T-cell Acute Lymphoblastic Leukemia: A Roadmap to Targeted Therapies

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ABSTRACT T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive hematologic malignancy characterized by aberrant proliferation of immature thymocytes. Despite an overall survival of 80% in the pediatric setting, 20% of patients with T-ALL ultimately die from relapsed or refractory disease. Therefore, there is an urgent need for novel therapies. Molecular genetic analyses and sequencing studies have led to the identification of recurrent T-ALL genetic drivers. This review summarizes the main genetic drivers and targetable lesions of T-ALL and gives a comprehensive overview of the novel treatments for patients with T-ALL that are currently under clinical investigation or that are emerging from preclinical research.

Significance: T-ALL is driven by oncogenic transcription factors that act along with secondary acquired mutations. These lesions, together with active signaling pathways, may be targeted by therapeutic agents. Bridging research and clinical practice can accelerate the testing of novel treatments in clinical trials, offering an opportunity for patients with poor outcome.

INTRODUCTION

T-cell acute lymphoblastic leukemia (T-ALL) arises from the accumulation of genetic lesions during T-cell development in the thymus, resulting in differentiation arrest and aberrant proliferation of immature progenitors. T-ALL accounts for only 10% to 15% of pediatric and up to 25% of adult ALL cases (1), with an overall survival (OS) of 80% in the pediatric setting that has been achieved using a risk-based stratification toward intensive multiagent combination chemotherapeutic protocols (2). OS rates for adult patients with T-ALL are lower than 50% due to higher treatment-related toxicities (1). Patients are assigned to standard-, medium-, or high-risk group based on initial steroid response and minimal residual disease (MRD) after the first two courses of chemotherapy (3, 4). The risk-based therapeutic regimen consists of steroids, microtubule-destabilizing agents (vincristine), alkylating agents (cyclophosphamide), anthracyclines (doxorubicin or daunorubicin), antimetabolites (methotrexate, MTX), nucleoside analogues (6-mercaptopurine, thioguanine, or cytarabine), and hydrolyzing enzymes (L-asparaginase), and in some cases, it is followed by stem cell transplantation. Some of these conventional chemotherapeutics have a lymphoid lineage–specific effect in ALL. In fact, lymphoblasts have low asparagine synthetase activity, and thus, they are very sensitive to exogenous asparagine depletion by L-asparaginase. Moreover, ALL blasts are susceptible to MTX treatment due to a higher accumulation of MTX-polyglutamate metabolites that increases MTX intracellular retention and its antileukemic effect in these cells (5). Risk-based intensification of the therapeutic regimen has greatly improved the survival rate for pediatric (6) and young adult patients treated on pediatric-based protocols (1). Nevertheless, still 1 of 5 pediatric patients with T-ALL dies within 5 years after first diagnosis from relapsed disease and therapy resistance (refractory disease) or from treatment-related mortalities, including toxicity and infections. Therefore, further intensification of the treatment protocol does not seem feasible for high-risk patients (6), and there is an urgent need for implementation of targeted therapies. Furthermore, molecular biomarkers, in addition to MRD detection, could improve the upfront identification of high-risk patients and therefore guide the treatment of these patients with an intensified chemotherapeutic regimen or, whenever available, targeted agents. Unfortunately, such genetic biomarkers are not yet included in the risk stratification of newly diagnosed patients with T-ALL.

The clinical testing of targeted agents in the oncology field has dramatically increased over the last years. Nevertheless, targeted treatment options for patients with T-ALL remain limited. In fact, unlike other leukemias such as chronic myeloid leukemia (CML) and Philadelphia-positive ALL, which are kinase-driven malignancies, the initiating events in T-ALL cause the ectopic expression of transcription factors

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Note: Supplementary data for this article are available at Blood Cancer Discovery Online (https://bloodcancerdiscov.aacrjournals.org/).

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Blood Cancer Discov 2021;2:19–31

doi: 10.1158/2643-3230.BCD-20-0093

(type A aberrations) that drive leukemogenesis. However, the additional genetic lesions that are required for full transformation into malignancy (the so-called type B mutations) potentially serve as druggable vulnerabilities. Therefore, the thorough investigation of T-ALL oncogenic molecular pathways and their intricate RNA and protein signaling networks that sustain proliferation and survival can offer opportunities for the implementation of personalized targeted therapies (7). Potential limitations to the use of targeted drugs in pediatric T-ALL include clonal heterogeneity of the disease, resulting in only partial elimination of leukemia cells upon therapy. Therefore, resistant clones may be selected and survive under the selective pressure of treatment (8, 9). Similar resistance mechanisms have already been demonstrated for conventional chemotherapeutics such as the glucocorticoid-selected *NR3C1* mutations (10–12) and the 6-mercaptopurine–selected *NT5C2* mutations in chemoresistant relapsed ALL (11, 13). Already in 2017, the Innovative Therapies for Children with Cancer (ITCC) Consortium advised a change in the setup of early-phase pediatric clinical trials in order to accelerate the access of interesting drugs to randomized trials (14). ITCC has proposed to extrapolate data from adult clinical trials as a starting point for *first-in-child* trial designs. In addition, ITCC suggested the addition of homogeneous expansion cohorts to assess pharmacodynamic and pharmacokinetic parameters for the therapeutic agents tested and to detect early signs of antitumor activities. Furthermore, it has become evident that molecular tumor profiling is needed to study cancer heterogeneity and to understand therapy-induced mutations and the insurgence of relapse (14). Supplementary Table S1 offers an overview of current clinical trials that investigate targeted agents for T-ALL. In the following paragraphs, we summarize the main recurrent T-ALL oncogenic drivers and targetable genetic lesions and highlight the most important preclinical and clinical evidence to implement promising drugs in clinical trials for patients with T-ALL. In particular, we discuss agents that target activated pathways by specific genomic lesions in T-ALL and drugs already approved for cancer treatment that are under clinical investigation for patients with T-ALL. Moreover, we briefly discuss novel therapeutic options for which promising preclinical results were obtained in T-ALL models and that should be taken into consideration for future research. The agents discussed here include modifiers of apoptosis; inhibitors of transcriptional regulators, signal transduction, and the cell cycle; and immunotherapies. Figure 1 offers a visual summary of the relevant targets and therapeutic agents described throughout this review.

