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Publication Date

2022

DOI

10.2147/ott.s265637

Peer reviewed

OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Targeting *TP53*-Mutated Acute Myeloid Leukemia: Research and Clinical Developments

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Abstract: *TP53* is a key tumor suppressor gene that plays an important role in regulating apoptosis, senescence, and DNA damage repair in response to cellular stress. Although somewhat rare, *TP53*-mutated AML has been identified as an important molecular subgroup with a prognosis that is arguably the worst of any. Survival beyond one year is rare after induction chemotherapy with or without consolidative allogeneic stem cell transplant. Although response rates have been improved with hypomethylating agents, outcomes remain particularly poor due to short response duration. Improvements in our understanding of AML genetics and biology have led to a surge in novel treatment options, though the clinical applicability of these agents in *TP53*-mutated disease remains largely unknown. This review will focus on the epidemiology, molecular characteristics, and clinical significance of *TP53* mutations in AML as well as emerging treatment options that are currently being studied.

Keywords: acute myeloid leukemia, *TP53* mutation, venetoclax, eprenetapopt, magrolimab

Introduction

Acute myeloid leukemia (AML) is a heterogeneous aggressive malignancy arising from clonal expansion of neoplastic hematopoietic precursor cells, which can occur de novo, after exposure to cytotoxic treatments, or after transformation from an antecedent hematologic disease. It is the most common acute leukemia in adults with an annual age-adjusted incidence rate of 4.3/100,000 rising to 15–20/100,000 above the age of 60 years.[1] Recent advances in next-generation sequencing (NGS) have revealed a stepwise process of mutational events, epigenetic dysregulation, and acquirement of copy number aberrations as main drivers of AML pathogenesis.[2–5] Leukemogenic mutations can often be detected in a small percentage of hematopoietic stem cell clones without any evidence of cytopenias or malignancy, a phenomenon referred to as clonal hematopoiesis of indeterminate potential (CHIP). Though the overall rate of progression from CHIP to AML is only 0.5–1.0% per year, mutations in the *TP53* gene have been associated with higher rates of AML than most other implicated genes.[6] In AML, certain genetic aberrations are associated with inferior outcomes, with those that affect the *TP53* gene being among the absolute worst. Somatically acquired *TP53* mutations constitute early events in the transformation of hematopoietic stem cells into pre-leukemia stem cells (preLSCs) and subsequently AML, and contribute substantially to its therapeutic resistance.[7] This review will focus on the role of *TP53* mutations in the prognosis and treatment of AML, with an emphasis on emerging therapies with the potential to improve outcomes in this challenging molecular subgroup.

Biology

Mutations in *TP53* are seen in nearly half of all tumors, making it the most consistently mutated gene in human malignancies.[8,9] Immunohistochemistry and real-time reverse transcription PCR (rt-PCR) can be used to detect *TP53* mutations, though NGS is preferred given its higher sensitivity.[10] Situated on chromosome 17p13.1, the *TP53* gene encodes a 393 amino acid phosphoprotein, p53, a transcription factor with critical tumor suppressor functions.[11,12] It contains five hallmark domains including the DNA-binding, oligomerization, proline-rich SH3, C-terminal regulatory,

Received: 31 January 2022
Accepted: 7 April 2022
Published: 21 April 2022

and N-terminal transactivation domains, the latter of which interacts with the negative regulator MDM2.[13,14] The *TP53* gene is known as the "guardian of the genome" given its importance in regulating cellular proliferation/differentiation associated with aberrant oncogene expression.[15] When provoked by cellular stressors such as DNA damage, hypoxia, and oncogene activation, it regulates a multitude of transcriptional targets involved in DNA repair, cell-cycle arrest, anti-angiogenesis, senescence, and induction of apoptosis.[8,11,16,17]

Thus, inactivation of *TP53* through gene mutation or deletion favors the action of oncogenes, ultimately promoting uncontrolled proliferation of neoplastic cells.[8,11,18,19] The role of p53 in mediating apoptosis is especially important in the setting of cytotoxic chemotherapy, where it has been associated with an inherent resistance to DNA damaging agents traditionally used to treat AML and other malignancies.[20–22]

