



**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-347 Blinatumomab

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

Blinatumomab

[zur Behandlung der akuten lymphatischen Leukämie, Philadelphia-Chromosom-negativ, in Remission, MRD-positiv]

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.

- Allogene Stammzelltransplantation
- Strahlentherapie (prophylaktische Schädelbestrahlung)

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:

- Tisagenlecleucel – Beschluss vom 15. Februar 2024
- Brexucabtagen Autoleucel – Beschluss vom 16. März 2023
- Ponatinib – Beschluss vom 20. November 2020
- Blinatumomab (Philadelphia-Chromosom-negativ, MRD-positiv) – Beschluss vom 15. August 2019
- Inotuzumab Ozogamicin – Beschluss vom 18. Januar 2018
- Blinatumomab (Philadelphia-Chromosom-negativ) – Beschluss vom 7. Dezember 2017

Richtlinie Methoden Krankenhausbehandlung:

Ausgeschlossene Methoden § 4:

Durchführung klinischer Studien hiervon unberührt

- Autologe Stammzelltransplantation bei akuter lymphatischer Leukämie (ALL) bei Erwachsenen

in klinischen Studien von der Erbringung zu Lasten der gesetzlichen Krankenkassen ausgeschlossen:

- Allogene Stammzelltransplantation mit alleiniger CD34-Selektion oder anderen Formen

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

Blinatumomab

[zur Behandlung der akuten lymphatischen Leukämie, Philadelphia-Chromosom-negativ, in Remission, MRD-positiv]

Kriterien gemäß 5. Kapitel § 6 Verfo

der In-vitro-Aufbereitung des Transplantats, wenn sie allein auf eine maximale, unspezifische T-Zell-Depletion abzielen, bei erwachsenen Patientinnen und Patienten mit akuter lymphatischer Leukämie (ALL) oder akuter myeloischer Leukämie (AML).

- Unberührt von diesem Ausschluss ist die Versorgung von erwachsenen Patientinnen und Patienten mit in-vitro-aufbereiteten Transplantaten bei folgenden Spendertypen:
 - Transplantate haploidentischer Spenderinnen oder Spender
 - Transplantate von Spenderinnen oder Spendern (verwandt oder nicht verwandt) mit einem Mismatch von mindestens 2 HLA-Merkmalen.
- Nicht Gegenstand der Bewertung war die Aufbereitung von Stammzellen zum Stammzellboost

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:

II. Zugelassene Arzneimittel im Anwendungsgebiet

Blinatumomab L01FX07 Blincyto	BLINCYTO wird als Monotherapie angewendet zur Behandlung von Erwachsenen mit Philadelphia-Chromosom-negativer, CD19- positiver B-Vorläufer-ALL in erster oder zweiter kompletter Remission mit einer minimalen Resterkrankung (minimal residual disease, MRD) von mindestens 0,1 %.
Chemotherapien	
Asparaginase L01XX02 Asparaginase E 5000 medac	Asparaginase 5000 (10000) E medac ist als Bestandteil einer antineoplastischen Kombinationstherapie der akuten lymphatischen Leukämie (ALL) im Kindes- und Erwachsenenalter [...] angezeigt.
Amsacrin L01XX01 Amsydil	Amsidyl wird angewendet zur Induktions- und Erhaltungstherapie der akuten myeloischen Leukämie und akuten lymphatischen Leukämie bei Erwachsenen nach Versagen konventioneller Therapien.
Crisantaspase L01XX02 Erwinase	Erwinase wird als Bestandteil einer krebshemmenden Kombinationstherapie bei akuter lymphatischer Leukämie (ALL) im Kindes- und Erwachsenenalter angewendet, hauptsächlich bei Patienten, die überempfindlich auf L-Asparaginase aus Escherichia coli, entweder nativ oder pegyliert (Pegaspargase), reagieren.
Cyclophosphamid L01AA01 Endoxan	Cyclophosphamid ist ein Zytostatikum und in Kombination mit weiteren antineoplastisch wirksamen Arzneimitteln bei der Chemotherapie folgender Tumoren angezeigt: – Remissionsinduktion und Konsolidierungstherapie bei akuter lymphatischer Leukämie
Cytarabin L01BC01 ARA-Cell	Das Arzneimittel wird in Kombination mit anderen Zytostatika in konventionellen Dosen eingesetzt zur: - Remissionseinleitung und Konsolidierung akuter lymphatischer Leukämien
Daunorubicin L01DB02 Daunoblastin	<u>Erwachsene</u> Remissionsinduktion bei akuten lymphoblastischen bzw. lymphatischen Leukämien (ALL) [...]. Die Anwendung erfolgt in Kombination mit anderen Zytostatika.
Doxorubicin L01DB01 Adrimedac	Induktions- und Konsolidierungstherapie bei akuter lymphatischer Leukämie. Doxorubicin wird in Kombinationschemotherapieschemata häufig zusammen mit anderen Zytostatika angewendet.
Mercaptopurin L01BB02 Xaluprine	Zur Behandlung von akuter lymphoblastischer Leukämie (ALL) bei Erwachsenen, Jugendlichen und Kindern.

II. Zugelassene Arzneimittel im Anwendungsgebiet

Methotrexat L01BA01 Methotrexat-GRY	Methotrexat in niedriger Dosierung wird angewendet zur Behandlung akuter lymphatischer Leukämien im Kindes- und Erwachsenenalter im Rahmen komplexer Therapieprotokolle in Kombination mit anderen zytostatischen Arzneimitteln zur remissionserhaltenden Therapie (bei systemischer Anwendung [...]).
Pegaspargase L01XX24 Oncaspar	Oncaspar® ist als Bestandteil einer antineoplastischen Kombinationstherapie bei akuter lymphatischer Leukämie (ALL) bei Kindern und Jugendlichen ab der Geburt bis zum Alter von 18 Jahren und bei Erwachsenen angezeigt.
Tioguanin L01BB03 Thioguanin-Aspen	Konsolidierungs-/Intensivierungsphase der Behandlung der akuten lymphatischen Leukämie (ALL).
Vincristin L01CA02 Vincristinsulfat-TEVA	Vincristinsulfat-TEVA® 1 mg/ml Injektionslösung wird entweder allein oder in Verbindung mit anderen Mitteln zur Krebstherapie angewendet zur Behandlung von: – akuter lymphatischer Leukämie
Vindesin L01CA03 Eldisine	Kombinationschemotherapie: - Remissionseinleitung und Konsolidierung bei akuter lymphatischer Leukämie
Glucocorticoide	
Dexamethason H02AB02 Dexamethason TAD	Behandlung von [...] akuter lymphatischer Leukämie [...] in Kombination mit anderen Arzneimitteln.
Prednison H02AB07 Prednison acis	Prednison acis wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen. Hämatologie/Onkologie: akute lymphoblastische Leukämie
Prednisolon H02AB06 Prednisolon acis	Prednisolon acis wird angewendet bei Erwachsenen, Kindern aller Altersgruppen und Jugendlichen. Hämatologie/Onkologie: akute lymphoblastische Leukämie
Monoklonale Antikörper	

II. Zugelassene Arzneimittel im Anwendungsgebiet

Inotuzumab Ozogamicin L01XC26 Besponsa	BESPONSA ist indiziert als Monotherapie für die Behandlung von Erwachsenen mit rezidivierender oder refraktärer CD22-positiver <u>B-Vorläufer-ALL</u> (akuter lymphatischer Leukämie).
CAR-T-Zellen	
Brexucabtagen Autoleucl L01XL06 Tecartus	Tecartus wird angewendet zur Behandlung von erwachsenen Patienten ab einem Alter von 26 Jahren mit rezidivierender oder refraktärer B-Zell-Vorläufer akuter lymphatischer Leukämie (ALL).
Tisagenlecleucel L01XL04 Kymriah	Kymriah wird angewendet zur Behandlung von: <ul style="list-style-type: none"> • Kindern, Jugendlichen und jungen erwachsenen Patienten im Alter bis einschließlich 25 Jahren mit refraktärer oder rezidivierender (Rezidiv nach Transplantation oder zweites oder späteres Rezidiv) akuter lymphatischer B-Zell-Leukämie (ALL).
Obecabtagen Autoleucl L01XL12 Aucatzyl ¹	Aucatzyl wird angewendet zur Behandlung von erwachsenen Patienten ab 26 Jahren mit rezidivierender oder refraktärer (r/r) B-lymphoblastischer Leukämie (B ALL).

Quellen: AMIce-Datenbank, Fachinformationen

¹ nicht auf dem deutschen Markt verfügbar, Stand Dezember 2025 (Zulassung EMA am 17. Juli 2025)

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

**Vorgang: 2025-B-347 (Beratung nach § 35a SGB V)
Blinatumomab**

Auftrag von: Abt. AM
Bearbeitet von: Abt. FB Med
Datum: 14. Januar 2026

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Abkürzungsverzeichnis

ALL	Acute Lymphoblastic Leukemia
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
AYA	Adolescent and young adult
CMR	Complete molecular response
COG	Children's Oncology Group
CR	Complete remission
DFCI	Dana-Farber Cancer Institute
DFS	Disease-free survival
ECRI	Emergency Care Research Institute
EFS	Event-free survival
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GvHD	Graft-versus-Host-Reaktion
HR	Hazard Ratio
HSCT	Hematopoietic stem cell transplantation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MRD	Measurable (minimal) residual disease
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NRSI	Non-randomized studies of interventions
OR	Odds Ratio
ORR	Overall response rate
OS	Overall survival
PFS	progression-free survival
Ph+	Philadelphia Chromosome–Positive
PR	Partial response
R/R	Relapsed/refractory
RR	Relatives Risiko
SAE	Serious adverse events

SCT	stem cell transplantation
SIGN	Scottish Intercollegiate Guidelines Network
SoC	standard of care
TKIs	Role of Tyrosine Kinase Inhibitors
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Erwachsene mit CD19-positiver B-Zell-Vorläufer ALL

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 lymphatische Leukämie* 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 17.12.2025 abgeschlossen. 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 703 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 vier Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews im AWG identifiziert.

3.2 Systematische Reviews

Jamil A et al., 2025 [2].

Impact of Minimal Residual Diseases Status and Depth of Response on Survival Outcomes in Blinatumomab-Treated Acute Lymphoblastic Leukemia - A Systematic Review and Meta-Analysis

Fragestellung

This review, therefore, aims to summarize evidence from both RCTs and single-arm studies on the efficacy of blinatumomab in managing B-ALL and thus provide a preliminary comparison to conventional chemotherapy.

Methodik

Population:

- primary population was patients with acute refractory or relapsed ALL

Intervention:

- blinatumomab

Komparator:

- standard chemotherapy

Endpunkte:

- primary outcomes of interest included overall survival (OS), event-free survival (EFS), complete remission rates (CR), minimal residual disease rates (MRD), and safety analysis.

Recherche/Suchzeitraum:

- [...] literature search for all articles published until July 2024.
- The initial search utilized 3 databases: PubMed, CENTRAL, and Science Direct.

Qualitätsbewertung der Studien:

- ROB2

Ergebnisse

Anzahl eingeschlossener Studien:

- [...] 21 studies, of which 3 were randomized controlled trials¹⁷⁻¹⁹ (Hogan et al., 2023; Locatelli et al., 2021; Dobret et al., 2021) and 18 were nonrandomized.^{11,14,20-35}

Charakteristika der Population/Studien:

TABLE 1. Characteristics of the Included Studies

References	Study design	Setting	Study arm	Sample size	Age (median/mean)	Male: female	Ph+, n (%)	Prior HSCT, n (%)	BM blasts before therapy, n (%)	Disease status pretreatment	Dosage	Follow-up period
Locatelli et al ¹⁷	RCT	47 centers in 13 countries	Blinatumomab	54	6 (1-17)	30:24	NR	0	<5%, 54 (100%)	NR	15 µg/m ² /d as a continuous intravenous infusion (IVI) for 4 wk According to the IntReALL HR 2010 protocol	22.4 mo
			Consolidation chemotherapy	54	5 (1-17)	22:32	NR	0	<5%, 51 (96.2%)	NR		
Dombret et al ¹⁸	RCT	101 centers in 21 countries	Blinatumomab (first salvage)	104	45.9 ± 18.0	61:43	NR	29 (27.9)	> 5 to <10%, 4 (3.8)	Primary refractory disease: 27 (26.0)	Consolidation dose 6-week cycle: 4 wk (9 µg/d during week 1 and 28 µg/d weeks 2 to 4), then two weeks with no treatment Maintenance dose (12-wk cycle)- 4 wk of 28 µg/d and then 8 wk of no treatment High-dose chemotherapy	NR
									10 to <50%, 22 (21.2)	First relapse with remission < 12 mo: 54 (51.9)		
				≥ 50%, 78 (75.0)	Untreated second or greater relapse: 2 (1.9)							
					Relapse after allo-HSCT: 21 (20.2)							
			Chemotherapy (first salvage)	63	43.1 ± 1 8.3	32:33	NR	20 (31.7)	> 5 to <10%, 2 (3.2)	Primary refractory disease: 18 (28.6)		
									10 to <50%, 16 (25.4)	First, relapse with remission < 12 mo: 29 (46.0)		
				≥ 50%, 45 (71.4)	Untreated second or greater relapse: 1 (1.6)							
					Relapse after allo-HSCT: 15 (23.8)							
Blinatumomab (second or later salvage)	167	37.7 ± 15.8	104:63	NR	65 (38.9)	> 5 to <10%, 5 (3.0)	Primary refractory disease: 88 (52.7)					
						10 to <50%, 38 (22.8)	First relapse with remission < 12 mo: 22 (13.2)					
	≥ 50%, 123 (73.7)	Untreated second or greater relapse: 30 (18.0)										
		Relapse after allo-HSCT: 25 (15.0)										
Chemotherapy (second or later salvage)	71	39.3 ± 16.2	45:26	NR	26 (36.6)	> 5- <10, 5 (7.0)	Primary refractory disease: 36 (50.7)					
						10% to <50%, 7 (9.9)	First relapse with remission < 12 mo: 8 (11.3)					
	≥ 50%, 59 (83.1)	Untreated second or greater relapse: 15 (21.1)										
		Relapse after allo-HSCT: 12 (16.9)										



Hogan et al ¹⁹	RCT	United States of America, New Zealand, Australia, and Puerto Rico	Blinatumomab	127	11 (7-15)	76:51	0	NR	NR	NR	15 µg/m ² /d for 28 d as a continuous infusion and then a rest period of 1 wk	3.5 y
			Chemotherapy group	128	10 (7-15)	76:52	0	NR	NR	NR	Two intensive chemotherapy blocks, followed by two continuation blocks and then a maintenance block	

Qualität der Studien:

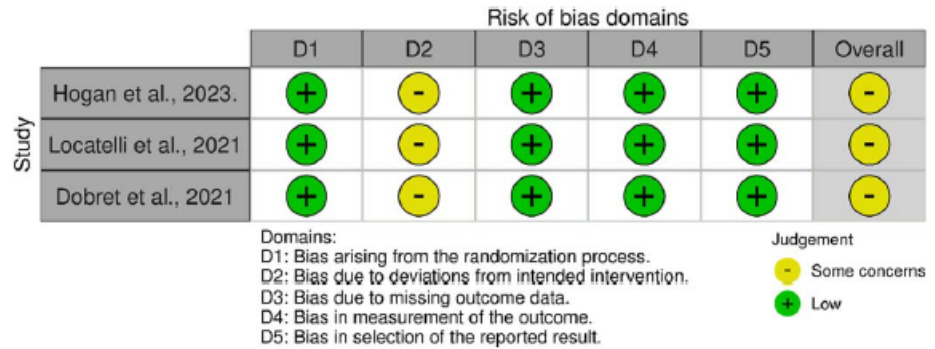


FIGURE 2. A risk of bias summary of the included RCTs. [full color online](#)

- All the studies had overall “some concerns” risk of bias outcomes due to “some concerns” on the bias due to deviations from the intended intervention.

Studienergebnisse:

- Survival: Three RCTs reported the OS of R/RALL patients treated with blinatumomab compared with those treated with chemotherapy. A meta-analysis of the fixed effects results showed that the OS was prolonged in patients treated with blinatumomab compared with those treated with chemotherapy (HR: 0.65; 95% CI: 0.51, 0.82; P=0.0003). There was no heterogeneity across the studies, I²=0% (Fig. 3).

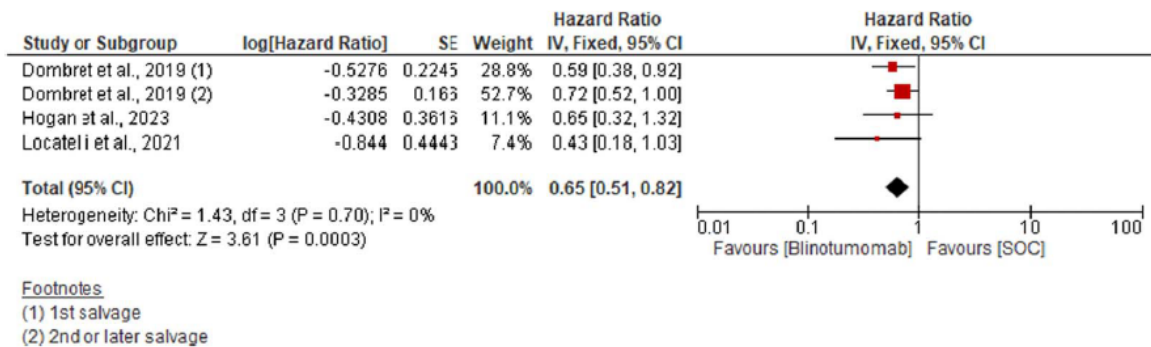


FIGURE 3. A forest plot comparing overall survival between blinatumomab and standard chemotherapy. [full color online](#)

- Disease-Free Survival (DFS): Three RCTs reported the DFS of R/R ALL patients treated with blinatumomab compared with those treated with chemotherapy. A meta-analysis of the fixed effects results showed that the DFS was prolonged in patients treated with blinatumomab compared with those treated with chemotherapy (HR: 0.57; 95% CI: 0.41, 0.80; P=0.001). There was moderate heterogeneity across the studies, I²=52% (Fig. 4).

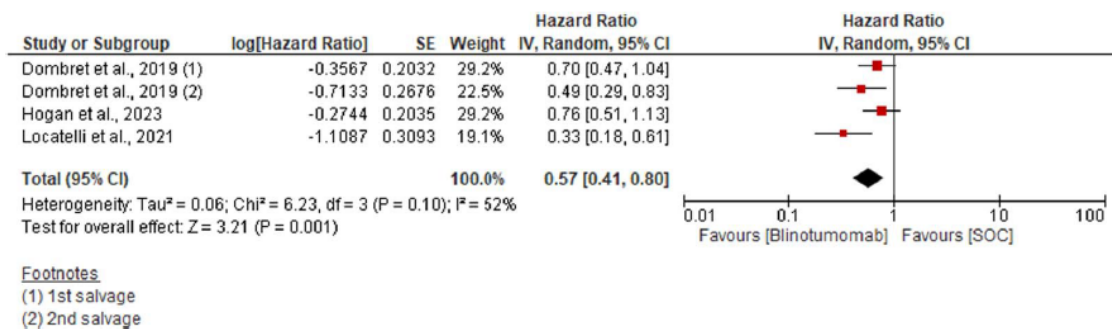
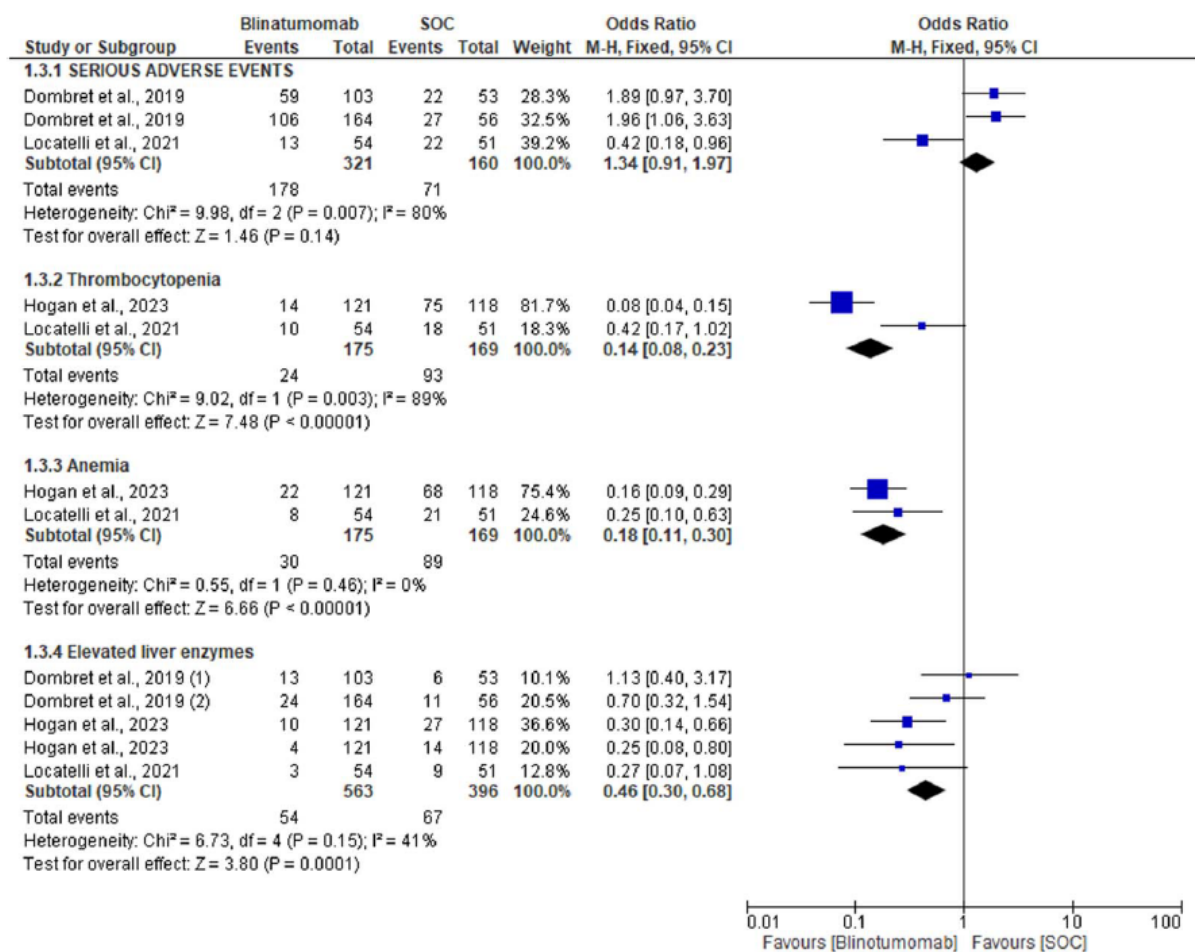


FIGURE 4. A forest plot for disease-free survival between blinatumomab and standard chemotherapy. [full color online](#)

- **Safety Analysis:** To determine blinatumomab's comparative safety and toxicity to standard chemotherapy, we used only the data from the three included RCTs. A pooled analysis of the outcomes showed that the incidence of serious adverse events was not significantly different between the patients treated with blinatumomab and those treated with standard chemotherapy (OR: 1.34; 95% CI: 0.91, 1.97; P= 0.14) (Fig. 7). Furthermore, further analysis of the incidence of thrombocytopenia, anemia, and liver toxicity found that the incidence of these adverse events was lower in the patients treated with blinatumomab (OR: 0.144; 95% CI: 0.08, 0.23; P<0.00001), (OR: 0.18; 95% CI: 0.11, 0.30; P< 0.00001), and (OR: 0.46; 95% CI: 0.30, 0.68; P=0.0001), respectively (Fig. 7).



