TP53-Mutated Myelodysplastic Syndrome and Acute Myeloid Leukemia: Biology, Current Therapy, and Future Directions

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ABSTRACT *TP53*-mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) form a distinct group of myeloid disorders with dismal outcomes. *TP53*-mutated MDS and AML have lower response rates to either induction chemotherapy, hypomethylating agent–based regimens, or venetoclax-based therapies compared with non–*TP53*-mutated counterparts and a poor median overall survival of 5 to 10 months. Recent advances have identified novel pathogenic mechanisms in *TP53*-mutated myeloid malignancies, which have the potential to improve treatment strategies in this distinct clinical subgroup. In this review, we discuss recent insights into the biology of *TP53*-mutated MDS/AML, current treatments, and emerging therapies, including immunotherapeutic and nonimmune-based approaches for this entity.

Significance: Emerging data on the impact of cytogenetic aberrations, *TP53* allelic burden, immunobiology, and tumor microenvironment of *TP53*-mutated MDS and AML are further unraveling the complexity of this disease. An improved understanding of the functional consequences of *TP53* mutations and immune dysregulation in *TP53*-mutated AML/MDS coupled with dismal outcomes has resulted in a shift from the use of cytotoxic and hypomethylating agent–based therapies to novel immune and nonimmune strategies for the treatment of this entity. It is hoped that these novel, rationally designed combinations will improve outcomes in this area of significant unmet need.

INTRODUCTION

TP53 is a tumor suppressor gene that encodes for the transcription factor p53, appropriately coined the "guardian of the genome." *TP53* is the most frequently mutated gene across all human cancers and carries an adverse prognosis with suboptimal responses to conventional therapies across multiple cancer types (1). Response to cytotoxic chemotherapy is highly dependent on the presence of intact p53 to enable the induction of apoptosis (2, 3). Consequently, *TP53*-mutated cancers respond poorly to cytotoxic chemotherapy. Despite being one of the most studied genes since its initial discovery about 40 years ago, it has so far been considered "undruggable." Similar to many *TP53*-mutated malignancies, *TP53*-mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) remain long-standing therapeutic challenges, with a dismal median survival of 5 to 10 months, irrespective of therapies used (4–6). In the last few years, some of the novel immune-harnessing and p53 structure-modulating agents have demonstrated encouraging early clinical activity in *TP53*-mutated AML/MDS, and are now being advanced in phase II/III registration studies. In this

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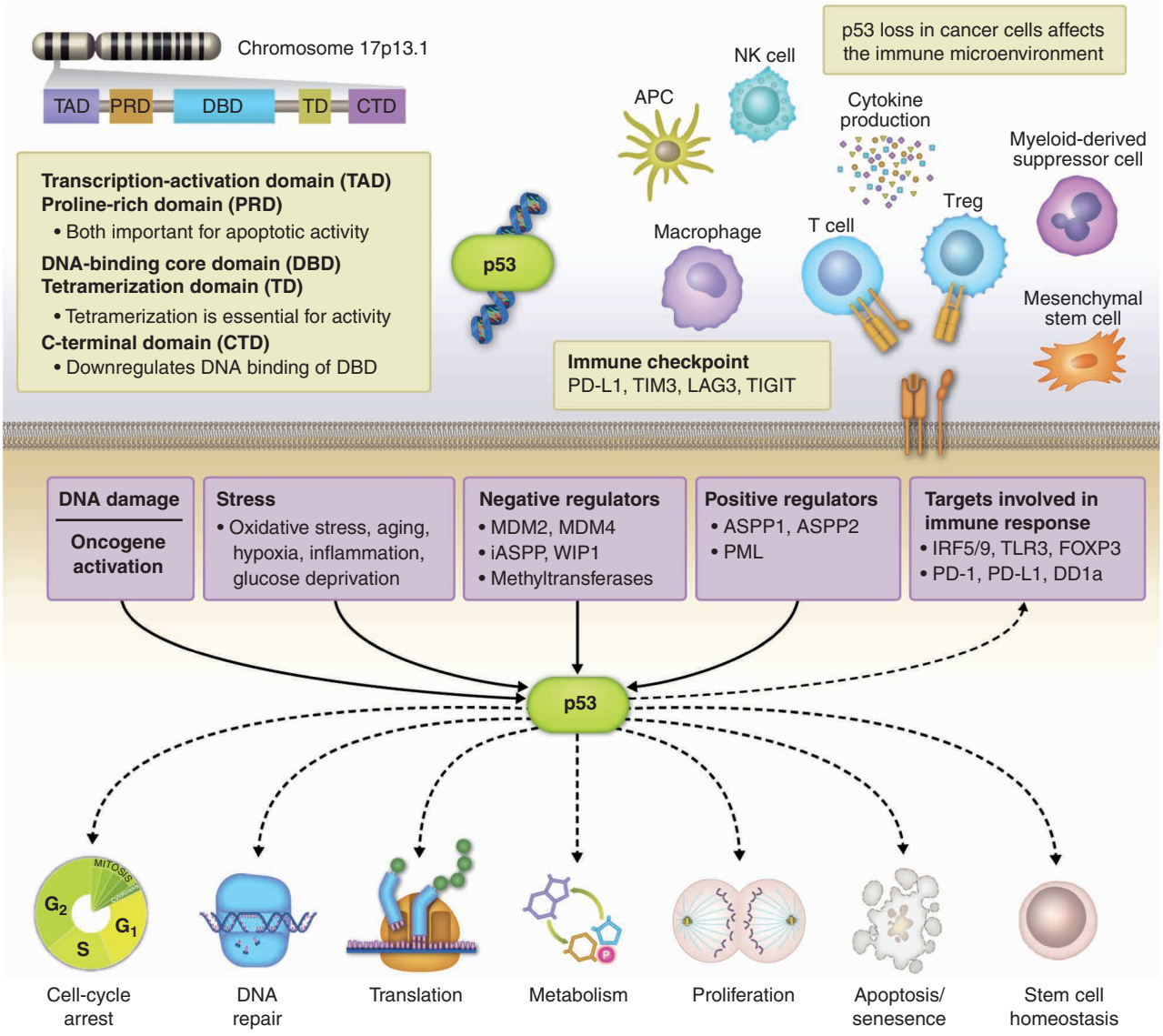

