Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2025-B-349 Blinatumomab

Stand: Februar 2026

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

Blinatumomab
[zur Behandlung pädiatrischer Patientinnen und Patienten mit rezidivierter oder refraktärer akuter lymphatischer Leukämie]

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:** • Blinatumomab (Philadelphia-Chromosom-negativ) – Beschluss vom 15. August 2019 • Blinatumomab (Kinder im Alter von 1 bis 18 Jahre) – Beschluss vom 20. Januar 2022 • Blinatumomab (Kinder im Alter von 1 Monat bis < 1 Jahr) – Beschlüsse vom 21. August 2025 • Tisagenlecleucel – Beschluss vom 15. Februar 2024 **ATMP-Qualitätssicherungs-Richtlinie:** Anlage I - CAR-T-Zellen bei B-Zell-Neoplasien (Stand: 14.06.2022) **Richtlinie Methoden Krankenhausbehandlung:** Methoden, deren Bewertungsverfahren ausgesetzt ist: • Allogene Stammzelltransplantation mit In-vitro-Aufbereitung (T-Zell-Depletion über Positivanreicherung oder Negativselektion) des Transplantats bei akuter lymphatischer Leukämie (ALL) und akuter myeloischer Leukämie (AML) bei Erwachsenen – Beschluss gültig bis 1. Juli 2021 (verbunden mit Beschluss zur Qualitätssicherung gemäß § 136 SGB V)
Die Vergleichstherapie soll nach dem allgemein anerkannten	

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

Blinatumomab
[zur Behandlung pädiatrischer Patientinnen und Patienten mit rezidivierter oder refraktärer akuter lymphatischer Leukämie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
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:	
Blinatumomab L01FX07 Blincyto	BLINCYTO wird als Monotherapie angewendet zur Behandlung von pädiatrischen Patienten im Alter von 1 Monat oder älter mit Hochrisiko-Erstrezidiv einer Philadelphia-Chromosom-negativen, CD19-positiven B-Zell-Vorläufer-ALL im Rahmen der Konsolidierungstherapie.
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.
Clofarabine L01BB06 Evoltra	Behandlung von akuter lymphoblastischer Leukämie (ALL) bei pädiatrischen Patienten, die nach mindestens zwei Vorbehandlungen ein Rezidiv erleiden oder refraktär sind, und wenn erwartet wird, dass keine andere Behandlungsoption zu einem dauerhaften Ansprechen führt. Sicherheit und Wirksamkeit sind in Studien mit Patienten beurteilt worden, die bei der Erstdiagnose ≤ 21 Jahre alt waren (siehe Abschnitt 5.1).

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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
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.
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

II. Zugelassene Arzneimittel im Anwendungsgebiet	
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	
Blinatumomab L01FX07 Blincyto	BLINCYTO wird als Monotherapie angewendet zur Behandlung von Erwachsenen mit CD19-positiver, rezidivierter oder refraktärer B-Vorläufer akuter lymphatischer Leukämie (ALL). Bei Patienten mit Philadelphia-Chromosom-positiver B-Vorläufer-ALL sollte die Behandlung mit mindestens 2 Tyrosinkinase-Inhibitoren (TKI) fehlgeschlagen sein, und sie sollten keine alternativen Behandlungsoptionen haben. 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 %. BLINCYTO wird als Monotherapie angewendet zur Behandlung von pädiatrischen Patienten im Alter von 1 Monat oder älter mit Philadelphia-Chromosom-negativer, CD19-positiver B-Vorläufer-ALL, die refraktär ist oder nach mindestens zwei vorangegangenen Therapien rezidiviert ist oder nach vorangegangener allogener hämatopoetischer Stammzelltransplantation rezidiviert ist. BLINCYTO wird als Monotherapie angewendet zur Behandlung von pädiatrischen Patienten im Alter von 1 Monat oder älter mit Hochrisiko-Erstrezidiv einer Philadelphia-Chromosom-negativen, CD19-positiven B-Vorläufer-ALL im Rahmen der Konsolidierungstherapie (siehe Abschnitt 4.2). BLINCYTO wird als Monotherapie angewendet zur Behandlung von erwachsenen Patienten mit neu diagnostizierter Philadelphia-Chromosom-negativer, CD19-positiver B-Zell-Vorläufer-ALL im Rahmen der Konsolidierungstherapie.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Koloniestimulierende Faktoren	
Filgrastim L03AA02 Nivestim	Filgrastim ist angezeigt zur Verkürzung der Dauer von Neutropenien sowie zur Verminderung der Häufigkeit neutropenischen Fiebers bei Patienten, die wegen einer malignen Erkrankung (außer chronisch-myeloischer Leukämie und myelodysplastischem Syndrom) mit üblicher zytotoxischer Chemotherapie behandelt werden und zur Verkürzung der Dauer von Neutropenien bei Patienten, die eine myeloablative Behandlung mit anschließender Knochenmarktransplantation erhalten, bei denen ein erhöhtes Risiko einer verlängerten schweren Neutropenie besteht. Die Sicherheit und Wirksamkeit von Filgrastim ist bei Erwachsenen und Kindern, die eine zytotoxische Chemotherapie erhalten, vergleichbar.
Lenograstim L03AA10 Granocyte	GRANOCYTE ist für Erwachsene, Heranwachsende und Kinder, die älter als 2 Jahre sind, indiziert: • Zur Verkürzung der Dauer von Neutropenien bei Patienten mit nicht-myeloischen malignen Erkrankungen, die sich einer myeloablativen Therapie mit anschließender Knochenmarktransplantation unterziehen und ein erhöhtes Risiko andauernder schwerer Neutropenien aufweisen.
CAR-T-Zellen	
Tisagenlecleucel L01XL04 Kymriah	Kymriah wird angewendet zur Behandlung von: • Kindern, Jugendlichen und jungen erwachsenen Patienten im Alter bis einschließlich 25 Jahren mit refraktärer oder rezidivierter (Rezidiv nach Transplantation oder zweites oder späteres Rezidiv) akuter lymphatischer B-Zell-Leukämie (ALL).

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-349 (Beratung nach § 35a SGB V) Blinatumomab

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

Inhaltsverzeichnis

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

Kinder (ab 1 Monat oder älter) mit einer Philadelphia-Chromosom-negativen, CD19-positiven 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 fünf 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

Da Silva AMP et al., 2025 [1].

Blinatumomab Versus Chemotherapy for Post-Induction Consolidation in First Relapse of B-Cell Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Fragestellung

We conducted a systematic review and meta-analysis to evaluate the efficacy and safety of blinatumomab compared to conventional chemotherapy as post-induction consolidation therapy in children, adolescents, and young adults with first relapse of B-ALL.

Methodik

Population:

- children, adolescents, and young adults with a first relapse of standard-risk B-ALL

Intervention:

- post-induction consolidation therapy with blinatumomab

Komparator:

- post-induction consolidation therapy with conventional chemotherapy

Endpunkte:

- […] reporting at least one predefined endpoint of interest, including disease-free survival (DFS), overall survival (OS), relapse rate, complete response (CR), adverse events (AEs), treatment-related mortality, need for salvage therapy, cumulative incidence of relapse, hematopoietic stem cell transplantation (HSCT), any AEs, anemia risk, white blood cell (WBC) decrease risk, deaths in remission, and MRD negativity at the end of cycle 1

Recherche/Suchzeitraum:

- extensive search of PubMed, Embase, the Cochrane Central Register of Controlled Trials, and ScienceDirect from inception to February 2025

Qualitätsbewertung der Studien:

- Version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- four RCTs

Charakteristika der Population/Studien:

- A total of 703 patients received Blinatumomab-based treatment, and correspondingly 703 patients received Chemotherapy alone across the included studies. The overall median age was 6 years (1-17) in the Blinatumomab group and 5 years (1-17) in the Chemotherapy group, with no significant age difference between groups. The proportion of female patients was 381 (54.2%) in the Blinatumomab group and 380 (54.1%) in the Chemotherapy group, indicating similar gender distribution across treatments.

Table 1 Baseline Characteristics of Included Studies.

Authors, y	Treatment	Sample Size (n)	Country	Study design	Female (n)	Age (y)[a]	No. of Consolidation Cycles	Type of Chemotherapy Regimen	MRD Assessment Method (Sensitivity)	Follow-Up (y)[a]
Gupta et al.[23]	Blinatumomab + Chemotherapy	417	AUS CAN NZ US	RCT	207	4.0 (1.0-9.9)	2 cycles	DEX,VCR, MP, IT, MTX	Flow cytometry (10^{-4}) + NGS (10^{-6})	2.5 (1.6-3.2)
	Chemotherapy	418			195	4.3 (1.0-10.0)				
Brown et al.[16]	Blinatumomab	105	AUS CAN NZ US	RCT	48	9 (6-16)	2 cycles	DEX, VCR, HD-MTX + LV, PEG-Asp, CTX, ETP, Ara-C, IT MTX, Erwinia Asp.	Flow cytometry (10^{-4})	2.9 (1.8-3.9)
	Chemotherapy	103			49	9 (5-16)				
Hogan et al.[24]	Blinatumomab	127	AUS CAN NZ US	RCT	51	11 (7-15)	3 cycles	DEX, VCR, PEG-Asp, CTX, ETP, Ara-C, MTX (IV and IT), LV, Erwinia Asp (if indicated).	Flow cytometry (10^{-4})	3.5 (2.5-4.7)
	Chemotherapy	128			52	10 (7-15)				
Locatelli et al.[25]	Blinatumomab	54	MULTICENTER	RCT	24	6 (1-17)	1 cycles	DEX, VCR, CTX, Ara-C, MTX, PEG-Asp, ETP, DNR, IFO	Flow cytometry (10^{-4}) + PCR(10^{-5})	1.87 (0.68-2.85)
	Chemotherapy	54			32	5 (1-17)				

Um total de 703 pacientes foram tratados com esquemas contendo Blinatumomabe, enquanto 703 receberam apenas quimioterapia nos quatro ensaios clínicos randomizados incluídos. A mediana de idade no grupo Blinatumomabe variou de 4,0 a 11 anos, enquanto no grupo quimioterapia variou de 4,3 a 10 anos, com distribuições etárias semelhantes. Pacientes do sexo feminino representaram 381 (54,2%) no grupo Blinatumomabe e 380 (54,1%) no grupo quimioterapia, indicando distribuição de gênero equivalente entre os grupos. Os protocolos de tratamento variaram entre os estudos, incluindo os esquemas AALL1731, InfReALL HR e UKALL-R3, com 1 a 3 ciclos de consolidação administrados. A avaliação da doença residual mensurável (MRD) foi realizada predominantemente por citometria de fluxo, com alguns estudos incorporando PCR ou sequenciamento de nova geração (NGS), com sensibilidades variando entre 10^{-4} e 10^{-6}. As características demográficas e de tratamento dos pacientes incluídos estão detalhadas na Tabela 1.
Abbreviations: AUS = Australia; CAN = Canada; CNS = Central Nervous System; CTX = Cyclophosphamide; DEX = Dexamethasone; DNR = Daunorubicin; ETP = Etoposide; HD-MTX = High-Dose Methotrexate; IFO = Ifosfamide; IT = Intrathecal; IV = Intravenous; LV = Leucovorin; MP = Mercaptopurine; MTX = Methotrexate; MRD = Measurable Residual Disease; NA = Not Available; NGS = Next-Generation Sequencing; n = Number; NZ = New Zealand; PCR = Polymerase Chain Reaction; PEG-Asp = Pegaspargase; RCT = Randomized Clinical Trial; US = United States; VCR = Vincristine; y = Years.
[a] mean (SD) or median (range) or percentual.

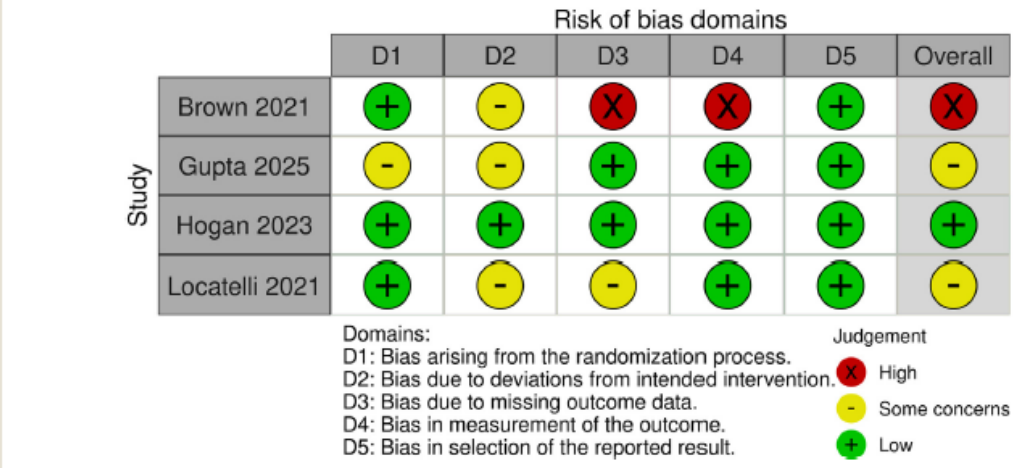
Table 2 Disease Profile and Risk Stratification in the Included Studies

Authors (y)	Treatment	CNS Status		Cytogenetic Risk Group		Marrow Relapse Months			Extramedullary Relapse (%)	Marrow + Extramedullary Relapse (%)	Risk Patients (n)		Any Adverse Event (%)
		CNS1[a] (%)	CNS2[a] (%)	Favorable (%)	Unfavorable (%)	< 18 (%)	18-36 (%)	≥ 36 (%)			High-Risk (%)	Intermediate (%)	
Gupta et al.[23]	Blinatumomab + Chemotherapy	399 (95.7)	18 (4.3)	127 (30.5)	NA	NA	NA	NA	NA	NA	301/605	417/835	NA
	Chemotherapy	407 (97.4)	11(2.6)	114 (27.3)							304/605	418/835	
Brown et al.[16]	Blinatumomab	NA	NA	21 (23.3)	7 (7.8)	18 (17.1)	41(39.0)	36 (34.3)	10 (9.5)	NA	69 (65.7)	36/105 (34.3)	99 (97)
	Chemotherapy			16 (17.6)	10 (11.0)	18 (17.5)	41 (39.8)	34 (33.0)	10 (9.7)		69 (67.0)	34/103 (33.0)	89 (92)
Hogan et al.[24]	Blinatumomab	NA	NA	39 (32.5)	5 (4.2)	NA	NA	NA	40 (31.5)	17 (13.4)	NA	NA	117 (97)
	Chemotherapy			37 (35.6)	2 (1.9)				41 (32.0)	15 (11.7)			105 (89)
Locatelli et al.[25]	Blinatumomab	NA	NA	8 (14.8)	7 (13.0)	19 (35.2)	32 (59.3)	3 (5.6)	10 (18.5)	NA	54 (100)	NA	54 (100)
	Chemotherapy			10 (18.5)	9 (16.7)	22 (40.7)	28 (51.9)	4 (7.4)	14 (25.9)				49 (96.1)

Abbreviations: NA = Not Available; y = years; n = number; RCT = Randomized Clinical Trials; CNS = Central Nervous System.
[a] n/total.

<u>Qualität der Studien:</u>

Figure 12 Traffic light plot showing the individual assessments according to each domain.



- The study by Hogan et al. 24 was classified as having an overall low risk of bias. However, two studies Gupta et al. 23 and Locatelli et al. 25 were identified as having some concerns in specific domains. Gupta et al. 23 exhibited shortcomings in the

randomization process (Domain 1) and allocation concealment (Domain 2), while Locatelli et al.25 not only demonstrated limitations in the treatment protocol but also showed issues affecting the outcomes (Domain 3). Finally, Brown et al. 16 presented a combination of concerns across multiple domains, contributing to a higher overall risk of bias classification. Despite these issues, most studies employed sound methodological designs, minimizing the potential impact of bias on the aggregated review results.

Studienergebnisse:

In a meta-analysis of:

- four studies, blinatumomab was associated with a higher DFS compared to chemotherapy (HR 0.59; 95% CI, 0.42-0.81; *P* < .01; I^2 = 48%, Figure 2).
- four studies, blinatumomab was associated with improved OS compared to chemotherapy (HR 0.57; 95% CI, 0.43-0.76; *P* < .01; I^2 = 0%, Figure 3).
- two studies, blinatumomab was associated with lower risk of cumulative incidence of relapse compared to chemotherapy (HR 0.26; 95% CI, 0.16-0.41; *P* < .01; I^2 = 0%, Figure 4).
- three studies, the relapse rate was lower in the blinatumomab group compared to chemotherapy, but without statistical significance (RR 0.53; 95% CI, 0.24-1.15; P = .11;I^2 = 87%, Figure 5).
- two studies, patients receiving blinatumomab were more likely to proceed to HSCT compared to chemotherapy (RR 1.43; 95% CI, 1.10-1.85; *P* < .01; I^2 = 62%, Figure 6).
- three studies, the incidence of any adverse event was slightly higher in the blinatumomab group compared to chemotherapy (RR 1.06; 95% CI, 1.02-1.10; *P* < .01; I^2 = 0%, Figure 7).
- three studies, anemia risk did not significantly differ between blinatumomab and chemotherapy (RR 0.87; 95% CI, 0.43-1.76; *P* = .70; I^2 = 82%, Figure 8).
- three studies, the risk of WBC decrease was slightly higher in the blinatumomab group (RR 1.16; 95% CI, 1.01-1.32; *P* < .05; I^2 = 0%, Figure 9).
- three studies, no statistically significant difference was observed between blinatumomab and chemotherapy for deaths in remission (RR 0.91; 95% CI, 0.43-1.95; *P* = .82; I^2 = 0%, Figure 10).
- two studies evaluating MRD negativity at the end of cycle 1 demonstrated greater benefit in the blinatumomab group compared to chemotherapy (RR 1.96; 95% CI, 1.40-2.76; *P* < .01; I^2 = 64%, Figure 11).

