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An Overview of Targeted Therapies in Acute Myeloid Leukemia

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ABSTRACT

Acute myeloid leukemia (AML) is the most aggressive adult leukemia, characterized by clonal differentiation arrest of progenitor or precursor hematopoietic cells. Intense preclinical and clinical research has led to regulatory approval of several targeted therapeutics, administered either as single agents or as combination therapies. However, the majority of patients still face a poor prognosis and disease relapse frequently occurs due to selection of therapy-resistant clones. Hence, more effective novel therapies, most likely as innovative, rational combination therapies, are urgently needed. Chromosomal aberrations, gene mutations, and epigenetic alterations drive AML pathogenesis but concurrently provide vulnerabilities to specifically target leukemic cells. Other molecules, either aberrantly active and/or overexpressed in leukemic stem cells, may also be leveraged for therapeutic benefit. This concise review of targeted therapies for AML treatment, which are either approved or are being actively investigated in clinical trials or recent preclinical studies, provides a flavor of the direction of travel, but also highlights the current challenges in AML treatment.

Acute myeloid leukemia (AML) is the most aggressive adult acute leukemia, which still has a high unmet clinical need. Although treatment outcomes have improved, and multiple new drugs have been licensed over the last few decades, most patients still face a dismal prognosis. Approximately 70% of AML patients are above the age of 65 years and are mostly treated with nonintensive chemotherapy. The current standard of care for this patient group is a combination of the BCL2 inhibitor venetoclax and the hypomethylating agent (HMA) azacitidine. The median survival is 14.5 months, and patients are usually not cured. The remaining 30% of patients, usually aged <60 years, are treated with >1 course of intensive combination chemotherapy, potentially combined with targeted therapies. Patients at high risk of treatment failure receive allogeneic stem cell transplantation (allo-SCT). Although the cure rates for this group are ~30%–70%, the majority of intensively treated patients still die of their disease.

A significant advance in AML biology and treatment has been the definition of the genetic and cytogenetic landscape of the disease.[1,2] This has provided genetic markers for diagnostic and prognostic purposes, as well as markers used to follow the depth of therapy response (also known as measurement of residual disease). In some cases, the discovery of genetic markers has led to the development of specific therapies targeting mutant proteins essential for AML propagation.

Therapeutic targets in AML can be broadly classified into 6 categories (Table 1; Figure 1).

FUSION PROTEINS: THE PARADIGM FOR TARGETED THERAPY IN MYELOID MALIGNANCIES

Recurrent chromosomal aberrations can generate fusion proteins, which cause differentiation block and sustain malignant transformation, but may also create a critical therapeutic vulnerability of leukemic cells.[3] The fusion protein stemming from the Philadelphia chromosome in chronic myelogenous leukemia (CML),[4] which generates the BCR-ABL1 oncogene with constitutive tyrosine kinase activity, is the exemplar of a targetable fusion protein in myeloid malignancy. Imatinib,[5] a specific inhibitor of the BCR-ABL1 kinase domain,[6] transformed the care of CML patients and introduced the concept of targeting products of somatic alteration in cancer. Targeted therapies have also revolutionized the treatment of acute promyelocytic leukemia (APL), caused by the promyelocytic leukemia-retinoic acid receptor alpha (PML-RARA) fusion oncoprotein,[7,8] which blocks granulocytic differentiation.[9] Patients now routinely receive all-trans retinoic acid (ATRA), which reverses transcriptional repression imposed by PML-RARA, thus promoting granulocyte differentiation. ATRA is combined with arsenic trioxide (ATO), which degrades PML-RARA, removing the oncogenic protein that sustains APL. A chemotherapy-free regimen combining ATRA and ATO has led to >90% overall survival (OS).[10,11] This approach highlighted the potential for differentiation therapy in leukemia[12] and demonstrated the importance of combining targeted therapies with synergistic mechanisms of action.[13]

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The therapeutic success in CML and APL has been harder to replicate for other oncogenic fusion proteins, especially those involving transcription factors. One approach to developing targeted therapy for AML driven by transcription factor fusion proteins is to target pathways downstream of these transcription factors. An example is the inhibition of Menin,[14] a required coactivator for MLL (KMT2A) fusion proteins. Menin and oncogenic MLL fusion proteins coordinately activate the transcription of *HOX* family members and *MEIS1*.[15,16] These observations, coupled with preclinical data showing promising activity of Menin inhibition,[17–19] prompted first-in-human clinical trials of multiple Menin inhibitors, namely revumenib,[20,21] ziftomenib,[22] and JNJ-6617 (NCT04811560), in *MLL*-rearranged and *NPM1*-mutated leukemia. As one may expect, second-site mutations in the *MEN1* gene, encoding Menin, confer resistance to revumenib.[21] MLL fusions also interact with the histone methyltransferase DOT1L, required for aberrant activation of target genes.[23] In a phase I study, the DOT1L inhibitor pinometostat showed limited single-agent activity in *MLL*-rearranged adult AML.[24] Pinometostat is now being evaluated in combination with azacitidine.[25]

