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REVIEW ARTICLE

New Approaches to the Management of Adult Acute Lymphoblastic Leukemia

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ABSTRACT

Traditional treatment regimens for adult acute lymphoblastic leukemia, including allogeneic hematopoietic cell transplantation, result in an overall survival of approximately 40%, a figure hardly comparable with the extraordinary 80% to 90% cure rate currently reported in children. When translated to the adult setting, modern pediatric-type regimens improve the survival to approximately 60% in young adults. The addition of tyrosine kinase inhibitors for patients with Philadelphia chromosome–positive disease and the measurement of minimal residual disease to guide risk stratification and postremission approaches has led to additional improvements in outcomes. Relapsed disease and treatment toxicity—sparing no patient but representing a major concern especially in the elderly—are the most critical current issues awaiting further therapeutic advancement. Recently, there has been considerable progress in understanding the disease biology, specifically the Philadelphia-like signature, as well as other high-risk subgroups. In addition, there are several new agents that will undoubtedly contribute to additional improvement in the current outcomes. The most promising agents are monoclonal antibodies, immunomodulators, and chimeric antigen receptor T cells, and, to a lesser extent, several new drugs targeting key molecular pathways involved in leukemic cell growth and proliferation. This review examines the evidence supporting the increasing role of the new therapeutic tools and treatment options in different disease subgroups, including frontline and relapsed or refractory disease. It is now possible to define the best individual approach on the basis of the emerging concepts of precision medicine.

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INTRODUCTION

In Western countries, new cases of adult acute lymphoblastic leukemia (ALL) occur at an annual rate of approximately one per 100,000, with a bimodal distribution decreasing at age 45 to 54 years and increasing again in people older than 55 years, totaling approximately 2,300 new cases per year for patients older than 15 years (n = 1,750 between ages 15 and 55 years) in the United States.[1,2] Over the past decade, we have witnessed an incredible therapeutic improvement. Currently, pediatric patients have an estimated 5-year overall survival (OS) approaching 90%.[3-5] Modern pediatric programs thrive on an intensified use of corticosteroids (mainly dexamethasone), antimetabolites (especially methotrexate and 6-mercaptopurine) and L-asparaginase/pegylated-asparaginase, and rely on minimal residual disease (MRD) analysis for additional dose intensification or allogeneic hematopoietic cell transplantation (HCT).[6-8]

RECENT ADVANCES USING PEDIATRIC REGIMENS IN ADULTS

The results in adult ALL, unfortunately, have not kept pace with those in pediatric ALL, with OS rates $< 45\%$[9] despite the addition of CNS prophylaxis, late intensification with prolonged maintenance chemotherapy, and an extensive use of HCT in high-risk (HR) subsets. Currently, pediatric-inspired regimens are being administered in young adult patients, leading to improvements in event-free survival (EFS) and OS rates as compared with historical controls.[10-13] This approach, initially reserved for adolescents and young adults (AYA; $<$ 40 years old)[10,14,15] and later applied to patients up to 50 to 60 years of age,[11,12,16] has increased the 5-year OS rate to $\geq$ 50%, and up to 70% to 80% in favorable subsets (ie, AYA, standard risk, MRD negative; Appendix Table A1, online only),[17] but not in older patients, whose survival decreases progressively to $<$ 20%.[2-4] Finally, allogeneic HCT is

ASSOCIATED CONTENT

Appendix
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Table 1. Summary of Clinical Evidence of Antibody Therapy in Acute Lymphoblastic Leukemia in Selected Clinical Trials

Target Antigen	Agents	Class	Clinical Trials			
			Patients	No.	Regimen	Study Results
CD19	Blinatumomab	BiTE (CD19 × CD3) antibody	MRD positive ($> 10^{-4}$)	21	Blinatumomab IVCI × 4 weeks	Phase II: 61% RFS rate at median follow-up of 33 months[35]
			MRD positive ($> 10^{-3}$)	116	Blinatumomab IVCI × 4 weeks (HCT after response)	Phase II: complete MRD response, 80% (78% at cycle 1); median OS, 38.9 months; and RFS, 23.6 months in MRD responders ($P = .002$ *v* nonresponders)[36]
			Relapsed/refractory	36	Blinatumomab IVCI × 4 weeks	Phase I/II: 69% CR/CRi with 88% MRD negative[37]
				189	Blinatumomab IVCI × 4 weeks	Phase II: 43% CR/CRi with 82% MRD negative; median OS of responders, 6.1 months *v* nonresponders, 3.5 months[38]
			Relapsed/ refractory (Ph−)	376	Blinatumomab IVCI × 4 weeks	Phase III *v* SOC: Improved CR/CRi 44 *v* 25%; MRD negative rate 76% *v* 48%; OS 7.7 *v* 4.0 months[39] ($P = .01$)
			Relapsed/ refractory (Ph+)	45	Blinatumomab IVCI × 4 weeks	36% CR/CRi (40% with T315I), with 88% MRD negative; median RFS, 6.7 months[40]
	SGN19a (denintuzumab mafodotin)	Immunoconjugate (monomethyl auristatin F)	Relapsed/ refractory	59	Weekly (days 1 and 8) or day 1 every 3 weeks	Phase I: 19% CR/CRi weekly arm and 35% in the every-3-week arm[41]
	SAR3419 (coltuximab ravtansine)	Immunconjugate (maytansine DM4)		36	Monotherapy weekly (escalating dose and selected dose in expansion cohort)	Study discontinued because of toxicity; overall response rate, 25.5%[42]
CD19/22	Combotox	Immunotoxin (ricin A chain)	Relapsed/refractory	17	Maximum tolerated dose, 7 mg/m^2	Phase I: one patient achieved partial remission[43]
CD20	Rituximab	Naked antibody	Newly diagnosed	282	Rituximab + hyper-CVAD	Phase II: Improved CMR, RFS, and OS in patients < 60 years old[44]
				263	Rituximab + chemotherapy	Phase II: improved rate of negative MRD, CRD, and 3-year OS[45]
				209	Rituximab + chemotherapy	Phase III: improved rate of 2-year EFS (65% *v* 52%, $P = .04$)[13]
	Ofatumumab	Naked antibody	Newly diagnosed	55	Ofatumumab + hyper-CVAD	Phase II: CR 98% and MRD negativity 93%; 3-year CRD rate, 78%; and OS, 68%[46]

(continued on following page)

Table 1. Summary of Clinical Evidence of Antibody Therapy in Acute Lymphoblastic Leukemia in Selected Clinical Trials (continued)

Target Antigen	Agents	Class	Clinical Trials			
			Patients	No.	Regimen	Study Results
CD22	Epratuzumab	Naked antibody	Relapsed/refractory	15	Epratuzumab + chemotherapy	Phase I: 60% CR, 40% MRD negative[47]
			Relapsed (first)	114	Epratuzumab + chemotherapy (two schedules of epratuzumab)	Phase II: 65% and 66% CR rates, 42% MRD negative rate (higher than historical controls)[48]
			Relapsed/refractory	32	Epratuzumab + clofarabine + cytarabine	Phase II: 52% CR/CRi rate; median OS, 5 months[49]
				20	Epratuzumab + hyper-CVAD	Phase II:CR/CRi, 33%; median OS, 3 months[50]
		Radioconjugate (^{90}Y-labeled)	Relapsed/refractory	17	^{90}Y-Epratuzumab days 1 and 8, dose level 1-4	Phase I: well tolerated, with three CRs; recommended dose for phase II study (2 × 10.0 mCi/m^2)[51]
	Inotuzumab	Immunconjugate (calicheamicin)	Relapsed/refractory	90	Inotuzumab every 3 to 4 weeks (n = 49 patients) or weekly (n = 41 patients)	Phase I/II: CR/CRi rate 58%, and 72% MRD negative rate[52]
				72	Inotuzumab weekly	Phase I/II; multicenter trial with CR/CRi rate of 68% and 84% MRD negative; median OS, 7.4 months[53]
				326	Inotuzumab weekly	Phase III *v* SOC: Improved CR rate 81% *v* 33%; MRD negative rate 78% *v* 28%; OS 7.7 *v* 6.7 months ($P = .04$)[54,99]
				59	Inotuzumab weekly + mini–hyper-CVD	Phase II: CR/CRi rate of 78%, with 82% MRD negative; median RFS and OS, 8 and 11 months, respectively; 1-year RFS in first salvage, 77%[55]
			Newly diagnosed, older age (> 60 years)	48	Inotuzumab weekly + mini–hyper-CVD	Phase II: 98% CR/CRi rate with 76% MRD negative; 2-year PFS, 52%; OS, 66% (*v* historical OS 36% ($P < .05$)[56,108]
	BL22 and moxetumomab pasudotox	Immunotoxin (*Pseudomonas* exotoxin)	Relapsed/refractory (children)	47	BL22 and moxetumomab pasudotox every other day × 6	Phase I: 32% objective response with 23% CR (n = 11, with 5 MRD negative)[57]
			Relapsed/refractory	16	BL22 and moxetumomab pasudotox every other day × 6	Phase I: overall response rate 13%, 2 CR/CRi; safe at higher dose level[58]
CD52	Alemtuzumab	Naked antibody	Newly diagnosed	24	Postremission in fourth treatment module	Phase I: median OS, 55 months; 1-log MRD reduction; immune suppression/toxicity led to study discontinuation[59]

Abbreviations: BiTE, bispecific T-cell engaging; CMR, complete molecular remission; CR, complete remission; CRD, complete remission duration; CRi, complete remission with incomplete neutrophil and/or platelet count recovery/; HCT, hematopoietic cell transplantation; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; hyper-CVD, cyclophosphamide, vincristine, dexamethasone; ICVI, intravenous continuous infusion; MRD, minimal residual disease; OS, overall survival; PFS, progression free-survival; Ph, Philadelphia chromosome; RFS, relapse-free survival; SOC, standard of care.

Table 2. Representative CD19 Chimeric Antigen Receptor T-Cell Studies for R/R and MRD+ B-Cell Precursor ALL

Study	Phase, Status	Population	Costimulatory Domain	Efficacy	Toxicity
Novartis (ELIANA)[60]	Phase II, FDA-approved (children and adolescents)	Pediatric/young adult (n = 92; effective infusion, n = 75)	4-1BB	CR/CRi 81%, all MRD negative; 1-year OS, 76%; 1 year EFS, 50%	77% CRS (48% to tocilizumab), 40% neurotoxicity (no cerebral edema)
Kite Pharma (ZUMA-3)[61]	Phase I/II	Adults (n = 11; infused, n = 10)	CD28	CR/CRi 75%, all MRD negative	Grade 3+ CRS, 20%; grade 3+ neurologic toxicity, 40%; one grade 5 MOF, CRS related (no cerebral edema)
Kite Pharma (ZUMA-4)[62]	Phase I/II, ongoing	Pediatric and adolescents (n = 5; infused, n = 4)	CD28	CR/CRi 100%, all MRD negative	No grade 3+ CRS; one grade 3 neurologic event
MSKCC[63]	Phase I	Adults (n = 32 R/R; n = 21 MRD+ [marrow blasts $< 0.01\%$ to $< 5\%$])	CD28	CR, 83%; CMR 67%; median EFS, 6.1 months (CMR *v* no CMR patients: 12.5 months *v* 3.1 months; $P < .001$). Median OS, 12.9 months (CMR *v* no CMR patients: 20.7 months *v* 6.6 months; $P < .001$)	26% severe CRS (one related death); grade 3-4 neurotoxicity, 42%
Juno Therapeutics[64]	Phase II (Rocket), discontinued	Adults (n = 32 R/R; n = 6 MRD+)	CD28	CR of 47% with 40% MRD negative. Median OS, 8.1 months	24% severe CRS; 53% neurotoxicity (five fatal cases of cerebral edema)

Abbreviations: CMR, complete molecular remission; CR, complete remission; CRi, complete remission with incomplete count recovery; CRS, cytokine release syndrome; EFS, event-free survival; FDA, US Food and Drug Administration; MOF: multiorgan failure; MRD, minimal residual disease; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; RFS, relapse-free survival; R/R, relapsed/refractory.

often considered in first complete remission (CR) in adults with HR disease to reduce the risk of relapse,[18] but potential benefits may be offset by transplant-related morbidity and mortality, especially in the elderly.[19]

Risk Stratification

Current risk stratification criteria reflect the clinical and prognostic heterogeneity of ALL and determine which patients should undergo more intensive treatment including HCT, due to the high risk of relapse. Besides patient-related characteristics, namely advanced age and poor performance status, recognized risk factors include hyperleukocytosis, early thymic-precursor (ETP) phenotype and adverse cytogenetics or genetics (ie, t(9;22)/*BCR-ABL1* rearrangement [Philadelphia chromosome positive (Ph+) ALL], Ph-like ALL, t(4;11)/*KMT2A-AFF1* rearrangement, hypodiploidy, mutated *TP53*, and other abnormalities).[20] In all studies, MRD has proven to be a major independent risk factor for relapse.[21] In contrast to MRD-negative patients (typically defined as having $<10^{-4}$ residual leukemic cells in their CR marrow compared with baseline), MRD-positive patients are seldom cured with chemotherapy alone. In prospective trials performed over the past 25 years, enrolling $>$ 1,500 patients,[22-24] OS was between 60% and 80% with chemotherapy alone in MRD-negative patients, even in HR subsets and Ph+ ALL.[25] Instead MRD-positive patients benefit partially from HCT, although with OS rates $\leq$ 50% in intention-to-treat analyses, due to the cumulative effects of pre- and post-transplantation relapse and transplant-related deaths.[26-28]

Current Therapeutic Limitations

The treatment of older patients represents a major obstacle,[29] and, at all ages, relapse affects one-third or more of the patients and remains an unsolved issue due to extremely poor results with standard salvage chemotherapy. An international study of 1,706 patients with refractory or recurrent (R/R) B-cell precursor (BCP) ALL reported 3-year survival rates of only 10%.[30] Results are worse in Ph+ ALL[31] and T-cell precursor (TCP) ALL, with some mitigation provided by nelarabine.[32] Another concern is high-grade toxicity causing death in remission, which increases with age and with transplants ($\geq$ 20% in most studies).