Figure 1. Different subunits of the p53 are coded by a gene located on chromosome 17p13.1. p53 resides over a highly connected hub involving multiple signal transduction pathways, including DNA damage response, oncogene activation, cellular stress, and its positive and negative regulators. In turn, p53 regulates numerous key cellular processes including cell cycling, genomic stability, cell metabolism, differentiation, proliferation, apoptosis, senescence, and others. In addition, downstream signaling through p53 influences the tumor microenvironment through a direct effect on several immunologic targets. APC, antigen-presenting cell; NK, natural killer; Treg, regulatory T cell.

review, we summarize the key biological implications of *TP53* mutations, their prognostic relevance to MDS and AML, and outcomes with currently approved therapies, and we discuss current and future directions for drug development for *TP53*-mutated AML/MDS.

TP53 MUTATION AND CANCER

TP53 is a 20-kb gene located on chromosome 17p13.1, which codes for at least 15 different isoforms and has two paralogs, p63 and p73, with similar structures and overlapping but distinct functions and upstream pathways (7). It presides over a highly connected intracellular hub involving multiple signal transduction pathways and consequently is affected by and in turn regulates numerous cellular processes. Some of the major functions of p53 include the regulation of genomic stability, cell cycling, proliferation, differentiation, apoptosis, senescence, autophagy, metabolism, and stem cell homeostasis throughout human life, highlighting the central role of this pathway in the healthy state (Fig. 1; refs. 8, 9).

More than 90% of cancer-related *TP53* mutations have structural losses of both alleles, and most result in loss or decreased function of genes in the p53 regulatory network, many of which are critical for growth arrest, routine apoptosis, and suppressing neoplasia (10). Mutations in *TP53* can be somatic or germline, can be contact or structural, and based on their functional consequences can be divided into the most frequent complete or partial loss of function to rarely silent or potentially gain of function (1, 11, 12). A majority of *TP53* hotspot mutations lead to loss of function, causing

an inability to trigger p21, downregulation of genes associated with apoptosis, and upregulation of proteins involved in cell-cycle progression (e.g., cyclin B1, cyclin E1, FOXM1, CDK1) and those involved in DNA damage response (CHK2, MSH6; ref. 10). However, the gain-of-function hypothesis has been challenged by elegant work demonstrating a dominant-negative effect of missense *TP53* mutations leading to the disruption of activity of the remaining wild-type p53 after tetramerization (13, 14). This was further supported by clinical analysis showing lack of a more aggressive phenotype, a similar comutational landscape, and comparable clinical outcomes and response to therapy between patients harboring missense and truncating *TP53* mutations, throwing doubt on the gain-of-function hypothesis. Seventy percent of all *TP53* mutations are nonhotspot mutations, and out of those, around 30% of the mutations, for example, those involving E180 and R181, while tumorigenic, behave very differently from p53-null and hotspot mutations (15). These partial loss-of-function mutant p53 proteins can retain 10% to 50% of transcriptional activity compared with wild-type p53, and accumulation of these mutants can rescue the transcriptional apoptosis defect and sensitize leukemia cells to chemotherapy (15). In contrast, mutations in other tumor suppressors, such as *RB1* and *VHL*, more homogenously lead to no protein expression at all (16).