Figure 2 Forest plot for disease-free survival, showing a significant benefit of blinatumomab over chemotherapy.

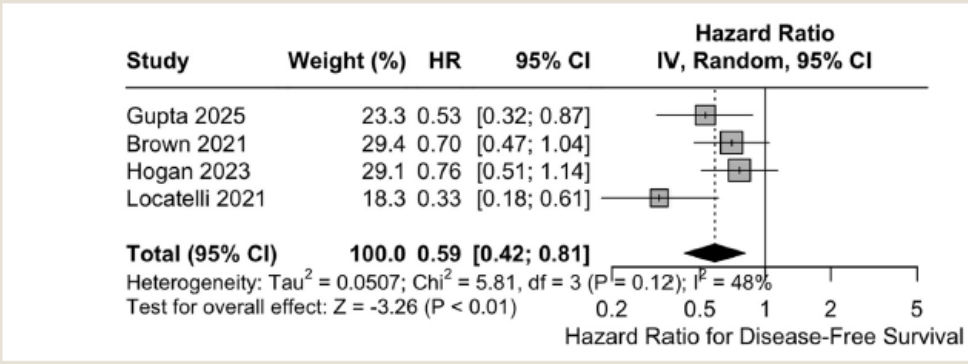


Figure 3 Forest plot for overall survival, demonstrating a reduced mortality risk with blinatumomab.

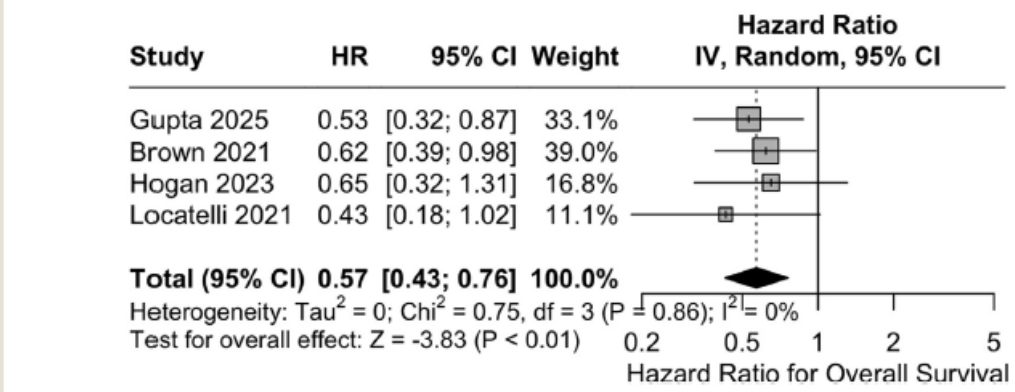


Figure 4 Forest plot for cumulative incidence of relapse, demonstrating a reduced risk with blinatumomab.

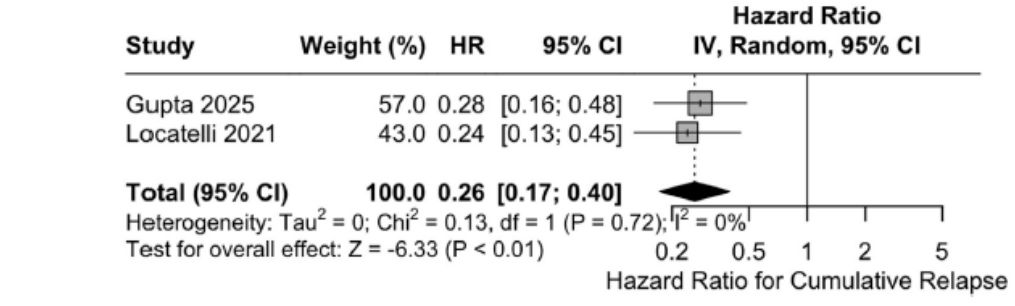


Figure 5 Forest plot for relapse rate, showing a trend toward lower relapse with blinatumomab, though not statistically significant.

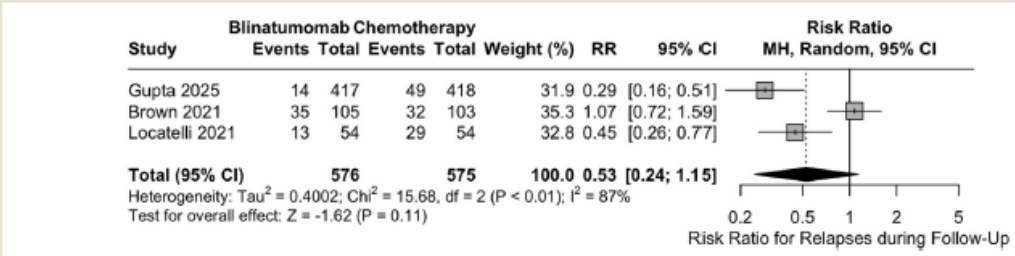


Figure 6 Forest plot for hematopoietic stem cell transplantation, indicating a higher likelihood of transplantation with blinatumomab.

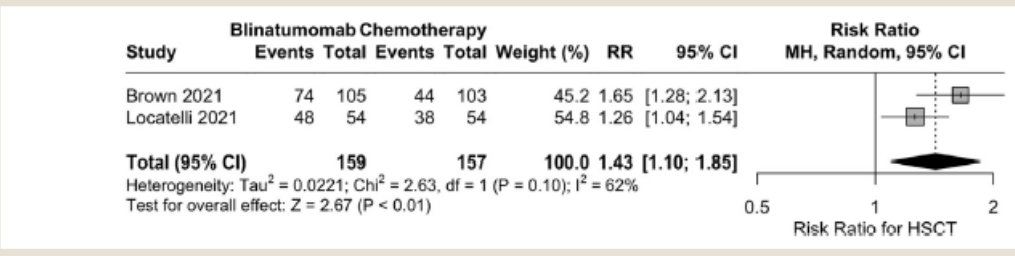


Figure 7 Forest plot for any adverse events, showing a slightly increased risk in the blinatumomab group.

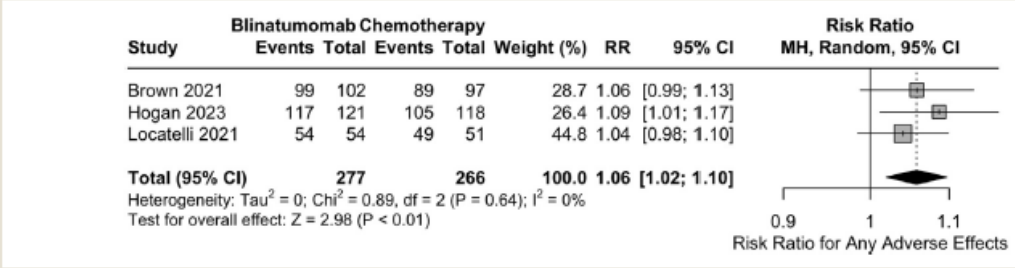


Figure 8 Forest plot for anemia risk, indicating no significant difference between treatment groups.

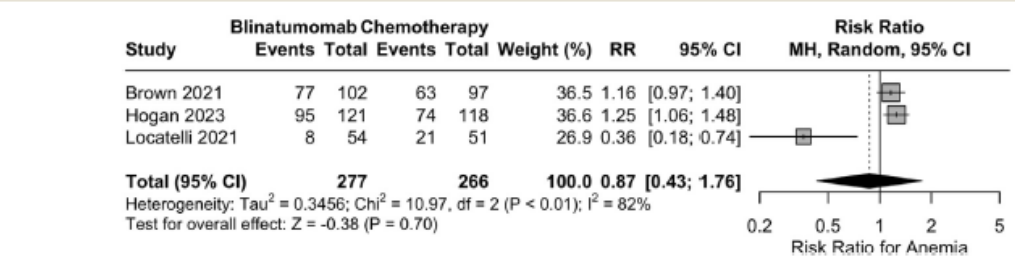


Figure 9 Forest plot for WBC decreases risk, demonstrating a slightly higher risk in the blinatumomab group.

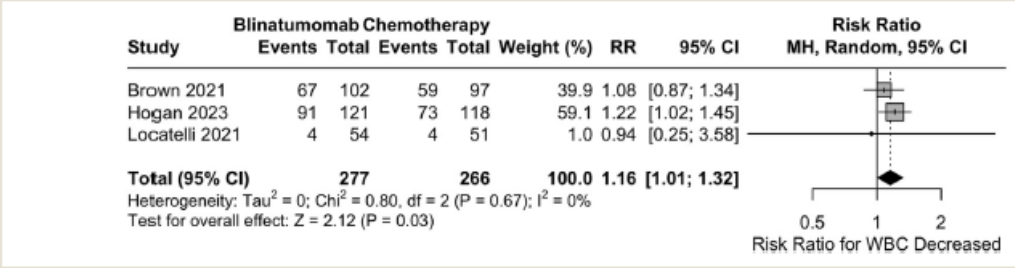


Figure 10 Forest plot for deaths in remission, showing no significant difference between blinatumomab and chemotherapy.

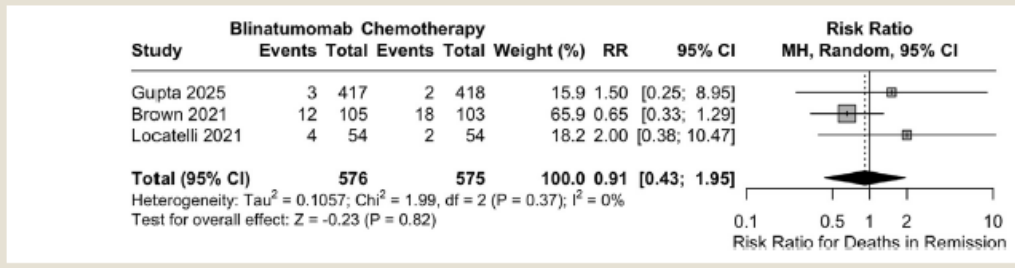
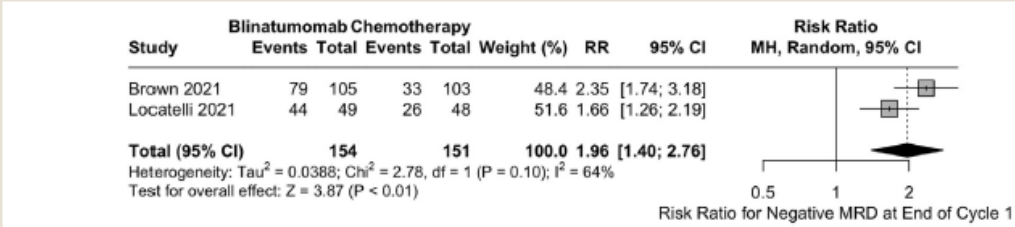


Figure 11 Forest plot for negative MRD at the end of cycle 1 favoured blinatumomab over chemotherapy.



Anmerkung/Fazit der Autoren

The meta-analysis of the selected studies, which evaluated the efficacy and safety of blinatumomab compared to conventional chemotherapy as post-induction consolidation therapy in children, adolescents, and young adults with first relapse of standard-risk BALL, supports the potential benefit of blinatumomab in improving survival outcomes and reducing relapse. However, given the heterogeneity in relapse rates and MRD negativity among the included studies, as well as variations in treatment protocols, these results should be interpreted with caution. Large-scale RCTs with standardized methodologies and longer follow-up periods are needed to validate these findings and enhance the integration of blinatumomab into clinical practice.

Kommentare zum Review

Es liegen weitere SRs zu dieser Fragestellung mit derselben Schlussfolgerung vor:

- Ogedegbe et al., 2025 [5]

3.3 Leitlinien

NCCN, 2025 [2,3].

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

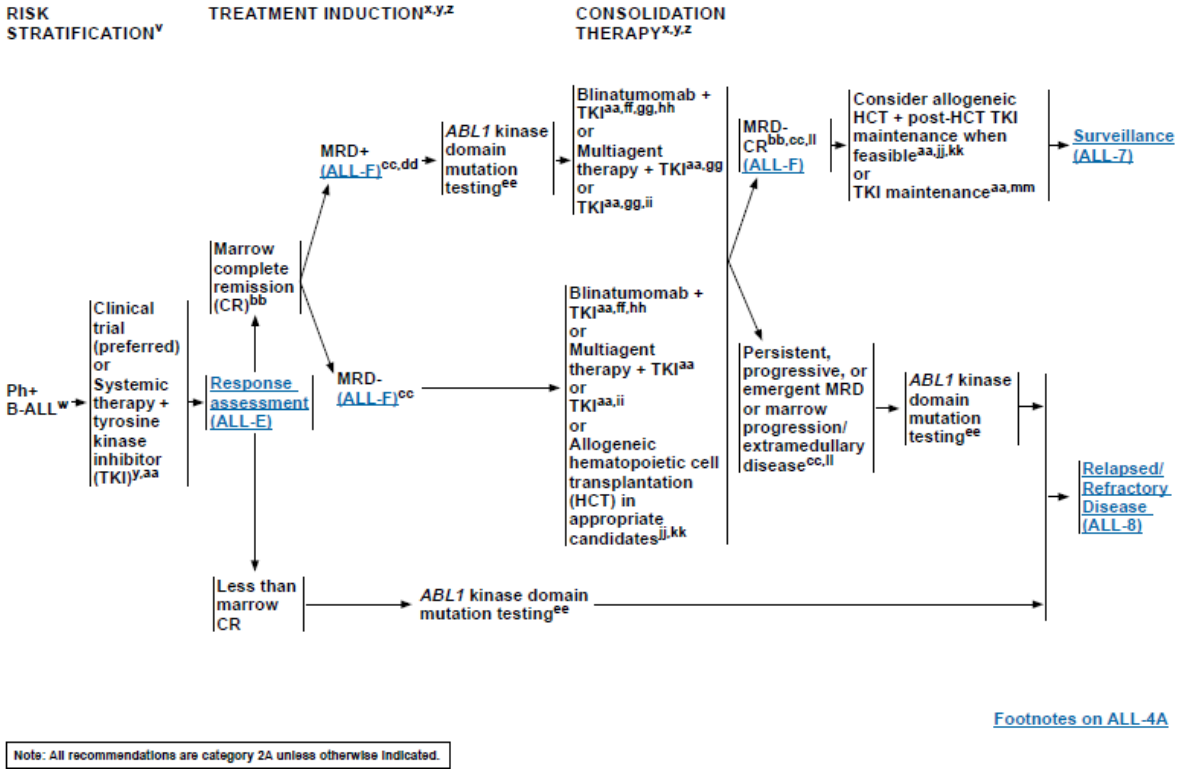
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there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

All recommendations are category 2A unless otherwise indicated.

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

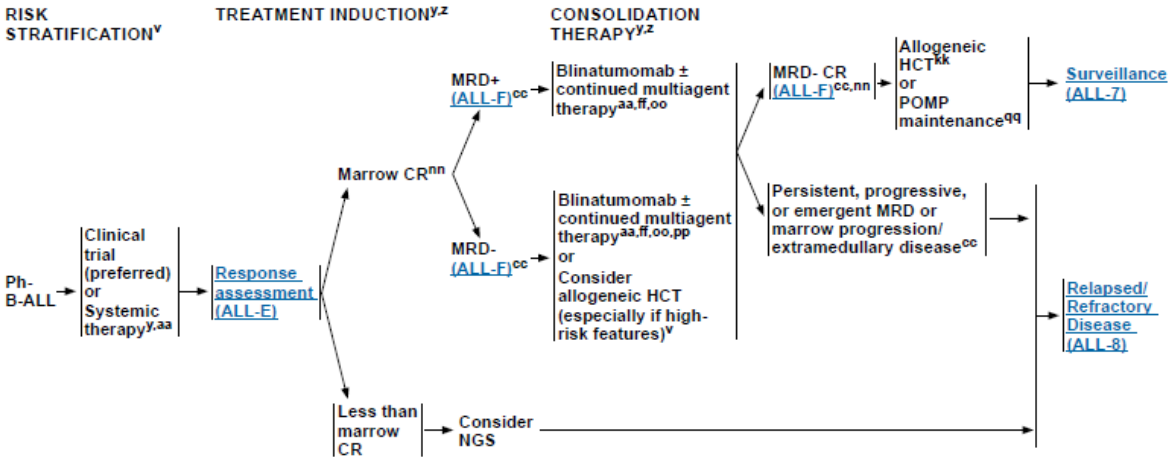
All recommendations are considered appropriate.