Footnotes

- (1) ALT
(2) AST

Anmerkung/Fazit der Autoren

The results of our analysis show that blinatumomab has superior efficacy to standard chemotherapy in managing R/R ALL. Furthermore, blinatumomab's safety profile is better than that of conventional chemotherapy. This superior efficacy and low toxicity make blinatumomab an effective alternative in treating R/R ALL. However, only a limited number of RCTs have evaluated the comparative effectiveness of blinatumomab. We, therefore, recommend that further RCTs be conducted to determine the comparative efficacy and enable the analysis of different prognosis factors that influence the effectiveness of blinatumomab.

Kommentare zum Review

- Es wurden ausschließlich die Ergebnisse der RCTs dargestellt.

3.3 Leitlinien

NCCN, 2025 [3,4].

National Comprehensive Cancer Network (NCCN)

Acute Lymphoblastic Leukemia / Version 2.2025 — June 27, 2025

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur aktuellen Therapie für Patienten mit CD19-positiver B-Zell-Vorläufer akuter lymphoblastischer Leukämie (ALL), 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 nicht zu**;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – **trifft teilweise zu**;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – **trifft zu**;
- Regelmäßige Überprüfung der Aktualität gesichert – **trifft zu**.

Recherche/Suchzeitraum:

- PubMed

LoE/GoR

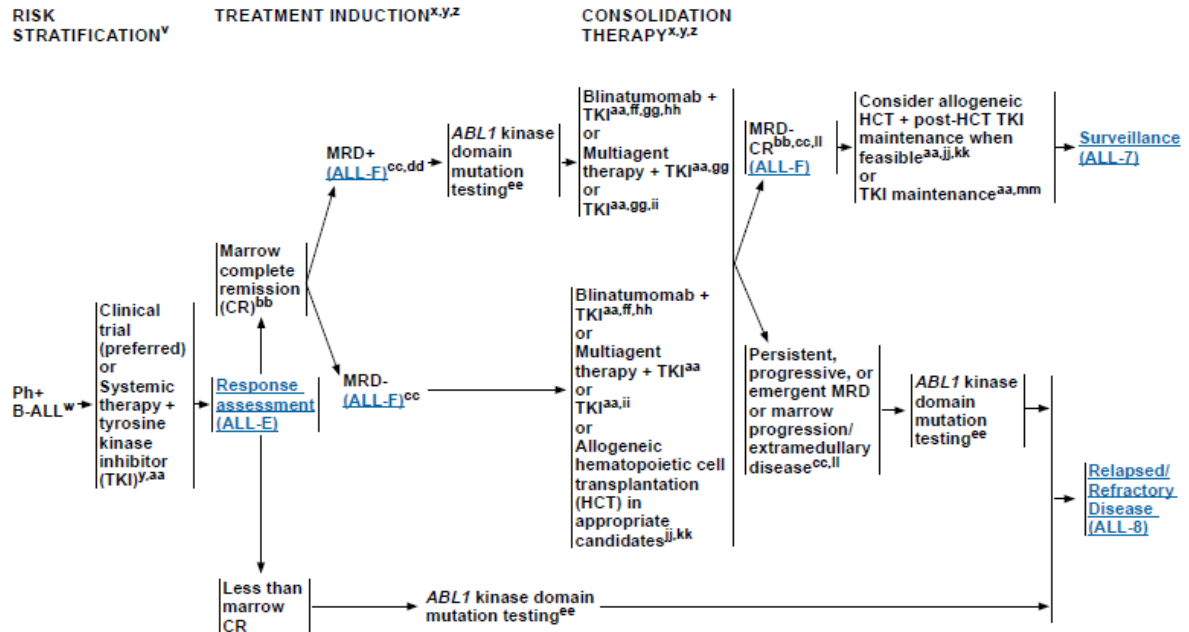
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥ 1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus ($\geq 85\%$ support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence,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



Footnotes on ALL-4A

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

FOOTNOTES FOR Ph+ B-ALL TREATMENT INDUCTION AND CONSOLIDATION THERAPY

^v [Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL \(ALL-2\)](#).

^w It is reasonable to approach the initial treatment of BP-CML with similar strategies to Ph+ ALL, with a goal of proceeding to HCT.

^x TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).

^y ALL treatment regimens include CNS prophylaxis. See [Evaluation and Treatment of Extramedullary Involvement \(ALL-B\)](#).

^z [Principles of Supportive Care \(ALL-C\)](#).

^{aa} [Principles of Systemic Therapy \(ALL-D\)](#).

^{bb} Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted. Assess for myelosuppression secondary to TKI and consider dose reduction.

^{cc} The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in immunoglobulin (Ig) and T-cell receptor (TCR) loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positivity.

^{dd} BCR::ABL1 quantitative RT-PCR (qPCR) positivity may reflect persistence in the myeloid compartment. Where feasible, flow sorting to isolate myeloid versus lymphoid cells for FISH/qPCR studies and/or NGS MRD may help to resolve. Of note, the presence of the Philadelphia chromosome in the myeloid compartment does not necessarily imply a diagnosis of CML with lymphoid blast transformation.

^{ee} See [ALL-D 1 of 27](#) for treatment options based on BCR::ABL1 mutation profile.

^{ff} [Principles of Supportive Care: Toxicity Management \(ALL-C 2 of 8\)](#).

^{gg} Consider using an alternative and more broadly acting TKI. See [Treatment options based on BCR::ABL1 mutation profile \(ALL-D 1 of 27\)](#).

^{hh} Blinatumomab + TKI is preferred in consolidation regardless of MRD status for those who have not previously received blinatumomab.

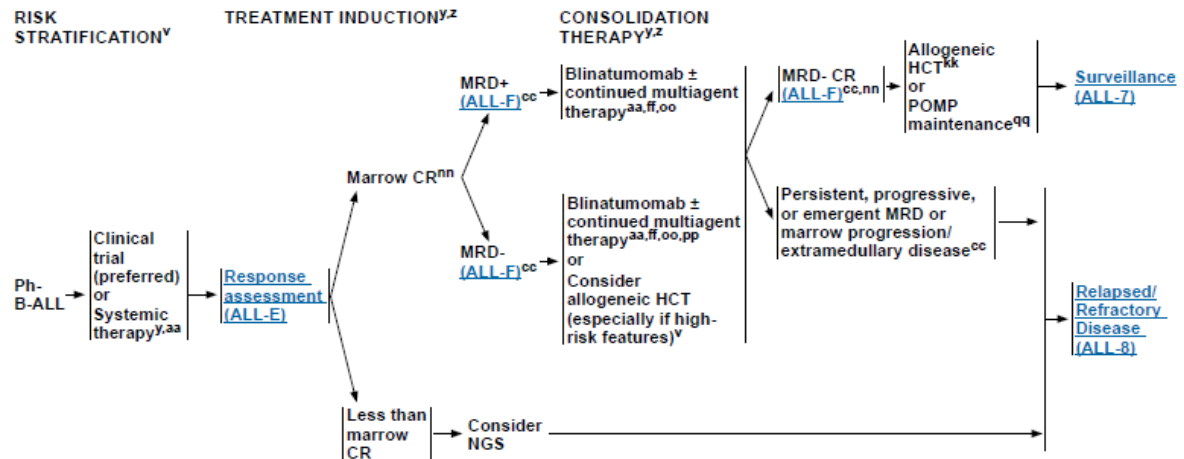
ⁱⁱ TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.

^{ll} Data suggest that for patients aged ≤21 years, particularly for those who achieve MRD negativity, allogeneic HCT may not offer an advantage over chemotherapy + TKI. Schultz KR, et al. J Clin Oncol 2009;27:5175-5181; Schultz KR, et al. Leukemia 2014;28:1407-1471.

^{kk} Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance.

^l Consider sequential MRD monitoring for patients with complete molecular remission (undetectable levels). Increased frequency may be indicated for detectable levels or for those discontinuing TKI.

^{mm} May include other elements of maintenance therapy, such as vincristine, corticosteroids, and IT therapy.



^v Cytogenetic and Molecular Prognostic Risk Stratification for B-ALL (ALL-2).

^y ALL treatment regimens include CNS prophylaxis. See Evaluation and Treatment of Extramedullary Involvement (ALL-B).

^z Principles of Supportive Care (ALL-C).

^{aa} Principles of Systemic Therapy (ALL-D).

^{cc} The preferred method of MRD quantification is an FDA-approved NGS-based assay to detect fusion genes or clonal rearrangements in Ig and TCR loci (does not require patient-specific primers), if available. Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for patients with ALL with MRD positivity.

^{ff} Principles of Supportive Care: Toxicity Management (ALL-C 2 of 8).

^{kk} Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance.

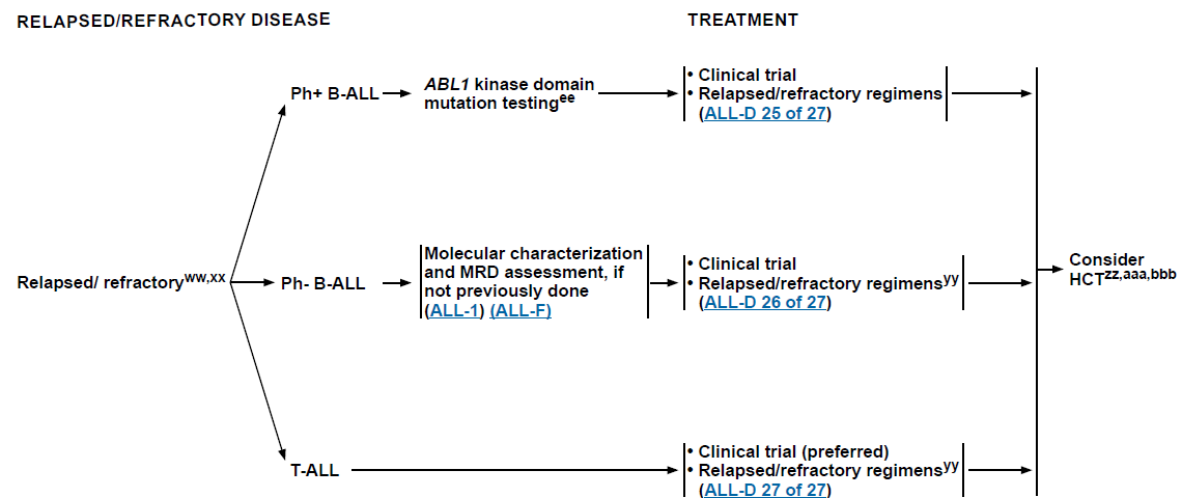
ⁿⁿ Adequate count recovery per protocol is recommended before transitioning to post-remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.

^{oo} Blinatumomab can be considered for consolidation in patients for whom multiagent therapy is contraindicated.

^{pp} Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910.

^{qq} May include other elements of maintenance therapy, such as blinatumomab and IT therapy.

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



^{ee} See ALL-D 1 of 27 for treatment options based on BCR::ABL1 mutation profile.

^{ww} Isolated extramedullary relapse (including CNS and testicular) requires systemic therapy to prevent relapse in marrow. Consider CNS prophylaxis for relapsed/refractory disease. The role of CNS prophylaxis in the setting of cellular therapy is still being studied.

^{xx} NCCN Guidelines for Palliative Care.

^{yy} For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same regimen used at initial diagnosis (for Ph-negative B-ALL, see ALL-D 9 of 27; for T-ALL, see ALL-D 18 of 27).

^{zz} The role of allogeneic HCT following cellular therapy is unclear.

^{aaa} If second remission is achieved prior to HCT and patient has not had a prior HCT, consolidative HCT is recommended.

^{bbb} For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.

PRINCIPLES OF SYSTEMIC THERAPY

GENERAL CONSIDERATIONS

- The ALL Panel considers adolescent and young adult (AYA) to be within the age range of 15–39 years. However, this age range is not a firm reference point because some of the recommended regimens have not been comprehensively tested across all ages. For additional considerations in the care of AYA patients with ALL, see the [NCCN Guidelines for Adolescent and Young Adult \(AYA\) Oncology](#).
- For infection risk, monitoring, and prophylaxis recommendations for immune and targeted therapies, see [INF-A in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#).
- For toxicity management for blinatumomab, inotuzumab ozogamicin, brexucabtagene autoleucl, tisagenlecleucl, and obecabtagene autoleucl, see [Principles of Supportive Care ALL C 2 of 6](#).
- Although there are limited data, the Panel recommends waiting at least 4 weeks from the completion of inotuzumab ozogamicin monotherapy and the start of conditioning therapy for allogeneic HCT to minimize risk of SOS. SOS occurred less frequently when fewer alkylators were used as part of the conditioning regimen. Kantarjian H, et al. *Cancer* 2013;119:2728-2736
- Leucovorin is always used in combination with high-dose methotrexate.
- Mesna is always used in combination with ifosfamide and used in combination with cyclophosphamide as clinically indicated.
- An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. Tbo-filgrastim is also an appropriate substitute for G-CSF.

Mutation Profile Principles

TREATMENT OPTIONS BASED ON BCR::ABL1 MUTATION PROFILE

Therapy	Contraindicated Mutations
Asciminib	A337T, P465S, M244V, or F359V/I/C
Bosutinib	T315I, V299L, G250E, or F317L
Dasatinib	T315I/A, F317L/V/I/C, or V299L
Nilotinib	T315I, Y253H, E255K/V, or F359V/C/I or G250E
Ponatinib	None

- Mutations contraindicated for imatinib are too numerous to include. There are compound mutations that can cause resistance to ponatinib, but those are uncommon following treatment with bosutinib, dasatinib, or nilotinib.
- Nilotinib may be preferred over bosutinib in patients with F317L mutation.
- Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease (PD) on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. *JAMA* 2024;331:1814-1823.

[Continued](#)

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

ALL-D

PRINCIPLES OF SYSTEMIC THERAPY

GENERAL CONSIDERATIONS

- For patients receiving mercaptopurine (6-MP), consider testing for *TPMT* gene polymorphisms, particularly in patients who develop severe neutropenia after starting 6-MP. Testing for both *TPMT* and *NUDT15* variant status should be considered, especially for patients of East Asian descent. Relling MV, et al. *Clin Pharmacol Ther* 2019;105:1095-1105.

Maintenance Principles

- Ph+ B-ALL
 - The optimal duration of TKI maintenance is unknown.
 - ◊ The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy.
 - ◊ TKI should be continued for at least 2 years post-HCT.
- Dose modifications for antimetabolites in maintenance should be consistent with the chosen treatment regimen. It may be necessary to reduce dose/eliminate antimetabolite in the setting of myelosuppression and/or hepatotoxicity.

CNS Prophylaxis Principles

- All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- Refer to specific references/protocols, and/or chemotherapy order templates (where available) for appropriate timing in phases of treatment.

Adults ≥65 Years or Adults with Substantial Comorbidities

- Adults who are ≥65 years benefit from therapy, despite higher treatment-related morbidity and mortality.
- Chronological age is a poor surrogate for fitness of therapy. Patients should be evaluated on an individual basis, including for the following factors: end-organ reserve, end-organ dysfunction, and performance status.
- Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.
- For tools to aid optimal assessment and care of adults ≥65 years with cancer, see the [NCCN Guidelines for Older Adult Oncology](#).
- Dose reduction of pegylated asparaginase (1000 IU/m²), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.^a
- The categorization of regimens as low, moderate, or high intensity is based on two factors: 1) the presence or absence of myelosuppressive cytotoxic agents; and 2) the relative dose intensity of the included agents.
- All regimens should include CNS prophylaxis, antimicrobial prophylaxis, and growth factor support.
- For appropriate fit individuals achieving remission, consideration of allogeneic HCT may be appropriate.

^a Patel AA, Heng J, Dworkin E, et al. Efficacy and tolerability of a modified pediatric-inspired intensive regimen for acute lymphoblastic leukemia in older adults. *EJHaem* 2021;2:413-420.

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

ALL-D

**PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL INDUCTION REGIMENS^b**

AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
<p>Preferred</p> <ul style="list-style-type: none"> • Clinical trial <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • TKI^{c,d} in combination with: <ul style="list-style-type: none"> ▶ Blinatumomab^{e,1-3} ▶ HyperCVAD⁴⁻⁸ <p>Useful in certain circumstances</p> <ul style="list-style-type: none"> • TKI^{c,d} in combination with: <ul style="list-style-type: none"> ▶ Corticosteroid^{9,10} ▶ Vincristine + dexamethasone¹¹ 	<p>Preferred</p> <ul style="list-style-type: none"> • Clinical trial <p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Low intensity <ul style="list-style-type: none"> ▶ TKI^{c,d} in combination with: <ul style="list-style-type: none"> ◊ Blinatumomab^{e,1-3} ◊ Corticosteroid^{f,9,10,12-14} ◊ Vincristine + dexamethasone¹¹ • Moderate intensity <ul style="list-style-type: none"> ▶ TKI^{c,d} + mini-hyperCVD¹⁵

[Regimen components on ALL-D 4 of 27](#)

- ^b There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).
- ^d Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
- ^e Prior to blinatumomab initiation, cytereduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10⁹/L. Foà R, et al. J Clin Oncol 2024;42:881-885.
- ^f TKI + corticosteroid as induction should be followed by TKI + multiagent therapy or TKI + blinatumomab consolidation unless TKI + corticosteroid is used in a palliative manner.

[References on ALL-D 8 of 27](#)

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

ALL-D

**PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL INDUCTION COMPONENTS^{b,g,h,i}**

AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline
<p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Blinatumomab^e + TKI^{c,d,1-3} • HyperCVAD⁴⁻⁸ + TKI^{c,d}: Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine <p>Useful in certain circumstances</p> <ul style="list-style-type: none"> • Corticosteroid + TKI^{c,d,f,9,10} • Vincristine + dexamethasone + TKI^{c,d,11}
Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
<p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Low intensity <ul style="list-style-type: none"> ▶ Blinatumomab^e + TKI^{c,d,1-3} ▶ Corticosteroid + TKI^{c,d,f,9,10,12-14} ▶ Vincristine + dexamethasone + TKI^{c,d,11} • Moderate intensity <ul style="list-style-type: none"> ▶ Mini-hyperCVD¹⁵ + TKI^{c,d}: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine

**PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL INDUCTION COMPONENTS FOOTNOTES**

- ^b There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).
- ^d Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.
- ^e Prior to blinatumomab initiation, cytereduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10⁹/L. Foà R, et al. J Clin Oncol 2024;42:881-885.
- ^f TKI + corticosteroid as induction should be followed by TKI + multiagent therapy or TKI + blinatumomab consolidation unless TKI + corticosteroid is used in a palliative manner.
- ^g All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^h For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
- ⁱ For patients who develop hypersensitivity to *Escherichia coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL CONSOLIDATION REGIMENS^b

- Blinatumomab + TKI^{c,d,j,1-3}
- Multiagent therapy^k + TKI^{c,d,4-8,11,15} (see [ALL-D 6 of 27](#))
- TKI^{c,d,l,9,10,12-14}

[Regimen components on ALL-D 6 of 27](#)

- ^b There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. *JAMA* 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).
- ^d Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/oder/daif/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. *JAMA* 2024;331:1814-1823.
- ^j Blinatumomab + TKI is preferred in consolidation regardless of MRD status for those who have not previously received blinatumomab.
- ^k Refer to induction regimen references, consolidation components on [ALL-D 6 of 27](#), or chemotherapy order templates (where available), for components if not listed.
- ^l TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.

[References on ALL-D 8 of 27](#)

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

ALL-D

PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL CONSOLIDATION COMPONENTS^{b,g,h,i}

AYA Patients without Substantial Comorbidities	Adults <65 years without Substantial Comorbidities	Adults ≥65 Years or Adults with Substantial Comorbidities
HyperCVAD ⁴⁻⁸ + TKI ^{c,d} ; Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine	Vincristine + dexamethasone + TKI ^{c,d,11} ; Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, high-dose methotrexate, vincristine	Mini-hyperCVD ¹⁵ + TKI ^{c,d} ; Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine
		Vincristine + dexamethasone + TKI ^{c,d,11} ; May use mini-hyperCVD ¹⁵ + TKI

- ^b There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, *BCR::ABL1* mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. *JAMA* 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).
- ^d Ponatinib has activity against *T315I* mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/oder/daif/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. *JAMA* 2024;331:1814-1823.
- ^g All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^h For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
- ⁱ For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

[References on ALL-D 8 of 27](#)

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

ALL-D



PRINCIPLES OF SYSTEMIC THERAPY
Ph-POSITIVE B-ALL MAINTENANCE THERAPY^{b,m}

- POMP (mercaptopurine, vincristine, methotrexate, prednisone) + TKI^{c,d}
- Vincristine + prednisone + TKI^{c,d}
- TKI^{c,d,l,n} monotherapy (if post-HCT or previously received blinatumomab + TKI)

^b There are data to support the benefit of rituximab in addition to multiagent therapy (excluding TKI + blinatumomab) for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).

^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. JAMA 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).

^d Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or PD on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). See package insert for more details (<https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>). The PhALLCON study shows improved MRD responses with ponatinib compared to imatinib. Jabbour E, et al. JAMA 2024;331:1814-1823.

^l TKI monotherapy is seldom effective as induction; however, it may be considered as consolidation/maintenance in those unfit for additional therapies.

^m Refer to induction regimen references or chemotherapy order templates (where available), for components. Include IT chemotherapy per protocol, or as clinically indicated.

ⁿ TKI should be continued for at least 2 years post-HCT. See [Discussion](#) for use of different TKIs in this setting. The recommended duration of TKI during maintenance chemotherapy is at least until completion of maintenance chemotherapy. The optimal duration of TKI is unknown in both settings.

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

ALL-D

Referenzen – Ph-positive B-ALL:

- 1 Foa R, Bassan R, Elia L, et al. Long-term results of the dasatinib-blinatumomab protocol for adult Philadelphia-positive ALL. J Clin Oncol 2024;42:881-885.
- 2 Gökbuget N, Zugmaier G, Dombret H, et al. Curative outcomes following blinatumomab in adults with minimal residual disease B-cell precursor acute lymphoblastic leukemia. Leuk Lymphoma 2020;61:2665-2673.
- 3 Kantarjian H, Short NJ, Haddad FG, et al. Results of the simultaneous combination of ponatinib and blinatumomab in Philadelphia chromosome-positive ALL. J Clin Oncol 2024;42:4246-4251.
- 4 Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood 2010;116:2070-2077.
- 5 Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. Blood 2004;103:4396-4407.
- 6 Thomas DA, Kantarjian HM, Cortes J, et al. Outcome after frontline therapy with the hyper-CVAD and imatinib mesylate regimen for adults with de novo or minimally treated Philadelphia chromosome (Ph) positive acute lymphoblastic leukemia (ALL) [abstract]. Blood 2008;112(Suppl 11):Abstract 2931.
- 7 Thomas DA, O'Brien SM, Faderl S, et al. Long-term outcome after hyper-CVAD and imatinib (IM) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL) [abstract]. J Clin Oncol 2010;28:Abstract 6506.
- 8 Jabbour EJ, Kantarjian H, Ravandi F, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. Lancet Oncol 2015;16:1547-1555.
- 9 Foa R, Vitale A, Vignetti M, et al. Dasatinib as first-line treatment for adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2011;118:6521-6528.
- 10 Vignetti M, Fazi P, Cimino G, et al. Imatinib plus steroids induces complete remissions and prolonged survival in elderly Philadelphia chromosome-positive patients with acute lymphoblastic leukemia without additional chemotherapy: results of the Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) LAL0201-B protocol. Blood 2007;109:3676-3678.
- 11 Chalandon Y, Thomas X, Hayette S, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood 2015;125:3711-3719.
- 12 Ottmann OG, Wassmann B, Pfeiffer H, et al. Imatinib compared with chemotherapy as front-line treatment of elderly patients with Ph-chromosome positive acute lymphoblastic leukemia. Cancer 2007;109:2068-2076.