More recently, it has been noted that *TP53* mutations also modulate diverse aspects of the innate and adaptive immune systems. Loss or dysfunction of p53 in solid tumors promotes tumor immune tolerance through downregulating antigen presentation, decreasing Toll-like receptor–mediated apoptosis, and increasing PD-L1 expression (17). However, mutant p53 also favorably modulates immune response by increasing NF-κB activity, increasing tumor-associated macrophage infiltration, eliciting B-cell response, and activating T cells—effects that potentially could be modulated with therapeutic intent (17). The differential impact of cytotoxic therapy on *TP53*-mutated cancer cells and *TP53* wild-type immune cells in the tumor microenvironment further adds to the stochastic complexity of these immune interactions and may affect cytokine production, immune synapse formation between antigen-presenting cells and T cells, and T-cell fate (18–20). With these diverse effects on various components of both the adaptive and innate immune systems, p53 is increasingly being recognized as a "guardian of immune integrity" (21).

TP53 MUTATION IN MDS AND AML

Clonal hematopoiesis is noted in the blood of 2% to 6% of patients with cancer, including clonal *TP53* variants that could represent a precursor lesion in diverse malignancies (22, 23). *TP53* abnormalities occur in nearly 5% to 10% of patients with *de novo* MDS and AML (24–26). This frequency is much lower than several other solid tumors—for example, uterine carcinosarcoma, esophageal adenocarcinoma, and lung squamous cell cancers in which *TP53* alterations are noted in more than 80% of cases. However, the frequency in AML/MDS goes up to 20% to 40% in older patients or those with therapy-related myeloid malignancies (6, 27). The frequency of *TP53* abnormalities further increases to 70% to 80% in patients with complex karyotype and in patients with loss of chromosome 17/17p, 5/5q, or 7/7q (28, 29). Therapy for a previous cancer, including radiation or chemotherapy, does not directly induce *TP53* mutations. Rather, preexisting progenitors that carry mutant *TP53* and are resistant to DNA damage expand under selective pressure from radiation or chemotherapy to give rise to *TP53*-mutated AML/MDS later in life (5, 30, 31). Although more than 70% of *TP53* abnormalities are missense substitutions clustering within the DNA-binding domain, diverse genetic aberrations in *TP53* with complex and varied functional consequences have been described in MDS and AML (1). These include chromosomal alterations leading to allelic gains or losses or frameshift insertions or deletions. The impact of these disruptions ranges from partial loss of function to complete loss of function (1, 26, 27). Among *TP53*-mutated MDS, "multihit" involvement with more than one genomic and/or chromosome 17 abnormality is noted in the majority of patients, including multiple mutations in 24% of patients, mutations with concomitant deletions in 22% of patients, and mutations with concomitant copy-number loss of heterozygosity in 21% of patients (26). Notably, recent data strongly support that *TP53* mutations, particularly multihit, results in similarly poor clinical outcomes, regardless of whether classified as MDS or AML, arguing for a revised *TP53* mutant myeloid entity encompassing both MDS and AML if the blast count is 10% to 19% (MDS/AML) or AML with mutated *TP53* if blasts are 20% to recognize this highly adverse-risk myeloid pathology (32–35).

Multihit *TP53*-mutated MDS/AML often represents a distinct stem cell disorder with a paucity of comutations in other myeloid malignancy–related genes, with comutations occurring in less than 25% of cases (36). This is consistent with *TP53* mutations being early truncal events in the MDS/AML pathogenesis in such cases, and consequently multihit *TP53* mutations or biallelic defects evolve to become dominant clones conferring resistance to current standard therapies and therefore carry a worse prognosis (26). Monoallelic *TP53* mutations (33%) on the other hand frequently have comutations in other genes, most commonly *TET2* (29%), *SF3B1* (27%), *ASXL1* (16%), and *DNMT3A* (16%), and are likely to be late subclonal events with varying impacts on outcomes (26). As accurate multihit analysis requires the determination of the allelic state by loss-of-heterozygosity mapping, clinically available conventional and cytogenetic techniques currently do not capture all biallelic patients. However, a reasonable determination of multihit state can be made if there is the presence of more than one *TP53* mutation, *TP53* mutation(s) in the setting of a missing chromosome 17p locus, or a variant allele frequency (VAF) >50%, which are 75% concordant with copy-neutral loss-of-heterozygosity variants (26). Nuclear p53 accumulation assessed by IHC may also serve as a surrogate for *TP53* mutation and copy-number status (37). Recent reports further show that blast count does not distinguish clinical course, and patients with *TP53* mutation with complex karyotype have similarly dismal outcomes irrespective of the initial diagnosis of AML or MDS or the baseline bone marrow blast percentage (32, 33). As a result, the International Consensus Classification has categorized *TP53*-mutated MDS with excess blasts and *TP53*-mutated AML as a group of high-risk myeloid neoplasms harboring *TP53* mutations to facilitate clinical trial conduct and regulatory approval for new drugs targeting this patient population.