ONCOGENIC DRIVERS AND T-ALL SUBTYPES

Historically, three main T-ALL differentiation stages were identified based on the expression of cluster of differentiation (CD) markers on the cell surface and were denoted as early/precortical, cortical, and mature in analogy with the thymocytes' developmental stages (15). With the rapid development of (cyto)genetic technologies and next-generation sequencing in the last two decades, it was possible to identify genetic drivers that, in case of T-ALL, are transcription factors that are ectopically activated due to chromosomal rearrangements or deletions (reviewed in ref. 7). Initially using gene expression profiling (16, 17), which has been replaced by the identification of recurrent genomic abnormalities via genome sequencing (18, 19), patients with T-ALL can be clustered in four main subtypes with characteristic oncogenic aberrations, namely early thymocyte progenitor (ETP)/immature-ALL, TLX, TLX1/NKX2.1 (originally denoted as proliferative subgroup), and TAL/LMO. Figure 2 illustrates the main features of each subtype. The ETP-ALL group includes the most immature T-ALL cases (approximately 10% of the total T-ALL cases) that present a gene expression profile similar to hematopoietic stem cells and myeloid progenitors, with a high expression of self-renewal genes including *LMO2, LYL1*, and *HHEX* and the antiapoptotic *BCL2* (20). The mechanisms for high BCL2 expression in ETP-ALL are still poorly understood—the expression of this antiapoptotic protein could reflect a stem cell–like feature of immature cells, or it could be due to STAT5 activation downstream of recurrent IL7 signaling pathway mutations within this subgroup (21, 22). ETP-ALL cases show increased expression of the transcription factor *MEF2C* or genetic aberrations of *MEF2C*-associated transcription regulators such as *SPI1, RUNX1, ETV6-NCOA2*, and *NKX2.5* (16). Interestingly, ETP-ALL blasts have higher mutational loads compared with blasts of other T-ALL subtypes (21, 22). In particular, although *NOTCH1*-activating mutations and cell-cycle regulators' *CDKN2A/2B*-inactivating mutations are relatively rare in ETP-ALL, recurrent activating aberrations involve kinase-encoding genes, such as *FLT3, NRAS, IL7R, JAK1*, and *JAK3* (21, 22). In addition, recurrent 5q deletions result in deletion of the *NR3C1* locus, encoding for the glucocorticoid receptor (GCR; refs. 22, 23). Interestingly, recent evidence demonstrated that reduced GCR expression can induce steroid resistance in T-ALL (12). Some ETP-ALL cases present genomic aberrations that activate genes of the *HOXA* locus. Such activating events have been correlated to chemoresistance and inferior outcome in adult ETP-ALL (24).

The TLX group includes immature cases that either lack a functional T-cell receptor (TCR) or present a γ/δ TCR, which is in line with early or γ/δ T-cell lineage development (DN2 stage). A recent study suggests that patients with γ/δ T-ALL have higher MRD levels after induction chemotherapy compared with other T-ALL cases (25). Common genetic lesions within the TLX group include rearrangements of the transcription factor *TLX3* (16, 17), mostly as consequence of recurrent *TLX3–BCL11B* translocations (26). These aberrations result in haploinsufficiency of the tumor suppressor *BCL11B* (27), which is a crucial regulator of the α/β lineage commitment during differentiation. Moreover, *TLX3*-rearranged T-ALLs often have *NOTCH1*-activating mutations (28) and aberrations in epigenetic regulators such as PHF6 and CTCF (18). Similar to various ETP-ALL cases, some TLX patients harbor alternative *HOXA*-driving events instead of *TLX3*-activating lesions (16).

The common features of the TLX1/NKX2.1 T-ALL group are genomic rearrangements involving either *TLX1* or *NKX2.1*, CD1 expression, and differentiation arrest at the cortical (DN3-DP) stage of T-cell development. These cases present higher expression of genes involved in cell-cycle regulation and progression, DNA duplication, and spindle assembly