13 Papayannidis C, Fazi P, Piciocchi A, et al. Treating Ph+ acute lymphoblastic leukemia (ALL) in the elderly: the sequence of two tyrosine kinase inhibitors (TKI) (nilotinib and imatinib) does not prevent mutations and relapse. Blood 2012;120:Abstract 2601.

14 Martinelli G, Piciocchi A, Papayannidis C, et al. First report of the GIMEMA LAL 1811 prospective study of the combination of steroids with ponatinib as frontline therapy of elderly or unfit patients with Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 2017;139:99.

15 Jen WY, Jabbour E, Short NJ, et al. A phase 2 trial of mini-hyper-CVD, blinatumomab, and ponatinib in Philadelphia positive acute lymphoblastic leukemia. Am J Hematol 2024;99:2229-2232.

**PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL INDUCTION REGIMENS^a**

Only for AYA Patients without Substantial Comorbidities: Frontline	For both AYA Patients & Adults <65 years without Substantial Comorbidities: Frontline	Only for Adults <65 years without Substantial Comorbidities: Frontline	Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Preferred <ul style="list-style-type: none"> Clinical trial CALGB 10403^{b,1} DFCI ALL regimen based on DFCI Protocol 00-01^{b,2} 	Preferred <ul style="list-style-type: none"> Clinical trial Other Recommended Regimens <ul style="list-style-type: none"> ECOG 1910³ HyperCVAD⁴⁻⁶ MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)^{b,7,8} 	Preferred <ul style="list-style-type: none"> Clinical trial Other Recommended Regimens <ul style="list-style-type: none"> Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹ 	Preferred <ul style="list-style-type: none"> Clinical trial Other Recommended Regimens <ul style="list-style-type: none"> Low Intensity <ul style="list-style-type: none"> Vincristine + prednisone¹² POMP¹³: mercaptopurine, vincristine, methotrexate, prednisone Moderate Intensity <ul style="list-style-type: none"> ALL-INITIAL-1¹⁴: Inotuzumab ozogamicin/dexamethasone (category 2B) ALLIANCE A041703¹⁵: Inotuzumab ozogamicin (category 2B) Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹ Modified DFCI 91-01 protocol¹⁶ Mini-hyperCVD^{17,18} Mini-hyperCVD + venetoclax¹⁷ High Intensity <ul style="list-style-type: none"> ECOG 1910³ Useful in certain circumstances <ul style="list-style-type: none"> ALLOLD07 (PETHEMA-based regimen)¹⁹ CALGB 9111²⁰ EWALL²¹ GMALL²² + rituximab for CD20-positive disease GRAALL²³

^a There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).

^b Pediatric-inspired regimen.

[Regimen components on ALL-D 10 of 27](#)

[References on ALL-D 16 of 27](#)

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

ALL-D

**PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL INDUCTION COMPONENTS^{a,c,d,e,f}**

AYA Patients without Substantial Comorbidities: Frontline
Preferred Regimens <ul style="list-style-type: none"> CALGB 10403^{b,1}: Daunorubicin, pegaspargase, prednisone, vincristine DFCI ALL regimen based on DFCI Protocol 00-01^{b,2}: Doxorubicin, high-dose methotrexate, pegaspargase, prednisone, vincristine
For both AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens <ul style="list-style-type: none"> ECOG 1910³: Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase, vincristine, rituximab for CD20-positive disease HyperCVAD⁴⁻⁶: Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine, rituximab for CD20-positive disease MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)^{b,7,8}: Cyclophosphamide, cytarabine, daunorubicin, mercaptopurine, pegaspargase, prednisone, vincristine
Only for Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens <ul style="list-style-type: none"> Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin

PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL INDUCTION COMPONENTS^{c,d,e,f}

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory
<p>Other Recommended Regimens</p> <ul style="list-style-type: none"> • Low intensity <ul style="list-style-type: none"> ▶ Vincristine + prednisone¹² ▶ POMP¹³: Mercaptopurine, vincristine, methotrexate, prednisone • Moderate intensity <ul style="list-style-type: none"> ▶ ALL-INITIAL-1¹⁴: Inotuzumab ozogamicin/Dexamethasone (category 2B) ▶ ALLIANCE A041703¹⁵: Inotuzumab ozogamicin (category 2B) ▶ Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin ▶ Modified DFCl 91-01 protocol¹⁶: Dexamethasone, doxorubicin, methotrexate, pegaspargase, vincristine ▶ Mini-hyperCVD^{17,18}: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, rituximab for CD20-positive disease ▶ Mini-hyperCVD + venetoclax¹⁷: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax • High intensity <ul style="list-style-type: none"> ▶ ECOG 1910⁹: Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase (age <55 years), vincristine, rituximab for CD20-positive disease <p>Useful in certain circumstances</p> <ul style="list-style-type: none"> • ALLOLD07 (PETHEMA-based regimen)¹⁹: Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine • CALGB 9111²⁰: Cyclophosphamide, daunorubicin, prednisone, pegaspargase, vincristine • EWALL²¹: Cyclophosphamide, dexamethasone, vincristine • GMALL²²: Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine, rituximab for CD20-positive disease • GRAALL²³: Cyclophosphamide, dexamethasone, doxorubicin, vincristine

PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL INDUCTION COMPONENTS FOOTNOTES

- ^a There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^b Pediatric-inspired regimen.
- ^c All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^d For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
- ^e For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
- ^f PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.

PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL CONSOLIDATION REGIMENS^{a,g}

- | |
|---|
| <ul style="list-style-type: none"> • Blinatumomab (preferred) + continued multiagent therapy^h • Blinatumomabⁱ |
|---|

[Regimen components on ALL-D 13 of 27](#)

- ^a There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^g Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673. Topp MS, et al. J Clin Oncol 2011;29:2493-2498; Litzow MR, et al. N Engl J Med 2024;391:320-333.
- ^h Refer to induction regimen references, consolidation components ([ALL-D 13 of 27](#)), or chemotherapy order templates, where available, for components if not listed.
- ⁱ Blinatumomab can be considered for consolidation in patients for whom multiagent therapy is contraindicated.

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

ALL-D

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS^{a,c,d,e,f,g}

AYA Patients without Substantial Comorbidities
Preferred Regimens <ul style="list-style-type: none"> • CALGB 10403^{b,1}: Cyclophosphamide, cytarabine, mercaptopurine, pegaspargase, vincristine • DFCI ALL regimen based on DFCI Protocol 00-01^{b,2}: Dexamethasone, doxorubicin, mercaptopurine, methotrexate, pegaspargase, vincristine
For both AYA Patients and Adults <65 years without Substantial Comorbidities
Other Recommended Regimens <ul style="list-style-type: none"> • ECOG 1910³: Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab • HyperCVAD⁴⁻⁶: Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine, rituximab for CD20-positive disease, with sequential blinatumomab • MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)^{b,7,8}: Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, high-dose methotrexate, pegaspargase, prednisone, thioguanine, vincristine
Only for Adults <65 years without Substantial Comorbidities
Other Recommended Regimens <ul style="list-style-type: none"> • Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin, with sequential blinatumomab

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS^{c,d,e,f,g}

Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline and Relapsed/Refractory
Other Recommended Regimens <ul style="list-style-type: none"> • Low intensity <ul style="list-style-type: none"> ▸ Vincristine + prednisone¹² ▸ POMP¹³: mercaptopurine, vincristine, methotrexate, prednisone • Moderate intensity <ul style="list-style-type: none"> ▸ ALL-INITIAL-1¹⁴: Cyclophosphamide, cytarabine, dexamethasone, idarubicin, high-dose methotrexate, pegaspargase, vincristine, with rituximab for CD20-positive disease ▸ ALLIANCE A041703¹⁵: Blinatumomab ▸ Inotuzumab ozogamicin + mini-hyperCVD⁹⁻¹¹: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin, with sequential blinatumomab ▸ Modified DFCI 91-01 protocol¹⁶: Dexamethasone, doxorubicin, mercaptopurine, pegaspargase, vincristine ▸ Mini-hyperCVD^{17,18}: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, rituximab for CD20-positive disease, with sequential blinatumomab ▸ Mini-hyperCVD + venetoclax¹⁷: Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax • High intensity <ul style="list-style-type: none"> ▸ ECOG 1910³: Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab
Useful in certain circumstances <ul style="list-style-type: none"> • ALLOLD07 (PETHEMA-based regimen)¹⁹: Cytarabine, high-dose methotrexate, pegaspargase • CALGB 9111²⁰: Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, pegaspargase, thioguanine, vincristine • EWALL²¹: Cytarabine, high-dose methotrexate, pegaspargase • GMALL²²: Cytarabine, methotrexate, rituximab for CD20-positive disease • GRAALL²³: Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, vincristine

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS FOOTNOTES

- ^a There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).
- ^b Pediatric-inspired regimen.
- ^c All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).
- ^d For full details on all phases of therapy, including induction IA; induction IB; CNS phase; early intensification; delayed intensification; continuation; consolidation IA, IB, IC, and II; reinduction I and II; and interim maintenance I and II, see attached references or chemotherapy order templates, where available.
- ^e For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.
- ^f PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in AYA patients aged 15 to ≤21 years and adults aged 18 to ≤21 years for more sustained asparaginase activity. Silverman LB, et al. Blood 2016;128:175; Angiolillo AL, et al. J Clin Oncol 2014;32:3874-3882.
- ^g Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910. Gokbuget N, et al. Leuk Lymphoma 2020;61:2665-2673. Topp MS, et al. J Clin Oncol 2011;29:2493-2498. Litzow MR, et al. N Engl J Med 2024;391:320-333.

PRINCIPLES OF SYSTEMIC THERAPY
Ph-NEGATIVE B-ALL MAINTENANCE THERAPY^{a,j}

- POMP (mercaptopurine, vincristine, methotrexate, prednisone)
- Blinatumomab alternating with POMP^k

^a There are data to support the benefit of rituximab in addition to multiagent therapy for AYA patients and adults aged <65 years without substantial comorbidities with CD20-positive disease (especially in patients aged <60 years).

^j Refer to induction regimen references, or chemotherapy order templates (where available), for components. Include IT chemotherapy per protocol, or as clinically indicated.

^k For maintenance in patients induced with inotuzumab ozogamicin + mini-hyperCVD + blinatumomab regimen or hyperCVAD + blinatumomab regimen.

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

ALL-D

Referenzen – Ph-negative B-ALL:

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- 2 DeAngelo DJ, Stevenson KE, Dahlberg SE, et al. Long-term outcome of a pediatric-inspired regimen used for adults aged 18-50 years with newly diagnosed acute lymphoblastic leukemia. *Leukemia* 2015;29:526-534.
- 3 Litzow MR, Sun Z, Mattison RJ, et al. Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults. *N Engl J Med* 2024;391:320-333.
- 4 Jabbour E, Short NJ, Jain N, et al. Hyper-CVAD and sequential blinatumomab for newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: a single-arm, single-centre, phase 2 trial. *Lancet Haematol* 2022;9:e878-e885.
- 5 Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. *J Clin Oncol* 2010;28:3880-3889.
- 6 Kantarjian H, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HyperCVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. *Cancer* 2004;101:2788-2801.
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- 11 Jabbour E, Short NJ, Senapati J, et al. Mini-hyper-CVD plus inotuzumab ozogamicin, with or without blinatumomab, in the subgroup of older patients with newly diagnosed Philadelphia chromosome-negative B-cell acute lymphocytic leukaemia: long-term results of an open-label phase 2 trial. *Lancet Haematol* 2023;10:e433-e444.
- 12 Hardisty RM, McElwain TJ, Darby CW. Vincristine and prednisone for the induction of remissions in acute childhood leukaemia. *Br Med J* 1969;2:662-665.
- 13 Berry DH, Pullen J, George S, et al. Comparison of

prednisolone, vincristine, methotrexate, and 6-mercaptopurine vs. vincristine and prednisone induction therapy in childhood acute leukemia. *Cancer* 1975;36:98-102.

14 Stelljes M, Raffel S, Alakel N, et al. Inotuzumab ozogamicin as induction therapy for patients older than 55 years with Philadelphia chromosome-negative B-precursor ALL. *J Clin Oncol* 2024;42:273-282.

15 Wieduwilt MJ, Yin J, Kour O, et al. Chemotherapy-free treatment with inotuzumab ozogamicin and blinatumomab for older adults with newly diagnosed, Ph-negative, CD22-positive, B-cell acute lymphoblastic leukemia: Alliance A041703. *J Clin Oncol* 2023;41:7006-7006.

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22 Goekbuget N, Beck J, Bruggemann M, et al. Moderate intensive chemotherapy including CNS prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German multicenter study group for adult ALL (GMALL). *Blood* 2012;120:1493.

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PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-POSITIVE B-ALL^{a,b}

Other Recommended Regimens

- TKI^c (dasatinib,^{1,2} imatinib,³ ponatinib,⁴ nilotinib,⁵ or bosutinib⁶)
 - ▶ The TKIs noted above may also be used in combination with any of the regimens noted on [ALL-D 3 of 27](#) that were not previously given.
- Asciminib + dasatinib⁷
- Blinatumomab ± TKI^{8,9}
- Inotuzumab ozogamicin ± TKI^{10,11}
- Tisagenlecleucel (patients aged <26 years and with refractory disease or ≥2 relapses and following therapy that has included 2 TKIs)¹²
- Brexucabtagene autoleucel (following therapy that has included TKIs)¹³
- Obecabtagene autoleucel (following therapy that has included TKIs)¹⁴
- The regimens listed on [ALL-D 26 of 27](#) for Ph-negative B-ALL may be considered for Ph-positive B-ALL refractory to TKIs.

^a All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^b The safety of relapsed/refractory regimens in adults ≥65 years or adults with substantial comorbidities has not been established. Please see [ALL-D 2 of 27](#) for additional information.

^c TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. Not all TKIs have been directly studied within the context of each specific regimen and the Panel notes that there are limited data for bosutinib in Ph+ ALL. Use of a specific TKI should account for anticipated/prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. Imatinib use in first line should be restricted to patients who cannot tolerate broader acting TKIs. Jabbour E, et al. *JAMA* 2024;331:1814-1823. For contraindicated mutations, see [ALL-D 1 of 27](#).

[References on ALL-D 25A of 27](#)

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

ALL-D

Referenzen – r/r Ph-positive B-ALL:

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- 7 Lusk MR, Murakami MA, Keating J, et al. Asciminib plus dasatinib and prednisone for Philadelphia chromosome-positive acute leukemia. *Blood* 2025;145(6):577589.
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- 12 Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with b-cell lymphoblastic leukemia. *N Engl J Med* 2018;378:439-448. 13 Shah BD, Ghobadi A, Oluwole OO, et al. KTE-X19 for relapsed/refractory adult B-cell acute lymphoblastic leukemia. *Lancet* 2021;398:491-502. 14 Roddie C, Sandhu KS, Tholouli E, et al. Obecabtagene autoleucel in adults with B-cell acute lymphoblastic leukemia. *N Engl J Med* 2024;391:2219-2230.

PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL^{a,b,c,d}

Preferred Regimens
<ul style="list-style-type: none"> • Blinatumomab (CD19 antigen directed) (category 1)¹ ± multiagent therapy • Inotuzumab ozogamicin (CD22 antigen directed) (category 1)² • Tisagenlecleucel (CD19 antigen directed) (patients aged <26 years and with refractory disease or ≥2 relapses)³ • Brexucabtagene autoleucel (CD19 antigen directed)⁴ • Obecabtagene autoleucel (CD19 antigen directed)⁵
Other Recommended Regimens ^e
<ul style="list-style-type: none"> • Inotuzumab ozogamicin + mini-hyperCVD with or without sequential blinatumomab (hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine)^{6,7} • Augmented HyperCVAD: hyperfractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, pegaspargase; alternating with high-dose methotrexate, cytarabine⁸ • Clofarabine alone⁹⁻¹² or in combination (eg, clofarabine, cyclophosphamide, etoposide)^{10,13,14} • MOPAD regimen: methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease¹⁵ • Fludarabine-based regimens <ul style="list-style-type: none"> ▶ FLAG-IDA: fludarabine, cytarabine, G-CSF ± idarubicin¹⁶ ▶ FLAM: fludarabine, cytarabine, mitoxantrone¹⁷ • Cytarabine-containing regimens: eg, high-dose cytarabine, idarubicin, IT methotrexate¹⁸ • Alkylator combination regimens: eg, etoposide, ifosfamide, mitoxantrone¹⁹ • Revumenib (KMT2A rearranged)^{f,20}

^a All regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^b For patients in late relapse (>3 years from initial diagnosis), consider treatment with the same regimen used at initial diagnosis (see ALL-D 9 of 27).

^c For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn should be substituted as a component of the multi-agent therapeutic regimen to complete the full treatment course.

^d PEG is substituted with Cal-PEG, an asparagine-specific enzyme, in patients aged 15 to ≤21 years for more sustained asparaginase activity. Silverman LB, et al. *Blood* 2016;128:175; Angiolillo AL, et al. *J Clin Oncol* 2014;32:3874-3882.

^e The safety of relapsed/refractory regimens in adults ≥65 years or adults with substantial comorbidities has not been established. Please see ALL-D 2 of 27 for additional information.

^f Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

[References on ALL-D 26A of 27](#)

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

ALL-D

Referenzen – r/r Ph-negative B-ALL:

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Management of Ph-Positive B-ALL

Initial Treatment in AYA Patients with Ph-Positive B-ALL

Ph-positive ALL is rare in children with ALL, occurring in only approximately 3% of pediatric cases compared with 25% of adult cases.³⁷ The frequency of Ph-positive ALL among AYA patients ranges from 5% to 25% and increases with age,^{112,121} although this subtype is still uncommon relative to the incidence in adults who are older. Historically, children and adolescents with Ph-positive disease had a poorer prognosis compared with patients with Ph-negative B-ALL. However, improvements in the treatment options are closing this gap.

Hematopoietic Cell Transplant

In a retrospective analysis of children with Ph-positive ALL treated between 1986 and 1996 (n = 326) with intensive chemotherapy regimens with or without allogeneic HCT, the 7-year EFS and OS rates were 25% and 36%, respectively.⁵⁵ This benefit with HCT versus chemotherapy alone was not observed with autologous HCT or with HCT from matched URDs. This study showed that allogeneic HCT from a matched related donor offered improvements in outcomes over chemotherapy alone.

In a subsequent analysis of outcomes in children with Ph-positive ALL treated between 1995 and 2005 but also without targeted TKIs, the 7-year EFS and OS rates were 32% and 45%, respectively.¹⁶⁸ Outcomes with allogeneic HCT from either matched related donors or URDs appeared similar, and HCT improved disease control over intensive chemotherapy alone.¹⁶⁸ Although this analysis showed an improved 7-year EFS rate, outcomes remained suboptimal in patients with Ph-positive ALL.

Allogeneic HCT has been considered the standard of care for AYA patients with Ph-positive ALL; however, its role has become less clear with the advent of BCR::ABL–targeted TKIs. Several studies evaluated the role of allogeneic HCT in the era of imatinib and whether imatinib-based therapies provided an additional benefit to HCT.

Blinatumomab

Treatment of adults with newly diagnosed Ph-positive ALL was evaluated in a phase II single-group trial using dasatinib chemotherapy-free induction followed by first-line consolidation therapy with blinatumomab.¹⁶⁹ Sixty-three patients, aged 24 to 84 years, were enrolled. At the end of induction, 29% of patients achieved a molecular response, which increased to 60% after 2 cycles of blinatumomab. ABL1 mutations occurred in six patients who experienced an increase in MRD, however were cleared upon treatment with blinatumomab. Few toxic effects of grade 3 or higher were observed, with CMV reactivation or infection occurring in six patients. As a result of high molecular response, OS and DFS at a median follow-up of 18 months was achieved in 95% and 88% (95% CI, 90–100; 80–97) of patients, respectively.¹⁷⁰ DFS was lower in the setting of IKZF1 deletions.

The safety and efficacy of blinatumomab in combination with TKIs has been evaluated in the treatment of Ph-positive ALL.¹⁷¹⁻¹⁷³ In a small retrospective study, adults with R/R Ph+ ALL (n = 9) and CML (n = 3) who had previously been treated with one line of chemotherapy and one class of TKIs were treated with the combination blinatumomab and a TKI (ponatinib, dasatinib, or bosutinib). Of the 12 total patients, 75% (9/12) achieved complete molecular responses with no cardiovascular adverse events.¹⁷¹

A single arm phase II study explored the chemotherapy free combination of blinatumomab plus ponatinib in 54 patients ≥ 18 years of age with newly diagnosed Ph-positive ALL.¹⁷⁴ With a median follow up of 24 months, complete molecular response rate by RT-PCR was 83%, with 98% achieving MRD negativity utilizing a highly sensitive NGS-based assay. Estimated 3-year OS and EFS were 91% and 77%, respectively. Only two patients went on to allogeneic HCT. Three patients had to discontinue blinatumomab secondary to adverse events, while nine patients discontinued ponatinib secondary to adverse events, including but not limited to coronary artery stenosis, cerebrovascular ischemia, and arterial thrombus.

TKIs Combined with HyperCVAD

A phase II study at MDACC evaluated imatinib combined with the hyperCVAD regimen in patients with previously untreated or minimally treated ALL (n = 54; median age, 51 years; range, 17–84 years); 14 patients underwent subsequent allogeneic HCT.¹⁶⁰ The 3-year OS rate for this regimen was 54%. Among the patients ≤ 40 years of age (n = 16), a strong trend was observed for OS benefit with allogeneic HCT (3-year OS rate, 90% vs. 33%; P = .05).¹⁶⁰ Among patients ≤ 60 years of age, no statistically significant difference was observed in the 3-year OS rate between patients who received HCT and those who did not (77% vs. 57%).

