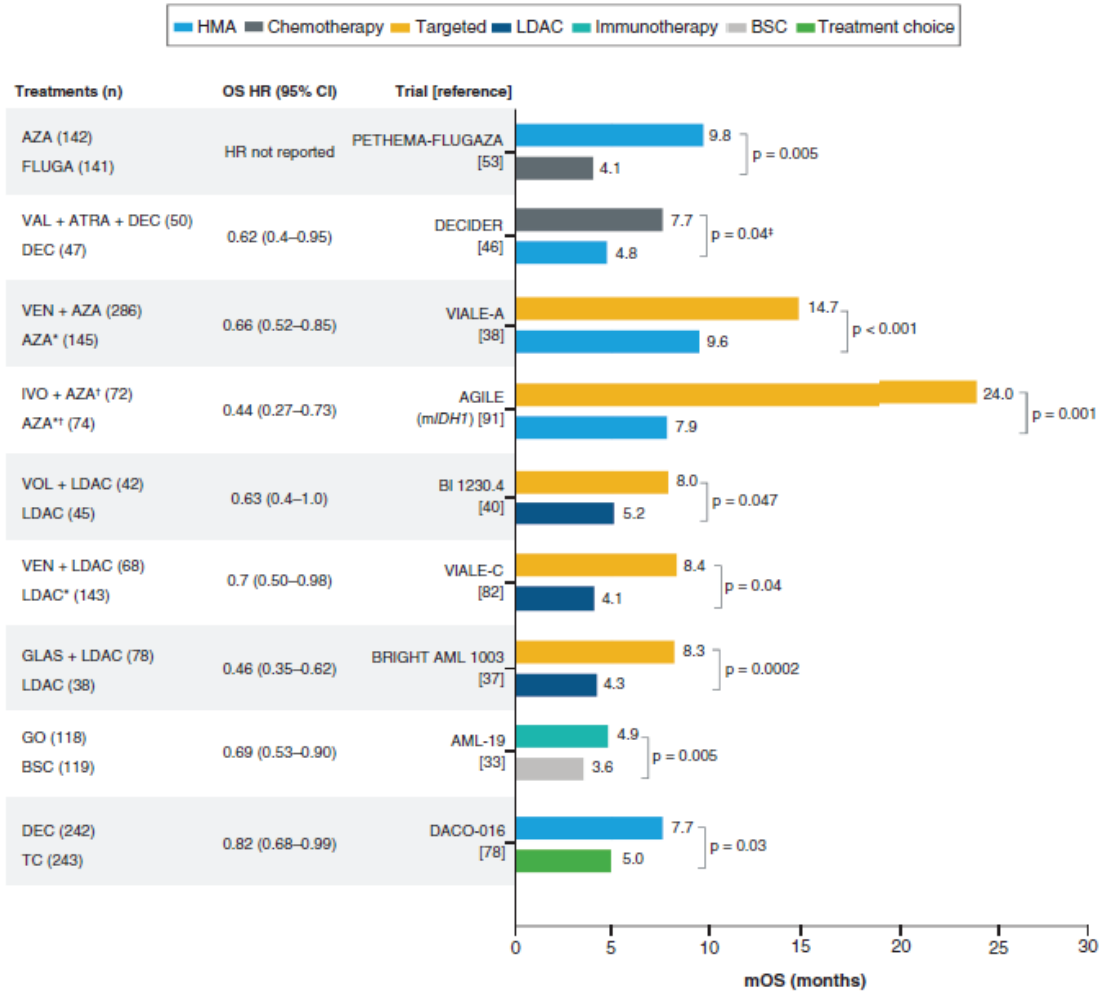


Figure 2. Comparison of mOS outcomes among trials with statistically significant differences between treatment groups.
*Added to placebo.
†AGILE specifically enrolled an mIDH1 population.
‡Two additional experimental groups included in the DECIDER trial – VAL + DEC and ATRA + DEC – are not included here; HRs and p-values reflect improvements in mOS in all three experimental groups vs DEC.
ATRA: All-trans retinoic acid; AZA: Azacitidine; BSC: Best supportive care; DEC: Decitabine; FLUGA: Fudarabine, cytarabine and filgrastim; GLAS: Glasdegib; GO: Gemtuzumab ozogamicin; HMA: Hypomethylating agent; HR: Hazard ratio; IVO: Ivosidenib; LDAC: Low-dose cytarabine; mOS: Median overall survival; n: Sample size; OS: Overall survival; TC: Treatment choice; VAL: Valproate; VEN: Venetoclax; VOL: Volasertib.

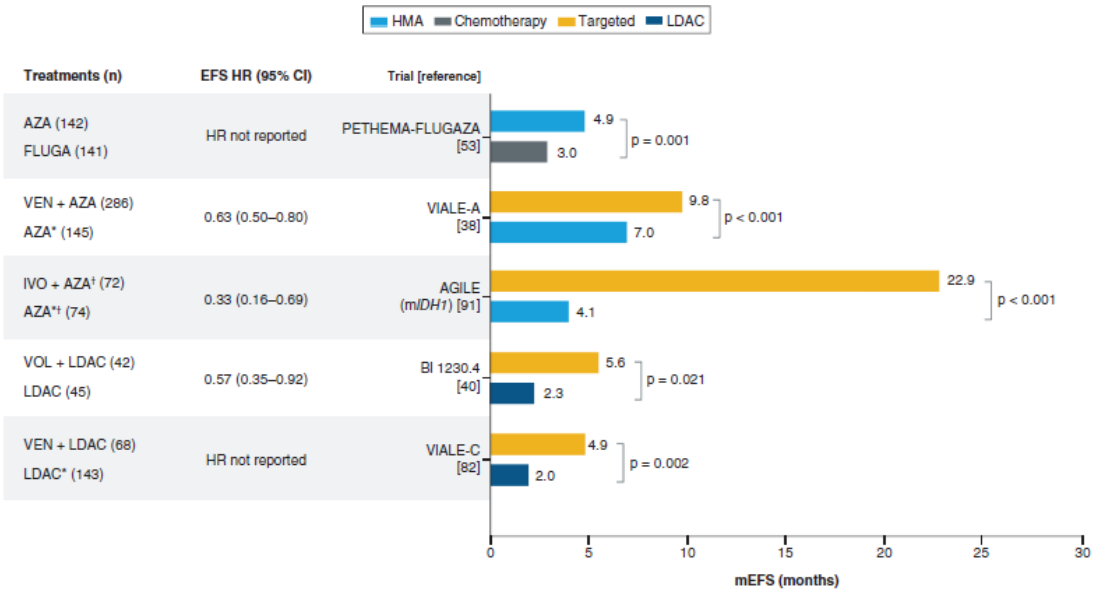


Figure 3. Comparison of median event-free survival outcomes among trials with statistically significant differences between treatment groups.
*Added to placebo.
†AGILE specifically enrolled an m*IDH1* population.
AZA: Azacitidine; DEC: Decitabine; EFS: Event-free survival; FLUGA: Fludarabine, cytarabine and filgrastim; HMA: Hypomethylating agent; HR: Hazard ratio; IVO: Ivosidenib; LDAC: Low-dose cytarabine; mEFS: Median event-free survival; n: Sample size; VEN: Venetoclax; VOL: Volasertib.