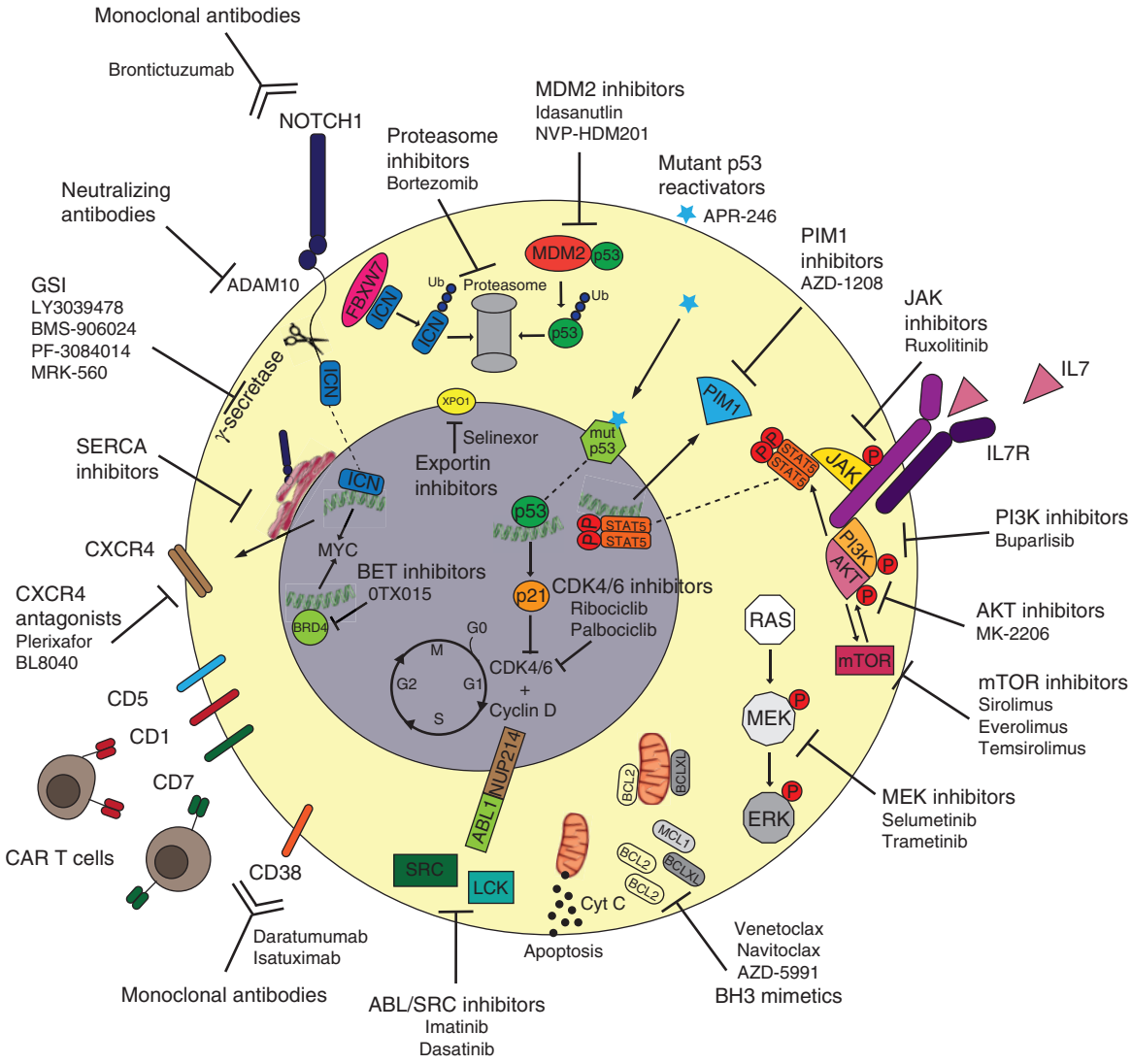

Figure 1. Targeted therapies to tackle T-ALL vulnerabilities. Oncogenic NOTCH1 signaling can be inhibited via different strategies such as monoclonal antibodies blocking the NOTCH1 receptor itself (brontictuzumab), monoclonal antibodies blocking the ADAM10 metalloprotease that releases extracellular NOTCH1, gamma-secretase inhibitors (GSI) preventing the release of intracellular ICN1, and SERCA inhibitors that block the maturation of NOTCH1 and its localization on the cell surface. Because NOTCH1-mutated T-ALL cases can present higher CXCR4 surface expression, CXCR4 antagonists (plerixafor and BL8040) can be used to tackle NOTCH1-driven T-ALL as well. Immunotherapy approaches for T-ALL include monoclonal antibodies against surface CD38 (daratumumab or isatuximab) as well as CAR T cells directed toward surface CD1, CD5, CD7, and CD38. The increased expression of antiapoptotic BH3 proteins such as BCL2 and BCLXL can be counteracted by the use of BH3 mimetics (venetoclax, navitoclax, and AZD-5991). The oncogenic signaling of ABL1 fusion proteins as well as aberrant activity of Src-family kinases can be inhibited by the tyrosine kinase inhibitors imatinib and dasatinib. The aberrant IL7R signaling cascade can be tackled using multiple targeted agents including JAK inhibitors (ruxolitinib), PIM1 inhibitors (AZD-1208), PI3K inhibitors (buparlisib), AKT inhibitors (MK-2206), mTOR inhibitors (sirolimus, everolimus, or temsirolimus), and MEK inhibitors (selumetinib or trametinib). APR-246 can bind mutant p53 and restore its wild-type, tumor-suppressor function, whereas MDM2 inhibitors (idasanutlin and NVP-HDM201) can prevent wild-type p53 ubiquitination and consequent degradation via the proteasome. Alternatively, tumor-suppressor proteins' degradation can be prevented by proteasome inhibitors (bortezomib). Increased activity of cell-cycle regulators CDK4/6 can be blocked by CDK inhibitors (ribociclib or palbociclib), whereas aberrant transcription induced by BRD4 can be targeted by BET inhibitors (OTX015). Nuclear trafficking of oncogenic mRNA and proteins can be targeted via XPO1 inhibitors (selinexor).

(16, 17). T-ALL cases with *TLX1* or *NKX2.1* aberrations have been associated with excellent treatment outcomes (reviewed in ref. 7).

The TAL/LMO T-ALL subgroup comprises nearly half of all pediatric patients with T-ALL, and it is characterized by ectopic expression of *TAL1* (either via translocation or *SIL–TAL1* deletion), *TAL2*, *LYL1*, *LMO1*, *LMO2*, or *LMO3* (driven by *TCRB* or *TCRAD* rearrangements; refs. 16, 17). Immunophenotypes of TAL/LMO patients mostly resemble late cortical ($CD4^+$ single positive or $CD8^+$ single positive) T-cell development stages. *PTEN* mutations are most common in this subgroup and have been associated with poor outcome (29). In addition, *PIK3R1*- or *PIK3CG*-activating lesions are frequent within this cluster (30, 31). Moreover, *TAL1*-rearranged cases

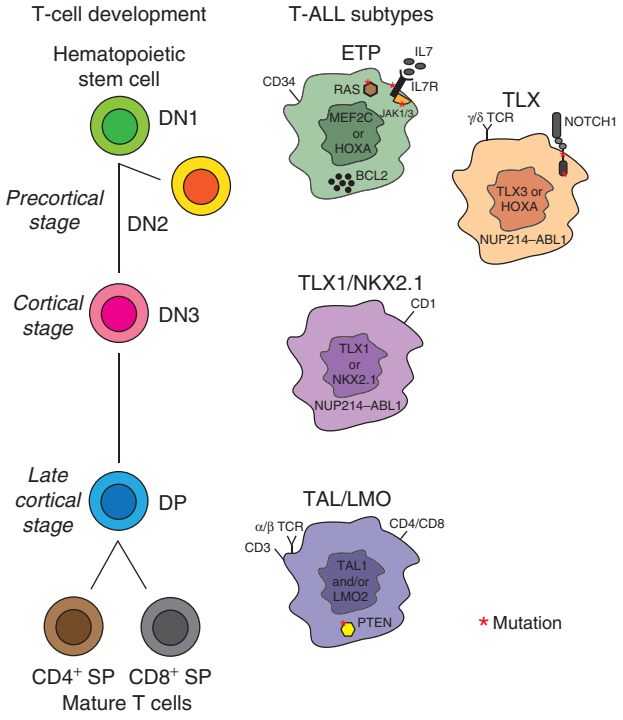

Figure 2. Thymocytes' developmental stages and T-ALL subtypes. The ETP-ALL subtype is driven by aberrant *MEF2C* or *HOXA* gene expression, presents frequent mutations in the IL7 signaling cascade, and shows higher BCL2 protein expression. Similarly to hematopoietic progenitors, ETP-ALL blasts express stem cell markers such as CD34. The TLX subgroup, driven by either *TLX3*- or *HOXA*-activating events, often presents *NOTCH1* mutations and, in some cases, expression of the γ/δ T-cell receptor (TCR), in analogy to the precortical γ/δ T-cell progenitors (DN2 stage). The TLX1/NKX2.1 subgroup is driven by either *NKX2.1* or *TLX1* aberrations. TLX-rearranged cases can present the oncogenic *NUP214–ABL1* fusion. The TAL/LMO subgroup, driven by the expression of the oncogenes *TAL1* and *LMO2*, includes the most mature T-ALL cases. As for late cortical (SP) T-cell progenitors, TAL/LMO blasts express mature T-cell surface markers such as CD4, CD8, CD3, and α/β TCR and often present *PTEN* mutations.

often have mutations in the ubiquitin-specific protease USP7 that regulates MDM2 and TP53 stability (18).

CURRENT AND NOVEL POSSIBILITIES FOR TARGETED THERAPY

In the following paragraphs, we will discuss various classes of drugs and biological agents that provide novel strategies for targeted treatment. These are classified as modifiers of apoptosis; inhibitors of transcription regulation, signal transduction, and the cell cycle; and immunotherapies.