Studies have shown the promising activity of other TKIs, including dasatinib and ponatinib when incorporated into frontline regimens for patients with ALL. In a phase II study from MDACC, dasatinib was combined with hyperCVAD and subsequent maintenance therapy in patients with previously untreated Ph-positive ALL (n = 35; median age, 53 years; range, 21–79 years; 31% were >60 years); four of the patients

received allogeneic HCT in CR1.¹⁷⁵ The 2-year OS and EFS rates were 64% and 57%, respectively. The efficacy and safety of ponatinib combined with hyperCVAD was examined in patients with Ph-positive ALL (n = 37; aged ≥ 18 years; median age, 51 years; 12 patients were ≥ 60 years) in a phase II prospective trial.¹⁵⁴ Of the 32 patients with disease with Ph-positive metaphases at the start of therapy, all 32 patients (100%) achieved an overall complete cytogenetic response. By multiparametric flow cytometry, 35 of 37 patients (95%) achieved MRD negativity after a median of 3 weeks of therapy.¹⁵⁴ However, it is worth noting that only half of the patients ≥ 60 years of age completed therapy with this regimen, and were switched to alternate TKIs. The 2-year OS and EFS rates were 80% and 81%, respectively. A follow-up study (n = 76; age ≥ 18 years; median age, 47 years) demonstrated long-term efficacy for ponatinib and hyperCVAD with a 3-year EFS rate of 70%.¹⁷⁶

Initial Treatment in Adults with Ph-Positive B-ALL

Historically, treatment outcomes for adult patients with Ph-positive ALL have been extremely poor. Before the era of targeted TKIs, the 3-year OS rates with chemotherapy regimens were generally <20%.¹⁷⁹

Hematopoietic Cell Transplant Allogeneic HCT, in the pre-imatinib era, resulted in some improvements over chemotherapy alone, with 2-year OS rates of 40% to 50%^{180,181} and 3-year OS rates of 36% to 44%.^{95,182} In the large, international, collaborative MRC UKALL XII/ECOG E2993 trial conducted in patients with previously untreated ALL, the subgroup with Ph-positive disease (n = 267; median age, 40 years; range, 15–60 years) was eligible for allogeneic HCT if its patients were <50 (in the ECOG E2993 trial) or <55 (in the MRC UKALL XII trial) years of age and had a matched sibling or matched URD.¹⁸³ Among the Ph-positive cohort, postremission treatment included matched sibling allogeneic HCT (n = 45), matched URD allogeneic HCT (n = 31), and chemotherapy alone (n = 86). The 5-year OS rate according to postremission therapy was 44%, 36%, and 19%, respectively, and the 5-year EFS rate was 41%, 36%, and 9%, respectively.¹⁸³ Both the OS and EFS outcomes for patients who underwent allogeneic HCT (related or unrelated) were significantly improved compared with those who received only chemotherapy. The incidence of transplant-related mortality was 27% with matched sibling allogeneic HCT and 39% with matched URD HCT. An intent-to-treat analysis of patients with a matched sibling donor versus those without a matched sibling donor showed no statistically significant difference in 5-year OS rates (34% vs. 25%, respectively).¹⁸³ The incorporation of imatinib in the treatment regimen for Ph-positive ALL has led to improvements in outcomes over chemotherapy alone.^{160,179,184}

Some retrospective studies suggest similar outcomes between myeloablative conditioning (MAC) and reduced-intensity conditioning (RIC) followed by allogeneic HCT in adult patients with Ph-positive ALL.^{185–187} The Center for International Blood and Marrow Transplant Research (CIBMTR) group conducted a multicenter retrospective analysis examining the efficacy RIC and MAC allogeneic HCT in adult patients with Ph-positive ALL (n = 197).¹⁸⁵ At a median follow-up of 4.5 years, the 1-year transplant-related mortality was significantly lower in the RIC versus MAC group (13% vs. 36%; P = .001), and 3-year OS rates were similar (39% vs. 35%, respectively).¹⁸⁵

TKIs Combined with HyperCVAD

Studies evaluating TKIs plus hyperCVAD have included both AYA and adult patients.^{154,160,175} For discussion of these studies, refer to the previous section (see Initial Treatment in AYA Patients with Ph-Positive ALL).

In a phase II trial, the combination of lower intensity mini-hyperCVD, ponatinib, and blinatumomab was evaluated among 12 patients ≥18 years of age with newly diagnosed Ph-positive ALL.¹⁸⁸ Induction consisted of 4 cycles of ponatinib and mini-hyperCVD alternating with mini-methotrexate

and cytarabine, with blinatumomab utilized in consolidation. Among patients with evaluable data, 78% achieved complete molecular remission. Three-year OS was 72%. Of note, 50% of patients were in CR at time of enrollment.

TKIs Combined with Multiagent Therapy

Several studies evaluating the efficacy of TKIs combined with multiagent therapy in patients with previously untreated ALL have shown improved outcomes, particularly when treatment was followed by allogeneic HCT.^{157,182,184,189,190}

PhALLCON is an ongoing phase III study comparing ponatinib versus imatinib combined with reduced-intensity chemotherapy in 245 patients (median age, 54 years) with newly diagnosed Ph-positive ALL.¹⁹¹ Treatment was continued for 20 cycles, through induction, consolidation, and post-consolidation. Following 20 cycles, single agent ponatinib or imatinib was continued until disease progression or unacceptable toxicity. Many patients discontinued study treatment, with the most common reasons being the decision to proceed with HCT, adverse events, and lack of efficacy. Seventy-eight patients remained on protocol at the time of data cutoff. Among these 78 patients, MRD negative CR rates were significantly higher among the ponatinib cohort compared to the imatinib cohort (34.4% vs. 16.7%; P = .002). Median follow up was 20.1 months. There was also a trend towards improved EFS (hazard ratio [HR] = 0.652; 95% CI, 0.385–1.104) and time to treatment failure with ponatinib (HR = 0.455), though survival data was not mature. Rates of treatment-emergent adverse events of any grade were comparable between the two cohorts. Based on this data, the FDA approved ponatinib with chemotherapy for adult patients with newly diagnosed Ph+ ALL on March 19, 2024.¹⁷⁸

TKIs Combined with Corticosteroids

The treatment of patients who are older with Ph-positive ALL may pose a challenge, because patients who are older or those with comorbidities may not tolerate aggressive regimens with multiagent therapy combined with TKIs.¹⁹² Several studies have evaluated outcomes with imatinib induction, with or without concurrent corticosteroids, in adults who are older with Ph-positive ALL. In a study that randomly assigned patients aged 54 to 79 years with Ph-positive ALL (n = 55; median age, 68 years; 94.5% were ≥60 years of age) to induction therapy with imatinib versus chemotherapy alone, followed by imatinib-containing consolidation therapy, the estimated 2-year OS rate was 42%; no significant difference was observed between induction treatment arms.¹⁹³ The median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to receive chemotherapy induction (23.5 vs. 12 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs. 90%; P = .005), which suggested that induction therapy with imatinib may be better tolerated than chemotherapy in patients in this age group with Ph-positive ALL.¹⁹³

In a study by GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; median age, 54 years; range, 24–76.5 years) received induction therapy with dasatinib and prednisone.¹⁵³ Twelve patients were >60 years of age. Postinduction therapy included no further therapy (n = 2), TKI only (n = 19), TKI combined with chemotherapy (n = 10) with or without autologous HCT (n = 4), or allogeneic HCT (n = 18). All patients experienced a CR after induction therapy. The median OS was 31 months and the median DFS (calculated from day +85) was 21.5 months. At 20 months, the OS and DFS rates were 69% and 51%, respectively.¹⁵³ T3151 mutation was detected in 12 of 17 cases of relapsed disease (71%).

In a small phase II study from GRAALL (AFR-09 study), patients ≥55 years of age with Ph-positive ALL (n = 29 evaluable; median age, 63 years) were treated with chemotherapy induction followed by a consolidation regimen with imatinib and methylprednisolone.¹⁹⁴ The 1-year OS rate in this study was significantly higher compared with the historical control population who received the same induction therapy but did not receive imatinib as part of consolidation (66% vs. 43%; P = .005), and the median OS in this study was longer than that of the control group (23 vs. 11 months, respectively). In addition, the 1-year RFS rate was significantly increased with the addition of imatinib (58% vs. 11%; P < .001).¹⁹⁴ A phase II study by GIMEMA (LAL0201-B study) also evaluated imatinib combined with corticosteroids in patients >60 years of age with Ph-positive ALL (n = 29 evaluable; median age, 69 years).¹⁹⁵ Patients received imatinib in combination with prednisone for induction. The estimated 1-year DFS and OS rates were 48% and 74%, respectively; the median OS was 20 months.¹⁹⁵ In a separate study from GIMEMA (LAL-1205), patients with Ph-positive ALL (n = 53 evaluable; age range, 24–76.5 years) received induction therapy with dasatinib and prednisone.¹⁵³ Postinduction therapy included no further therapy (n = 2), TKI only (n = 19), TKI combined with chemotherapy (n = 10) with or without autologous HCT (n = 4), or allogeneic HCT (n = 18). All patients experienced a CR after induction therapy. The median OS was 31 months and the median DFS (calculated from day +85) was 21.5 months. At 20 months, the OS and DFS rates were 69% and 51%, respectively.¹⁵³

A phase II study from GIMEMA (LAL1811) also evaluated the efficacy and safety of ponatinib and prednisone in adult patients aged 27 to 85 years with untreated Ph-positive ALL (n = 42 evaluable; median age, 68 years).¹⁹⁶ Dose reduction of ponatinib was allowed for adverse events. At week 24, the primary endpoint of the study, complete hematologic response, was prematurely reached in 75% of patients. During the study, 75 adverse events were reported; 36 were related to ponatinib.¹⁹⁶

TKIs Combined with Vincristine and Dexamethasone

The phase II GRAALL study (GRAAPH-2005) compared induction therapy with high-dose imatinib (800 mg daily, days 1–28) combined with vincristine and dexamethasone (arm A) versus imatinib (800 mg daily, days 1–14) combined with hyperCVAD (arm B) in patients <60 years of age with previously untreated Ph-positive ALL.^{197,198} Eligible patients proceeded to HCT (allogeneic or autologous) after induction/consolidation phases. The primary endpoint was noninferiority of the less intensive arm A regimen in terms of MRD response (BCR::ABL/ABL ratio <0.1% by quantitative PCR) after induction/consolidation. In an early report from this study (n = 118; n = 83 evaluable; median age, 42 years), 52 patients proceeded to HCT (allogeneic, n = 41; autologous, n = 11). The estimated 2-year OS rate was 62%, with no significant difference between patients who received imatinib with vincristine and dexamethasone and those who received imatinib with hyperCVAD (68% vs. 54%, respectively).¹⁹⁷ The 2-year DFS rate was 43%, with no significant difference between induction arms (54% vs. 32%, respectively).

In an updated analysis from the GRAAPH-2005 study with a median follow-up of 4.8 years ($n = 268$; median age, 47 years), the CR rate was higher in arm A compared to arm B (98% vs. 91%; $P = .006$), but MRD response rates after 2 cycles of therapy were similar between arm A and arm B (66.1% vs. 64.5%).¹⁹⁹ The estimated 5-year EFS and OS rates were 37.1% and 45.6%, respectively, and no significant differences were observed between arm A and arm B.¹⁹⁹ Among patients who proceeded to allogeneic HCT or autologous HCT after MRD response, the outcomes were similar in terms of the 5-year post-transplant RFS (48.3% vs. 46.1%) and OS (56.7% vs. 55.1%) rates. This study suggests that outcomes with less intensive chemotherapy regimens (using high-dose imatinib) may offer similar benefits to more intensive imatinib-containing chemotherapy regimens.¹⁹⁹

In the EWALL-Ph-01 study, induction therapy with dasatinib combined with low-intensity chemotherapy (vincristine and dexamethasone) was evaluated in patients ≥ 55 years of age with Ph-positive ALL ($n = 71$; median age, 69 years; range, 58–83 years). The CR rate after induction was 96% and MRD response (BCR::ABL1/ABL1 ratio $\leq 0.1\%$) was observed in 65% of patients.²⁰⁰ At 3 years, the RFS, EFS, and OS were 33% (95% CI, 22%–44%), 31% (95% CI, 21%–42%), and 41% (95% CI, 29%–52%), respectively.²⁰⁰ At 5 years, the cumulative incidence of relapse was 54% (95% CI, 42%–66%). These studies suggest that the use of TKIs in combination with less intensive therapies (eg, corticosteroids with or without vincristine) may provide an alternative treatment option for patients who are older with Ph-positive ALL for whom intensive regimens are not appropriate.

TKIs in Maintenance Therapy

Collectively, the incorporation of TKIs into the therapeutic regimen has demonstrated improved outcomes for adult patients with Ph-positive ALL, particularly when administered before allogeneic HCT. Given that patients can experience relapse following allogeneic HCT, strategies are needed to prevent disease recurrence. One strategy involves the incorporation of post-HCT maintenance therapy with TKIs, which has been investigated in several studies. In a small prospective study in patients with Ph-positive leukemias who underwent allogeneic HCT ($n = 15$ with ALL; median age, 37 years; range, 4–49 years), imatinib was administered from the time of engraftment until 1 year after HCT.²⁰¹ The median time after HCT until initiation of imatinib was short, at 27 days (range, 21–39 days). Molecular remission (by PCR) was observed in 46% of patients (6 of 13) prior to HCT and 80% (12 of 15) after HCT. Two patients died after hematologic relapse and one patient died due to acute respiratory distress syndrome approximately 1 year post-HCT. At a median follow-up of 1.3 years, 12 patients (80%) were alive without detectable disease.²⁰¹ This was one of the first prospective studies to show the feasibility of administering imatinib maintenance early in the post-HCT period (< 90 days) when the leukemic tumor burden tends to be low.

Maintenance therapy with imatinib was also evaluated in a prospective study in patients who underwent allogeneic HCT ($n = 82$; median age, 28.5 years; range, 3–51 years).²⁰² Imatinib was scheduled for a period of 3 to 12 months (until three consecutive tests were negative for BCR::ABL transcripts or sustained molecular CR for at least 3 months). Among the patients who received imatinib ($n = 62$), the median time after HCT until initiation of imatinib was 70 days (range, 20–270 days). In this group of patients, 84% were alive with a molecular CR at a median follow-up of 31 months.²⁰² Imatinib was discontinued in 16% of patients receiving treatment due to toxicities. The remaining patients ($n = 20$) who did not receive maintenance with imatinib (due to cytopenias, infections, graft-versus-host disease [GVHD], or patient choice) constituted the non-imatinib group. The estimated 5-year relapse rate was significantly lower with imatinib compared with no imatinib (10% vs. 33%; $P = .0016$) and the estimated 5-year DFS (81.5% vs. 33.5%; $P < .001$) and OS rates (87% vs. 34%; $P < .001$) were significantly longer with imatinib compared with no imatinib.²⁰²

The previous study was not designed as a randomized controlled trial, and the number of patients in the non-imatinib group was small. A multicenter randomized trial evaluated imatinib given prophylactically ($n = 26$) compared with imatinib given at the time of MRD detection (ie, molecular recurrence; $n = 29$) in patients who underwent allogeneic HCT with a planned duration of imatinib therapy for 1 year.²⁰³ MRD was defined by the appearance of BCR::ABL transcripts, as assessed by quantitative RT-PCR performed at a central laboratory. In the prophylactic arm, imatinib was started in 24 patients (92%) at a median time of 48 days (range, 23–88 days) after HCT. In the MRD-triggered arm, imatinib was started in 14 patients (48%) at a median time of 70 days (range, 39–567 days) after HCT. Imatinib was discontinued prematurely in the majority of patients in both arms (67% in the prophylaxis arm; 71% in the MRD-triggered arm), primarily because of toxicities.²⁰³ Ongoing CR was observed in 81% of

patients in the prophylaxis arm (median follow-up, 30 months) and in 78% of patients in the MRD-triggered arm (median follow-up, 32 months). No significant differences were found between the prophylaxis and MRD-triggered arms in terms of relapse rate (8% vs. 17%), 5-year DFS (84% vs. 60%), EFS (72% vs. 54%), or

OS (80% vs. 74.5%).²⁰³ However, MRD positivity was predictive of relapse regardless of treatment arm; the 5-year RFS rate was significantly lower among patients with detectable MRD compared with those who achieved MRD negativity (70% vs. 100%; $P = .017$). Moreover, early MRD positivity (within 100 days after HCT) was associated with significantly decreased EFS compared with late MRD detection (median, 39 months vs. not reached [NR]; 4-year EFS, 39% vs. 65%; $P = .037$).²⁰³ This trial suggested that imatinib given post-allogeneic HCT (either prophylactically or based on MRD detection) resulted in low relapse rates and durable remissions. However, imatinib may not provide benefit for patients who experience early molecular relapse or persistent MRD following HCT. Although no randomized controlled trials have yet been conducted to establish the efficacy of TKIs (compared with observation only or other interventions) following allogeneic HCT, the collective results from these studies suggest that TKI maintenance may have a potential role in reducing the relapse risk in this setting.

Treatment of Relapsed Ph-Positive B-ALL

The treatment of patients who experience relapse after initial therapy for ALL remains a challenge, because these patients have a very poor prognosis. Several large studies using conventional chemotherapy for adults with relapsed disease have reported a median OS of 4.5 to 6 months, and a 5-year OS rate of 3% to 10%.²⁰⁴⁻²⁰⁷ One major factor associated with poorer survival outcomes after subsequent therapy for relapsed ALL is the duration of response to frontline treatment. In an analysis of data from the PETHEMA (Programa Español de Tratamientos en Hematología) trials, patients with disease that relapsed >2 years after frontline therapy had significantly higher 5-year OS rates than the groups with disease that relapsed within 1 to 2 years or within 1 year of frontline therapy (31% vs. 15% vs. 2%; $P < .001$).²⁰⁵ Similarly, in the MRC UKALL XII/ECOG E2993 trial, patients with disease that relapsed >2 years after initial diagnosis and frontline therapy had a significantly higher 5-year OS rate than those whose disease relapsed within 2 years (11% vs. 5%; $P < .001$).²⁰⁴ In the pre-imatinib era, patients with Ph-positive B-ALL who experienced relapse after frontline therapy had dismal outcomes; subgroup data from the large, prospective trials LALA-94 and MRC UK XII/ECOG E2993 showed a median OS of 5 months and a 5-year OS rate of 3% to 6% among patients subsequently treated for relapsed Ph-positive B-ALL.^{204,206}

Hematopoietic Cell Transplant

Treatment options are extremely limited for patients with Ph-positive B-ALL who experience relapse after receiving consolidation with allogeneic HCT. Some investigators have reported on the feasibility of inducing a second molecular CR with dasatinib in those who have experienced an early relapse after first allogeneic HCT, which allowed for a second allogeneic HCT.^{208,209} Studies that include donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in those who experience relapse after allogeneic HCT have reported little to no benefit, though it has been suggested that this is due to excessively high leukemic burden.^{210,211} Indeed, published case reports have suggested that the use of DLI for residual disease or molecular relapse (as noted by levels of BCR::ABL fusion mRNA measured with PCR) after allogeneic HCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse.²¹²⁻²¹⁴ Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT.^{215,216} Although these approaches are promising, only limited data are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapsed disease.

Tyrosine Kinase Inhibitors

The emergence of resistance poses a challenge for patients who experience relapse after initial treatment with TKI-containing regimens. Point mutations within the ABL kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated as mechanisms of resistance.²¹⁷⁻²¹⁹ The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.^{220,221} Moreover, ABL kinase domain mutations may be present in a small group of patients not yet treated with imatinib even before initiation of any TKI therapy.^{222,223}

CNS relapse has been reported in both patients with disease responsive to imatinib therapy (isolated CNS relapse with CR in marrow) and patients with disease resistant to imatinib therapy.²²⁴⁻²²⁷ The concentration of imatinib in the cerebrospinal fluid (CSF) has been shown to be approximately 2 logs lower than that achieved in the blood, suggesting that this agent does not adequately penetrate the blood-brain

barrier to ensure CNS coverage.^{225,227} A study showed that among patients with ALL treated with imatinib and who did not receive routine prophylactic IT therapy or cranial irradiation, 12% developed CNS leukemia.²²⁶ Patients with imatinib-resistant disease who developed CNS disease rapidly died from progressive disease (PD); conversely, patients with imatinib-sensitive disease who developed isolated CNS relapse could be successfully treated with IT therapy with or without cranial irradiation.^{224,226}

Dasatinib and nilotinib are second-generation TKIs that have shown greater potency in inhibiting BCR::ABL compared with imatinib, and retention of antileukemic activity in cells with certain imatinib-resistant ABL mutations.^{158,228-230} In addition, dasatinib has better CNS penetration than imatinib, and therefore may have advantages in preventing CNS relapse. Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL that is resistant to imatinib treatment.²³¹⁻²³³ A randomized phase III study examined the activity of dasatinib administered as once-daily (140 mg daily) versus twice-daily (70 mg twice daily) dosing in patients with Ph-positive leukemia resistant to imatinib²³²; the once-daily dosing resulted in a higher response rate (major cytogenetic response) than the twice-daily dosing (70% vs. 52%). Although the median OS was shorter with the once-daily dosing (6.5 vs. 9 months), the median progression-free survival (PFS) was longer (4 vs. 3 months).²³² These differences in outcomes between the dosing arms were not statistically significant.

Dasatinib in combination with the hyperCVAD regimen (hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was investigated in a phase II trial that included patients with Ph-positive relapsed ALL (n = 19) and lymphoid blast phase (BP) CML (n = 15).²³⁴ An overall response rate (ORR) of 91% was obtained, with 26 patients (84%) achieving complete cytogenetic remission, 13 patients (42%) achieving a complete molecular response, and 11 patients (35%) achieving a major molecular response. There were nine patients who went on to receive allogeneic HCT, including two patients with ALL. In the patients with relapsed ALL, 30% remained in complete remission at 3 years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), two patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of BCR::ABL and SRC family kinases,^{235,236} was approved in September 2012 by the FDA for the treatment of chronic, accelerated phase (AP), or BP Ph-positive CML in adult patients with disease resistant to prior TKI treatment based on an open-label, multicenter phase I/II trial.²³⁶ Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia [AP CML (n = 79), BP CML (n = 64), or ALL (n = 24)] who were previously treated with at least one TKI.^{237,238} Of the 22 evaluable patients with ALL, two patients (9%) attained or maintained a confirmed overall hematologic response by 4 years.²³⁷ Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).^{237,238}

Ponatinib is a third-generation TKI that was initially approved by the FDA in December 2012 for the treatment of adult patients with chronic, AP, or BP Ph-positive CML or Ph-positive ALL, with resistance to prior therapy, and was added as a treatment option for R/R Ph-positive ALL in 2013. Though temporarily removed from the market in November 2013, ponatinib distribution resumed in December 2013 following revision to both the prescribing information and risk evaluation and mitigation strategies program to address the risk for serious cardiovascular adverse events. This TKI has been shown to inhibit both native and mutant forms of BCR::ABL (including those resulting from T315I mutation) in preclinical studies.²³⁹ In a multicenter, open-label, phase II study (PACE trial; n = 449), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs.²⁴⁰ Major hematologic response was observed in 41% of the subgroup with Ph-positive ALL (n = 32). In the subset of patients with Ph-positive ALL with ABL T315I mutation (n = 22), major hematologic response was observed in 36%.²⁴⁰ Common overall treatment-related adverse events in the PACE trial included thrombocytopenia (37%), rash (34%), and dry skin (32%). Additionally, arterial thrombotic events were observed and 7.1% of patients experienced cardiovascular events,²⁴⁰ though dose reduction may impart a lower risk.

Not all imatinib-resistant ABL mutations are susceptible to the newer TKIs. For instance, dasatinib is not as active against cells harboring the ABL mutations T315I, V299L, and F317L.^{219,229,241,242} Thus, for patients with disease resistant to TKI therapy, it becomes important to identify potential ABL mutations that may underlie the observed resistance to treatment. A panel of experts from the European LeukemiaNet published recommendations for the analysis of ABL kinase domain mutations in patients with CML, and treatment options according to the presence of different ABL mutations.²⁴³ (See Principles of Systemic Therapy in the algorithm for TKI treatment options for Treatment Options Based on BCR::ABL1 Mutation Profile).