Table 1

Therapeutic Targets in AML

Type of Target	Targets
Genetic Targets	Fusion Oncoproteins, FLT3, IDH1/2, p53, KIT
Targets involved in apoptosis	BCL2, MCL-1, BCL-XL, MDM2
Signaling molecules or nuclear receptors	RAS pathway, SYK, RARα
Epigenetic regulators	Menin, DOT1L
Surface proteins and/or molecules involved in immune signaling	Smoothened, CD33, CD123, CD47, SIRPα, AXL, TIM-3, CLL-1, PD-1/PD-L1, and CTLA-4 axes
Transcription factors and other molecules subject to targeted protein degradation	EZH2, GSPT1

GENETIC TARGETS RESULTING FROM SOMATIC MUTATION AND OTHER ABERRANTLY ACTIVE TARGETS

Driver somatic mutations, which produce mutated proteins imparting a fitness advantage to AML cells, also provide an opportunity to develop targeted therapies (Table 2). For example, gain-of-function mutations in the *FLT3* gene, encoding a transmembrane receptor tyrosine kinase (RTK), are found in ~30% of younger AML patients and at lower frequency in older patients. Most *FLT3* mutations occur as internal tandem duplications (*FLT3*-ITD) within the gene locus encoding the juxtamembrane domain or as point mutations within the locus encoding the tyrosine kinase domain activation loop (*FLT3*-TK). Mutant FLT3 proteins transmit a constitutively active ligand-independent signal to aberrantly activate prosurvival and proproliferative RAS/MAPK, PI3K/AKT, and JAK/STAT pathways.[26] Type I FLT3 inhibitors, such as midostaurin, gilteritinib, and crenolanib, bind the kinase active conformation, inhibiting both FLT3-ITD and FLT3-TK proteins. Type II FLT3 inhibitors, including

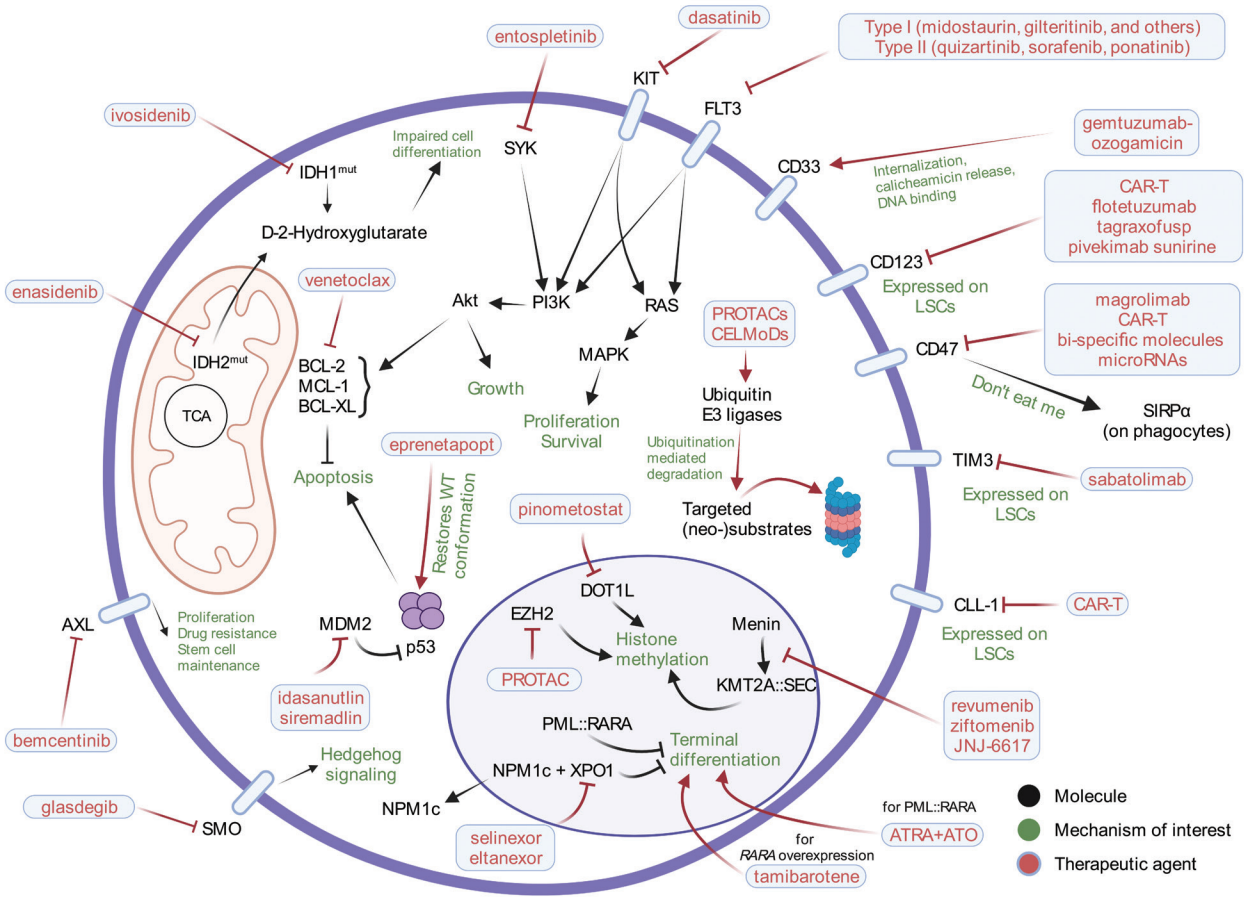

Figure 1. Overview of therapeutic agents and targeted pathways in AML. Schematic overview of targeted molecules found either on the AML cell surface or within the cytoplasm, nucleus, or mitochondria of AML cells. The molecules used as therapeutic agents are labeled in red. Targeted molecules are labeled in black. Cellular mechanisms involved or targeted molecule expression patterns are labeled in green. AML = acute myeloid leukemia.