Modifiers of Apoptosis

BH3 Mimetics

Encouraged by significant responses of the BCL2 inhibitor venetoclax (ABT-199) in chronic lymphatic leukemia (32), BH3 mimetics became of great interest for the treatment of various hematologic malignancies. The sensitivity toward BH3 mimetics can be determined by BH3 profiling, a functional screening method that determines the "priming of death" state in cells by measuring specific BCL2 family member (e.g., BCL2, BCLXL, and/or MCL1) dependencies (33). BH3 profiling of T-ALL cell lines and patient blasts identified a dependency on BCL2 in ETP-ALL and BCLXL in the remaining subtypes of T-ALL (34). Consequently, immature/ETP-ALL cells are most responsive to venetoclax, whereas other T-ALL subtypes are more sensitive to navitoclax (ABT-263) treatment, respectively (34, 35). The BCL2/BCLW/BCLXL inhibitor navitoclax induces significant cell death in both T-ALL and B-cell precursor (BCP)-ALL patient-derived xenograft (PDX) models (36), but it can induce severe thrombocytopenia *in vivo*. First reports on pediatric and adult patients with relapsed/refractory T-ALL treated with venetoclax alone or combined with navitoclax showed promising results (37, 38). However, various resistance mechanisms toward venetoclax treatment have been reported in several hematologic malignancies including T-ALL, such as acquired *BCL2* mutations, altered mitochondrial fitness, or MCL1 upregulation (36, 39–41). Combination treatment of venetoclax with other BH3 mimetics or PI3K/AKT/mTOR inhibitors significantly increases cell toxicity and overcomes venetoclax-induced resistance (39, 40). The MCL1 inhibitor S63845 also induces efficient cell death in various T-ALL cell lines as single treatment (39), therefore serving as an interesting alternative to venetoclax, especially given the limited dependency on BCL2 in most patients with T-ALL (34). Measuring BCL2 family dependencies can enable guided application of different BH3 mimetics for individualized medicine. In addition, the mitochondrial priming for apoptosis correlates with clinical responses in ALL and predicts for chemosensitivity, empowering the use of BH3 profiling as a functional screen in pediatric leukemia (42).

Transcriptional Regulator Inhibitors

NOTCH1 Inhibitors

Over 70% of T-ALL cases present *NOTCH1*-activating mutations *(gain-of-function)*, and up to 25% of patients harbor mutations in the *FBXW7* gene (18), which mediates the proteasomal degradation of NOTCH1. Gamma-secretase inhibitors (GSI) have been extensively studied as potential treatment for NOTCH1-activated tumors. Despite promising preclinical results, GSI failed during clinical trials due to insufficient efficacy (even in presence of *NOTCH1* mutations) and excessive gastrointestinal toxicity caused by the concomitant inhibition of NOTCH2 in the gut epithelium (reviewed in ref. 43). Preclinical data showed that simultaneous corticosteroid administration can relieve gastrointestinal toxicity and enhance the GSI antitumor activity (44). Current clinical trials are investigating whether combined GSI and dexamethasone administration could be an effective therapeutic approach (NCT02518113 and NCT01363817). As an alternative strategy, Habets and colleagues showed a safe, selective GSI targeting of NOTCH1 signaling in T-ALL using a PSEN1 inhibitor (MRK-560; ref. 45). Although intestinal epithelial cells express both PSEN1 and PSEN2 subunits of the γ-secretase proteolytic complex, T-ALL cells express only PSEN1. *In vivo* preclinical data showed that γ-secretase inhibition by MRK-560 has antileukemic activity without causing intestinal toxicity in mouse xenografts derived from patients with T-ALL, offering a promising alternative therapeutic

approach for NOTCH1-activated T-ALL cases (45). It is fair to question whether, despite high prevalence of *NOTCH1* mutations in T-ALL, GSI is a valid strategy to efficiently and safely target this mutant protein and the consequent altered transcriptional program.

Additional strategies to block aberrant NOTCH1 signaling include monoclonal antibodies (46) or sarco-endoplasmic reticulum Ca^{2+}-ATPase (SERCA) inhibitors that block NOTCH1 protein maturation by preventing its localization on the cell membrane (47). Other approaches to tackle oncogenic NOTCH1 involve the targeting of molecules that are activated upon NOTCH1-induced signaling. For example, it has been reported that GSI-resistant T-ALL cells express lower levels of the antiapoptotic protein MCL1. Because MCL1 can counteract the inhibition of BCL2 and BCLXL, cells with lower MCL1 expression are vulnerable to navitoclax treatment (48). At last, another emerging druggable player within NOTCH1 oncogenic signaling is CXCR4 (CD184), the chemokine receptor for CXCL12 that is released by stromal cells in the thymus. CXCR4 is upregulated in NOTCH1-driven T-ALL and promotes survival and proliferation in the bone marrow niche (reviewed in ref. 49). Therefore, CXCR4 antagonists, which are already largely used in the clinic to promote stem cells' mobilization into the bloodstream, could be repurposed as a therapeutic option for patients with leukemia. In fact, the novel CXCR4 inhibitor BL8040 is now in phase II clinical trial for patients with relapsed T-ALL/lymphoblastic lymphoma (LBL; Supplementary Table S1). Together, these studies show that there is potential for targeting mutant NOTCH1 or its downstream signaling.

BET Inhibitors

Bromodomain (BRD)-containing proteins affect gene transcription via binding to acetylated histones. Their functions include remodeling of the chromatin, modifying histones, and modulating transcription itself (50). The BRD and extraterminal (BET) family of BRD-containing proteins consists of four members: BRD2, BRD3, BRD4, and the testis-specific BRDT. One of the first small molecules developed to selectively inhibit BET proteins was JQ1 (50). In leukemia, BRD4 activity can drive aberrant MYC expression. Because *MYC* is an important and direct NOTCH1 target gene (51), *NOTCH1*-mutated T-ALL cases have increased MYC expression. In preclinical T-ALL models, JQ1 competes with BRD4, resulting in reduced MYC expression, decreased cell proliferation, and impaired tumor growth (52). Moreover, JQ1 treatment can synergize with vincristine (53) and with the BCL2 inhibitor venetoclax (54). Interestingly, T-ALL cells that acquire resistance to GSIs remain responsive to BRD4 inhibition by JQ1 (55), indicating that *NOTCH1*-mutated patients could benefit from BET inhibitor treatment. In addition to *MYC*, JQ1 also lowers the transcription of another important NOTCH1 target gene, the IL7 receptor (*IL7R*; ref. 56). Moreover, another BRD4-dependent transcription factor, ETS1, can cooperate with NOTCH1 during leukemogenesis. Because Ets1 deletion sensitizes T-ALL cells to GSI (57), targeting NOTCH1 transcriptional cofactors could offer an alternative strategy to treat NOTCH1-driven T-ALL cases.