Empfehlungen



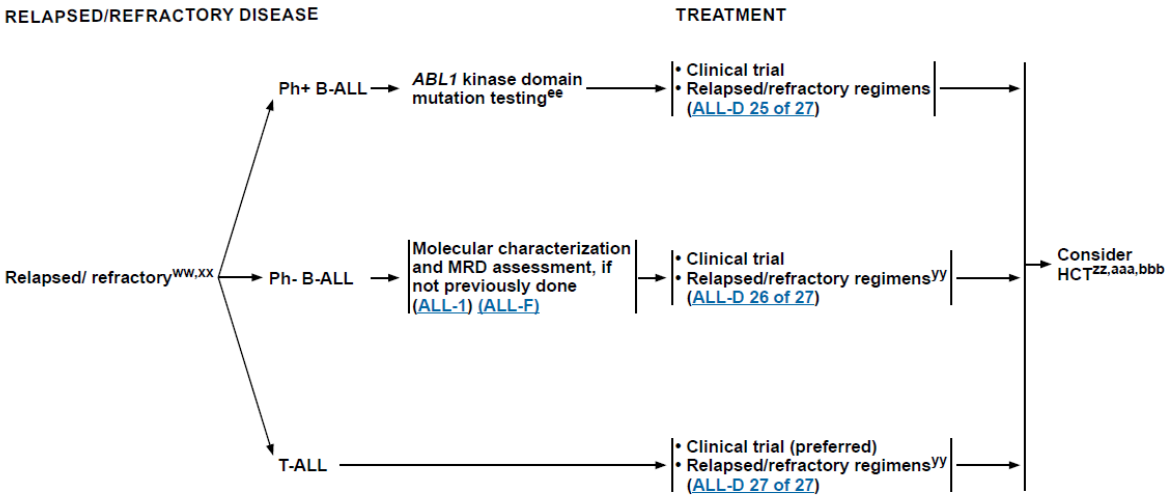
FOOTNOTES FOR Ph+ B-ALL TREATMENT INDUCTION AND CONSOLIDATION THERAPY

[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 6).
[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.
[jj] 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;28:1467-1471.
[kk] Favored for poor risk B-ALL (ALL-2) and/or slow/incomplete MRD clearance.
[ll] 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 6).
[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 autoleucel, tisagenlecleucel, and obecabtagene autoleucel, 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.

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/m^2), 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.

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

Preferred
• Clinical trial
 	
Other Recommended Regimens
• TKI[c,d] in combination with:
  ▸ Blinatumomab[e,1-3]
  ▸ HyperCVAD[4-8]
 	
Useful in certain circumstances
• TKI[c,d] in combination with:
  ▸ Corticosteroid[f,9,10]
  ▸ Vincristine + dexamethasone[11]
	Preferred
	• Clinical trial
	
	Other Recommended Regimens
	• Low intensity
	  ▸ TKI[c,d] in combination with:
	  ◊ Blinatumomab[e,1-3]
	  ◊ Corticosteroid[f,9,10,12-14]
	  ◊ Vincristine + dexamethasone[11]
	• Moderate intensity
	  ▸ TKI[c,d] + mini-hyperCVD[15]

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, cytoreduce with TKI plus corticosteroid to a peripheral WBC count of <10 x 10^9/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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-POSITIVE B-ALL INDUCTION COMPONENTS[b,g,h,i]

AYA Patients and Adults <65 years without Substantial Comorbidities: Frontline
Other Recommended Regimens • **Blinatumomab[e] + TKI[c,d,1-3]** • **HyperCVAD[4-8] + TKI[c,d]:** Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, alternating with high-dose methotrexate, dose-adjusted cytarabine **Useful in certain circumstances** • **Corticosteroid + TKI[c,d,f,9,10]** • **Vincristine + dexamethasone + TKI[c,d,11]**
Adults ≥65 Years or Adults with Substantial Comorbidities: Frontline & Relapsed/Refractory
Other Recommended Regimens • **Low intensity** ‣ **Blinatumomab[e] + TKI[c,d,1-3]** ‣ **Corticosteroid + TKI[c,d,f,9,10,12-14]** ‣ **Vincristine + dexamethasone + TKI[c,d,11]** • **Moderate intensity** ‣ **Mini-hyperCVD[15] + 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.
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[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/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.
[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.

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		**Mini-hyperCVD[15] + TKI[c,d]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine
Vincristine + dexamethasone + TKI[c,d,11]: Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, high-dose methotrexate, vincristine		**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/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.
[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.

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.

Referenzen – Ph-positive B-ALL:

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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 • Clinical trial • CALGB 10403[b,1] • DFCI ALL regimen based on DFCI Protocol 00-01[b,2]	Preferred • Clinical trial Other Recommended Regimens • ECOG 1910[3] • HyperCVAD[4-6] • MSKCC ALL regimen based on CCG-1882 regimen (if aged ≥18 to <60 years)[b,7,8]	Preferred • Clinical trial Other Recommended Regimens • Inotuzumab ozogamicin + mini-hyperCVD[9-11]	Preferred • Clinical trial Other Recommended Regimens • Low Intensity ‣ Vincristine + prednisone[12] ‣ POMP[13]: mercaptopurine, vincristine, methotrexate, prednisone • Moderate Intensity ‣ ALL-INITIAL-1[14]: Inotuzumab ozogamicin/ dexamethasone (category 2B) ‣ ALLIANCE A041703[15]: Inotuzumab ozogamicin (category 2B) ‣ Inotuzumab ozogamicin + mini-hyperCVD[9-11] ‣ Modified DFCI 91-01 protocol[16] ‣ Mini-hyperCVD[17,18] ‣ Mini-hyperCVD + venetoclax[17] • High Intensity ‣ ECOG 1910[3] Useful in certain circumstances • ALLOLD07 (PETHEMA-based regimen)[19] • CALGB 9111[20] • EWALL[21] • GMALL[22] + rituximab for CD20-positive disease • GRAALL[23]

[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

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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 • **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 • **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase, vincristine, rituximab for CD20-positive disease • **HyperCVAD[4-6]:** 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 • **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** 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
Other Recommended Regimens • **Low intensity** ‣ **Vincristine + prednisone[12]** ‣ **POMP[13]:** Mercaptopurine, vincristine, methotrexate, prednisone • **Moderate intensity** ‣ **ALL-INITIAL-1[14]: Inotuzumab ozogamicin/Dexamethasone (category 2B)** ‣ **ALLIANCE A041703[15]: Inotuzumab ozogamicin (category 2B)** ‣ **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin ‣ **Modified DFCI 91-01 protocol[16]:** Dexamethasone, doxorubicin, methotrexate, pegaspargase, vincristine ‣ **Mini-hyperCVD[17,18]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine, rituximab for CD20-positive disease ‣ **Mini-hyperCVD + venetoclax[17]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax • **High intensity** ‣ **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, mercaptopurine, pegaspargase (age <55 years), vincristine, rituximab for CD20-positive disease **Useful in certain circumstances** • **ALLOLD07 (PETHEMA-based regimen)[19]:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine • **CALGB 9111[20]:** Cyclophosphamide, daunorubicin, prednisone, pegaspargase, vincristine • **EWALL[21]:** Cyclophosphamide, dexamethasone, vincristine • **GMALL[22]:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, vincristine, rituximab for CD20-positive disease • **GRAALL[23]:** 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]

- **Blinatumomab (preferred) + continued multiagent therapy[h]**
- **Blinatumomab[i]**

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.

PRINCIPLES OF SYSTEMIC THERAPY

Ph-NEGATIVE B-ALL CONSOLIDATION COMPONENTS[a,c,d,e,f,g]

AYA Patients without Substantial Comorbidities
Preferred Regimens • **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 • **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab • **HyperCVAD[4-6]:** 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 • **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** 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

- **Low intensity**
  - **Vincristine + prednisone[12]**
  - **POMP[13]:** mercaptopurine, vincristine, methotrexate, prednisone
- **Moderate intensity**
  - **ALL-INITIAL-1[14]:** Cyclophosphamide, cytarabine, dexamethasone, idarubicin, high-dose methotrexate, pegaspargase, vincristine, with rituximab for CD20-positive disease
  - **ALLIANCE A041703[15]:** Blinatumomab
  - **Inotuzumab ozogamicin + mini-hyperCVD[9-11]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, inotuzumab ozogamicin alternating with cytarabine, methotrexate, inotuzumab ozogamicin, with sequential blinatumomab
  - **Modified DFCI 91-01 protocol[16]:** 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 + venetoclax[17]:** Hyperfractionated cyclophosphamide, vincristine, dexamethasone, alternating with methotrexate, cytarabine; venetoclax
- **High intensity**
  - **ECOG 1910[3]:** Cyclophosphamide, cytarabine, daunorubicin, dexamethasone, etoposide, mercaptopurine, high-dose methotrexate, pegaspargase, vincristine, rituximab for CD20-positive disease, alternating with blinatumomab

Useful in certain circumstances

- **ALLOLD07 (PETHEMA-based regimen)[19]:** Cytarabine, high-dose methotrexate, pegaspargase
- **CALGB 9111[20]:** Cyclophosphamide, cytarabine, dexamethasone, doxorubicin, mercaptopurine, pegaspargase, thioguanine, vincristine
- **EWALL[21]:** Cytarabine, high-dose methotrexate, pegaspargase
- **GMALL[22]:** Cytarabine, methotrexate, rituximab for CD20-positive disease
- **GRAALL[23]:** 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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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 bosutinib[6]) ‣ 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 + dasatinib[7] • 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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PRINCIPLES OF SYSTEMIC THERAPY

REGIMENS FOR RELAPSED OR REFRACTORY Ph-NEGATIVE B-ALL[a,b,c,d]

Preferred Regimens
• **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]
• **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, cytarabine[8] • **Clofarabine alone[9-12] or in combination** (eg, clofarabine, cyclophosphamide, etoposide)[10,13,14] • **MOpAD regimen:** methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease[15] • **Fludarabine-based regimens** ▸ **FLAG-IDA:** fludarabine, cytarabine, G-CSF ± idarubicin[16] ▸ **FLAM:** fludarabine, cytarabine, mitoxantrone[17] • **Cytarabine-containing regimens:** eg, high-dose cytarabine, idarubicin, IT methotrexate[18] • **Alkylator combination regimens:** eg, etoposide, ifosfamide, mitoxantrone[19] • **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 withallogeneic 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 T315I 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 historicalcontrol 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 ≤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 Hematologia) 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 CD19250 (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 x 109/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 allogenic 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 note 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-hyperCVD 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 autoleucel and obecabtagene autoleucel are CAR-T cell therapy options for AYA and adult patients with R/R Ph-positive B-ALL following therapy that has included TKIs. Tisagenlecleucel 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 tisagenlecleucel is unclear. Persistence of tisagenlecleucel 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 × 109/L for B-ALL; >100 × 109/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 (AALL-0232). 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 Gökbuget et al281 examined the efficacy of blinatumomab in an expanded cohort (n = 116) using a higher threshold for MRD positivity (hematologic CR with MRD ≥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 ≥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 ≥10-3 and/or a post-consolidation MRD ≥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 ATRIALL 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 ≥10-3 and/or post-consolidation MRD ≥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 (≥1x10-4).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 ≥50% or cellularity ≤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 ECOG1910.309Consolidation 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 autoleucel and obecabtagene autoleucel are additional options for AYA and adult patients with R/R Ph-negative B-ALL. Tisagenlecleucel 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 tisagenlecleucel is unclear. As previously discussed, persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia has been associated with durable clinical responses without subsequent allogeneic HCT.255

NCCN, 2025 [4].

National Comprehensive Cancer Network (NCCN)

Pediatric acute lymphoblastic leukemia, Version 01.2026 – August 11, 2025

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter höherwertiger Evidenz, hinsichtlich der Fragestellung zur aktuellen Therapie für Kinder mit einer Philadelphia-Chromosom-negativen, CD19-positiven B-Zell-Vorläufer-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

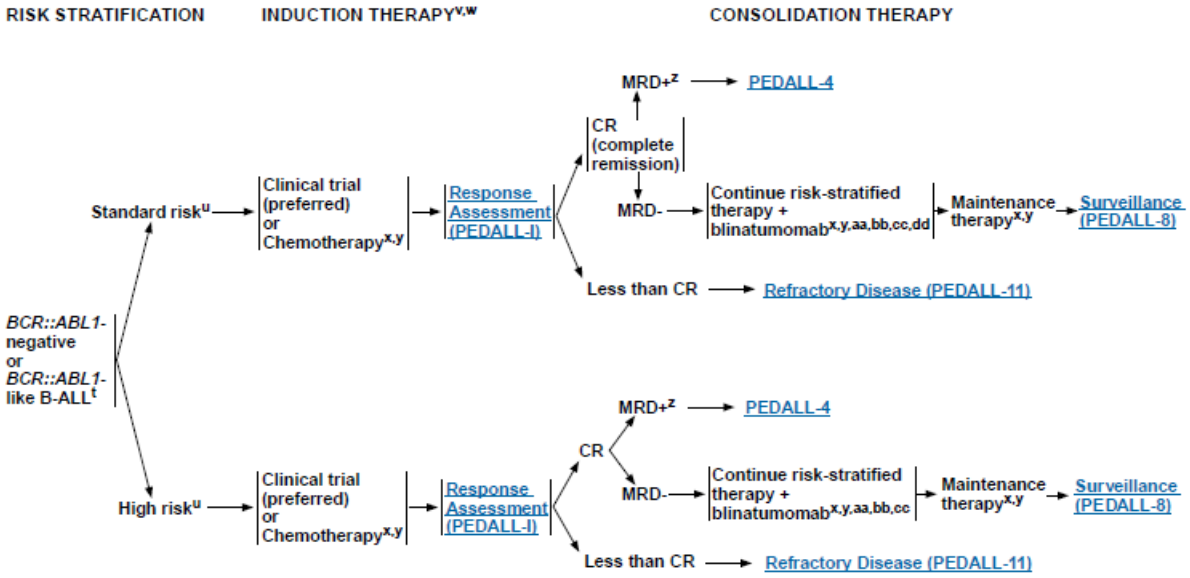
NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

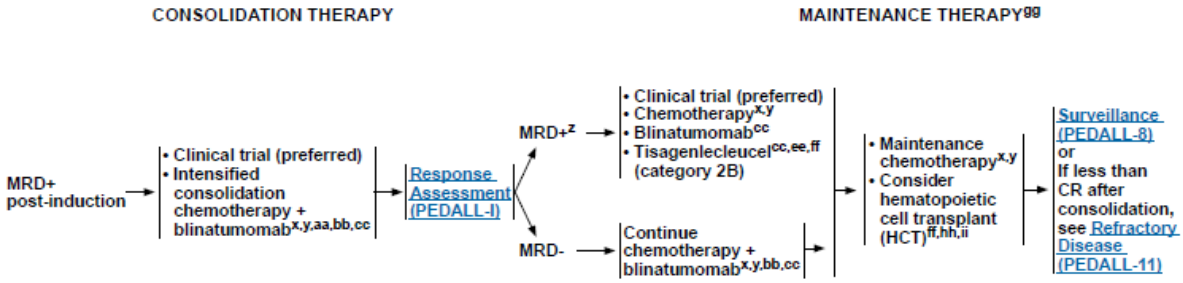
Empfehlungen



Footnotes on PEDALL-3A

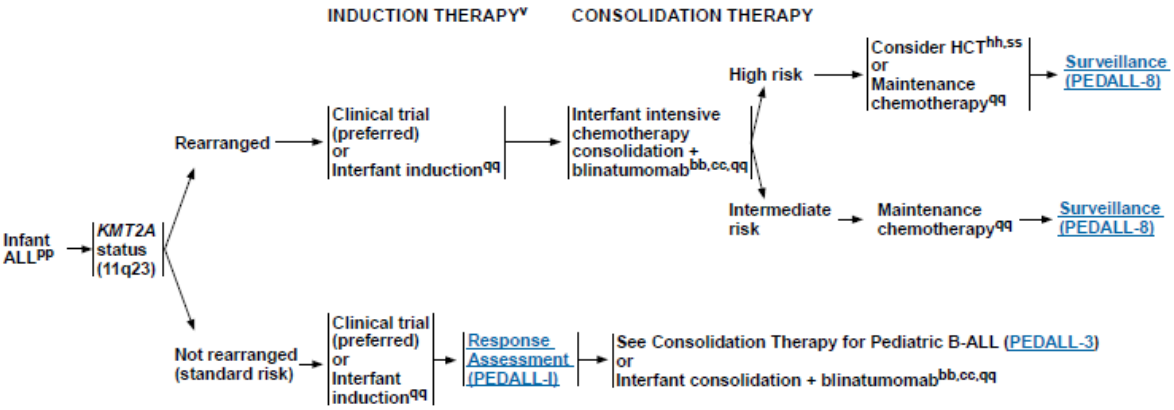
FOOTNOTES

[t] For patients with Down syndrome, see Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).
[u] See Risk Stratification Definitions (PEDALL-F).
[v] Principles of Supportive Care (PEDALL-C).
[w] Several retrospective studies have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved event-free survival (EFS) compared to same-aged patients treated on adult ALL regimens. Stock W. Hematology Am Soc Hematol Educ Program 2010;2010:21-29. Seibel NL. Hematology Am Soc Hematol Educ Program 2008:374-380.
[x] Principles of Systemic Therapy (PEDALL-G).
[y] For patients with *BCR::ABL1*-like ALL, tyrosine kinase inhibitors (TKIs) may be considered. For more information, see Principles of Systemic Therapy (PEDALL-G).
[z] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[aa] Risk Stratification Definitions for Post-Induction Therapy (PEDALL-F, 2 of 3).
[bb] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome (CRS) and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[cc] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[dd] For patients with an expected very favorable outcome, the benefit of blinatumomab should be weighed with potential toxicities, including increased infection risk.