Table 2

Overview of Targeted Therapies in Acute Myeloid Leukemia, Which are Either Approved or Are Being Investigated in Clinical Trials

Target	Therapeutic(s)	Mechanism of Action
PML-RARA	All-trans retinoic acid + arsenic trioxide	PML-RARA configuration change, which results in coregulator exchange; sumoylation and degradation of PML-RARA
Menin	Revumenib	Menin-MLL interaction inhibition
	Ziftomenib	Menin-MLL interaction inhibition
	JNJ-6617	Menin-MLL interaction inhibition
DOT1L	Pinometostat	Specific DOT1L inhibition via conformational change
FLT3	Type I (targeting FLT3-ITD and FLT3-TK) Midostaurin Crenolanib Gilterinib	FLT3 inhibition, binds FLT3 receptor in active conformation
	Type II (targeting FLT3-ITD) Quizartinib Sorafenib	FLT3 inhibition, binds FLT3 receptor in inactive conformation
Several kinases (KIT, SRC family, BCR-ABL, others)	Dasatinib	ATP-competitive protein tyrosine kinase inhibition
Mutated IDH1	Ivosidenib	Selective allosteric inhibition of mutant IDH1
Mutated IDH2	Enasidenib	Selective allosteric inhibition of mutant IDH2
Mutant p53	Eprenetapopt	Covalent p53 core domain binding, partial restoration of WT function
XPO1	Selinexor	Selective XPO1 inhibition
	Eltanexor	Selective XPO1 inhibition
SYK	Entospletinib	Selective SYK inhibition
RARα	Tamibarotene	RARα agonism
BCL2	Venetoclax	BCL2 sequestration (BH3-mimetic)
MCL-1	Murizatoclax	Selective MCL-1 inhibition
MEK	Cobimetinib	Selective MEK1 inhibition
MDM2	Idasanutlin	p53-MDM2 interaction inhibition
	Siremadlin	p53-MDM2 interaction inhibition
Smoothened	Glasdegib	Inhibition of the translocation of Smoothened to the primary cilium
CD33	Gemtuzumab ozogamicin	Gets internalized, subsequent calicheamicin causes DNA double-strand breaks
CD123	Tagraxofusp	Anti-CD123 antibody fused to diphtheria toxin, gets internalized and blocks protein synthesis via eEF2 inhibition
	Pivekimab sunirine	Anti-CD123 antibody fused to indolinobenzodiazepine pseudodimer payload, leading to DNA alkylation and single-strand breaks
CD3/CD123	Flotetuzumab, UCART123v1.2	Anti-CD3/CD123 bispecific antibody; recruitment of T cells to CD123-expressing cells
CLL-1	CAR-T cells	Recruitment of T cells to CLL-1-expressing cells
TIM-3	Sabatolimab	Anti-TIM-3 monoclonal antibody—blockage of ligand binding
CD47/SIRPα	Magrolimab, TTI-621	Inhibition of the CD47-SIRPα axis
AXL	Bemcentinib	Selective AXL inhibition
CTLA-4	Ipilimumab	Anti-CTLA-4 monoclonal antibody—immune checkpoint inhibition
PD-1	Nivolumab, pembrolizumab	Anti-PD-1 monoclonal antibody—immune checkpoint inhibition
GSPT1	CC-90009	Linkage of GSPT1 to an E3 ubiquitin ligase—promotes GSPT1 degradation

quizartinib and sorafenib, bind the kinase-inactive conformation and are only active against FLT3-ITD. These inhibitors decrease FLT3 autophosphorylation, reducing FLT3 signaling.

Following successful phase III clinical trials, midostaurin[27] was approved in combination with chemotherapy in frontline *FLT3*-mutated AML, while gilteritinib was approved as single-agent in *FLT3*-mutated relapsed or refractory AML (R/R AML).[28] In addition, results of a phase III trial of quizartinib combined with intensive chemotherapy showed superior OS compared with intensive chemotherapy alone,[29] and a decision on regulatory approval is awaited. A common mechanism of resistance to FLT3 inhibitors arises from secondary mutations in the ATP-binding region within the FLT3 kinase domain,[30,31] which seem to be inhibitor-specific.[31] Alternatively, activating mutations in genes encoding members of downstream RAS/MAPK or JAK/STAT pathways, or persistent activation of pathways downstream of FLT3 due to stimulation from microenvironmental factors, can be selected by treatment and mediate resistance.[32–36] Accordingly, preclinical data indicate that combining FLT3 and MEK inhibition could be more efficient in causing leukemic cell death.[34,37] FLT3 inhibitors are actively being evaluated in combination with venetoclax,[38] venetoclax/azacitidine,[39] venetoclax/ASTX727,[40] and as single agents post allo-SCT[41,42] (NCT02997202) or postchemotherapy[43] (NCT02668653 for quizartinib with chemotherapy or as continuation therapy).

