Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2021-B-291-z Venetoclax

Stand: September 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Venetoclax **[zur Behandlung erwachsener Patienten mit neu diagnostizierter akuter myeloischer Leukämie (AML), die nicht für eine intensive Chemotherapie geeignet sind.]**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „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: - Glasdegib (Beschluss vom 09. Februar 2021) - Decitabin (Beschluss vom 02. Mai 2013) Anlage VI zum Abschnitt K der Arzneimittel-Richtlinie (Stand: 10. April 2021) 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:	
Venetoclax L01XX52 Venclyxto®	<u>Anwendungsgebiet laut Zulassung:</u> 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.
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 Alexan®	Alexan wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur - Remissionseinleitung, Konsolidierung und Erhaltungstherapie akuter, nichtlymphatischer Leukämien
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.
Doxorubicin L01DB01 Doxorubicinhydrochlorid Bendalis®	[…] Remissionsinduktion bei akuter myeloischer Leukämie […]
Etoposid	<u>Entscheidung der Europäischen Komission zur Harmonisierung der Fachinformation von Etopophos:</u>

II. Zugelassene Arzneimittel im Anwendungsgebiet	
L01CB01 Etopophos®	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)
Glasdegib L01XX63 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.
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.
Idarubicin L01DB06 Zavedos®	Erwachsene: Zavedos ist zur Remissionsinduktion und Konsolidierung bei akuten myeloischen Leukämien (AML, ANLL) im Erwachsenenalter angezeigt.
Mitoxantron L01DB07 Mitoxantron Teva®	Mitoxantron ist indiziert zur Behandlung der akuten myeloischen Leukämie (AML) bei Erwachsenen.
Tioguanin L01BB03 Tioguanin-Aspen	Induktions- und Konsolidierungsphase der Behandlung der akuten myeloischen Leukämie (AML).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2021-B-291-z (Venetoclax)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	7. Juli 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AE	Adverse events
AML	Acute Myeloid Leukemia
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AZA	Azacytidine
BM	Bone marrow
CBF	Core binding factor
CCR	Conventional care regimens
CMML	Chronische myelomonozytäre Leukämie
CR	Complete remission
DEC	Decitabine
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HiDAC	High-dose cytarabine
HMA	Hypomethylating agents
HR	Hazard Ratio
HSCT	Hematopoietic stem cell transplantation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LDAC	Low-dose cytarabine
LoE	Level of Evidence
MDS	Myelodysplastic syndrome
NCCN	National Comprehensive Cancer Network
ND-AML	Newly Diagnosed AML
NICE	National Institute for Health and Care Excellence
NRCT	Non-randomized controlled trial
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
RBC	Red blood cell
RCT	Randomized controlled trial
RR	Relatives Risiko
R/R-AML	Relapsed/Refractory AML

SC	Subcutaneously
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
VEN	Venetoclax
WHO	World Health Organization

1 Indikation

Erwachsenen mit neu diagnostizierter oder sekundärer AML (insbesondere Patienten, die nicht für eine intensive Chemotherapie geeignet sind).

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *akute myeloische Leukämie (AML)* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 29.07.2020 durchgeführt, die Folgerecherche am 23.02.2021. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 677 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen 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. Nachträglich wurde die aktualisierte Anlage VI zum Abschnitt K der Arzneimittelrichtlinie des Gemeinsamen Bundesausschusses identifiziert und in die Synopse aufgenommen. Basierend darauf, wurden insgesamt 8 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse

G-BA, 2021 [2].

Richtlinie des Gemeinsamen Bundesausschusses über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (Arzneimittel-Richtlinie/AM-RL): Anlage VI zum Abschnitt K. Verordnungsfähigkeit von zugelassenen Arzneimitteln in nicht zugelassenen Anwendungsgebieten (sog. Off-Label-Use). Stand: 10.04.2021

XIV. Hydroxycarbamid bei chronischer myelomonozytärer Leukämie

1. Hinweise zur Anwendung von Hydroxycarbamid bei chronischer myelomonozytärer Leukämie gemäß § 30 Absatz 2 AM-RL

a) Nicht zugelassenes Anwendungsgebiet (Off-Label-Indikation):

Patienten/innen mit einer chronischen myelomonozytären Leukämie (CMML), definiert nach der FAB-Klassifikation mit einer Monozytose > 1.000/µl im Blut und einem Blastenanteil im Knochenmark < 30 %, bei denen eine Indikation für eine zytostatische Therapie besteht (siehe „Spezielle Patientengruppe“) oder bei Patienten mit CMML nach Übergang in eine akute myeloische Leukämie (AML, Blastenanteil im Knochenmark ≥ 30 %), die eine Kontraindikation für eine aggressive Induktionschemotherapie mit einem konventionellen AML-Protokoll aufweisen.

b) Behandlungsziel:

Palliative Therapie zur Überlebenszeitverlängerung

c) Folgende Wirkstoffe sind zugelassen:

Für eine Untergruppe der CMML-Patienten/innen ist 5-Azacitidine zugelassen:

Patienten, die nicht für eine Behandlung mit allogener Stammzelltransplantation geeignet sind und eine CMML mit 10 – 29 % Knochenmarkblasten ohne myeloproliferative Störung aufweisen.

d) Spezielle Patientengruppe:

CMML-Patienten/innen, bei denen eine Indikation zur zytostatischen Chemotherapie besteht.

Eine Indikation zur zytostatischen Chemotherapie besteht in der Regel, wenn zwei der folgenden Merkmale vorliegen:

Leukozyten > 16.000/µl, Hämoglobin < 10 g/dl, Thrombozyten < 100.000/µl, Blasten im Knochenmark > 5 %, Splenomegalie > 5 cm unterhalb Rippenbogen

und / oder wenn eines der folgenden Merkmale vorliegt:

zytologisch oder histologisch nachgewiesene Beteiligung anderer Organe als Milz, Leber und Lymphknoten, histologisch gesicherte Hautbeteiligung, zytologisch gesicherter Befall bei Pleura- / Perikarderguss oder Aszites.

Diese Merkmale sichern, dass keine Niedrigrisikopatienten therapiert werden. Nach heutigem Kenntnisstand sind zudem erhöhter Laktatdehydrogenase-Wert und ungünstiger Karyotyp als weitere Risikomerkmale zu nennen.

e) Patienten, die nicht behandelt werden sollten:

Patienten mit Leukozyten < 5.000/µl, sofern keine zytologisch oder histologisch nachgewiesene therapiebedürftige Organbeteiligung vorliegt (siehe „Spezielle Patientengruppe“).

f) Dosierung:

Initiale Dosis: 2 x 500 mg Hydroxycarbamid per os täglich.

Bei viszeraler Beteiligung, drohendem oder bereits erfolgten AML-Übergang: initiale Dosis 2 x 1.000 mg Hydroxycarbamid per os täglich.

Die weitere Dosierung soll dem Leukozytenverlauf angepasst werden. Es sollen Leukozytenwerte zwischen 5.000/µl und 10.000/µl angestrebt werden. In den Dosierungsempfehlungen der Phase 3-Studie von Wattel et al. (1996) wurde als maximale Tagesdosis 2 x 2 g angegeben.

Bei ausgeprägter Granulo- und/oder Thrombozytopenie sind engmaschige Blutbildkontrollen erforderlich und rechtzeitig eine Dosisreduktion von Hydroxycarbamid bzw. supportive Maßnahmen wie Antibiotikaprophylaxe und/oder Thrombozytentransfusionen in Erwägung zu ziehen.

g) Behandlungsdauer:

Es handelt sich um eine orale Dauertherapie, die so lange fortgeführt wird, wie die CMML ausreichend kontrolliert werden kann.

h) Wann sollte die Behandlung abgebrochen werden?

Die Hydroxycarbamidtherapie soll abgebrochen werden, wenn auch bei der maximal tolerablen Dosis eine ausreichende Kontrolle der Leukozytose oder der Organinfiltration nicht (mehr) erreicht werden kann.

i) Nebenwirkungen/Wechselwirkungen, wenn diese über die zugelassene Fachinformation hinausgehen oder dort nicht erwähnt sind:

Insbesondere bei ausgeprägter Leukozytose muss mit der Entwicklung eines Tumorlysesyndroms gerechnet werden. Deshalb sind entsprechende Vorsichtsmaßnahmen zu ergreifen, eine ausreichende Diurese ist zu gewährleisten und ggf. die Gabe von Allopurinol in Betracht zu ziehen.

Häufige Nebenwirkungen sind Granulozytopenie, Anämie, Thrombozytopenie und Hautreaktionen.

Die Fachinformation ist unbedingt zu beachten.

j) Weitere Besonderheiten

Die Behandlung soll von einem Facharzt/ einer Fachärztin für Innere Medizin, Hämatologie und Onkologie durchgeführt werden.

k) Zustimmung des pharmazeutischen Unternehmers:

Die folgenden pharmazeutischen Unternehmer haben für ihre Hydroxycarbamid-haltigen Arzneimittel eine Anerkennung des bestimmungsgemäßen Gebrauchs abgegeben (Haftung des pharmazeutischen Unternehmers), sodass ihre Arzneimittel für die vorgenannte Off-Label-Indikation verordnungsfähig sind:

1 A Pharma GmbH, axicorp Pharma GmbH, EMRAmed Arzneimittel GmbH, EurimPharm Arzneimittel GmbH, Hexal AG und medac Gesellschaft für klinische Spezialpräparate mbH.

Nicht verordnungsfähig sind in diesem Zusammenhang die Hydroxycarbamid-haltigen Arzneimittel der Firmen A.C.A. Müller ADAG Pharma AG, Addmedica, ADL Pharma GmbH, BERAGENA Arzneimittel GmbH, Bristol-Myers Squibb GmbH, CC-Pharma GmbH, kohlpharma GmbH, Medicopharm AG und Pharma Westen GmbH, da keine entsprechende Erklärung vorliegt.