Asciminib plus Dasatinib

Asciminib is an allosteric inhibitor of BCR::ABL1 currently FDA approved for the treatment of chronic phase (CP) Ph-positive CML with T315I mutation or CP Ph-positive CML without T315I mutation that has previously been treated with TKIs. In a phase I study including 24 patients with Ph-positive ALL, the combination of asciminib with dasatinib was evaluated.²⁴⁴ Patients received a 28-day course of induction consisting of asciminib, dasatinib, and prednisone, followed by asciminib and dasatinib indefinitely or until allogeneic HCT. Eighty-four percent of patients achieved complete hematologic remission at day 28. By day 84, the complete hematologic remission rate had improved to 100%, with 89% achieving MRD negativity by multicolor flow cytometry.

Blinatumomab

In December 2014, the FDA approved blinatumomab for the treatment of relapsed or refractory Ph-negative precursor B-ALL (see Treatment of Relapsed Ph-Negative ALL for a detailed discussion of blinatumomab). In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-ALL (Ph-negative and Ph-positive). A follow-up, open-label, single-arm, multicenter, phase II study evaluated the efficacy and safety of blinatumomab in patients with R/R Ph-positive ALL who experienced disease progression after imatinib and at least one second- or third-generation TKI (n = 45).²⁴⁵ During the first 2 cycles of blinatumomab, 36% achieved complete remission or complete remission with partial hematologic recovery, and 88% of these responders achieved

a complete MRD response.²⁴⁵ Notably, responses were independent of T315I mutation status (see Initial Treatment in AYA Patients with Ph-Negative ALL for a discussion of studies related to blinatumomab and chemotherapy-resistant MRD).

In a phase II study that included 14 patients with R/R Ph-positive ALL, the chemotherapy free combination of blinatumomab plus ponatinib was evaluated.²⁴⁶ Patients received up to 5 cycles of ponatinib and continuous IV blinatumomab, followed by single agent ponatinib. Among patients with R/R disease with evaluable data, 92% achieved an overall response, with 79% achieving a complete molecular response.

Inotuzumab Ozogamicin

Following the generation of encouraging single-agent phase II data,²⁴⁷ a randomized study was conducted comparing inotuzumab ozogamicin (InO) with standard intensive chemotherapy regimens in Ph-negative or Ph-positive ALL in first or second relapse, defined as >5% marrow blasts (n = 326). Compared to standard therapy, InO produced a significantly higher CR/CRi rate (80.7% vs. 29.4%; P < .001) and higher MRD-negative rates (78.4% vs. 28.1%; P < .001).²⁴⁸ Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with Ph-positive leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic sinusoidal obstruction syndrome (SOS), observed in the InO group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs. 3.1 months; P = .03), median PFS (5 vs. 1.8 months; P < .001), and mean OS (13.9 vs. 9.9 months; P = .005).²⁴⁸ In August 2017, InO received full approval from the FDA for the treatment of R/R precursor B-ALL.

CAR T Cells

Currently, HCT is the only cure for R/R ALL, but many patients are not eligible for transplant based on age or progression of the disease. The generation of chimeric antigen receptor (CAR) T cells to treat ALL represents a significant advance in the field and has shown significantly greater OS than current regimens.²⁴⁹ Pre-treatment with CAR T cells has served as a bridge for transplant, and patients who were formerly unable to be transplanted due to poor remission status achieve a CR and ultimately proceed to transplantation. CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to engender a response against a leukemic cell-surface antigen, most commonly CD19/250 (see Treatment of Relapsed Ph-Negative ALL for a detailed discussion of CAR T cells). CAR T-cell therapy with tisagenlecleucel was recommended for accelerated approval by the FDA Oncologic Drug Advisory Committee in July 2017 and fully approved by the FDA in August 2017 for the treatment of patients <26 years of age with R/R precursor B-ALL. In October 2021, the FDA approved the second CAR T-cell therapy for adults with relapsed or refractory B-ALL: brexucabtagene autoleucel. This treatment is the first CAR T-cell therapy for patients ≥26 years of age in this setting. The 3rd CAR T-cell therapy for adults with relapsed or refractory B-ALL, obecabtagene autoleucel, was approved on November 8, 2024.

NCCN Recommendations for Ph-Positive B-ALL

AYA and Adult Patients with Ph-Positive B-ALL

The Panel recommends that Ph-positive B-ALL AYA and adult patients <65 years of age and no substantial comorbidities be treated in a clinical trial, when possible. In the absence of an appropriate clinical trial,

other recommended induction therapy options include would comprise multiagent therapy, blinatumomab, or corticosteroids blinatumomab or hyperCVAD combined with a TKI. Prior to initiation of blinatumomab, cytoreduction to a peripheral WBC count of $<10 \times 10^9/L$ is recommended, which can frequently be achieved with a TKI plus corticosteroid.¹⁷⁰ TKI options include (in alphabetical order): bosutinib, dasatinib, imatinib, nilotinib, or ponatinib. However, the Panel notes that not all TKIs have been studied within the context of each regimen, and there are limited data for bosutinib in Ph-positive B-ALL. Use of a specific TKI should account for anticipated or prior TKI intolerance, dose used, BCR::ABL1 mutations, and disease-related features. The PhALLCON study suggests improved MRD responses with ponatinib compared to imatinib.¹⁹¹ Imatinib use in first-line treatment should be restricted to patients who cannot tolerate broader acting TKIs. Additional induction options that may be useful in certain circumstances include a TKI in combination with either a corticosteroid or with vincristine and dexamethasone.

Treatment regimens should include adequate CNS prophylaxis for all patients. It is also important to adhere to the treatment regimens for a given protocol in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. For AYA patients and adults <65 years without substantial comorbidities, there are data to support the benefit of rituximab in addition to multiagent therapy (excluding immunotherapy) in the setting of CD20-positive disease.

For AYA and adult (<65 years of age) patients experiencing a marrow CR after initial induction therapy, an MRD assessment should be performed prior to consideration of consolidation therapy (see NCCN Recommendations for MRD Assessment). Given the complexity of MRD management, referral to or consultation with a center with expertise is recommended for any patient with ALL with MRD positivity. BCR::ABL1 qPCR positivity may reflect persistence in the myeloid compartment. Where feasible, flow sorting to isolate myeloid versus lymphoid cells for FISH/qPCR studies and/or NGS MRD may help to resolve. Of note, the presence of the Philadelphia chromosome in the myeloid compartment does not necessarily imply a diagnosis of CML with lymphoid blast transformation.

Adequate count recovery per protocol is necessary before transitioning to post remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow up for MRD may be warranted. Myelosuppression secondary to TKI should also be assessed, and consideration should be made for dose reduction.

Consolidation therapy options in the setting of MRD positivity or negativity may include blinatumomab combined with a TKI,^{170,246} continuation of multiagent therapy or corticosteroid combined with a TKI, or single agent TKI. In cases of MRD positivity, using an alternative and more broadly acting TKI is recommended. ABL1 kinase domain mutation testing is also recommended, though mutations associated with asciminib resistance can occur outside of the kinase domain. Relevant BCR::ABL1 mutations should be considered as outlined in the algorithm table titled, Treatment Options Based on BCR::ABL1 Mutation Profile. Ponatinib has activity against T315I mutations and is effective in treating patients with resistant or PD on multiple TKIs; however, it is associated with a high frequency of serious vascular events, such as stroke, heart attack, or tissue ischemia (see package insert for more details).

Allogeneic HCT is another consolidation option in the setting of MRD negativity for appropriate candidates. Many variables determine eligibility for allogeneic HCT, including donor availability, depth of remission, comorbidities, and social support.²⁵¹ The optimal time for a patient to receive allogeneic HCT is unclear; however, proceeding to allogeneic HCT with MRD is not optimal. In AYA patients ≤ 21 years of age, emerging data suggest that allogeneic HCT may not confer an advantage over multiagent combined with TKIs.²⁵²

Following consolidation therapy, repeat MRD assessment is recommended (see NCCN Recommendations for MRD Assessment). If MRD negativity is achieved following consolidation, options include maintenance TKI or allogeneic HCT followed by post-HCT TKI. TKI should be started as soon as feasible post-transplant. Although the optimal duration of post-transplant or maintenance TKI is unknown, TKI should be continued for at least 2 years post-transplant. Sequential MRD assessments should be considered for patients who have achieved a complete molecular remission (undetectable levels). The frequency may be increased if MRD levels are detectable or for those discontinuing TKI.

For patients receiving a maintenance TKI, weekly methotrexate and daily 6-MP may be added to the maintenance regimen, as tolerated; however, the doses of these antimetabolite agents may need to be reduced in the setting of hepatotoxicity or myelosuppression. Individuals who inherit a nonfunctional variant allele of the TPMT gene are known to be at high risk of developing hematopoietic toxicity (in particular, severe neutropenia) after treatment with 6-MP.¹⁴⁶ Testing for the TPMT gene polymorphism should be considered in patients receiving 6-MP as part of maintenance therapy, particularly those who experience severe bone marrow toxicities (see Role of MRD Evaluation).

In the setting of persistent, progressive, or emergent MRD, marrow progression, or development of extramedullary disease following consolidation therapy, ABL1 kinase domain mutation testing is recommended, followed by treatment for R/R disease (see Patients with Relapsed/Refractory Ph-Positive B-ALL). As noted previously, mutations associated with asciminib resistance can occur outside of the kinase domain.

Adult Patients ≥ 65 Years of Age with Ph-Positive B-ALL

For adult patients with Ph-positive B-ALL ≥ 65 years of age or with substantial comorbidities, the Panel recommends treatment in a clinical trial, when possible. In the absence of an appropriate clinical trial, other recommended therapies can be broken down into low and moderate intensity categories. Low intensity induction therapy options include TKI in combination with either blinatumomab, a corticosteroid, or vincristine and dexamethasone. A moderate intensity induction therapy option is TKI combined with mini-hyperCVAD rather than hyperCVAD. Treatment regimens should include adequate CNS prophylaxis for all patients, and a given treatment protocol should be followed in its entirety. Although the age cutoff indicated in the guidelines has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as age, performance status, end-organ function, and end-organ reserve. Dose modifications for patients age and performance status should also be considered.

For adult patients who are ≥ 65 years of age or who have substantial comorbidities, consolidation therapy is recommended to follow the same treatment preferences and considerations noted for AYA and adult patients (see NCCN Recommendations for Ph-Positive B-ALL; AYA and Adult Patients with Ph-Positive B-ALL).

Patients with Relapsed/Refractory Ph-Positive B-ALL

Mutation testing for the ABL1 kinase domain is recommended in patients with Ph+ B-ALL that have experienced relapse after or have disease refractory to initial TKI-containing therapy. The Panel has largely adopted the recommendations for treatment options based on ABL mutation status for CML, as published by the European LeukemiaNet.²⁴³ If not administered during initial induction, TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are recommended options for patients with R/R Ph+ B-ALL. The PhALLCON study suggests improved MRD responses with ponatinib compared to imatinib.¹⁷⁷

For second- and third-generation TKIs, relevant BCR::ABL1 mutations should be considered as outlined in the algorithm table titled, Treatment Options Based on BCR::ABL1 Mutation Profile.

For all patients with R/R Ph-positive B-ALL, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (ie, different from the TKI used as part of induction therapy) alone, TKI combined with systemic therapy regimens as previously discussed in the frontline setting, or TKI combined with corticosteroids (especially for patients who are older who may not tolerate multiagent combination therapy). Other options include asciminib plus dasatinib or blinatumomab or InO with or without a TKI. Compared to standard care, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic SOS, and increased risk of post-HCT non-relapse mortality.²⁵³ Although there are limited data, it is recommended to wait at least 4 weeks from InO monotherapy and the start of conditioning for allogeneic HCT to minimize risk of SOS. SOS has been shown to occur less frequently when less alkylators are used as part of the conditioning regimen.²⁵⁴

Brexucabtagene autoleucl and obecabtagene autoleucl are CAR-T cell therapy options for AYA and adult patients with R/R Ph-positive B-ALL following therapy that has included TKIs. Tisagenlecleucl is also an option for patients < 26 years of age and with refractory disease or ≥ 2 relapses and following therapy that has included 2 TKIs.

If patients who have not yet undergone transplant experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucl is unclear. Persistence of tisagenlecleucl in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT. In the global registration trial, estimated 3-year RFS rates were 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT.²⁵⁵ Further study will be required before conclusive recommendations can be made. In the absence of an appropriate clinical trial, for patients with T-ALL that is refractory to TKIs, regimens for R/R Ph-negative ALL can be considered. (See Treatment of Relapsed Ph-Negative ALL).

Management of Ph-Negative ALL

Initial Treatment in AYA Patients with Ph-Negative ALL

The AYA population with ALL can pose a unique challenge given that patients may be treated with either a pediatric or an adult protocol, depending on local referral patterns and institutional practices. The NCCN Guidelines for ALL are intended to apply to AYA patients treated in an adult oncology setting. For recommendations and discussion regarding the treatment of AYA patients with ALL in a pediatric oncology setting, see the NCCN Guidelines for Pediatric ALL (available at www.NCCN.org).

Retrospective analyses based on cooperative group studies from both the United States and Europe have consistently shown the superior outcomes for AYA patients (age range, 15–21 years) treated on pediatric versus adult ALL regimens. In the AYA population, 5-year EFS rates ranged from 63% to 74% for patients treated on a pediatric study protocol versus 34% to 49% for those receiving the adult protocol.^{92,93,121,256,257} In a retrospective comparative study that analyzed outcomes of AYA patients (age range, 16–20 years) treated on a pediatric CCG study protocol (n = 197; median age, 16 years) versus an adult CALGB study protocol (n = 124; median age, 19 years), patients treated on the pediatric regimen compared with those on the adult regimen had significantly improved 7-year EFS (63% vs. 34%, respectively; P < .001) and OS (67% vs. 46%, respectively; P < .001) rates.¹²¹ Moreover, AYA patients treated on the adult protocol experienced a significantly higher rate of isolated CNS relapse at 7 years (11% vs. 1%; P = .006). The substantial improvements in outcomes observed with the pediatric regimen in this study, and in the earlier retrospective analyses from other cooperative groups, may be largely attributed to the use of greater cumulative doses of drugs, such as corticosteroids (prednisone and/or dexamethasone), vincristine, and L-asparaginase, and to earlier, more frequent, and/or more intensive CNS-directed therapy compared with adult regimens.¹²¹ Given the success seen with multiagent intensive therapy regimens for pediatric patients with ALL, several clinical trials have evaluated pediatric-inspired regimens for the AYA patient population.

Hematopoietic Cell Transplant

For AYA patients with Ph-negative ALL in first CR, allogeneic HCT may be considered for high-risk cases—particularly for patients with disease that is MRD positive any time after induction; or patients with elevated WBC counts; or patients with B-ALL and poor-risk cytogenetics [eg, hypodiploidy, KTM2A (MLL) rearrangement] at diagnosis. A large multicenter trial (LALA-94 study) evaluated the role of postinduction HCT as one of the study objectives in adolescent and adult patients with ALL receiving therapy for previously untreated ALL (n = 922; median age, 33 years; range, 15–55 years).⁹⁵ Patients were stratified into four risk groups: 1) Ph-negative standard-risk disease [defined as achievement of CR after 1 course of chemotherapy; absence of CNS disease; absence of t(4;11), t(1;19), or other 11q23 rearrangements; WBC count <30 × 10⁹/L]; 2) Ph-negative high-risk ALL (defined as patients with non-standard-risk disease and without CNS involvement); 3) Ph-positive ALL; and 4) evidence of CNS disease. After induction therapy, patients with Ph-negative high-risk ALL were eligible to undergo allogeneic HCT if a matched sibling donor was available; those without a sibling donor were randomized to undergo autologous HCT or chemotherapy alone.⁹⁵ Among the subgroup of patients with Ph-negative high-risk ALL (n = 211), the 5-year DFS and OS rates were 30% (median, 16 months) and 38% (median, 29 months), respectively. Based on intent-to-treat analysis, outcomes in patients with Ph-negative high-risk ALL were similar for autologous HCT (n = 70) and chemotherapy alone (n = 59) in terms of median DFS (15 vs. 11 months), median OS (28 vs. 26 months), and 5-year OS rate (32% vs. 21%).⁹⁵ Outcomes were improved in patients with Ph-negative high-risk ALL and those with CNS involvement allocated to allogeneic HCT. The median DFS was 21 months for these patients, and the median OS has not yet been reached; the 5-year OS rate was 51%.⁹⁵ Thus, it appears that in patients with Ph-negative high-risk disease, allogeneic HCT in first CR improved DFS outcomes, whereas autologous HCT did not result in significant benefit compared with chemotherapy alone.

In the PETHEMA ALL-93 trial, adult patients with high-risk ALL [defined as having at least one of the following criteria: 30–50 years of age; WBC count ≥25 × 10⁹/L; presence of t(9;22), t(4;11), or other 11q

rearrangements; and t(1;19)] received postremission induction therapy (n = 222 eligible; median age, 27 years; range, 15–50 years) with allogeneic HCT (n = 84; if matched related donor available), autologous HCT (n = 50), or chemotherapy alone (n = 48).²⁵⁸ Based on intent-to-treat analysis of data from patients with Ph-negative high-risk disease, no significant advantage was observed in a donor versus no-donor comparison of median DFS (21 vs. 38 months), median OS (32 vs. 67 months), 5-year DFS rate (37% vs. 46%), or 5-year OS rate (40% vs. 49%). In addition, when the analysis was conducted based on the actual postremission treatment received, no significant differences were noted between treatment arms for 5-year DFS rates (50% for allogeneic HCT; 55% for autologous HCT; and 54% for chemotherapy alone).²⁵⁸

The role of allogeneic HCT in adults with ALL was also evaluated in the large multicenter MRC UKALL XII/ECOG E2993 study (n = 1913; age range, 15–59 years).⁹⁶ In this study, high risk was defined as ≥ 35 years of age; time to CR > 4 weeks from induction; elevated WBC counts ($> 30 \times 10^9/L$ for B-ALL; $> 100 \times 10^9/L$ for T-ALL); or the presence of Ph chromosome. All other patients were considered to have standard-risk disease. Patients experiencing a remission with induction therapy were eligible to undergo allogeneic HCT if a matched sibling donor was available or, in the absence of a sibling donor, were randomized to undergo autologous HCT or chemotherapy. The 5-year OS rate was higher for patients randomized to chemotherapy alone compared with autologous HCT (46% vs. 37%; P = .03). A donor versus no-donor comparison in all patients with Ph-negative ALL showed that the 5-year OS rate was significantly higher in the donor group than in the no-donor group (53% vs. 45%; P = .01). This advantage in OS outcomes for the donor group was observed for patients with standard-risk disease (62% vs. 52%; P = .02) but not for those with Ph-negative high-risk disease (41% vs. 35%).⁹⁶ This was partly because of the high rate of non-relapse mortality observed with the donor group compared with the no-donor group in patients with high-risk disease (36% vs. 14% at 2 years). Among patients with standard-risk disease, the non-relapse mortality rate at 2 years was 19.5% for the donor group and 7% for the no-donor group. Relapse rate was significantly lower in the donor group than in the no-donor group for both patients with standard-risk disease (24% vs. 49%; P < .001) and those with high-risk disease (37% vs. 63%; P < .001).⁹⁶ Nevertheless, the high non-relapse mortality rate in the donor group among patients with high-risk disease seemed to diminish the advantage of reduced risk for relapse in this group. This study suggested that allogeneic HCT in first CR was beneficial in patients with standard-risk ALL.

The benefit of matched sibling allogeneic HCT in adults with standard-risk ALL was also reported by the HOVON cooperative group. In a donor versus no-donor analysis of patients with standard-risk ALL undergoing postremission therapy with matched sibling allogeneic HCT or autologous HCT, the donor arm was associated with a significantly reduced 5-year relapse rate (24% vs. 55%; P < .001) and a higher 5-year DFS rate (60% vs. 42%; P = .01) compared with the no-donor arm.²⁵⁹ In the donor group, the non-relapse mortality rate at 5 years was 16% and the 5-year OS rate was 69%.²⁵⁹

As evidenced by the previously described studies, matched sibling HCT has been established as a valuable treatment strategy for patients with both standard and high-risk Ph-negative ALL, but subsequent studies have examined the role of URD transplants in high-risk Ph-negative ALL. In a retrospective analysis of 169 patients who underwent URD HCT during first CR, 60 patients (36%) had one poor prognostic factor and 97 (57%) had multiple risk factors. The 5-year survival rate was 39%, which is higher than survival rates reported in studies of patients with high-risk disease receiving chemotherapy alone.²⁶⁰ The most significant percentage of treatment-related mortality occurred in patients who were given mismatched donors compared to partially or well-matched donors. There was no significant difference in outcome between patients < 35 years of age and patients > 35 years of age, suggesting that URD transplants may be an option for patients who are older. In a follow-up retrospective study by the same group, RIC was evaluated to lower treatment-related mortality.²⁶¹ RIC conditioning most commonly comprised busulfan (≤ 9 mg/kg), melphalan (150 mg/m²), low-dose total body irradiation (TBI) (< 500 cGy single dose or < 800 cGy fractionated), or fludarabine plus TBI of 200 cGy. RIC is more prominent in the treatment of patients who are older; therefore, the median age for patients receiving full-intensity (FI) conditioning was 28 years (range, 16–62 years), and for patients receiving RIC, the median age was 45 years (range, 17–66 years). Despite the variation in age, results from the study have shown no difference in relapse (35% vs. 26%; P = .08) or in treatment-related mortality (FI, 33%; 95% CI, 31%–36% vs. RIC, 32%; 95% CI, 23%–43%; P = .86) at 3 years.²⁶¹ The 3-year survival for HCT was similar following first CR (FI, 51%; 95% CI, 48%–55% vs. RIC, 45%; 95% CI, 31%–59%) and second CR (FI, 33%; 95% CI, 30%–37% vs. RIC, 28%; 95% CI, 14%–44%). The DFS was similar in both groups following first CR (FI, 49%; 95% CI, 45%–53% vs. RIC, 36%; 95% CI, 23%–51%) and in second CR (FI, 32%; 95% CI, 29%–36% vs. RIC, 27%; 95% CI, 14%–43%).²⁶¹

A systematic review and meta-analysis of published randomized trials on post-remission induction therapy in adults with ALL reported a significant reduction in all-cause mortality with allogeneic HCT in first CR (RR, 0.88; 95% CI, 0.80–0.97) compared with autologous HCT or chemotherapy.²⁶² A subgroup analysis showed a significant survival advantage with allogeneic HCT in standard-risk ALL, whereas a nonsignificant

advantage was seen in high-risk ALL.²⁶² Autologous HCT in first remission was not shown to be beneficial relative to chemotherapy in several large studies and meta-analyses.^{95,96,262,263}

DFCI ALL Regimen Based on DFCI Protocol 00-01

A multicenter phase II trial evaluated the pediatric-inspired regimen based on the DFCI Childhood ALL Consortium Protocol 00-01 in AYA and adult patients (aged 18–50 years) with previously untreated ALL; 20% of the patients in this study had Ph-positive disease.²⁶⁴ The treatment regimen comprised induction (vincristine, doxorubicin, prednisone, L-asparaginase, and high-dose methotrexate), triple IT therapy, intensification, and maintenance. Among the 75 patients with evaluable data, the estimated 2-year EFS and OS rates were 72.5% and 77%, respectively.²⁶⁴ Adverse events included one death from sepsis (during induction), pancreatitis in nine patients (12%; including 1 death), osteonecrosis in two patients (3%), thrombosis/embolism in 14 patients (19%), and neutropenic infection in 23 patients (31%).²⁶⁴ After a median follow-up of 4.5 years, the 4-year DFS rate for patients with Ph-negative ALL ($n = 64$) and those who achieved CR was 71% (95% CI, 58%–81%), and the 4-year OS rate for all patients with Ph-negative ALL was 70% (95% CI, 58%–79%).²⁶⁵ A phase II successor trial was initiated to determine whether PEG could be substituted for L-asparaginase in this regimen.²⁶⁶ A high frequency of asparaginase toxicities precipitated reverting to L-asparaginase during induction and a dose-reduction of PEG during consolidation. After 4 weeks, the CR rate was 89%, and with a median follow-up of 39 months, the estimated 3-year DFS and OS rates were 73% and 75%, respectively.²⁶⁶ These data suggest that intensive pediatric regimens are feasible, with potential modifications, in young adults with previously untreated ALL; however, further follow-up data are needed to evaluate long-term survival outcomes.