Activating mutations in *KIT*, encoding another RTK upstream of PI3K/AKT, RAS/MAPK, and JAK/STAT pathways, occur in a subset of core-binding factor (CBF) AML patients. Notably, KIT D816 mutations have been associated with poorer outcomes in chemotherapy-treated patients.[44] Dasatinib is a multikinase inhibitor active against KIT, SRC family, BCR-ABL, and other kinases. Phase II clinical trials of dasatinib with intensive chemotherapy reported favorable event-free survival and cumulative incidence of relapse in newly diagnosed CBF AML patients.[45,46] Notably, survival outcomes were compared favorably with a historical control group treated with chemotherapy alone.[45] Ongoing adequately powered phase III trials will better elucidate dasatinib's role in this setting (NCT02013648).

Approximately 20% of AMLs harbor hotspot gain-of-function mutations in *IDH1* and *IDH2*, encoding isocitrate dehydrogenase (IDH) enzymes.[47] Wild-type IDH catalyzes the conversion of isocitrate to α-ketoglutarate (α-KG) in the tricarboxylic acid (TCA) cycle. Neomorphic mutant IDH catalyzes the production of the oncometabolite 2-hydroxyglutarate (2-HG)[48] from α-KG, resulting in competitive inhibition of α-KG-dependent enzymes, including ten-eleven translocation (TET) family of 5-methylcytosine hydroxylases[49] and Jumonji-C domain histone demethylases.[50,51] This leads to DNA hypermethylation and impaired hematopoietic differentiation.[52] The small molecules ivosidenib and enasidenib, allosteric inhibitors of mutant IDH1 and IDH2, respectively, reverse DNA hypermethylation and promote differentiation.[47] Both agents were approved by the FDA for the treatment of *IDH*-mutated AML.[53–55] Notably, cooccurring *RUNX1* and *NRAS* mutations, as well as a more stem-like transcriptional state of leukemic cells, correlated with poorer responses to mutant IDH inhibition and may mediate primary resistance.[56,57] Unsurprisingly, when mutant IDH inhibitors are used as monotherapy, disease relapse occurs by selecting therapy-resistant clones that have acquired multiple genetic resistance mechanisms.[56,58] These include *TET2*, *BCOR*, *FLT3*, and RAS pathway mutations, as well as mutations in transcription factors involved in hematopoietic differentiation, which may re-establish differentiation block.[56,58] Restoration of 2-HG through either secondary *IDH* mutations,[59,60] which compromise inhibitor binding, or via selection of mutations on the gene encoding the second IDH isoform (isoform switching),[58,59,61] have also been reported. Consequently, both ivosidenib and

enasidenib are being tested in combination with chemotherapy, HMAs, and venetoclax.[53,62–64]

TP53 mutations occur in 8%–12% of AML patients, a significant proportion of which also have complex or monosomal karyotypes.[65] These genetic features correlate with universally poor prognosis.[2,66] The small molecule eprenetapopt covalently binds to the core domain of p53,[67] which mediates the cooperative DNA binding of p53. In some cases, this leads to appropriate refolding and restoration of p53 function. Eprenetapopt demonstrated encouraging activity in early-phase trials when combined with azacitidine[68,69] and when administered post allo-SCT,[70] but this activity was not validated in a phase III trial in *TP53*-mutated higher-risk MDS, which failed to meet its primary end point of a higher complete remission (CR) rate (NCT03745716).

Approximately, 30% of AML patients harbor hotspot mutations in exon 12 of the *NPM1* gene,[2,71] causing a frameshift that forms a novel C-terminal nuclear export signal (NES) and causes loss of a nucleolar localization signal. This results in the NPM1c neomorphic oncoprotein with predominantly cytoplasmic localization.[72,73] Due to the novel C-terminal NES, NPM1c is more efficiently exported from the nucleus and binds with higher affinity to the nuclear exporter XPO1 (CRM1).[74] It has been proposed that increased nuclear export of NPM1c hijacks several proteins from the nucleus, including PU.1[75] and CTCF,[76] thus disrupting their normal function.[74] Furthermore, NPM1c interferes with the p53 pathway by destabilizing the Arf tumor suppressor.[77] Notably, *NPM1*-mutated AML typically displays a high expression of *HOXA*/*HOXB* cluster and *MEIS1* genes,[78] which depends on NPM1c.[79] In this regard, 2 recent studies have demonstrated that the nuclear portion of NPM1c directly regulates the transcription of several target genes, including *HOX* family and *MEIS1*.[80,81] In fact, NPM1c binds chromatin through the interaction with XPO1 and cooperates with MLL/Menin activity, likely underscoring favorable activity of Menin and DOT1L inhibitors in *NPM1*-mutated AML models.[82,83] Notably, combined inhibition of XPO1 and Menin showed a synergistic decrease in *HOX* and *MEIS1* expression, decreased colony-forming capacity of AML blasts, and induction of differentiation in model systems.[80,81] The XPO1 inhibitor selinexor has shown promise in early trials on patients with hematologic malignancies, including AML,[84] while the next-generation XPO1 inhibitor eltanexor demonstrated reduced toxicity compared with selinexor in preclinical models.[85] Hence, there is a sound rationale for testing the combination of XPO1 and Menin inhibitors in *NPM1*-mutated AML patients.