2. Anforderungen an eine Verlaufsdokumentation gemäß § 30 Abs. 4 AM-RL:

entfällt

G-BA, 2013 [3].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 02. Mai 2013 - **Decitabin**

Anwendungsgebiet

Dacogen® ist indiziert zur Behandlung erwachsener Patienten ab einem Alter von 65 Jahren mit neu diagnostizierter de novo oder sekundärer akuter myeloischer Leukämie (AML) gemäß der Klassifikation der Weltgesundheitsorganisation (WHO), Induktionstherapie nicht in Frage kommt.

Vergleichstherapie

Decitabin ist zugelassen als Arzneimittel zur Behandlung eines seltenen Leidens nach der Verordnung (EG) Nr. 141/2000 des Europäischen Parlaments und des Rates vom 16. Dezember 1999 über Arzneimittel für seltene Leiden. Gemäß § 35a Absatz 1 Satz 10 des Fünften Buches Sozialgesetzbuch (SGB V) gilt der medizinische Zusatznutzen durch die Zulassung als belegt.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Geringer Zusatznutzen

3.2 Cochrane Reviews

Es wurden keine relevanten Quellen identifiziert.

3.3 Systematische Reviews

Liu B et al., 2020 [5].

The efficacy and adverse events of venetoclax in combination with hypomethylating agents treatment for patients with acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and adverse effects of venetoclax(VEN) in combination with hypomethylating agents(HMAs) in acute myeloid leukemia(AML) or myelodysplastic syndrome(MDS).

Methodik

Population:

- AML or MDS patients

Intervention:

- Venetoclax in combination with azacytidine (AZA) or decitabine (DEC)

Komparator:

- k.A.

Endpunkte:

- primary outcome: overall CR rate.
- secondary outcome: ORR, median OS and the rate of grade 3–4 adverse events including decreased white blood cell count, thrombocytopenia, anemia and febrile neutropenia.

Recherche/Suchzeitraum:

- PubMed, Cochrane Library, Embase, Google Scholar and ClinicalTrials.gov.
- Until August 2020

Qualitätsbewertung der Studien:

- Newcastle-Ottawa Scale and Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 retrospective cohort studies, 5 NRCTs and 1 RCT

Table 2. The study design and treatment regimen used in the included studies.

Study	Diseases	Regimen
Aldoss, et al. [8]	De novo AML: 58 Therapy-related AML: 10 Secondary AML: 22	AZA + VEN: 9; DEC + VEN: 81 5-day DEC: 33; 10-day DEC: 48
Asghari et al. [9]	AML-MRC: 38 Therapy-related AML: 10	AZA + VEN: 40; DEC + VEN: 31
Ball et al. [10]	MDS-EB1: 14 MDS-EB2: 25 MDS-RS MLD: 2 MDS-U: 1	VEN starting dose: 400 200 mg, ≤100 mg, AZA + VEN: 23; DEC + VEN: 19
DiNardo et al. [4]	De novo AML: 109 Secondary AML: 36	-Dose escalation phase(AZA/ DEC: 22/23): VEN: from 20 mg to a target dose of 400, 800, 1200 mg/d orally. AZA: 75 mg/m^2 day1-7, IV; DEC: 20 mg/m^2 day1-5 IV. -Dose-expansion phase(AZA/DEC: 50/50): VEN: from 100 mg to a target dose of 400, 800 mg/d orally. AZA: 75 mg/m^2 day1-7, IV; DEC: 20 mg/m^2 day1-5 IV.
Lou, et al. [11]	Primary refractory AML: 16 Relapsed AML: 32	VEN: from 100 mg with a 3-day ramp to target dose of 400 mg/d orally. AZA: 75 mg/m^2 day1-7, H.
Maiti et al. [12]	New diagnosed AML: 40 Secondary AML: 28 Relapsed/refractory AML: 33	VEN: 400 mg/d orally on day1-28 in cycle 1. DEC: 20 mg/m^2 day1-10 IV(until CR/CRi), followed by 5-day cycles.
Mittal et al. [13]	Relapsed/refractory AML: 11	AZA + VEN: 8; DEC + VEN: 3
Rausch et al. [14]	De novo AML: 69 Secondary AML: 40 Therapy-related AML: 12	-DEC 20 mg/m^2 d1-5/d1-10: 110 -AZA 75 mg/m^2 d1-7: 11 -VEN 400 mg/d or >400 mg/d orally × 7-30d
Wei et al. [15]	Treatment-Naive Higher-Risk MDS: 59	-randomized cohort: VEN 400/800 mg daily + AZA 75 mg/m^2 d1-7 -dose escalation cohort: VEN 100/200/400 mg daily + AZA 75 mg/m^2 d1-7 -safety expansion cohort: VEN 400 mg daily + AZA 75 mg/m^2 d1-7
Winters et al. [16]	Older Newly Diagnosed AML: 30	VEN from 100 mg with a 4-day ramp to target dose of 600 mg/d orally + AZA 75 mg/m^2 d1-7
Winters, et al. [17]	Older Newly Diagnosed AML: 30	VEN: from 100 mg with a 3-day ramp to a target dose of 400 mg/d orally, for 28-day cycles. AZA: 75 mg/m^2 day1-7, IV/H
Zeidanet al. [18]	Relapsed/refractory MDS: 46	-C1 group(22): VEN monotherapy 400 and 800 mg/d for 28-day cycles -C2 group(24): VEN + AZA 100, 200 and 400 mg daily for 14 of 28-day cycles + AZA 75 mg/m^2 d1-7
DiNardo et al, [4]	-AML(C1 group) De novo: 214; Secondary: 72 -AML(C2 group) De novo: 110; Secondary: 35	-C1 group(286): VEN: from 100 mg with a 3-day ramp to a target dose of 400 mg/d orally, for 28-day cycles. AZA: 75 mg/m2 day1-7, IV/H -C2 group(145): VEN placebo. AZA: 75 mg/m2 day1-7, IV/H

- Abbreviations: IV, Intravenous; H, Subcutaneous.

Charakteristika der Population:

- A total of 934 AML and 125 MDS patients, aged between 18 and 91 years, of whom more than 50% were male and elderly (>60 years). Most patients (>50%) were considered to have unfavourable- risk AML and MDS according to the genetic risk stratification used in all studies

Qualität der Studien:

- The cohort studies and NRCTs were evaluated using the Newcastle-Ottawa Scale, with scoring between 7 and 9 and considered 'high quality'; the RCT was evaluated using the Cochrane risk of bias tool, which was scored 5 and also considered 'high quality'.

Studienergebnisse:

- Overall analysis (AML and MDS patients)
  - Seven cohort studies and 5 NRCTs were analyzed by random-effects model and the results showed pooled overall CR rate after treatment with VEN + HMA regimen was 56% (95% CI, 51-62%, I2 = 51%),
  - while the pooled ORR was 68% (95% CI, 61–75%, I2 = 67%).
  - Results showed moderate heterogeneity.
  - A total of 7 studies reported median OS, and a descriptive systematic evaluation of median OS was observed in the range of 4.9–17.5 months.
  - The CR and median OS in VEN + AZA groups was 66.4% and 14.7 months, respectively, in the study by DiNardo et al.
  - A total of 8 studies reported adverse events, with cytopenia and infection being the most common grade 3– 4 adverse events, and adverse events were combined for 7 of these studies. The pooled rate of febrile neutropenia was 47%(95% CI, 36-58%, I2 = 84%). The pooled rate of grade 3–4 decreased white blood cell count was 42%(95% CI, 30-54%, I2 = 77%). The pooled rate of grade 3–4 anemia was 28% (95% CI, 14-48%, I2 = 86%). The pooled rate of grade 3–4 thrombocytopenia was 33%(95% CI, 14–58%,

I2 = 96%). In the study by DiNardo et al., the incidences of grade 3–4 adverse events in patients who received VEN + AZA regimen were 42% of the patients with febrile neutropenia, 20% with decreased white blood cell count, 26% with anemia, 45% with thrombocytopenia, respectively.

- Subgroup analysis
  - pooled overall **CR rate of 68% (95% CI 55-79%, I2 = 84%, Figure 4) for the ND-AML group** 39% (95% CI 30-48%, I2 = 28%, Figure 4) for R/R-AML, and 61% (95% CI 50-71%, I2 = 25%) for MDS.

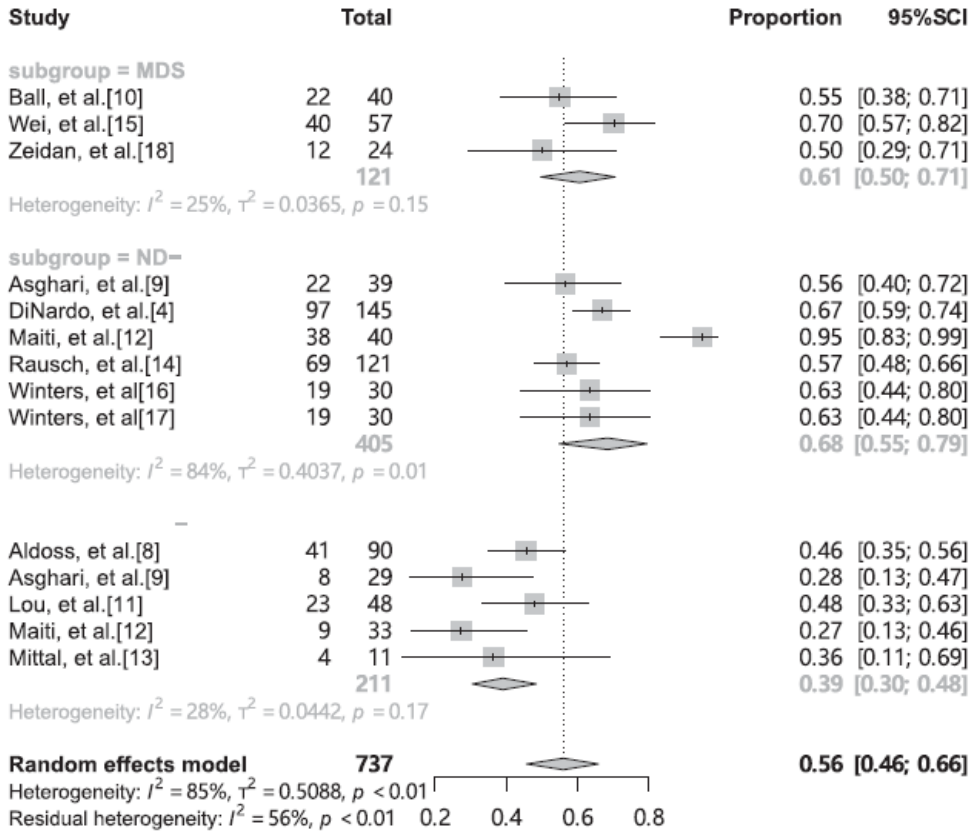


Figure 4. Forest plots of the pooled CR rate for different disease types.