Chromothripsis, or chromosome shattering, is a catastrophic event leading to extensive chromosomal rearrangement (38). Chromothripsis serves as an additional adverse-risk biological characteristic associated with *TP53* mutation and complex karyotype in AML/MDS. Such massive shattering and reassembly of chromosomes correlates with genomic instability and defines a subset of complex karyotype AML/MDS with even worse outcomes (39, 40).

In a recent survey of more than 500 *TP53*-mutant AML cases, three quarters harbored a missense variant, most commonly R248, R273, and Y220, with other variants, such as *TP53* deletion as well as frameshift and nonsense alterations being less common. It was also found that *TP53* copy-number loss was extremely prevalent—identified in 70% of AML cases with a concomitant *TP53* abnormality (37). AML survival appeared worse for patients who had either a concomitant *TP53* mutation and *TP53* copy-number loss or when multiple *TP53* mutations were present. It is possible that certain *TP53* hotspot variants confer a biological fitness advantage, especially if the restraining effect of the wild-type allele is also lost. Alternatively, deletion of chromosome 17p may result in an allelic loss of other haploinsufficient tumor suppressors that may further enhance the oncogenic potential of mutant *TP53* via p53 independent mechanisms (41). Experimental CRISPR/Cas9 genome modeling has demonstrated that human AML cell lines expressing $TP53^{missense/+}$ have a competitive growth advantage *in vivo* over haploinsufficient $TP53^{+/-}$ isogenic lines, suggesting a dominant-negative effect (13). $TP53^{missense/-}$ cells, however, were also competitively more potent than $TP53^{missense/+}$ cells with the wild-type allele retained, consistent with clinical observations in which p53 loss of heterozygosity is often selected for at the time of clinical progression, including after venetoclax-based therapy (42). The biological dominance of *TP53* missense variants in AML supports the ongoing therapeutic search for new compositions with therapeutic potential to revert aberrant p53 protein function to normal.

TP53 mutational burden has also emerged as a significant prognostic factor in AML and MDS, with a correlation with response to certain standard therapies. A VAF over 6% is associated with inferior overall survival (OS) and progression-free survival in lower-risk MDS. In high-risk MDS (HR-MDS), increasing VAF strongly correlates with risk of complex cytogenetics, and a VAF >40% was an independent covariate for poor OS (43, 44). These data were validated in a larger cohort that showed that the hazard of death increased by 1.02 per 1% increase in VAF among all MDS (45). In patients with newly diagnosed AML with monoallelic *TP53* mutations, an increasing VAF (<20% vs. 20%–40% vs. >40%) did not affect the response rates or the overall dismal survival with hypomethylating agent (HMA)–based therapies, with or without venetoclax, but an increasing VAF was associated with progressively lower response rates and inferior OS in the context of cytarabine-based regimens (46, 47).

p53 also plays a vital role in the normal function and homeostasis of hematopoietic stem cells (HSC) and the bone marrow microenvironment. During normal hematopoiesis, intact p53 mediates the quiescence of HSCs and preservation of genomic stability. Loss or dysfunction of p53 leads to enhanced self-renewal of HSCs, and other supporting oncogenic aberrations can lead to their transformation into leukemia stem cells (LSC; ref. 36). p53 is activated in response to DNA damage with consequent transcriptional activation of several genes, resulting in DNA repair or cell-cycle arrest and apoptosis (2). An impaired apoptosis pathway likely contributes to resistance to cytotoxic chemotherapy or venetoclax-based therapies in multihit *TP53*-mutated MDS/AML (46, 48, 49). Haploinsufficiency of genes located on chromosome 5q—for example, *CSNK1A1*, *EGR1*, *APC*—cooperate with loss of or mutations in *TP53* to confer a survival advantage in HSCs (50, 51). Degradation of the remaining CK1α leading to increased p53-mediated apoptosis is the key mechanism of benefit with lenalidomide in MDS with del(5q) (52). Expansion of preexisting clones or emergence of new clones with *TP53* mutations consequently contributes to treatment failure and disease progression in lower-risk MDS with del(5q) treated with lenalidomide (53, 54). Other notable genomic associations with *TP53*-mutated MDS/AML include amplifications involving *EPOR/JAK2* in patients with acute erythroid leukemia, which is characterized by multihit *TP53* mutations (55, 56). Germline mutations in ERCC excision repair 6 like 2 (*ERCC6L2*) have been linked to genomic instability and somatic *TP53* mutations leading to AML with erythroid differentiation (57).