Cancer cells often use superenhancer structures to restore and sustain oncogene expression. Guo and colleagues (58) showed that JQ1-resistant leukemic cells can restore MYC expression via enhancer remodeling. However, combined BET and cyclin-dependent kinase (CDK) 7 (transcriptional regulator) inhibition in JQ1-resistant cells effectively abrogates MYC expression. Pharmacologic targeting of CDK7 results in decreased enhancer activity in T-ALL and epigenetic reprogramming, in particular for NOTCH1-related enhancers that are not affected by GSI treatment (59). CDK7 inhibition also effectively disrupts the TAL1 superenhancer (60), highlighting that disruption of oncogenic transcription complexes may be an effective approach for T-ALL treatment when direct targeting of mutant genes, proteins, or pathways is not possible. Therefore, the investigation of the epigenetic state of leukemia cells can provide additional insights to guide the use of targeted treatments. Despite promising results in preclinical models, JQ1 has a very short half-life that limits its applicability as a therapeutic agent *in vivo*. Nevertheless, several novel BET inhibitors have been developed by multiple companies, and they are currently under investigation in oncology trials, highlighting the great interest in these epigenetic drugs and their potential application (61). Among these novel agents, OTX015 was proven effective in preclinical leukemia models (62).

Signal Transduction Inhibitors

ABL1/Src-Family Kinase Inhibitors

Unlike B-cell ALL (B-ALL) cases, patients with T-ALL with *ABL1* fusions are rare (18, 63). The most common *ABL1* aberration in T-ALL is the *NUP214–ABL1* fusion due to an episomal amplification of the 9q34 region, which was one of the few discovered T-ALL lesions that can be directly targeted by a kinase inhibitor (63). Usually, *NUP214–ABL1* rearrangements are particularly present at the subclonal level (64). Novel *ZBTB16–ABL1* and *ZMIZ1–ABL1* fusions have been identified in rare T-ALL cases (ref. 65 and unpublished observations), resulting in sensitivity toward imatinib and dasatinib treatment in preclinical models (65). Interestingly, in 2017, Frismantas and colleagues identified a subgroup of patients with T-ALL who are highly sensitive to dasatinib treatment *in vitro* despite the absence of *ABL1* aberrations, suggesting a role for the SRC kinase as a putative novel target for therapy (66). Other studies proposed the lymphocytic-specific kinase LCK, which is often highly expressed in T-ALL, as a prime dasatinib target in T-ALL (67, 68). Based on these preclinical data, patients presenting high SRC phosphorylation and/or increased LCK expression could potentially benefit from dasatinib treatment. Therefore, in addition to genomic analyses, further investigation of the phospho-proteome could highlight aberrantly activated proteins (7) that could serve as biomarkers for dasatinib responsiveness when *ABL1* abnormalities are not present.

JAK Inhibitors

JAK–STAT pathway activation in T-ALL is mainly observed in the context of IL7-induced signaling or caused by activating mutations in the *IL7R* gene or in genes encoding downstream effectors (e.g., *JAK1, JAK3*, or *STAT5*) that are recurrently found at diagnosis (18, 21, 69). Active JAK–STAT signaling leads to the upregulation of various antiapoptotic

and prosurvival proteins including BCL2 and PIM1 and contributes to steroid resistance (21, 70, 71). Ruxolitinib, an FDA-approved JAK1/2 inhibitor for the treatment of myeloproliferative neoplasms (MPN) and graft-versus-host disease (GvHD), blocks JAK–STAT signaling regardless of the presence of mutations (72). In T-ALL, ruxolitinib shows efficacy in IL7-responsive T-ALL and ETP-ALL (69). Ruxolitinib treatment can synergize with dexamethasone treatment to overcome IL7-induced steroid resistance in patients with T-ALL and ETP-ALL. Multiple trials are underway to test the efficacy of ruxolitinib for JAK-mutated T-ALL (Supplementary Table S1) or Philadelphia-like BCP-ALL with CRLF2 rearrangements and/or JAK mutations (NCT2723994, NCT03117751, and NCT02420717) despite the fact that the clinical responses to ruxolitinib in MPNs seem rather limited (73). This indicates that the role of JAK inhibitors should be carefully considered in future treatment regimens of T-ALL.

PIM1 Inhibitors

When exploring alternative treatment options for aberrant JAK–STAT signaling, *PIM1* was identified as a direct STAT5 transcriptional target gene that is also upregulated by physiologic IL7-induced signaling (71, 74, 75). Expression of the prosurvival PIM1 kinase is mainly observed in precortical T-ALL, with the highest expression in the TLX and ETP-ALL subtypes (71, 74, 76, 77). This is in agreement with the higher occurrence of activating mutations in the IL7R signaling pathway in these T-ALL subtypes, including *JAK1/3* and *STAT5B* mutations (18, 21, 22, 78). PIM1 inhibition has proven efficacy in T-ALL using *in vitro* and *in vivo* models, with an increased effect observed for ETP-ALL blasts (74, 77). Both phospho-STAT5 and PIM1 expression levels can be used as a predictive biomarker for response to JAK inhibitors (74). PIM1 inhibition paradoxically results in enhanced MAPK–ERK signaling and may explain the observed synergy of combined PIM1 and MEK inhibitor treatment (74, 79). In addition, synergistic effects of PIM1 inhibitors in combination with venetoclax or dexamethasone have been observed (77, 80), indicating that PIM1 could be a valuable therapeutic target to counteract unfavorable hallmarks of immature/ETP-ALL cases such as high BCL2 expression and steroid resistance.

PI3K–AKT–mTOR Inhibitors

High PI3K–AKT–mTOR signaling is frequently observed in T-ALL and can be caused by a variety of cellular events, including activating mutations in *PI3K* or *AKT*, inactivating lesions in the tumor-suppressor gene *PTEN*, or posttranslational modification of these molecules (21, 30, 31, 81). *PTEN*-inactivating events are predominantly observed in patients with T-ALL that belong to the TAL/LMO subtype. PTEN loss is associated with poor prognosis in T-ALL, resulting in higher risk of disease relapse (29, 30, 81, 82). In addition, IL7R signaling mutations that frequently occur in ETP-ALL and TLX subtypes also activate the downstream PI3K–AKT pathway and correlate with steroid resistance and inferior event-free survival (21, 78). Pan-PI3K inhibitors have shown higher efficacy in inhibiting cell growth and survival of T-ALL cell lines compared with inhibitors that target only specific catalytic subunit(s) of PI3K (83). Preclinical *in vitro* studies demonstrate synergy between PI3K inhibitors and several chemotherapeutic agents, including doxorubicin, nelarabine, and glucocorticoids (21, 84, 85). Moreover, dual PI3K/mTOR inhibitors seem to be even more effective and also synergize with a wide range of chemotherapeutics (85–88).

The effects of the first-generation allosteric mTOR inhibitors rapamycin (sirolimus) and rapalogs RAD001 (everolimus) and CCI-779 (temsirolimus) have been largely investigated in T-ALL (86, 89, 90). These inhibitors target only mTORC1 and can paradoxically activate AKT via PI3K/mTORC2 in some cell types (reviewed in ref. 91). Second-generation ATP-competitive dual mTORC1/mTORC2 inhibitors are more efficient in inducing apoptosis in T-ALL blasts because they also interfere with more downstream PI3K–AKT–mTOR signaling effectors, including a strong inhibition of 4EBP1 phosphorylation (92). The stronger cytotoxic effects and broad PI3K–AKT pathway regulation of dual inhibitors (e.g., PI3K/mTOR and mTORC1/mTORC2 inhibitors) compared with PI3K- or mTORC1-only inhibitors provide evidence that dual inhibitors are more suitable for future clinical trials (91, 93).