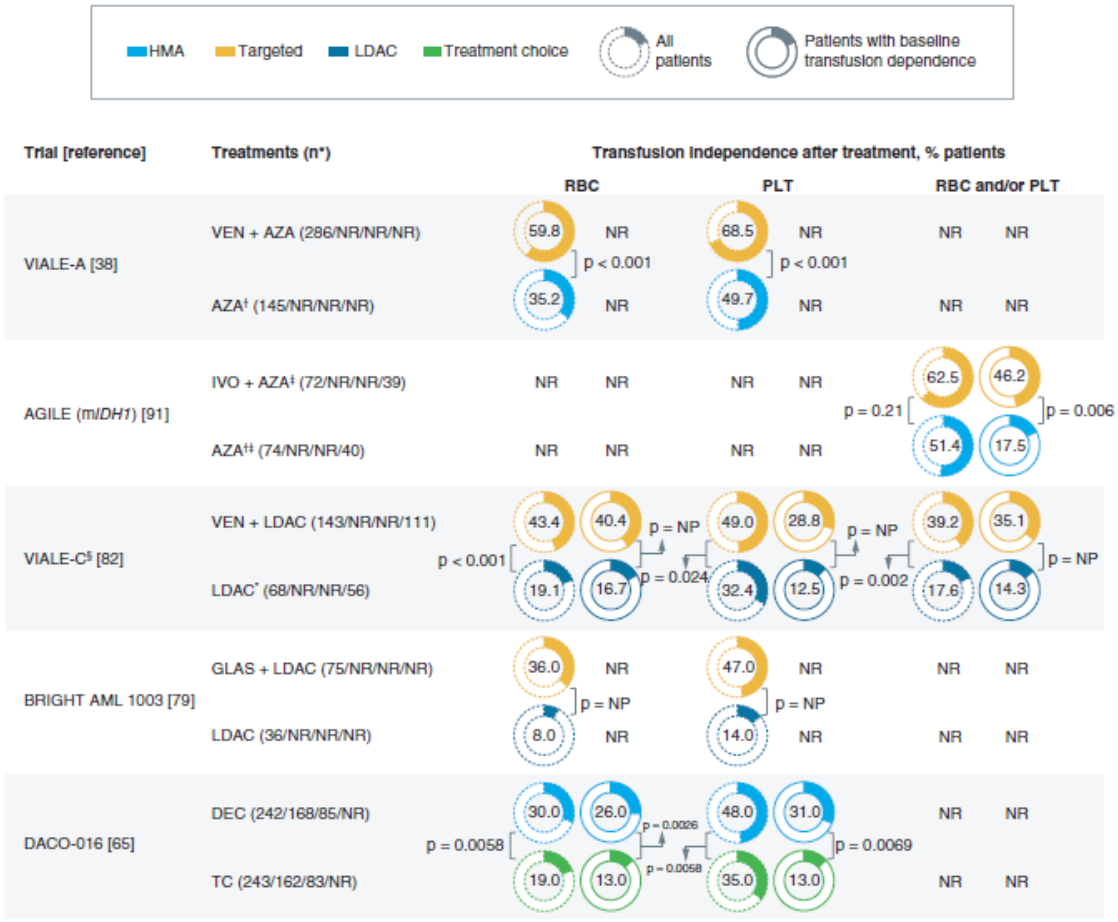


Figure 4. Post-baseline transfusion-independence rates in trials that showed statistically significant differences in median overall survival.

*n, all patients/number of patients with baseline RBC transfusion dependence/number of patients with baseline PLT transfusion dependence/number of patients with baseline RBC and/or PLT transfusion dependence.
†Added to placebo.
‡AGILE specifically enrolled an mIDH1 population. §6-month follow-up to primary data cut-off.
AZA: Azacitidine; DEC: Decitabine; GLAS: Glasdegib; HMA: Hypomethylating agent; IVO: Ivosidenib; LDAC: Low-dose cytarabine; NP: Not performed; NR: Not reported; PLT: Platelet; RBC: Red blood cell; TC: Treatment choice; VEN: Venetoclax.

- The AGILE trial [49] investigated the combination of ivosidenib plus azacitidine in previously untreated patients with mIDH1 AML ineligible for induction chemotherapy. A 16-month improvement in mOS was seen with ivosidenib plus azacitidine compared with azacitidine plus placebo (24.0 months vs 7.9 months; HR = 0.44; 95% CI: 0.27–0.73; p = 0.001); a 19-month improvement was observed in mEFS (22.9 months vs 4.1 months; HR = 0.39; 95% CI: 0.24–0.64; p < 0.001). Similarly, OS and EFS rates continually improved over 24 months in patients who received ivosidenib plus azacitidine compared with those who received azacitidine plus placebo
- In a subgroup analysis of patients with genomic variations, the mOS did not differ between the treatment groups among patients with mIDH1 and, in the IDH2 subpopulation, the OS benefit with azacitidine was similar to the overall population. Although the number of observations in this subanalysis was limited (n = 34 patients with mIDH1 AML; n = 36 patients with mIDH2 AML), the trial reported a numerically lower mOS in the azacytidine treated group with mIDH

Summary points

- Treatment options for newly diagnosed patients with acute myeloid leukemia (AML) ineligible for induction chemotherapy are expanding.
- Of the novel therapies, targeted drugs (venetoclax [BCL-2 inhibitor] and ivosidenib [IDH1 inhibitor]) have shown the most consistent and highest survival benefits, when combined with azacitidine.
- Screening for genetic mutations is now a standard part of the initial clinical workup in AML.
- *IDH1* mutations in AML are rare, making it challenging to conduct phase III clinical trials in patients with m*IDH1* AML.
- Ivosidenib is the only targeted drug that has been studied (in combination with azacitidine) specifically in patients with m*IDH1* AML in a phase III trial; it showed a significant improvement in overall survival by 16 months compared with the control group of azacitidine plus placebo.
- Venetoclax plus azacitidine showed an improvement of 5 months compared with the control group of azacitidine plus placebo in a *post hoc* analysis of patients with m*IDH*1 in a phase III trial.
- Added toxicities should be considered when using combination therapies in patients with AML.
- Patients initiating on combination therapies should be closely monitored as they have an increased risk of bone marrow suppression and infections, such as pneumonia.
- Unlike the other studies with combination therapies, the trial comparing ivosidenib plus azacitidine with azacitidine plus placebo showed similar frequencies of adverse events in the two groups, as well as a decrease in the frequency of infectious complications with ivosidenib plus azacitidine, possibly due to the increase in absolute neutrophil count that is seen with ivosidenib.
- Patients initiating on targeted therapies such as ivosidenib, glasdegib, gilteritinib, and enasidenib should be monitored for differentiation syndrome as well as QTc prolongation.

Anmerkung/Fazit der Autoren

Patients with AML who are ineligible for IC have historically had poor outcomes with the available treatment options. Novel therapies have improved clinical outcomes in this patient population, with targeted therapy combined with an HMA showing the most promising results. Adding ivosidenib or venetoclax to azacitidine or adding volasertib, venetoclax or glasdegib to LDAC significantly improved OS. In line with the most recent NCCN and ELN guidelines [6,15], ivosidenib in combination with azacitidine in mIDH1 AML and venetoclax in combination with azacitidine in the general AML population showed the most promising results. Some treatment-specific AEs highlighted in this SLR require attention during treatment, and management recommendations have been developed for these.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2025 [6].

Acute myeloid leukemia; version 3.2026

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur Behandlung erwachsener Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, die für eine Standard- Induktionschemotherapie nicht geeignet sind, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium; **trifft teilweise zu, keine Patientenvertretung.**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; **trifft nicht zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz; **unklar**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt; **trifft nicht zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt; **trifft teilweise zu**
- Regelmäßige Überprüfung der Aktualität gesichert; **trifft zu**

Recherche/Suchzeitraum:

Nicht angegeben

LoE/GoR

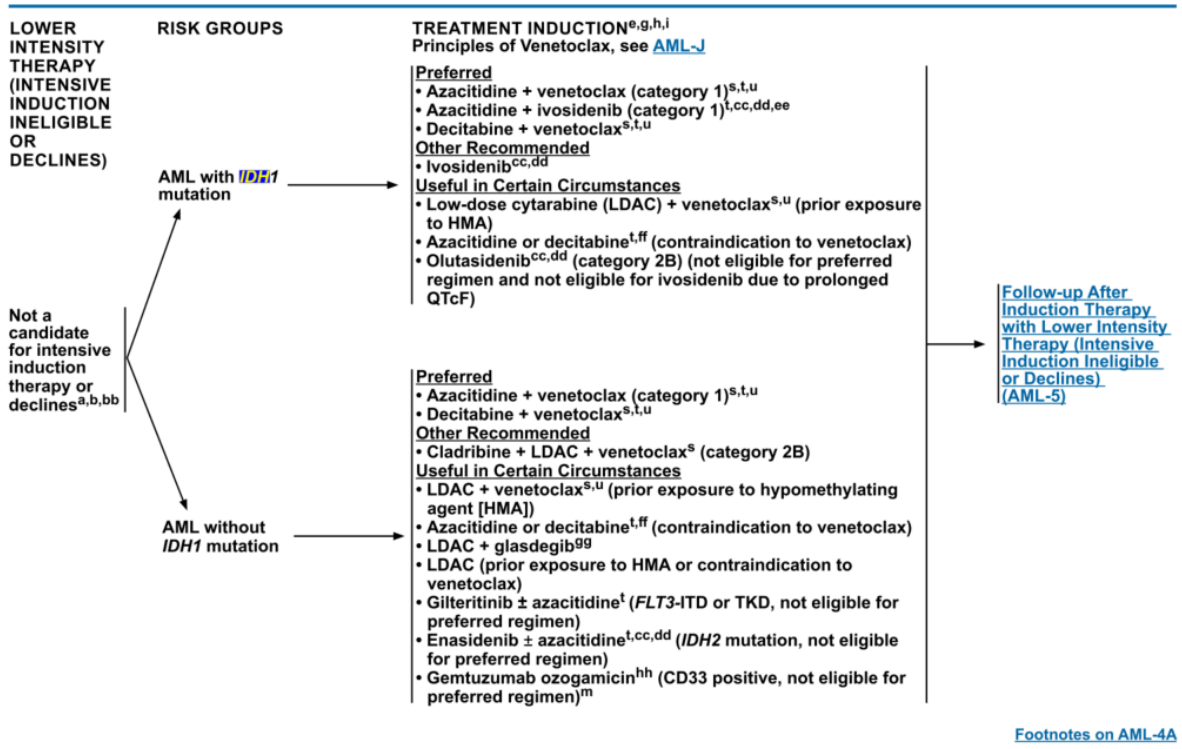
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Empfehlungen



AML-4

FOOTNOTES FOR LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE OR DECLINES)

[a] Patients with elevated blast counts are at risk for tumor lysis and organ dysfunction secondary to leukostasis. Measures to rapidly reduce the WBC count include leukapheresis, hydroxyurea, and/or a single dose of cytarabine. Prompt institution of definitive therapy is essential.