[x] Principles of Systemic Therapy (PEDALL-G).
[y] For patients with *BCR::ABL1*-like ALL, TKIs may be considered. For more information, see Principles of Systemic Therapy (PEDALL-G).
[z] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[aa] Risk Stratification Definitions for Post-Induction Therapy (PEDALL-F, 2 of 3).
[bb] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/oder/daf/index.cfm).
[cc] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[ee] The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. See Tisagenlecleucel section in the Principles of Systemic Therapy (PEDALL-G, 10 of 13).
[ff] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K). Bone marrow MRD positivity, with or without B-cell aplasia, has been shown to be highly predictive of relapse following tisagenlecleucel. Pulsipher MA, et al. Blood Cancer Discov 2022;3:66-81. See Minimal Residual Disease (PEDALL-J).
[gg] To confirm adherence to oral chemotherapy during maintenance therapy, clinicians can take a detailed history, perform pill counts, and/or measure metabolites.
[hh] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[ii] HCT should be more strongly considered in the setting of MRD positivity.

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

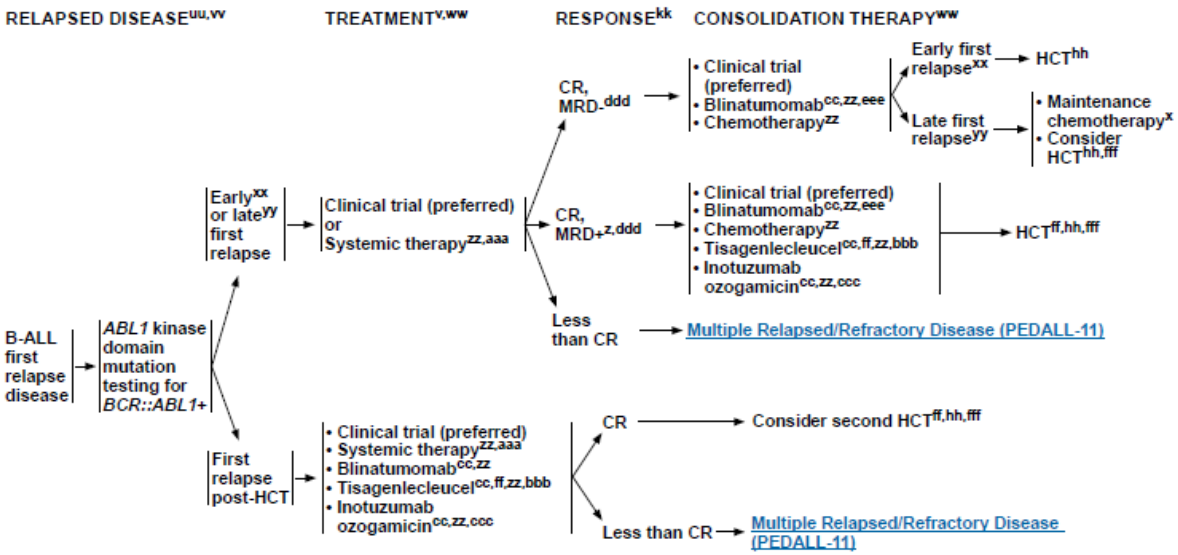


Infant Risk Group Definitions[rr]:

Risk Group	Features[z]
High	*KMT2A*-rearranged; *and* Age <3 mo with any WBC count or age <6 mo with WBC count ≥300,000; *or* Remains MRD+ after intensive consolidation therapy (any age/WBC count)
Intermediate	*KMT2A*-rearranged and not high risk
Standard	*KMT2A* not rearranged

[v] Principles of Supportive Care (PEDALL-C).
[z] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).
[bb] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/oder/daf/index.cfm).
[cc] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[hh] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[pp] Special Considerations for Patients with Down Syndrome and Infants (PEDALL-E).
[qq] Principles of Systemic Therapy for Infant ALL (PEDALL-G, 2 of 13).
[rr] Reproduced with permission: Brown P, Pieters R, Biondi A. How I treat infant leukemia. Blood 2019;133:205-214.
[ss] If donor available, prefer non-total body irradiation (TBI)-based prep regimen and age ≥6 mo at time of HCT.

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



Footnotes on PEDALL-9A

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

FOOTNOTES

[v] Principles of Supportive Care (PEDALL-C).

[x] Principles of Systemic Therapy (PEDALL-G).

[z] The threshold for MRD positivity may vary based on the protocol being followed and/or the assay being used. For further information, see Minimal Residual Disease (PEDALL-J).

[cc] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).

[ff] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K). Bone marrow MRD positivity, with or without B-cell aplasia, has been shown to be highly predictive of relapse following tisagenlecleucel. Pulsipher MA, et al. Blood Cancer Discov 2022;3:66-81. See Minimal Residual Disease (PEDALL-J).

[hh] Principles of Hematopoietic Cell Transplant (PEDALL-K).

[kk] MRD and morphologic marrow response should be assessed after induction, and if not MRD negative, repeat assessment after consolidation therapy. Assess MRD at additional time points based on chemotherapy regimen and response as indicated. See Minimal Residual Disease (PEDALL-J).

[uu] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

[vv] NCCN Guidelines for Palliative Care.

[ww] For *BCR::ABL1+* ALL add TKI to the treatment; see Regimens for Relapsed/Refractory *BCR::ABL1*-positive ALL (PEDALL-G, 8 of 13).

[xx] Early relapse is defined as <36 mo from initial diagnosis for isolated or combined bone marrow relapse OR <18 mo from initial diagnosis for isolated extramedullary relapse.

[yy] Late relapse is defined as ≥36 mo from initial diagnosis for isolated or combined bone marrow relapse OR ≥18 mo from initial diagnosis for isolated extramedullary relapse.

[zz] Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-G, 7 of 13).

[aaa] If patients experience relapse >3 months from initial diagnosis, consider treatment with the same induction regimen. For *BCR::ABL1*-negative, *BCR::ABL1*-like and *BCR::ABL1*-positive B-ALL, see PEDALL-G (1 of 13); for T-ALL, see PEDALL-G (2 of 13).

[bbb] See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-G, 10 of 13).

[ccc] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic sinusoidal obstructive syndrome (SOS) and increased risk of post-HCT non-relapse mortality. For details, see inotuzumab ozogamicin prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.

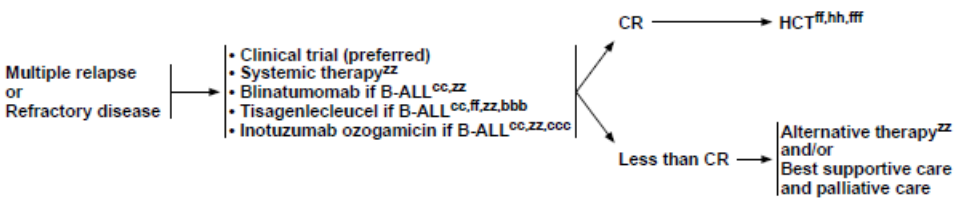
[ddd] Minimal Residual Disease (PEDALL-J).

[eee] This recommendation for blinatumomab pertains only to patients with bone marrow relapse with or without extramedullary involvement (Locatelli F, et al. JAMA 2021;325:843-854; Brown PA, et al. JAMA 2021;325:833-842; Hogan LE, et al. J Clin Oncol 2023; 41:4118-4129).

[fff] For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HCT should be considered.

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

MULTIPLE RELAPSE/REFRACTORY DISEASE[uu,vv]



[v] Principles of Supportive Care (PEDALL-C).
[cc] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[ff] The role of allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel in peripheral blood and persistent B-cell aplasia have been associated with durable clinical responses without subsequent HCT. In the global registration trial, 3-year relapse-free survival was 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT (Laetsch TW, et al. J Clin Oncol 2023;41:1664-1669). See Principles of Hematopoietic Cell Transplant (PEDALL-K). Bone marrow MRD positivity, with or without B-cell aplasia, has been shown to be highly predictive of relapse following tisagenlecleucel. Pulsipher MA, et al. Blood Cancer Discov 2022;3:66-81. See Minimal Residual Disease (PEDALL-J).

[hh] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[uu] Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.
[vv] NCCN Guidelines for Palliative Care.
[zz] Principles of Systemic Therapy for Relapsed/Refractory ALL (PEDALL-G, 7 of 13).
[bbb] See Tisagenlecleucel in the Principles of Systemic Therapy (PEDALL-G, 10 of 13).
[ccc] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic SOS and increased risk of post-HCT non-relapse mortality. For details, see inotuzumab ozogamicin prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.
[fff] For patients with MRD-positive second CR, it is recommended to receive an additional 1–2 courses of therapy to achieve an MRD-negative result prior to allogeneic HCT. However, some patients may not be able to achieve MRD negativity and proceeding to allogeneic HCT should be considered.

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

PRINCIPLES OF SYSTEMIC THERAPY[a,b,c]

Regimens for *BCR::ABL1*-Negative B-ALL
Regimen Components and Risk Stratification Applications on PEDALL-G (3 of 13)

Preferred	Other Recommended
• Clinical trial	• Standard risk (SR)-favorable arm of COG AALL1731 (for NCI standard-risk favorable B-ALL; based on COG AALL0932 regimen)[d,e,1] • SR-avg blinatumomab arm of COG AALL1731[d,e,2] • SR-high blinatumomab arm of COG AALL1731[d,e,2] • COG AALL0932 LR-M regimen[d,1] • Standard arm of COG AALL1732 regimen[d] (based on COG AALL1131 regimen[3-5]) • DFCI ALL Protocol 16-001 (based on DFCI ALL protocol 11-001[6,7]) • Total Therapy XVII regimen (based on Total Therapy XVI regimen[6])

Regimens for *BCR::ABL1*-Like B-ALL
Regimen Components and Risk Stratification Applications on PEDALL-G (4 of 13)

Preferred	Other Recommended
• Clinical trial	• COG AALL1131 regimen[d,3-5] + dasatinib[8] • COG AALL1521 regimen[d] ± ruxolitinib • DFCI-ALL Protocol 16-001 + dasatinib • Total Therapy XVII regimen + dasatinib[9] • Total Therapy XVII regimen ± ruxolitinib[9]

Regimens for *BCR::ABL1*-Positive B-ALL
Regimen Components and Risk Stratification Applications on PEDALL-G (5 of 13)

Preferred	Other Recommended
• Clinical trial	• Standard arm of COG AALL1631[d] (based on COG AALL1122/EsPhALL regimen): imatinib or dasatinib; combined with a high-risk backbone of the Berlin-Frankfurt-Münster (BFM) regimen[10] • COG AALL0622 regimen[11]: dasatinib; post-induction intensified chemotherapy based on POG/CCG regimens[12,13] • Total Therapy XVII regimen plus dasatinib on Day 15

Continued

FOOTNOTES

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; IT triple therapy [ITT] with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] While blinatumomab is recommended for patients with disease meeting the SR-avg or SR-high definitions of AALL1731, for sites without access to blinatumomab it is reasonable to follow the control (no blinatumomab) arms which are based on AALL0932. It is also reasonable to treat patients with disease meeting the SR-favorable definition as per the SR-avg arm of AALL1731 with blinatumomab. Assessment of MRD with a high sensitivity NGS assay post-induction may aid the decision to administer blinatumomab in patients with SR-favorable disease.

PRINCIPLES OF SYSTEMIC THERAPY[a,b]

Regimens for T-ALL[f,g,h,i]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended
• Clinical trial	• COG AALL1231 regimen[d,j,14] • COG AALL0434 regimen[d,j,15] • DFCI-ALL Protocol 16-001 (based on DFCI ALL protocol 11-001[6,7]) • SJCRH regimen based on Total Therapy XVII Regimen

Regimens for Infant ALL[c]

Regimen Components and Risk Stratification Applications on PEDALL-G (6 of 13)

Preferred	Other Recommended
• Clinical trial	• Interfant regimens + blinatumomab[16-20]

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[f] Incorporation of nelarabine is reasonable post-induction for all patients with T-ALL, especially those who are MRD+ or have CNS disease at diagnosis. Strongly consider including nelarabine in post-induction therapy for patients who do not achieve CR after induction therapy.
[g] CNS-directed therapy with IT chemotherapy is recommended during all phases of therapy in all patients.
[h] Cranial radiation should be considered for CNS-3 patients and is reasonable for other patients with high-risk T-ALL.
[i] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[j] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.

Continued
References

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

PEDALL-G

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,c,k]

The regimen components outlined in these tables represent the most recently published studies.

BCR::ABL1-Negative ALL	Induction	Consolidation
COG AALL1731 regimen[e,2]	SR arm: dexamethasone, vincristine, pegaspargase/calaspargase[l]; IT therapy: cytarabine then MTX	SR-favorable arm: mercaptopurine,[b] vincristine; IT therapy: MTX
		SR-avg arm: mercaptopurine,[b] vincristine; blinatumomab[m]; IT therapy: MTX
		SR-high arm: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase[l] + blinatumomab[m]; IT therapy: MTX
COG AALL0932 LR-M regimen[b,d,1,21] (SR)	SR arm: dexamethasone, vincristine, pegaspargase/calaspargase[l]; IT therapy: cytarabine then MTX	SR-low/avg arm: mercaptopurine,[b] vincristine; IT therapy: MTX
COG AALL1131 regimen[b,d,3-5,22] (HR)	HR arm: prednisone or dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin; IT therapy: cytarabine then MTX	HR arm: cyclophosphamide, cytarabine, mercaptopurine,[b] vin4cristine, pegaspargase/calaspargase[l] + blinatumomab[m]; IT therapy: MTX
DFCI ALL Protocol 11-001 regimen[6,7]	Prednisone, vincristine, pegaspargase/calaspargase,[l] doxorubicin, IT cytarabine, then IT triple therapy (ITT)[a]	SR arm: high-dose MTX, vincristine, pegaspargase/calaspargase,[l] mercaptopurine,[b] dexamethasone; + blinatumomab[m]; IT therapy: MTX or ITT[a]
		HR/VHR[n] arms: high-dose MTX, vincristine, pegaspargase/calaspargase,[l] mercaptopurine,[b] dexamethasone, doxorubicin, dexrazoxane + blinatumomab[m]; IT therapy: MTX or ITT[a]
Total Therapy XVI regimen[23]	Prednisone, vincristine, daunorubicin, pegaspargase/calaspargase,[l] cyclophosphamide, cytarabine, mercaptopurine (6-MP),[b] ITT[a]	LR arm: high-dose MTX, mercaptopurine,[b] + blinatumomab,[m] ITT[a]
		SR/HR arm: high-dose MTX, mercaptopurine,[b] + blinatumomab[m]; ITT[a]

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

FOOTNOTES

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[e] While blinatumomab is recommended for patients with disease meeting the SR-avg or SR-high definitions of AALL1731, for sites without access to blinatumomab it is reasonable to follow the control (no blinatumomab) arms which are based on AALL0932. It is also reasonable to treat patients with disease meeting the SR-favorable definition as per the SR-avg arm of AALL1731 with blinatumomab. Assessment of MRD with a high sensitivity NGS assay post-induction may aid the decision to administer blinatumomab in patients with SR-favorable disease.
[k] 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 References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[m] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[n] VHR arm also includes cyclophosphamide, cytarabine, and etoposide.

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,c,k]

BCR::ABL1-like B-ALL	Induction	Consolidation
COG AALL1131 regimen + dasatinib[b,d,3,5,8]	Vincristine, dexamethasone or prednisone, daunorubicin, pegaspargase/calaspargase[l]; IT therapy: cytarabine then MTX	For *CRLF2*- with *ABL* class kinase fusion: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase,[l] + dasatinib + blinatumomab[m]; IT therapy: MTX
COG AALL1521 regimen + ruxolitinib[b,d,24]		For *CRLF2*+ or *CRLF2*- with *JAK2* fusions, *EPOR* rearrangements, *SH2B3* alterations, *IL7R* insertions/deletions: cyclophosphamide, cytarabine, mercaptopurine,[b] vincristine, pegaspargase/calaspargase,[l] + ruxolitinib + blinatumomab[m]; IT therapy: MTX
DFCI-ALL Protocol 16-001 regimen + dasatinib[6,7]	For *ABL* class kinase fusion: DFCI-ALL Protocol 16-001 VHR arm: dexamethasone, vincristine, pegaspargase/calaspargase,[l] doxorubicin, cyclophosphamide, cytarabine, mercaptopurine[b] + dasatinib; IT therapy: cytarabine then ITT[a] or MTX	For *ABL* class kinase fusion: high-dose MTX, mercaptopurine,[b] dexamethasone, vincristine, cyclophosphamide, etoposide, high-dose cytarabine, pegaspargase/calaspargase,[l] doxorubicin + dasatinib + blinatumomab[m]; IT therapy: MTX
Total Therapy XVII regimen + dasatinib[9] or **Total Therapy XVII regimen ± ruxolitinib[9]**	For *ABL* class kinase fusion: Total Therapy XVII regimen + dasatinib[21]	For *ABL* class kinase fusion: Total Therapy XVII regimen (either LR or SR/HR arm) + dasatinib + blinatumomab[m,8]
	For mutations associated with JAK-STAT pathway activation: Total Therapy XVII regimen ± ruxolitinib	For mutations that are associated with JAK-STAT pathway activation: Total Therapy XVII regimen (SR/HR arm) + blinatumomab[m] ± ruxolitinib

Risk groups: low risk (LR), standard risk (SR), high risk (HR), very high risk (VHR).

Continued

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[k] 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 References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[m] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).