MSKCC ALL Regimen Based on CCG-1882 Regimen

The MSKCC ALL trial based on the pediatric CCG-1882 regimen has studied the regimen of daunorubicin, vincristine, prednisone, and methotrexate with augmented PEG in patients between 18 and 60 years of age with newly diagnosed ALL ($n = 51$).^{267,268} The augmented arm included one long-lasting PEG dose in each cycle of the 6 total scheduled doses. Each dose of PEG (2000 IU/m² IV) was preceded with hydrocortisone for hypersensitivity prophylaxis followed by 1 to 2 weeks of oral steroids. Patients on this trial received a mean of 3.8 doses per patient with 45% of patients receiving all 6 doses, while 20% of patients discontinued treatment based on toxicity. The 7-year OS was 51% (58% of these patients had Ph-negative disease) and the 7-year DFS was 58%. The dose of PEG was lower than the FDA-approved dose of 2500 IU/m² and adjustments to the dosing interval were made to be ≥ 4 weeks. This deviated from the pediatric protocol to account for the difference in drug enzymatic activity in adults. Study data suggest that adaptation of the pediatric regimen to the adult population may be feasible with modifications to reduce toxicity.

CALGB 10403 Regimen

A multicenter phase II Intergroup study (CALGB 10403) was conducted to evaluate a pediatric-inspired regimen in the treatment of AYA patients with Ph-negative ALL. One of the study objectives was to compare the outcomes of patients treated in this trial with those of a similar group of patients (in regard to age and disease characteristics) treated by pediatric oncologists in the COG trial (AALL0232). The treatment protocol included a 4-drug induction regimen with IT cytarabine and IT methotrexate, consolidation, interim maintenance, delayed intensification, maintenance (for 2–3 years), and radiotherapy (for patients with testicular or CNS disease or those with T-ALL). Results from 295 patients with evaluable data (median age, 24 years; range 17–39 years) reported two post-remission deaths and 3% overall treatment-related mortality.²⁶⁹ The median EFS was 78.1 months (95% CI, 41.8 months – NR) and the 3-year EFS rate was 59% (95% CI, 54%–65%). The estimated 3-year OS rate was 73% (95% CI, 68%–78%).²⁶⁹ It was also noted that post-induction MRD positivity, Ph-like gene expression signatures, and obesity were associated with worse treatment outcomes.²⁶⁹

COG AALL0434 Regimen

Nelarabine is a nucleoside metabolic inhibitor and a prodrug of ara-G, approved for the treatment of patients with T-ALL with disease that has not responded to or that has relapsed after at least 2 chemotherapy regimens. The randomized phase III COG study (AALL0434) evaluated the safety of nelarabine as part of frontline therapy, using the augmented BFM chemotherapy regimen, with or without nelarabine, and showed that the toxicity profiles were similar between patients with high-risk T-ALL who received nelarabine ($n = 47$) and those who did not ($n = 47$).²⁷⁰ No significant differences were observed in the occurrence of neurologic adverse events between these groups, including peripheral motor neuropathy, peripheral neuropathy, or CNS neurotoxicity. The incidence of adverse events such as febrile neutropenia and elevation of liver enzymes was also similar between treatment groups. These initial safety data suggest that nelarabine may be better tolerated in frontline regimens than in the R/R setting.²⁷⁰

Results from the efficacy phase of this study evaluated data from 1895 patients with newly diagnosed T-ALL and T-LL.²⁷¹ Patients were randomized to receive escalating dose methotrexate without leucovorin rescue and PEG or high-dose methotrexate with leucovorin rescue. Patients with intermediate and high-risk T-ALL and T-LL all received prophylactic or therapeutic cranial irradiation and were randomized into arms with or without nelarabine (650 mg/m²/day). The 4-year DFS rate for patients with T-ALL in the nelarabine arm (n = 323) versus those who did not receive nelarabine (n = 336) was 88.9% ± 2.2% and 83.3% ± 2.5%, respectively (P = .0332).²⁷¹ Compared to the high-dose methotrexate and nelarabine arm, use of escalating-dose methotrexate and nelarabine appeared to enhance the 4-year DFS rates.²⁷¹ Another report from the COG AALL0434 study determined that compared to high-dose methotrexate, escalating-dose methotrexate combined with augmented BFM chemotherapy improves DFS and OS outcomes in patients with T-ALL.²⁷²

A single-arm phase II study from the MDACC evaluated the efficacy of hyperCVAD plus nelarabine as frontline therapy in adults with T-ALL (n = 23).²⁷³ With a median follow-up of 30.4 months (range, 2.4–69.2 months), the CR rate for patients with T-ALL was 89%; however, a trend for inferior DFS and OS was observed for patients with ETP-ALL.²⁷³ After a median follow-up of 42.5 months, the 3-year complete remission duration and OS rates were 66% (95% CI, 52%–77%) and 65% (95% CI, 51%–76%), respectively.²⁷⁴ These studies suggest that for patients with T-ALL, the addition of nelarabine to frontline therapy may be a promising approach.

HyperCVAD with or without Rituximab or Blinatumomab

The hyperCVAD regimen constitutes another commonly used ALL treatment regimen for adults. A phase II study from MDACC evaluated hyperCVAD in adolescents and adults with previously untreated ALL (n = 288; median age, 40 years; range, 15–92 years; Ph-positive in 17%).²⁰

The median OS for all patients was 32 months and the 5-year OS rate was 38%, with a median follow-up of 63 months. Among the patients with Ph-negative ALL (n = 234), the 5-year OS rate was 42%.²⁰ Among patients who experienced a CR (92% of all patients), the 5-year CR duration rate was 38%.²⁰ Death during induction therapy occurred in 5% of patients, and was more frequent among patients ≥60 years of age. The 5-year OS in patients >60 years of age was 17%.²⁰ A subsequent retrospective review from the same institution suggested that this may be related to higher rates of death in remission (34%) relative to patients <60 years of age (7%).²⁷⁵

Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (generally defined as CD20 expression on >20% of blasts) was found to be associated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.^{42,276} Given the prognostic significance of CD20 expression in these patients, treatment regimens incorporating the CD20 monoclonal antibody rituximab have been evaluated. A phase II study from MDACC evaluated hyper-CVAD with or without rituximab in patients with newly diagnosed Ph-negative B-lineage ALL (n = 282; median age, 41 years; range, 13–83 years).¹⁶⁴ Among the subgroup of patients with CD20-positive ALL who were treated with hyperCVAD combined with rituximab, the 3-year CR duration and OS rates were 67% and 61%, respectively. In addition, among patients <60 years of age with CD20-positive disease, modified hyperCVAD plus rituximab resulted in a significantly improved CR duration (70% vs. 38%; P < .001) and OS rate (75% vs. 47%; P = .003) compared with the standard hyperCVAD regimen without rituximab.¹⁶⁴ No significant differences in outcomes with the addition of rituximab were noted for the subgroup of patients with CD20-negative disease. Notably, patients ≥60 years of age with CD20-positive disease demonstrated higher rates of MRD negativity with the inclusion of rituximab; however, this did not translate into a survival benefit, again largely due to increased mortality in CR. It is worth noting that this high rate of death in CR for patients ≥60 years of age may relate to anthracycline intensification as opposed to rituximab.²⁷⁷

Another phase II study from MDACC evaluated hyperCVAD and sequential blinatumomab in patients with newly diagnosed Ph-negative B-ALL (n = 38; median age, 37 years).²⁷⁸ Treatment consisted of 4 cycles of hyperCVAD followed by 4 cycles of blinatumomab consolidation. Maintenance consisted of 15 cycles of alternating POMP for 3 cycles and blinatumomab for 1 cycle. Three-year RFS was estimated at 73%, with no relapses >2 years from the start of therapy. Grade 3 CRS occurred in one patient (3%), while four patients (11%) had grade 3 neurological events related to blinatumomab.

Blinatumomab

Blinatumomab has shown promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al²⁷⁹ evaluated the efficacy of blinatumomab in patients with MRD-positive Ph-negative B-ALL (n = 21; age range, 20–77 years). Patients were considered to have MRD-positive disease if they had never achieved MRD negativity before blinatumomab or had experienced a hematologic CR with MRD ≥10⁻⁴. After blinatumomab treatment, 16

of 20 patients with evaluable data were determined to have achieved MRD negativity at a detection threshold of 10^{-4} .²⁷⁹ After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.²⁸⁰ Gökbüget et al²⁸¹ examined the efficacy of blinatumomab in an expanded cohort ($n = 116$) using a higher threshold for MRD positivity (hematologic CR with MRD $\geq 10^{-3}$). After one 28-day cycle of blinatumomab, 88 of 113 patients with evaluable data achieved a complete MRD response, and the RFS rate at 18 months was 54%.²⁸¹ In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective “bridge to transplant” in patients with MRD-positive disease. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.²⁸²⁻²⁸⁴ In March 2018, the FDA approved blinatumomab use for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease $\geq 0.1\%$ (see Treatment of Relapsed Ph-Negative B-ALL for discussion of studies related to blinatumomab use in R/R B-ALL).

Initial Treatment in Adults with Ph-Negative ALL

Hematopoietic Cell Transplant

Studies evaluating HCT in first CR for AYA patients with Ph-negative ALL have generally been inclusive of adult patients and therefore have been discussed previously (see Initial Treatment in AYA Patients with Ph-Negative ALL). More aggressive therapies are being considered for patients who are older or less fit. A retrospective study of 576 adults >45 years of age compared RIC or MAC allogeneic HCT from HLA-matched siblings.¹⁸⁷ Patients who received RIC ($n = 127$) versus MAC ($n = 449$) showed no statistically significant difference in leukemia-free survival ($P = .23$; HR, 0.84), thereby supporting the incorporation of more aggressive treatments for this population.¹⁸⁷

CALGB 9111 Regimen

The CALGB 9111 study evaluated the impact of adding granulocyte colony-stimulating factor (G-CSF) after intensive therapy (CALGB 8811 Larson regimen; a 5-drug induction regimen comprising vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) on neutrophil recovery in adults with ALL ($n = 198$; median age, 35 years; range, 16–83 years).²⁸⁵ Patients were randomized to receive either placebo or G-CSF beginning 4 days after induction, and the G-CSF group continued G-CSF treatment during consolidation. Although the addition of G-CSF did not result in a significant impact in OS or DFS, patients in the G-CSF group had significantly shorter durations of neutropenia and thrombocytopenia, a higher CR rate, and lower induction mortality ($P = .04$) compared to patients in the placebo group.²⁸⁵ Among the 41 patients >60 years of age randomized to G-CSF ($n = 21$) or placebo ($n = 20$), G-CSF use was associated with lower induction mortality (10% vs. 25%); however, this did not meet statistical significance. The reduction observed with induction mortality was accompanied by a similarly non-significant increase in CR rate for those receiving G-CSF (81% vs. 55%; $P = .1$). For the entire group ≥ 60 years of age, median OS was improved to 12 months, but 3-year OS remained poor at 17%.²⁸⁵

GRAALL- 2014 Regimen

Studies involving the GRAALL-2005 regimen investigated the addition of rituximab for CD20-positive disease in both AYA and adult patients.^{286,287} The role of standard-dose versus hyperfractionated cyclophosphamide during first induction and late intensification in adults with newly diagnosed Ph-negative ALL was evaluated in a subsequent report from the GRAALL-2005 trial.²⁸⁸ After a median follow-up of 5.2 years, randomization to the hyperfractionated cyclophosphamide arm did not increase the CR rate or prolong EFS or OS rates, and tolerability to this regimen was poor in patients ≥ 55 years of age.²⁸⁸

The GRAALL-2014 study aimed to improve outcomes of the GRAALL-2005 by reducing chemotherapy intensity in patients aged 45 to 59 years and modifying the indication for HCT to only a post-induction MRD $\geq 10^{-3}$ and/or a post-consolidation MRD $\geq 10^{-4}$.²⁸⁹ Compared to GRAALL-2005, induction death rate was significantly reduced in GRAALL-2014 among patients aged 45 to 59 years (3% vs. 11%; $P = .001$). CR rate was also higher in this age group in GRAALL-2014 (92% vs. 86%; $P = .05$), attributed to a higher need for second induction due to the reduced-intensity of first induction. In light of MRD-based HCT indication, fewer patients proceeded to HCT on GRAALL-2014, leading to an increase in 3-year CIR (35% vs. 28%; $P = .01$), though a reduction in 3-year cumulative incidence of transplant related mortality (5% vs. 11%; $P < .001$) and OS (71% vs. 64%; $P = .002$).

In the phase II GRAALL-2014 T ATRIAL study of adult patients with T-ALL, patients were deemed to be at high risk based on the presence of RAS/PTEN alterations or lack of NOTCH1/FBXW7 mutations.^{116,290} Patients in the high risk group were offered 2 cycles of nelarabine combined with etoposide and cyclophosphamide during consolidation and another 3 cycles during maintenance, though some received standard of care without nelarabine.²⁹⁰ Following 1 cycle, patients with MRD $\geq 10^{-3}$ and/or post-consolidation MRD $\geq 10^{-4}$ were eligible for HCT. When censored at time of transplant, the addition of

nelarabine was associated with a significant reduction in CIR (P = .045) and a non-significant prolongation of DFS (P = .075). The benefit of nelarabine was similar in patients in the high-risk group who were not eligible for transplant, with a significant reduction in CIR (P = .045) and a non-significant prolongation of DFS (P = .06). While patients with ETP-ALL did not benefit from nelarabine, the addition of nelarabine in patients with non-ETP ALL led to significant improvements in both CIR (P = .025) and DFS (P = .048).

MSKCC ALL Regimen

Based on CCG-1882 Regimen Studies evaluating MSKCC ALL regimen have included both AYA and adult patients.^{267,268} For discussion of these studies, refer to the previous section (see Initial Treatment in AYA Patients with Ph-Negative ALL).

HyperCVAD with or without Rituximab or Blinatumomab

Studies evaluating hyperCVAD with or without rituximab or blinatumomab have included both AYA and adult patients.^{20,164,278} For discussion of these studies, refer to the previous section (see Initial Treatment in AYA Patients with Ph-Negative ALL).

A separate phase II MDACC study evaluated the use of hyperCVAD with or without blinatumomab in patients ≥ 60 years of age with newly diagnosed Ph-negative B-ALL.²⁹¹ Treatment consisted of 4 cycles of mini-hyperCVD followed by 4 cycles of blinatumomab consolidation. Maintenance therapy consisted of 3 cycles of POMP alternating with 1 cycle of blinatumomab for a total of 12 cycles. Five-year PFS was 44%. The most common grade 3–4 events were hematological. Six patients (8%) developed SOS, four of which were fatal.

Mini-hyperCVD plus Venetoclax

Venetoclax is a selective BCL2 inhibitor that is currently FDA approved for treatment of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) as well as in combination with hypomethylating agents (HMAs) or low-dose cytarabine for treatment of newly diagnosed AML in those ≥ 75 years or those with comorbidities precluding intensive induction chemotherapy. It has also been studied in the treatment of R/R T-ALL.

An ongoing phase Ib/II study is investigating the combination of venetoclax with mini-hyperCVD in the treatment of patients ≥ 55 years or ≥ 50 years with BMI ≥ 35 kg/m² with newly diagnosed Ph-negative B-ALL or T-ALL (n = 30; median age, 68 years).²⁹² Patients received hyperCVAD along with venetoclax (with ramp up for cycle 1) for 21 days out of a 28-day cycle for up to 8 cycles or until allogeneic HCT, followed by venetoclax in addition to POMP maintenance for up to 2 years. Eighty-three percent of patients achieved MRD-negative CR by a median of 1 cycle). Among those who achieved CR, 44% proceeded to allogeneic HCT in CR1. With a median follow-up of 16.4 months, estimated 12-month OS and EFS were 82.1% and 82.9%, respectively. Estimated 24-month OS and RFS were 74.6% and 67.8%, respectively. The addition of venetoclax did not slow count recovery, with a median time of 34 days between the 1st and 2nd cycles of therapy.

Inotuzumab Ozogamicin

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyperCVD) was evaluated in adults with a median age of 68 years with newly diagnosed Ph-negative ALL and an ECOG performance status ≤ 3 (n = 52; interquartile range, 64–72 years).²⁹³ Compared to hyperCVAD, mini-hyperCVD has no anthracycline and is composed of reduced doses of dexamethasone (50% reduction), methotrexate (75% reduction), and cytarabine (given every 12 hours at 0.5 g/m² on days 2 and 3). In this study, InO was given on day 3 of the first 4 courses at 1.3–1.8 mg/m² for cycle 1, followed by 1.0–1.3 mg/m² for subsequent cycles.²⁹³ In addition, maintenance therapy with dose-reduced POMP (6-MP, vincristine sulfate, methotrexate, and prednisone) was given for 3 years. With a median follow-up of 29 months, the 2-year PFS was 59% (95% CI, 43%–72%).²⁹³ Some of the most frequent grade 3 and 4 adverse events were prolonged thrombocytopenia (81%), infections during induction and consolidation (52% and 69%, respectively), and hyperglycemia (54%).²⁹³ In this study, SOS occurred in four patients (8%).

A phase II study evaluated InO monotherapy in 26 patients (median age, 46 years; range, 19–70 years) with B-cell ALL in CR1 or beyond with positive MRD ($\geq 1 \times 10^{-4}$).²⁹⁴ After a median of 3 cycles (range, 1–6 cycles; 69% of patients achieved MRD negativity. Two-year RFS and OS rates were 54% and 60%, respectively. Eight percent of patients developed SOS and the remainder of adverse events were noted to be low grade.

In the ongoing phase II INITIAL-1 trial, InO combined with dexamethasone is being investigated as an induction regimen for patients ≥ 55 years of age (n = 43; median age, 64 years; age range, 56–80 years)

with newly diagnosed Ph-negative B-ALL.²⁹⁵ Up to 3 cycles of InO/dexamethasone induction were given, followed by up to 6 cycles of GMALL consolidation adapted by age and maintenance therapy. All

patients achieved CR/CRi following 2 to 3 cycles of InO/dex. Following cycle 2, 53% of patients achieved MRD negativity, while 30% achieved MRD negativity following cycle 3. With a median follow-up of 2.7 years, 1-year EFS and OS were 88% and 91%, respectively. Three-year EFS and OS were 55% and 73%, respectively.

In the ongoing phase II Alliance A041703 trial, the chemotherapy-free regimen of inotuzumab ozogamicin for induction followed by blinatumomab consolidation is being investigated in patients ≥ 60 years of age ($n = 33$; median age, 71 years; range, 60–84 years) with newly diagnosed Ph-negative B-ALL with no plans for allogeneic HCT.²⁹⁶ Induction course IA included InO at a dose of 0.8 mg/m² on day 1 followed by 0.5 mg/m² on days 8 and 15 of a 21-day cycle. Those with adequate cytoreduction, defined as bone marrow (BM) blasts $\geq 50\%$ or cellularity $\leq 20\%$, went on to receive either induction IB (InO, 0.5 mg/m² on days 1, 8, and 15 of a 28-day cycle) if CR/CRi was achieved or induction IC (InO, 0.8 mg/m² on days 1, 8, and 15 of a 28-day cycle) if having not achieved CR/complete remission with incomplete hematologic recovery (CRI). Those with inadequate cytoreduction to induction IA or those without events in induction IA, IB, or IC began blinatumomab consolidation. Those achieving CR/CRi with InO received a total of three 28-day cycles of blinatumomab, while all others received a total of 4 cycles. The cumulative CR rate through induction InO courses was 85% and for blinatumomab consolidation was 97%. With a 22-month median follow-up, 1-year EFS was 75% (95% CI, 61%–92%) and 1-year OS was 84% (95% CI, 72%–98%).

GRAALL-SA1 Regimen

In an effort to decrease toxicity, the GRAALL-SA1 study compared the efficacy and toxicity of pegylated liposomal doxorubicin (Peg-Dox) to continuous infusion doxorubicin (CI-Dox) in patients ≥ 55 years of age with ALL.²⁹⁷ In this moderate-intensity regimen containing vincristine, dexamethasone, and cyclophosphamide, patients were randomized to receive either CI-Dox ($n = 31$; 12 mg/m²/day) or Peg-Dox ($n = 29$; 40 mg/m²).²⁹⁷ Compared to the CI-Dox arm, the Peg-Dox arm was significantly associated with reduced toxicity and fewer infections, but there was no survival benefit: the induction mortality rate was 8% (CI-Dox arm, 7% vs. Peg-Dox arm, 10%), the frequency of refractory disease after induction was 10% (CI-Dox arm, 17% vs. Peg-Dox arm, 3%; $P = .1$), and the CR rate was 82% (CI-Dox arm, 90% vs. Peg-Dox arm, 72%; $P = .1$).²⁹⁷ At 2 years, the estimated death in CR was 26.5% (CI-Dox arm, 37% vs. Peg-Dox arm, 19%), and the OS and EFS rates were statistically similar at 35% and 24% in the CI-Dox and Peg-Dox arms, respectively.²⁹⁷

GMALL Regimen

In a prospective trial, the GMALL group evaluated the efficacy of a moderate-intensity regimen in adults aged 55 to 85 years with Ph-negative ALL ($n = 268$).²⁹⁸ The induction therapy consisted of induction I (dexamethasone, vincristine, idarubicin) and induction II (cyclophosphamide, cytarabine), with rituximab added for patients with CD20-positive disease. The original treatment protocol (group 1) was modified to evaluate CNS prophylaxis with liposomal cytarabine and alternative consolidation with asparaginase (group 2); and after induction, 1 cycle with 500 U/m² PEG was scheduled to evaluate feasibility (group 3). The reported overall CR rate was 76% ($n = 203$), and the CR rates in groups 1, 2, and 3 were 72%, 86%, and 82%, respectively.²⁹⁸ The 5-year OS rate was 23%, and the 2-year OS rates observed in groups 1 and 2 were 33% and 52%, respectively.²⁹⁸ A major finding from this study included the importance of the ECOG performance status before the onset of ALL (ECOGb) at predicting induction mortality. Patients with an ECOGb score ≥ 2 correlated with higher induction mortality rates compared to those with an ECOGb score of 0 to 1 (53% vs. 7%, respectively; $P < .0001$).²⁹⁸ In addition, the study showed that consolidation with native *Escherichia coli* asparaginase and PEG was feasible and well tolerated, and was associated with improvements in CR rates and 2-year OS in this aged 55 to 85 years patient subset.²⁹⁸

PETHEMA-Based Regimen

The Spanish PETHEMA group conducted phase II prospective studies in patients aged 56 to 79 years with Ph-negative ALL (ALLOLD07; $n = 56$).^{299,300} The ALLOLD07 protocol was based on a protocol from EWALL, and treatment comprised a 4-week induction with dexamethasone, vincristine, idarubicin, cyclophosphamide, and cytarabine, followed by consolidation with intermediate-dose methotrexate and native *E. coli* asparaginase. The CR rate was 74% with an early death rate of 13%. The median DFS was 8 months with a median OS of 12 months. This trial included other adapted regimens for Ph-positive ALL and mature B-ALL groups, but the outcomes were poorest in the Ph-negative ALL group.³⁰⁰

Modified DFCI 91-01 Protocol

A retrospective analysis examined the efficacy of a modified version of a DFCI pediatric protocol, DFCI 91-01,^{301,302} in adults with newly diagnosed ALL ($n = 51$; age range, 60–79 years).³⁰³ Induction consisted

of dexamethasone (in place of prednisone), doxorubicin, cytarabine, and reduced doses of methotrexate, vincristine, and native asparaginase. For patients who achieved CR, the median time to recurrence was 30 months (range, 1–94 months).³⁰³ In patients with Ph-negative disease (n = 35), the CR rate was 71%, with induction mortality and primary refractory rates of 20% and 9%, respectively.³⁰³ The DFS rate amongst those achieving CR was 57.4% (95% CI, 32.8%–75.8%), while the overall estimated 5-year OS was 40.5% (95% CI, 20%–60.2%).³⁰³

Low-Intensity Chemotherapy and Corticosteroids

For adults who are older with ALL who may also have multiple comorbidities, the utility of traditional chemotherapy backbones based on vincristine, corticosteroids, and an anthracycline is limited largely due to treatment-related toxicities.³⁰⁴ Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP.^{305–308} While these regimens are unlikely to generate cure, they can palliate the disease and extend survival, with clinical outcomes similar to those achieved with more intensive protocols. It is important to note that adults who are older with ALL and multiple comorbidities have not typically qualified for clinical trials. To improve clinical outcomes, trials designed specifically for this population are needed. These should include novel, personalized approaches based on immunophenotype and/or genetic mutation status.