Anmerkung/Fazit der Autoren

The addition of VEN to HMAs may provide significant clinical benefit for AML/MDS patients, where response rates are better in MDS and ND-AML than in R/R-AML, but attention should be paid to the possible increased risk of febrile neutropenia. However, there is still a need for RCT to comprehensively evaluate the efficacy and adverse effects of the VEN + HMAs regimen in patients with AML and MDS.

Wen B et al., 2020 [8].

Indirect comparison of azacitidine and decitabine for the therapy of elderly patients with acute myeloid leukemia: a systematic review and network meta-analysis.

Fragestellung

A systematic review and network meta-analysis were performed to indirectly compare the efficacy and safety of decitabine and azacitidine in elderly AML patients.

Methodik

Population:

- elderly AML patients

Intervention/Komparator

- azacitidine or decitabine, and compared the two drugs against each other, or compared them to standard supportive care, or placebo

Endpunkte:

- mortality, complete and partial responses, and haematologic improvement

Recherche/Suchzeitraum:

- PubMed, Medline, Web of Science, EMBASE and Cochrane Library through May 14, 2019.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool / GRADE

Ergebnisse

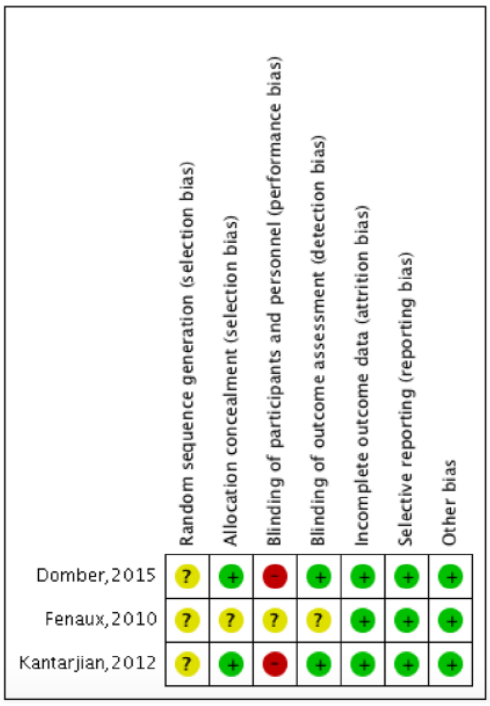
Anzahl eingeschlossener Studien:

- 3 trials

Charakteristika der Population:

- The three RCTs involved a total number of 1086 patients with an age range of 64–91 years old. Two RCTs compared of azacitidine (75 mg/m2/day, SC × 7 days) and the conventional care regimens (CCR), including lowdose cytarabine (LDAC) or best supportive care (BSC) or intensive chemotherapy (IC), and included 601 patients (296 azacitidine and 305 CCR; age average 74; range 64–91 years old). The other RCT compared decitabine (20 mg/m2, IV, QD × 5 days/4 weeks) to the CCR including supportive care or cytarabine and included 485 patients (242 decitabine and 243 CCR; age average 73; range 64–91 years old).

Qualität der Studien:



Studienergebnisse:

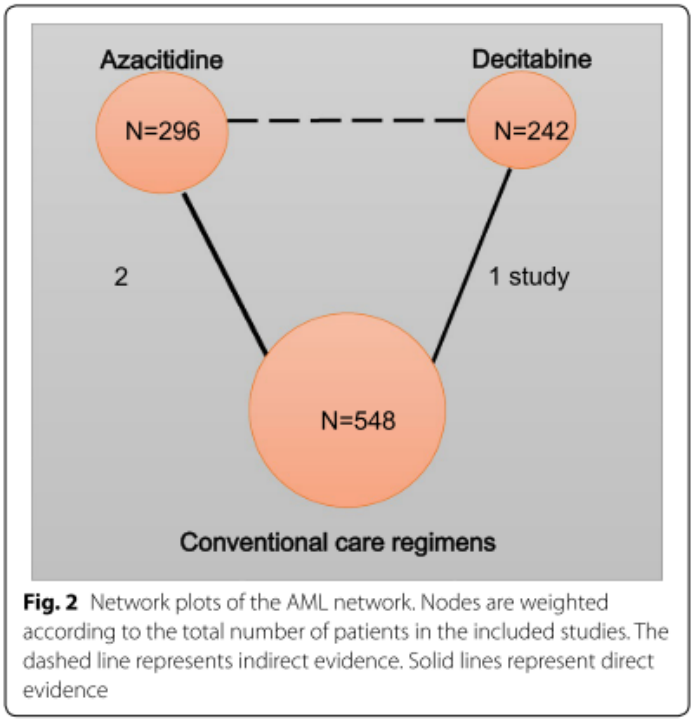


Fig. 2 Network plots of the AML network. Nodes are weighted according to the total number of patients in the included studies. The dashed line represents indirect evidence. Solid lines represent direct evidence

- Direct comparisons showed that azacitidine significantly reduced mortality (RR = 0.90, 95% CI 0.83–0.98, p < 0.001, I2 = 94.0%), while decitabine did not show improvement in mortality rates compared to CCR (RR = 0.97, 95% CI 0.92–1.02). Higher complete responses were reported in both groups as compared to CCR.
- Indirect head-to-head comparisons showed that azacitidine significantly reduced the mortality rate (RR = 0.83 95% CI 0.77–0.90, I2 = 82.8%) and anemia (RR = 0.68, 95% CI 0.52–0.90, I2 = 82.2%). Patients in the azacitidine group were more likely to achieve

complete response (CR) compared to decitabine (RR = 1.66, 95% CI 1.17–2.35, I2 = 65.3%, low certainty). There was no statistically significant difference found in other study outcomes including partial response rate, neutropenia and thrombocytopenia. Similarly, azacitidine showed improved overall survival by SUCRA analysis compared to decitabine (74.7% vs. 47.1%).

Anmerkung/Fazit der Autoren

Compared to CCR, azacitidine or decitabine yields both better outcomes, including mortality, overall response, and improvement of haematological parameters. For indirect head-to-head comparisons, low certainty of evidence was found when comparing azacitidine and decitabine. The superiority of either agent cannot be confirmed in this study and head-to-head clinical trials are still required to provide more information about the efficacy and safety of the two agents. In addition, other factors including adverse effects, patient preferences and cost, are also important and should be taken into consideration in the final choice between the two agents.

Kommentare zum Review

- The consistency of the network could not be evaluated because there were no closed loops
- Heterogeneity and publication bias could not be obtained because of the small number of trials investigating each agent
- direct and indirect head-to-head comparisons were performed with low or moderate of the certainty of the evidence
- Subgroup analysis could not be assessed due to the paucity of data. → unklar ob Patienten vorbehandelt oder nicht.

He PF et al., 2017 [4].

Efficacy and safety of decitabine in treatment of elderly patients with acute myeloid leukemia: A systematic review and metaanalysis

Fragestellung

The purpose of this study was to assess what is currently known about the efficacy and safety of decitabine in elderly AML patients by performing a meta-analysis.

Methodik

Population:

- previously untreated elderly AML (≥ 60 Jahre)

Intervention:

- decitabine

Komparator:

- k.A.

Endpunkte:

- CR, overall response rate (ORR) and overall survival (OS)

Recherche/Suchzeitraum:

- PubMed, Web of Science, Embase and Cochrane Library
- Bis Februar 2017

Qualitätsbewertung der Studien:

- Cochrane Collaboration's Risk of Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- N=9 (n=718 Patienten)

Charakteristika der Population:

Table 1: General characteristics of the included studies

First Author	Year	Country	Study-center	Phase	Dose and schedule of decitabine	Trial Sponsor
Jacob et al. [10]	2015	India	NR	NR	20 mg/m² 5-days 4 weeks	NR
Yan et al. [11]	2012	America	Single-center	Phase II	20 mg/m² 10-days 4 weeks	National Cancer Institute
Ritchie et al. [12]	2013	America	Single-center	NR	20 mg/m² 10-days 4 weeks	Leukemia Fighters™
Cashen et al. [13]	2010	America	Multicenter	Phase II	20 mg/m² 5-days 4 weeks	NR
Blum et al. [14]	2010	America	Single-center	Phase II	20 mg/m² 10-days 4 weeks	National Cancer Institute
Tawfik et al. [15]	2014	America	Single-center	NR	20 mg/m² 5-days 4 weeks	National Cancer Institute
Kantarjian et al. [16]	2012	America	Multicenter	Phase III	20 mg/m² 5-days 4 weeks	MDACC and others
Lübbert et al. [17]	2011	Germany	Multicenter	Phase II	15 mg/m² 3-days 6weeks*	European LeukemiaNet
Park et al. [18]	2016	Korea	Single-center	NR	20 mg/m² 5-days 4 weeks	Yonsei University

Abbreviations: NR: Not Reached; 15 mg/m² 3-days 6weeks*: 15 mg/m², three times daily on 3 consecutive days. MDACC: M.D. Anderson Cancer Center.