Alternatively, the oncogenic signaling of the PI3K–AKT–mTOR axis can also be targeted by direct AKT inhibition. The allosteric AKT inhibitor MK-2206 inhibits AKT and impairs downstream activation of mTORC1, mTORC2, GSK3, and FOXO in various T-ALL cell lines (94). In addition, MK-2206 synergizes with steroids in primary samples of patients with T-ALL (21, 94). ATP-competitive AKT inhibitors like AZD5363 also demonstrate cytotoxic effect against T-ALL cells *in vitro* (95).

MEK Inhibitors

The presence of mutations in *N*- and *K-RAS* genes at diagnosis, which strongly activate the MAPK–ERK signaling, predicts for inferior outcome in both patients with BCP- and T-ALL (82, 96–98). In addition, a high prevalence of these mutations in patients with ALL is found at relapse (10). Although not significantly enriched in relapsed T-ALL, the presence of *RAS* mutations in relapsed pediatric patients with T-ALL predicts for extremely poor outcome (99). *MAPK–ERK*-activating mutations, which may be selected under the pressure of treatment, can contribute to steroid resistance (21, 78, 100). MEK inhibitors induce cell death in *RAS*-mutant cells and synergize with glucocorticoids in primary T-ALL patient cells and *in vivo* BCP-ALL models (21, 97, 101, 102). These findings led to the ongoing SeluDex trial that combines the MEK inhibitor selumetinib with dexamethasone for the treatment of relapsed adult and pediatric patients with BCP- and T-ALL (NCT03705507; Supplementary Table S1). As IL7R and JAK1 signaling mutations strongly activate downstream MEK–ERK signaling, in addition to the JAK-STAT and PI3K-AKT pathways, and strongly provoke steroid resistance in T-ALL (21), patients having such IL7R signaling mutations should also become eligible for selumetinib treatment.

Cell-Cycle Inhibitors

CDK Inhibitors

More than 70% of T-ALL cases downregulate *CDKN2A/B* (18), negative regulators of CDK4/6, either via recurrent gene deletions, sporadic mutations, or promoter hypermethylation

(103). Therefore, the CDK4/6 inhibitors palbociclib and ribociclib could be potential therapeutic options for patients with T-ALL. Palbociclib induces cell-cycle arrest in T-ALL cells and can suppress leukemia progression in animal models (104). Moreover, another preclinical study proved that the CDK4/6 inhibitor ribociclib can act synergistically with glucocorticoids and mTOR inhibitors in both T-ALL cell lines and murine models (90). Current phase I clinical trials for relapsed/refractory pediatric ALL (Supplementary Table S1) are investigating the tolerability of the combination of ribociclib with everolimus and dexamethasone (NCT03740334) or the addition of palbociclib to the standard reinduction chemotherapeutic regimen (NCT03792256). Other aberrations involving cell-cycle regulators include overexpression of the NOTCH1 target Cyclin D3 and CDK6 (18, 19, 21, 65, 99). Moreover, deletions of *CDKN1B* ($p27^{KIP1}$), which is a negative regulator of the Cyclin E–CDK2 complex, have been reported in about 13% of patients with T-ALL (18). Therefore, inhibitors targeting CDK2 might be of interest for the treatment of T-ALL as well. In 2017, Moharram and colleagues reported the efficacy of the CDK1/2/5/9 inhibitor dinaciclib in preclinical T-ALL models (105). Despite the promising results, a clinical trial had already shown only transient effect of dinaciclib treatment for adult patients with leukemia (106).

Nelarabine

Active cell cycle may increase the sensitivity to nucleoside analogue treatment. Nelarabine is a purine nucleoside analogue that inhibits DNA synthesis and shows higher efficacy in T-ALL compared with other malignancies. Whether this is an exclusive T-ALL effect still remains debatable. Nevertheless, T-lymphoblasts show higher accumulation of nelarabine-active metabolite ara-G with consequent increased cytotoxicity compared with other hematopoietic cells (107), making T-ALL cells more susceptible to this treatment. At the moment, it is the only novel drug approved for the treatment of relapsed T-ALL/LBL cases. As a single agent for relapsed or refractory T-ALL in children and young adults, nelarabine had a response rate of over 50% (108). In adults, these response rates were somewhat lower (36% achieved complete remission), but they still provided encouraging results for relapsed cases by inducing clinical remissions that facilitated access to stem cell transplantation (109). However, nelarabine treatment can have significant neurologic side effects depending on other central nervous system (CNS)–directed therapy, in particular in children older than 10 years of age (110). The results of nelarabine safety and efficacy trials in patients with T-ALL/lymphoma highlight considerable single-agent activity in the relapse setting that facilitates disease control. Moreover, nelarabine can be combined with other drugs with nonoverlapping toxicities. The Children's Oncology Group recently published the results of a randomized phase III trial investigating the addition of nelarabine to the chemotherapeutic treatment for newly diagnosed pediatric and young adult patients with T-ALL. The increased disease free-survival rate as well as the decreased CNS relapse incidence without excessive toxicity support the inclusion of nelarabine into frontline therapy for pediatric T-ALL, especially for high-risk cases (111).

Drugs Targeting Mutant p53

Mutations that inactivate p53 are rare in patients with T-ALL at diagnosis (1%–6%) but show an increased incidence at relapse and correlate with poor prognosis (18, 99). A recent study showed that p53-mutant subclones that were detected at first relapse can give rise to clonal p53 mutations detectable in post–stem cell transplantation relapses. Furthermore, in these patients, p53 mutations correlated with an extremely short time to relapse (112). Various reactivators of mutant p53 that induce restoration of the wild-type conformation are in preclinical investigation (113). Interestingly, leukemic blasts from a patient with T-ALL who relapsed after stem cell transplantation showed sensitivity *ex vivo* to the p53 reactivator APR-246 (112). APR-246 has already shown promising results for p53-mutant patients affected by other hematologic malignancies (NCT00900614) and could be a suitable option for patients with T-ALL who relapse after stem cell transplantation and present with p53 mutations.

Drugs Targeting Wild-Type p53

The p53 signaling pathway can be impaired despite the presence of wild-type p53 by overexpression of physiologic p53 inhibitors such as MDM2 or MDM4. In fact, p53 activity can be restored by targeting the E3 ubiquitin ligase MDM2. The MDM2 antagonist idasanutlin disrupts the MDM2–p53 interaction and prevents p53 degradation. Currently, idasanutlin has reached phase I/II clinical trial investigation for pediatric ALL (NCT04029688). Furthermore, another MDM2 inhibitor, NVP-HDM201, is currently being investigated in a phase I/II clinical trial for wild-type p53 tumors, including relapsed ALL (NCT02143635). Lastly, the MDM2/MDM4 stapled peptide ALRN-6924 has reached clinical investigation in pediatric patients with relapsed ALL (NCT03654716).