Blinatumomab

The referenced studies evaluating the efficacy of blinatumomab at eradicating MRD during or after multiagent therapy included both AYA and adult patients.^{279–281} For a discussion of these studies, refer to the previous section (see Initial Treatment in AYA Patients with Ph-Negative ALL).

ECOG-ACRIN E1910 Regimen

In contrast to prior studies investigating blinatumomab as a means of eradicating MRD during or after multiagent therapy, this phase III trial investigated whether blinatumomab could improve outcomes in patients receiving chemotherapy who had achieved MRD negativity (<0.01%).³⁰⁹ Patients with newly diagnosed Ph-negative B-ALL between the ages of 30 to 70 years initially received multiagent induction therapy with a BFM-like regimen adapted from E2993/UKALLXII. PEG was added for patients <55 years of age and rituximab was added for CD20 positivity. Following induction, patients who achieved a CR/CRi remained on study and proceeded to intensification with high dose methotrexate and pegaspargase for CNS prophylaxis. Thereafter, MRD status was assessed by 6-color flow cytometry. Patients were randomized to receive either 4 cycles of consolidation chemotherapy or 2 cycles of blinatumomab followed by 3 cycles of consolidation chemotherapy, followed by a 3rd cycle of blinatumomab, followed by another cycle of consolidation chemotherapy, and finally a 4th cycle of blinatumomab. However, following the FDA approval of blinatumomab for patients with MRD positive disease, those with MRD positivity in the trial were no longer randomized and assigned to the blinatumomab arm. All patients received POMP maintenance therapy for a total of 2.5 years. Patients were referred for allogeneic HCT at provider discretion. For the entire cohort, CR/CRi rate following induction was 81%. For those who achieved MRD negativity, the addition of blinatumomab led to significant improvement on OS. With a median follow-up of 43 months, 3-year OS was 85% for the blinatumomab arm compared to 68% for the consolidation chemotherapy arm (95% CI, 0.23–0.73; P = .002). Three-year RFS also favored the blinatumomab arm, at 80% vs. 64% (95% CI, 0.32–0.87).

Based on initial data, in June 2024, the FDA expanded the approval of blinatumomab to include adult and pediatric patients ≥1 month with Ph-negative B-ALL in the consolidation phase of multiphase chemotherapy.

Treatment of Relapsed Ph-Negative ALL

Despite major advances in the treatment of childhood ALL, approximately 20% of pediatric patients experience relapse after initial CR to frontline treatment regimens.^{310–312} Among those who experience relapse, only approximately 30% experience long-term remission with subsequent therapies.^{165,313,314} Based on a retrospective analysis of historical data from COG studies (for patients enrolled between 1998 and 2002; n = 9585), early relapse (<18 months from diagnosis) was associated with very poor outcomes, with an estimated 5-year survival (from time of relapse) of 21%.³¹⁰ For cases of isolated bone marrow relapse, the 5-year survival estimates among early (n = 412), intermediate (n = 324), and late (n = 387) relapsing disease were 11.5%, 18.0%, and 43.5%, respectively (P < .0001). Intermediate relapse was defined as relapse occurring 18 to 36 months from time of diagnosis; late cases were defined as relapse occurring ≥36 months from time of diagnosis. For cases of isolated CNS relapse, the 5-year survival estimates among early (n = 175), intermediate (n = 180), and late (n = 54) relapsing disease were 43.5%, 68.0%, and 78.0%, respectively (P < .0001).³¹⁰ Based on multivariate analysis (adjusted for both timing and site of relapse), age (>10 years), presence of CNS disease at diagnosis, male gender, and T-cell lineage

disease were found to be significant independent predictors of decreased survival after relapse.³¹⁰ In a separate analysis of data from one of the above COG studies (CCG-1952), the timing and site of first relapse were significantly predictive of EFS and OS outcomes, even among the patients with standard-risk ALL (n = 347; based on NCI criteria: aged 1 to <10 years and WBC count <50 × 10⁹/L).³¹⁵ Early bone marrow relapse (duration of first CR <36 months) was associated with significantly shorter estimated 3-year EFS (30% vs. 44.5%; P = .002) and OS (35% vs. 58%; P = .001) rates compared with late bone marrow relapse.³¹⁵ Similarly, early isolated extramedullary relapse (duration of first CR <18 months) was associated with significantly shorter estimated 3-year EFS (37% vs. 71%; P = .01) and OS (55% vs. 81.5%; P = .039) rates compared with late extramedullary relapse. In a multivariate regression analysis, early bone marrow and extramedullary relapse were independent predictors of poorer EFS outcomes.³¹⁵

Data from patients with disease relapse after frontline therapy in the MRC UKALL XII/ECOG E2993 study and PETHEMA studies showed that the median OS after relapse was only 4.5 to 6 months; the 5-year OS rate was 7% to 10%.^{204,205} Approximately 20% to 30% of patients experience a second CR with second-line therapies.^{205,207} Factors predictive of more favorable outcomes after subsequent therapies included younger age and a first CR duration of more than 2 years.^{183,205} Among younger patients (aged <30 years) whose disease relapsed after experiencing a first CR duration longer than 2 years with frontline treatment in PETHEMA trials, the 5-year OS rate from the time of first relapse was 38%.²⁰⁵

Hematopoietic Cell Transplant

HCT is the only potentially curative modality for R/R ALL. Based on findings from evidence-based review of the published literature, the American Society for Blood and Marrow Transplantation guidelines recommend HCT over chemotherapy alone for adults with ALL experiencing a second CR.³¹⁶ Several studies have shown that for AYA patients in second CR, allogeneic HCT may improve outcomes, particularly for patients who have early bone marrow relapse or have other high-risk factors.^{313,314,317} Seemingly contradictory data were reported in the COG CCG-1952 study that showed prognosis after early bone marrow relapse in patients with standard-risk ALL (aged 1 to <10 years and WBC count <50 × 10⁹/L) remained poor with no apparent advantage of HCT, regardless of timing (ie, early or late) of bone marrow relapse.³¹⁵ However, data were not available on the conditioning regimen used for HCT in this study for comparison with other trials. The UKALLXII/ECOG2993 trial (n = 609; age range, 15–60 years) examined the efficacy of transplantation after relapse in a subgroup of patients with relapsed ALL who had not received prior transplant.²⁰⁴ Patients treated with HCT demonstrated a superior OS at 5 years compared to those treated with chemotherapy alone.²⁰⁴ The CIBMTR group conducted an analysis of outcomes of patients with ALL (n = 582; median age, 29 years; range, <1 to 60 years) who underwent transplant during relapse.³¹⁸ At 3 years, OS rates were 16% (95% CI, 13%–20%).³¹⁸ Response to therapy for relapsed/refractory disease prior to HCT may also predict outcome. One retrospective study has shown 3-year OS and EFS estimates of 69% and 62% (respectively) for patients in second or later MRD-negative remission at the time of HCT, similar to the outcomes of those who underwent HCT in MRD-negative first remission at the same center.¹⁸⁶

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in patients with R/R B-precursor ALL (n = 25).^{284,319} Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 patients with R/R Ph-negative B-ALL that demonstrated a CR or CR with incomplete platelet recovery (CRp) in 43% of patients within the first 2 cycles of treatment.^{283,320} In a follow-up prospective, multicenter, randomized, phase III trial, patients with R/R B-cell precursor ALL (n = 405) were assigned to receive either blinatumomab (n = 271) or standard chemotherapy (n = 134).²⁸² The OS was longer in the blinatumomab group, with median OS at 7.7 months, compared to the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93; P = .01).²⁸² Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard chemotherapy group with respect to both CR with full hematologic recovery (CR, 34% vs. 16%; P < .001) and CR with full, partial, or incomplete hematologic recovery (CR, CR with partial hematologic recovery [CRh], or CRi, 44% vs. 25%; P < .001).²⁸² Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.²⁸²

There are significant and unique side effects to blinatumomab treatment compared to other established regimens. The most significant toxicities noted in clinical studies are CNS events and cytokine release syndrome (CRS). Neurologic toxicities have been reported in 50% of patients (median onset, 7 days) and grade 3 or higher neurologic toxicities, including encephalopathy, convulsions, and disorientation, have occurred in 15% of patients.³²¹ CRS typically occurs within the first 2 days following initiation of blinatumomab infusion.³²¹ Symptoms of CRS include pyrexia, headache, nausea, asthenia, hypotension,

increased transaminases, and increased total bilirubin. The incidence of adverse events can be reduced with monitoring for early intervention at onset of symptoms. However, the serious nature of these events underscores the importance of receiving treatment in a specialized cancer center that has experience with blinatumomab.

Inotuzumab Ozogamicin

Clinical studies described earlier include patients with relapsed or refractory Ph-positive and Ph-negative ALL.^{247,248} For discussion of these studies, see Treatment of Relapsed Ph-Positive ALL.

In a phase II study, the efficacy and safety of InO combined with low-intensity chemotherapy (mini-hyperCVD) was evaluated in adults with R/R B-ALL (n = 59; median age, 35 years; range, 18–87 years).³²² The response rate was 78%, with 35 of these patients achieving CR (59%).³²² The overall MRD negativity rate among responders was 82%. With a median follow-up of 24 months, the median RFS and OS were 8 and 11 months, respectively. The 1-year RFS and OS rates were 40% and 46%, respectively. When using this regimen, the risk of SOS should be considered in patients with previous liver damage and among transplant candidates. In this study, SOS occurred in 9 patients (15%).³²²

In a subsequent report, to reduce the risk of SOS and improve outcomes, the investigators amended the protocol by lowering the weekly InO doses and including 4 cycles of blinatumomab in the consolidation phase.³²³ In a cohort of adults with Ph-negative B-ALL treated in first relapse (n = 48; median age, 39 years; range, 18–87 years), the rates of SOS prior to the protocol amendment and after the protocol amendment were 13% (n = 5 of 38) and 0% (n = 0 of 10), respectively.³²³ In addition, based on propensity score matching, the combination of InO with mini-hyperCVD with or without blinatumomab resulted in better outcomes than inotuzumab alone or intensive chemotherapy for relapsed/refractory disease.³²³ Long-term follow up data from a total of 96 patients revealed an ORR of 80%, with 57% achieving a CR. Among responders, the overall MRD negativity rate was 83%.³²⁴ Patients treated at first relapse had better outcomes than patients treated at second relapse or 3rd relapse and beyond, with ORR rates of 91%, 59%, and 57%, respectively. Similarly, rates of MRD negativity were higher among patients treated at first relapse compared to those treated at second relapse or beyond, at 88% and 67%, respectively. Forty-six percent of patients ultimately went on to allogeneic HCT. Estimated 3-year OS was 33% in the entire cohort and 48% among patients who proceeded to allogeneic HCT. Sixteen percent of patients underwent allogeneic HCT developed SOS compared to 6% of patients who did not proceed to allogeneic HCT.

CAR T Cells

One of the early treatments for patients with advanced ALL included adoptive cell therapy to induce a graft-versus-leukemia effect through allogeneic HCT or DLI. However, this method resulted in a significant risk of GVHD. To circumvent this issue, current advances are focused on the use of the patient's own T cells to target the tumor. The generation of CAR T cells to treat ALL is a significant advancement in the field.^{249,325,326} CAR T-cell therapy relies on the genetic manipulation of a patient's T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.²⁵⁰ Briefly, T cells from the patient are harvested and engineered with a receptor that targets a cell surface tumor-specific antigen (eg, CD19 antigen on the surface of leukemic cells). The ability of CAR T cells to be reprogrammed to target any cell-surface antigen on leukemic cells is advantageous and avoids the issue of tumor evasion of the immune system via receptor down regulation.²⁵⁰ The manufacture of CAR T cells requires ex vivo viral transduction, activation, and expansion over several days to produce a sufficient cell number to engender disease response.³²⁷ Following infusion, debulking of tumors occurs in <1 week and these cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

There are several clinical trials using CAR T cells that differ in the receptor construct for patients with relapsed or refractory ALL. One of the first CAR constructs to be investigated, termed 19-28z—which links the CD19 binding receptor to the costimulatory protein CD28—demonstrated an overall CR in 14 out of 16 patients with relapsed or refractory B-ALL following infusion with CAR T cells.³²⁸ This average remission rate is significantly improved compared to the average remission rate for patients receiving standard-of-care chemotherapy following relapse (88% vs. approximately 30%).^{204,328-330} Furthermore, 7 out of 16 patients were able to receive an allogeneic HCT, suggesting that CAR T cells may provide a bridge to transplant.³²⁸ No relapse has been seen in patients who underwent allogeneic HCT (follow-up, 2–24 months); however, 2 deaths occurred from transplant complications. Follow-up data of adults enrolled on this trial (n = 53) showed an 83% CR rate after the infusion and 32 patients achieved an MRD-negative CR.³³¹ At a median follow-up of 29 months (range, 1–65 months), the median OS was 12.9 months (95% CI, 8.7–23.4 months) and subsequent allogeneic HCT did not appear to improve survival.³³¹ In contrast, data in children and young adults treated on another clinical trial at the National Institutes of Health/National Cancer Institute with a similar CAR construct suggested consolidative allogeneic HCT post-

CAR T-cell therapy might be associated with superior outcomes (2-year cumulative incidence of relapse post-transplant, 9.5%; 5-year EFS post-transplant, 62%).³³²

Other CD19-targeted constructs have been investigated—some comprising an alternative costimulatory protein, 4-1BB—have shown similar results to the 19-28z CAR T cells in terms of overall CR.³³³

Relevant in this context are data from the ELIANA trial of CTL019 (tisagenlecleucel) in 75 children and young adults with R/R B-ALL, which demonstrated an overall remission rate of 81% within 3 months of infusion, all of which were notably MRD negative.³³⁴ These results led to the approval of CTL019 by the FDA in August 2017 for the treatment of patients <26 years of age with R/R precursor B-ALL. The efficacy of CTL019 in children and young adults with R/R B-ALL in the non-trial setting was recently confirmed using registry data from the CIBMTR. This retrospective analysis showed morphologic CR in 85% of patients.³³⁵ MRD negativity was reported in 99% of patients who had achieved a CR with available data. A comparable proportion of patients experienced durable responses at 12 months in the CIBMTR cohort compared to patients treated on the ELIANA clinical trial (61% and 67%, respectively). At the last update of the ELIANA data at the 2019 American Society of Transplantation and Cellular Therapy (ASTCT) Annual Meeting (median follow-up, 24 months), the median duration of remission and OS was NR and the 24-month RFS probability in responders was 62%. Survival probability curves plateaued after 1 year. Consolidation with allo-HCT after CTL019 was reported in only 9% of patients who had achieved a CR. These updated results suggest treatment with CTL019 in children and young adults with R/R B-ALL could be curative in a subset of patients in the absence of consolidative allo-HCT.³³⁶

The single-arm, open-label, international multicenter phase 2 ZUMA-3 clinical trial assessed the efficacy of the CAR T-cell product KTE X19 (brexucabtagene autoleucel) in 71 adults with R/R B-ALL.³³⁷ The primary endpoint, the rate of overall CR or CRi by central assessment, was met (71%; 95% CI, 57–82; $P < .0001$). Secondary endpoints were also met: 76% of patients experienced MRD-negative CR, the median duration of remission was 12.8 months, the median RFS was 11.6 months, and the median OS was 18.2 months.³³⁷ Brexucabtagene autoleucel had a manageable safety profile. The most common grade 3 or higher adverse events were anemia (49%) and pyrexia (36%). It is also being evaluated in children and young adults ≤ 21 years of age with R/R ALL in the ZUMA-4 trial (NCT02625480).

A phase Ib/II multicenter study investigated the anti-CD19 CAR T-cell therapy obecabtagene autoleucel in adults ≥ 18 years with R/R B-ALL ($n = 127$ with evaluable data; median age, 47 years).^{338,339} All patients had received at least two prior lines of therapy. In a cohort of patients with morphologic disease, the ORR was 77%, with 55% achieving CR. Among all patients who received obecabtagene autoleucel, including patients with both morphologic disease and MRD, ORR was 78% and median EFS and OS were 11.9 months and 15.6 months, respectively. Among those who achieved response, 17% proceeded to allogeneic HCT in MRD-negative CR. Grade ≥ 3 CRS or immune effector cell-associated neurotoxicity syndrome (ICANS) occurred in 2.4% and 7.1% of patients, respectively.

As with blinatumomab, T-cell and CAR T-cell activation can be accompanied by severe CRS and neurologic toxicity (ICANS), as well as infectious risks—though treatment-related mortality remains low.³³⁴ While side effects from CAR T cells can be severe, they are reversible in most cases. CRS is clinically characterized by high fever, hypotension, tachycardia, and hypoxia; ICANS includes delirium, aphasia, headaches, tremor, focal deficits, and cerebral edema. Higher CRS and ICANS severity have been reported in patients with B-ALL compared to patients with NHL after CD19 CAR T-cell therapy.³⁴⁰ It is recommended to evaluate CRS and ICANS severity using the ASTCT consensus criteria.³⁴¹ Tocilizumab (interleukin-6 receptor antagonist) and corticosteroids are the cornerstone of CRS and ICANS management. An FDA-approved biosimilar is an appropriate substitute for tocilizumab. Expert consensus clinical guidelines were recently published by the Society of Immunotherapy of Cancer to guide toxicity management.³⁴²

Nelarabine

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-ALL who have unresponsive or relapsed disease after at least two chemotherapy regimens. A phase II study of nelarabine monotherapy in children and adolescents with R/R T-ALL or T-cell NHL ($n = 121$) showed a 55% response rate among the subgroup with T-ALL with first bone marrow relapse ($n = 34$) and a 27% response rate in the subgroup with a second or greater bone marrow relapse ($n = 36$).¹⁶⁵ Major toxicities included grade 3 or higher neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in adults with R/R T-ALL or T-cell lymphoblastic leukemia in a phase II study ($n = 39$; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-ALL, $n = 26$).¹⁶⁷ The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median DFS and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.¹⁶⁷

There are limited studies of nelarabine combination regimens in adults with R/R T-ALL. In a study by Commander et al, pediatric patients with R/R T-ALL (n = 7; range, 1–19 years) were treated with nelarabine, etoposide, and cyclophosphamide.³⁴³ In addition, all patients received IT prophylaxis with methotrexate or triple IT therapy with methotrexate, cytarabine, and hydrocortisone. All patients experienced a CR after 1 or 2 courses of therapy. The most common adverse events attributed to nelarabine were grade 2 and 3 sensory and motor neuropathy and musculoskeletal pain.³⁴³ In phase I of the NECTAR trial, pediatric patients with R/R T-ALL and T-LL (range, 1–21 years) were also treated with nelarabine, etoposide, and cyclophosphamide.³⁴⁴ Of nine patients with T-ALL with evaluable data, there were two CRs, one partial CR, and one CR in the bone marrow/partial response (PR) in an extramedullary site for a response rate of 44%.³⁴⁴

Augmented HyperCVAD

A phase II study from the MDACC evaluated an augmented hyperCVAD regimen (that incorporated asparaginase, intensified vincristine, and intensified dexamethasone) as therapy in adults with R/R ALL (n = 90; median age, 34 years; range, 14–70 years; median 1 prior regimen).³⁴⁵ Among patients with evaluable data (n = 88), the CR rate was 47%; an additional 13% experienced a CRp and 5% experienced a partial remission. The 30-day mortality rate was 9% and median remission duration was 5 months. The median OS for all patients with evaluable data was 6.3 months; median OS was 10.2 months for patients who experienced a CR. In this study, 32% of patients were able to proceed to HCT.³⁴⁵

Clofarabine

Clofarabine is a nucleoside analog approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is relapsed or refractory after at least two prior regimens. In a phase II study of single-agent clofarabine in pediatric patients who have undergone heavy pretreatment with R/R ALL (n = 61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%.³⁴⁶ Single-agent clofarabine in this setting was associated with severe liver toxicities (generally reversible) and frequent febrile episodes including grade 3 or 4 infections and febrile neutropenia.³⁴⁶ Phase II studies evaluating the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with R/R ALL have resulted in response rates ranging from 44% to 52%.^{347,348} This combination has been associated with prolonged and severe myelosuppression, febrile episodes, severe infections (including sepsis or septic shock), mucositis, and liver toxicities including fatal SOS (the latter occurring in the post-allogeneic HCT setting).³⁴⁷

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study by Miano et al,³⁴⁹ pediatric patients with R/R ALL (n = 24; median age, 7.6 years; range, 1–20 years) were treated with clofarabine, etoposide, and cyclophosphamide, and 42% (10 of 24) of patients experienced treatment response, with a 24-month OS rate of 25%.³⁴⁹ In a study from GRAALL, adults with R/R ALL (n = 55) were treated with clofarabine in combination with conventional chemotherapy (cyclophosphamide [ENDEVOL cohort; median age, 53 years; range, 18–78 years], or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and PEG [VANDEVOL cohort; median age, 34 years; range, 19–67 years]). Patients in the ENDEVOL cohort achieved a CR of 50% (9 of 18) and patients in the VANDEVOL cohort yielded a CR rate of 41% (15 of 37); the median OS was 6.5 months after a median follow-up of 6 months.³⁵⁰ The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%.³⁵⁰ Because the use of clofarabine-containing regimens require close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL, preferably in the context of a clinical trial.