Other molecules, which are aberrantly expressed and/or active, rather than mutant, have also been targeted therapeutically. One exemplar is the non-RTK SYK that has been shown to cooperate both with FLT3-ITD[86] and HOXA9/MEIS1.[87] In a phase Ib/II study in previously untreated AML patients, the SYK inhibitor entospletinib combined with induction chemotherapy led to composite CR of 70%, with potentially improved OS in patients with high basal *HOXA9* and *MEIS1* expression.[88] A phase II trial of entospletinib combined with induction and consolidation chemotherapy in newly diagnosed *NPM1*-mutated/*FLT3*-ITD-wild-type AML patients reported a composite CR rate of 78% and a median duration of response of 15.7 months.[89] A phase III trial of entospletinib with chemotherapy in previously untreated *NPM1*-mutated AML patients is ongoing (NCT05020665).

Interestingly, the *RARA* gene is overexpressed in a significant proportion of non-APL AML and MDS patients. This has provided the impetus for the development of the RARα agonist tamibarotene. In preclinical models of RARα-high AML, tamibarotene induced AML differentiation, reminiscent of ATRA activity in APL.[90] A phase II clinical trial combining tamibarotene and azacitidine showed that 61% of evaluable RARα-high patients achieved CR or CR with incomplete hematological recovery (CRi).[91] Ongoing trials are testing tamibarotene with venetoclax/azacitidine in newly diagnosed AML or with azacitidine in higher-risk myelodysplastic syndrome (MDS) (NCT04905407 and NCT04797780).

TARGETS INVOLVED IN APOPTOSIS

Regulation of apoptosis is often aberrant in cancer.[92] A significant proportion of AML cells are highly dependent on the antiapoptotic BCL2 protein for their survival.[93,94] Furthermore, BCL2 is overexpressed in functionally defined leukemia stem cells (LSCs).[95] Concordantly, high levels of BCL2 correlate with chemoresistance in AML.[96] The BH3-mimetic venetoclax is a selective BCL2 inhibitor that sequesters BCL2, thus precluding its binding to proapoptotic proteins. Venetoclax demonstrated efficacy when combined with azacitidine or low-dose cytarabine (LDAC) in treatment-naïve AML patients.[97,98] These combinations are now the standard of care for AML patients unfit for intensive chemotherapy.

Importantly, response to venetoclax, or venetoclax combinations, varies with the genetic subtype of AML. *IDH1/2*-mutated AML has high response rates and more durable remissions to venetoclax.[99] These clinical observations are concordant with preclinical data showing that *IDH*-mutated AML cells are highly dependent on BCL2 for survival due to the inhibition of cytochrome c oxidase by 2-HG, which decreases the threshold for apoptosis.[100] Of note, remission rates for *IDH2*-mutated patients treated with venetoclax/azacitidine were particularly high, even when compared with *IDH1*-mutated patients.[101] For *IDH1*-mutated AML, venetoclax has also recently been combined with ivosidenib and ivosidenib/azacitidine, resulting in encouraging preliminary response rates.[63] Poorer responses to venetoclax/azacitidine have been noted with *FLT3*– (in the absence of *NPM1* mutation), *TP53*–, and *RAS*-mutated AML.[102,103] Interestingly, venetoclax combined with the protein translation inhibitor omacetaxine showed encouraging preclinical activity in *RUNX1*-mutated AML models.[104]

Despite these promising results, multiple mechanisms of resistance to venetoclax have been described in AML.[105] For example, the selection of the monocytic differentiation program[106] is associated with increased expression and function of the antiapoptotic protein MCL-1. Consistent with MCL-1 mediating venetoclax resistance, several preclinical studies have shown that inhibition of BCL2 and MCL-1 synergize in AML models.[107–109] Clinical trials with MCL-1 inhibitors have been ongoing for some time but have been complicated by on-target cardiac toxicity (NCT03465540). An additional mechanism of venetoclax resistance includes the selection of clones with mutations in *FLT3*, *TP53*, and genes mediating RAS/MAPK signalling.[105] Hence, to potentially mitigate resistance, rational combinations of venetoclax or venetoclax/azacitidine with inhibitors of FLT3,[38,39,105,110] MEK,[111,112] or MDM2[113,114] are being actively studied in preclinical and clinical settings. By combining clonal tracking and RNA-Seq at single-cell resolution, we are currently investigating the mechanisms of therapy response and resistance to venetoclax and ivosidenib +/– azacitidine.[63]