The Challenge of New Management Options

Despite these constraints, the management of adult ALL can be improved. This new era started with the advent of tyrosine kinase inhibitors (TKI) for Ph+ ALL,[33] flourished with immunotherapy for BCP ALL and is now empowered by novel immunotherapeutics (Tables 1 and 2)[13,34-64] and several small molecules targeting critical metabolic pathways (Fig 1; Tables 3 and 4), used alone or in combination in specific ALL subsets (Fig 2). More robust data on toxicity, dosing, and therapeutic implications are required and will be generated by ongoing trials (Appendix Tables A2-A7, online only); however, some of these agents could improve the cure rate and prompt a shift in the therapeutic regimens for ALL. The most promising agents currently available are those targeting cell membrane antigens (namely, CD19, CD20, and CD22) and major molecular pathways controlling cell proliferation and apoptotic response (ie, multiple kinases and members of Bcl-2, TP53, RAS, mTOR/PI3K, pre-B/B-cell receptor, and NOTCH networks). Furthermore, new molecular and drug profiling techniques might become essential to define targets and compounds deserving evaluation in trials or individual patients. This new strategy is still largely speculative, especially in frontline therapy, because molecular sequencing and new drug-sensitivity screening models have not yet been sufficiently tested or validated in early clinical trials. This review focuses on the rationale supporting this change and illustrates

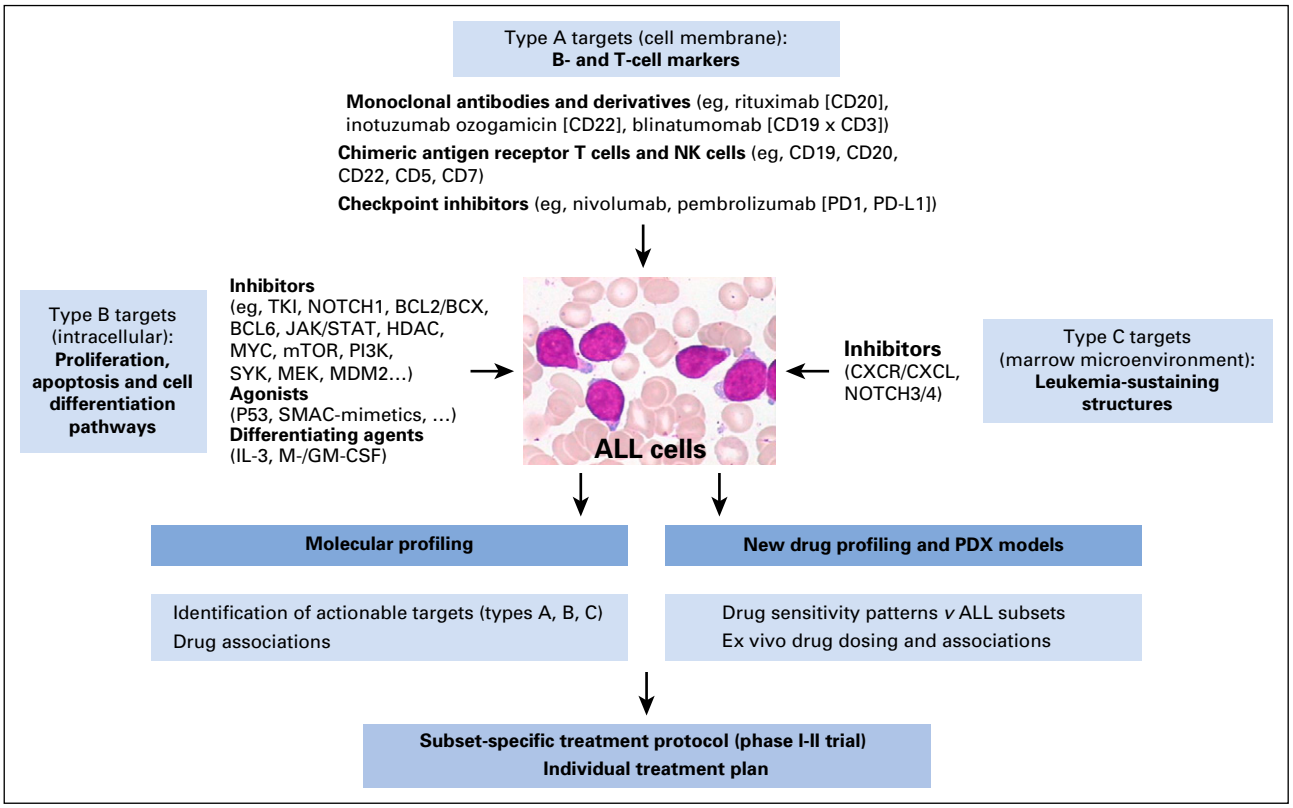

Fig 1. Actionable targets and drugs for innovative therapeutics in adult ALL. New therapeutic targets are membrane markers associated with B- or T-cell functions (type A), intracellular molecules involved in the regulation of key cell proliferation and differentiation pathways (type B), and receptors involved in the interaction with the supportive marrow niche (type C). Examples are shown for each category. Multitargeted therapy is possible, and synergy with chemotherapy is reported. Molecular profiling and new-drug profiling techniques can help identify suitable targets and the more active compounds and drug combinations to be exploited in clinical trials of subset- and patient-specific therapy. ALL, acute lymphoblastic leukemia; NK, natural killer; PDX, patient-derived xenograft.

how new treatment approaches and related experimental work are likely to modify and improve the management of adult ALL.

ACTIONABLE TARGET AND DRUG SCREENING

Molecular Profiling

Although targets for immunotherapy can be identified by diagnostic immunophenotype, ALL subtype classification and target identification rely mostly on molecular genetics for the detection of gene rearrangements, translocations, and actionable recurrent mutations with genome-wide technologies.[65-69] In the era of precision medicine, molecular profiling has gained in importance for the management of this disease. New concepts for targeted therapies and combinatory approaches with immunotherapy and/or chemotherapy require sophisticated experimental modeling and are now increasingly entering clinical development (Fig 2; Appendix Tables A2-A10).

Drug Profiling Platforms

Because the molecular classification of ALL is often insufficient to capture the complex biology of the disease and provide a predictive guide for treatment,[70] functional screening approaches are being explored to generate drug response profiles directly from clinical samples, leading to proof-of-concept results and raising interest in exploring this approach in clinical trials (Fig 3). The first screening platform tested a customized library of kinase inhibitors,[71] leading to a prospective trial in relapsed acute myeloid leukemia. The Primary Blood Cancer Encyclopedia project, which integrates short-term drug testing data with transcriptome and DNA methylome analysis, strongly supported the value of phenotypic screening in hemato-oncology.[72] Some platforms are based on large viability assays for high-throughput testing[72-74] with the advantage of simplicity and lower costs, and other, more sophisticated platforms are based on automated microscopy, which can discriminate leukemia cells with the normal microenvironment at the single-cell level.[75,76] Functional screens of ALL samples maintained on mesenchymal stromal cells identified unexpected dependencies in defined HR ALL subtypes,[77] captured response heterogeneity across ALL subtypes, efficiently discriminated patients on the basis of drug sensitivity[75,78,79] and detected new pathways and vulnerabilities in resistant disease.[75,77-80]

New Disease Models

Drug development can be accelerated using humanized mouse models with primary leukemia[81,82] that enable systematic preclinical drug testing.[83,84] Patient-derived xenograft (PDX) biobanks integrate extensive genomic and clinical information,[75,85-88] mirror the clonal architecture of leukemia initiating cells,[89-92] maintain the genetic composition of the

Table 3. Major BCP and TCP ALL Subsets of Interest for Molecular Targeted Therapy in Adult ALL: Subset Identification Through Cytogenetics/Genetics and Genome-Wide Technologies

ALL Subset	Prevalence; Prognosis	Main Aberration	Other Aberration
BCP ALL			
BCR-ABL1+/ t(9;22)(q34;q11.2) (Ph+)	20% to approximately 50%, increasing with age; unfavorable, improved by TKI	*BCR-ABL1* rearrangement	Deletions of *IKZF1* and *CDKN2A/B*; ABL1 mutations (recurrence/resistance)
Ph-like	10%-15% of childhood ALL, 27% of AYA, 20% in adult ALL; unfavorable	Gene expression profile similar to *BCR-ABL1+* ALL except for lack of *BCR-ABL1* rearrangement	Deletions of *IKZF1, TCF3*, *EBF1*, *PAX5*, and *VPREB1;* dic(9;20) and *iAMP21; CRLF2* deregulated; *JAK* members mutations; rearrangements involving *ABL1*, *JAK2*, *CRLF2*, *PDGFRB*, *EBF1*
*KMT2A-AFF1+/*t(4;11)(q21; q23.3), *KMT2A*-rearranged/t(v; 11q23.3)	Approximately 5% (*MLL-KMT2A+*); unfavorable	*KMT2A-AFF1 or KMT2A*-other partner-gene rearrangement	Few additional aberrations; *KRAS*, *NRAS*, *FLT3*, *NF1*, *PTPN11*, and *PIK3R1* mutations; epigenetic regulatory gene mutations
TCF3-PBX1+/t(1;19)(q23;p13)	10%-15%; relatively favorable with intensive therapy	*TCF3-PBX1* rearrangement	Deletions of *PAX5* and *CDKN2A/B*
iAMP21	Approximately 2%; unfavorable	—	Deletions of *IKZF1*, *CDKN2A/B*, *PAX5*, *ETV6*, and *RB1*; chromosome X gain; *P2RY8-CRLF2* rearrangement
Hypodiploid, further classified as near-haploid (24-30 chromosomes) and low-hypodiploid (31-39 chromosomes)	Children: 0.5% of both near-haploid or low-hypodiploid, adults: low hypodiploid 3%-4%; poor prognosis	TP53, RAS, PI3K, and IKZF members	—
t(v;14q32)	< 5%, higher incidence in adolescents; unfavorable	*IGH* fusion with partner genes *CRLF2*, *ID4*, *CEBP*, *BCL2*, *EPOR*, *LHX4*, and *IL-3*	CDKN2A deletions
Translocations/deletions/ mutations in Xp22.3/Yp11.3	≤ 7%, > 50% in Down syndrome ALL, 50% in *BCR-ABL1*-like ALL; unfavorable	*CRLF2-IGH, P2RY8-CRLF2* rearrangements	*JAK1/2* mutations (≤ 50%); *IKZF1* deletions in HR ALL
9p13 deletions/translocations	Approximately 25%, possibly involved in leukemogenesis; no effect on outcome	*PAX5* fusion with partner genes *ETV6*, *ELN*, *POM121*, *PML*, *FOXP1*, *MLLT3*, *JAK2*, *C20orf112*, *AUTS2*, *CHFR*, *SOX5*, *POM121C*	—
7p12.2 focal deletions/mutations	40% overall; 15% in childhood and 50% in adult ALL; unfavorable/ controversial prognosis	Deletion of *IKZF1*	—
TCP ALL			
TAL and *LMO* rearrangements/ del(1)(p32), t(1;14)(p32;q11), t(1;7)(p32;q34), t(7;9)(q34;q32), t(11;14)(p15;q1), t(11;14) (p13;q1), t(7;11)(q35;p13)	30%-40%; favorable, partly depending on additional lesions	*SIL-TAL1* rearrangement, TCR rearrangements with *TAL1, TAL2, LMO1, LMO2*	*PTEN* mutations and deletions, *MYC* rearrangements
HOXA aberrations/inv(7) (p15q34), t(7;7)(p15;q34), t(10;11)(p13;q14), t(v;11q23), del(9)(q34),	Approximately 20%-25%; outcome depending on additional lesions	*TCR-HOXA* rearrangement, *MLLT10* and *MLL* rearrangements with various partners, *SET-NUP214* rearrangement	*IL7R* and *JAK1/3* mutations
TLX3-5q35 rearrangement/ t(5;14)(q35;q32)	20%-24% childhood ALL, 10% adult ALL	*TLX3-BCL11B* rearrangement	—
TLX1-10q24 rearrangements/ t(7;10)(q34;q24), t(10;14), (q24;q11)	3%-8% childhood ALL, 20%-30% adult ALL	*TCR-TLX11* rearrangement	*PTPN2* mutations and deletions, *PHF6* mutations, *NUP214-ABL1* and *EML1-ABL1* rearrangements
NKX2-1/NKX2-2 rearrangements/ inv(14)(q11.2q13), t(7;14) (q34;q13), inv(14)(q13q32.33), t(14;20)(q11;p11)	6%	*TCR/IGH-NKX2-* or *NKX2-2* rearrangements	—
LYL/MEF2C rearrangement and immature cluster/t(7;19), (q34;p13), del(5)(q14)	3%-17%; unfavorable, survival improved by intensive treatment	*TCR* with *LYL1* and *MEF2C* rearrangements	*JAK1/3* mutations, *IL7R, N-RAS, FLT3*, epigenetic modulators (ie, *IDH1/2, DNMT3A, EZH2, EED, SUZ12, SETD2* and *EP300*), transcription factors (ie, *RUNX1, ETV6, GATA3* and *IKZF1*); *RUNX1-AFF3, ETV6-NCOA2, BCL11B-*

NOTE. Dashes indicate no data.
Abbreviations: ALL, acute lymphoblastic leukemia; AYA, adolescents and young adults; BCP, B-cell precursor; HR, high risk; TCP, T-precursor; TKI, tyrosine kinase inhibitor.