[b] Poor performance/functional status and a comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy. Web-based tools available to evaluate the probability of CR and early death after standard induction therapy in patients aged ≥60 years with AML can be found at: Walter RB, et al. J Clin Oncol 2011;29:4417-4423; Borlenghi E, et al. J Geriatr Oncol 2021;12:550-556. Consider the use of geriatric assessment for patients with AML ≥60 years of age. Ritchie EK, et al. Blood Adv 2022;6:3812-3820; Min GJ, et al. Blood 2022;139:1646-1658; Saad M, et al. Blood 2020;136:2715-2719; Klepin H, et al. Blood 2013;121:4287-4294. See NCCN Guidelines for Older Adult Oncology.

[e] Principles of Supportive Care for AML (AML-F).

[g] Consider referral to palliative care for consultation at the start of induction. El-Jawahri A, et al. JAMA Oncol 2021;7:238-245. See NCCN Guidelines for Palliative Care.

[h] General Considerations and Supportive Care for Patients Who Prefer Not to Receive Blood Transfusions (AML-D).

[i] Principles of Systemic Therapy for AML (AML-E).

[m] Threshold for CD33 is not well-defined and may be ≥1% by flow cytometry.

[s] Venetoclax combination regimens may be continued for patients whose disease demonstrates clinical improvement (CR/CRi), with consideration of subsequent transplant, where appropriate. DiNardo CD, et al. Lancet Oncol 2018;19:216-228; Wei A, et al. Blood 2017;130:890; DiNardo CD, et al. Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629. Kadia TM, et al. J Clin Oncol 2022;40:3848-3857.

[t] Patients whose disease has progressed to AML from MDS after significant exposure to HMAs (ie, azacitidine, decitabine) may be less likely to derive benefit from continued treatment with HMAs compared to patients who are HMA-naïve. Alternative treatment strategies should be considered. DiNardo CD, et al. Blood 2019;133:7-17.

[u] Patients with cytopenias with disease in remission should take breaks between cycles. For more details about cycle length, see Principles of Venetoclax (AML-J).

[bb] For patients who decline induction chemotherapy and/or targeted therapy, best supportive care may include hydroxyurea and/or transfusion support.

[cc] Response to treatment with IDH inhibitors may take 3–5 months.

[dd] IDH inhibitors increase the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids. Monitor closely for differentiation syndrome and initiate therapy to resolve symptoms according to indications. Note that differentiation syndrome can occur later (up to several months after induction).

[ee] This regimen is approved for patients with newly diagnosed AML with an *IDH1* mutation who met at least one of the following criteria: aged >75 years, baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, creatinine clearance (CrCl) <45 mL/min, or other comorbidity. Montesinos P, et al. N Engl J Med 2022;386:1519-1531.

[ff] Response may not be evident before 3–4 cycles of treatment with HMAs (ie, azacitidine, decitabine). Continue HMA treatment until progression if patient is tolerating therapy. Similar delays in response are likely with novel agents in a clinical trial, but endpoints will be defined by the protocol.

[gg] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL) and has been associated with an improved overall survival (OS) in a randomized trial. Cortes JE, et al. Leukemia 2019;33:379-389.

[hh] Regimens that include gemtuzumab ozogamicin have limited benefit in poor-risk disease.

Note: All recommendations are category 2A unless otherwise indicated.

AML-4A

PRINCIPLES OF SYSTEMIC THERAPY FOR AML[a,p]
LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE OR DECLINES)
(AML-4)

Therapy	Regimen
Azacitidine + venetoclax[i,j,20,23]	Azacitidine 75 mg/m² SC or IV days 1–7 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg days 3 and beyond)
Azacitidine + ivosidenib (*IDH1* mutation)[p,27]	Azacitidine 75 mg/m² SC or IV (days 1–7 or days 1–5, 8, and 9 of each 28-day cycle) and ivosidenib 500 mg PO once daily on days 1–28
Decitabine + venetoclax[i,j,20,21,28]	Decitabine 20 mg/m² IV (days 1–5 or days 1–10) and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg day 3 and beyond)
Ivosidenib[29] (*IDH1* mutation)	500 mg PO once daily on days 1–28 of a 28-day cycle
LDAC + venetoclax[i,j,30]	LDAC 20 mg/m²/day SC days 1–10 of each 28-day cycle and venetoclax PO once daily (100 mg day 1, 200 mg day 2, 400 mg day 3 and 600 mg days 4 and beyond)
Azacitidine[31,32]	75 mg/m² SC or IV days 1–7 of each 28-day cycle
Decitabine[33,34]	20 mg/m² IV days 1–5 of each 28-day cycle
Olutasidenib[35,36]	150 mg PO twice daily on days 1–28 of a 28-day cycle
Cladribine + LDAC + venetoclax[37]	Induction: Cladribine 5 mg/m² days 1–5 and LDAC 20 mg SC twice daily days 1–10 and venetoclax PO once daily (100 mg day 1, 200 mg day 2, and 400 mg days 3–21 of each 28-day cycle)[q] Consolidation Courses 1, 4–5, 8–9, 12–13, 16–17: Cladribine 5 mg/m² days 1–3 and LDAC 20 mg SC twice daily days 1–10 and venetoclax PO 400 mg days 1–21 of a 28-day cycle Consolidation Courses 2–3, 6–7, 10–11, 14–15: Azacitidine 75 mg/m² SC or IV days 1–7 and venetoclax PO 400 mg days 1–21 of a 28-day cycle

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see AML-1 through AML-9). The charts in this section delineate systemic therapy regimens that can be used and provide some additional details.
[i] Patients with cytopenias with disease in remission should take breaks between cycles. For more details about cycle length, see AML-J.
[j] Principles of Venetoclax Use With HMA or LDAC (AML-J).
[p] This regimen is approved for patients with newly diagnosed AML with an *IDH1* mutation who met at least one of the following criteria: aged >75 years, baseline ECOG performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin >1.5 times the upper limit of normal, CrCl <45 mL/min, or other comorbidity. Montesinos P, et al. N Engl J Med 2022;386:1519-1531.
[q] If CR/CRi not achieved following induction, a second course of induction can be administered.

References on AML-E 11 of 14

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY FOR AML[a,b]
LOWER INTENSITY THERAPY (INTENSIVE INDUCTION INELIGIBLE OR DECLINES) (AML-4)

Therapy	Regimen
LDAC + glasdegib[r,38]	LDAC 20 mg SC every 12 hours (days 1–10 of each 28-day cycle) + glasdegib (100 mg PO daily on days 1–28)
LDAC[33]	20 mg/m²/day SC (days 1–10 of each 28-day cycle)
Gilteritinib (*FLT3*-ITD or TKD)[39]	Gilteritinib 120 mg PO once daily on days 1–28 of a 28-day cycle
Gilteritinib + azacitidine (*FLT3*-ITD or TKD)[39]	Gilteritinib 120 mg PO once daily on days 1–28 + azacitidine 75 mg/m² SC or IV on days 1–7 of each 28 day cycle
Azacitidine + enasidenib (*IDH2* mutation)[40]	Azacitidine 75 mg/m² SC or IV on days 1–7 of each 28-day cycle + enasidenib 100 mg daily on days 1–28
Enasidenib[41] (*IDH2* mutation)	100 mg PO once daily on days 1–28 of a 28-day cycle
Gemtuzumab ozogamicin (CD33 positive)[c,1,42]	6 mg/m² IV on day 1 and 3 mg/m² IV on day 8
See AML-4 for other lower intensity regimens that were previously used for induction	

[a] An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[b] Specific recommendations, Categories of Evidence and Consensus, and Categories of Preference vary based on patient and disease characteristics (see AML-1 through AML-9). The charts in this section delineate systemic therapy regimens that can be used and provide some additional details.
[c] A meta-analysis showing an advantage with gemtuzumab ozogamicin included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.
[r] This regimen is for treatment of newly diagnosed AML in patients who are ≥75 years of age, or who have significant comorbid conditions (ie, severe cardiac disease, ECOG performance status ≥2, baseline creatinine >1.3 mg/dL) and has been associated with an improved OS in a randomized trial. Cortes JE, et al. Leukemia 2019;33:379-389.