References

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

PRINCIPLES OF SYSTEMIC THERAPY

Regimen Components[a,i,k]

T-ALL	Induction	Consolidation
COG AALL1231 regimen[b,d,o,14]	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] daunorubicin[o]; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine[o]; IT therapy: MTX
COG AALL0434 regimen[b,d,15]	Prednisone, vincristine, pegaspargase/calaspargase,[l] daunorubicin; IT therapy: cytarabine and MTX	Cyclophosphamide, cytarabine, mercaptopurine,[b] pegaspargase/calaspargase,[l] vincristine, nelarabine; IT therapy: MTX
DFCI ALL 16-001 based on DFCI-ALL Protocol 11-001	Dexamethasone, vincristine, pegaspargase/calaspargase,[l] doxorubicin; IT therapy: cytarabine then ITT[a]	Cyclophosphamide, cytarabine, mercaptopurine,[b] IT therapy: MTX or ITT[a]
SJCRH regimen based on Total Therapy XVII regimen	Prednisone, vincristine, pegaspargase/calaspargase,[l] cyclophosphamide, daunorubicin, mercaptopurine,[b] cytarabine[p]; ITT[a]	High-dose MTX, mercaptopurine,[b] pegaspargase/calaspargase[l]; ITT[a]

Infant ALL	Induction	Consolidation[q,r]
Interfant regimens[c,16-18]	Prednisone, dexamethasone, vincristine, cytarabine, daunorubicin, pegaspargase/calaspargase,[l] MTX; IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone)	Intermediate-risk and HR arms: Chemotherapy consolidation: cyclophosphamide, mercaptopurine,[b] cytarabine, MTX, prednisone, pegaspargase/calaspargase[l] + blinatumomab[m,16]
		LR arm: Identical approach as pediatric ALL risk-stratified chemotherapy based on genetics and MRD response (see PEDALL-J) or interfant consolidation (see above)

Risk groups: low risk (LR), high risk (HR).

FOOTNOTES

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[b] See Pharmacogenomics (PEDALL-H) for recommended dosing alterations for 6-MP and 6-TG.
[c] Blinatumomab is incorporated into frontline therapy as a postremission approach based on data from AALL1731 as well as the ECOG1910 study in adults. Gupta S, et al. N Engl J Med 2025;392:875-891. Litzow MR, et al. N Engl J Med 2024;391:320-333. Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[d] This regimen contains 6-TG as a part of delayed intensification. For full details on other systemic agents incorporated into all phases of therapy, such as induction/induction IA, consolidation/induction IB, interim maintenance phases, intensification phases, delayed intensification, continuation phases, and maintenance, see References.
[l] The Panel believes it is reasonable to use bortezomib with BFM backbone chemotherapy in patients with pediatric T-LL, because it was shown to improve EFS/OS in T-LL but not leukemia (Teachey DT, et al. J Clin Oncol 2022;40:2106-2118).
[k] 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; IM I; and interim maintenance I and II, see References.
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[m] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[o] It is reasonable to transition patients treated with AALL1231 induction to the AALL0434 backbone with nelarabine post-induction.
[p] Patients treated on the high-risk arm of St. Jude Children's Research Hospital (SJCRH) TXVII receive an intensification phase.
[q] IT therapy: cytarabine, prednisone (if initial CNS involvement, MTX, prednisone).
[r] For patients with MRD ≥5 x 10^{-4} at the EOI, myeloid type consolidation therapy (eg, ADE/MAE) can be considered (Stutterheim J, et al. J Clin Oncol 2021;39:652-662).

PRINCIPLES OF SYSTEMIC THERAPY

Regimens for Relapsed/Refractory ALL[s,t]

BCR::ABL1-negative ALL[a]

Preferred	Other Recommended
• Clinical trial	• UKALL R3 regimen[25] • COG AALL01P2 regimen[26] • ALL-REZ BFM 90 regimen[27] • COG AALL07P1 regimen[28] • COG AALL1331 regimen[u,29] • Blinatumomab[m,u,30-33] • Revumenib (*KMT2A*r R/R *BCR::ABL1*-negative ALL)[v,34] • Tisagenlecleucel (refractory disease or ≥2 relapses)[m,w,x,35] ‣ Consider participation in a clinical trial for relapsed/refractory B-ALL targeting CD19, CD22, or other antigens, or for relapse following HCT ‣ Consider participation in a clinical trial with humanized or fully human CAR T-cell binding domains • Inotuzumab ozogamicin ± mini-hyper-CVD (cyclophosphamide, vincristine, dexamethasone)[m,y,36-38] • Clofarabine-containing regimens (eg, clofarabine, cyclophosphamide, etoposide)[39,40] • Fludarabine-based regimens: FLAG-IDA (fludarabine, cytarabine, G-CSF ± idarubicin)[41] • High-dose cytarabine-based regimens (eg, high-dose cytarabine, pegaspargase/calaspargase[l])[42] • Venetoclax-containing regimen: eg, venetoclax, vincristine, pegaspargase/calaspargase,[l] prednisone or dexamethasone[43]

Continued

[a] All regimens include CNS prophylaxis with systemic therapy (eg, MTX, cytarabine) and/or IT therapy (eg, IT MTX, IT cytarabine; ITT with MTX, cytarabine, corticosteroid).
[l] For patients who develop hypersensitivity to *E. coli*-derived asparaginase, ERW-rywn can be substituted as a component of the multiagent chemotherapeutic regimen to complete the full treatment course.
[m] Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 of 18).
[s] Principles of Hematopoietic Cell Transplant (PEDALL-K).
[t] Guidelines for managing specific sites of extramedullary relapse (ie, testicular) are included in the protocols listed.
[u] Blinatumomab may cause severe, life-threatening, or fatal adverse events, including CRS and neurologic toxicities. Experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instructions for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdosing and overdosing. For details, see blinatumomab prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[v] Revumenib can cause fatal or life-threatening differentiation syndrome. If differentiation syndrome is suspected, immediately initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.
[w] Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under REMS. For details, see tisagenlecleucel prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).
[x] Principles of Systemic Therapy - CD19-targeting CAR T-Cell Therapy (PEDALL-G 10 of 13)).
[y] Inotuzumab ozogamicin is associated with potentially fatal or life-threatening hepatic SOS and increased risk of post-HCT non-relapse mortality. For details, see inotuzumab ozogamicin prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). Ursodiol prophylaxis can be considered for prevention of SOS with use of inotuzumab ozogamicin.

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

References

PRINCIPLES OF SYSTEMIC THERAPY
CD19-targeting CAR T-Cell Therapy[aa]

Tisagenlecleucel[w]

- The FDA label indication for the use of tisagenlecleucel is for patients <26 years of age and CD19+ B-ALL that is refractory or with ≥2 relapses. Of note, there has been limited published experience with the use of CAR T-cell therapy in infants <12 months of age.
  - Relapse includes medullary and/or extramedullary disease. CAR T cells have shown activity against extramedullary disease.
- Prior to apheresis for T-cell collection, consider avoidance of agents that may significantly impact the absolute lymphocyte count and/or T-cell function.
- The following lymphodepletion regimen is suggested prior to infusion of tisagenlecleucel (with alternatives allowed):
  - Fludarabine (30 mg/m² IV daily for 4 days)
  - Cyclophosphamide (500 mg/m² IV daily for 2 days starting with first dose of fludarabine)
  - Infuse tisagenlecleucel 2 to 14 days after completion of the lymphodepleting chemotherapy. Recommend evaluation of response 28 days after tisagenlecleucel infusion.
- Recommendations for toxicity management of CRS or neurotoxicity are included in the tisagenlecleucel package insert. Tocilizumab and corticosteroids are the main options used to manage CRS and neurotoxicity.[50,51] See the American Society for Transplantation and Cellular Therapy (ASTCT, formerly ASBMT) consensus grading[52] and CARTOX management guidelines[53] for detailed CAR T-cell toxicity grading, monitoring, and management. Hemophagocytic lymphohistiocytosis (HLH)-like toxicities, also known as immune effector cell-associated HLH-like syndrome (IEC-HS), are another potential toxicity following CAR-T cell therapy.[54]
- The role of consolidative allogeneic HCT following tisagenlecleucel is unclear. Persistence of tisagenlecleucel (persistence of B-cell aplasia) and negative NGS MRD have been associated with durable clinical responses without subsequent HCT.[35,55] Bone marrow MRD positivity, with or without B-cell aplasia, has been shown to be highly predictive of relapse following tisagenlecleucel.[55] See Minimal Residual Disease (PEDALL-J).
- Encourage patient participation in the Center for International Blood and Marrow Transplant Research (CIBMTR) Cellular Therapy Registry.[bb]
- Strongly consider NGS-based MRD testing post CAR T-cell therapy.[55]
- For recommendations on management of tisagenlecleucel-induced immunosuppression, see Principles of Supportive Care: Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel (PEDALL-C, 15 OF 18).

[w] Tisagenlecleucel is associated with CRS, including fatal or life-threatening reactions. Do not administer to patients with active infection or inflammatory disorders. Treat severe or life-threatening CRS with tocilizumab. Neurologic toxicities, which may be severe or life-threatening, can occur following treatment, including concurrently with CRS. Monitor for neurologic events after treatment. Provide supportive care as needed. Tisagenlecleucel is available only through a restricted program under REMS. For details, see tisagenlecleucel prescribing information (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm).

[aa] For information regarding obecabtagene autoleucel, a CD19-targeting CAR T-cell therapy FDA approved for AYA and adult patients ≥18 years of age, see the NCCN Guidelines for Acute Lymphoblastic Leukemia.

[bb] The CIBMTR tracks safety and efficacy data following commercial CAR T-cell therapy. For details and cellular therapy data collection forms, see https://www.cibmtr.org/DataManagement/DataCollectionForms/Pages/index.aspx.

References

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

PEDALL-G

Referenzen – Principles of systemic therapy:

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PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Indications for HCT (B-cell) in First Remission

- Unfavorable cytogenetics
  - Consider HCT if *MLL/KMT2A* mutation (<6 months in age) with high-risk features (PEDALL-7).[a,1]
- MRD
  - Consider HCT if MRD ≥0.01% post-consolidation (week 9–12 from diagnosis).[b,2]
- Other considerations
  - The role of HCT for patients with hypodiploid ALL in CR1 has not yet been established, even in patients who are MRD-positive at end-induction.[3-8]
    - ◊ HCT for hypodiploid ALL may be considered in the setting of a clinical trial.
  - HCT is not routinely indicated for *BCR::ABL1*+ ALL in CR1 (while on TKI plus systemic chemotherapy) provided that the patient has achieved MRD negativity (<0.01%) post-consolidation and is being treated on an intensive pediatric regimen plus TKI. Consider HCT (for *BCR::ABL1*+ ALL) if relapse (any time point), or MRD ≥0.01% (by week 9–12).[9,10]
  - For patients who are MRD positive (≥0.01%) at end-induction, there is insufficient evidence to suggest a survival advantage for HCT, even in patients with kinase activating mutations (ie, *IKZF1, CDKN2A/B, PDGFRB, ABL1, ABL2, CSF1R, JAK2, CRLF, EPOR*) or iAMP21.

Indications for HCT (B-cell) in Non-First Remission Settings

- Induction failure (M3 marrow): Recommend HCT after achieving MRD-negative status.
- CR2: Consider HCT based upon timing of relapse (or refractory disease) and leukemic phenotype; see PEDALL-K (2 of 5).
- CR3: Recommend HCT.
- For a patient with CNS involvement at the time of relapse (or refractory disease), consider a CNS boost at the time of administration of TBI. For those without CNS involvement at the time of relapse (or refractory disease), there is no clear evidence that CNS boost will prevent subsequent CNS relapse.[11,12]
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

Indications for HCT (T-cell)

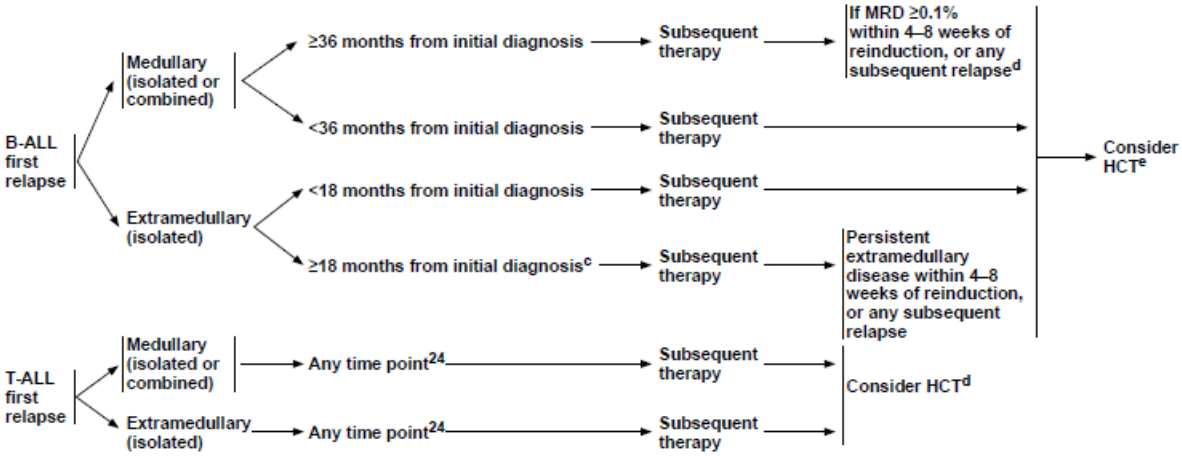
- HCT should be considered for:
  - Patients with MRD positivity (>0.1%) at completion of consolidation. Additional therapy should be given prior to HCT to achieve MRD negativity. See PEDALL-G (9 of 13).
  - Induction failure (M3 marrow).[13]
  - Patients with medullary or extramedullary relapse (any time point).[14] See PEDALL-K (2 of 5).
- For relapsed/refractory disease, see PEDALL-K (2 of 5).

[a] The Interfant-99 study noted a potential benefit for HCT in children aged <6 months with *MLL* rearrangements plus either poor day 8 (induction) response to systemic corticosteroids, or WBC count at initial diagnosis >300 x 10^9/L.
[b] MRD based upon flow cytometry, PCR, or NGS.

Continued
References

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

TIME TO RELAPSE[15-23]



[c] For late bone marrow or isolated extramedullary relapses, if patient achieves MRD-negative CR2 with reinduction/therapy for relapsed disease, no HCT is indicated.
[d] The recommendations may differ based on the treatment regimen. Consideration of HCT can also be made in the setting of MRD of 0.01%–0.09% given an increased risk of relapse. Hogan LE, et al. J Clin Oncol 2023;41:4118-4129; Parker C, et al. Lancet 2010;376:2009-2017.
[e] Consideration for HCT depends upon donor availability and patient's clinical status at the time of potential HCT.

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

PRINCIPLES OF HEMATOPOIETIC CELL TRANSPLANT

Donor Type
- Unrelated vs. related donor
  - In children/young adults undergoing HCT for ALL, there is no survival advantage (event-free survival [EFS] or overall survival [OS]) by donor type when comparing use of matched unrelated donors to matched related donors.[25]
- Umbilical cord blood (UCB)[26-28]
  - Allows rapid procurement and more lenient human leukocyte antigen (HLA) matching.
    - ◊ No outcome differences are noted in HCT for childhood leukemia when comparing UCB versus matched related/matched unrelated donors.[26]
    - ◊ There are possible lower relapse rates using UCB versus matched unrelated donor if the patient achieves MRD positivity pre-HCT.[27]
    - ◊ There is no survival advantage for double (vs. single) UCB HCT in children/young adults, when a single cord unit with adequate cell dose is available.[28]
- The role of haploidentical transplants for childhood leukemia has been examined in several single and multicenter studies, with potential efficacy and favorable toxicity profiles. Haploidentical transplants (with post-transplant cyclophosphamide or T-cell depletion such as αβ-depletion) may be considered as an alternative donor source, especially if no HLA-matched donor is available.[29-32]

Donor Cell Source
- When comparing bone marrow to peripheral blood stem cells (PBSCs) as the donor cell source, there is no survival advantage for use of PBSCs in matched unrelated donor transplantation. Higher graft-versus-host disease (GVHD) rates with equivalent survival are noted with PBSCs (vs. marrow) in recipients of matched unrelated donor transplants. The optimal donor cell source (marrow vs. PBSCs) has not been clearly defined with either matched related donor or haploidentical donor transplants. Due to increased risks of acute and chronic GVHD with PBSCs, the use of PBSCs should be considered with caution for HCT in children/young adults with ALL.[33,34]

Conditioning Regimen
- Both TBI and non-TBI–containing regimens have been used in HCT for children and young adults with ALL. Randomized controlled trials indicate that TBI is superior to non-TBI–containing regimens for children with ALL.[35-37] Non-TBI–containing regimens are under current investigation.
- The use of TBI in conditioning regimens for ALL demonstrated a disease-free survival advantage seen regardless of donor source (matched related vs. unrelated HCT).[37]
- For infants: If donor available, prefer non–TBI-based prep regimen and age ≥6 months at time of HCT.[38] See PEDALL-G, 2 of 13.

Impact of Pre-HCT MRD Status
- An increased risk of relapse has been noted in children with ≥0.1% MRD pre-HCT for ALL, suggesting the need to attain an MRD level <0.1% prior to HCT.[39,40] An increased risk of relapse has also been noted in children with an MRD of 0.01%–0.09%.[41,42]
- The absence of detectable MRD by NGS before and after HCT may be associated with favorable outcomes.[43]

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Treatment Considerations: AYA Patients

Historically, the AYA population has been treated on either a pediatric or an adult ALL regimen, depending on referral patterns and the institution. Several retrospective studies from both the United States and Europe have shown that AYA patients (15–21 years of age) treated on a pediatric protocol have substantially improved EFS compared to same-aged patients treated on adult ALL regimens.19,20 Comparison of adult and pediatric protocols has shown that adults received lower doses of nonmyelosuppressive chemotherapy and less intense IT chemotherapy regimens.195,196 Adult protocols also entail a greater use of allogeneic HCT compared to pediatric protocols, but the benefits of HCT in the AYA population have not been sufficiently studied, and the available data have conflicting findings.197-201 However, this is a significant difference between the way adult and pediatric patients are treated and may be a variable in the treatment of AYA patients. Thus, the choice of initial treatment regimen can have a profound impact on overall clinical outcomes in AYA patients.