Epidemiology

TP53 mutations are found in about 5–15% of AML cases.[23,24] In 75% of these cases, it is the only mutated gene identified on NGS.[25] *TP53* alterations are associated with older age in AML, occurring in up to 25% of cases in elderly individuals.[24] Though *TP53* mutations occur across all morphological subtypes of AML, they are more frequently seen in acute erythroblastic leukemia, therapy-related AML (t-AML), and in AML that has progressed from an underlying myeloproliferative neoplasm, where it can be found in up to a third of cases.[26–28] The mutation can be germline, in which case there is a tendency to develop other solid tumor malignancies, a condition referred to as Li-Fraumeni syndrome.[29,30] Sporadic mutations are also seen, in which case carcinogen exposure is often implicated.[31,32] The higher frequency of *TP53* mutations in t-AML appears to be related to expansion of pre-existing chemotherapy-resistant hematopoietic stem cell clones carrying age-related *TP53* mutations rather than direct induction of *TP53* mutation by cytotoxic chemotherapy.[33]

TP53 Mutation Characteristics

Greater than 80% of oncogenic *TP53* mutations have been reported as missense mutations, with "hot spots" noted in various arginine residues (R175H, R248Q, R273C, R282). Other mutation types have been reported, including insertions, deletions, nonsense, and frameshift mutations.[34,35] In most cases, the mutation occurs in the DNA-binding domain, with about a quarter of the remaining mutations located widely throughout the other domains.[36] These mutations typically lead to loss of function of p53′s tumor suppressive capabilities, although some mutations (in codons 175, 248, 173, 282) can lead to gain of function, often through binding of mutated p53 to other tumor suppressor proteins such as p63 and p73.[14,37–39] *TP53* can also be deleted through loss of the short arm of chromosome 17 (band 17p13.1).[40] In addition to somatic mutations and cytogenetic aberrancies involving the *TP53* gene, p53 dysregulation can occur through over-expression of its canonical negative regulators (Mdm2, Mdm4, $p14^{ARF}$).[41] Co-occurring mutations involving other commonly mutated AML genes (eg, *DNMT3A, FLT3, IDH1, IDH2, NPM1, TET2*) is seen in only a minority of cases, while chromothripsis, complex karyotype, and recurrent karyotypic structural aberrations, especially involving chromosomes 5, 7, and 17, are seen more frequently.[2,42,43]

Prognosis

Risk stratification in AML plays an important role in both prognostication and determining the best overall treatment approach. Various risk stratification models exist, with the most widely utilized in clinical practice being the European LeukemiaNet (ELN) system. This system was largely based on cytogenetic analysis prior to 2017.[44]

In recent years, improvements in rt-PCR and genomic sequencing have allowed for more routine access to molecular analysis and subsequent adjustments to the ELN risk stratification. In 2012, a molecular analysis of 841 AML patients defined five distinct prognostic subgroups that outperformed cytogenetic analysis alone. *TP53*-mutated disease represented the "very unfavorable group" associated with a three-year OS of 0%.[45] In a 2016 study regarding 1540 patients enrolled in three trials investigating treatment with intensive chemotherapy, driver mutations involving 111 cancer-associated genes along with cytogenetic findings were combined to identify 11 molecular classes with distinct clinical outcomes. In addition to the eight recurrent cytogenetic abnormalities that had already been described in AML, three additional classes emerged: AML with *TP53* mutations, chromosomal aneuploidies, or both (13%), AML with mutations of chromatin and RNA-splicing regulators (18%), and AML with $IDH2^{R172}$ mutations (1%). The *TP53*-mutated class was

associated with a particularly dismal prognosis, especially when a complex karyotype was also present, with each having an independent and additive effect on prognosis.[23] A 2015 analysis of the genetic ontogeny of AML used sequencing of 82 myeloid malignancy target genes to identify three clinicopathologically distinct subgroups in a cohort of patients enrolled in the ACCEDE trial with secondary-AML (s-AML) or t-AML. These subgroups included secondary-type, *TP53* de novo/pan-AML-type, and *TP53*-mutated, the latter of which was associated with reduced median OS (4.0 vs 8.5 months) in s-AML and increased chemoresistance in t-AML.[46] The ELN subsequently updated its risk stratification in 2017 to include *TP53* mutation as an independent adverse-risk indicator, associated with an estimated five-year overall survival (OS) of 20% and 6% in those treated with intensive chemotherapy aged <60 and ≥60, respectively.[47]

The variant allele frequency (VAF) for *TP53* mutations appears to play a role in prognosis as well. Higher *TP53* VAFs were associated with a significant increase in the relative hazards on OS in elderly patients treated with low-intensity therapies.[48] In patients treated with low-dose cytarabine, a VAF >40% was independently associated with higher rates of relapse and worse RFS and OS, which was not true for patients that were treated with a hypomethylating agent (HMA).[49] Outcomes with high-intensity therapies appear to depend less on *TP53* VAFs, with similar OS, EFS, and CR rates even with VAF <20%.[50] This may be the result of expanding subclones that are selected for during treatment and suggests that subclonal *TP53* mutations should be considered in prognostication.