Supplementary Table 1: Baseline characteristics of patients in the included studies

First Author	No. patients	Median age (years)	Gender (male %)	AML type (%)		BM blast (%)		Cytogenetics-risk (%)		
				De novo	secondary	< 30	≥ 30	favorable	intermediate	poor
Jacob et al. [10]	15	65	80	87	13	13	60	33	47	20
Yan et al. [11]	16	75	50	NR	NR	31	69	NR	NR	NR
Ritchie et al. [12]	52	75	44	NR	NR	NR	NR	NR	53	45
Cashen et al. [13]	55	74	51	23	71	33	67	NR	65	35
Blum et al. [14]	53	74	64	NR	NR	NR	NR	40	NR	30
Tawfik et al. [15]	34	75	50	53	41	56	35	3	32	38
Kantarjian et al. [16]	242	73	57	64	36	27	71	NR	63	36
Lübbert et al. [17]	227	72	61	49	51	3	95	1	45	32
Park et al. [18]	24	73	50	92	8	NR	NR	13	67	13

BM blast: Bone Marrow blast; NR: Not Reported;

Qualität der Studien:

- Based on the risk of bias assessment criteria, included 9 studies were classified into class B. Sensitivity analyses indicated that excluding any single study did not significantly affect the pooled outcomes, suggesting the results of our meta-analysis were stable.

Studienergebnisse:

- **CR**
  - 8 Studien: Pooled estimate for overall CR rate was 27% (95% CI 19%–36%). In subgroup analysis of therapy schedule, data from 3-days 6 weeks course showed that CR rate was 13% (95% CI 9%–18%), and the 5-days 4 weeks course showed a CR rate of 17% (95% CI 13%–21%). The patients treated with 10-days 4 weeks course achieved a significantly higher CR rate of 45% (95% CI 37%–54%) than the other two courses ($P < 0.001$).
- **ORR**
  - 8 Studien: Pooled estimate for ORR of decitabine treated patients was 37% (95% CI 28%–47%). Subgroup analysis of ORR with 3-days 6 weeks course was 26% (95% CI 20%–32%) and 5-days 4 weeks course was 29% (95% CI 22%–37%). Patients treated with the 10-days 4 weeks course showed a relatively higher ORR of 53% (95% CI 37%–

70%). In the different treatment schedule, ORR presented a consistent pattern with CR, 10-days 4 weeks course showed significantly better response than the other two courses (P = 0.001).

- **OS**
  - 6 Studien: Pooled estimate of OS was 8.09 months (95% CI 5.77–10.41). In subgroup analysis of therapy schedule, OS of 5-days 4 weeks course was 6.40 months (95% CI 4.24–8.56) and 10-days 4 weeks course was 11.30 months (95% CI 8.26–14.34). Subgroup analysis showed that 10-days 4 weeks course achieved a relatively prolonged survival.
- **Safety**
  - 7 Studien: random-effects model was applied. Myelosuppression was the most common toxicity observed in decitabine treated patients.
  - high risks of treatment related AEs: thrombocytopenia 40% (95% CI 28%– 53%), febrile neutropenia 38% (95% CI 23%–53%), neutropenia 37% (95% CI 22%–51%), anemia 36% (95% CI 23%–48%) and fatigue 15% (95% CI 4%– 26%). Occurrence of treatment associated infections was 36% (95% CI 24%–48%), pneumonia (25%) and sepsis (9%) were the most frequent infectious complications.
  - Decitabine treatment related ED rates were analysed in six studies [10, 12, 14–17], random-effects model were adopted. Death within 30-days was 7% (95% CI 2%–11%) and 60-days mortality was 17% (95% CI 11%–22%). Subgroup analysis of the association between ED rate and decitabine course with 5-days and 10-days was 31% (95% CI 13%-49%) and 19% (95% CI 11%–26%). ED rates analyses showed that there was no significant difference in mortality between 5-days and 10-days courses treatment (P = 0.072).

Anmerkung/Fazit der Autoren

This meta-analysis showed that decitabine brought considerable treatment response in elderly AML patients. Preliminary data indicated longer exposure times to decitabine showed an improved response rate and relatively prolonged survival. The dose schedule of decitabine did not seem to affect ED rate with patients receiving 10-days decitabine (19%) compared with those received 5-days course (31%). Neutropenia and thrombocytopenia related to myelosuppression were common during decitabine treatment. Prospective clinical trials that directly compared decitabine courses are still needed to confirm the more optimal administration.

In conclusion, our meta-analysis suggests that decitabine is an effective and well-tolerated therapeutic alternative with acceptable side effects in elderly AML patients. To improve the overall response and maintain durable remission, further studies should focus on determining the best administration schedule and developing the optimal combination with decitabine.

3.4 Leitlinien

National Comprehensive Cancer Network (NCCN), 2021 [6].

Acute Myeloid Leukemia

Leitlinienorganisation/Fragestellung

Diagnosis and Treatment of AML in adults

Methodik

Grundlage der Leitlinie

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

- Repräsentatives Gremium – trifft zu.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu.
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft nicht zu (unzureichend dargelegt, siehe unten).
- 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 (Verbindung zu Evidenz nur über Hintergrundtext indirekt zu erkennen).
- Regelmäßige Überprüfung der Aktualität – trifft zu.

Recherche/Suchzeitraum:

- Prior to the update of this version of the NCCN Guidelines for AML, an electronic search of the PubMed database was performed to obtain key literature in AML published since the previous Guidelines update. […] The PubMed database was chosen […].

LoE/ GoR

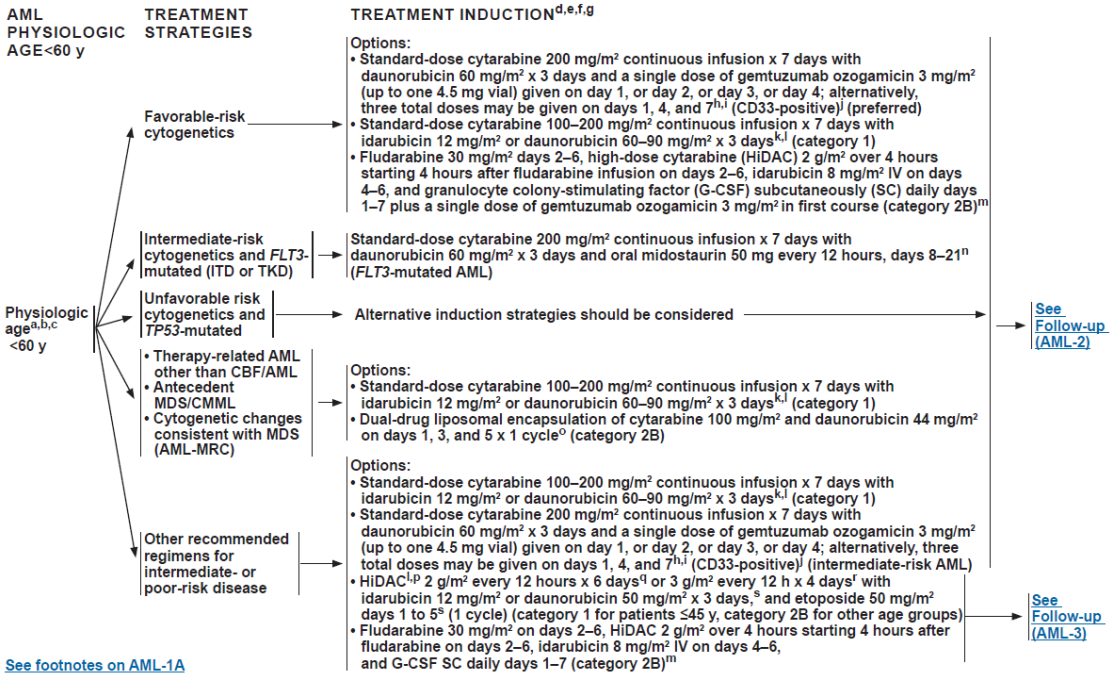
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus 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



Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AML-1

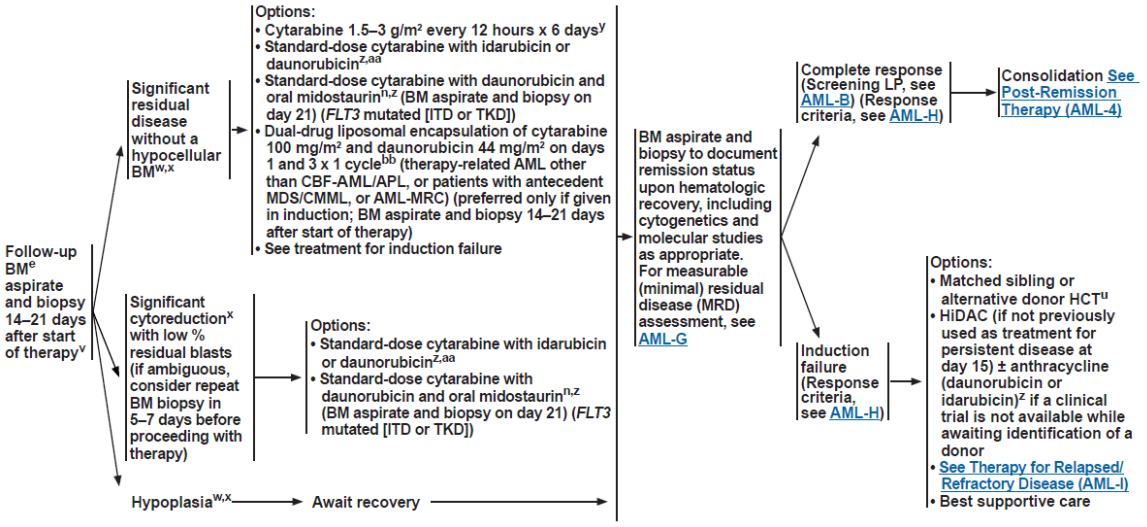
FOOTNOTES FOR TREATMENT INDUCTION (PHYSIOLOGICAGE <60 YEARS)