Besides induction of apoptosis, BCL2 inhibition also decreases levels of oxidative phosphorylation (OxPhos) in functionally defined LSCs.[95] Moreover, the venetoclax/azacitidine treatment disrupts amino acid uptake[115] and the TCA cycle,[116] with consequent decrease in OxPhos and energy metabolism in these cells. Consistently, resistance to venetoclax/azacitidine arises from upregulation of fatty acid oxidation, which replenishes energy production,[117] and from increased nicotinamide levels,[118] which promote both fatty acid oxidation and amino acid metabolism, thus driving OxPhos. Hence, variations in central energy metabolism represent an important resistance mechanism to venetoclax/azacitidine and correlate with mutations in *TP53*[119] and genes mediating RAS/MAPK signaling.[117] Importantly, MCL-1

inhibition decreased fatty acid oxidation and engraftment of venetoclax/azacitidine-resistant LSCs.[117] These studies not only further highlight the potential benefits of MCL-1 inhibition in venetoclax/azacitidine-resistant AML but also encourage clinical investigation of agents targeting intermediate metabolism, with key considerations regarding treatment specificity.

SURFACE PROTEIN TARGETING

Several therapeutic strategies target proteins expressed on the AML cell surface (Table 2). One target is the smoothened transmembrane protein, which mediates Hedgehog signaling by activating GLI transcription factors in proximity to the cellular structure known as primary cilium. Glasdegib inhibits the translocation of smoothened to the primary cilium, thus blunting GLI activation.[120] Although there is limited knowledge about the exact role of this pathway in AML, encouraging data from a phase II clinical trial showed that the addition of glasdegib to LDAC improved median OS compared with LDAC alone (8.8 months versus 4.9 months), in older or unfit AML and high-risk MDS patients.[121] This led to the licensing of a smoothened inhibitor glasdegib combined with LDAC in the USA (2018) and in the EU (2020). A current phase III trial is evaluating glasdegib in combination with intensive chemotherapy or azacitidine in previously untreated AML patients (NCT03416179).

CD33 and CD123 molecules are generally found on subsets of hematopoietic cells but are highly expressed on the AML cell surface in most patients.[122] Gemtuzumab ozogamicin is a humanized anti-CD33 monoclonal antibody conjugated to the cytotoxic drug calicheamicin. Upon binding to CD33, gemtuzumab ozogamicin is internalized, and calicheamicin is released, causing DNA double-strand breaks, which trigger cell death. Gemtuzumab ozogamicin has been approved in combination with intensive chemotherapy for newly diagnosed AML.[123,124] Interestingly, gemtuzumab ozogamicin, in combination with intensive chemotherapy, has maximal benefit in good prognosis CBF AML, but the reasons for this are still not entirely clear.

Tagraxofusp is a recombinant anti-CD123 (IL-3 receptor alpha chain) antibody fused to diphtheria toxin. When bound to CD123, tagraxofusp is internalized and blocks protein synthesis via eEF2 inhibition. Tagraxofusp has shown clinical benefit in blastic plasmacytoid dendritic cell neoplasm, a specific form of myeloid malignancy with high CD123 expression.[125] Tagraxofusp has also been combined with azacitidine or venetoclax/azacitidine in CD123-positive AML and MDS patients. Eight of the 9 previously untreated AML patients and 3 of 4 of previously untreated MDS patients achieved CR/CRi.[126] Of note, 2 responding AML patients and 3 responding MDS patients were *TP53*-mutated. Another anti-CD123 antibody-drug conjugate, pivekimab sunirine, which causes DNA alkylation,[127] led to objective response rates (ORR) of 51% when combined with venetoclax/azacitidine in CD123-positive R/R AML, with auspicious activity in the *FLT3*-ITD subgroup, where ORR was 82%.[128]

Bispecific antibodies, typically bispecific T-cell engagers, recruit T cells to tumors via an anti-CD3 moiety by binding to a tumor-specific antigen. An exemplar is blinatumomab, used to treat B-cell acute lymphoblastic leukemia. The success of blinatumomab has triggered enormous activity in this therapeutic area with variations in the mechanisms of action. One example is the concept of dual affinity retargeting antibodies such as flotetuzumab, an anti-CD3/CD123 bispecific antibody.[129] In phase 1 of 2 studies, 26.6% R/R AML patients who did not respond to induction therapy or who experienced early relapse postinduction therapy achieved CR/CRh with a median OS of 10.2 months. Interestingly, a 10-gene signature derived from diagnostic bone marrow was predictive of CR.

Chimeric antigen receptor (CAR) T-cell therapy has been transformative in lymphoid malignancy. CD19-directed CAR-T led the initial wave of therapies,[130–132] which was recognized by the American Society of Clinical Oncology[133] as the advance of the year in 2018. Between 2018 and 2023, 5 CAR-T cell therapies targeting CD19 or B-cell maturation antigen were authorized for sale. However, finding a suitable antigen target for AML that is not present on normal myeloid cells has been a challenge. CD123-directed CAR-T cells showed promising antileukemic activity in vitro and in vivo, with limited toxicity toward healthy hematopoietic cells.[134] A phase I trial evaluated UCART123v1.2, an allogeneic anti-CD123 T-cell product, in 16 CD123-positive R/R AML patients.[135] Four patients showed evidence of activity, including 1 long-term CR. Another approach has been universal CAR-T therapy with inducible activity of the CD123-targeting module. In a phase I trial of 14 CD123-positive R/R AML, 3 patients achieved CR/CRi, with 4 partial responses.[136] Anti-CD123 CAR-T cells have also been tested in pediatric R/R AML patients[137] in a phase I study. CAR-T cells against the surface molecule CLL-1 have shown some promise, with 7 of 10 R/R AML patients achieving CR/CRi in a phase I trial.[138]