The relationship between prognosis and the *TP53* mutation allelic state is still largely unknown at this time in AML. In the MDS setting, multi-hit *TP53*-mutant disease is an independent predictor of OS and transformation to AML, while monoallelic *TP53*-mutant disease may have a prognosis that is similar to wild-type.[51] Further analysis will be required to assess for a similar possibility in the AML setting.

The functional subtype of *TP53* mutation may also have an impact on prognosis. In an analysis of 9833 DNA sequence variants in human p53-null cells, certain variants were associated with greater expansion in in vitro cultures, which was used to generate a relative fitness score (RFS).[52] This score was applied to 83 *TP53*-mutated patients intensively treated with German-Austrian AML study group protocols, which demonstrated better median OS (12.9 vs 5.5 months) in patients with low-risk scores when compared to those with high-risk scores.[53] This indicates that functional characterization of *TP53* mutants may play an important role in refining the prognostic significance of *TP53* mutations.

Treatments

Intensive Chemotherapy

High-intensity chemotherapy, typically with a combination of cytarabine and an anthracycline, has long been considered the standard treatment approach in fit patients. However, the most recent NCCN guidelines recommend considering alternative induction strategies in *TP53*-mutated disease.[54] The discouraging outcomes after treatment with aggressive chemotherapy is reflected by the inclusion of *TP53* mutations in the adverse-risk category in the ELN risk-stratification system. This scoring system was developed by analyzing outcomes from patients enrolled in Phase 3 clinical trials involving treatment with cytarabine plus doxorubicin or mitoxantrone-based induction.[47] Other studies have revealed response rates ranging from 20% to 42% with a median OS of 4–9 months after treatment with induction chemotherapy.[23,24,26,42,55,56] *TP53* mutation has also been identified as a predictor of inferior response to CPX-351, a newer liposomal form of cytarabine and daunorubicin that is approved for treatment of t-AML and AML with MRC.[57] Median OS was similar for *TP53*-mutant patients treated with CPX-351 vs 7+3 induction.[58] Despite these observations, intensive cytotoxic therapy does still offer an advantage over no treatment, supported by an improved median OS (8 vs 1.7 months).[55] Although high-intensity treatments may be appropriate in the right clinical situation, newer therapies that do not require activation of *TP53* in response to DNA damage are likely the future to overcoming these poor outcomes.

Hypomethylating Agents

Epigenetic modifications resulting from DNA hypermethylation events at CpG islands have been associated with transcriptional silencing of genes involved in cell cycle regulation and other important growth regulators that suppress leukemogenesis.[59,60] The HMAs, decitabine (DEC) and azacitidine (AZA), are cytosine analogs that inhibit DNA methyltransferases, ultimately leading to reversal of DNA hypermethylation patterns and renewed transcription of previously

silenced tumor suppressor genes.[60,61] These agents have shown surprising activity in *TP53*-mutated disease and ELN adverse-risk in general, with higher response rates than those historically seen with high-intensity chemotherapy.

The first study to report such results evaluated a 10-day course of DEC in 113 patients with AML or MDS, revealing a complete response with (CR) or without hematologic recovery (CRi) in 100% of the 21 patients with *TP53*-mutated disease in comparison to 41% of the 46 patients with *TP53* wild-type disease, and no difference in OS [Table 1].[62] A Phase 2 trial compared 5-day and 10-day DEC dosing schedules in elderly AML patients, which demonstrated similar response rates and OS for each dosing schedule. A subgroup analysis of the *TP53*-mutated cases revealed response rates of 29% (2/7) and 47% (8/17) in the 5- and 10-day dosing schedules, respectively, which were not significantly different from response rates seen in the other subgroups (diploid cytogenetics, adverse-risk cytogenetics, de novo AML, and t-AML). Median OS was also similar between *TP53*-mutated and wild-type patients in the 5-day arm (5.5 vs 4.9 months), with a trend towards worse median OS in the 10-day arm (4.7 vs 8.3 months) that was not statistically significant.[63] Like DEC, AZA has also demonstrated similar response rates in *TP53*-mutated disease, although this has not translated into improved survival outcomes.[64,65,66] Despite the higher response rates with HMA therapy, these do not appear to be durable, with the longest remissions occurring in rare patients achieve *TP53* mutation clearance.[63,67]

The mechanism accounting for the increased sensitivity of *TP53*-mutated disease to HMAs remains largely unknown at this time. One investigation into the gene-regulatory effects of HMAs in AML cells with monosomal karyotype (including deletion of 17p) revealed that hemizygous tumor suppressor genes are more sensitive to decitabine-mediated induction, resulting in derepression and restoration to expression levels seen in diploid cells.[68] This could partially explain the activity of HMAs when p53 aberration is due to del 17p or in *TP53*-mutated disease that is associated with a monosomal karyotype. Further studies will be needed to elucidate the mechanism of HMA activity in *TP53*-mutated disease without any karyotypic abnormalities.