[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 apheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.
[b] Poor performance status and a comorbid medical condition, in addition to age, are factors that influence ability to tolerate standard induction therapy.
[c] Patients with CBF-AML and core abnormalities may benefit from the addition of gemtuzumab ozogamicin. Consider screening with fluorescence in situ hybridization (FISH) to identify translocations/abnormalities associated with CBF-AML.
[d] See Principles of Supportive Care for AML (AML-E).
[e] See Monitoring During Therapy (AML-F).
[f] Consider referral to palliative care for consultation at the start of induction. LeBlanc T, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc T, et al. J Oncol Pract.2017;13:589-590. See NCCN Guidelines for Palliative Care.
[g] See General Considerations and Supportive Care for AML Patients Who Prefer Not to Receive Blood Transfusions (AML-D)
[h] Burnett AK, et al. J Clin Oncol 2011;29:369-377. Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules; Hills RK, et al. Lancet Oncol 2014;15:986-996.
[i] Patients who receive transplant shortly following gemtuzumab ozogamicin administration may be at risk for developing sinusoidal obstruction syndrome (SOS). Wadleigh M, et al. Blood 2003;102:1578-1582. If transplant is planned, note that prior studies have used a 60- to 90-day interval between the last administration of gemtuzumab ozogamicin and HCT.
[j] Threshold for CD33 is not well-defined and may be ≥1%.
[k] ECOG reported a significant increase in complete response rates and overall survival using daunorubicin 90 mg/m² x 3 days versus 45 mg/m² x 3 days in patients <60 years of age. Fernandez HF, et al. N Engl J Med 2009;361:1249-1259. If there is residual disease on days 12–14, the additional daunorubicin dose is 45 mg/m² x 3 days. Burnett AK, et al. Blood 2015;125:3878-3885.
[l] For patients with impaired cardiac function, other cytarabine-based regimens alone or with other agents can be considered. See Discussion.
[m] Burnett AK, et al. J Clin Oncol 2013;31:3360-3368.
[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.
[o] There are limited data supporting the use of this regimen in patients aged <60 years. Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.
[p] The use of high-dose cytarabine for induction outside the setting of a clinical trial is still controversial. While the remission rates are the same for standard- and high-dose cytarabine, two studies have shown more rapid marrow blast clearance after one cycle of high-dose therapy. Kern W and Estey EH. Cancer 2006;107:116-124. However, one study showed that high-dose cytarabine may improve the outcome for younger patients. Willemze R, et al. J Clin Oncol 2014;32:219-228.
[q] Weick JK, et al. Blood 1996;88:2841-2851.
[r] Bishop JF, et al. Blood 1996;87:1710-1717.
[s] Willemze R, et al. J Clin Oncol 2014;32:219-228.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AML-1A

AML PHYSIOLOGICAGE <60 y
AFTER STANDARD-DOSE CYTARABINE INDUCTION/RE-INDUCTION[f,t,u]



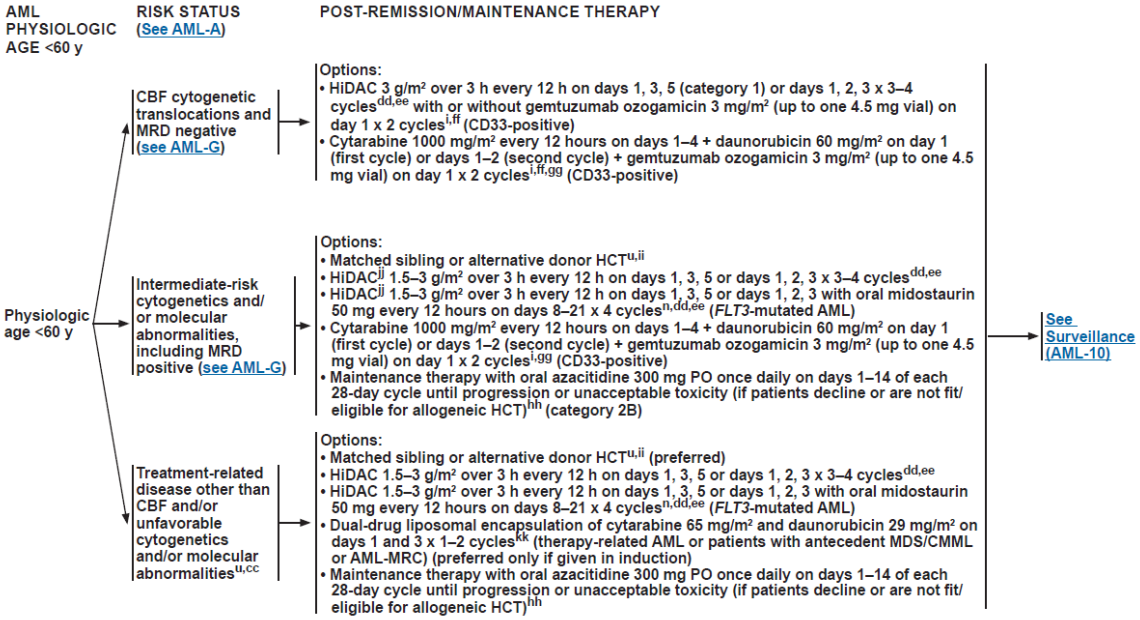
See footnotes on AML-2A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES FOR TREATMENT AFTER STANDARD-DOSE CYTARABINE INDUCTION/RE-INDUCTION (PHYSIOLOGIC AGE <60 YEARS)

[e] See Monitoring During Therapy (AML-F).
[f] Consider referral to palliative care for consultation at the start of induction. LeBlanc T, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc T, et al. J Oncol Pract 2017;13:589-590. See NCCN Guidelines for Palliative Care.
[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.
[t] Consider clinical trials for patients with targeted molecular abnormalities.
[u] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For induction failure, alternative therapy to achieve remission is encouraged prior to HCT.
[v] There are limited prospective data to support this recommendation. Othus M, et al. Leukemia 2016;30:1779-1780.
[w] If ambiguous, consider repeat BM biopsy in 5–7 days before proceeding with therapy.
[x] Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).
[y] For re-induction, no data are available to show superiority with intermediate or high-dose cytarabine.
[z] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.
[aa] If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.
[bb] Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



See footnotes on AML-4A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES FOR POST-REMISSION/MAINTENANCE THERAPY (PHYSIOLOGIC AGE <60 YEARS)

[i] Patients who receive transplant shortly following gemtuzumab ozogamicin administration may be at risk for developing sinusoidal obstruction syndrome (SOS). Wadleigh M, et al. Blood 2003;102:1578-1582. If transplant is planned, note that prior studies have used a 60- to 90-day interval between the last administration of gemtuzumab ozogamicin and HCT.

[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.

[u] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For induction failure, alternative therapy to achieve remission is encouraged prior to HCT.

[cc] *FLT3*-ITD mutation is a poor-risk feature in the setting of otherwise normal karyotype, and these patients should be considered for clinical trials where available.

[dd] Mayer RJ, et al. N Engl J Med 1994;331:896-903; Jaramillo S, et al. Blood Cancer J 2017;7:e564.

[ee] Alternate dosing of cytarabine for postremission therapy has been reported (see Discussion). Jaramillo S, et al. Blood Cancer J 2017;7:e564.

[ff] Meta-analyses showing an advantage with gemtuzumab ozogamicin have included other dosing schedules. Hills RK, et al. Lancet Oncol 2014;15:986-996.

[gg] This regimen may also be used in patients with *KIT* mutations because the outcomes are similar in patients without *KIT* mutations.

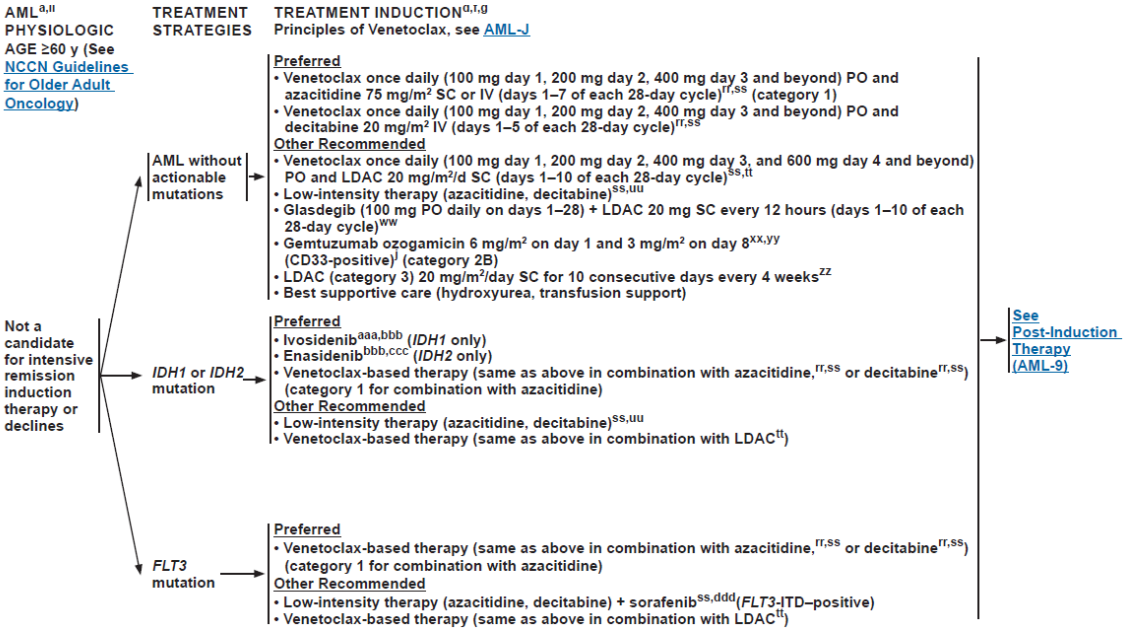
[hh] This is a maintenance therapy and is not intended to replace consolidation chemotherapy, which can be curative in some cases. In addition, fit patients with intermediate- and/or adverse-risk cytogenetics may benefit from HCT in first CR, and there are no data to suggest that maintenance therapy with oral azacitidine can replace HCT. The panel also notes that the trial did not include younger patients or those with CBF-AML; it was restricted to patients ≥55 years of age with intermediate or adverse cytogenetics who were not felt to be candidates for HCT. Most patients received at least 1 cycle of consolidation prior to starting oral azacitidine. Wei AH, et al. Blood 2019;134 (Suppl_2):LBA-3.