Table 4. Major BCP and TCP ALL Subsets of Interest for Molecular Targeted Therapy in Adult ALL: Main Molecular Targets for Available or Developmental Targeted Therapy

ALL Subsets	Dysfunctional Gene Category	Molecular Targets	Targeting Agents
BCP: *BCR-ABL1+* (Ph+), Ph-like, *TCF3-PBX1+*	Kinase aberrations	*BCR-ABL1, PDGFRB, MERTK, ICK, TNK2*	TKI
TCP: *NUP214-ABL1+, EML1-ABL1+*	Kinase aberrations	*BCR-ABL1, PDGFRB, MERTK, ICK, TNK2*	TKI
Various (BCP and TCP)	*JAK/STAT* deregulation	*JAK1/2, CRLF2, IL7R, PTPRC, PTPN2*	*JAK* inhibitors, mTOR inhibitors
	*PI3K/PTEN/AKT/*mTOR deregulation	*PTEN, N/K-RAS, AKT, PI3K*	PI3K/mTOR dual inhibitors, allosteric MEK1/2 inhibitor
KMT2A-rearranged, hyperdiploid and hypodiploid, *FLT3*-mutated TCP	*RAS* signaling deregulation	*FLT3, N/K-RAS*	FLT3 inhibitors, mTOR inhibitors, PI3K/mTOR dual inhibitors, allosteric MEK1/2 inhibitor
KMT2A-rearranged	Epigenetic deregulation	*CREBBP, SETD2, DOT1L*	DOT1L inhibitors, histone deacetylase inhibitors
MLL-rearranged, *TCF3-HLF+*	Apoptosis deregulation	*BCL2*	Bcl-2 inhibitors
TCP	*NOTCH1* mutations	*NOTCH1*	γ-Secretase inhibitors

Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; TCP, T-cell precursor; TKI, tyrosine kinase inhibitor.

xenografted sample,[75,77,89,93] and enable testing of new agents on samples from clinically representative cohorts of patients, providing survival cues and a longer window for combinatorial drug testing. Impressive results have been reported from a first trial assessing drug sensitivity in patients with refractory hematologic malignancies, using multiparametric image-based immunocytometry to distinguish the effect of drugs on malignant and normal blood cells.[76] Of 48 patients, informative results could be used for 17 who received assay-guided treatment, including two patients with BCP ALL, resulting in responses in eight patients (one with ALL). These results will stimulate the design of larger clinical studies on specific disease entities to capture the full potential

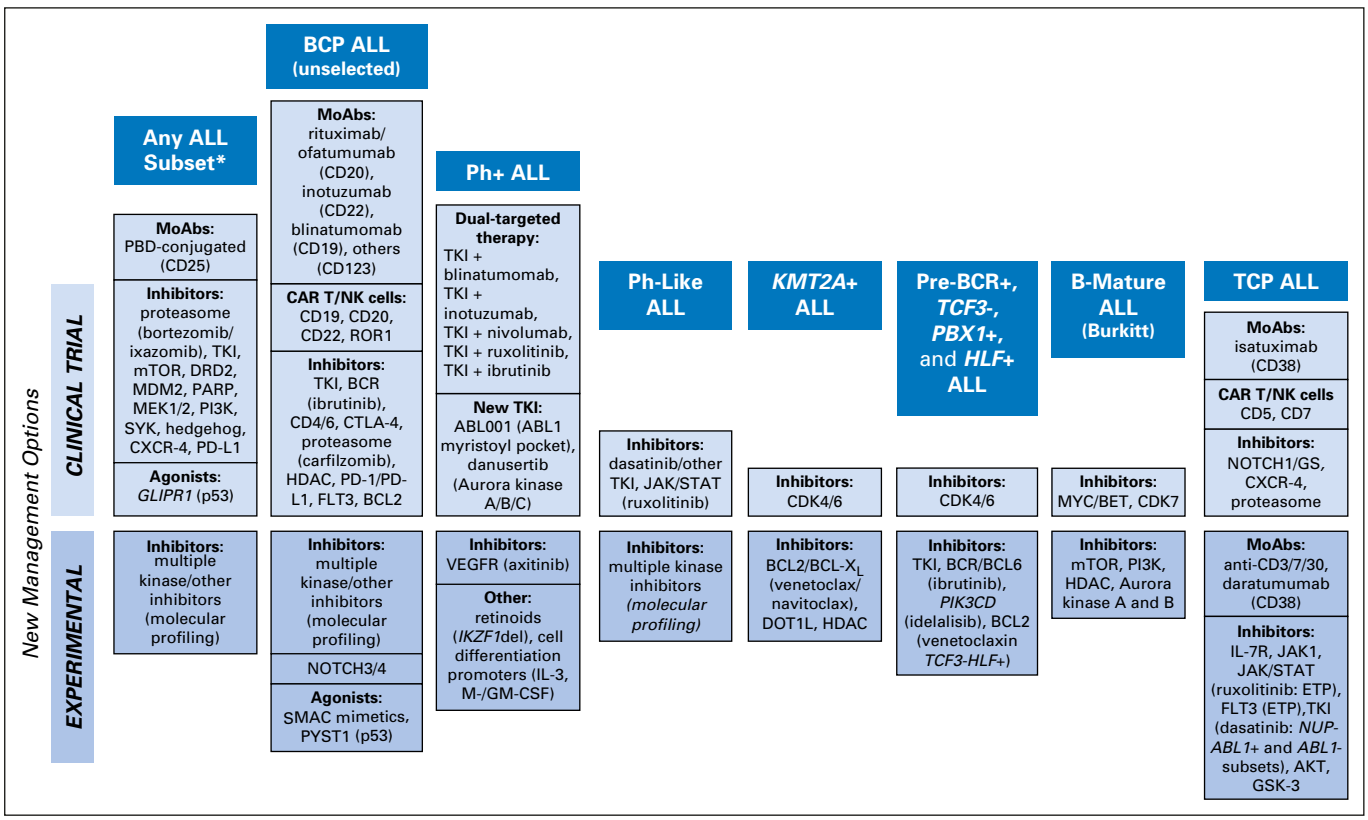

Fig 2. Subset-specific approaches with new therapeutics in adult ALL. Clinical and preclinical experimental approaches with new management options for adult ALL and subsets. Clinical trial evidence extracted from ClinicalTrials.gov repository, accessed April 2017. ALL, acute lymphoblastic leukemia; CAR, chimeric antigen receptor; BCP, B-cell precursor; MoAb, monoclonal antibody; NK, natural killer; PBD, pyrrolobenzodiazepine; TCP, T-cell precursor; TKI, tyrosine kinase inhibitor. (*) By trial eligibility

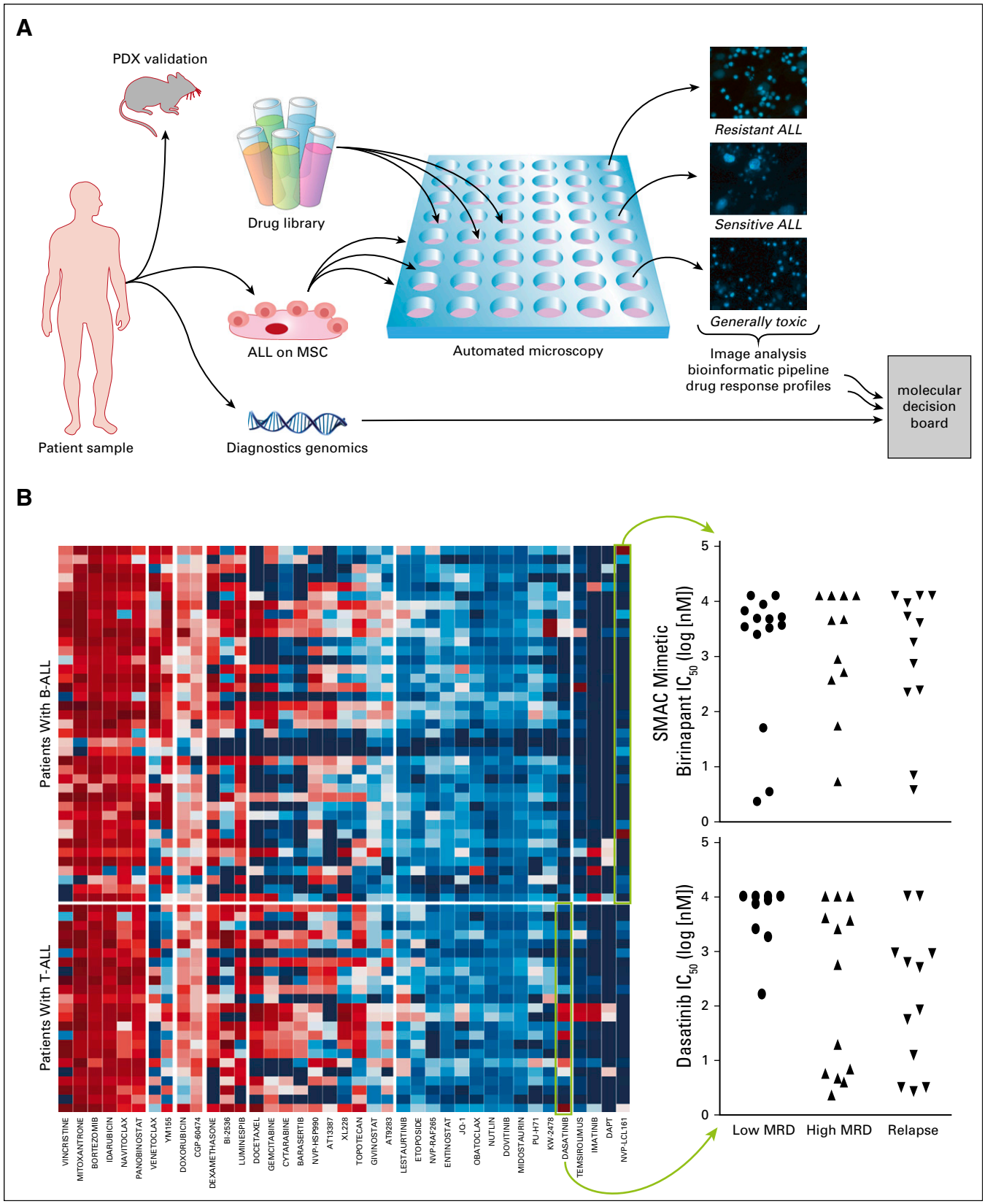

Fig 3. Drug response profiling of primary patient samples. (A) Workflow for phenotypic screens of cocultures of primary ALL cells on human MSCs using large-scale automated microscopy. Generation of PDXs provides a renewable source of representative ALL cells for mechanistic research but may also be invaluable for deeper coclinical validation experiments depending on the clinical situation. (B) Example of drug response profiling output. IC_{50} values on the basis of (continued on next page)

of drug response profiling with the aims of avoiding unnecessary toxicity of inappropriate salvage regimens and improving responses in selected subgroups.

Functional Drug Screening for Molecularly Unclustered ALL

The usefulness of functional drug screening is being explored in patients with ALL not included in specific molecular clusters. For example *BCL2*-dependent ALL was identified by screening PDX models for sensitivity to BH3 mimetics, including venetoclax,[75,77,85,94,95] and drug combinations established to overcome resistance.[75,96] Similarly, selective sensitivity to alternative RIP-1–dependent cell-death pathways (eg, necroptosis by SMAC [second mitochondrial-derived activator of caspases] mimetics) not exploited by current antileukemic agents were discovered.[80,97] PDX models have also been used to elucidate the critical dependence on altered metabolic function.[98-100] This underscores the importance of cross-referencing drug responses over many samples in a structured database to establish the effective and expected dose-response range for relevant outliers (ie, drug-sensitivity patterns not predicted by the molecular ALL subset).

NEW MANAGEMENT OPTIONS WITH IMMUNOTHERAPEUTICS

Rituximab

In BCP ALL, the expression of CD20 confers a poor prognosis.[101] Rituximab, a chimeric anti-CD20 antibody, was evaluated in combination with chemotherapy for untreated patients with Ph− CD20+ BCP ALL. At the MD Anderson Cancer Center (MDACC), rituximab was added to the first four courses of the hyper-CVAD (cyclophosphamide, vincristine, doxorubicin) regimen.[44] The results demonstrated an improved CR duration, a lower relapse rate, and an improved OS, but only in patients younger than 60 years as compared with historical controls (70% *v* 38%, $P < .001$; and 75% *v* 47%, $P = .003$). Comparable data were produced by the German adult ALL Study Group.[45] The French-Belgian-Swiss Group for Research on Adult ALL evaluated the addition of rituximab in a phase III study using a pediatric-inspired regimen[13]: Patients 18 to 59 years old received 16 to 18 rituximab doses, resulting in improved 2-year EFS from 52% to 65% ($P = .004$) due to a decreased relapse rate with no increase in toxicity.