Despite improved outcomes for AYA patients treated on pediatric-inspired regimens versus adult ALL regimens, studies have shown poorer outcomes among patients in the AYA group compared with children <10 years.202 This may be attributed to factors that are based on biology and social differences. Compared to the pediatric population, AYA patients have a lower frequency of favorable chromosomal or cytogenetic abnormalities, such as hyperdiploidy or ETV6::RUNX1203; a greater incidence of poor-risk cytogenetics, including BCR::ABL1-positive ALL, hypodiploidy, and complex karyotype204; and a higher incidence of ETP-ALL.43,205 Furthermore, the positive prognostic values of the ETV6::RUNX1 mutation and hyperdiploidy are greater in the pediatric population, suggesting that the benefits decline with age.203

The effects of the treatment are also shown to be different in the AYA population compared to the pediatric population. In vitro studies showed that ALL cells from children >10 years are more resistant to chemotherapy compared to the cells from children <10 years.206 The COG AALL0232 study reported an initial delay in response to induction therapy in AYA patients aged 16 to 30 years compared to younger patients (aged 1–15 years).207 The number of patients who had negative end-induction MRD was significantly lower in the cohort aged 16 to 30 years compared to the younger cohort (59% vs. 74%; P < .0001), with fewer patients achieving M1 marrow on day 15 of induction (67% vs. 80%, respectively; P = .0015). In addition to the biological differences, the social component of treating AYA patients is important. Enrollment in clinical trials has been shown to improve patient outcomes208; however, only 2% of AYA patients enroll in clinical trials compared to the 60% enrollment of pediatric patients.209 Pediatric patients have been shown to be more adherent to treatment protocols compared to AYA patients,210 which may be due to greater parental supervision of the treatment and better health insurance coverage.211

Treatment Considerations: Vulnerable Populations

Infant ALL (<12 months of age) makes up 2% to 5% of pediatric ALL and represents a high-risk ALL group due to lack of response to treatment and treatment-related complications.32,212 This is due in part to a high incidence of early bone marrow, CNS, and extramedullary relapse.213 Infants with ALL also have an increased incidence of poor prognostic features, including high initial WBC count, massive organomegaly, thrombocytopenia, CNS leukemia at diagnosis, or KMT2A gene rearrangements at chromosome band 11q23—which is the most common molecular genetic rearrangement in infant ALL.32,213,214

Children with trisomy 21 (Down syndrome) have an increased risk of ALL, although the basis for this increased risk is unknown.32,114,215 ALL in children with Down syndrome is associated with unique features, including the absence of ALL in patients <1 year of age; a lower incidence of favorable and

unfavorable cytogenetics; increased sensitivity to MTX; and an increased susceptibility to infections.215 Some reports have determined that ALL in children with Down syndrome frequently expresses CRLF2, which is associated with mutated JAK2.216,217 Historically, children with ALL and Down syndrome have been shown to have poorer outcomes relative to non-Down syndrome–related ALL.218 These differences may be due to poor adherence of physicians to protocol guidelines,219 and an increased susceptibility to treatment-related toxicities and infections. In biologically defined subsets, current data suggest that the outcomes for children with ALL and Down syndrome are comparable to those of non-Down syndrome–related ALL.215,220 For both infants and children with Down syndrome with ALL, it is essential to use protocols that have demonstrated safety in these patient populations and that incorporate aggressive and tailored supportive care measures (see Special Considerations for Patients with Down Syndrome and Infants in the algorithm).

Management of BCR::ABL1-Negative or BCR::ABL1-Like B-ALL

Front-Line Management of BCR::ABL1-Negative or BCR::ABL1-Like ALL

The management of de novo BCR::ABL1-negative and BCR::ABL1-like B-ALL is complex and current regimens are based on a number of trials referenced in the algorithm, which are summarized below.

COG AALL0331 and AALL0932

The COG AALL0331 trial helped establish the benefit of intensifying therapy for patients with EOI MRD >0.01%, which is now part of all COG protocols. This trial enrolled 5377 patients with standard-risk B-ALL and used a 3-drug induction without anthracyclines (ie, dexamethasone, vincristine, and pegaspargase), with post-induction assignment into refined risk groups based on genetics and early response (ie, standard-risk low, standard-risk average, and standard-risk high).270 At the EOI, patients were randomized to receive standard consolidation (6-MP, vincristine, and IT MTX) versus intensified consolidation (cyclophosphamide, cytarabine, 6-MP, vincristine, pegaspargase, and IT MTX).270 The 6-year EFS and OS for all evaluable patients with standard-risk disease were 89% and 96%, respectively, and intensified consolidation did not significantly improve outcomes for patients with standard-risk–average disease.270 Patients with standard-risk–high disease (day 15 bone marrow ≥5% blasts and/or day 29 MRD ≥0.1%) were non-randomized to intensified consolidation and two intensified IM and DI phases, resulting in 6-year continuous CR and OS rates of 86% and 93% of patients, respectively.270

Due to the intensification of pre-maintenance therapy and modern risk stratification, the COG AALL0932 study, a randomized phase III trial, was designed to optimize maintenance therapy in newly diagnosed pediatric B-ALL by asking two questions: 1) Will a higher dose (40 mg/m2/dose) for weekly oral MTX be superior to standard dose (20 mg/m2/dose)?; and 2) Will a reduced frequency of vincristine and dexamethasone pulses (from every 4 weeks to every 12 weeks) impact outcomes? The 5-year DFS (95.1% [95% CI, 93.3%–96.8%] vs. 98.8% [95% CI, 97.9%–99.7%]; P = .92) and OS rates (94.2% [95% CI, 92.2%–96.1%] vs. 98.1% [95% CI, 97.0%–99.2%]; P = .89) for patients with average-risk disease who received oral MTX 20 mg/m2/dose versus 40 mg/m2/dose were similar, suggesting that higher MTX starting dose does not improve outcomes.151

The 5-year DFS for patients with average-risk disease randomized to receive vincristine and dexamethasone pulses every 4 weeks versus every 12 weeks was 94.1% (95% CI, 92.2%–96.0%) versus 95.1% (95% CI, 93.3%–96.9%) (P = .86). The 5-year OS for the every-4-week versus every-12-week regimens was 98.3% (95% CI, 97.2%–99.4%) versus 98.6% (95% CI, 97.7%–99.6%) (P = .69).151 This study highlighted excellent outcomes in patients randomized to vincristine/dexamethasone pulses every 12 weeks, despite receiving one third of the amount of pulses used in standard of care in COG trials.

A separate study from the Japanese Children's Cancer Group (ALL-B12) evaluating the effectiveness of vincristine/dexamethasone pulses every 4 weeks in patients ≤19 years with newly diagnosed B-ALL found no difference in 5-year EFS rates among patients with disease meeting NCI standard-risk criteria who received pulses compared to those in whom pulses were omitted (P = .73).271

COG AALL0232 and AALL1131

The AALL0232 trial enrolled 2154 patients between the ages of 1 and 30 years who were diagnosed with high-risk B-cell ALL.272 In this study patients were randomly assigned to receive dexamethasone versus prednisone during induction and HD-MTX versus Capizzi-MTX plus pegaspargase during IM1. HD-MTX showed improved 5-year EFS (79.6% vs. 75.2%; P = .008) and OS (88.9% ± 1.2% vs. 86.1% ± 1.4%; P = .025) rates compared to Capizzi-MTX. No statistically significant difference was reported in the occurrence of

mucositis, neurotoxicity, osteonecrosis, or other toxicities. The ALL0232 trial compared dexamethasone 10 mg/m2/day for 14 days to prednisone 60 mg/m2/day for 28 days. Dexamethasone showed improved outcomes during induction in patients <10 years of age; however, it was associated with a higher risk of osteonecrosis in patients ≥10 years of age. These data suggest that age may be an important factor for the selection of a corticosteroid.272

Relative to pediatric patients with standard-risk B-ALL, patients with high-risk B-ALL experience high relapse rates and worse clinical outcomes.185,248 Some approaches to combat this are investigating the integration of new agents into treatment after induction. The COG AALL1131 study was a phase III trial for patients aged 1 to 30 years with newly diagnosed high-risk B-ALL.153,273,274 Patients enrolled in this trial received a standard 4-drug induction (dexamethasone/prednisone, vincristine, daunorubicin, and pegaspargase). The high-risk stratum of this study was designed to compare post-induction CNS prophylaxis with standard-of-care IT MTX versus triple IT therapy including MTX, hydrocortisone, and cytarabine.274 Randomization was closed early after a futility boundary had been crossed, concluding that triple IT therapy was not superior to IT MTX. Neither 5-year post-induction DFS or OS rates statistically favored triple IT therapy over standard MTX; thus, IT MTX remains standard-of-care CNS prophylaxis in this setting. Another experimental arm of this study was designed to evaluate the safety and efficacy of clofarabine, cyclophosphamide, and etoposide as part of multiagent chemotherapy.273 However, infectious toxicities precipitated the closure of this study arm. Another experimental arm investigated whether substituting post-induction chemotherapy (cyclophosphamide, cytarabine, and 6-MP) with cyclophosphamide and etoposide would improve the 4-year DFS of pediatric patients with very-high-risk B-ALL.153 This substitution was not superior to the control arm. Given this experience, future therapeutic approaches will examine the utility of targeted agents. In this context, the COG has investigated the incorporation of dasatinib for newly diagnosed patients with high-risk BCR::ABL1-like B-ALL harboring ABL-class lesions (AALL1131),41 and is investigating ruxolitinib for newly diagnosed patients with high-risk BCR::ABL1-like ALL harboring CRLF2 rearrangements and/or a mutation that activates the JAK-STAT pathway (AALL1521).154,275 In addition, trials investigating whether the combination of immunotherapies with chemotherapy improves outcomes have been performed; a study of blinatumomab combined with chemotherapy in standard-risk B-ALL (AALL1731) has been completed (see Blinatumomab below)148; a study of InO combined with chemotherapy and blinatumomab in high-risk B-ALL (AALL1732) is ongoing (NCT03959085).

DFCI ALL Protocols 05-001, 11-001, and 16-001

The DFCI ALL Consortium Protocol 05-001 enrolled 678 children and adolescent patients (aged 1–18 years) with newly diagnosed BCR::ABL1-negative B-ALL, and tested a new risk stratification system.117 At study entry, patients were classified as having standard-risk or high-risk disease and a 4-drug induction was used (prednisone, vincristine, doxorubicin, and pegaspargase).117 After achieving CR, patients with high EOI MRD (≥10-3 via PCR analysis of patient-specific Ig or TCR rearrangements) and/or adverse cytogenetics (KMT2A rearrangement or hypodiploidy) were reclassified as having very-high-risk disease and received intensified therapy.117 Among all patients, the 5-year EFS and OS rates were 87% (95% CI, 84%–89%) and 93% (95% CI, 90%–94%), respectively. The 5-year DFS rates for the standard-risk (n = 407), high-risk (n = 176), and very-high-risk (n = 65) groups were 94%, 84%, and 79%, respectively.

To refine risk classification for future trials, the prognostic significance of alternative age and WBC count thresholds, alternative EOI MRD levels, and IKZF1 deletion status were examined. The IKZF1 deletion was associated with inferior 5-year EFS and higher cumulative incidence of relapse, including among patients with low MRD.117 Further analysis of outcome by age demonstrated that patients with BCR::ABL1-negative B-ALL aged 10 to 14.99 years had similar EFS to those <10 years of age, whereas those ≥15 years of age had a significantly worse outcome.117 The DFCI protocol 16-001 incorporated some changes to risk stratification for B-ALL, including the use of: 1) 15 years as a cut-off to distinguish standard risk versus high risk; 2) prospective determination of IKZF1 deletionstatus; and 3) assessment of MRD via NGS assay to identify patients with very-high-risk disease.117

The DFCI ALL Consortium Protocol 11-001 evaluated the efficacy and toxicity of calaspargase compared to standard pegaspargase in pediatric patients (aged 1–21 years) with newly diagnosed ALL or LL (n = 239).143 Patients were randomized to receive IV standard pegaspargase (n = 120) or calaspargase (n = 119) and EOI MRD was assessed in patients with ALL by real-time quantitative PCR. Of 230 evaluable patients, 99% of patients in the standard pegaspargase group and 95% of patients in the calaspargase group achieved a CR (P = .12), and there was no difference in the frequency of EOI MRD between the two groups. In addition, a 3-week dosing schedule of calaspargase and a 2-week dosing schedule of standard pegaspargase had similar safety profiles and nadir serum asparaginase activity (SAA). The 5-year EFS (± standard error [SE]) was 84.9% (± 3.4%) for pegaspargase and 88.1% (± 3.0%) for calaspargase (P = .65).

St. Jude Total Therapy XV–XVII Studies

In the St. Jude Total XV study, 498 evaluable patients with newly diagnosed ALL (aged 1–18 years) were enrolled, with study aims of determining whether prophylactic cranial irradiation could be safely omitted in all patients and determining the impact on overall EFS.125 Induction was comprised of multiagent chemotherapy (prednisone, vincristine, daunorubicin, L-asparaginase, cyclophosphamide, cytarabine, and 6-MP), and upon hematopoietic recovery, MRD was assessed prior to intensified consolidation/continuation therapy according to risk-stratified groups. Of 498 patients, 492 (98.8%) entered CR (low risk, 99.6%; standard risk, 99.5%; and high risk, 90.4%). The 5-year EFS and OS estimates were 85.6% and 93.5%, respectively.125 This study demonstrated that prophylactic cranial irradiation could be omitted without compromising OS.

In the Total XVI study, investigators evaluated whether a higher dose of pegaspargase (3500 U/m2 vs. 2500 U/m2) and early intensification of triple IT therapy would improve systemic and CNS control in pediatric patients with ALL (n = 598).276 Patients with features associated with increased risk of CNS relapse received two extra doses of IT therapy during the first 2 weeks of remission induction. The 5-year EFS and OS rates were 88.2% and 94.1%, respectively, with a cumulative risk of any CNS relapse of 1.5%.276 Higher doses of pegaspargase did not affect treatment outcome, and patients with features associated with increased risk for CNS relapse experienced significantly lower CNS relapse than patients with similar features in the Total XV study.276

The Total XVII study incorporated novel precision medicine strategies based on genomic features and targeted treatment.109 Some of these approaches include the use of NGS-based diagnostics. In addition, the Total XVII study investigated the use of dasatinib in patients with disease with ABL-class chimeric fusions identified by RNA sequencing, and ruxolitinib in patients with disease with alterations that activate the JAK-STAT signaling pathway.109

Blinatumomab

Blinatumomab is a bispecific T-cell–engaging antibody that directs CD3-positive effector memory T cells to CD19-positive target cells, inducing cell death.277,278 Blinatumomab first showed promising clinical efficacy as a means of eradicating persistent MRD following upfront chemotherapy. In a multicenter, single-arm, phase II study, Topp et al192 evaluated the efficacy of blinatumomab in patients with MRD-positive BCR::ABL1-negative B-ALL (n = 21; age range, 20–77 years). MRD positivity was defined as never having achieved MRD negativity before blinatumomab or having experienced a hematologic remission with MRD ≥10-4. After blinatumomab treatment, 16 of 20 evaluable patients achieved MRD negativity at a detection threshold of 10-4.192 After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.279 Gökbuget et al280 examined the efficacy of blinatumomab in an expanded cohort (n = 116; age range, 18–76 years) using a higher threshold for MRD positivity (hematologic CR with MRD ≥10-3). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients achieved a complete MRD response, and the RFS rate at 18 months was 54%.280 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 positivity. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in pediatric and adult patients with R/R B-precursor ALL.191,281-283 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 (CR2) with MRD defined as disease ≥0.1% (see Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL for discussion of studies related to blinatumomab use in R/R B-ALL).

More recently, the efficacy of 4 cycles of intensive chemotherapy (hyper-CVAD [hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone] alternating with HD-MTX and cytarabine) followed by 4 cycles of blinatumomab consolidation and maintenance alternating between 3 cycles of POMP (6-MP, vincristine, MTX, and prednisone) and 1 cycle of blinatumomab is being evaluated in an ongoing single-arm, phase II trial.284 In this trial, which is enrolling patients ≥14 years of age with newly diagnosed BCR::ABL1-negative B-ALL, the estimated 3-year RFS was 73%, with no patients relapsing >2 years following the start of treatment.

In contrast to prior studies investigating blinatumomab as a means of eradicating MRD during or after multiagent therapy, the phase III ECOG-ACRIN E1910 trial investigated whether blinatumomab could improve outcomes in adult patients receiving chemotherapy who had achieved MRD negativity (<0.01%).149 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. Polyethylene glycol (PEG) was added for patients <55 years of age and rituximab was added for CD20 positivity. Following induction, patients who achieved a CR/CR with incomplete count recovery (CRi) remained on study and proceeded to intensification with HD-MTX 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 2 cycles of

consolidation chemotherapy, followed by a third cycle of blinatumomab, followed by another cycle of consolidation chemotherapy, and finally a fourth cycle of blinatumomab. However, following the FDA approval of blinatumomab for patients with MRDpositive 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 in 3-year OS and RFS (85% and 80% for the blinatumomab arm versus 68% and 64%, respectively; P = .002 for OS).