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Continued

Note: All recommendations are category 2A unless otherwise indicated.

mutations (biallelic) of *CEBPA* but not in the setting of a single mutation of the gene. The 8-year OS rates reported in this study for patients with double-mutant–positive, single-mutation, and wild-type *CEBPA* genes were 54%, 31%, and 34%, respectively.[74] The revised 2016 WHO classification of AML redefined mutated *CEBPA* to indicate that biallelic mutations (and not single *CEBPA* mutations) are associated with improved prognosis.[34]

More recent studies have investigated the prognostic significance of *CEBPA* mutations or insertions/deletions in the bZIP region, irrespective of biallelic status.[76-78] In a report from the Children's Oncology Group (COG), *CEBPA* mutations in 2958 children and young adults with newly diagnosed AML were evaluated, including a cohort with a single *CEBPA*-bZIP mutation and a cohort harboring a second *CEBPA* mutation (*CEBPA*-double-mutated [*CEBPA*-dm]).[76] EFS was identical between the two *CEBPA* cohorts (64%) and OS was similar, at 81% for the *CEBPA*-dm cohort and 89% for the *CEBPA*-bZIP cohort ($P = .259$). Outcomes were worse in the *CEBPA* wild-type cohort, with EFS of 46% and OS of 61% (both $P < .001$). This study highlighted favorable outcomes in the setting of *CEBPA*-bZIP domain mutations, irrespective of monoallelic or biallelic status.

A retrospective analysis of 240 adult patients with AML with *CEBPA* mutations revealed improved EFS in the setting of *CEBPA*-dm and *CEBPA*-bZIP mutations compared to CEBPA mutations affecting the N-terminal transactivation domains (*CEBPA*^{smTAD}), at 20.7, 17.1, and 5.7 months, respectively.[77] Similarly, OS was significantly improved in the setting of *CEBPA*-dm and *CEBPA*-bZIP mutations compared to *CEBPA*^{smTAD} mutations, at 103, 63, and 13 months, respectively.

An additional retrospective analysis evaluated prognosis in 1028 patients with AML with *CEBPA* mutations.[78] The presence of *CEBPA*-bZIP mutations was associated with higher CR rates compared to AML without *CEBPA*-bZIP mutations (90.2% for all age groups, 92.7% for patients ≤70 years of age; $P < .001$). AML with *CEBPA*-bZIP mutation was also associated with longer OS than AML without *CEBPA*-bZIP mutation (not reached [NR] vs. 945 days for all age groups; $P < .001$ and NR vs. 1296 days for patients ≤70 years of age and in the setting of intermediate-risk karyotype; $P < .001$). Similarly, AML with *CEBPA*-bZIP mutation was associated with longer median time to relapse than AML without *CEBPA*-bZIP mutation (NR vs. 612 days for all age groups; $P < .001$ and NR vs. 671 days for patients ≤70 years of age and in the setting of intermediate-risk karyotype; $P < .001$). The favorable prognostic significance of *CEBPA*-bZIP mutations was also observed in the setting of single-mutated *CEBPA*-sm (OS for all patients, $P = .008$; OS for patients ≤70 years of age and in the setting of intermediate-risk karyotype, $P = .008$; cumulative incidence of relapse for all patients, $P = .063$; cumulative incidence of relapse for patients ≤70 years of age and in the setting of intermediate-risk karyotype, $P = .026$). Multivariate analysis revealed that in patients ≤70 years of age, the presence of a *CEBPA*-bZIP mutation was found to be the strongest predictor of improved OS (hazard ratio [HR], 0.3287; 95% CI, 0.1852–0.5834; $P < .001$)

IDH1/2 Mutations

Mutations in *IDH1* have been reported in 6% to 9% of AML cases, with a higher frequency among patients with NK-AML (8%–16%).[58,79-84] *IDH1* mutations were found to occur concurrently with NK-AML and *NPM1* mutations.[79-82,84] Additionally, these mutations have been associated with wild-type *CEBPA* and the absence of *FLT3* abnormalities.[82]

Findings from published reports on the prognostic effects of *IDH1* mutations have been inconsistent. Although some studies showed no prognostic effect of *IDH1* mutations on OS when considering all *IDH* mutations (*IDH1* and *IDH2* combined) or in the overall patient population,[79-82] *IDH1* mutations correlated with significantly worse outcomes in the subgroup of patients with NK-AML with favorable- or intermediate-risk disease.[79,82,84] In the subgroup of patients <60 years of age with favorable-risk AML (*NPM1* mutation without *FLT3*-ITD), *IDH1* mutations were associated with a significantly decreased 5-year DFS rate (42% vs. 59%; *P* = .046) and a trend for decreased OS rate (50% vs. 63%) compared with wild-type *IDH*.[82] In another study, *IDH* mutations (*IDH1* and *IDH2* combined) were associated with significantly inferior 5-year RFS rates (37% vs. 67%; *P* = .02) and OS rates (41% vs. 65%; *P* = .03) in the subgroup of patients with favorable-risk AML (NK-AML with *NPM1* mutation without *FLT3*-ITD).[84] This prognostic significance was observed when *IDH1* and *IDH2* mutations were separately analyzed, although patient numbers were small for each subgroup and statistical significance was reached only for the RFS analysis.[84] *IDH1* mutations were also associated with worse EFS and OS outcomes among the subgroup of patients with intermediate-risk NK-AML (wild-type *NPM1* without *FLT3*-ITD).[79] Mutations in *IDH2* have been reported in 8% to 12% of AML cases,[58,79,80,84,85] with a higher frequency of 19% among those with NK-AML.[82] The presence of *IDH2* mutations was mutually exclusive with *IDH1* mutation in nearly all cases.[79,80,82] Mutations have been identified in R172 and R140 of the *IDH2* gene, with the R140 mutation occurring more frequently.[82,84,85] Interestingly, the *IDH2*-R172 mutation seemed to be mutually exclusive with *NPM1* mutations and *FLT3*-ITD.[82,84,85]

Reports on the prognostic effect of *IDH2* mutations have also been inconsistent. Some studies have reported the lack of prognostic value of *IDH2* mutations,[79,80,84] whereas others have reported favorable outcomes with *IDH2* mutations.[58,85] In one study, an association was found between *IDH2* mutations and poorer prognosis in the subgroup of patients with NK-AML and otherwise favorable risk (*NPM1* mutation without *FLT3*-ITD).[84] However, in another study, the *IDH2* mutation (restricted to *IDH2*-R140) was associated with improved survival among the overall study population, and among the subgroup of patients with favorable risk (intermediate-risk AML with *NPM1* mutation without *FLT3*-ITD).[58] In this latter subgroup, the presence of *IDH1* or *IDH2* mutations was associated with a significantly increased 3-year OS rate compared with *NPM1* mutation without *FLT3*-ITD and without *IDH1* or *IDH2* mutations (89% vs. 31%; *P* < .0001). These results seem to suggest that in patients with NK-AML without *FLT3*-ITD, *NPM1* mutations confer a survival benefit only in the presence of concurrent *IDH* mutations.[58]

The prognosis of IDH1- or IDH2-mutated AML is more recently being impacted by the increasingly use of lower-intensity treatment options including venetoclax-based regimens and *IDH1/2* inhibitors. In a retrospective study that evaluated 556 patients with newly diagnosed AML with *IDH1*, *IDH2*, or *NPM1* mutations, *IDH1* mutations were associated with an increased risk of death compared to *IDH2* mutations; however, this risk was partially negated by treatment with lower intensity, venetoclax-based regimens.[86] OS rates were similar between patients with *IDH2*-mutated/*NPM1*-wild type, *IDH2*-mutated/*NPM1*-wild type, and *IDH*-wild type/*NPM1*-mutated AML that were treated with venetoclax-based regimens. While there was a trend towards improved survival with intensive chemotherapy in the setting of *IDH2*-mutated AML with co-occurring *NPM1* mutations compared to without *NPM1* mutations (*P* =.77), there was a significant improvement in survival with venetoclax-based therapy in the setting of *IDH1*-mutated AML with concurrent *NPM1*

mutations compared to without *NPM1* mutations (*P* = .0056). In another study including 81 patients (median age, 74 years) with newly diagnosed AML treated with venetoclax combined with a hypomethylating agent (HMA) or LDAC, CR was achieved in 82% of patients with *IDH1*-mutated AML and in 100% of patients with *IDH*-2 mutated AML.[87] *IDH1/2* inhibitors used alone or in combination with venetoclax have also improved outcomes for *IDH*-mutated AML, with remission rates of >40% to 50% single agent and >60% to 70% when combined with venetoclax. [88-91]