[ii] Patients may require at least one cycle of high-dose cytarabine consolidation while donor search is in progress to maintain remission. Patients may proceed directly to transplant following achievement of remission if a donor (sibling or alternative) is available.

[jj] There is no evidence that HiDAC is superior to intermediate doses (1.5 g/m² daily x 5 days) of cytarabine in patients with intermediate-risk cytogenetics.

[kk] Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



See footnotes on AML-6A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES FOR TREATMENT INDUCTION (PHYSIOLOGICAGE ≥60 YEARS)

[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 apheresis, hydroxyurea, and/or a single dose of cytarabine (1–2 g). Prompt institution of definitive therapy is essential.

[d] See Principles of Supportive Care for AML (AML-E).

[f] Consider referral to palliative care for consultation at the start of induction. LeBlanc T, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc T, et al. J Oncol Pract.2017;13:589-590. See NCCN Guidelines for Palliative Care.

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

[j] Threshold for CD33 is not well-defined and may be ≥1%.

[ll] There is a web-based scoring tool available to evaluate the probability of complete response and early death after standard induction therapy in elderly patients with AML: http://www.aml-score.org/. Krug U, et al. Lancet 2010;376:2000-2008. A web-based tool to predict CR and early death can be found at: https://www.fhcrc-research.org/TRM/Default.aspx?GUID=1358501B-C922-4422-84F0-0E6C67D8F266 and Walter RB, et al. J Clin Oncol 2011;29:4417-4423.Factors in decisions about fitness for induction chemotherapy include age, performance status, functional status, and comorbid conditions. See NCCN Guidelines for Older Adult Oncology.

[rr] This regimen may be continued for patients who demonstrate 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; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.

[ss] Patients who have 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.

[tt] Wei AH, et al. J Clin Oncol 2019;37:1277-1284.

[uu] In patients with AML with *TP53* mutation, a 10-day course of decitabine may be considered (Welch JS, et al. N Engl J Med 2016;375:2023-2036). 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.

[ww] 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. Blood 2016;128:99.

[xx] Amadori S, et al. J Clin Oncol 2016;34:972-979.

[yy] Regimens that include gemtuzumab ozogamicin will not benefit patients with poor-risk disease.

[zz] Kantarjian HM, et al. J Clin Oncol 2012;30:2670-2677.

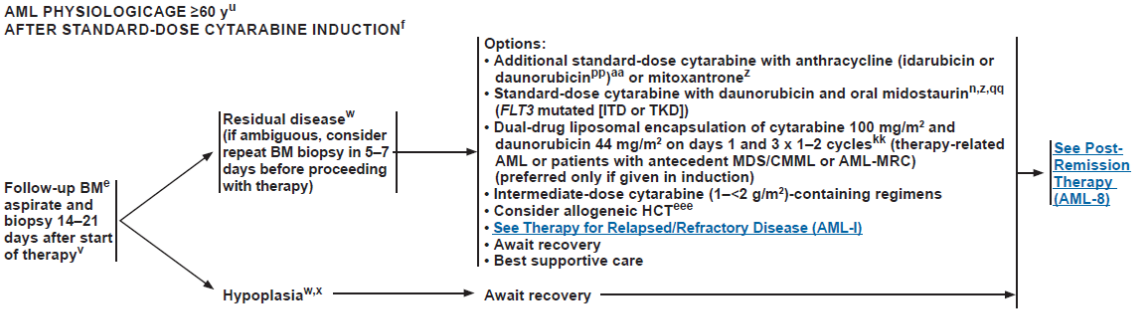
[aaa] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:463-471.

[bbb] When using this agent, 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).

[ccc] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.

[ddd] Ohanian M, et al. Am J Hematol 2018;93:1136-1141.

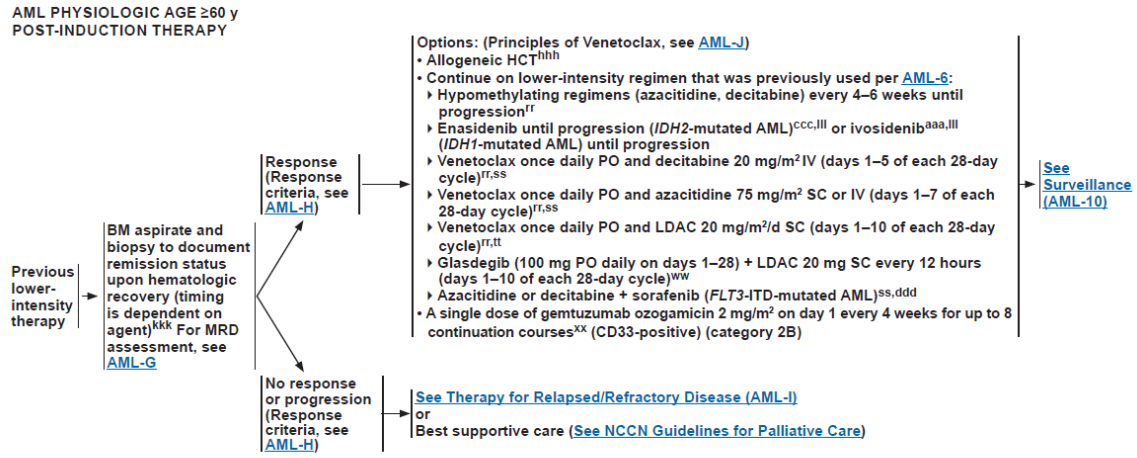
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[e] See Monitoring During Therapy (AML-F).
[f] Consider referral to palliative care consultation at the start of induction. LeBlanc T, et al. Curr Hematol Malig Rep 2017;12:300-308 and LeBlanc T, et al. J Oncol Pract 2017;13:589-590. See NCCN Guidelines for Palliative Care.
[n] This regimen is for *FLT3* mutation-positive AML (both ITD and TKD mutations). While midostaurin was not FDA approved for maintenance therapy, the study was designed for consolidation and maintenance midostaurin for a total of 12 months. Stone RM, et al. N Engl J Med 2017;377:454-464.
[u] Begin alternate donor search (haploidentical, unrelated donor, or cord blood) if no appropriate matched sibling donor is available and the patient is a candidate for allogeneic HCT. For induction failure, alternative therapy to achieve remission is encouraged prior to HCT.
[v] There are limited prospective data to support this recommendation. Othus M, et al. Leukemia 2016;30:1779-1780.
[w] If ambiguous, consider repeat BM biopsy in 5–7 days before proceeding with therapy.
[x] Hypoplasia is defined as cellularity less than 20% of which the residual blasts are less than 5% (ie, blast percentage of residual cellularity).
[z] For regimens using high cumulative doses of cardiotoxic agents, consider reassessing cardiac function prior to each anthracycline/mitoxantrone-containing course. Karanes C, et al. Leuk Res 1999;23:787-794.
[aa] If daunorubicin 90 mg/m² was used in induction, the recommended dose for daunorubicin for reinduction prior to count recovery is 45 mg/m² for no more than 2 doses. Analogously, if idarubicin 12 mg/m² was used for induction, the early reinduction dose should be limited to 10 mg/m² for 1 or 2 doses.
[kk] Lancet JE, et al. J Clin Oncol 2018;36:2684-2692.
[pp] The complete response rate and 2-year overall survival in patients between 60 and 65 years of age treated with daunorubicin 90 mg/m² are also comparable to the outcome for idarubicin 12 mg/m²; the higher dose daunorubicin did not benefit patients >65 years of age (Löwenberg B, et al. N Engl J Med 2009;361:1235-1248).
[qq] The RATIFY trial studied patients aged 18–60 y. An extrapolation of the data suggests that older patients who are fit to receive 7+3 should be offered midostaurin since it seems to provide a survival benefit without undue toxicity. Schlenk RF, et al. Blood 2019;133:840-851.
[eee] Allogeneic transplant is a reasonable option in patients who experience failure after re-induction with certain regimens (eg, intermediate- or high-dose cytarabine), and have identified donors available to start conditioning within 4–6 weeks from start of induction therapy. Patients without an identified donor would most likely need some additional therapy as a bridge to transplant. HCT may be appropriate for patients with a low level of residual disease post-induction (eg, patients with prior MDS who reverted back to MDS with <10% blasts). It is preferred that this approach be given in the context of a clinical trial. For patients with residual disease after 1 cycle of induction chemotherapy who would not tolerate another intensive salvage, consider a venetoclax-based regimen.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AML-7



[rr] This regimen may be continued for patients who demonstrate 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; Wei A, et al. Haematologica 2017; Abstract S473; DiNardo CD, Blood 2019;133:7-17; DiNardo CD, et al. N Engl J Med 2020;383:617-629.
[ss] Patients who have 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.
[tt] Wei AH, et al. J Clin Oncol 2019;37:1277-1284.
[ww] 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). Cortes JE, et al. Blood 2016;128:99-99.
[xx] Amadori S, et al. J Clin Oncol 2016;34:972-979.
[aaa] DiNardo CD, et al. Blood 2017;130:725; DiNardo CD, et al. Blood 2017;130:639; Roboz GJ, et al. Blood 2020;135:463-471.
[ccc] Stein EM, et al. Blood 2015;126:323; DiNardo CD, et al. Blood 2017;130:639.
[ddd] Ohanian M, et al. Am J Hematol 2018;93:1136-1141.
[hhh] Patients who are deemed as candidates for HCT and who have an available donor should be transplanted in first remission.
[kkk] Response to treatment with enasidenib or ivosidenib may take 3–5 months.
[lll] Enasidenib or ivosidenib increases the risk for differentiation syndrome and hyperleukocytosis that may require treatment with hydroxyurea and steroids.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

AML-9

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Sekeres MA et al., 2020 [7].