Based on data from the ECOG-ACRIN E1910 trial149 and a phase III randomized trial from Locatelli and associates investigating blinatumomab consolidation in children with relapsed B-ALL285 (see Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-like ALL), the FDA approved blinatumomab for adult and pediatric patients ≥1 month with BCR::ABL1-negative B-ALL in the consolidation phase of multiphase chemotherapy.286

In a phase III trial (COG AALL1731), the safety and efficacy of blinatumomab incorporated into frontline therapy as a postremission approach was investigated in pediatric patients (n = 1440; median age 4.3 years) with standard-risk B-ALL.148 Patients deemed to have an average or high risk of relapse were randomized to chemotherapy alone or chemotherapy plus blinatumomab. In the chemotherapy plus blinatumomab arm, blinatumomab was administered as two, nonsequential 28-day cycles, one before and one following IM. IT MTX was given on day 1 of each blinatumomab cycle. Estimated 3-year DFS ± standard error in the entire cohort treated with chemotherapy plus blinatumomab was 96% ± 1.2% compared to 87.9% ± 2.1% with chemotherapy alone (difference in restricted mean survival time, 72 days; P < .001). Three-year OS was similar between the two arms (98.4% ± 0.9% vs. 97.1% ± 1.1%, respectively). DFS advantage was noted with blinatumomab plus chemotherapy in both patients at average and high risk of relapse, at 97.5% ± 1.3% vs. 90.2% ± 2.3% and 94.1% ± 2.5% vs. 84.8% ± 3.8%, respectively. The rate of ≥ grade 3 sepsis and catheterrelated infections was significantly higher in patients with an average risk of relapse that received chemotherapy plus blinatumomab compared to chemotherapy alone (14.8% vs. 5.1%; P < .001), though rates were similar among patients at high risk of relapse (20.9% vs. 17%; P = .28). CRS was rare in the chemotherapy plus blinatumomab arm.

Hematopoietic Cell Transplant

For pediatric and AYA patients with BCR::ABL1-negative ALL in CR1, allogeneic HCT may be considered for patients who: 1) have persistent MRD positivity at EOC (regardless of genetic features); or 2) have high-risk genetic features and have persistent MRD positivity at the EOI.248 In the latter group, it should be noted that some studies have examined the role of HCT in pediatric patients with hypodiploid B-ALL, and it is unclear whether HCT improves outcomes when given in CR1 in patients with MRD positivity at the EOI.287-290 However, HCT for hypodiploid ALL may be considered in the context of a clinical trial.

Management of Relapsed or Refractory BCR::ABL1-Negative or BCR::ABL1-Like ALL

The outcomes of pediatric patients with R/R B-ALL have been historically poor. In addition, the number of previous regimens utilized in the relapsed/refractory setting and duration of CR1 impact outcomes.261,291,292 In the guidelines, early relapse is defined as disease that recurs <36 months from initial diagnosis for isolated or combined bone marrow relapse or <18 months from initial diagnosis for isolated extramedullary relapse. Late relapse is defined as disease that recurs ≥36 months from initial diagnosis for isolated or combined bone marrow relapse or ≥18 months from initial diagnosis for isolated extramedullary relapse. In general, HCT is the only known curative therapy for early relapse of B-ALL. For patients with late relapses of B-ALL or late isolated CNS relapses of T-ALL, chemotherapy alone may be sufficient.256,291 It has also been reported that patients who received CAR T cells can maintain long-term remission without subsequent HCT.193 Several trials referenced in the algorithm have developed regimens that are currently used to treat R/R B-ALL, and these studies are summarized below.

ALL-REZ BFM 90

The ALL Relapse BFM 90 (ALL-REZ BFM 90) trial was designed to improve prognosis for pediatric patients with relapsed ALL (<19 years of age; n = 525) through additional multi-chemotherapy blocks.293 The patients were stratified into three risk groups: A (early bone marrow relapses; n = 126); B (late bone marrow relapses; n = 183); and C (isolated extramedullary relapses; n = 64). Patients with early bone marrow or T-ALL relapse (poor prognosis group/PPG; n = 152) were eligible for experimental regimens. After treatment with this regimen, 440 patients (84%) achieved CR2, 25 patients died during induction, and 60 patients (11%) did not experience a response. A majority of patients in each group achieved CR2 (Group A: 83%; Group B: 94%; and Group C: 100%).293 In addition, 117 patients received HCT in CR2. Significant differences existed between strategic groups: probability of EFS (pEFS)(A) = .17 ± .03; pEFS(B) =

.43 ± .04; pEFS(C) = .54 ± .06; pEFS(PPG) = .15 ± .03; log-rank P < .001.293 Significant predictors of EFS in multivariate analyses included time point, site of relapse, immunophenotype, and HCT.293

COG AALL01P2

In the COG AALL01P2 study, 124 pediatric patients aged 1 to 21 years with relapsed ALL were treated with 3 blocks of reinduction chemotherapy, with an upfront randomization in block order (arm A = blocks 1, 2, 3; arm B = blocks 1, 3, 2).294 Patients with CNS leukemia were nonrandomly assigned to arm B to allow early introduction of high-dose cytarabine, and patients with mature B-ALL and Down syndrome were excluded.294 In addition, patients with BCR::ABL1-positive ALL received imatinib with all chemotherapy blocks. Of 117 patients evaluable for response in block 1, 81.2% achieved a CR2. For early relapses (defined as recurrence <36 months after initial diagnosis) versus late relapses (defined as recurrence ≥36 months after initial diagnosis), the CR2 rates were 68% ± 6% and 96% ± 3% (P < .0001), respectively.294 One objective of this study was to determine the feasibility of measuring MRD in a single COG central reference laboratory at the completion of each block to monitor the kinetics of response. The absence of MRD at the end of the first month of reinduction therapy was associated with better outcomes in all patients.294 In addition, subsequent blocks of therapy reduced the MRD burden in 40 (71%) of 56 patients with MRD positivity after block 1.

UKALL R3

The UKALL R3 trial investigated the outcomes of pediatric patients with relapsed ALL aged 1 to 18 years (n = 239).256 Patients were stratified into standard-, intermediate-, or high-risk groups based on the duration of CR1, site of relapse, and immunophenotype. In addition, patients were randomized to receive mitoxantrone or idarubicin on days 1 and 2 of induction.256 After three blocks of therapy, all patients in the high-risk group and patients in the intermediate-risk group with post-induction high MRD (≥10-4 cells) received HCT. The estimated 3-year PFS and OS rates in the mitoxantrone versus idarubicin groups were 64.6% versus 35.9% (P = .0004) and 69% versus 45.2% (P = .004), respectively.256 After a median follow-up of 84 months, PFS of all randomly assigned patients was 60% (95% CI, 54%–70%). Of 92 patients who received HCT, 58 (63%) remained in CR2, 13 (14%) died of complications, and 21 (23%) relapsed after HCT.291 Of 70 patients who continued on chemotherapy, 49 (70%) remained in CR2, 2 (3%) died of complications, and 19 (27%) relapsed. At 5 years, the PFS was 56% (95% CI, 46%–65%) in patients with high MRD and 72% (95% CI, 60%–81%) in patients with low MRD (<10-4 cells; P = .0078).291

COG AALL07P1

Bortezomib is a proteasome inhibitor that has demonstrated some activity in relapsed pediatric ALL.295-297 The COG AALL07P1 phase II study tested the hypothesis that adding bortezomib to reinduction chemotherapy in pediatric patients experiencing first relapse would increase CR2 rates.295,298 Of the evaluable patients treated with bortezomib and chemotherapy (n = 135; B-ALL, n = 103; T-ALL, n = 22; T-LL, n = 10), overall CR2 rates were 68% ± 5% for patients with precursor B-ALL (<21 years of age), 63% ± 7% for very early relapse (<18 months from diagnosis), and 72% ± 6% for early relapse (18–36 months from diagnosis).295 The CR2 rate for patients with relapsed T-ALL was 68% ± 10%.

Clofarabine-Based Regimens

Clofarabine is a second-generation purine analog that has demonstrated single-agent activity in R/R pediatric ALL299,300 and is approved by the FDA as monotherapy for pediatric patients aged 1 to 21 years with R/R ALL treated with at least two previous regimens. Other clinical studies have evaluated its use in combination with chemotherapy.301,302 A phase II study evaluated the efficacy and safety of clofarabine, etoposide, and cyclophosphamide in pediatric patients with R/R ALL (aged 1–21 years; n = 25).301 The overall response rate (ORR) was 44% (7 CR, 4 CR with partial recovery) with a 67.3-week median duration of remission censored at last follow-up.301

Fludarabine-Based Regimens

A regimen of high-dose cytarabine and fludarabine followed by granulocyte colony-stimulating factor (G-CSF) (ie, FLAG alone) or combined with idarubicin (FLAG-IDA) yields response rates ranging from 39% to 83% in adult patients with R/R ALL.303-306 In a study by Gabriel et al, 32 pediatric patients (median age, 10.4 years; range, 1.7–15.5 years) with high-risk leukemias, including relapsed ALL (n = 13), primary refractory ALL (n = 3), relapsed AML (n = 13), primary refractory AML (n = 1), and secondary AML (n = 2), were given the FLAG-IDA regimen.307 Overall, 23 (71.9%) of 32 patients achieved a CR after a single course of FLAG-IDA. In patients with relapsed ALL, 10 (76.9%) of 13 achieved a CR, and in patients with primary refractory ALL, 2 of 3 achieved a CR—1 after a second course of FLAG-IDA and both had BCR::ABL1-positive disease.307 Overall, 22 of the 23 patients who achieved remission (10 AML and 12 ALL) proceeded to HCT after further consolidation with 2 to 3 courses of the FLAG regimen.

High-Dose Cytarabine-Based Regimens

In a study by the CCG, 52 pediatric patients with R/R ALL received high-dose cytarabine and L-asparaginase.308 By day 28, 10 patients had died from the disease and treatment-related complications. Of the 42 evaluable patients, 22 (42% of all patients) achieved CR2.308 However, 16 of the 22 patients who entered CR2 subsequently relapsed, and the median duration of CR2 was 3 months (range, 0.7–19 months).308

Venetoclax-Based Regimens

In a phase I open-label study, the safety and efficacy of venetoclax combined with chemotherapy was evaluated in patients <25 years of age with R/R ALL.309 ORR was 56% with venetoclax combined with dexamethasone, vincristine, and pegaspargase. The combination was well tolerated and responses were seen in patients with a variety of mutations, including KMT2A rearrangements.

Blinatumomab

Blinatumomab is a component of the growing arsenal of immunotherapies for cancer treatment, and is a bispecific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in AYA and adult patients with R/R B-precursor ALL (n = 25).283,310 Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 AYA and adult patients with R/R BCR::ABL1-negative B-cell ALL that demonstrated a CR or CR without platelet recovery in 43% of patients within the first 2 cycles of treatment.282,311 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).281 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).281 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).281 Of note, prespecified subgroup analyses of patients with high bone marrow count (≥50%) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.281

In a phase I/phase II open-label study, the safety and efficacy of blinatumomab was evaluated in children <18 years of age with R/R B-ALL.191 Based on phase I data, the recommended dosage of blinatumomab was 5 µg/m2/day for the first 7 days, followed by 15 µg/m2/day afterwards.191 Of the 70 patients who received this dosage, 27 (39%) achieved CR within the first 2 cycles, 14 (52%) of whom achieved complete MRD response.191

In a phase III trial, COG AALL1331, the efficacy of blinatumomab versus chemotherapy was evaluated in pediatric patients (aged 1–30 years) with intermediate- or high-risk B-ALL in first relapse (n = 208).312 In this study, after re-induction chemotherapy (Block 1 of UKALLR3), patients were randomized to receive either two intensive chemotherapy blocks (arm A; n = 103) or two 4-week blocks of blinatumomab (arm B; n = 105). Randomization was halted early, not due to the triggering of the pre-defined DFS stopping rule, but due to the combination of higher DFS and OS, lower rates of serious adverse events, and higher rates of MRD negativity with blinatumomab compared to chemotherapy. At a median of 2.9 years, DFS favored the blinatumomab group, but was not statistically significant (54.4% vs. 39.0%; hazard ratio [HR], 0.70; 95% CI, 0.47–1.03; P = .06), though the study was limited by early termination of randomization. The 2-year OS rate was statistically significant in favor of blinatumomab (71.3% vs. 58.4% in the chemotherapy group; HR, 0.62; 95% CI, 0.39–0.98; P = .04). In addition, a greater percentage of patients in the blinatumomab arm achieved MRD negativity after the first cycle of randomized therapy (75% vs. 32% in the chemotherapy group; P < .001), and this significant difference persisted following the second cycle of randomized therapy (66% vs. 32% in the chemotherapy group; P < .001). A higher percentage of patients in the blinatumomab arm were able to proceed to HCT (70% vs. 43% in the chemotherapy group; P < .001).

In another randomized phase III trial,285 after induction therapy and two rounds of consolidation chemotherapy, 108 pediatric patients with high-risk B-ALL in first relapse were randomized to 1 cycle of blinatumomab versus chemotherapy for third consolidation prior to HCT. The 24-month EFS rate was 66.2% (95% CI, 50.1%–78.2%) in the blinatumomab arm compared to 27.1% (95% CI, 13.2%–43.0%) in the consolidation chemotherapy arm (HR, 0.33; 95% CI, 0.18–0.61; P < .001). Benefit for blinatumomab was seen across all specified subgroups and was independent of MRD status at the EOI or before the start of therapy. There was not a significant benefit in OS with blinatumomab compared to consolidation chemotherapy (HR, 0.43; 95% CI, 0.18–1.01). MRD remission by PCR was observed in a higher proportion of patients in the blinatumomab arm compared to the consolidation chemotherapy arm (90% vs. 54%, absolute percentage difference, 35.6% [95% CI, 15.6%– 52.5%]). This benefit was also seen in the subgroup of patients with detectable MRD at baseline (93% vs. 24%, absolute percentage difference, 69.1% [95% CI,

45.4%–85.5%]). A total of 88.9% of patients in the blinatumomab arm proceeded to HCT compared to 70.4% in the consolidation chemotherapy arm. A post hoc analysis of the study reported similar findings, with more patients achieving MRD <10–4 by PCR following third consolidation with blinatumomab compared to chemotherapy (81.5% vs. 48.1%, respectively; P = .0367).313 Among patients with baseline MRD ≥10–4 (at end of second consolidation) who achieved MRD negativity after blinatumomab, 91% achieved MRD <10–4 by day 15.

There are significant and unique side effects to blinatumomab treatment compared to the current standard-of-care regimens. In addition, blinatumomab requires prolonged exposure for efficacy due to a short half-life (mean ± standard deviation [SD]) of 1.25 ± 0.63 hours.314 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. CRS typically occurs within the first 2 days following initiation of blinatumomab infusion (see prescribing information for further details).145 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.

An arm of the phase III COG AALL1331 trial investigated the survival benefit of adding blinatumomab to chemotherapy in 255 patients (aged 1– 30 years) with low-risk B-ALL in first relapse.257 Following reinduction, patients were randomized to receive chemotherapy alone versus chemotherapy intercalated with three 4-week cycles of blinatumomab. While there was no significant DFS or OS benefit with the addition of blinatumomab for the overall cohort, blinatumomab did improve outcomes in patients with bone marrow relapse, with or without extramedullary relapse. For this specific patient cohort, the 4-year DFS and OS rates for those who received chemotherapy plus blinatumomab compared to chemotherapy alone were 72.7% ± 5.8% versus 53.7% ± 6.7 (P = .015) and 97.1% ± 2.1% versus 84.8% ± 4.8% (P = .020), respectively. However, for patients with isolated extramedullary relapse, 4-year DFS was poor for both arms, at 36.6% ± 8.2% for blinatumomab versus 38.8% ± 8.0% for chemotherapy (P = .62). Four-year OS rates were also similar for those with isolated extramedullary relapse, at 76.5% ± 7.5% for blinatumomab versus 68.8% ± 8.6% for chemotherapy (P = .53).

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 donor lymphocyte infusions. However, this method resulted in a significant risk of graft-versus-host disease (GVHD). To circumvent this issue, current advances are focused on the use of one's own T cells to target the B-ALL cells. The generation of CAR T cells to treat B-ALL is a significant advancement in the field.193,315-317 The treatment of patients with CAR T cells has served as a bridge for transplant, enabling patients who were formerly unable to receive a transplant due to poor remission status to achieve a CR and ultimately transplantation. It is also reported that patients who received CAR T cells can maintain long-term remission without subsequent HCT.193 In a systematic review and meta-analysis of 38 studies utilizing CD19-directed CAR T-cell therapy in both children and adults (n = 2134) with R/R B-ALL, median EFS and OS were 13.3 months and 36.2 months, respectively, with an ORR of 76%.318 CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to generate a response against a leukemic cell-surface antigen, most commonly CD19.319 Briefly, T cells from the patient are harvested and engineered to express a chimeric T-cell receptor that targets a cell surface tumor antigen (eg, CD19 on B-ALL cells). CAR T cells can be engineered to target any cell-surface antigen on leukemic cells, and even more than one antigen, which may help avoid the issue of tumor evasion via receptor down regulation. Studies of CAR T cells targeting antigens other than CD19 are ongoing.319 The manufacturing of CAR T cells currently requires ex vivo viral transduction, activation, and expansion over several days to weeks to produce a sufficient cell number to engender disease response.320 Following infusion, debulking of tumors occurs in less than a week and these CAR T cells may remain in the body for extended periods of time to provide immunosurveillance against relapse.