DNMT3A Mutations

The *DNMT3A* mutations have been reported in 18% to 22% of AML cases,[58,92,93] with a frequency of 29% to 34% in those with NK-AML.[94-96] R882 is the most commonly mutated residue. This mutation has also been observed in conjunction with *NPM1* mutations and *FLT3* mutations.[93,95,96] Data concerning the prognostic significance of *DNMT3A* mutations have thus far been conflicting. Some studies in the overall AML population and in patients with intermediate-risk disease reported no significant effect of *DNMT3A* mutations on survival outcomes,[58,95] whereas other studies have shown a negative prognostic effect in the overall population or specific subgroups.[92-94,96] Studies have shown significantly decreased OS outcomes among patients with *DNMT3A*-mutated AML compared with patients with *DNMT3A* wild-type AML (median OS, 12–21 vs. 40–41 months).[92,93] Significantly decreased OS with *DNMT3A* mutations has also been reported in the subgroup of patients with NK-AML who have wild-type *NPM1* with or without *FLT3*-ITD, or *NPM1* mutation in the presence of *FLT3*-ITD, but not in the favorable subgroup with *NPM1* mutation without *FLT3*-ITD.[93] A study reported that in patients <60 years of age with NK-AML, the presence of *DNMT3A* mutations was associated with significantly decreased OS compared with the wild-type gene (5-year OS rate, 23% vs. 45%; *P* = .02).[96] Another study also showed that in patients <60 years of age with NK-AML, a *DNMT3A* mutation was associated with significantly decreased DFS (3-year rate, 20% vs. 49%; *P* = .007) and a trend toward decreased OS.[94] In this latter study, non-R882 *DNMT3A* mutations were significantly associated with poorer outcomes in patients <60 years of age but not R882 mutations; in contrast, *DNMT3A*-R882 mutations (but not non-R882 mutations) in patients ≥60 years of age were associated with significantly decreased DFS (3-year rate, 3% vs. 21%; *P* = .006) and OS (3-year rate, 4% vs. 24%; *P* = .01).[94] The authors concluded that the prognostic relevance of *DNMT3A* mutations may depend on age and mutation type. Currently, the interactions of *IDH1* or *IDH2* and *DNMT3* mutations with other molecular changes require further investigation to determine the prognostic value in patients with NK-AML. Although commercial testing is available for *FLT3* and *CEBPA*, most of the other genetic mutations are not available for testing outside of the research setting. Other candidate genes that are associated with an adverse impact on outcome are *TET2* and *RUNX1*.[97,98]

KIT Mutations

KIT mutations have been reported in approximately 20% of patients with CBF-AML.[51,99] Studies have shown that *KIT* mutations are associated with decreased remission duration (eg, EFS and RFS) and decreased OS in patients with AML with t(8;21).[45,51,53,99] However, the association of *KIT* mutations on CBF-AML with inv(16) is less clear than the data for t(8;21), with several studies showing no association.[45,99,100] In an analysis from the German-Austrian AML Study Group, the frequency and prognostic impact of secondary genetic lesions were evaluated in patients with CBF-AML who were treated in prospective trials (n = 176).[101] Secondary chromosomal abnormalities were found in 39% of cases, with the most common abnormalities being trisomy 22 (18%), trisomy 8 (16%), and 7q deletion (5%). Secondary genetic lesions were found in 84% of cases,

Alberta Health Services (AHS), 2024 [1,2].

Acute myeloid leukemia; version 7 - *Clinical practice guideline LYHE-006*

Zielsetzung/Fragestellung

What is the optimal management of the acute myeloid leukemias in Alberta at the present time?

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur Behandlung erwachsener Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, die für eine Standard- Induktionschemotherapie nicht geeignet sind, wird die LL ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium – **trifft teilweise zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – **trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz – **trifft teilweise zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – **trifft zu**
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – **unklar**
- Regelmäßige Überprüfung der Aktualität gesichert – **trifft zu**

Recherche/Suchzeitraum:

- Pubmed and Medline

LoE/GoR

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Empfehlungen

Table 6. 2022 ELN risk classification by genetics at initial diagnosis[17].

Risk Category	Genetic Abnormality
Favorable	• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ CBFB::MYH11†,‡ • Mutated NPM1†,§ without FLT3-ITD • bZIP in-frame mutated CEBPA‖
Intermediate	• Mutated NPM1†,§ with FLT3-ITD • Wild-type NPM1 with FLT3-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/MLLT3::KMT2A†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearranged# • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ GATA2, MECOM(EVI1) • t(3q26.2;v)/MECOM(EVI1)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2‡‡ • Mutated TP53ª

†Mainly based on results observed in intensively treated patients. Initial risk assignment may change during the treatment course based on the results from analyses of measurable residual disease.
‡Concurrent KIT and/or FLT3 gene mutation does not alter risk categorization .
§AML with NPM1 mutation and adverse-risk cytogenetic abnormalities are categorized as adverse-risk.
‖Only in-frame mutations affecting the basic leucine zipper (bZIP) region of CEBPA, irrespective whether they occur as monoallelic or biallelic mutations, have been associated with favorable outcome.
¶The presence of t(9;11)(p21.3;q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.
#Excluding KMT2A partial tandem duplication (PTD).
**Complex karyotype: ≥3 unrelated chromosome abnormalities in the absence of other class-defining recurring genetic abnormalities; excludes hyperdiploid karyotypes with three or more trisomies (or polysomies) without structural abnormalities.
††Monosomal karyotype: presence of two or more distinct monosomies (excluding loss of X or Y), or one single autosomal monosomy in combination with at least one structural chromosome abnormality (excluding core-binding factor AML).
‡‡For the time being, these markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes.
ªTP53 mutation at a variant allele fraction of at least 10%, irrespective of the TP53 allelic status (mono- or biallelic mutation); TP53 mutations are significantly associated with AML with complex and monosomal karyotype.

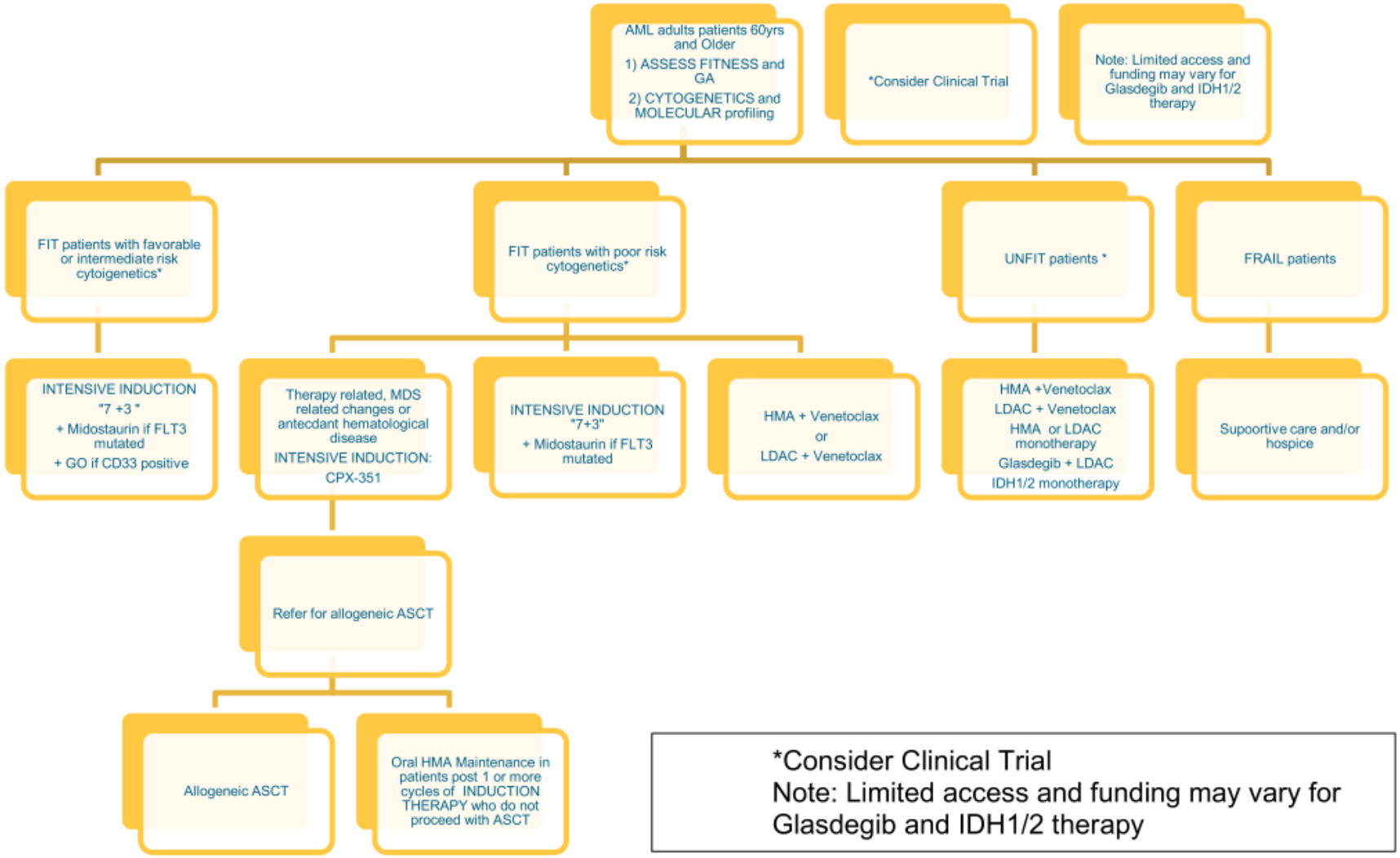
Recommendations

Recommendation
Venetoclax and Azacitidine is recommended for patients with AML who are unfit for induction therapy. The use of mold-active azole is suggested as antifungal prophylaxis and venetoclax dose adjustments are needed when using with CYP3A4 inhibitors. Assessment of HMA + Ven response is suggested by cycle 2 and venetoclax dose changes are suggested once remission is achieved.