Blinatumomab

New antibody constructs have shown promise for R/R ALL.[102] Blinatumomab, a bispecific T-cell engager construct, received US Food and Drug Administration and European Medicines Agency approval. Blinatumomab simultaneously targets CD19 (present on most BCP ALL cells) and CD3 (present on cytotoxic T cells) and acts to bring ALL cells into proximity of T cells, which are capable of tumor eradication. In a phase II study,[38] 189 adult patients with Ph− R/R BCP ALL received blinatumomab with 43% (n = 81 of 189) of them achieving CR or CR with defective hematologic recovery, and 40% of responders able to successful transition to allogeneic HCT Importantly, 60 of 73 evaluable patients with CR (82%) achieved MRD negativity. Results were similar in the phase III trial, with a 44% CR or CR with defective hematologic recovery rate in the blinatumomab arm compared with 25% in patients receiving chemotherapy,[39] and a 76% rate compared with 48% in patients whose disease turned MRD negative. Although generally well tolerated, grade 3 or higher cytokine release syndrome (CRS) and neurologic toxicity was seen in 4.9% and 9.4% of patients, respectively. Blinatumomab was tested as a single agent in patients with R/R Ph+ ALL; it induced a CR rate of 36% associated with 88% MRD-negative status[40] and, in Ph− MRD-positive ALL, achieved an excellent response rate of 78%, with prolonged survival, occasionally without HCT.[36,103] Resistance mechanisms include a defective T-memory or regulator-cell response, PD1/PD-L1 overexpression,[104] and emergence of CD19-negative subclones.[105]

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (INO) is an anti-CD22 antibody conjugated to calicheamicin; it is in late clinical development. A phase I/II study demonstrated a CR/ incomplete hematologic recovery rate of 68%, with 84% of responding patients achieving MRD negativity.[53] In a recent phase III trial, INO was superior to salvage chemotherapy for R/R ALL. Among the first 218 patients randomly assigned to treatment arm, 81% of those assigned to INO achieved CR, compared with 29% who received the standard of care, with a higher percentage of MRD-negative cases (78% *v* 28%; $P < .001$).[54] Duration of remission and OS favored INO, as confirmed by a long-term update reporting a 2-year rate of 22.8% versus 10% in standard-care group (P .001).[106] However, hepatotoxicity was more frequent in the INO group (51% *v* 34%), including incidence of sinusoidal obstruction syndrome (13% *v* < 1%). Although most of the cases occurred after HCT, sinusoidal obstruction syndrome developed in five patients (3%) receiving INO therapy alone.[107] Given the proven efficacy of this compound on these studies, INO is being combined with chemotherapy in the frontline setting. Using a mini-hyper-CVD (cyclophosphamide, vincristine, dexamethasone) regimen with INO in elderly patients, 47 of 48 evaluable patients (98%) achieved a CR/incomplete hematologic recovery (n = 35 CR), coupled with flow-cytometric MRD-negative status in 76%. Two-year progression-free survival and OS were 52% and 66%, respectively.[56,108]

Chimeric Antigen Receptor T Cells

Cellular immunotherapy with CD19-directed chimeric antigen receptor (CAR) T cells represents another promising approach for R/R disease. Anti-CD19 CAR T cells have been the most

(Continued). dose-response curves with eight datapoints after 72-hour exposure of ALL cells to a selection of drugs are shown as a heatmap (red responses in the nanomolar range; deep blue represents resistance in the 10-μM range). Two examples of individual strong activity to the SMAC mimetic birinapant and to dasatinib are provided, with validation in an extended set of ALL PDX. ALL, acute lymphoblastic leukemia; B-ALL, B-cell (or Burkitt) acute lymphoblastic leukemia; IC_{50}, half maximal inhibitory concentration; MRD, minimal residual disease; MSC, mesenchymal stromal cell; NK, natural killer; PDX, patient-derived xenograft; SMAC, second mitochondrial-derived activator of caspases; T-ALL, T-cell acute lymphoblastic leukemia.

extensively studied in trials using second-generation receptors, which comprise three components: an extracellular antigen-recognition domain derived from the single-chain variable fragment of a monoclonal antibody, an intracellular signaling domain (the CD3z chain from the T-cell receptor), and a costimulatory domain (most commonly, 4-1BB or CD28).[109-111] Initial phase I/II studies using the CTL019 construct reported a 90% CR rate in 30 patients (n = 25 children, n = 5 adults).[110] In addition, 88% of the patients who achieved a CR were MRD negative. Responses were durable, with seven relapses and 19 ongoing remissions (2 to 24 months) and with 15 patients receiving no additional therapy. High rates of CAR T-cell persistence (68%) and associated B-cell aplasia was reported at 6 months. In collaboration with Novartis, CTL019 was administered to 75 children and young adults, with 81% achieving CR and concurrent MRD-negative status. At a median follow-up of 10.6 months, 29 remained in CR. One-year EFS and OS were 50% and 76%, respectively.[60] This led to the approval of tisagenlecleucel (Kymriah; Novartis, Basel, Switzerland), the first CAR product in the United States.

The outcomes in adult patients treated with CAR T cells has been less impressive, with median EFS and OS of 6.1 months and 12.9 months, respectively.[63] CAR T cells but not natural killer cells[112] could also be effective against CNS leukemia.[113] Although anti-CD19 CAR T cells can generate rapid and impressive responses, therapy is associated with a unique set of severe adverse effects. The two major toxicities include CRS and neurotoxicity. In the CTL019 study, all patients experienced signs and symptoms of CRS, with eight of 30 patients requiring transfer to the intensive care unit.[110] Fortunately, tocilizumab, an anti-IL6 receptor antibody, was found effective and has become the mainstay of management for severe CRS, because it is well tolerated and rapidly effective in most cases. Current approaches include optimization of the CAR T-cell product in defined proportions of CD4 and CD8 T-cell subsets, development of humanized CARs, CARs with two costimulatory domains, allogeneic CARs, and CARs against other antigens such as CD22.

NEW MANAGEMENT OPTIONS IN MOLECULARLY DEFINED ALL SUBSETS

Ph + ALL

Outcome of Ph+ ALL was dramatically improved by TKIs.[114-118] Single-agent imatinib or dasatinib plus corticosteroids therapy, pioneered by the Gruppo Italiano Malattie Ematologiche dell'Adulto[114,119] induced CR virtually in all patients without risk of induction death. With TKI-chemotherapy combinations, CR rate exceeded 95% but death occurred in 2% to 7% of the cases. In a randomized trial from the French-Belgian-Swiss Group for Research on Adult ALL,[116] a combination of de-escalated chemotherapy plus TKI resulted in less induction toxicity and noninferior CR and survival results compared with standard chemotherapy plus TKI. In a MDACC study, ponatinib combined with hyper-CVAD led to an excellent 83% 2-year OS, even without HCT.[115] In elderly and/or frail patients (median age, 68 years; range, 27 to 85 years), ponatinib monotherapy resulted in 87.5% 1-year OS, associated with a 45% molecular response rate in a Gruppo Italiano Malattie Ematologiche dell'Adulto study.[120] Postremission consolidation is still based on intensive chemotherapy (plus TKI) and HCT, when feasible. This "global" strategy led to survival rates approaching 50%, thus meaning we still need to improve.

Chemotherapy-free trials with TKI-immunotherapy combinations (eg, TKI-blinatumomab) are ongoing (Clinicaltrial.gov identifier: NCT02744768) and will clarify the place of this antibody construct especially in eradicating MRD. As for other ALL subsets, MRD persistence is associated with recurrence, whereas its negativity may identify patients with favorable prognosis in whom the indication for HCT could be reconsidered to spare morbidity and mortality.[25] With these premises, relapse remains relatively frequent and is often sustained by mutations, the most deleterious being T315I. New, potentially active agents include axitinib,[73] a vascular endothelial growth factor receptor inhibitor active in T315I-mutant disease; a new TKI, danusertib[121]; and ABL001 (asciminib),[122] a novel allosteric TKI that binds to the myristoyl pocket of ABL1, causing an inactive kinase conformation (Clinicaltrial.gov identifier: NCT02081378, a phase I trial for patients intolerant/refractory to standard TKI). Notably, a drug-sensitivity testing platform[123] allowed the identification of axitinib as a selective inhibitor of the T315I mutation.[73]

As for combinatory studies, of interest is the simultaneous administration of dasatinib, ruxolitinib, and dexamethasone, which research in vitro was shown to restore cytokine dependency, inhibit STAT3 and STAT5 activation, and prevent leukemia initiating cell growth and acquisition of mutations (Clinicaltrial.gov identifier: NCT02494882),[124] and the combination of ruxolitinib with nilotinib (Clinicaltrial.gov identifier: NCT01914484). In cases with IKZF1 impairment, retinoids can induce *IKZF1* re-expression, stimulate cell maturation. and restore in vitro TKI sensitivity.[125] Moreover, promoters of myelomonocytic differentiation can successfully induce Ph+ ALL cells into nonleukemic monocytes/macrophages.[126]

Ph-Like ALL

The Ph-like subgroup, initially identified by gene expression profiling, accounts for approximately 20% of adult BCP ALL cases, with a prevalence in AYA. These cases are characterized by a transcriptional profile similar to that of Ph+ ALL but lacking the t(9;22)/*BCR-ABL1* rearrangement.[127-130] Instead, the underlying genomic lesions are heterogeneous, making its recognition difficult and uneven among trials. *CRLF2* rearrangements are detected in approximately 50%; lesions affecting ABL class genes (ie, *ABL1*, *ABL2*, *CSF1R*, *PDGFRA*, *PDGFRB*) in approximately 10%; and JAK/STAT genes (ie, *JAK1-3*, *IL7R*, and *CRLF2* mutations) in $< 10\%$. Rearrangements in other TKs and the *EPOR* gene are extremely rare. *IKZF1* deletions occur in $\leq 80\%$ of cases. Patients with Ph-like ALL have a poorer outcome when compared with other BCP ALL subsets and it is not yet clear whether they should receive an HCT up front, on the basis of MRD persistence only.[128,131] Given the activated kinome profile, several groups are testing the combination of TKIs with chemotherapy. Children's Oncology Group is testing ruxolitinib in patients with *CRLF2* rearrangements and/or JAK-STAT deregulation (Clinicaltrial.gov identifier: NCT02723994) or dasatinib in untreated patients (Clinicaltrial.gov identifier: NCT02883049), while MDACC is testing these drugs in pretreated patients (Clinicaltrial.gov identifier: NCT02420717) with disappointing results.[132] Other experimental

approaches use a variety of inhibitors on the basis of the individual molecular profile. The pan-TKI ponatinib could be effective regardless of the underlying genetic lesion.[133]

MLL-*Rearranged ALL*

The prognosis of t(4;11)/*KMT2A-AFF1*+ and other *MLL*-rearranged ALLs is poor and could be improved by new targeted approaches. *MLL* (ie, *KMT2A*) rearrangements are associated with high levels of H3K79 methylation catalyzed by the DOTL1 enzyme. Therefore, DOT1L inhibitors, particularly EPZ-5676 (pinometostat), have been tested in R/R cases (Clinicaltrial.gov identifiers: NCT02141828 and NCT01684150) in both pediatric and adult cohorts.[134] Furthermore, *MLL*-rearranged cases express high levels of Bcl-2, BAX, and BIM, but relatively low levels of BCL-XL and MCL-1, a mechanism directly sustained by *KMT2A* rearrangement on *BCL2* expression and partly mediated by interaction with H3K79me2/3. As a consequence, in vitro and xenograft model studies showed that the Bcl-2 inhibitor venetoclax induces cell killing in synergy with chemotherapy.[85,135,136] In addition, histone deacetylase inhibitors (HDACis) can exert synergistic activity with cytarabine by repressing cytidine deaminase.[137]

TCF3-*Rearranged ALL*

TCF3-PBX1+ ALL associated with t(1;19) represents approximately one-half of the cases of the newly recognized pre–B-cell receptor (BCR)+ subset and is characterized by a favorable outcome with intensive treatment. These cases could be targeted by dasatinib because they overexpress many TKs,[138] including the BCR-dependent TK ROR1[139] and Mer TK, which correlates with risk of CNS progression,[140] by idelasib due to the high levels of *PIK3CD*[141] and ibrutinib via downmodulation of the pre-BCR signaling on *BCL6*.[98,142,143]

Instead, *TCF3-HLF*+ ALL is a very HR subset associated with t(17;19), often with high levels of *BCL2* expression recalling venetoclax as a potential therapeutic compound.[77] Drug response profiling predicted robust resistance to conventional drugs and confirmed a unique sensitivity to venetoclax. Combination therapy with dexamethasone, vincristine, and venetoclax in PDX from two patients maintained CR for up to 1 year.[77]

Hypodiploid BCP ALL

Hypodiploid ALL is a rare, poor prognostic subtype including near-haploid (24 to 31 chromosomes), low hypodiploid (32 to 39 chromosomes), and high hypodiploid (40 to 43 chromosomes) ALL.[144] RAS and PI3K pathways are frequently altered in near-haploid ALL, whereas TP53 and IKZF members are often mutated in low hypodiploid ALL, pinpointing functional targeting using PI3K and PI3K/mTOR inhibitors.[144,145] Germline mutational screening of *TP53* should always be performed in these cases.

Other BCP ALL Subsets

Many other actionable deletions or mutations are emerging in BCP ALL (and sometimes TCP ALL).[127,144,146-148] These involve pathways affecting lymphoid development, cell cycle, regulation of transcription, lymphoid and RAS signaling, epigenetic modifications, cytokine receptors, TK expression, and the JAK/STAT phosphorylation system (Tables 3 and 4). Focus is now on downstream members of the RAS pathway, namely the MEK and PI3K inhibitor BEZ235 (Clinicaltrial.gov identifier: NCT01756118), the allosteric MEK1/2 inhibitor selumetinib, trametinib, steroids, and FLT3 inhibitors (ie, lestaurtinib, midostaurin, and quizartinib, all being evaluated in phase I-II and III trials, respectively; Clinicaltrial.gov identifiers: NCT 00866281, NCT00557193, and NCT01411267). Among epigenetic regulators, the HDACis vorinostat and panobinostat are being investigated in phase I-II trials for R/R disease (Clinicaltrial.gov identifiers: NCT01483690, NCT01321346, and NCT01321346); however, there have been reports of toxicity.[148a] JAK2 inhibitors (ruxotilinb) and Bcl-2 inhibitors might be used in cases harboring target mutations. SMAC mimetics, directly acting on apoptosis and necroptosis pathways, proteasome inhibitors, and checkpoint inhibitors, have shown in vitro activity and are being studied (Supplemental Data). The role of inhibitors of molecules involved in interaction with the marrow niche (ie, NOTCH3 and NOTCH4) is still largely undetermined[149]; targeting SCD and SPP1 genes and proteins[150] and vascular endothelial growth factor A (with bevacizumab) could be useful against CNS leukemia.[151]

B-ALL (mature B/Burkitt leukemia)

MYC rearrangements are the hallmark of B-ALL, leading to escape from cell-cycle control and a high proliferative rate. Thus, inhibition of *MYC*-related pathways is an attractive option for refractory disease. MYC inhibitors JQ1 and THZ1 target MYC/MAX heterodimerization and CDK7 (THZ1), whereas dependency of MYC activation on multiple enhancers and so-called super-enhancers, such as a BET proteins and PI3K, are targeted by mTOR or HDACis, Aurora kinase A and B, and other BET inhibitors (namely, I-BET 151, GSK525762, and CPI-0610).[152] New phase I trials are underway.