Venetoclax

The BCL-2 inhibitor, venetoclax (VEN), is approved for newly diagnosed and relapsed/refractory AML in combination with a HMA, a regimen which has become an important tool in treating elderly patients and those who are not candidates for high-intensity therapy.[69,70] Initial trials involving DEC plus VEN found *TP53* status to be a statistically significant predictor of response in a *post-hoc* exploratory analysis. The CR/CRi rate of 47%, median duration of response (DoR) of 5.6 months, and median OS of 7.2 months appeared favorable when compared to historical controls.[69] A subsequent retrospective analysis involving 32 patients with *TP53* mutations echoed these results, demonstrating a CR/CRi rate of 67% and 38% in the frontline and relapsed/refractory setting, respectively, with responses seen in those that underwent previous hematopoietic stem cell transplantation. Baseline VAF was comparable among responders vs nonresponders and similar outcomes were seen with 5- and 10-day schedules of DEC.[71]

More recent data have reported conflicting results. A *post-hoc* analysis of a phase 2 trial involving 10-day DEC plus VEN revealed significantly inferior rates of CR/CRi (57% vs 77%), MRD negativity by flow cytometry (29% vs 59%), median OS (5.2 vs 19.4 months), and median RFS (3.4 vs 18.9 months) in *TP53*-mutated disease when compared to wild-type. These patients were also compared to patients receiving 10-day DEC alone on a separate prospective clinical trial with similar baseline characteristics, which demonstrated higher ORR (66% vs 53%) and MRD negativity (29% vs 25%) with the addition of VEN, but no significant difference in OS or RFS.[72] An analysis of *TP53*-mutated patients with poor-risk cytogenetics enrolled in the phase 3 trial that led to the approval of AZA plus VEN revealed higher CR rates (41% vs 17%) similar median DoR (6.54 vs 6.7 months), and similar median OS (5.17 vs 4.9 months) for the combination when compared to AZA alone.[73] A retrospective study involving 238 patients treated with VEN and non-venetoclax-based regimens similarly showed higher response rates, but no difference in OS or RFS with venetoclax-based regimens, regardless of age or intensity of treatment.[74] *TP53* mutation was also found to be associated with worse OS in the relapsed/refractory setting in retrospective analyses.[75–77] In vitro studies have supported inactivation of *TP53* as a mediator of VEN resistance, as well as other genes that regulate the mitochondrial apoptotic network (*BAX, PMAIP1, TFPD1*).[78,79] Although venetoclax-based combination therapies have high response rates and improved ability to attain disease control, the short-lived nature of these responses does not necessarily translate into improved survival outcomes [Table 1], highlighting the continued need for adequate consolidation strategies.

Table 1 Approved Drugs with Activity in TP53-Mutated AML

Study	Design	Treatment	Patients	Wildtype ORR	TP53-Mutated ORR	Wildtype OS	TP53-Mutated OS
Welch, et al[62]	Prospective, Uncontrolled	DEC 20 mg/m2 for 10 days of 28 day cycle	116 with AML/ MDS (12 TP53-mutated AML)	53%	100%	15.4 Months	12.7 Months
Short, et al[63]	Prospective, Randomized Phase 2	DEC 20 mg/m2 for 5 or 10 days of 28 day cycle	71 with AML ≥60 years old (21 with TP53 mutations)	43% in 5- day arm 40% in 10-day arm (p=0.78)	29% in 5-day arm 47% in 10-day arm (p=0.40)	5.5 months in 5-day arm 8.3 months in 10-day arm	4.9 months in 5-day arm, 4.7 months in 10-day arm
Bally, et al[64]	Prospective	AZA 75 mg/m2 for 7 days of 28 day cycle	62 patients with AML/MDS (23% with TP53 mutations)	51%	43%	23.7 months	12.4 months
DiNardo, et al[69]	Prospective, Phase 1b	AZA +VEN (49%) or DEC +VEN (51%)	145 AML (36 with TP53 mutations)	73% (CR +CRi)	47% (CR +CRi)	17.5 months (for entire cohort)	7.2 months
DiNardo, et al[70]	Prospective, Phase 3, Randomized, Double-blind	AZA 75 mg/m2 for 7 days of 28 day cycle with VEN vs AZA alone	431 AML (52 with TP53 mutations)	36.7% in AZA/VEN arm vs 17.9% in AZA arm (for entire cohort)	55.3% in AZA/ VEN arm vs 0% in AZA arm (P<0.001)	14.7 months in AZA/ VEN arm vs 9.6 months in AZA arm (for entire cohort)	5.17 months in AZA/VEN arm vs 4.9 months in AZA arm (by *post-hoc* analysis in those with poor-risk cytogenetics)
Kim, et al[72]	*Post-hoc* analysis of Phase 2 trial	DEC 20 mg/m2 for 10 days of 28 day cycle with VEN	118 AML (53 with TP53 mutations)	89%	66%	19.4 months	5.2 months
Venugopal, et al[74]	Retrospective	VEN based vs non-VEN based regimens	239 TP53-mutated AML	NA	43% with VEN vs 32% without VEN (CR rates) (p=0.06)	NA	6.6 months with VEN vs 5.7 months without (p=0.4)
Morsia, et al[75]	Retrospective	DEC or AZA plus VEN	44 AML (9 with TP53 mutations)	50% (CR + CRi in the entire cohort)	44% (CR + CRi)	11 months (in the entire cohort)	8 months