Recommendation
Venetoclax and LDAC may be given for patients with AML who are unfit for induction therapy and unable to receive HMA + venetoclax therapy. However, venetoclax is not funded for this indication. If venetoclax is not available, LDAC alone is an acceptable alternative.

Recommendation
Enasidenib and ivosidenib are not currently funded in Canada. However, given the results of the above phase 3 trial, the combination of ivosidenib plus azacitidine would be an acceptable alternative to ven-aza as frontline treatment for unfit patients with IDH1 mutated AML, if available.

Figure 3: Summary treatment recommendations for elderly AML patients.



Appendix A: Chemotherapy Regimens

7&3

• Cytarabine 200 mg/m2/dcontinuous infusion days 1-7(consider 100 mg/m2/d if age >60)
• Idarubicin 12 mg/m2/ or daunorubicin 60 mg/m2/d days 1-3

7&3&GO

• Cytarabine 200 mg/m2/dcontinuous infusion days 1-7(consider 100 mg/m2/d if age >60)
• Idarubicin 12 mg/m2/ or daunorubicin 60 mg/m2/d days 1-3
• Gemtuzumab Ozogomycin 3 mg/m2 days 1, 4, 7

7&3 & Midostaurin

• Cytarabine 200 mg/m2/dcontinuous infusion days 1-7(consider 100 mg/m2/d if age >60)
• Idarubicin 12 mg/m2/ or daunorubicin 60 mg/m2/d days 1-3
• Midostaurin 50 mg twice daily days 8-21

CPX-351 induction

• Daunorubicin 44 mg/m2 and Cytarabine 100 mg/m2 liposome on Days 1,3,5
• (reinduction only days 1,3)

NOVE

• Mitoxantrone 10 mg/m2/d days 1-5
• Etoposide 100 mg/m2/d days 1-5

NOVE-HiDAC

• Mitoxantrone 10 mg/m2/d days 1-5
• Etoposide 100 mg/m2/d days 1-5
• Cytarabine 1.5 g/m2(1.0 g/m2 if >age 60) every 12 hours on days 6-7.

FLAG-Ida

• Fludarabine 30 mg/m2/d days 1-5
• Cytarabine 2 g/m2/d days 1-5
• Idarubicin 8 mg/m2/d days 1-3
• G-CSF 300 µm s/c od starting day 7

HiDAC

• Cytarabine 3 g/m2 every 12 hours on days 1, 3 and 5

HiDAC & GO

• Cytarabine 3 g/m2 every 12 hours on days 1, 3 and 5
• Gemtuzumab Ozogomycin 3 mg/m2 day 1 (for 2 cycles)

HiDAC & Midostaurin

• Cytarabine 3 g/m2 every 12 hours on days 1, 3 and 5
• Midostaurin 50 mg twice daily days 8-21

CPX-351 consolidation

• Daunorubicin 29 mg/m2 and Cytarabine 65 mg/m2 liposome on Days 1,3,5

Intermediate Dose Cytarabine

• Cytarabine 1 g/m2 every 12 hours on days 1, 3 and 5

Azaciticine/Venetoclax

First cycle

• Azacitidine 75mg/m2 s/c days 1-7

• Venetoclax ramp up to maximum 400 mg daily dose for 28 days (depending on co-administered medications)

• Subsequent cycles dictated by response, co-administered medications and cytopenias

Azacitidine

• Azacitidine 75mg/m2 s/c days 1-7 or days 1-5, 8,9

Low Dose Cytarabine

• Cytarabine 20 mg s/c days 1-10 q 4-5 weeks

• Cytarabine 40 mg s/c days 1-10 q 4-5 weeks

Oral Azacytidine

• 300mg po daily for 14 days, repeat every 28 days until disease progression or unacceptable toxicity (5).

Treatment Options

Azacytidine (AZA) was studied in older patients (median age 75 years) with AML with > 30% blasts in a randomized phase III study. Azacytidine was associated with a trend towards better OS compared to conventional care regimens (CCR, standard induction chemotherapy, LDAC, or supportive care only) (10.4 months vs. 6.5 months, P=0.10).83 AZA was compared to CCR in another phase III trial, in patients with low bone marrow blast counts of 20–30% (median age 70 years).84 In this study, azacytidine was associated with improved OS (24.5 months vs. 16 months, P=0.05), as well as shorter fewer hospitalizations and number of days spent in the hospital.84

Venetoclax + HMA: A phase Ib escalation and expansion trial for older patients (median age 74 years) ineligible for intensive chemotherapy evaluated venetoclax (400 or 800 mg) with a HMA (decitabine 20 mg/m2/day for 5 days or azacytidine 75 mg/m2/day for 7 days) in 28-day cycles.85 Poor risk cytogenetics was present in 49% of subjects. Venetoclax 400 mg combined with HMA was associated with 73% CR + CRi. CR + CRi occurred in 67% of all dosed patients. CR +CRi was achieved in 60% of those with poor risk cytogenetics and 65% for patients ≥ 75 years.85 Median duration of CR+CRi was 11.3 months. Median survival was 17.5 months although, not reached in Venetoclax 400 mg cohort.85 The phase III trial of venetoclax (target dose 400 mg) with azacytidine (75mg/m2 SC day 1-7) in 28-day cycles compared to azacytidine-placebo in elderly AML treatment naïve patients, demonstrated OS benefit favoring combination therapy. In a cohort of 431 patients, with median age of 76 years, the median OS was 14.7 months versus 9.6 months (HR 0.66, p <0.001) with composite CR rates of 66.4% vs 28.3%, (p <0.001) in favor of combination. Key adverse events included nausea (any grade 44%), febrile neutropenia and grade 3 neutropenia (42%) as well as grade 3 thrombocytopenia (45%). Serious adverse events were reported in 83% (combo therapy) versus 73% (Aza-placebo therapy).86 Overall, the incidence of tumor lysis syndrome (TLS) with HMA/venetoclax in AML is low when the WBC count is not elevated [link]. It is suggested that hydration and allopurinol prophylaxis are still routinely recommended for the first cycle of therapy but can be safely discontinued if there is no evidence of TLS. Inpatient hospitalization is not required for initiation of therapy but should be considered if frequent outpatient monitoring is challenging, or if the patient may be at increased risk for complications based on leukocytosis (WBC >25), impaired renal function, or other comorbid conditions. It is suggested that WBC be lowered to <25 with hydroxyurea or cytarabine before initiating venetoclax therapy to minimize tumor lysis risk.87

Initiation of venetoclax includes a 3-day ramp-up and in absence of required dose adjustments, venetoclax is provided as: 100 mg once on Day 1, 200 mg once on day 2, and 400 mg once daily on day 3 and beyond. When using strong or moderate CYP3A4 inhibitor such as posaconazole or fluconazole, the dosing of venetoclax is reduced by 80% and 50%, respectively. See Table 10 for summary of drug interactions and venetoclax dose reductions.86, 87 As patients are usually severely neutropenic for at least 3 weeks during induction, prophylactic antimicrobials are recommended, e.g. antibacterial such as levofloxacin (not cipro due to drug interaction with venetoclax), antifungal (e.g. posaconazole, adjusting the venetoclax dose accordingly) and valacyclovir.

The combination therapy of HMA + venetoclax works quickly, with a median time to response of approximately 1 month. Since most patients will begin treatment with cytopenias and nearly all patients will have cytopenias by the end of the first cycle, it is suggested to repeat a staging bone marrow be performed ~day 21; if blast excess persists, commence the next cycle by day 29 without treatment dose interruption. A bone marrow assessment is suggested within first 2 cycles of treatment in all cases. This is performed to determine whether cytopenias are therapy-related or due to persistent AML. Identifying response early is crucial as continuation of venetoclax without temporary holds or delays in the subsequent cycles may result in prolonged aplasia and a higher risk of serious infections.86, 87

If patients are in CR—defined as <5% blasts, it is recommended to pause venetoclax and delay initiation of the second cycle for up to 14 days or until recovery of neutropenia, at minimum neutrophils ≥0.5 × 109/L. The effect of venetoclax is most pronounced on neutrophils, so often neutropenia is therapy-related. If persistent disease exists (>5% blasts), treatment should continue without delay and without a change in the venetoclax dose or schedule, with plan for a repeat biopsy before the third cycle to reassess response. If there has not been a meaningful blast reduction or hematologic response after 3-4 cycles of therapy, consider stopping treatment if alternate options exist. The presence of NPM1 and/or IDH mutation is associated with higher rates of clinical response while the presence of signaling mutations, particularly FLT3-ITD, and/or biallelic TP53 mutations pose high relapse risk.88

Once remission achieved, the main challenge in successfully keeping patients on continued treatment while avoiding grade 3/4 hematologic toxicities, most notably neutropenia. Consider decreasing venetoclax dosing days especially if hematologic recovery takes >14 days after interrupting venetoclax for neutropenia and/or thrombocytopenia. Consider stepwise reductions in venetoclax dosing: 21 days → 14 days → 10 days. Additional reductions to consider include reducing HMA dose intensity by 25-50% if prolonged cytopenias persist with marrow hypocellularity If prolonged or severe cytopenias are recurrent after achieving remission, the recommendation is to decrease the number of days of venetoclax per cycle rather than reduction of the dose of venetoclax. Although data are limited, it does not appear that a shorter duration of venetoclax post remission compromises durability of response.87, 89 [abstract link]

Additional strategies for limiting the depth and duration of cytopenias post remission include additional use of supportive G-CSF for grade 3/4 neutropenia to support ongoing cycles. If cytopenias worsen at any point during treatment or do not respond to dose pauses/adjustments, a repeat marrow evaluation is recommended to rule out disease progression.