TCP ALL

TCP ALL accounts for approximately 25% of ALL cases and is further classified according to maturation stage (ie, early-, cortical-, and mature T). With modern pediatric-based regimens adopting MRD or risk-oriented intensification, outcome of TCP ALL may be excellent and superior to that of BCP ALL. Among actionable molecular lesions,[153] the most frequent is *NOTCH1* mutation. NOTCH1 and the strictly associated γ-secretase inhibitors were tested in late-stage disease, with some responses of short duration and considerable gut toxicity.[154] The best study reported one CR and an overall 32% response rate in 25 patients with relapsed disease.[155] Theoretically, targeting NOTCH1-related overexpression of chemokine receptor CCR7 and its ligand CCL19 could reduce the risk of CNS disease.[156] Many other targeting agents are being investigated, often in combination, like γ-secretase inhibitors and AKT inhibitors to revert glucocorticoid resistance[157-159] (Fig 2; Tables 3 and 4). Moreover, induction of T-cell receptor signaling led to apoptosis mimicking thymic negative selection,[160] and targeting contact structures with the marrow microenvironment (ie, CXCR4, CXCL12) reduces proliferation and the propagation potential of leukemic stem cells.[161,162] Notably, PDX and drug screening models identified a subset of refractory T-ALL responsive to dasatinib in a nanomolar range,

correlating with strong responses in vivo after resistance to multiple other treatments.[75]

ETP ALL

This peculiar diagnostic subset (with weak or absent CD5 expression and mixed T-lympho/myeloid phenotype and genotype) is associated with poor outcome unless treated with very intensive MRD-based chemotherapy or HCT in first CR.[163] ETP ALL is characterized by abnormalities typically observed in myeloid disorders, including mutations in RUNX1, ETV6, GATA3, IDH1, IDH2, DNMT3A,[164,165] and the JAK/STAT pathway. In an experimental PDX model, ETP ALL was exquisitely sensitive to ruxolitinib, which abrogated IL-7–induced STAT5 phosphorylation.[166] Furthermore, FLT3 inhibitors might be considered, because mutations are detected in approximately 35% of cases.[167]

FUTURE DIRECTIONS

We are entering an intensive phase of clinical investigations with new agents. To take advantage of these new treatment options, we will have to gradually shift from R/R ALL to the frontline setting, where treatment resistance is less likely to occur.[168] We will certainly need to develop solutions to integrate functional and genomic data for reference bioinformatics tools supporting clinical decisions, in accordance with studies in patients with cancer including acute myeloid leukemia and childhood ALL.[169-171] For the exploration of individualized or subset-specific treatment forms, it will be crucial to design prospective clinical studies with modular elements to evaluate optimal strategies for chemotherapy,[172] immunotherapy, and combinations of molecularly targeted drugs and synergistic drug pairs,[74,173] and detect activity in the early clinical trials more rapidly to pilot subsequent therapeutic developments.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHOR CONTRIBUTIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

New Approaches to the Management of Adult Acute Lymphoblastic Leukemia

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Appendix

Table A1. Results of Recent Trials With Pediatric Elements for Adolescent and Young Adult Patients and Adult Patients With Ph− ALL

Study*	No.	Age (years), mean or median (range)†	CR (%)	DFS (%)	CRD (%)	OS (%)	EFS (%)	FUP (years)‡	Annotations
JALSG ALL-202U (Sakura T, et al: Blood 120, 2012 [abstr 1464])	138	19 (16-24)	97	71	—	74	—	4	Allo-HCT in t(4;11)+
UKALL 2003 (Hough R et al, Br J Haematol 172:439-451, 2015)	229	16-24	97	—	—	76.4	72.3	5-y	CR rate calculated upon induction failures (2.6%); EFS correlating with MRD risk class ($P = .0001$)
GMALL 05/93 07/03 (Goekbuget N, et al: Blood 122, 2013 [abstr 839])	642 887	15-35	88 91	—	49 61	46 65	—	5	07/03: intensified Peg-Asp, dexamethasone, and HD consolidation; allo-HCT in HR or MRD+; $P < .05$ for CRD and OS
GIMEMA 1398 [Testi AM, et al: Haematologica 99:259, 2014 (suppl 1; abstr S725)]	61	18-35	98	—	—	72.3	—	2	—
GMALL 07/03; (Goekbuget N, et al: Blood 116, 2010 [abstr 494])	1,226	35 (15-55)	91	—	61 (SR cohort 1) 74 (SR cohort 2) 60 (AYA cohort 1) 78 (AYA cohort 2)	60 (cohort 1) 67 (cohort 2) 68 (SR cohort 1) 80 (SR cohort 2) 77 (AYA cohort 1) 86 (AYA cohort 2)	—	3	Peg-Asp 1,000 and 2,000 UI/m^2 (cohort 1 and cohort 2), × 7 in SR; allo-HCT if HR or MRD+; $P <$ .05 for CRD and OS in SR cohort 2
MDACC augmented BFM (Rytting ME, et al: Am J Hematol 91:819-823, 2016)	106	22 (13-39)	93	—	60	53	—	5	Allo-HCT in t(4;11)+ or MRD+; MRD- *v* MRD+ on days 29-84: OS 75% *v* 40%-22% ($P = .004$); CRD 64%-63% *v* 33%-26% ($P = .017$); CRD/OS comparable to hyper-CVAD
US Intergroup C10403 (Stock W, et al. Blood 124, 2014 [abstr 796])	296	24 (17-39)	—	—	—	78	66	2	Ph-like signature: EFS, 52% *v* 81% ($P = .04$); MRD-day 28: EFS, 100% ($P <$ .0006)
NOPHO ALL2008 (Toft N, et al: Leukemia 32: 606-615, 2018)	221	26 (18-45)	—	—	—	—	73 87 (SR) 78 (IR) 66 (HR) 61 (HCT)	5	Allo-HCT if day 29 MRD > 5% or day 79 ≥ 0.1%
Saudi Arabia/Egypt (Alabdulwahab AS, et al: Leuk Res 60:58-62, 2017)	73	< 50 (37 ≥ 21)	91 (D), 84 (H)	71 (D) 42 (H)	—	73 (D) 48.5 (H)	—	3	Comparing D (n = 43) with H (n = 30); better OS with D protocol ($P = .04$)
DFCI 01-175[12]	82	28 (18-50)	78	66 (B) 87 (T)	—	68 (B) 76 (T)	—	4	Allo-HCT in t(4;11)+, +8, t(9;12)+; intensified L-Asp
DFCI 06-254 (DeAngelo DJ, et al: Blood 126:80, 2015 [abstr])	89	32 (18-50)	89	80	—	75	—	3	Intensified Peg-Asp (toxicity reduced from 2,500 to 2,000 UI/m^2 and from 16 to 10 doses)
GRAALL 2003[11]	225	31 (15-60)	93.5 53 (> 45 y)	—	61 (15-45 y) 53 (> 45 y)	60 64 (15-45 years) 47 (> 45 years)	55	3.5	Allo-HCT in t(4;11)+, HR or MRD > 10^{-2}, age ≤ 55 years
GRAALL 2003, 2005 (Beldjord K, et al: Blood 123:3739-3749, 2014)	955	35 (15-60)	92	—	—	57	—	5	Allo-HCT in HR MRD and oncogenetics significantly affecting risk of relapse

(continued on following page)

Table A1. Results of Recent Trials With Pediatric Elements for Adolescent and Young Adult Patients and Adult Patients With Ph− ALL (continued)

Study*	No.	Age (years), mean or median (range)†	CR (%)	DFS (%)	CRD (%)	OS (%)	EFS (%)	FUP (years)‡	Annotations
RAALL 2009 (Parovichnikova EN, et al: Blood 124:3662, 2014 [abstr])	250	30 (15-60)	87	69.3 71.5 (< 30 y) 61.2 (≥ 30 y)	—	65.6 73.6 (< 30 years) 52.7 (≥ 30 years)	—	4	Allo-HCT in HR
PETHEMA HR-11 (Ribera J-M, et al: Blood 128:180, 2016 [abstr])	126	30-60	86	40 (L-Asp) 58 (Peg-Asp)	—	60 (L-Asp) 57 (Peg-Asp)	—	3	HR only, for allo-HCT if MRD+; comparable MRD response L-Asp *v* Peg-Asp
NILG 10/07 (Bassan R, et al: Blood 128:176, 2016, [abstr])	163	41 (17-67)	87	55 48 (B) 61 (T)	—	52 48 (B) 74 (T)	—	5	Allo-HCT in MRD+ or very HR; MRD highly predictive of outcome
JALSG ALL 202-O (Sakura T, et al: Leukemia 32: 626-632, 2018; 2017)	344	24-65	86	42	—	52	—	5	Phase III trial (MTX 0.5 *v* 3 g/m^2: DFS 32% *v* 56%; *P* = .015)

NOTE. Dashes indicate no data.

Abbreviations: ALL, acute lymphoblastic leukemia; allo-HCT, allogeneic hematopoietic cell transplantation; B, B-precursor ALL; CR, complete remission; CRD, duration of complete remission; D, Dana Farber consortium protocol; DFCI, Dana Farber Cancer Institute; DFS, disease-free survival; EFS, event-free survival; FUP, follow-up; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; GMALL, German Multicenter Group for Adult ALL; GRAALL, Group for Research on Adult ALL; H, hyper-CVAD protocol; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; HD, high dose; HR, high risk; IR, intermediate risk; JALSG, Japan Adult Leukemia Study Group; L-Asp, L-asparaginase; MDACC, MD Anderson Cancer Center; MRD, minimal residual disease; MTX, methotrexate; NILG, Northern Italy Leukemia Group; NOPHO, Nordic Society of Pediatric Haematology and Oncology; OS, overall survival; Peg-Asp, pegylated asparaginase; Ph, Philadelphia chromosome; PETHEMA, Programa Español de Tratamientos en Hematologia; RAALL, Russian Adult ALL Group; SR, standard risk; T, T-precursor ALL.

*Studies are ordered by increasing patient age. There were a minimum of 50 patients; outcome estimates at ≥3 years except GIMEMA 1398 and US Intergroup C10403, for which 2-year results are reported.

†Age given as mean (range) or range.

‡Number of years of CR/DFS/CRD/OS/EFS estimates.