Immunotherapies

Antibody-Based Therapy

Monoclonal antibodies can be applied in immunotherapies and have entered various trials for T-cell lymphoma (reviewed and summarized in ref. 114). Surprisingly, only a few have been considered in the treatment of ALL, such as anti-CD38 antibodies. CD38 is a transmembrane receptor that is expressed on subsets of myeloid, lymphoid, and some nonhematologic cells. The anti-CD38 monoclonal antibody daratumumab was initially developed for multiple myeloma and was approved by the FDA in 2015 and the European Medicines Agency in 2016 as a single agent for patients with relapsed/refractory multiple myeloma. CD38 is also a promising target for T-ALL as it is robustly and consistently expressed on T-ALL and ETP-ALL blasts at diagnosis, during chemotherapy treatment, and at relapse (115). Moreover, daratumumab displayed great efficacy in 14 of 15 PDX models in NSG mice (115). Of note, the cytotoxic efficacy of daratumumab in NSG mice—that do not have B, T, and natural killer cells, and complement factors—seems therefore independent of T-cell–mediated or complement-dependent cytotoxicity. CD38 expression on regulatory B and T cells as well as on myeloid suppressor cells results in their depletion by

daratumumab, which could boost antitumor responses (116). Clinical trials will reveal whether daratumumab has an even higher efficacy than that observed in NSG mice, as both T-cell–mediated toxicity and repression of regulatory cells will be active in patients with T-ALL. Recently, daratumumab was successfully administered for compassionate use to 3 patients with CD38-positive ALL who experienced multiple relapses, with 1 patient who relapsed after an allogeneic stem cell transplantation (117). Two patients had T-ALL, whereas the third had a CD19/CD22-negative pre–B-ALL, and all three achieved an MRD-negative remission after daratumumab treatment. Trials combining daratumumab treatment with standard chemotherapy for pediatric and young adult patients with ALL are in phase II (NCT03384654; EudraCT 2017-003377-34). Another anti-CD38 monoclonal antibody that is under clinical investigation is isatuximab. An isatuximab trial for adult patients with T-ALL in the United States was closed prematurely due to lack of response, whereas the NCT03860844 trial for pediatric patients with refractory/relapsed acute leukemia is still ongoing.

Preclinical evidences suggest that TCR-expressing T-ALL blasts can be targeted by anti-CD3 antibodies. In fact, the activation of persistent TCR signaling induced by antibodies engaging CD3 leads to cell death *in vitro* and *in vivo* (118), suggesting a novel targeted therapeutic option for T-ALL cases that present TCR expression.

Cellular Therapy

Genetically engineered autologous chimeric antigen receptor T (CAR T) cells have been used successfully as therapy for various malignancies including relapsed ALL. An extensive review recently addressed the challenges and potential solutions for the use of CAR T cells in T-cell malignancies and lists all currently ongoing trials (119). Initially, the challenge to harvest sufficient mature T cells from patients with T-cell malignancies without any lymphoblast contamination hampered the development of CAR T cells against T-ALL/LBL. Most of the CAR T therapies developed so far are dependent on harvesting sufficient autologous and healthy T cells from a single patient. The production of allogenic CAR T cells would eliminate this challenge by using genetically modified T cells from a healthy donor (reviewed in ref. 120). In addition, the fratricide effect—the paradigm that CAR T cells share the same surface markers with their malignant T-cell targets—would rapidly self-extinguish the CAR T cells. After the first approval of the anti-CD19 CAR T for the treatment of pediatric patients with relapsed B-ALL, many different surface proteins have been investigated for the development of novel CAR T therapies directed toward T-cell malignancies, including CD5, CD7, CD1, and CD38. One of the advantages of anti-CD5 CAR T cells is the rapid internalization of CD5 from their cell surface, resulting in a limited and transient fratricide effect (121). Nevertheless, the internalization of CD5 can happen on blasts as well, offering an escape mechanism for leukemia cells that needs to be taken into account. Currently, a phase I anti-CD5 CAR T-cell trial is ongoing for patients with CD5-positive T-ALL or T-cell lymphoma (NCT03081910). As CD5 is expressed on most T-ALL subtypes, while it is absent or expressed at low levels on ETP-ALL cells, there is need for additional CAR T cells that can target ETP-ALL as well. CD7 is a promising target on T lymphoblasts but is also highly expressed on effector T cells. To minimize the fratricide effect, the CRISPR-Cas9 gene editing technology has been used to remove the endogenous *CD7* gene from these CAR T cells (122). A clinical trial using these modified anti-CD7 CAR T cells for treating CD7-positive T-ALL/LBL has been designed (NCT03690011). However, because CD7 is expressed on all thymocytes and T cells, patients receiving CD7 CAR T-cell treatment risk a lifelong T-cell depletion and immunodeficiency that might impair a broad use in the clinic. In order to avoid such side effects and to regulate the activity of these cellular therapies, some CARs have been designed to express an inducible suicide gene (e.g., caspase 9) that can be selectively activated upon administration of a small molecule (reviewed in ref. 123). As an alternative strategy to target CD7, second-generation, fratricide-resistant anti-CD7 CAR T cells have been developed using T cells from healthy donors (UCART7; ref. 124). These CAR T cells have been genetically altered not only to be *CD7* deficient but also to lack the *TCRAD* gene to eliminate the risk for an allogenic CAR T-cell–mediated GvHD. Of note, such an allogenic product can be immediately available for treatment of multiple patients as an "off-the-shelf" product. Promising results on the use of another allogeneic anti-CD7 CAR T-cell treatment were presented at the American Association for Cancer Research virtual meeting in April 2020. Wang and colleagues reported the preliminary exciting data on the efficacy of a single infusion of TruUCAR GC027 (Gracell Biotechnologies) after 6 days of lymphodepleting chemotherapy in 5 adult patients with refractory/relapsed T-ALL enrolled in a phase I clinical trial in China (ChiCTR1900025311). Four patients achieved complete response at day 28 with manageable cytokine release syndrome and absence of neurotoxicities and GvHD, whereas 1 patient who had received the lowest CAR T dose relapsed. Three of 4 patients remained in complete remission at day 161 of follow-up. Future evaluations will investigate the duration of the remissions induced by this treatment (125).

CD1a is another promising target for refractory or relapsed cortical T-ALL (126). Moreover, CD1a is expressed only during the proliferative phase of thymocyte development and not on immature progenitor cells or mature T cells, limiting the risk of complete immunodeficiency after treatment. Recently, the development of fratricide-resistant anti-CD1a CAR T cells for the treatment of CD1a-positive T-ALL has been reported (126). However, because patients with CD1-positive cortical T-ALL have been associated with excellent outcomes, it is not known what percentage of patients with relapsed T-ALL will express CD1 and thus benefit from such a CAR T therapy.