Venetoclax + LDAC: VIALE-C was a Phase III randomized trial of Venetoclax (600 mg daily) with LDAC versus LDAC alone in AML who were ineligible for IC (median age 76 years). This study included 20% of patients who had received prior HMA. The planned primary analysis showed a 25% reduction in risk of death with venetoclax plus LDAC vs LDAC alone (hazard ratio [HR], 0.75; 95% confidence interval [CI], 0.52-1.07; P = .11), with non-significant median OS of 7.2 vs 4.1 months, respectively. Additional 6-month follow-up demonstrated a significant difference with median OS of 8.4 months for the venetoclax arm (HR, 0.70; 95% CI, 0.50-0.98; P = .04). Composite CR rates were 48% and 13% for venetoclax plus LDAC and LDAC alone, respectively. Grade ≥3 adverse events (venetoclax vs LDAC alone) were febrile neutropenia (32% vs 29%), neutropenia (47% vs 16%), and thrombocytopenia (45% vs 37%). Venetoclax plus LDAC demonstrates clinically meaningful improvement in remission rate and OS vs LDAC alone, with a manageable safety profile. Results confirm venetoclax plus LDAC as an alternative frontline treatment for unfit AML patients. This option is targeted for patients who are unable or unwilling to received Azacytidine subcutaneously at treatment centers.90, 91

Venetoclax-based regimens have become very common in AML elderly treatment but challenges with this non-curative chemotherapy regimen still exist. Common challenges include tumor lysis syndrome, severe bone marrow suppression, and drug-drug-interactions. Data from real-world experience are emerging92 and practical guidance are available.86

Other Oral AML therapies: Glasdegib, a hedgehog pathway inhibitor, was studied in a phase II randomized trial for older patients with AML or high-risk MDS (median age 76 years) unfit for intensive chemotherapy. (Cortes et al., 2019)Glasdegib 100 mg oral daily was administered continuously with LDAC 20 mg SC BID x 10 days per 28 day cycles. Median OS was 8.8 (6.9-9.9) months with glasdegib/LDAC and 4.9 (3.5-6.0) months vs LDAC monotherapy (hazard ratio, 0.51; 80% CI, 0.39-0.67, P = 0.0004) CR was achieved in 17.0% versus 2.3% patients in the glasdegib/LDAC and LDAC arms, respectively, (P < 0.05). It was considered well tolerated and safe therapy with nonhematologic grade 3/4 toxicities of pneumonia (16.7%) and fatigue (14.3%).93 Glasdegib received FDA approval for treatment of AML in older or unfit patients but is not CADTH approved for use in Canada.

For patients with IDH1/2 mutant AML, Ivosidenib and enasidenib target IDH1 and IDH2 mutations respectively and were initially approved in the relapsed/refractory (R/R) setting. [link]

Mutations in isocitrate dehydrogenase 2 (IDH2) occur in ~12% of AML patients. Mutated IDH2 proteins neomorphically synthesize 2-hydroxyglutarate resulting in DNA and histone hypermethylation, this leads to block in cellular differentiation. Use of inhibitors lead to cellular differentiation and maturation. IDH2 inhibitor, Enasidenib 100 mg once daily showed ORR of 40.3%,

with a median response duration of 5.8 months in R/R AML. Median OS was 9.3 months, and in ~20% of patients who attained CR, OS was 19.7 months.94 Enasidenib was studied in phase I/II trial newly diagnosed mutant-IDH2 AML (N=39), median age was 77 years (range 58-87). ORR was 30.8% with CR of 18%. At a median follow-up of 8.4 months, the median duration of any response was not reached (NR). Median overall survival was 11.3 months and was NR for responders. A median number of enasidenib cycles was 6.0 (range 1-35) with most common treatment-related adverse event being indirect hyperbilirubinemia (31%).95 A phase II study of newly diagnosed, mutant-IDH2 AML patients (median age 75 years), assigned enasidenib 100 mg oral daily plus azacytidine (n=68) compared to azacytidine only (n=33). 74% in the

combination group vs 36%; in azacytidine monotherapy group achieved an OR (odds ratio 4·9 [95% CI 2·0-11·9]; p=0·0003).
Common treatment-related grade 3 or 4 adverse events with combination were thrombocytopenia. Serious treatment-related adverse events were reported in 43% patients in the combination group and 44% patients in the azacytidine-only group: including febrile neutropenia, differentiation syndrome and pneumonia. Overall, enasidenib plus azacytidine was well tolerated and significantly improved ORR versus azacytidine monotherapy, suggesting that this regimen for elderly treatment naïve AML.96
Isocitrate dehydrogenase 1 (IDH1) mutations occur in 6 to 10% of AML patients. In the phase 1 doseescalation and dose-expansion study of ivosidenib 500 mg PO daily in IDH1-mutated R/R AML. CR or CR with partial hematologic recovery was achieved in 30% and ORR was 41.6% with median duration of responses ranging 6.5 – 9.3 months treatment was well-tolerated. Specifically, IDH differentiation syndrome occurs with therapy and presents with significant neutrophil-predominant leukocytosis and nonspecific symptoms such as fever, hypotension, and effusions. This occurred in 16% of patients.97, 98
An open-label, single-arm, multicenter clinical trial of single-agent ivosidenib (500 mg PO daily) used for newly diagnosed AML with an IDH1 mutation included patients ≥75 years. Twenty-eight patients were treated (median age 77 years; range: 64–87 years); with majority (79%) having therapy-associated or myelodysplasia-related AML. CR+CRh was achieved in 12/28 patients (42.9%) and based on the results, the FDA approved use in newly diagnosed IDH1 mutated AML.98
Ivosidenib plus azacytidine combination was also studied in an open-label, multicenter, phase Ib trial for newly diagnosed elderly AML with mutated IDH1 ineligible for intensive therapy. Ivosidenib 500 mg once daily continuously with subcutaneous azacytidine 75 mg/m2 on days 1-7 in 28-day (median age, 76 years; range, 61-88 years). Median treatment duration was 15.1 months (range, 0.3-32.2 months with ORR of 78.3% and CR was 60.9%. With median follow-up of 16 months, median duration of response in responders had not been reached. The 12-month OS was 82.0%. Treatmentrelated grade ≥ 3 adverse events occurring in > 10% of patients were neutropenia (22%), anemia (13%), thrombocytopenia (13%), and QTC prolongation (13%). All grade IDH differentiation syndrome (17%). This combination was overall well tolerated, and responses were deep and durable, with most complete responders achieving IDH1 mutation clearance.99
Phase 3 studies involving IDH1-mutated AML patients ineligible for intensive induction chemotherapy treated with ivosidenib (500 mg once daily) and subcutaneous or intravenous azacytidine (75 mg m2 x 7 days in 28-day cycles) versus matched placebo and azacytidine also showed significant benefit. The primary end point was event-free survival, defined as the time from randomization until treatment failure (i.e., the patient did not have complete remission by week 24), relapse from remission, or death from any cause, whichever occurred first. In the intention-to-treat population of 146 patients: 72 in the ivosidenib-and-azacytidine group and 74 in the placebo-and-azacytidine group, with a median follow-up of 12.4 months, EFS was significantly longer in the ivosidenib-and-azacytidine group than in the placebo-and-azacytidine group (hazard ratio for treatment failure, relapse from remission, or death, 0.33; 95% confidence interval [CI], 0.16 to 0.69; P = 0.002). Median OS was 24.0 months with ivosidenib and azacitidine versus 7.9 months with placebo and azacitidine (hazard ratio for death, 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Grade 3 or higher AEs included febrile neutropenia (28% with ivosidenib and azacytidine and 34% with placebo and azacytidine) and neutropenia (27% and 16%, respectively). Bleeding events of any grade was 41% and 29%, respectively with any grade of infection being 28% with ivosidenib and azacytidine and 49% with placebo and azacytidine. Differentiation syndrome of any grade occurred in 14% of the patients receiving ivosidenib and azacytidine and 8% of those receiving placebo and azacytidine.100
Overall, a meta-analysis of 1109 IDH-mutated AML patients from 10 articles (11 cohorts) found a CR rate, ORR rate, and 2-year OS rate, of relapsed or refractory (R/R) IDH-mutated AML (394 patients) were 21%, 40%, 15% with median OS and median EFS of 8.21 months and 4.73 months, respectively.
In contrast, for newly diagnosed IDH mutated AMLs (N=715) the CR rate, and ORR rate, were 47%, and 65%, respectively. The 2-year survival (OS) rate and 2-year event-free survival (EFS) rates were 45% and 29%, respectively. Gastrointestinal adverse events were the most frequently occurring all-grade adverse events and hematologic adverse events were the most frequently occurring ≥ grade 3 adverse events.101
A systematic review of RCTs concluded an objective response (OR) was reported in 63-74% of the patients with IDH inhibitors (ivosidenib for IDH-1 and enasidenib for IDH-2) + azacytidine as compared to 19-36 % of the patients with azacytidine monotherapy in newly diagnosed medically unfit AML patients. OR was reported in 39.1-46 % of the AML patients who relapsed/refractory. Survival rates were significantly improved with the use of ivosidenib. ≥Grade 3 IDH differentiation syndrome and QT prolongation were reported in 3.9-10 % and 2-10 % of the patients, respectively. IDH inhibitors have been found to be safe and effective in treating both treatment naïve and R/R AML. However, no survival benefit was reported with enasidenib. More randomized multicenter doubleblinded clinical studies are needed to confirm these results and compare them with other targeting agents.102