Table A2. Registered or ongoing trials (n = 25) With Innovative Therapeutics For Relapsed/Refractory, MRD-Positive or Untreated Adult B-Precursor Ph− ALL*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/ Outcome Measures
Relapsed/refractory						
Albert Einstein College of Medicine/11-04-146	NCT01408160	≥ 18 (18)	Deglycosylated ricin A chain-conjugated CD19/CD22 immunotoxins	Yes (cytarabine)	I	Dose-limiting toxicity
University of California/UCDCC 266	NCT02997761	≥ 18 (20)	Ibrutinib (BCR inhibitor), blinatumomab (CD19 × CD3 bispecific antibody)	No	II	CR rate
ADC Therapeutics/ADCT-402-102	NCT02669264	≥ 12 (60), any subset	ADCT-42 (CD19)	No	I	Dose-limiting toxicities and maximum tolerated dose
Amgen/20130265	NCT02412306	≥ 18 (57)	Blinatumomab	No	I/II	Dose-limiting toxicities and CR rate
MDACC/2015-0870	NCT03094611	≥ 12 (48), CD22+ ALL	Inotuzumab (calicheamicin-conjugated CD22 immunotoxin)	No	II	CR rate
NCI/COG-ALL1331	NCT02101853	1-30 (598), including AYA	Blinatumomab	Yes (intensive)	III	Disease-free survival
University of Ulm/AMLSG 23-14	NCT02310243	≥ 18 (50), *MLL* rearranged	Palbociclib (CDK4/CDK6 inhibitor)	No	I/II	Adverse events/maximum tolerated dose
Affimed GmbH/AFM11-102	NCT02848911	≥ 18 (50), CD19+, any subset	AFM11 (CD19 × CD3)	No	I	Maximum tolerated dose
NCI/10030	NCT02879695	≥ 16 (30), CD19+, any subset	Blinatumomab, Nivolumab (anti-PD-1), ipilimumab (CTLA-4 inhibitor)	No	I	Adverse events, toxicities, maximum tolerated dose
MDACC/2014-0521	NCT02420717	≥ 10 (92), Ph-like, short -	Ruxolitinib (*JAK2* inhibitor)/ Dasatinib	Yes (hyper-CVAD)	II	CR rate
COG	NCT02723994	≥ 10 (170); Ph-like	Ruxolitinib (*JAK2* inhibitor)	Yes (modified aBFM regimen)	II	Event-free survival at 3 years
NCI	NCT02883049	1-31 (5437), Ph-like	Dasatinib	Yes	III	Outcome description
SWOG/S1312	NCT01925131	≥ 18+ (38), CD22+, any subset	Inotuzumab	Yes (CVP)	I	Maximum tolerated dose
Xencor/XmAb14045-01	NCT02730312	≥ 18 (66), CD123+, any subset	XmAb14045 (CD123 × CD3)	No	I	Maximum tolerated dose
Janssen Research and Development/CR107241	NCT02454270	≥ 18 (221), any type (including B-cell lymphoma)	Duvortuxizumab (CD19 × CD3 dual-affinity retargeting protein)	No	I	Recommended phase II dose/overall response rate
MRD positive						
MDACC/2014-0844	NCT02458014	≥ 18 (40), MRD CD19+, any subset	Blinatumomab	No	II	Relapse-free survival
Johann Wolfgang Goethe University Hospital/GMALL-MOLACT1-BLINA 2015-000733-76	NCT03109093	≥18 (30), B-precursor MRD ALL (also after prior HCT)	Blinatumomab	No	II	MRD response, continuous CR, relapse-free survival
Untreated						
ECOG/E1910	NCT02003222	30-70 (360)	Blinatumomab	Yes (intensive)	III	Improved OS
NCI/S1318	NCT02143414	≥ 65 (44), including Ph and Ph-like	Blinatumomab, Dasatinib	Yes	II	Improved OS
MDACC/2010-0091	NCT01371630	≥ 60 (206)	Inotuzumab	Yes (low intensity)	I/II	Maximum tolerated dose
NCI/ALL1131	NCT02883049	1-30 (5437), including AYA, HR or Ph-like	Dasatinib (Ph-like)	Yes (intensive BFM-type)	III	Improved DFS
University of California/UCDCC 246	NCT02293109	18-64 (18)	Carfilzomib	Yes (hyper-CVAD)	I	Safety, tolerability, dosing
DFCI/14-200	NCT02228772	51-75 (28)	Ixazomib (20 S proteasome inhibitor)	Yes	I	Safety and maximum tolerated dose
MDACC/2014-0845	NCT02877303	≥ 14 (60)	Blinatumomab	Yes (hyper-CVAD)	II	Relapse-free survival
MDACC/2010-0708	NCT01363128	Any age (80)	Ofatumumab (CD20)	Yes (hyper-CVAD)	II	ALL control and safety
MDACC/2014-0396	NCT02419469	12-30 (100), including AYA	Ofatumumab (CD20)	Yes (augmented BFM)	II	Relapse-free survival
Unspecified disease status						
Regeneron Pharmaceuticals/ *R*-1979-ONC-1504	NCT02651662	≥ 18 (100), CD20 ALL (any subset)	REG2810 (anti-PD-1), REGN1979 (CD20 × CD3)	Not reported	I	Treatment-emergent adverse events

Abbreviations: aBFM, augmented Berlin-Frankfurt-Münster; ALL, acute lymphoblastic leukemia; AYA, adolescents and young adults; BCR, B-cell receptor; BFM, Berlin-Frankfurt-Münster; COG, Children's Oncology Group; CR, complete remission; CVP, cyclophosphamide, vincristine, prednisone; CR, complete response; DFCI, Dana Farber Cancer Institute; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; MDACC, MD Anderson Cancer Center; MRD, minimal residual disease; NCI, National Cancer Institute; OS, overall survival; Ph, Philadelphia chromosome; SWOG, Southwest Oncology Group.

*Ph+ ALL is included when "any subset" is added (extracted from ClinicalTrials.gov website, accessed April 2017).

Table A3. Registered or Ongoing Trials (n = 7) With Innovative Therapeutics for Relapsed/Refractory or Untreated Adult B-Precursor Ph+ Acute Lymphoblastic Leukemia*

Institution/Trial Denomination	ClinicalTrials.gov identifier	Patient Age, Years (No.)	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/Outcome Measures
Relapsed/refractory						
Northwestern University/NU 15H13	NCT02819804	≥ 18 (22)	Nivolumab (with dasatinib)	No	I	Dose-limiting toxicity
Novartis Pharmaceuticals/ CABL001X2101	NCT02081378	≥ 18 (250)	ABL001 (selected allosteric ABL1 inhibitor)	No	I	Dose-limiting toxicity
Danusertib	EudraCT number 2007-004070-18	≥ 18 (37)	Danusertib	No	I	Dose-limiting toxicity
MDACC/2014-0435	NCT02311998	≥ 18 (80), CD22+	Inotuzumab (with bosutinib)	No	I/II	Maximum tolerated dose
University Health Network Toronto/ OZM-051	NCT01914484	≥ 18 (32)	Ruxolitinib (with nilotinib)	No	I/II	Maximum tolerated dose/major cytogenetic response
Untreated						
GIMEMA/D-ALBA	NCT02003222	≥ 18 (60)	Blinatumomab (after dasatinib)	No	II	MRD negativity after induction at two cycles of blinatumomab
MSKCC/14-272	NCT02494882	≥ 40 (12) (patients with relapsed disease allowed)	Ruxolitinib (with dasatinib)	No	I	Clinical response
University of Utah/ HCI85188	NCT02815059	≥ 60 (24)	Ibrutinib (with dasatinib)	No	I	Adverse events

Abbreviations: GIMEMA; Gruppo Italiano Malattie Ematologiche dell'Adulto; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; MRD, minimal residual disease; Ph+, positive for Philadelphia chromosome.
*Extracted from ClinicalTrials.gov website, accessed April 2017.

Table A4. Registered or Ongoing Trials (n = 4) With Innovative Therapeutics for Relapsed/Refractory or Untreated Adult T-Precursor Acute Lymphoblastic Leukemia*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.)	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/ Outcome Measures
Relapsed/refractory						
Washington University/ 201606146	NCT02763384	≥ 18 (20)	BL-8040 (CXCR-4 inhibitor)	Yes (nelarabine)	II	Safety and tolerability
Eli Lilly and Co./14548	NCT02518113	≥ 2 (92, including adults)	LY3039478 (*NOTCH* inhibitor; with dexamethasone)	No	I/II	Dose-limiting toxicities/CR
Sanofi/ACT14596	NCT02999633	≥ 16 (39)	Isatuximab (CD38)	No	II	Objective response rate
Untreated						
NCI/AALL1231	NCT02112916	Age 2-30 (1,400), including AYA	Bortezomib	Yes (intensive, BFM-type)	III	Improved event-free survival

Abbreviations: AYA, adolescents and young adults; B, B-precursor ALL; BFM, Berlin-Frankfurt-Münster; CR, complete response; NCI, National Cancer Institute; T, T-precursor ALL.
*Extracted from ClinicalTrials.gov website, accessed April 2017.

Table A5. Registered or Ongoing Trials (n = 13) With Innovative Therapeutics for Relapsed/Refractory, MRD-Positive or Untreated Adult ALL, Unspecified Subset and/or Other Leukemias*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/ Outcome Measures
Relapsed/refractory						
ADC Therapeutics/301-002	NCT02588092	≥ 18 (60), CD25+ ALL	ADCT-301 (PBD-conjugated CD25 immunotoxin)	No	I	Dose-limiting toxicity
Children's Mercy Hospital/ MERCY01	NCT02535806	1-39 (10), including AYA	Bortezomib	Yes	II	Adverse events
OHSU Knight Cancer Institute/ IRB00007195	NCT01620216	≥ 18 (24), including nonlymphoid leukemia	Dasatinib or nilotinib or sunitinib or sorafenib or ponatinib (based on kinase inhibition profile obtained on primary patient samples)	No	II	Clinical activity (decrease of ≥ 25% in bone marrow blast counts)
Daiiki Sankyo/DS3032-A-U102	NCT02319369	≥ 18 (100), including nonlymphoid leukemia	DS302-b (*MDM2* inhibitor)	No	I	Maximum tolerated dose
Children's Hospital of Philadelphia/10-007444	NCT01162551	≤ 25 (17), including AYA; second/greater relapse)	Sirolimus (mTOR inhibitor)	Yes (oral methotrexate)	II	Efficacy and toxicity
NCI/150093	NCT02390752	3-35 (45), including AYA, nonlymphoid leukemia/other tumors)	PLX3397 (multitargeted TKI)	No	I/II	Determine phase II dose/antitumor activity
University of Washington/ 9226	NCT02551718	≥ 3 (15), including adults, nonlymphoid leukemias, prior exhaustion of two treatment lines	Various agents† (based on high-throughput drug sensitivity assay)	Various agents	Pilot	Feasibility within 21 days (drug combination)
NCI/COG ADVL1411	NCT02116777	1-30 (148), including AYA and solid tumors	Talazoparib (PARP inhibitor)	Yes (temozolomide)	I/II	Maximum tolerated dose and antitumor activity
MDACC/2014-0731	NCT02392572	≥ 18 (120), including nonlymphoid leukemias	ONC201 (DRD2 inhibitor)	No	I/II	Maximum tolerated dose
MDACC/2013-0116	NCT02089230	≥ 18 (57), including nonlymphoid leukemias, not suitable for standard therapy	MEK 162 (MEK inhibitor)	No	I/II	Maximum tolerated dose
MRD positive						
University of Washington/ 9458	NCT02767934	≥ 18 (21)	Pembrolizumab (anti-PD-L1)	No	II	MRD negativity
Gilead Sciences/GS-US-339-1560	NCT02404220	≥ 18 (35)	Entospletinib (SYK inhibitor)	Yes (vincristine, prednisone)	I	Adverse events and dose-limiting toxicities
Untreated						
Medical College of Wisconsin/ PRO25835	NCT02578511	≥ 18 (18)	Ixazomib	Yes (POMP-D maintenance)	I	Maximum tolerated dose

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group; MDACC, MD Anderson Cancer Center; MRD, minimal residual disease; NCI, National Cancer Institute; OHSU, Ohio State University; NCI, National Cancer Institute; PBD, pyrrolobenzodiazepine dimer; TKI, tyrosine kinase inhibitor.

*Extracted from ClinicalTrials.gov website, accessed April 2017.

†Afatinib, arsenic trioxide, axitinib, bexarotene, bosutinib, cabazitaxel, cabozantinib, carfilzomib, ceritinib, crizotinib, dabrafenib, dasatinib, erlotinib, everolimus, gefitinib, imatinib, lapatinib, nilotinib, pazopanib, ponatinib, rapamycin, regorafenib, romidepsin, ruxolitinib, sorafenib, sunitinib, temsirolimus, trametinib, tretinoin.

Table A6. Registered or Ongoing trials (n = 12) With Innovative Therapeutics After HCT Relapse and After, During or Before HCT in Adult ALL*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/ Outcome Measures
After HCT relapse						
MSKCC/11-038	NCT01430390	Any age (12), CD19+ BCP ALL or lymphoma	Expanded EBV-specific allogeneic T-cytotoxic cells	No	I	Safety/persistence of escalating doses of allogeneic modified T cells
Masonic Cancer Center, University of Minnesota/ HM2013-12	NCT01885897	≥ 18 (61), ALL and other leukemias	ALT-803 (IL-15 superagonist complex)	No	I/II	Safety/efficacy, toxicity, incidence of acute and chronic GvHD
Case Comprehensive Cancer Center/CASE1916	NCT03104491	16-75 (44), CD22+ BCP ALL	Inotuzumab ozogamicin (calicheamicin-conjugated anti-CD22)	No	I/II	Maximum tolerated dose, posttransplant relapse, response rate
After HCT						
University of Colorado, Denver/ NCI-2013-00824	NCT01841333	≥ 18 (28), ALL and AML	PF-04449913 (Hedgehog inhibitor)	No	II	RFS and remission duration
Sidney Kimmel Comprehensive Cancer Center/IRB00125679	NCT03114865	≥ 18 (12), CD19+ BCP ALL, HR and/or MRD+ before HCT	Blinatumomab	No	I	OSOS, DFS, MRD response
MDACC/2015-0576	NCT02807883	18-70 (30), BCP ALL, HCT beyond CR1 or MRD+	Blinatumomab	No	II	Feasibility, OS and PFS
Fate Therapeutics/PT-001	NCT02743351	18-70 (70), ALL and AML	ProTmune (FT1050/PGE2 inhibitor and FT4145/CXCR4 inducer, enhancing programmed T-cell alloreactivity and antitumoral properties)	No	I/II	Adverse event, acute GvHD CMV viremia and disease, febrile neutropenia
During or before HCT						
Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran/INCMNSZ REF 917	NCT02605460	18-60 (20), ALL and AML	CXCR-4 antagonist	Yes (busulfan, cyclophosphamide)	II	OS and DFS
Kiadis Pharma/CR-AIR-009	NCT02999854	18-70 (195), ALL and AML	ATIR101 (haploidentical graft depleted of T-alloreactive cells)	Yes (*v* post-HCT cyclophosphamide arm)	III	GvHD, RFS and OS, transplant mortality
Kiadis Pharma/CR-AIR-008	NCT02500550	18-65 (15), ALL and AML	ATIR101	No	II	Incidence of grade III/ IV GvHD, time to T-cell reconstitution, transplant-related mortality, relapse and survival rates
First Affiliated Hospital of Wenzhou Medical University/ 20170316	NCT03110640	5-70 (20), CD19+ BCP ALL, other leukemia	Autologous anti-CD19 CAR-T followed by allogeneic HCT	Yes (fludarabine, cyclophosphamide)	I	Safety/feasibility of autologous CD19 CAR T cells before HCT
Bellicum Pharmaceuticals/BP-HM-001	NCT01744223	18-65 (36), ALL and AML	BPX-501 modified donor T cells reactive to AP1903 self-destruct switch (mismatch donors)	No	I/II	BPX-501 dose that produces no more than day 100 45% grade II-IV aGVHD, OS and DFS, GvHD response to AP1903

Abbreviations: aGVHD, acute graft-versus-host disease; ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; BCP, B-cell precursor; CAR, chimeric antigen receptor; CMV, cytomegalovirus; DFS, disease-free survival; EBV, Epstein-Barr virus; GvHD, graft-versus-host disease; HCT, hematopoietic cell transplantation; HR, high risk; MDACC, MD Anderson Cancer Center; MSKCC, Memorial Sloan Kettering Cancer Center; OS, overall survival; PFS, progression-free survival; RFS, relapse-free survival.