American Society of Hematology (ASH)

American Society of Hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults

Zielsetzung/Fragestellung

These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about management of AML in older adults.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft teilweise zu (systematische Suchstrategie dargestellt; Cochrane Collaboration's risk-of-bias tool soll zur Stuidenbewertung herangezogen worden sein, Ergebnisse diesbezüglich sind aber nicht ausreichend dargestellt; Evidenzbewertung mit Grade ist dargestellt);
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft teilweise zu (es hat ein Panel-Meeting stattgefunden, formale Konsenusrozesse werden aber nicht beschrieben; ein externes Begutachtungsverfahren hat stattgefunden)
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Verbindung zu Evidenz nur über Hintergrundtext indirekt zu erkennen);
- Regelmäßige Überprüfung der Aktualität gesichert – trifft teilweise zu ("After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions").

Recherche/Suchzeitraum:

- searches were updated on 24 May 2019
- Medline, Embase

LoE/GoR

- The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the guideline panel recommends" are used for strong recommendations, and "the guideline panel suggests" for conditional recommendations.

Recommendations

Recommendation 1. For older adults with newly diagnosed AML who are candidates for such therapy, the American Society of Hematology (ASH) guideline panel recommends offering antileukemic therapy over best supportive care (strong recommendation based on moderate certainty in the evidence of effects +++).

- A total of 15 studies were included in the evidence syntheses regarding benefits and harms for identified health outcomes.[62,64,85-97]

- Given the challenges in randomizing patients to intensive or less-intensive treatments, most of the included studies were observational.[62,85,86,93,95,96] Two were randomized clinical trials (RCTs).[94,96] One study was an RCT[64] in which patients were preselected by their physicians as appropriate candidates for either intensive therapy, less-intensive therapy, or best supportive care and then randomized to their preselected conventional-care treatment or to azacitidine.
- Eleven studies, all classified as observational, addressed the comparison between intensive antileukemic therapy and best supportive care.[62,64,85-93] Ten studies addressed the comparison between less-intensive antileukemic therapy and best supportive care.[62,64,88-90,92,94-97]

Recommendation 3. For older adults with AML who achieve remission after at least a single cycle of intensive antileukemic therapy and who are not candidates for allogeneic hematopoietic stem cell transplantation (HSCT; allo-HSCT), the ASH guideline panel suggests postremission therapy over no additional therapy (conditional recommendation based on low certainty in the evidence of effects ++).

- Remarks: In some settings, patients may receive 2 cycles of intensive antileukemic therapy even if they achieve remission after the first one. In those settings, the panel considered the second cycle of intensive therapy to be postremission therapy.
- Twelve studies addressing different postremission therapy strategies informed this question.
- In 2 studies, researchers compared no postremission therapy to 1 cycle of consolidation therapy (evidence profile 1). One was a RCT in which researchers reported mortality and time torecurrence in 297 participants,[138] and another was an observational study in which researchers reported time to recurrence in 132 participants.[139]
- In 1 observational study, researchers reported the outcomes for 48 patients who received 1 cycle of consolidation plus 1 cycle of postremission therapy with gemtuzumab ozogamicin or 1 cycle of consolidation therapy plus autologous HSCT (auto-HSCT; evidence profile 2).[140]
- In 4 studies, 3 RCTs with 258 participants[70,141,142] and 1 observational study with 126 patients,[106] researchers compared mortality and time to recurrence between patients who received 2 cycles of consolidation therapy and patients who received 1 cycle(evidence profile 3).
- In 1 RCT, researchers compared the outcomes of 6 cycles of ambulatory postremission therapy vs those of 1 cycle of consolidation therapy in 164 participants (evidence profile 4).[66]
- In 1 RCT, researchers compared 3 cycles of postremission therapy with those of 2 cycles of consolidation plus auto-HSCT in 25 participants (evidence profile 5).[143]
- In 1 RCT, researchers compared 3 cycles of postremission therapy with gemtuzumab ozogamicin vs no therapy in 232 participants (evidence profile 6).[144]
- In 2 observational studies, researchers compared auto-HSCT vs no therapy in 503 patients (evidence profile 7).[145,146]

Recommendation 4a. For older adults with AML considered appropriate for antileukemic therapy but not for intensive antileukemic therapy, the ASH guideline panel suggests using either of the options when choosing between hypomethylating-agent monotherapy and

low-dose-cytarabine monotherapy (conditional recommendation based on moderate certainty in the evidence of effects +++).

- 3 RCTs provided evidence for the comparison between azacytidine monotherapy and low-dose cytarabine monotherapy,[64,101,130] and 1 RCT[156] and 1 observational study[155] compared the effects of low-dose cytarabine monotherapy with the effects of decitabine monotherapy. In addition, there was 1 observational study comparing the effects of low-dose cytarabine monotherapy and either 1 of the hypomethylating agents.[96]
- Within the category of hypomethylating agents, 3 observational studies compared the effects of decitabine monotherapy and azacitidine monotherapy.[153,159,162]
- We did not find any randomized data comparing 5-day and 10-day decitabine monotherapy that met inclusion criteria (though 1 study of 71 patients[169] undergoing Bayesian randomization to 5-day or 10-day decitabine monotherapy showed similar overall response rates and OS) and thus were not able to make formal recommendations about these 2 decitabine regimens.
- Similarly, although there were some data suggesting superiority of azacitidine to decitabine, we did not find a compelling difference between the 2 drugs, and the panel does not recommend 1 drug over the other.

Recommendation 4b. For older adults with AML considered appropriate for antileukemic therapy (such as hypomethylating agents [azacitidine and decitabine] or low-dose cytarabine) but not for intensive antileukemic therapy, the ASH guideline panel suggests using monotherapy with 1 of these drugs over a combination of 1 of these drugs with other agents (conditional recommendation based on low certainty in the evidence of effects ++).

- Remarks: For patients treated with combination therapy, the agents for which there is evidence of effectiveness are low-dose cytarabine in combination with glasdegib, based on a small randomized trial, and hypomethylating agents or low-dose cytarabine in combination with venetoclax, based on promising data from phase 2 trials. These recommendations may change (favoring combination therapies over monotherapy) with upcoming reporting of results from randomized trials.
- 6 RCTs compared low-dose cytarabine monotherapy with low-dose cytarabine combination,[148-150,152,154,161]
- 3 RCTs compared the effects of azacitidine monotherapy with those of azacitidine combinations[151,157,158] and 1 RCT compared the effects of decitabine monotherapy with a decitabine combination.[160]
- In addition, 1 observational study compared the effects of low-dose cytarabine combination and hypomethylating agents.[122]

Recommendation 5. For older adults with AML who achieve a response after receiving less-intensive therapy, the ASH guideline panel suggests continuing therapy indefinitely until progression or unacceptable toxicity over stopping therapy (conditional recommendation based on very low certainty in the evidence of effects +).

- We did not find any comparative studies addressing this question in older adults with AML. The panel used 2 sources of indirect evidence to inform the judgments regarding desirable and undesirable effects. First, 2 RCTs compared the outcomes for patients who received less-intensive antileukemic therapy with those for patients who received conventional care, including best supportive care.[64,101] In both studies, patients received at least 6 cycles of azacitidine for 7 consecutive days (each cycle was 28 days). The researchers do not describe how many patients achieved a response after a specific number of cycles (and thus, we could not determine how many cycles beyond response

patients received) and report only that, overall, 27.8% of patients achieved a hematologic response (CR or CRi) in 1 study[64] and 18% did in the other study.[101]

- Second, we conducted a survey among the panel members to systematically collect their experiences. The survey was based on the panelists' best recollection of experiences because it was not feasible to collect information from clinical records given the timelines for the development of these guidelines.

Recommendation 6. For older adults with AML who are no longer receiving antileukemic therapy (including those receiving end-of-life care or hospice care), the ASH guideline panel suggests having red blood cell (RBC) transfusions be available over not having transfusions be available (conditional recommendation based on very low certainty in the evidence of effects). There may be rare instances where platelet transfusions may be of benefit in the event of bleeding, but there are even less data to support this practice and it is anticipated that platelet transfusions will have little or no role in end of- life or hospice care (+).

- We did not find any comparative studies addressing this question in older adults with AML. The panel decided to use indirect evidence, obtained from 2 published systematic reviews of the literature, neither of which was focused on older adults with AML, to inform this question.[163,164] The first systematic review focused on the effects of RBC transfusions for patients receiving palliative care.[163] The mean age of patients included in the studies ranged from 64 through 70 years, and it was specified (only in some of the studies) that the patients had terminal malignancies or advanced nonmalignant disease.
- The second systematic review focused on the effects of transfusions, both RBC and platelets, in palliative-care patients with cancer.[164] The authors described the outcomes for patients of all ages, with hematological malignancies and solid tumors. The outcomes of interest were measured in different ways across studies and therefore could only be summarized narratively. For most of these outcomes, there are only noncomparative data, given that most of the studies included in both systematic reviews were case series.

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Alberta Health Services (AHS), 2019 [1].

Acute Myeloid Leukemia

Leitlinienorganisation/Fragestellung

To identify the management options for acute myeloid leukemias in adults including chemotherapy, hematopoietic stem cell transplantation, and palliation.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Leitliniengruppe: Alberta Provincial Hematology Tumour Team (hematologists, medical oncologists, radiation oncologists, nurses, hematopathologists, and pharmacists)
- Systematische Literaturrecherche auf Basis von PICO Fragen (mehrere Datenbanken)
- Formulierung der Empfehlung auf Grundlage der Evidenz
- Bei Einigkeit über Empfehlung informeller Konsensusprozess, ansonsten auch formeller Konsensuprozess möglich (z.B. Delphi)
- Interessenkonflikte: no direct industry involvement in the development or dissemination of guidelines. Some members of the Provincial Tumour Teams are involved in research funded by industry or have other such potential conflicts of interest. However, all GWG members are asked to declare and discuss conflicts of interest prior to commencement of guideline development.