As discussed in the previous section, CD38 is widely expressed on T lymphoblasts, thus the development of anti-CD38 CAR T has also been pursued (127). Recently, the treatment of a relapsed adult patient with B-ALL was reported with the occurrence of serious side effects including cytokine release syndrome and damage to lung and liver tissues that also express the CD38 antigen (128). Therefore, caution and accurate target choices are warranted to extend the repertoire of safe and effective CAR T-cell treatments.

OTHER PROMISING TARGETED TREATMENTS IN DEVELOPMENT

Oncology drug development is constantly growing, and several potential novel candidates have recently been put into the spotlight. New, potentially promising compounds that should be kept in consideration for upcoming studies will be discussed below.

OBI-3424 is a *first-in-class* targeted treatment for liquid and solid tumors that overexpress the Aldo-Keto Reductase 1 c3 (AKR1C3) enzyme such as castrate-resistant prostate cancer and hepatocellular carcinoma. AKR1C3 is also expressed in T-ALL, with the exclusion of *TLX1/3*-rearranged cases (129). OBI-3424 is a prodrug that releases a potent DNA-alkylating component upon intracellular reduction by AKR1C3. This agent has shown promising cytotoxic activity in T-ALL cell lines and PDXs that express AKR1C3 (129). In September 2017, OBI-3424 received FDA orphan drug designation for AKR1C3-expressing tumors, including ALL, and it is currently being investigated in a phase I/II clinical trial for solid tumors (NCT03592264).

Selinexor (KPT-330) is a selective inhibitor of Exportin-1 (XPO1) that has recently been approved in combination with dexamethasone for the treatment of refractory/relapsed multiple myeloma. XPO1 is the key player in nuclear export of receptors (e.g., NR3C1), tumor-suppressor proteins (e.g., p53 and pRB) but also oncogenic mRNAs transcribed from *MDM2, BCL2*, and *MYC*, which will be retained in the nucleus upon XPO1 inhibition. Selinexor treatment is currently being investigated in a phase I clinical trial for relapsed pediatric acute leukemia (NCT02091245). Furthermore, the second-generation XPO1 inhibitor *eltanexor* (KPT-8602) can induce cytotoxicity and apoptosis in ALL models and can enhance the efficacy of dexamethasone treatment (130).

Histone deacetylases (HDAC) are key enzymes in chromatin remodeling and epigenetic gene regulation. HDACs are frequently overexpressed in cancer, including T-ALL. Samples of patients with T-ALL demonstrate higher HDAC1 and HDAC4 but lower HDAC5 levels compared with B-ALL (131). The pan-HDAC inhibitor *panobinostat* has shown anti-leukemic activity in T-ALL preclinical models (132), and it is under clinical investigation for relapsed acute leukemia (Supplementary Table S1). The same applies for *vorinostat*, which is already approved for the treatment of refractory/relapsed cutaneous T-cell lymphoma.

Additional epigenetic regulators that can be pharmacologically targeted are DNA methyltransferases. DNA methyltransferase inhibitors *decitabine* and *azacitidine* induce chromatin hypomethylation with a consequent alteration in gene transcription. They have been approved for the treatment of myelodysplastic syndromes and are currently being investigated in early-phase clinical trials for pediatric patients with ALL (Supplementary Table S1). In 2016, Lu and colleagues showed that decitabine pretreatment enhanced chemosensitivity of preclinical models of ETP-ALL (133). One year later, the successful treatment of a relapsed adult patient with ETP-ALL with decitabine was reported (134), therefore offering a promising opportunity for salvage therapy of ETP-ALL cases.

An alternative way to target oncogenic signaling pathways is by tackling protein stability or degradation. Cancer cells become addicted to the rapid elimination of tumor-suppressor proteins or may require higher protein turnover to sustain their metabolism. Therefore, processes involved in protein degradation can provide leukemia-specific vulnerabilities that can be effectively targeted. *Bortezomib*, a *first-in-class* proteasome inhibitor, is approved for the treatment of refractory multiple myeloma. It inhibits the 26S subunit of the proteasome, impairing protein degradation that results in cell-cycle arrest and eventually apoptosis. A recent report of the Children's Oncology Group highlights the safety of bortezomib during reinduction chemotherapy for pediatric relapsed ALL and provided encouraging results for T-ALL, with an increase in patients achieving complete remission (135). Another way of altering protein stability and activity is through inhibition of the Nedd8-activating enzyme (NAE). NAE is an ubiquitin-like protein that regulates the activity and the protein–protein interactions of NF-kB and cullins, which are essential cell-cycle regulators (136). Preclinical data showed that the NAE inhibitor *pevonedistat* (MLN4924) can induce cell-cycle arrest and apoptosis in T-ALL models (136). Both bortezomib and pevonedistat are currently under clinical investigation for patients with ALL (Supplementary Table S1).

Aurora kinases (AURK) are mitotic regulators often overexpressed in cancer, including pediatric ALL (137). The AURKA inhibitor alisertib (MLN8237) had shown promising results for both ALL and lymphoma cells *in vitro* (138). Unfortunately, a phase II clinical trial from the Children's Oncology Group reported objective response after alisertib single-agent treatment in less than 5% of the pediatric patients with recurrent/refractory advanced solid tumor or acute leukemia (139). Recent evidence elucidates a role for AURKB in inhibiting proteasomal degradation of MYC, thus stabilizing this oncogenic protein (140). *In vitro* treatment of T-ALL cells with the AURKB inhibitor barasertib (AZD1152) leads to reduced MYC protein levels (140) and enhanced cell death (140, 141). Furthermore, AZD1152 can act in synergy with vincristine (140).

CONCLUSIONS

The outcome for children diagnosed with T-ALL has dramatically improved in the last decades. Nevertheless, therapy resistance, disease relapse, treatment-related death, and long-term detrimental side effects for cancer survivors remain serious issues to be solved. In addition, the lack of predictive biomarkers at diagnosis remains an unmet need for patients with T-ALL. In this review, we presented an overview of the current state of drug development and ongoing clinical trials that are of interest for the T-ALL field, integrating preclinical evidence and clinical data. Several molecular tumor profiling protocols have been initiated in Europe (e.g., MOSCATO-01, iTHER, and ESMART; ref. 142) to identify actionable lesions for targeted treatment in specific subgroups of patients. This highlights the importance of bridging preclinical research with clinical practice to accelerate the use of promising novel drugs in effective new treatment combinations for patients with T-ALL.

Authors' Disclosures

No disclosures were reported.

Acknowledgments

This study was supported by Dutch Cancer Society (KWF Kankerbestrijding, grant number KWF2016_10355, to V. Cordo') and Stichting Kinderen Kankervrij (grant number KiKa219, to J.C.G. van der Zwet; grant number KiKa295, to K. Canté-Barrett).

Received June 4, 2020; revised October 8, 2020; accepted October 28, 2020; published first November 24, 2020.

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