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2025) am 09.07.2025

#	Suchschritt
1	[mh "Leukemia, Myeloid, Acute"]
2	acute:ti,ab,kw
3	(myeloid* OR myelogen* OR myeloblast* OR myelocyt* OR nonlymphoblast* OR nonlymphocyt* OR (non NEXT (lymphocyt* OR lymphoblast*))):ti,ab,kw
4	leu*mia*:ti,ab,kw
5	#2 AND #3 AND #4
6	AML:ti,ab,kw
7	#1 OR #5 OR #6
8	#7 with Cochrane Library publication date from Jul 2020 to present
9	#7 with Cochrane Library publication date from Jul 2023 to present
10	#8 NOT #9

Leitlinien und systematische Reviews in PubMed am 09.07.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	Leukemia, Myeloid, Acute[mh]
2	acute[tiab]
3	myeloid*[tiab] OR myelogen*[tiab] OR myeloblast*[tiab] OR myelocyt*[tiab] OR nonlymphoblast*[tiab] OR nonlymphocyt*[tiab] OR non-lymphoblast*[tiab] OR non-lymphocyt*[tiab]
4	leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab]
5	#2 AND #3 AND #4
6	AML[tiab]
7	#1 OR #5 OR #6
8	(#7) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
9	(#8) AND ("2020/07/01"[PDAT] : "3000"[PDAT])

#	Suchschritt
10	(#9) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
11	(#7) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
12	(#11) AND ("2020/07/01"[PDAT] : "3000"[PDAT])
13	(#12) NOT "The Cochrane database of systematic reviews"[Journal]
14	(#13) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
15	(#14) NOT (#10)
16	(#15) AND ("2023/07/01"[PDAT] : "3000"[PDAT])
17	#15 NOT #16

Iterative Handsuche nach grauer Literatur, abgeschlossen am 10.07.2025, überprüft am 25.11.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- National Cancer Institute (NCI)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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Beteiligung von Fachgesellschaften und der AkdÄ zu Fragen der Vergleichstherapie nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Verfahrens-Nr.: 2025-B-312

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO)
Sachverständige	
Datum	30. Dezember 2025

Indikation
Behandlung von Erwachsenen mit neu diagnostizierter akuter myeloischer Leukämie (AML) mit einer Isocitrat-Dehydrogenase-1 (IDH1)-R132-Mutation, die für eine Standard- Induktionschemotherapie nicht geeignet sind
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Für die Therapie von Patientinnen und Patienten (Pat.) mit neu diagnostizierter Akuter Myeloischer Leukämie (AML) und Nachweis einer IDH-R132-Mution, die für eine Standard-Induktionschemotherapie nicht geeignet sind, werden diese Optionen empfohlen:

- Azaziditin + Ivosidenib oder
- Azaziditin / Decitabin + Venetoclax

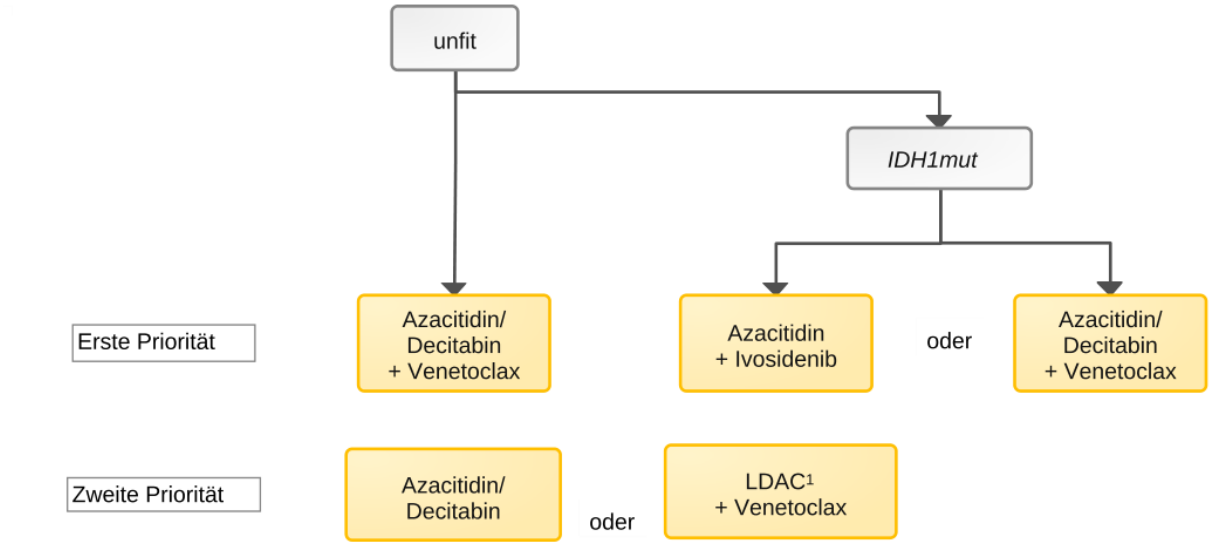
Fragestellung

Die Empfehlungen haben sich seit unserer letzten gutachterlichen Stellungnahme zu dieser Indikation (2024-B-327) nicht grundlegend geändert.

Stand des Wissens

Die Therapieoptionen für Pat., die für eine Standard- Induktionschemotherapie nicht geeignet sind, haben sich in den letzten Jahren deutlich erweitert [1, 2]. Ein aktueller Algorithmus ist in der Abbildung dargestellt [2].

Therapie-Optionen für die Primärtherapie unfitter Pat.



Legende:
nicht kurative intendierte Therapie;
[1] LDAC – niedrig dosiertes Ara-C;

Für unfitte Pat. mit neudiagnostizierter IDH1-mutierter AML-Mutation wurde der IDH1-Inhibitor Ivosidenib im Rahmen der randomisiert-plazebo-kontrollierten AGILE-Studie in Kombination mit Azacitidin evaluiert. Gegenüber Azacitidin und Placebo erhöhte die Hinzunahme von Ivosidenib die CR-Rate von 15% auf 47%. Die Dauer des Ansprechens war unter Ivosidenib-Azacitidin-Therapie deutlich länger als unter Azacitidin mit Placebo. Im Ergebnis erreichten Patienten mit der Ivosidenib-Kombination ein medianes Gesamtüberleben von 24,0 Monaten gegenüber 7,9 Monaten im Placebo-Arm (HR 0,44; p=0,001) [3].

Unabhängig von einer spezifischen molekularen Aberration steht für Pat., die nicht eine intensive Therapie geeignet sind, die Kombination aus einem hypomethylierenden Agens (HMA) wie Azacitidin oder Decitabin plus Venetoclax zur Verfügung. Einen direkten Vergleich beider Optionen gibt es nicht. In der kleinen IDH1-Kohorte aus der Zulassungsstudie für Venetoclax (VIALE-A) beträgt die CR-Rate 27% versus 47% in der Ivosidenib-Studie (AGILE), während die kombinierte CR/CRh-Rate mit Venetoclax bei 61% versus 53% in der AGILE-Studie liegt. Das mediane OS lag in der AGILE-Studie bei 29,3 Monaten und in der IDH1-Subgruppe der VIALE-A-Studie bei 15 Monaten, während die relative Risikoreduktion (HR) mit Venetoclax sich in einer HR von 0,19 äußert, gegenüber 0,42 in der AGILE-Studie mit Ivosidenib. In der Ivosidenib-Studie ist die Rate von ausgeprägten Zytopenien und febrilen Neutropenien niedriger als mit Venetoclax [4, 5].

Auf Grund des fehlenden direkten Vergleichs werden beide Therapie-Optionen gleichwertig für die Erstlinientherapie empfohlen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen in der o.g. Indikation, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?
Die verschiedenen Optionen sind oben dargestellt.

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