*Extracted from ClinicalTrials.gov website, accessed April 2017.

Table A7. Registered or Ongoing Trials (n = 45) With Cellular Immunotherapy for Relapsed/Refractory or MRD-Positive Adult ALL*

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/Outcome Measures
Relapsed/refractory						
Kite Pharma/KCE-C19-103	NCT02614066	≥ 18 (75), BCP ALL	KTE-C19 (autologous CD19 CAR T)	Yes (fludarabine, cyclophosphamide)	I/II	Safety/toxicity and dose-limiting toxicity, overall CR rate, duration of remission, MRD response, OS
Institute of Hematology and Blood Diseases Hospital/ XH-CD19CART-001	NCT02975687	18-70 (20), BCP ALL, including Ph+	CD19 CAR T	No	I	CR and DFS, safety/toxicity, persistence of CAR T cells
Affiliated Hospital to Academy of Military Medical Sciences/307-CTC-CAR T	NCT02186860	18-65 (5), BCP ALL	3rd generation CAR T (CD28, CD137)	No	I	Safety/toxicity, antileukemic effect
City of Hope Medical Center/ 13447 NCI-2014-01060	NCT02146924	≥ 18 (48), BCP ALL	CAR T (autologous; CD19, CD28)	No/yes (lymphodepletion ± cetuximab	I	Safety/toxicity, CR rate, persistence of CAR T cells
Henan Cancer Hospital/ HenanCH080	NCT02924753	4-70 (20), BCP ALL	CART-19 (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, antitumor activity, persistence of CAR T cells
Servier/CL1-68587-002	NCT02746952	16+ (12), BCP ALL	UCART19 (allogeneic)	No	I	Safety/toxicity, antileukemic activity, MRD response, DFS, OS rate
Cellular Biomedicine Group/ CBMG2016003	NCT03018093	14-75 (20), BCP ALL including Ph+	C-CAR-011	No	I	Dose-limiting toxicity, overall response and survival rate, MRD response
UNC Lineberger Comprehensive Cancer Center/LCCC 1541-ATL	NCT03016377	1+ (40), BCP ALL	iC9-CAR19 (autologous); AP1903 (tacrolimus analog)	No	I	Safety/toxicity, persistence of CAR T cells, overall response, overall, event-free and disease-free rates, optimal dose of AP1903
FHCRC/2639.00 NCI-2013-00073	NCT01865617	≥ 18 (169), BCP ALL	CD19CAR-4-1BB-CD3zeta-EGFRt-expressing T lymphocytes (autologous)	No/yes (lymphodepleting regimen)	II/II	Safety/toxicity, persistence of CAR T cells, CR, OS and PFS rates
Wuhan Sian Medical Technology /CART-CD19-01	NCT02965092	up to 60 (20), BCP ALL	Second generation CAR-T cells (CD19, CD137)	No	I	Safety/toxicity, antileukemic effect
FHCRC/9364 NCI-2017-00421	NCT03103971	≥ 18 (66), BCP ALL	Anti-CD19CAR-4-1BB-CD3zeta-EGFRt-expressing CD4+/CD8+ T lymphocytes (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, pharmacokinetic profile, antitumor activity, PFS and OS survival rates
University of Pennsylvania/ UPCC 21413	NCT02030847	≥ 18 (24), BCP ALL including Ph+	CART-19 (autologous)	No	II	Safety/toxicity (number of adverse events)
Beijing Sanwater Biologic Technology/IT1601-CART19	NCT02810223	1-60 (20), BCP ALL	CART-19 (autologous)	No	I	Safety/toxicity (number of adverse events)
Shanghai Unicar-Therapy Bio-medicine Technology /UnicarTherapy	NCT03064269	10-60 (10), BCP ALL, CNS+	CD19 CAR-T	No	I	Safety/toxicity, CR rate
The First People's Hospital of Yunnan/LXUN	NCT02968472	≥ 0.5 (30), BCP ALL	4SCAR19 (autologous)	No	I	Safety/toxicity, antitumor activity
University College, London/ UCL 14/0529	NCT02443831	≤ 24 (18), B-lineage ALL including Burkitt's leukemia/ lymphoma	CD19 CAR T (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, molecular response and duration of response, persistence of CAR T cells, incidence of hypogammaglobulinemia, relapse and OS rate
Novartis Pharmaceuticals/ CCTL019B2205J 14BT022	NCT02228096	1-21 (67), BCP ALL including Ph+	CTL019 T cells	No	II	Overall response rate, safety/toxicity
University of Pennsylvania/ 16CT022	NCT02906371	1-24 (39), BCP ALL including Ph+	CTL019 autologous T-cells (with tocilizumab)	No	I/II	Frequency of cytokine release syndrome grade 4, CR rate, MRD response, duration of remission
University College, London/ UCL/16/0530	NCT02935257	16-65 (20), BCP ALL	CD19CAT-41BBZ CAR T-cells (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, feasibility of manufacturing CAR T cells
Baylor College of Medicine/ H-31970 SAGAN	NCT01853631	≤ 75 (64), BCP ALL	CD19.CAR/28 and CD19.CAR/28.137 T cells (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, persistence of CAR T cells, tumor response
Sheba Medical Center/ SHEBA-15-2076-AT-CTIL	NCT02772198	1-39 (40) BCP ALL	CD19 CAR T cells (autologous)	Yes (fludarabine, cyclophosphamide)	I/II	Safety/toxicity and feasibility, persistence of CAR T cells
Baylor College of Medicine/ H40466, MAGENTA	NCT03081910	≤ 75 (14), T-ALL	CD5.CAR/28zeta CAR T cells (autologous)	Yes (fludarabine, cytoxan)	I	Safety/toxicity, overall response rate
The Affiliated Hospital of the Chinese Academy of Military Medical Sciences/ CART-ALL-2015	NCT02799550	≥ 60 (10), BCP ALL	CART-19 (allogeneic)	Yes (vindesine, mitoxantrone, cyclophosphamide, peg-aspargase, dexamethasone)	I	Safety/toxicity and overall response, DFS and OS rates
University of Pennsylvania/ 13BT022	NCT02374333	1-24 (50), BCP ALL	huCART19 (autologous)	No	I	Safety/toxicity
Shenzhen Institute for Innovation and Translational Medicine/SIITM20160115	NCT03076437	1-80 (36), BCP ALL	CD19-CAR transduced T cells (autologous)	Yes (fludarabine, cyclophosphamide)	I/II	Safety/toxicity and feasibility, clinical response, persistence of CAR T cells
Shenzhen Second People's Hospital/201504001	NCT02456350	1-85 (36), BCP ALL	CD19-CAR transduced T cells (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity and clinical response
MDACC/2016-0641	NCT03056339	18-65 (36), BCP ALL	iC9/CAR.19/IL15-transduced CB-NK cells (umbilical and cord-blood derived); AP1903 (tacrolimus analog)	Yes (fludarabine, cyclophosphamide)	I/II	Optimal dose, safety/toxicity, CR rate
University of Pennsylvania/15-012219	NCT02650414	1-24 (15), BCP ALL including Ph+	CART22 cells (autologous)	No/yes (lymphodepleting regimen)	I	Safety toxicity, overall response and CR rate, duration of remission
Chinese PLA General Hospital/ CHN-PLAGH-BT-001	NCT01735604	18-90 (50), BCP ALL	CD20-CAR transduced T cells (autologous)	No	I/II	Safety/toxicity, persistence of CAR T cells, antitumor responses
Case Comprehensive Cancer Center/CASE2Z16	NCT02890758	≥ 18 (54), any subset	NK cells (allogeneic non-HLA matched donor), ALT803	No	I	Maximum tolerated dose, antitumor activity
Chinese PLA General Hospital/ CHN-PLAGH-BT-020	NCT03097770	5-90 (20), BCP ALL	CD19/20-CAR transduced T cells (autologous or allogeneic)	No	I/II	Safety/toxicity, antitumor responses, persistence of CAR T cells
The Second Affiliated Hospital of Henan University of Traditional Chinese Medicine/ DHHUTCM20160106	NCT02685670	5-70 (20), BCP ALL	αCD19-TCRz-CD28 and αCD19-TCRz-CD137 (autologous)	Yes (fludarabine, cyclophosphamide)	I/II	Safety/toxicity, CR rate, persistence of CAR T cells, duration of remission, OS
Chinese PLA General Hospital/ CHN-PLAGH-BT-005	NCT01864889	5-90 (12), BCP ALL	CD19-CAR transduced T cells (autologous)	No	I	Safety/toxicity, antitumor response, persistence of CAR T cells
PersonGen BioTherapeutics (Suzhou) /PG-019-001	NCT02819583	≥ 18 (10), BCP ALL	PCAR-019 (autologous)	No	I/II	Safety/toxicity, objective response rate
FHCRC/9330 NCI-2015-01753	NCT02706392	≥ 18 (60) ROR1+ ALL, other B-cell malignancies	ROR1 CAR-specific T lymphocytes (autologous)	Yes (fludarabine, cyclophosphamide)	I	Safety/toxicity, persistence of CAR T cells, antitumor activity
PersonGen BioTherapeutics (Suzhou) /PG-107-002	NCT02742727	≥ 18 (10), T-precursor ALL	CD7 CAR-pNK cells (allogeneic)	No	I/II	Safety/toxicity, clinical response, persistence of CAR-pNK cells
PersonGen BioTherapeutics (Suzhou) /PG-119-001	NCT02892695	3-80 (10), BCP ALL	CD19 CAR-NK cells (allogeneic)	No	I/II	Safety/toxicity and optimal dose, objective response
PersonGen BioTherapeutics (Suzhou) /PG-019-002	NCT02851589	≥ 14 (10), BCP ALL	PCAR-019 (autologous)	No	I/II	Safety/toxicity, objective response

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Table A7. Registered or Ongoing Trials (n = 45) With Cellular Immunotherapy for Relapsed/Refractory or MRD-Positive Adult ALL* (continued)

Institution/Trial Denomination	ClinicalTrials.gov Identifier	Patient Age, Years (No.), ALL Subset	Study Drug	Associated Chemotherapy	Trial Design (phase)	Primary Objective/Outcome Measures
Seattle Children's Hospital/ PLAT-02	NCT02028455	1-26 (80), BCP ALL	CD19 specific CAR T cells EGFRt +/− (autologous), ± cetuximab	Yes (lymphodepletion)	I/II	Safety/toxicity and maximum tolerated dose, CR rate (MRD−), feasibility, persistence of CAR T cells
GIMEMA/LAL 2013	NCT02185781	≥ 60 (6), MRD+ Ph+ ALL	NK cells (autologous)	No	I	Maximum tolerated and recommended final dose, safety/toxicity, feasibility, immunologic modifications, MRD response, OS, time to progression
National University Health System Singapore/ NKCARCD19	NCT01974479	0-80 (20), BCP MRD+ ALL	CD19 redirected NK cells (allogeneic haploidentical)	No	II	MRD response
Fujian Medical University/ CART-19-02	NCT03027739	1-60 (20), BCP MRD+ ALL	CART-19	No	II	Leukemia-free survival, safety/toxicity
University of Pennsylvania/ 825668	NCT02935543	≥ 18 (24), BCP MRD+ ALL	CART 19 (autologous)	No	I/II	MRD response, OS rate, duration of remission, relapse- and event-free survival rates, feasibility, safety/ toxicity
National University Health System, Singapore/ NKCARCD19	NCT01974479	0-80 (20), BCP MRD+ ALL	CD19 redirected NK cells (allogeneic/ haploidentical)	No	II	MRD monitoring

Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; CAR, chimeric antigen receptor; CR, complete remission; DFS, disease-free survival; FHCRC, Fred Hutchinson Cancer Research Center; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; MDACC, MD Anderson Cancer Center; MRD, minimal residual disease; NK, natural killer; OS, overall survival; Ph+, positive for Philadelphia chromosome; pNK, peripheral natural killer.
*Extracted from ClinicalTrials.gov website, accessed April 2017.