https://doi.org/10.2147/OTT.S265637 DovePress

Magrolimab

CD47 is a macrophage checkpoint protein that is expressed on the surface of a variety of cells where it functions as a "don't eat me" signal by interacting with signal regulatory protein α (SIRPα) on the surface of macrophages and inhibiting phagocytosis.[80] CD47 expression is elevated on AML cells, where it aids in evasion of the immune system.[81,82] Magrolimab is an anti-CD47 IgG4 monoclonal antibody that stimulates antibody-dependent cellular phagocytosis and T-cell mediated cytotoxicity through inhibition of the CD47/SIRPα signaling access.[83]

Preclinical studies have demonstrated the ability of AZA to upregulate the "eat me" signal, calreticulin, in mouse xenograft models, which has inspired the combination of magrolimab plus AZA that is currently being evaluated in a Phase 1b trial.[84] The trial includes untreated, induction chemotherapy-ineligible or relapsed/refractory AML patients and intermediate to very-high risk untreated or relapsed/refractory MDS patients. Preliminary results have revealed an ORR of 63% (27/43) for the AML cohort, with elimination of LSCs (defined as CD34+/CD38-) in 71% of responding patients. The *TP53*-mutant cohort ORR, CR, and CRi rates were 69% (20/29), 45% (13/29), and 14% (4/29), respectively, with a median DoR of 7.6 months. The median OS for *TP53* mutant and wild-type patients was 12.9 months and 18.9 months, respectively. The combination was well tolerated in both studies with a safety profile comparable to AZA monotherapy. Aged red blood cells express CD47 leaving them susceptible to on-target hemolytic anemia with magrolimab treatment. Despite this, worsening anemia was only reported in about one-third of patients, with >50% becoming red blood cell transfusion-independent at some point throughout the course of therapy.[85]

Given the results of these studies, phase 3 trials are currently ongoing comparing AZA plus magrolimab to AZA plus VEN or intensive chemotherapy. A phase 1/2 trial is also assessing the safety and efficacy of magrolimab plus AZA in combination with VEN in newly diagnosed and relapsed/refractory AML. Preliminary results have reported a CR/CRi rate of 94% (15/16) in newly diagnosed patients with complete cytogenetic response and MRD negativity by flow cytometry rates of 75% and 55%. The *TP53*-mutant cohort achieved a CR/CRi rate of 100% (7/7), with and MRD negative rate of 57% (4/7).[86] Additional follow up will be needed to determine whether these responses are associated with improved survival outcomes [Table 2].

Eprenetapopt (APR-246)

Eprenetapopt (APR-246), a PRIMA-1 analog, is a first-in-class small molecule that targets *TP53*-mutant cancer cells through reactivation of p53 function.[87,88] The active component is methylene quinuclidinone, a decomposition product of eprenetapopt that covalently binds cysteine residues in mutant p53, shifting the equilibrium in favor of the wild-type p53 conformation through thermodynamic stabilization.[89] Increasing oxidative stress through depletion of glutathione and induction of ferroptosis also contributes to eprenetapopt's mechanism of action.[90,91]