TIM-3 is a surface receptor preferentially expressed on AML cells with LSC function compared with normal HSCs.[139] Moreover, TIM-3 marks dysfunctional and/or exhausted subsets of T cells in viral infections and cancer.[140,141] Concordantly, xenograft data in nonobese diabetic-severe combined immunodeficiency (NOD-SCID) mice showed a decrease in AML reconstitution and LSC function following antibody targeting of TIM-3.[142] Sabatolimab, an anti-TIM-3 monoclonal antibody, combined with HMAs, achieved a CR/CRi rate of 30% in the Revised International Prognostic Scoring System for high-/very high-risk MDS and newly diagnosed AML patients unfit for intensive chemotherapy.[143] More extensive phase II/III clinical trials are currently evaluating the efficacy of sabatolimab in multiple regimens.[144]

An alternative targeted strategy harnesses autologous innate immunity to specifically kill leukemic cells. CD47 (integrin-associated protein) is a surface molecule mediating *don't eat me* signals. This occurs via CD47-SIRPα interactions, which inhibit macrophage-mediated phagocytosis.[145] Notably, CD47 is upregulated both on LSC-enriched and nonenriched AML cells, compared with normal hematopoietic cells, predicting poor outcome.[146,147] Targeting the CD47-SIRPα axis has thus led to multiple drugs in preclinical and clinical development, including monoclonal antibodies, fusion proteins, bispecific antibodies, small molecules, RNA interference, and CD47-directed CAR-T cells. Importantly, anti-CD47 monoclonal antibodies stimulated AML cell phagocytosis in vivo while sparing normal HSCs.[146] This encouraged the development of magrolimab, a humanized anti-CD47 antibody, which was well-tolerated in R/R AML patients in the CAMELLIA phase 1 trial.[148] Results from a subsequent phase IB trial combining magrolimab with azacitidine in 95 untreated intermediate/high- and very high-risk MDS patients have just been reported. Sixty-two percent of patients had poor-risk cytogenetics, and 26% had a *TP53* mutation.[149] The combination was well-tolerated, the CR rate was 33%, and the duration of the overall response was 9.8 months. Median OS was not reached with a median 17.1-month follow-up. About 40% of *TP53*-mutated patients achieved CR and had a median OS of 16.1 months. Results from a phase Ib trial of magrolimab+azacitidine in 87 previously untreated AML patients, 72 of which *TP53*-mutated (median variant allele frequency of 61%), have also just been reported (Daver et al, invited revision resubmitted at *Journal of Clinical Oncology*). About 79.2% of *TP53*-mutated patients had adverse-risk cytogenetics according to the European LeukemiaNet (ELN) 2017 classification. Totally 28 (32.2%) patients achieved CR, including 23 (31.9%) patients with *TP53* mutations. Median OS in *TP53*-mutated patients was 9.8 months and 18.9 months in *TP53*-wild-type patients. Magrolimab has also been combined with venetoclax/azacitidine in a phase I/II study, displaying an ORR of 80% in newly diagnosed AML and 75% in venetoclax-naïve R/R AML.[150] Of note, 63% of newly diagnosed *TP53*-mutant patients achieved

CR/CRi. Three phase III trials of magrolimab combinations in previously untreated higher-risk MDS and AML patients are in progress and will determine its clinical role (NCT04313881, NCT05079230, and NCT04778397). Other approaches targeting the CD47-SIRPα axis include the fusion protein TTI-621 (SIRPα-IgG1 Fc), which inhibited the growth of AML xenografts,[151] leading to its evaluation in early-phase clinical trials for hematological malignancies.[152] In addition, the bispecific molecule PD1xCD47 BsAb HX009 has very recently shown antileukemic activity in a patient-derived xenograft model of AML.[153]

MicroRNAs repress gene expression by selective binding to the 3′ untranslated regions of target genes, which induces mRNA degradation and inhibition of translation.[154] In a preclinical study, miR-708 was shown to negatively regulate *CD47* expression and to inhibit T-ALL engraftment.[155] These alternative approaches might thus hold promise in reactivating antileukemic autologous innate immunity.

AXL is a member of the TAM family of RTK exerting pleiotropic effects in cancer, including the potentiation of migratory capabilities.[156] *Axl* overexpression correlates with poor prognosis in AML,[157] and *Axl* expression is an independent prognostic factor in de novo AML.[158] Bemcentinib is a selective small molecule AXL inhibitor, which is well-tolerated as single agent by AML patients who relapsed after treatment with HMAs.[159] In an ongoing phase II trial, bemcentinib is being investigated in AML patients either as single agent or in combination with LDAC or decitabine.[160]

While immune checkpoint inhibition has shown great promise in several solid tumors, results in AML have been disappointing after some initial encouraging data with ipilimumab (CTLA-4 inhibition) in relapsed patients post allo-SCT.[161] Since then, CTLA-4 (ipilimumab) and PD-1 (nivolumab and pembrolizumab) inhibitors have shown modest efficacy in phase I and II trials[161–169] and when combined with azacitidine in R/R AML.[170] Furthermore, PD-1 inhibition combined with chemotherapy showed some efficacy in newly diagnosed AML,[167] and PD-1 inhibition combined with venetoclax-azacitidine is being evaluated (NCT04284787).