Recherche/Suchzeitraum:

- The 2015, 2017, 2018 and 2019 updates involved review of the Pubmed and Medline

LoE / GoR

- Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations.
- no use of formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations including:
  - Description of all known benefits and possible harms
  - Evidence summary, quality/quantity/consistency of discussion
  - Discussion of the role of clinical experience, theory, values and opinions in developing the recommendation

Recommendation

Supportive care:

- Red blood cell transfusions for symptomatic anemia.
- Platelets should be transfused at a threshold of 10 x 109/L if there is no evidence of bleeding or to keep a platelet level of around 50 x 109/L if there is active bleeding.
- Tumor lysis prophylaxis should be initiated in all patients.
- Antifungal prophylaxis should be considered during all phases of chemotherapy.

- Antifungal prophylaxis should be considered during all phases of chemotherapy depending on local incidence of invasive fungal infections[29,98.]
- In a large randomized trial in AML patients receiving induction and post-remission chemotherapy, posaconazole prophylaxis was associated with a lower incidence of invasive Aspergillosis and lower mortality compared with fluconazole or itraconazole[100].

- Therapy of febrile neutropenia should include empiric broad spectrum antibiotics according to IDSA guideline. [101]
- The use of growth factor support should be individualized and should be considered in those with documented life-threatening infections. Recent use of G-CSF can increase the blast count in a bone marrow specimen obtained to determine remission status, however immunophentoyping may be useful in this situation if the leukemic cells are known to have an abnormal phenotype. Pegylated growth factors have not been studied in this setting.
- Steroid eye drops are recommended during the administration of intermediate to high dose cytarabine. These patients should also be screened for cerebellar toxicities before each dose of cytarabine.

<u>Transplant eligible patients</u>

- In transplant eligible patients treatment consists of induction and consolidation chemotherapy along with a FLT3 inhibitor in FLT3 positive cases
  - Induction: Chemotherapy should consist of standard-dose cytarabine with an anthracycline, so called 7&3 chemotherapy (see appendix A for regimens). Studies looking at higher doses of cytarabine in induction have not shown an increased CR rate but have demonstrated an increased treatment related mortality[103-105]. At count recovery or about day 28-35 from the start of chemotherapy a bone marrow aspirate should be done to determine remission status. The likelihood of establishing a CR with one cycle of induction chemotherapy varies amongst prognostic groups but overall is in the order of 60-70%. Consider repeating cytogenetic analysis if initially abnormal as part of the remission documentation[29].Other regimens such as FLAG (fludarabine + high-dose cytarabine + G-CSF) or NOVE (mitoxantrone + etoposide) may need to be considered in the case of significant left ventricular dysfunction.
  - Re-induction: If CR is not achieved after one cycle of induction chemotherapy another attempt is appropriate.
  - Consolidation can consist of further cycles of chemotherapy alone or in association with a hematopoietic stem cell transplant depending on risk of relapse.[103,104]

    i. Good risk – chemotherapy alone.[106-111]

    ii. Intermediate risk – consider transplantation. [26,107,109,112-116]

    iii. High risk – transplantation.
- FLT3 Mutation Positive Patients: If not enrolled on a clinical trial with a FLT3 inhibitor, midostaurin should be added for these patients on day 8 of each induction and consolidation treatment cycle[49]
- Relapse:
  - Re-induction: An attempt at achieving a CR should be attempted. If the remission was greater than one year 7&3 chemotherapy can be used again. Otherwise other regimens such as FLAG-Ida, NOVE, NOVE-HiDAC, or HiDAC are appropriate. Participation in a clinical trial is encouraged.

  - Hematopoietic stem cell transplantation: If a stem cell transplant was not done in first CR it should be undertaken once a second CR has been achieved. The ideal donor would be an allogeneic matched related or unrelated donor, or if necessary a related haploidentical donor or cord blood unit.

- Palliation
  - If comorbid conditions affect the ability to proceed with optimal aggressive therapy, treatment with either low-dose cytarabine (LDAC) or azacitidine is recommended as these have been shown to increase overall survival compared to supportive care alone[90,91]. Azacitidine is recommended for patients with 20-30% marrow blasts with dysplasia and for patients with adverse risk cytogenetics, based on two Phase III randomized trials[92,93]. For patients with >30% blasts and intermediate risk cytogenetics, LDAC and azacitidine have similar survivals [94]; LDAC has the advantage of lower cost and the potential for at-home administration.
  - The recommended dose of azacitidine is 75 mg/m^2/day subcutaneously for 7 days, every 28 days, for at least six cycles[95]. This is also an appropriate approach in the setting of primary induction failure not eligible for further intensive therapy, or relapse, particularly after allogeneic stem cell transplantation. The most commonly used dosing for LDAC is 20 mg subcutaneously twice daily for 10 days[90], repeated every 4-5 weeks; 40 mg once daily may be used for home care administration. At least 4 cycles should be used, unless there is clear evidence of progression earlier. In patients not responding to LDAC, azacitidine may be utilized; however, LDAC does not appear to be effective in azacitidine failures.
  - For patients not able or willing to receive these treatments, or not responding to these, supportive care alone is appropriate, with hydroxyurea to control circulating blast counts.

<u>Transplant ineligible patients</u>

- In transplant ineligible patients treatment options consist of palliation, low dose cytarabine, azacitidine or induction chemotherapy, depending on performance status and risk stratification. Strong consideration should be given to enrollment into a clinical trial.
  - Due to the poor outcomes in this group, clinical trials are particularly important. However, if none are available, azacitidine would be appropriate therapy in older patients with high-risk cytogenetics who are not considered candidates for allogeneic HSCT. In other elderly non-fit patients, low-dose cytarabine would also be appropriate.
  - Induction: In patients with an ECOG performance status of 2 or less and no prohibitive comorbid conditions, standard 7&3 induction chemotherapy is appropriate[127], particularly in patients with core-binding factor leukemias. If consideration is being given to consolidation therapy or re-induction in the case of primary induction failure, a bone marrow aspirate should be performed to document remission. If no further therapy is planned this can be omitted.
  - Consolidation: Consolidation chemotherapy in this group of patients is controversial. There is evidence to suggest that low-dose, prolonged ambulatory treatment should be preferred to intensive chemotherapy[123]; however intermediate dose cytarabine can be considered if the patient maintains a good performance status, normal renal function, and has a good or normal karyotype. Consolidation has not been shown to prolong survival in patients with high risk karyotypes. There is limited retrospective data which suggests azacitidine may be appropriate in this setting, although prior cytotoxic therapy was associated with a decreased marrow response rate, azacitidine

treatment still prolonged overall survival[128]. LDAC may also be considered in patients in CR who are not suitable candidates for further intensive chemotherapy.

- Relapse: In this age group, if acute leukemia recurs palliation with best supportive care or azacitidine is indicated if there are no available clinical trials.

CHEMOTHERAPY REGIMENS

7&3

- Cytarabine 200 mg/m^2/d continuous infusion days 1-7(consider 100 mg/m^2/d if age >60)
- Idarubicin 12 mg/m^2/d or daunorubicin 60 mg/m^2/d days 1-3

NOVE

- Mitoxantrone 10 mg/m^2/d days 1-5
- Etoposide 100 mg/m^2/d days 1-5

NOVE-HiDAC

- Mitoxantrone 10 mg/m^2/d days 1-5
- Etoposide 100 mg/m^2/d days 1-5
- Cytarabine 1.5 g/m2(1.0 g/m^2 if >age 60) every 12 hours on days 6-7

FLAG-Ida

- Fludarabine 30 mg/m^2/d days 1-5
- Cytarabine 2 g/m^2/d days 1-5
- Idarubicin 10 mg/m^2/d days 1-3
- G-CSF 300 µm s/c od starting day 7

HiDAC

- Cytarabine 3 g/m^2 every 12 hours on days 1, 3 and 5

Intermediate Dose Cytarabine

- Cytarabine 1 g/m^2 every 12 hours on days 1, 3 and 5

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews Reviews (Issue 2 of 12, February 2021) am 23.02.2021

#	Suchfrage
1	[mh “Leukemia, myeloid, acute”]
2	acute:ti,ab,kw
3	leu*mia*:ti,ab,kw
4	(myeloid* OR myelogen* OR myeloblast* OR myelocyt*):ti,ab,kw
5	AML:ti,ab,kw
6	#1 OR (#2 AND #3 AND #4) OR #5
7	#6 with Cochrane Library publication date from Feb 2016 to present

Systematic Reviews in Medline (PubMed) am 23.02.2021

#	Suchfrage
1	Leukemia, myeloid, acute[mh]
2	Acute[tiab]
3	leukemia*[tiab] OR leukaemia*[tiab] OR leucemia*[tiab] OR leucaemia*[tiab]
4	myeloid*[tiab] OR myelogen*[tiab] OR myeloblast*[tiab] OR myelocyt*[tiab]
5	AML[tiab]
6	#1 OR (#2 AND #3 AND #4) OR #5
7	(#6) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR

	treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
8	((#7) AND ("2016/02/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))

Leitlinien in Medline (PubMed) am 23.02.2021

#	Suchfrage
1	Leukemia, myeloid, acute[mh]
2	Acute[tiab]
3	(Leukemia*[tiab] OR leukaemia*[tiab] OR Leucemia*[tiab] OR leucaemia*[tiab])
4	(Myeloid*[tiab] OR Myelogen*[tiab] OR Myeloblast*[tiab] OR Myelocyt*[tiab])
5	AML[tiab]
6	(#1 OR (#2 AND #3 AND #4) OR #5)
7	((#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti]))
8	(((#7) AND ("2016/02/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]))

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