MOpAD Regimen

A single-arm trial evaluating the efficacy of the MOAD regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) in adults with newly diagnosed ALL (n = 55) demonstrated a CR rate of 76% with a median CR duration of over 12 months.³⁵¹ A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability,³⁵² and examined the safety and efficacy of the MOpAD regimen (methotrexate, vincristine, PEG-L-asparaginase, and dexamethasone) in adults with relapsed or refractory ALL (n = 37).³⁵³ For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, nilotinib) were added to the regimen and if patients had CD20-positive B-ALL, rituximab was added to the regimen. The CR and ORR rates were 28% and 39%, respectively, with a median duration of response of 4.3 months.³⁵³ Patients with Ph-positive ALL achieved CR and ORR rates of 50% and 67%, respectively.³⁵³ This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

TKIs

Studies evaluating other novel TKIs in targeting specific genetic subtypes have been evaluated for the treatment of R/R T-ALL disease. While daratumumab has efficacy in its application for MRD, it has been reported to have potential preclinical benefit in T-ALL with positive CD38 expression.³⁵⁴ The use of the selective BCL2 inhibitor, venetoclax, has been retrospectively analyzed in the treatment of R/R T-ALL. In this analysis, 60% of patients receiving venetoclax plus various chemotherapeutic agents such as hyperCVAD, nelarabine, or decitabine, achieved remission in marrow blasts, with the median OS of 7.7 months.³⁵⁵ Proteasome inhibition with the use of bortezomib in combination with chemotherapeutic agents has been suggested to improved relapse response rates in patients with T-ALL. In a phase II COG study, patients with ALL were treated with reinduction chemotherapy plus bortezomib.³⁵⁶ Patients with relapsed T-ALL showed a CR rate of 68%, with end of induction MRD significantly predicting survival.³⁵⁶

Revumenib

In the ongoing phase II AUGMENT-101 study the safety and efficacy of the oral menin inhibitor revumenib was evaluated in adult and pediatric patients ≥ 30 days old ($n = 94$; 57 with efficacy-evaluable data) with primary refractory or relapsed KMT2Ar acute leukemia, including 14 patients with ALL.³⁵⁷ Many patients (43.6%) had received ≥ 3 prior lines of therapy and 50% of patients had undergone prior allogeneic HCT.

Patients received revumenib 163 mg (or 95 mg/m² for those weighing < 40 kg) every 12 hours in 28-day continuous cycles. Dose of revumenib could be increased to 276 mg (or 160 mg/m² if weight < 40 kg) if no concomitant strong CYP3A4 inhibitor was being utilized; however, this did not occur on study and is rare in R/R acute leukemia, as most patients require fungal prophylaxis with azoles. Among patients with evaluable data, the CR/CRh rate was 22.8%. ORR was 63.2% with 68.2% of patients achieving MRD negativity. Among those who achieved response, 38.9% were able to proceed to allogeneic HCT and half of these patients receive revumenib maintenance therapy following HCT.

The most common adverse effects were nausea/vomiting/diarrhea, febrile neutropenia (grade ≥ 3 in 37.2% of patients), and edema. Grade ≥ 3 differentiation syndrome occurred in 16% of patients and grade ≥ 3 QTc prolongation occurred in 13.8% of patients.

Based on this data, the FDA approved revumenib for R/R acute leukemia with a KMT2A translocation in adult and pediatric patients ≥ 1 year.

NCCN Recommendations for Ph-Negative B-ALL

AYA and Adult Patients < 65 Years without Substantial Comorbidities with Ph-Negative B-ALL

The Panel recommends that AYA and adult patients < 65 years without substantial comorbidities with Ph-negative B-ALL (regardless of risk group) be treated in a clinical trial, where possible. In the absence of an appropriate clinical trial, the recommended induction therapy should comprise systemic therapy regimens.

For AYA patients, preferred systemic therapy regimens are regimens based on pediatric-inspired protocols, the DFCI-00-01 and CALGB 10403 regimens. Multiagent therapy protocols based on data from multiinstitution studies such as ECOG1910 and single-institution studies, including CCG-1882 (if ≥ 18 years) and hyperCVAD (with or without rituximab), are also recommended.

For patients < 65 years of age and without substantial comorbidities, recommended systemic therapy regimens include multiagent therapy such as those based on protocols from the ECOG1910 regimen, hyperCVAD with or without sequential blinatumomab (with or without rituximab), the MSKCC ALL regimen (CCG-1882 regimen; if < 60 years), and InO with mini-hyperCVD with or without blinatumomab.

Treatment regimens should include adequate CNS prophylaxis for all patients. It is important to adhere to the treatment regimens for a given protocol in its entirety. Testing for TPMT gene polymorphism should be considered for patients receiving 6-MP as part of maintenance therapy, especially in those who experience severe bone marrow toxicities.

Following induction, a response assessment is recommended. For patients experiencing less than a marrow CR, NGS testing may be considered prior to therapy for R/R disease. For patients experiencing a marrow CR following initial induction therapy, MRD status should be assessed (see NCCN Recommendations for MRD Assessment). If the resulting MRD status is negative, continuation of the multiagent therapy protocol with blinatumomab or blinatumomab monotherapy for consolidation may be considered. Blinatumomab should be incorporated into therapy as a post-remission approach based on data from ECOG1910.³⁰⁹ Consolidation with allogeneic HCT may also be considered, especially in the setting of high-risk features. If MRD is positive following treatment induction, blinatumomab with or

without continued multiagent therapy is recommended. Adequate count recovery per protocol is necessary before transitioning to post remission therapy, even in the presence of MRD negativity. If count recovery is not achieved, additional follow-up for MRD may be warranted.

Following consolidation therapy, repeat MRD assessment is recommended. In the setting of MRD negative CR following consolidation, POMP maintenance therapy or allogeneic HCT are recommended.

Allogeneic HCT is favored for individuals with B-ALL with poor risk cytogenetic and molecular alterations, or in the setting of slow or incomplete MRD clearance. In the setting of persistent progressive, or emergent MRD, marrow progression, or new extramedullary disease, treatment for R/R disease is recommended (see Patients with Relapsed/Refractory Ph-Negative B-ALL).

Adults ≥65 Years or Patients with Substantial Comorbidities with Ph-Negative B-ALL

For adults ≥65 years of age or patients with substantial comorbidities with Ph-negative B-ALL, the Panel recommends treatment in a clinical trial, where possible. Although the age cutoff indicated in the guidelines has been set at 65 years, it should be noted that chronologic age alone is not a sufficient surrogate for defining fitness; patients should be evaluated on an individual basis to determine fitness for therapy based on factors such as performance status, end-organ function, and end-organ reserve.

For patients ≥65 years of age or patients with substantial comorbidities, other recommended induction therapy options can be broken down by intensity. Low-intensity options include vincristine with prednisone or POMP. Moderate intensity options include InO monotherapy (a category 2B option based on ALLIANCE A041703), InO combined with dexamethasone (a category 2B option based on ALL-INITIAL-1), InO combined with mini-hyperCVD, the modified DFCI 91-01 protocol, and mini-hyperCVD with or without venetoclax. ECOG1910 is a high-intensity option. Other regimens that may be useful in certain circumstances include the PETHEMA-based regimen ALLOLD07, CALGB9111, EWALL, GMALL with rituximab for CD20-positive disease, and GRAALL.

Dose modifications may be required for systemic therapy agents, as needed. MRD assessment and consolidation approach after initial treatment induction would be similar to that for AYA and adult patients <65 years without substantial comorbidities with Ph-B-ALL, with appropriate dose modifications (see AYA and Adult Patients <65 Years without Substantial Comorbidities with Ph-Negative B-ALL).

For recommendations on the treatment of adults with mature B-ALL, refer to the NCCN Guidelines for B-Cell Lymphomas (available at www.NCCN.org).

Patients with Relapsed/Refractory Ph-Negative B-ALL

For patients with R/R Ph-negative B-ALL, molecular characterization and MRD assessment are recommended, if not previously done. The approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, relapses occurring ≥3 years from initial diagnosis), retreatment with the same induction regimen is a reasonable option. For other patients, participation in a clinical trial is preferred, when possible. In the absence of an appropriate trial, for patients with R/R Ph-negative precursor B-ALL, recommended category 1 options include blinatumomab with or without multiagent therapy or InO. As previously mentioned, InO is associated with increased hepatotoxicity, including fatal and life-threatening hepatic SOS, and increased risk of post-HCT non-relapse mortality.²⁵³

Brexucabtagene autoleucl and obecabtagene autoleucl are additional options for AYA and adult patients with R/R Ph-negative B-ALL. Tisagenlecleucl is also an option for patients <26 years of age and with refractory disease or ≥2 relapses. Other options that may be considered include subsequent multiagent therapy, with regimens containing clofarabine, InO with mini-hyperCVD with or without sequential blinatumomab, augmented hyperCVAD, MOpAD regimen, or other fludarabine-, cytarabine-, or alkylator-containing regimens.^{324,358-361} Revumenib is a targeted therapy option for those with R/R KMT2A rearranged Ph-negative B-ALL. If patients who have not yet undergone transplant experience a second CR prior to transplant, consolidative allogeneic HCT should be strongly considered. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. However, the role of allogeneic HCT following treatment with tisagenlecleucl is unclear. As previously discussed, persistence of tisagenlecleucl in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT.²⁵⁵

Alberta Health Services, 2023 [1].

Acute lymphoblastic leukemia in adults

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur aktuellen Therapie für Patienten mit CD19-positiver B-Zell-Vorläufer akuter lymphoblastischer Leukämie (ALL), 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

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

Summary of Recommendations

Treatment of Ph/BCR-ABL negative ALL

1. Eligible adults under age 60 should be treated with a pediatric-based protocol.
 - a. In Alberta the current standard regimen is the modified Dana Farber Cancer Institute (DFCI) protocol.
 - b. Patients with co-morbidities, or those unable to tolerate the full DFCI protocol, may be treated with a less intensive regimen, such as the modified DFCI protocol for patients age 60 or over.
2. Fit adults age 60-75 should be treated with curative intent.

- a. The Princess Margaret Hospital modified DFCl protocol for adults above age 60 has produced favourable results in this population compared to other regimens and may be used. Other curative-intent regimens are also acceptable.
3. Patients over age 75, or those under age 75 with major co-morbidities precluding intensive chemotherapy, should be considered for palliative chemotherapy with corticosteroids and vincristine +/- low- dose asparaginase, followed by low-dose maintenance chemotherapy if CR is achieved.

Treatment of Ph/BCR-ABL positive ALL

1. Ph/BCR-ABL positive patients who are fit for chemotherapy should be treated with a BCR-ABL tyrosine kinase inhibitor (TKI) combined with induction and post-remission therapy.

- a. A less intensive induction regimen with corticosteroids, vincristine and TKI (e.g. Chalandon protocol) is preferred for initial induction, as it produces higher CR rates due to lower induction mortality. In younger, fit patients, this should be followed by intensification (e.g. HyperCVAD Part B + TKI, as per the Chalandon protocol).
- b. Patients achieving a hematologic CR should be continued on post-remission chemotherapy + TKI. This may consist of the modified Princess Margaret Hospital DFCl CNS, intensification and maintenance phases, or HyperCVAD + TKI. Asparaginase should not be used due to increased toxicity when used concurrently with TKI.
- c. Imatinib (600 – 800mg per day), is currently the standard first line TKI drug.
 - i. Patients with intolerance to, or not achieving an adequate response to, imatinib should be switched to a second generation TKI such as dasatinib
 - ii. Ponatinib should be used in patients with a T315I mutation
 - iii. For patients with CNS disease at diagnosis, dasatinib should be used upfront due to its superior CNS penetration.
- d. Patients with Ph/BCR-ABL positive ALL who are elderly, or otherwise unfit for intensive chemotherapy or transplant, should be treated with the Chalandon induction protocol cycle A, or corticosteroids + TKI, followed by low-dose maintenance chemotherapy + TKI.
- e. TKIs should be continued indefinitely in patients who are not transplanted.
- f. Patients not transplanted should be closely monitored for disease progression with serial PCR testing every 3 months. Reappearance of PCR positivity, if confirmed, should prompt a change in TKI and referral for allogeneic HSCT, if a potential candidate.
- g. Patients with persistence of, or reappearance of BCR-ABL transcripts by PCR, should have mutational testing, specifically to look for the presence of a T315I mutation.

Role of MRD (minimal or measurable residual disease) assessments

1. Ph/BCR-ABL negative patients should have MRD assessments following induction chemotherapy, or by week 16, by flow cytometry or molecular techniques.

- a. MRD positive B-ALL patients, defined as > 0.1% of mononuclear cells by flow (>10³), should receive immuno-therapy using 1-2 cycles of blinatumomab with an intent to achieve MRD negativity.
- b. MRD positive T-ALL patients should receive intensified chemotherapy with an intent to achieve MRD negativity.
- c. MRD positive patients post-intensive induction or at week 16, defined as > 0.1% of mononuclear cells by flow, should be considered for allogeneic HSCT in CR1, as these patients are at higher risk of relapse.

2. Ph/BCR-ABL positive patients should have MRD assessments following induction chemotherapy, or by week 16, by quantitative PCR.

- a. Patients who are MRD positive by PCR at the end of a two-cycle induction using the Chalandon protocol, or by week 16 using other protocols, should be switched to a second generation TKI such as dasatinib. If already on a 2nd generation TKI, the patient should be switched to ponatinib. The TKI should be combined with either chemotherapy or blinatumomab.
- b. MRD positive patients at these timepoints should be referred for allogeneic HSCT in CR1, as per below.

Role of allogeneic stem cell transplantation

1. Allogeneic HSCT should not be routinely performed in patients with Ph/BCR-ABL negative ALL in CR-1. However, patients with the following high-risk features should be considered for HSCT:

- i. t(4;11) with MLL (KMT2A) rearrangement
- ii. Early T-cell precursor (ETP) ALL
- iii. Lack of attainment of hematologic CR with first induction
- iv. MRD positivity at end of induction or by week 16, as per above.
- v. Inability to deliver sufficient asparaginase dosing during intensification therapy
- a. There is no clear evidence that other cytogenetic abnormalities, or specific cell surface markers, constitute high risk features when using a pediatric-based regimen
- b. It is also not clear whether patients with a high-risk feature at baseline who achieve MRD negativity after induction therapy require a transplant.

2. Fit BCR-ABL positive patients up to age 70 may be considered for allogeneic HSCT in CR-1.

- a. Patients with BCR-ABL positivity by PCR, either post-induction or by week 16 (depending on the regimen), should be referred for allogeneic HSCT, as per 6.1.3. If an HLA matched related or unrelated donor is unavailable, a haploidentical transplant should be considered.
- b. Patients achieving early MRD negativity by PCR, either post-induction or by week 16 (depending on the regimen), may be continued on post-induction chemotherapy together with TKI without a transplant. Transplant is also an option in these patients.
- c. Reappearance of PCR positivity with monitoring, if confirmed, should prompt a referral for allogeneic HSCT, if a potential candidate, as per above.

CNS prophylaxis

1. Intrathecal chemotherapy: All patients should receive intrathecal chemotherapy prophylaxis, starting with the initiation of induction therapy, and continuing through maintenance therapy, for 11-12 total doses.

- a. If the initial CSF is positive, intrathecal chemotherapy should be administered twice weekly until CSF clearance is confirmed on at least 3 occasions.

2. Cranial Radiation: Cranial radiation may be omitted from CNS prophylaxis, unless there is evidence of fixed CNS disease.

Supportive care

1. Antimicrobial prophylaxis against PJP and HSV/VZV should be used from induction through the completion of maintenance therapy. Antifungal prophylaxis should be used during intensive induction therapy.

2. Asparaginase therapy requires close monitoring for liver toxicity, pancreatitis, hypertriglyceridemia and VTE.
 - a. Anticoagulation prophylaxis should be considered during intensification therapy. Documented VTE should be treated with full-dose anticoagulation but asparaginase therapy can generally be resumed after several weeks if stable or improved.
 - b. Asparaginase therapeutic drug monitoring should be routinely performed in all patients at the end of the first intensification cycle, at a later cycle and after any dose reduction, targeting a trough level of > 0.1 U/L.
 - c. Dose reductions should be considered for grade 2 or greater hepatic toxicity.
 - d. Pancreatitis requires discontinuation of asparaginase.
3. Prophylaxis against corticosteroid-induced osteoporosis and gastritis should be used.

Relapsed ALL

1. Transplant-eligible BCR-ABL negative B-ALL patients should be treated with an antibody-based regimen, either blinatumomab or inotuzumab (if CD22 positive).
2. BCR-ABL positive patients relapsing on an imatinib-based regimen should be treated with a second generation or third generation TKI + either chemotherapy, inotuzumab or blinatumomab. If a T315I mutation is detected, ponatinib plus blinatumomab or chemotherapy should be used.
3. T-ALL patients should receive a non-cross resistant re-induction chemotherapy regimen, or nelarabine.
4. Transplant eligible patients should be considered for allogeneic HSCT in CR-2, if not performed in CR-1.

CAR T-Cell Therapy:

1. Indicated for fit B-ALL patients relapsing after allogeneic HSCT, refractory to 2 induction regimens, or relapsed and not considered suitable candidates for HSCT.
2. Patients should be referred for apheresis prior to administering salvage immunosuppressive chemotherapy such as corticosteroids or cyclophosphamide, to avoid interfering with the quality of the product.
3. Patients should in most cases receive bridging/cytoreductive therapy following apheresis, to prevent clinical deterioration due to disease progression and to achieve cytoreduction prior to CAR T infusion. This may consist of either chemotherapy or antibody-based therapy.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 12 of 12, December 2025) am 17.12.2025

#	Suchschritt
1	[mh "Leukemia, Lymphoid"]
2	(acute OR pr*cursor):ti,ab,kw
3	(leu*mia* OR lymphoma*):ti,ab,kw
4	((lymphat* OR lymphocyt* OR lymphoblast* OR lymphoid* OR biphenotypic OR mixed* OR hybrid) OR (b NEXT cell) OR (t NEXT cell) OR (b NEXT lineage) OR (t NEXT lineage)):ti,ab,kw
5	{AND #2-#4}
6	((b NEXT all) OR (t NEXT all) OR (b NEXT cell NEXT all) OR (t NEXT cell NEXT all) OR (pre NEXT b NEXT cell NEXT all) OR (pre NEXT b NEXT all) OR (b NEXT lineage NEXT all) OR (t NEXT lineage NEXT all)):ti,ab,kw
7	{AND #3, #6}
8	{OR #1, #5, #7}
9	#8 with Cochrane Library publication date from Dec 2020 to present
10	#8 with Cochrane Library publication date from Dec 2023 to present
11	#9 NOT #10

Leitlinien und systematische Reviews in PubMed am 16.12.2025

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, Lymphoid[mh]
2	leuk*mia*[tiab] OR leuc*mia*[tiab] OR lymphoma*[tiab]
3	(#2) AND (acute[tiab] OR precursor[tiab] OR praecursor[tiab])
4	(#3) AND (lymphat*[tiab] OR lymphocyt*[tiab] OR lymphoblast*[tiab] OR lymphoid*[tiab] OR biphenotypic[tiab] OR hybrid[tiab] OR mixed*[tiab] OR b-cell[tiab] OR t-cell[tiab] OR b-lineage[tiab] OR t-lineage[tiab])
5	(#2) AND (b-all[tiab] OR b-cell-all[tiab] OR t-all[tiab] OR t-cell-all[tiab] OR pre-b-all[tiab] OR pre-b-cell-all[tiab] OR b-lineage-all[tiab] OR t-lineage-all[tiab])
6	#1 OR #4 OR #5

#	Suchschritt
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	((((#7) AND ("2020/12/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MeSH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
9	(#6) 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 metasyntes*[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])
10	((((#9) AND ("2020/12/01"[PDAT] : "3000"[PDAT])) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
11	(#10) NOT (#8)
12	(#11) AND ("2023/12/01"[PDAT] : "3000"[PDAT])
13	#11 NOT #12

Iterative Handsuche nach grauer Literatur, abgeschlossen am 17.12.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- American Society of Clinical Oncology (ASCO)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

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 2. **Jamil A, Qureshi Z, Riaz R, Akram H, Jamil R, Kichloo A, et al.** Impact of minimal residual diseases status and depth of response on survival outcomes in Blinatumomab-treated acute lymphoblastic leukemia: a systematic review and meta-analysis. *Am J Clin Oncol* 2025;48(6):290-301.
 3. **National Comprehensive Cancer Network (NCCN).** Acute lymphoblastic leukemia, evidence block, vers. 02.2025 [online]. 06.2025. Plymouth Meeting (USA): NCCN; 2025. [Zugriff: 17.12.2025]. (NCCN Guidelines with Evidence Blocks). URL: https://www.nccn.org/professionals/physician_gls/pdf/all_blocks.pdf.
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- [B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol* 2016;75:40-46. <https://doi.org/10.1016/j.jclinepi.2016.01.021>

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-347

Verfasser	
Institution	DGHO Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie
Sachverständige	
Datum	15. Januar 2026

Indikation
zur Behandlung von Erwachsenen mit Philadelphia-Chromosom-negativer, CD19-positiver B-Zell-Vorläufer-ALL in erster oder zweiter kompletter Remission mit einer minimalen Resterkrankung (minimal residual disease, MRD) von mindestens 0,1 %.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?
Zusammenfassung
Standard in der Behandlung von Patientinnen und Patienten (Pat.) mit Philadelphia-Chromosom-negativer, CD19-positiver B-Zell-Vorläufer-ALL in erster oder zweiter kompletter Remission mit einer minimalen Resterkrankung (minimal residual disease, MRD) von mindestens 0,1 % ist Blinatumomab.
Stand des Wissens
Basis der Empfehlung sind die auch zulassungsrelevanten Daten der Phase-II-Studie BLAST mit 116 Pat. Die Studie war mit wesentlicher deutscher Beteiligung durchgeführt worden. Hier führte Blinatumomab bei Pat. mit dem Nachweis minimaler Resterkrankung (MRD) von mindestens ³ (0,1%) zu einer MRD-Ansprechrage von 78% nach einem Therapiezyklus. Im Vergleich zu einer retrospektiven historischen Kohorte mit Polychemotherapie führt der frühe Einsatz von Blinatumomab zur Verlängerung des Gesamtüberlebens und des hämatologischen rezidivfreien Überlebens [1, 2]. Das mediane Überleben lag bei 36 Monaten. Pat. mit molekularem Ansprechen auf die Blinatumomab-Therapie hatten eine signifikant bessere Überlebenswahrscheinlichkeit als Pat. ohne Ansprechen [2, 3].
Das Muster der Nebenwirkungen entsprach dem Einsatz von Blinatumomab im Rezidiv bzw. bei Refraktärität. Im Vordergrund der schweren Nebenwirkungen stehen Neutropenie und neurologische Symptome. Ebenso wie beim Einsatz von Blinatumomab in der Rezidivsituation sind die Nebenwirkungen weniger ausgeprägt als unter intensiver Chemotherapie.

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?

Blinatumomab bereits ab einem MRD- Niveau von 0.01% gefolgt von einer Stammzelltransplantation ist der Standard in dieser Therapiesituation. Im Fall von Kontraindikationen und/oder Rezidiv nach Blinatumomab-basierter Therapie werden alternative Immuntherapien erwogen z.B. Inotuzumab Ozogamicin im MRD-Setting.

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