Two phase 1b/2 studies have been conducted evaluating the combination of eprenetapopt with AZA, which was shown to have synergistic cytotoxicity in *TP53*-mutated AML cell lines and in vivo models.[92] The first of these trials involved patients with *TP53*-mutated intermediate to very high risk MDS or oligoblastic AML (20–30% blasts) [Table 2].[93] The second study involved a similar patient population, though AML with any blast percentage was permitted and eprenetapopt/AZA maintenance could be administered for up to one year if allogeneic HCT was performed.[94] An analysis of the 100 patients combined in these two trials revealed an ORR, CR rate, NGS negativity rate, MRD negativity rate, and median OS after allogeneic HCT of 69%, 43%, 40%, 6%, 11.8 months, and 16.1 months, respectively. In the AML population, ORR and CR rate were 64% and 36%, respectively. Isolated *TP53* mutation was predictive of higher CR rate (52% vs 30%). Those with biallelic *TP53* mutations or complex karyotype experienced higher CR rates than those without either of these features (49% vs 8%). Patients who responded and proceeded to allogeneic HCT had a median OS that was not reached vs 9.1 months in allogeneic HCT patients who did not respond.[95]

Ongoing trials are evaluating eprenetapopt in other clinical settings and combinations. A phase 2 study evaluating eprenetapopt with AZA as maintenance therapy for up to one year in *TP53*-mutated MDS and AML has released preliminary results for the 33 patients that have been enrolled, demonstrating a median RFS of 368 days and median OS of 586 days.[96] A phase 1 trial involving eprenetapopt in combination with AZA and VEN has also published preliminary data for the first 30 patients, with a CR and CR/CRi rate of 37% and 53%, respectively.[97] A phase 3 trial comparing AZA to AZA plus eprenetapopt in MDS patients failed to reach its primary endpoint according to a 2020 press release, though

Table 2 Emerging Therapies for TP53-Mutated AML

Drug	Mechanism of Action	Trial	Study Design	Preliminary Data
Magrolimab[85]	Anti-CD47 mAb	NCT03248479	Phase 1b evaluating magrolimab plus AZA in untreated, induction chemotherapy ineligible-AML or r/r AML	ORR 63% (27/43) in de novo AML ORR 69% (20/29) in TP53-mutant cohort Median OS 18.9 months for TP53 wild-type Median OS 12.9 months for TP53-mutant
Magrolimab	Anti-CD47 mAb	NCT04778397	Phase 3 Trial comparing AZA plus magrolimab to AZA plus VEN or intensive chemotherapy in TP53-mutated AML	
Magrolimab	Anti-CD47 mAb	NCT04435691	Phase 1/2 trial evaluating AZA plus magrolimab and VEN in newly diagnosed and r/r AML	
Magrolimab	Anti-CD47 mAb	NCT05079230	Phase 3, randomized, double-blind trial evaluating magrolimab vs placebo in combination with VEN and AZA in untreated, chemotherapy ineligible-AML	
Magrolimab[86]	Anti-CD47 mAb	NCT04778410	Phase 2 trial evaluating magrolimab in combination with other therapies: Cohort 1: Magrolimab + AZA + Ven Cohort 2: Magrolimab + MEC in r/r AML Cohort 3: Magrolimab + CC-486 in AML with MRD-negative CR/CR1	De novo and R/R AML: CR + CRi rate 94% (15/16), MRD negativity rate 55%. TP53 Mutant Cohort: CR + CRi rate 100% (7/7) MRD negativity rate 57%
Eprenetapopt[93]	Stabilization of wt p53	NCT03072043	Phase 1b/2 trial evaluating eprenetapopt + AZA in TP53-mutant MDS and oligoblastic AML	ORR 64%, CR rate 36%, median OS 10.8 months in the 11 AML patients
Eprenetapopt[94]	Stabilization of wt p53	NCT03588078	Phase 2 trial evaluating eprenetapopt + AZA in TP53-mutant MDS and AML	AML with <30% Blasts: ORR 45%, CR rate 27%, median OS 13.9 months AML with >30% Blasts: ORR 14%, CR rate 0%, median OS 3.0 months
Eprenetapopt[97]	Stabilization of wt p53	NCT04214860	Phase 1 trial evaluating eprenetapopt + AZA + VEN in TP53-mutant myeloid malignancies	CR and CR + CRi rate of 37% and 53% for the first 30 patients receiving the regimen
Eprenetapopt	Stabilization of wt p53	NCT03745716	Phase 3 trial comparing eprenetapopt + AZA vs AZA alone in TP53-mutated MDS	Combination CR rate 33.3% AZA CR rate 22.4% (P=0.13)
Flotetuzumab[107]	Anti-CD3ε /CD123 Bispecific DART	NCT2152956	Phase 1/2 trial evaluating flotetuzumab in r/r AML and MDS	CR in 47% (7/15) with median OS of 10.3 months in TP53-mutated cohort on *post-hoc* analysis
Nivolumab	Anti-PD-1 mAb	NCT04277442	Pilot study evaluating nivolumab with AZA + VEN in TP53-mutated AML	
Atezolizumab	Anti-PD-1 mAb	NCT03922477	Phase 1b study evaluating atezolizumab in combination with magrolimab in r/r AML	
Atorvastatin	HMG-CoA Reductase Inhibitor	NCT03560882	Pilot study evaluating atorvastatin in p53 mutant and wild-type malignancies (including AML)	

(*Continued*)

Table 2 (Continued).