Table A8. Preclinical Studies With Targeted Therapy for ALL (Any Subset)

Therapeutic Target	Targeting Agent	Main Findings or Notes	Study
CXCR-4	Plerixafor	Enhancing chemosensitivity and sensitizing *MLL*+ ALL to *FLT3* inhibitor (lestaurtinib)	Sison EAR, et al; Oncotarget 5:8947-8958, 2014
mTOR	Sirolimus	Inhibitory effects in synergy with methotrexate	Teachey DT, et al; Blood 111:705-714, 2008
Proteasome, CK2	Bortezomib, CX-4945	Synergistic NF-κB mediated apoptosis	Buontempo F, et al; Oncotarget 7:1323-1340, 2015
Bcl-2 /Bcl-xL-	ABT-737	Synergy with mTOR inhibitor CCI-779	Iacovelli S, et al; Oncotarget 6:32089-32103, 2015
	Venetoclax, navitoclax	Venetoclax for r-*MLL*+, navitoclax others (BCP, TCP)	Kahw SL, et al; Blood 128:1382-1395, 2016
Chk1/2	Prexasertib	Potential synergy with TKI and chemotherapy	Ghelli A, et al, Oncotarget 7:53377-53391, 2016
c-Myc	Shikonins	—	Zhao Q, et al; Oncotarget 6:38934–38951, 2015
	CK2 inhibitor TBB	Ikaros activation and c-*MYC* downregulation	Ge Z, et al; Oncotarget 6:42300-42311, 2015
	TGR-1202	*MYC* silencing in synergy with carfilzomib	Deng C, et al; Blood 129:88-99, 2017
JNK	SP600125	Increasing *PAX5* and restoring glucocorticoid sensitivity	Nicholson L, et al; Br J Haematol 171: 595–605, 2015
HSP90	PU-H71	Active on *JAK1/2* mutant leukemia	Kucine N, et al; Blood 126:2479-2483, 2015
p53	SB225002*	Upregulating p53-related *GLIPR1* gene	de Vasconcellos JF: PLoS One 10:e0134783, 2015
Reactive oxygen species detoxification	Erastin, BSO, auranofin	Potentiating activity of SMAC-mimetic LCL-161	Hass C, et al; Biochem Pharmacol 105:14-22, 2016
MerTK	UNC2025	Increasing sensitivity to methotrexate and more active in TCP ALL	DeRyckere D, et al; Clin Cancer Res 23:1481-1492, 2017
Survivin	YM155	Potentiated by dasatinib in Ph+ subset	Chang BH, et al; J Hematol Oncol 8:39, 2015
LEPR	1-day fasting*	Upregulating LEPR gene with inhibition of ALL development and ALL cell differentiation	Lu Z, et al; Nat Med 23:79-90, 2017

NOTE. Data were generated using ALL cell lines or patient-derived samples; most studies included ex vivo PDX models. Dashes indicate no data.
Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; Ph+, positive for Philadelphia chromosome; PDX, patient-derived xenograft; SMAC, second mitochondrial-derived activator of caspases; TCP, T-cell precursor; TKI, tyrosine kinase inhibitor.
*Compounds inhibited molecular pathways stimulating cell growth and proliferation; agonists upregulating mechanisms related to cell death.

Table A9. Preclinical Studies With Targeted Therapy for BCP ALL and Subsets

ALL Subtype	Therapeutic Target	Targeting Agent	Main Findings or Notes	Study
BCP Ph+				
	PYST1 (Erk activation)	BCI*	Induction of p53-mediated cell death	Shojaee S, et al: Cancer Cell 28:114-128, 2015
	JAK-2	Ruxolitinib	Sensitivity restored by dasatinib and synergy with dasatinib/dexamethasone	Appelman et al[24]
	VEGFR-1 and T315I mutant	Axitinib	*BCR-ABL1* T315I inhibition	Pernovska T, et al: Nature 519:102-105, 2015
	T315I	Danusertib	Activity against *BCR-ABL1* T315I (toxicity reported)	Bortakur G, et al: Haematologica 100: 898-904, 2015
	Myristoyl pocket of ABL1	Asciminib	Activity on different site of *ABL1*	Wylie et al[122]
	MDM2	Nutlin-3	Restoring p53-mediated apoptosis	Trino S, et al: Oncotarget 7: 12951-12961, 2016
	Macrophage reprogramming pathway	IL-3, M-CSF, GM-CSF, FLT3L, IL-7	Ph+ BCP ALL blast reprogrammed into $CD14^{high}/CD19^{low}$ nonleukemic macrophage-like cells	McClellan et al[126]
	Retinoid X receptor	Bexarotene, carbacyclin, ATRA, 9- and 13-cis RA*	Inducing expression of *IKZF1* and potentiating dasatinib activity	Churchman et al[125]
	Bcl-2	Venetoclax	In synergy with dasatinib (induction of LYN proapoptotic *BCL-2*–like protein)	Leonard et al[96]
	Reactive oxygen species	Verteporfin*	Synergistic effects with dasatinib	Morishita T, et al: Oncotarget 7:10182-10192, 2016
BCP KTM2A+ (MLL+)				
	FLT-3	PKC412	—	Torelli GF, et al: Br J Haematol 130:43-50, 2005
	MEK, RAS	Trametinib, selumetinib, MEK162	—	Kerstjens M, et al: Oncotarget 8: 14835–14846, 2017
	Bcl-2	Venetoclax	In synergy with DOT1L inhibitors and chemotherapy	Benito et al[135]
		Venetoclax, navitoclax	Demonstrated synergy with cyclophosphamide	Ackler et al[136]
	MDM2	RG7112*	Upregulating p53	Richmond J, et al: Clin Cancer Res 21: 1395-1405, 2015
	Bcl-2 /Bcl-xL-	Venetoclax, navitoclax	Navitoclax active in B-other subsets	Khaw et al[85]
	HDAC	Romidepsin	Synergy with cytarabine	Cruickshank et al[137]
BCP unselected/other				
	Integrin alpha4	Natalizumab	Inhibition of stromal adhesion with drug sensitization (nilotinib in Ph+)	Hsieh YT, et al: Blood 121:1814-1818, 2013
	Proteasomes, histone deacetylase (HDAC)	Bortezomib, HDCA inhibitor	Synergistic inhibition	Bastian L, et al: Clin Cancer Res 19: 1445-1457, 2013
	Pre-BCR/*SYK*	INPP5D inhibitor*	*SYK* hyperactivation causing negative B-cell selection	Chen Z, et al: Nature 521:357-361, 2015
	Bcl-2 /Bcl-xL-	Disulfiram/copper	—	Deng M, et al: Oncotarget 7:82200-82212, 2016
	HDAC	LAQ824, WT161, Merck60	Stronger effects from HDAC1 and HDAC2 inhibitors	Stubbs MC, et al: Clin Cancer Res 21: 2348-2358, 2015
	HDAC, mTOR	Vorinostat/panobinostat, rapamycin/analogs	—	Beagle BR, et al: Oncotarget 6:2088-2100, 2015
	FLT3, PI3K/mTOR pathway	Quizartinib/crenolanib, BEZ235/rapamycin	—	Messina M, et al: Oncotarget 7:13886-13901, 2016
	JAK1/2	AZD1480	Synergy with with *MEK* inhibitor selumetinib	Suryani S, et al: Mol Cancer Ther 14: 364-374, 2015
	MEK 1 / B-Raf	Trametinib/sorafenib	Restoring prednisone sesnsitivity in *RAS* mutant ALL	Aries IM, et al: Haematologica 100: e132-e136, 2015
	Smac	BV6*	NF-κB activation and TNFα-induced apoptosis	Schirmer M, et al: Cell Death Dis 7: e2052, 2016
		Birinapant*	Activating RIP-1 apoptosis/necroptosis	McComb et al[80]
TCF3-HLF+	Bcl-2	Venetoclax	Highly sensitive, synergy with corticosteroids/chemotherapy	Fischer et al[77]
TCF3-PBX1+ and pre-BCR+	PI3K-delta	Idelalisib	—	Eldfors et al[77]
	BCL-6 (SYK, *c-Src,* BTK)	PRT062607, dasatinib, ibrutinib	Downstream *BCL-6* inhibition	Geng et al[98]
	SYK	PRT318, PRT260607	—	Kohrer S, et al: Leukemia 30:1246-1254, 2016
	SYK, BLK, MERTK, ROR1	Dasatinib	TK overexpression, ROR silencing	Messina et al[138] Bicocca et al[139]
	BCL-6	RI-BPI,	Expected synergy with *SYK* inhibitors and other *BTK* inhibitor ibrutinib	Deucher et al[142]
	SRC, BTK	Dasatinib		Kim et al[143]
CD22+	CD22ΔE12	CD22ΔE12-RTM nanoparticles	—	Uckun FU, et al: EBioMedicine 2:554-562, 2015

NOTE. Data were generated using ALL cell lines or patient-derived samples; most studies included ex vivo PDX models. Dashes indicate no data.
Abbreviations: ALL, acute lymphoblastic leukemia; BCP, B-cell precursor; HDCA, histone deacetylase; PDX, patient-derived xenograft; Ph+, positive for Philadelphia chromosome; TK, tyrosine kinase.
*Compounds inhibited molecular pathways stimulating cell growth and proliferation; agonists upregulating mechanisms related to cell death.

Table A10. Preclinical Studies With Targeted Therapy for TCP ALL

ALL Subtype	Therapeutic Target	Targeting Agent	Main Findings or Notes	Study
TCP				
	CD3	Anti-CD3/CD28 and CD3ε antibodies*	Triggering TCR signaling induces apoptosis	Trinquand et al[160]
	CD7	CD7-nanobody toxin	*Pseudomonas* exotoxin A	Tang J, et al: Oncotarget 7:34070-34083, 2016
	CD38	Daratumumab	Active in 14 of 15 pediatric T-ALL PDX models	Bride KL, et al: Blood 131:995-999, 2018
	Bcl-2	Venetoclax	Synergy with chemotherapy; most active in *TLX3*+ and *HOXA*+ subsets	Peirs et al[95]
			More effective in ETP ALL than other T-ALL subsets	Chongaile TN, et al: Cancer Discov 4:1074-1087, 2014
	IRAK-1/4	*IRAK* inhibitors	Reducing MCL1 stability; synergy with ABT-737 and vincristine	Li Z, et al: J Clin Invest 125:1081-1097, 2015
		IRAK1/4 inhibitors	Partial inhibition of proliferation and reversal of corticosteroid resistance	Dussiau C, et al: Oncotarget 6:18956-18965, 2015
	NOTCH1-4	12 (BMS-906024)	Pan-*NOTCH* inhibitor	Gavai AV, et al: ACS Med Chem Lett 6:523-527, 2015
	NOTCH3	MOR antibodies	Inhibiting *NOTCH3* mutated T-ALL	Bernasconi-Elias P, et al: Oncogene 35: 6077-6086, 2016
	Wnt	XAV-939	Targeting hypoxic, leukemia-initiating cell-rich population	Giambra V, et al: Blood 125:3917-3927, 2015
	CXCL-12/ CXCR-4	CXCR4-inh AMD3465	CXCL12 production by vascular endothelial cells mantains T-ALL; CXCL12 and CXCR4 genetic deletion suppresses T-ALL	Pitt et al[161]
			CXCR4 critical to T leukemogenecity; expression mediated by contactin and calcineurin	Passaro et al[162]
		BMS-936564/MDX-1338	Fully human anti-CXCR4 antibody	Kuhne MR, et al: Clin Cancer Res 19:357-366, 2012
	HDAC	Givinostat	—	Pinazza M, et al: Cell Death Dis 7: e2047, 2016
	Glutaminase	BPTES	Inhibition of glutaminolysis and autophagy in synergy with NOTCH inhibition by DBZ	Herranz D, et al: Nat Med 21:1182-1189, 2015
	Hedgehog	GANT61, vismodegib	T-ALL with high GLI1 expression	Dagklis A, et al: Blood 128:2642-2654, 2016
	HSP90	AUY922	Downregulating *TYK2* and *BCL-2*	Akahane K, et al: Leukemia 30:219-228, 2016
	CK2	CX-4945	Inhibiting IL-7R mutant T-ALL, in synergy with *JAK* inhibitors	Melao A, et al: Hematologica 101:1368-1379, 2016
	CDK4/6	LEE011	Synergy with glucocorticoids and mTOR inhibitor; antagonism with chemotherapy	Pikman Y, et al: Clin Cancer Res 23:1012-1024, 2016
	JAK/STAT pathway	Ruxolitinib	Inhibition IL-7 associated *STAT5* hyperactivation in ETP ALL	Maude et al[166]
	TYK2	JAK inhibitor 1, AG490	—	Sanda T, et al: Cancer Discov 3:564-577, 2013
	NEDD8-activating enzyme E1C	MLN4924	—	Han K, et al: Oncotarget 7:23812-23824, 2016
	PI3K/mTOR AKT/mTOR, c-Myc	Rapamycin, JQ1 (bromodomain inhibitor)	Targeting leukemia-initiating cells	Schubbert S, et al: Cancer Res 74:7048-7059, 2014
	PI3K/mTOR AKT/mTOR,	IPI-145 (pan *PI3K* inhibitor)	More efficient than isoform-selective PI3K inhibitors	Lonetti A, et al: Oncotarget 6:10399-10414, 2016
		AZD8835/8186, AZD5363, AZD2014	Identification of sensitive T-ALL subsets	Lynch JT, et al: Oncotarget 7:22128-22139, 2016
		AS605240	Synergistic with glucococorticoids; antagonistic interaction with anthracycline and methotrexate unless administered after 48 hours	Bortolini Silveira A, et al: Oncotarget 6: 13105-13118, 2015
	hLAT1	JPH2013	—	Rosilio C, et al: Leukemia 29:1253-1266, 2015
	Calcineurin (Cn)-nuclear factor/GSK-3	Cn/*GSK-3* inhibitors	Dual inhibition increasing proteosomal degradation of X-linked inhibitor of apoptosis (in pre-/pro-T ALL)	Tosello V, et al: Leukemia 30:812-822, 2016
	Src TK *LCK*	Dasatinib	Activity in *TAL1/SIL-TAL1* subset	Laukkanen S, et al: Blood Cancer J 7:e604, 2017
	LCK	Dasatinib, bosutinib, nintedanib, WH-4-023	Restoring sensitivity to dexamethasone in glucocorticoid-resistant leukemic cells	Serafin V, et al: Blood 130:2750-2751, 2017

NOTE. Data were generated using ALL cell lines or patient-derived samples; most studies included ex vivo PDX models. Dashes indicate no data.
Abbreviations: ALL, acute lymphoblastic leukemia; ETP, early thymic precursor; PDX, patient-derived xenograft; TCP, T-cell precursor; TCR, T-cell receptor.
*Compounds inhibited molecular pathways stimulating cell growth and proliferation; agonists upregulating mechanisms related to cell death.