TARGETED PROTEIN DEGRADATION

The cellular protein degradation machinery can be therapeutically leveraged to degrade proteins that cancer cells depend on (Table 2). The ubiquitin/proteasome system, composed of E3 ubiquitin ligase complexes, ubiquitinates damaged and unwanted proteins, directing them toward proteasomal degradation. In this context, the therapeutic agent acts as molecular glue, linking E3 ubiquitin ligases to target proteins (termed neosubstrates). For example, the small molecules thalidomide, lenalidomide, and pomalidomide link neosubstrates to cereblon, a member of the CRL4 E3 ubiquitin ligase complex. This leads to the degradation of proteins essential for multiple myeloma or MDS cell survival.[171] Subsequent development of Cereblon E3 ligase modulating drugs (CELMoDs) allowed the targeting of new neosubstrates by linking them to cereblon-containing E3 ligases. One CELMoD being investigated in AML is CC-90009[172]: This molecule promotes the degradation of GSPT1, which coregulates the termination of protein translation. In preclinical studies, GSPT1 degradation inhibited AML cell survival and proliferation.[173] Of note, CC-90009 efficacy may depend on AML differentiation stage.[174] CC-90009, as a single agent and in combination with other targeted approaches, is being evaluated in phase I trials in AML patients (NCT02848001 and NCT04336982). We are currently investigating clonal and molecular determinants of response and resistance to this treatment.

One limitation of the above approaches is the requirement for neosubstrates to contain a common *degron* peptide recognized by cereblon. Proteolysis-targeting chimeras (PROTACs) bind both to the target protein (via a PROTAC warhead) and to an E3 ubiquitin ligase enzyme via a linker domain connected to the E3 ligand.[3] This allows degrading proteins without the requirement for a common *degron* peptide. PROTACs are being investigated in hematological malignancies, for example, to target BCL2 in chronic lymphocytic leukemia.[175] The PROTAC technology has recently been designed to specifically degrade EZH2, the core member of the PRC2 complex with histone methyltransferase activity.[176] Mounting evidence suggests that EZH2 inhibits differentiation and promotes AML maintenance.[177–179] A recent study further identified a noncatalytic role of EZH2 in MLL-rearranged AML caused by the direct binding of EZH2 to cMYC and p300, which promotes malignant cell growth.[176] The novel PROTAC MS177, which promotes EZH2 degradation via cereblon, disrupted both the PRC2-dependent and cMYC-dependent EZH2 activity, inhibiting leukemic cell growth in vitro and in vivo.[176] Hence, this study exemplifies how PROTACs may be particularly effective in abolishing additional noncatalytic functions of targeted proteins. PROTACs might prove effective against transcription factors with oncogenic function in AML, such as WT1, MEIS1, or HOX family members.

CHALLENGES AHEAD: HOW TO OVERCOME THEM?

Novel targeted therapies are revolutionizing AML therapy, but fundamental challenges persist. The selection of resistant clones under therapy pressure causes treatment failure and relapse. An integrated characterization of genetic and molecular landscapes in longitudinal patient samples is needed to better understand putative resistance mechanisms. Emerging single-cell approaches coupling somatic genotypes with cellular readouts are potent tools to describe clonal complexity.[180] Complementing these technologies, our group recently integrated clonal readout with chromatin accessibility profiling at single-cell resolution, linking genetic and epigenetic disease evolution.[181] Going forward, this approach will elucidate clone-specific epigenetic mechanisms underlying disease relapse.

An obstacle to cure is the failure to eradicate quiescent LSCs, the seed of malignant growth most frequently residing in leukemic progenitor and/or precursor populations.[182,183] Hence, a better understanding of mechanisms driving aberrant self-renewal of LSCs is necessary and might lead to novel therapeutic targets.

In the context of disease prevention, the study of preleukemic clonal outgrowths, occurring years before leukemia onset, is critical. We and others are actively exploring molecular landscapes underlying human clonal hematopoiesis,[184–186] to elucidate pathways leading to early clonal dominance predating myeloid malignancy.

Going forward, better coordination between basic, translational, and clinical research is critical to maximize the value of technological advances. This will not only boost research through improved sample availability but also will lead to the rapid implementation of new technologies in clinical settings. Larger multicenter trials are warranted for the efficient delivery of promising therapeutic agents. Moreover, the process of drug discovery and clinical evaluation will benefit from increased collaboration between governments, industries, trial centers, and academic research. Finally, huge steps are needed to improve science communication between patients, their families, researchers, clinicians, and the public, to keep the primary focus on improving patients' lives.

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AUTHOR CONTRIBUTIONS

ST and FAR did writing and original draft preparation. PV did writing, review, and editing. All authors have read and agreed to the final version of the article.

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The authors have no conflicts of interest to disclose.

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