Drug	Mechanism of Action	Trial	Study Design	Preliminary Data
Arsenic Trioxide	Multiple	NCT03381781	Prospective, uncontrolled trial evaluating ATO + DEC + ara-C	
Idasanutlin	MDM2 Inhibitor	NCT02670044	Phase IB study of VEN + cobimetinib and VEN plus idasanutlin in cytotoxic therapy-ineligible r/r AML	

there was a statistically insignificant trend towards improved CR rate in the combination arm (33.3% vs 22.4%). The most common grade ≥3 adverse events reported with eprenetapopt in these trials were reversible neurologic phenomena (40%), febrile neutropenia (33–37%), diarrhea (50%), vomiting (39%), and hematologic toxicity that was similar to AZA monotherapy.[94–97]

Immunotherapy

Aside from magrolimab, several other immunotherapeutic approaches have been tried in AML, mostly with limited success. Checkpoint inhibition with PD-1, PD-L1, and CTLA-4 blockade has revolutionized treatment of various solid tumors. Increased expression of PD-L1 and PD-1 has been described on bone marrow AML blasts and infiltrating CD8+ T cells, with *TP53*-mutation, relapsed/refractory disease, and disease that has progressed after treatment with HMAs even more likely to express PD-L1.[98] Previous exposure to HMAs has also been associated with upregulation of CTLA-4.[99] Other biomarkers often associated with response to immunotherapies that have been identified in *TP53*-mutated AML include greater infiltration by CD8+ T-cells, resting memory NK/CD4+T cells, and higher tumor mutational burden.[100]

Trials have been completed involving checkpoint immune blockade either alone or in combination with other agents. Though activity was demonstrated with both AZA plus nivolumab in the relapsed/refractory setting and nivolumab plus cytarabine/idarubicin in the frontline, *TP53* mutation was not predictive of response in the former and was associated with nonresponse in the latter.[101,102] A phase 2 trial of pembrolizumab after high-dose cytarabine in the relapsed/refractory setting revealed a CR rate of 40% in the *TP53*-mutated population, although there were only 5 patients included in the study.[103]

Bispecific dual affinity retargeting antibodies (DARTs) have provided an additional immunotherapeutic approach in lymphoid neoplasms that has been more challenging in AML given its greater diversity of cell surface antigens. Flotetuzumab is a bispecific DART against CD3ε and CD123 which encourages the formation of an immunologic synapse between cytotoxic T cells and AML cells in an MHC-independent fashion.[104] Given that CD123 expression is augmented in primary induction failure and early relapse AML, a phase 1/2 study was conducted involving this patient population where the CR/CRh/CRi rate was 30.0% and median OS was 10.2 months.[105,106] A *post-hoc* analysis of bone marrow samples collected from patients on this trial demonstrated a CR in 47% (7/15) of *TP53*-mutated cases with a median OS of 10.3 months and two CRs that persisted for >6 months. Responders were also more likely to have higher tumor inflammation signature, *FOXP3, CD8A*, inflammatory cytokine, and *PD1* gene expression scores at baseline.[107] Novel combinations including immunotherapeutics are currently being assessed in clinical trials [Table 2].

Allogeneic Hematopoietic Stem Cell Transplantation

Allogeneic stem cell transplant is the most common consolidation strategy offered to young patients with adverse-risk AML, as it is generally the only reasonable chance for cure. Outcomes in the TP53-mutated population tend to be among the poorest. A retrospective analysis by the European Society for Blood and Marrow Transplantation of 139 patients with 17p abnormalities who underwent hematopoietic stem cell transplant (HCT) in CR1 revealed a 2-year OS and leukemia-

free survival (LFS) of 28% and 24%, respectively.[108] Another study of AML patients undergoing allogeneic HCT after achieving CR1 with intensive chemotherapy induction found *TP53* mutation to be a member of the "adverse molecular-genetic profile" group associated with the worst outcomes, including a lower 2-year OS (24.9% vs 57.9%) and lower relapse-free survival (23.7% vs 57.9%) in comparison to patients not in this group.[109] Despite these findings, some patients do appear to achieve long-term survival in the presence of certain clinical features. An analysis of 83 patients who underwent allogeneic HCT for *TP53*-mutated AML or MDS revealed three independent factors that predicted worse OS, including Karnofsky performance status ≤80%, HCT comorbidity index >4, and disease not in CR1/2 at the time of transplant. Patients with 0, 1, and ≥2 of these factors had one-year OS rates of 67%, 39%, and 17%, respectively.[110] With the improved CR rates and lesser toxicity associated with many novel agents, allogeneic HCT will likely continue to remain an important tool in the curative approach to *TP53*-mutated AML.