A study of 25 children and 5 adults infused with autologous T cells transduced with a CD19-directed CAR (CTL019) lentiviral vector showed a morphologic CR in 90% (27 out of 30) of patients within a month of treatment and an OS of 78% (95% CI, 65%–95%) and EFS of 78% (95% CI, 51%–88%) at 6 months.321 There were 19 patients in sustained remission, 15 of whom received no further therapy.

The pivotal phase II ELIANA trial investigated the use of the CD19-directed CAR T-cell therapy tisagenlecleucel in 75 children and young adults with R/R B-ALL and demonstrated an overall remission rate of 81% within 3 months of infusion, all of which were notably MRD negative.193 This high response rate was associated with OS rates of 90% and 76% at 6 and 12 months, respectively. As with blinatumomab,

T-cell activation was accompanied by severe CRS and neurologic toxicity, as well as higher infectious risks—though treatment-related mortality remained low.193 Given these data, CTL019/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 aged <26 years with R/R precursor B-cell ALL. Recent long-term follow-up data, with a median follow-up of 38.8 months, demonstrated an overall remission rate of 82%.322 Three-year EFS and OS rates were 44% and 63%, respectively. Estimated 3-year RFS rates were 52% and 48% with and without censoring for subsequent therapy, with only 22% of patients proceeding to HCT.

A systematic review compared the efficacy of tisagenlecleucel to historical standard-of-care R/R regimens for children and AYA patients with R/R B-ALL.323 In the intention-to-treat analysis, tisagenlecleucel was associated with significantly higher ORR (P < .001), lower hazard of death (P < .001), and higher adjusted OS probability at 4 years (44.05% vs. 32.86%) when compared to historical standard of care.

In a pilot clinical trial, 74 children and AYA patients (age range 1–29 years) with R/R B-ALL or B-LL were treated with huCART19, a humanized CD19 CAR T-cell product.324 There were two cohorts: those with prior CAR exposure (retreatment cohort, n = 33) and those without prior CAR exposure (CAR-naïve cohort, n = 41). ORR was 98% for the CAR-naïve cohort (100% for patients with B-ALL) and 68% for the retreatment cohort at one month post infusion. RFS for the CAR-naïve cohort at 12 and 24 months was 85% and 74%, respectively, compared to 74% and 58% in the retreatment cohort. This study highlighted durable remissions in children and AYA patients with R/R B-ALL, even after previous CAR T-cell therapy.

The side effect profile of CAR T cells differs substantially from those observed with standard therapies (ie, chemotherapy, HCT) (see Principles of Supportive Care; Toxicity Management for Inotuzumab Ozogamicin, Blinatumomab, and Tisagenlecleucel in the algorithm). While side effects from CAR T cells may be severe, they have been reversible. Adverse events are attributed to CRS and macrophage activation that occur in direct response to adoptive cell transplant resulting in high fever, hypotension, breathing difficulties, delirium, aphasia, and neurologic complications. Tocilizumab, a monoclonal antibody against interleukin-6 receptor; siltuximab, an antagonist of interleukin-6; and corticosteroids are the main options used to manage CRS and neurotoxicity symptoms.325,326 Hemophagocytic lymphohistiocytosis (HLH)-like toxicities, also known as immune effector cell-associated HLH-like syndrome (IEC-HS), can present with elevated ferritin, hepatosplenomegaly, and coagulopathy, and represent another potential toxicity following CAR-T cell therapy.327 By definition, IEC-HS occurs independently in time from CRS, usually after the resolution of CRS. Several groups have developed comprehensive guidelines regarding grading systems for and management of CAR T-cell– associated toxicities.328,329

A post-hoc analysis of pooled data from five clinical trials that included 195 patients between the ages of 1 to 29 years with R/R CD19-positive ALL or lymphocytic lymphoma compared the safety and efficacy of CD19-directed CAR T-cell therapy in those with and without CNS involvement at relapse.330 There was no significant difference in rates of CR at 28 days post infusion (97% vs. 94%; P = .74), RFS (60% vs. 60%; P = .50), or OS at 2 years (83% vs. 71%; P = .39) between the CNS-positive and CNS-negative cohorts. Additionally, the incidence and severity of CRS and neurotoxicity were not significantly different between the two groups, though the study required control of CNS disease both at time of enrollment and CAR T-cell infusion.

A phase II trial evaluated the safety and efficacy of the coadministration of CD19- and CD22-directed CAR T cells in patients ≤20 years with R/R B-ALL, including those with extramedullary relapse.331 Ninety-nine percent of patients with hematologic relapse or refractory disease achieved MRDnegative CR. The 12-month EFS among this entire cohort was 73.5%, improved to 85% among those who proceeded to HCT. Among patients with isolated testicular and CNS relapse, 12-month EFS was 95% and 68.6%, respectively. Eighty-eight percent of patients experienced CRS and 20.9% of patients experienced neurotoxicity. Neurotoxicity was associated with three deaths.

Another phase II study evaluated the administration of sequential CD19-directed and CD22-directed CAR T-cell therapies in patients aged 1 to 18 years with R/R B-cell ALL. Patients first received CD19-directed CAR T-cell therapy, followed by CD22-directed CAR T-cell therapy upon achievement of CRi or MRD negative CR. Among patients who received the target dose of 0.5 x 106 to 5.0 x 106 cells/kg, including two patients who did not receive CD22-directed cells, 97% achieved an objective response at the 3-month mark. Eighteen-month EFS and DFS (censored for transplant) were 79% and 80%, respectively, with an OS of 96%. Nineteen percent of patients experienced grade 3–4 CRS while 5% of patients experienced grade 3–4 neurotoxicity. B-cell aplasia was noted in 45% of patients with evaluable data at data cutoff.

Inotuzumab Ozogamicin

InO is a calicheamicin-based antibody-drug conjugate targeting CD22. Following the generation of encouraging single-agent phase II data,332 a randomized study was conducted comparing InO with

standard intensive chemotherapy regimens in BCR::ABL1-negative or BCR::ABL1-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).333 Notably, responses were consistent across most subgroups, including those with high marrow burden, and those with BCR::ABL1-positive leukemia. The overall incidence of severe adverse events was similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease 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).333 In August 2017, InO received full approval from the FDA for the treatment of adults with R/R precursor B-cell ALL.

In an analysis of patients ≥60 years of age with newly diagnosed BCR::ABL1-negative ALL who were treated on phase II clinical trials with either intensive hyper-CVAD versus the combination of InO and mini-hyper-CVD (mini-hyperfractionated cyclophosphamide, vincristine, and dexamethasone), with or without blinatumomab, there was a trend for higher CR rate and lower rate of death in the InO plus mini-hyper-CVD arm. The 3-year EFS rate for InO plus mini-hyper-CVD was 49% compared to 29% for hyper-CVAD (P = .001). The 3-year OS rates were 54% versus 32%, respectively (P = .002).334

The phase II COG trial AALL1621 assessed the safety and efficacy of InO in 48 pediatric and AYA patients aged 1 to 21 years with R/R CD22-positive B-ALL.335 CR/CRi was 58.3% and 66.7% of patients with CR or CRi had MRD <0.01%. Of patients who subsequently proceeded to HCT, 28.6% developed grade 3 sinusoidal obstruction syndrome (SOS).

Another phase II study assessed the safety and efficacy of InO in pediatric patients aged ≥1 to <18 years with R/R CD22-positive B-ALL.336 Of the 27 evaluable patients, estimated ORR (including CR, CR with insufficient platelet recovery [CRp], and CRi) was 81.5%, with 81.8% of patients with response achieving MRD negativity. One-year EFS was 36.7% and OS was 55.1%, with a median follow-up of 16 months. Eighteen patients received subsequent consolidation therapy (14 with HCT, 2 with CAR T-cell therapy, and 2 with CAR T-cell therapy followed by HCT). Seven patients developed SOS, of which 6 were ≥ grade 3.

While pediatric experience with InO is relatively limited, based on available data, InO was FDA approved for pediatric patients aged ≥1 year with relapsed/refractory CD22-positive B-ALL on March 6, 2024. InO is also associated with potentially fatal or life-threatening hepatic SOS, especially after HST,337,338 as well as an increased risk of post-HCT non-relapse mortality (see prescribing information for further details).145 Ursodiol prophylaxis can be considered for prevention of SOS with use of InO.339

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; age range 1.3-75 years) with primary refractory or relapsed KMT2Ar acute leukemia, including 14 patients with ALL.194 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 with evaluable data 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 febrile 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.

Hematopoietic Cell Transplant

For patients with early relapse of B-ALL, HCT is the only currently established curative modality. 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.340 At 3 years, OS rates were 16% (95% CI, 13%–20%).340 Based on findings from an evidence-based review of the published literature, the

American Society for Transplantation and Cellular Therapy (ASTCT) guidelines recommend HCT for pediatric patients with ALL in CR2 after experiencing an early marrow relapse.341

NCCN Recommendations for BCR::ABL1-Negative or BCR::ABL1-Like ALL

Front-Line Management

The Panel recommends that pediatric and AYA patients with BCR::ABL1-negative or BCR::ABL1-like ALL be treated in a clinical trial when possible. In the absence of an appropriate clinical trial, patients are initially grouped according to risk criteria (see Risk Stratification Definitions, Initial Risk Group Stratification in the algorithm), and induction therapy consists of multiagent chemotherapy (see Principles of Systemic Therapy; Regimens for BCR::ABL1-Negative B-ALL or Regimens for BCR::ABL1-Like B-ALL in the algorithm.

Patients who achieve MRD-negative CR after induction will continue risk-stratified therapy plus blinatumomab. Blinatumomab is incorporated into frontline therapy as a post-remission approach based on data COG AALL1731148 as well as the ECOG1910 study in adults.149 While blinatumomab is recommended for patients with disease meeting the SR-avg or SR-high definitions of COG AALL1731,148 for sites without access to blinatumomab it is reasonable to follow the control (no blinatumomab) arms which are based on AALL0932.151 It is also reasonable to treat patients with disease meeting the SR-favorable definition as per the SR-avg arm of AALL1731 with blinatumomab. For patients with an expected very favorable outcome, the benefit of blinatumomab should be weighed with potential toxicities, including increased infection risk. Assessment of MRD with a high sensitivity NGS assay post-induction may aid the decision to administer blinatumomab in SR-favorable patients.

Patients with MRD-positive CR after induction may undergo intensified consolidation therapy plus blinatumomab. If MRD remains persistent, other options include blinatumomab or tisagenlecleucel (category 2B recommendation). The use of tisagenlecleucel in this setting is strongly recommended in the context of a clinical trial. In all circumstances, HCT may be considered as part of consolidation or maintenance therapy, though should be more strongly considered in the setting of MRD positivity. The role of allogeneic HCT following tisagenlecleucel is unclear, however. Persistence of tisagenlecleucel in peripheral blood (persistent B-cell aplasia) and negative NGS MRD, with or without B-cell aplasia, have been associated with durable clinical responses without subsequent HCT.269,322 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.322 Patients with less than CR after induction should be treated as having refractory disease.

R/R Management

For pediatric and AYA patients with BCR::ABL1-negative or BCR::ABL1-like ALL experiencing early or late first relapse, the Panel recommends initial treatment with systemic therapy. If patients experience CR (CR2) with MRD negativity, the options are to receive blinatumomab or continue on systemic therapy and receive maintenance therapy or HCT if feasible based on the risk of subsequent relapse. If patients experience CR2 with MRD positivity, or are experiencing first relapse after a prior HCT, in addition to chemotherapy, blinatumomab, tisagenlecleucel, or InO may be considered prior to either a first or second HCT. In instances of both CR2 with MRD negativity or positivity, the recommendation for blinatumomab applies to patients with bone marrow relapse, with or without extramedullary relapse.257,285,312 If patients experience less than a CR (ie, multiple relapse), treatment options include chemotherapy, blinatumomab, tisagenlecleucel, or InO ± mini-hyper-CVD, and they may receive HCT as consolidation therapy if their disease

subsequently responds to therapy. Long-term remissions have also been reported after tisagenlecleucel treatment without subsequent HCT; thus, the role of HCT following tisagenlecleucel is unclear.193 If the disease does not respond to therapy, alternative treatment options may be considered with best supportive and palliative care.

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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 metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
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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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-349

Verfasser	
Institution	Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO) Gesellschaft für Pädiatrische Onkologie und Hämatologie (GPOH)
Datum	TT.MM.JJJJ

Indikation
zur Behandlung von pädiatrischen Patienten im Alter von 1 Monat oder älter mit Hochrisiko-Erstrezidiv einer Philadelphia-Chromosom-negativen, CD19-positiven B-Zell-Vorläufer-ALL im Rahmen der Konsolidierungstherapie.
Fragen zur Vergleichstherapie
Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Zusammenfassung

Pädiatrische Patientinnen und Patienten (Pat.) im Alter von 1 Monat oder älter mit Hochrisiko-Erstrezidiv einer Philadelphia-Chromosom-negativen, CD19-positiven B-Zell-Vorläufer-ALL im Rahmen der Konsolidierungstherapie haben eine sehr schlechte Prognose. Die Therapie erfolgt patientenindividuell. Sie sollte im Rahmen von Studien erfolgen.

Wir weisen darauf hin,

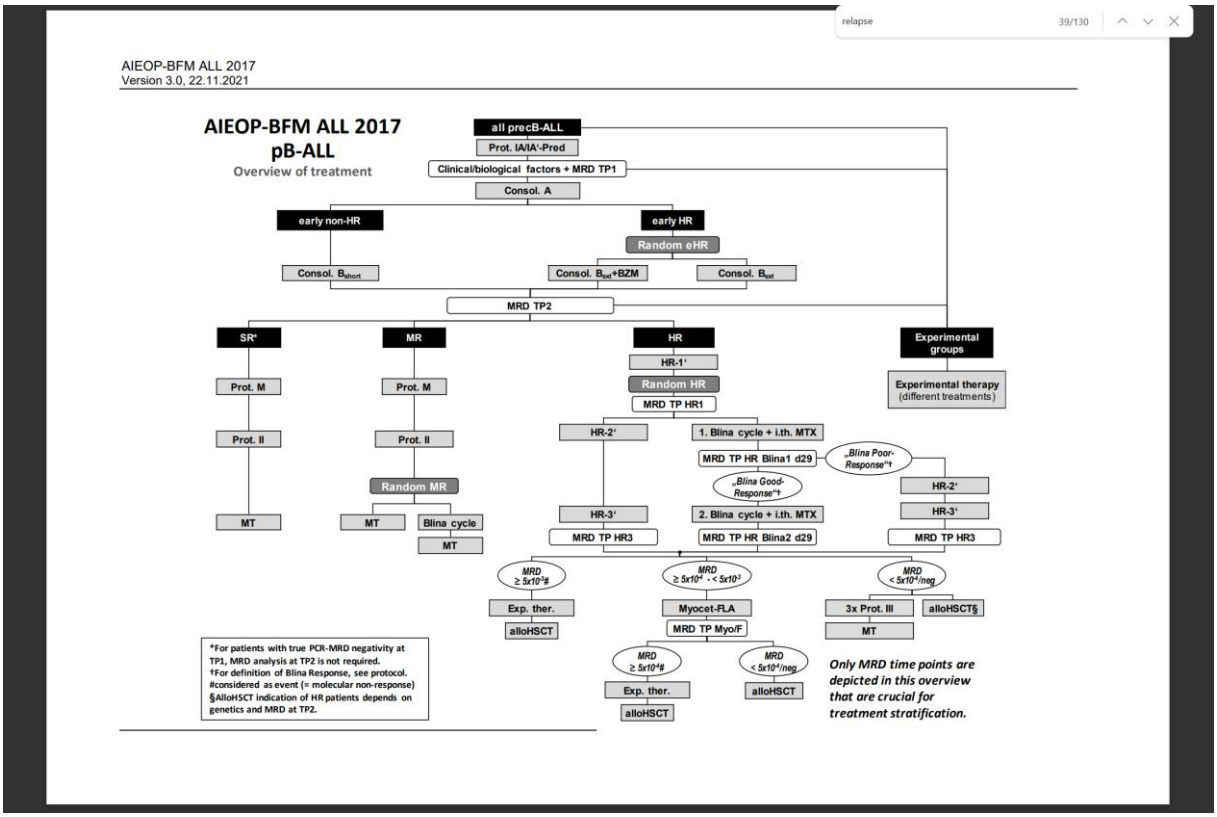
- dass in der Regel eine allogene Stammzelltransplantation bereits aufgrund der initialen Hochrisiko-Situation stattgefunden hat,
- dass die Therapieresistenz in Deutschland regelhaft auf der Basis der MRD-Positivität festgestellt wird.

Fragestellung

Sowohl die Festlegung einer zweckmäßigen Vergleichstherapie im Rahmen einer frühen Nutzenbewertung als auch eine Studienplanung sollte die oben genannten Punkte (Vortherapie, Definition von Therapieresistenz) berücksichtigen.

Stand des Wissens

Die Therapie von pädiatrischen Pat. erfolgt nach dem AIEOP-BFM ALL-Studienprotokoll, siehe Abbildung [1].



Dieses sieht zum einen eine frühe Identifikation refraktärer leukämischer Blasten mittels des Nachweises von Minimal Residual Disease (MRD) und eine frühe Risikostratifikation mit Integration der allogenen Stammzelltransplantation (allo HSCT) vor.

Im Rezidiv erfolgt die Therapie patientenindividuell. Entscheidend ist vor allem die Vortherapie einschl. bereits stattgehabter allogener Stammzelltransplantation.

Neue Ansätze setzen insbesondere auf den frühen Einsatz innovativer Formen der Immuntherapie.

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?
Ja, diese sind oben dargestellt.

Referenzliste:

1. AIEOP-BFM ALL 2017