Future Treatment Approaches

Several other strategies are currently being tested to overcome treatment resistance in *TP53*-mutated AML by direct targeting of the p53 protein in an effort to degrade its mutant form or restore its wild-type functions [Table 2]. Statins have demonstrated the ability to induce degradation of mutant p53 by reducing mevalonate-5-phosphate formation, which increases CHIP ubiquitin ligase-mediated degradation of mutant p53.[111] Preclinical studies demonstrating the ability of these agents to synergize with doxorubicin and inhibit growth of *TP53*-mutated AML cells as well as a general vulnerability to mevalonate reduction in *TP53*-mutated tumors have inspired the opening of a phase 1 trial of atorvastatin in *TP53*-mutated malignancies.[112–114] Arsenic trioxide has been shown to induce degradation of mutant p53 via a proteasomal pathway involving upregulation of Pirh2 E3 ligase, which is currently being studied in a clinical trial in combination with DEC and cytarabine in patients with *TP53*-mutated AML.[115,116] Histone deacetylase inhibitors and heat shock protein 90 inhibitors have proven ability to degrade mutant p53, though this has not translated into clinical activity in early phase trials for AML and other myeloid neoplasms.[117–121] MDM2 inhibitors have proven clinical activity in *TP53* wild-type disease, though their use in *TP53*-mutant disease remains in question and may require the use of additional agents in combination.[120] Other agents are aimed at restoring the wild-type function of mutant p53 or targeting the G2M point and other pathways that *TP53*-mutant cancers depend on. These agents have demonstrated promising preclinical data that has not yet been translated into clinical studies.[121–123]

Conclusion

The presence of a molecular aberration impairing the function of the *TP53* gene has been identified as a poor prognostic indicator in AML, with dismal outcomes following standard induction chemotherapy and consolidation with allogeneic HCT. Higher VAFs have been associated with worse outcomes and will likely play a role in risk-stratifying patients with even finer precision than currently available models. The use of hypomethylating agents with or without VEN has produced higher response rates than induction chemotherapy, though median OS continues to be around a year with these treatments. Emerging treatments involve novel therapeutic mechanisms that have led to increased optimism about the ability to exploit *TP53* mutations therapeutically. Efforts to improve immunotherapeutics have included targeting of new receptors and use of bispecific DARTs. Direct targeting of mutated p53 protein with eprenetapopt has led to some initial success. Although these therapies have demonstrated promising results in early phase clinical trials, larger randomized trials are still needed to confirm their benefit over approved treatments, and it may ultimately require combination of these therapies in order to achieve adequate responses that are also durable. Recent data have suggested that *TP53*-mutated AML and MDS with excess blasts (MDS-EB) should be one disease entity due to their similar biological behavior and survival outcomes.[124] Given the relative rarity of *TP53*-mutated AML, this adaptation could help simplify future clinical trial design and eliminate existing drug approval barriers, allowing more efficient access to *TP53* targeted therapy. As further treatments for AML and other myeloid disorders are developed, continued focus on outcomes in the *TP53*-mutated population will be required to identify additional agents with activity in this setting. *TP53*-mutated disease remains a challenging AML subgroup with a continued need for more effective treatment options.

Author Contributions

EMG and BAJ: All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

Brian A Jonas reports consultant/advisor for AbbVie, BMS, Celgene, Genentech/Roche, Gilead, GlycoMimetics, Jazz, Pfizer, Servier, Takeda, Tolero, and Treadwell; protocol steering committee for GlycoMimetics; data monitoring committee for Gilead; travel reimbursement from AbbVie; and research funding to his institution from 47, AbbVie, Accelerated Medical Diagnostics, Amgen, AROG, BMS, Celgene, Daiichi Sankyo, F. Hoffmann-La Roche, Forma, Genentech/Roche, Gilead, GlycoMimetics, Hanmi, Immune-Onc, Incyte, Jazz, Loxo Oncology, LP Therapeutics, Pfizer, Pharmacyclics, Sigma Tau, and Treadwell. The authors report no other conflicts of interest in this work.

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