Poor outcomes with available therapies prompted investigations into the immune architecture and cytokine milieu of *TP53*-mutated MDS/AML, with the goal of identifying potential immunotherapeutic approaches. *TP53*-mutated MDS and AML have an enrichment of immunoinhibitory checkpoints including PD-L1 on HSCs, TIM3 on myeloid-derived suppressor cells (MDSC), and LAG3 and TIGIT on bulk bone marrow blasts (20, 58, 59). Furthermore, *TP53*-mutated MDS and AML have an immune-dampened microenvironment with upregulation of *FOXP3* transcription, an increase in $ICOS^{hi}$ (activated) regulatory T cells and PD-1^{lo} MDSCs, a decrease in $OX40^{+}$ cytotoxic T cells and $ICOS^{+}$ and 4-$1BB^{+}$ natural killer cells, as well as marked impairment of CD3–CD28-stimulated T cells to secrete immune-effector Th1 cytokines (polyfunctionality; refs. 20, 58, 60). IFNγ signaling is well recognized as a major driver of response to immune-checkpoint inhibition in solid tumors. Although studies in *TP53*-mutated AML show that IFNγ signaling may be a biomarker of response to the CD123 × CD3ε dual-affinity receptor targeting (DART) antibody flotetuzumab, there is debate about whether the increased IFNγ signal is a reflection of T-cell fitness in the tumor microenvironment or a sequela of increased inflammation in response to cell death after chemotherapy causing heightened IFNγ production (20, 60). Although bulk RNA analysis of bone marrow has shown high IFNγ signaling before therapy in *TP53*-mutated AML responders to flotetuzumab, single-cell CD3–CD28-stimulated T-cell cytokine profiling has suggested decreased IFNγ and Th1 cytokine secretion by T cells in newly diagnosed and relapsed or refractory (R/R) *TP53*-mutated AML (20, 60). In addition, *TP53*-mutated AML showed upregulation of proinflammatory Th17 genes, NF-κB, PI3K–AKT signaling, and other markers of immune senescence. One could postulate that these aspects may not only affect response to standard therapies but also potentially abrogate the development of a robust graft-versus-leukemia effect (20).

In summary, these data point toward a profound immune dysregulation, with features of immunosenescence with an overall immune-evasive phenotype, which could potentially

be leveraged to develop novel immunotherapy approaches for *TP53*-mutated MDS/AML.

CURRENT THERAPIES FOR *TP53*-MUTATED MDS AND AML

HMAs are the current standard approach for newly diagnosed HR-MDS and offer an overall response rate (ORR) of 17% to 77% [encompassing complete remission (CR), marrow complete remission (mCR), partial response (PR), and hematologic improvement (HI)] in patients with *TP53*-mutated MDS, with International Working Group (IWG) CR in 10% to 25%, and a median OS of 8.2 to 12.4 months, with one study reporting an ORR of 100% ($n = 9$) with the 10-day regimen of decitabine (45, 61, 62). In MDS, *TP53* deletions are associated with significantly lower response rates to HMAs, and *TP53* VAF more than 40% confer significantly worse outcomes with a median OS of 4.1 to 7.7 months with HMA therapy (Table 1; refs. 29, 45). In a large cohort of patients with MDS and oligoblastic AML who underwent sequential genomic testing during HMA therapy, *TP53* mutation was a strong negative predictor with a median OS of 9.7 months (HR, 2.33; $P = 0.001$). Importantly, a clearance of *TP53* mutations (i.e., to VAF of <5%) was a strong predictor of improved outcomes to HMA therapy, particularly in patients who were bridged to allogeneic stem cell transplantation (allo-SCT; HR 0.28; $P = 0.001$; ref. 44).

In *TP53*-mutated AML, first-line therapy with low-intensity chemotherapies—for example, HMAs or low-dose cytarabine–based regimens—demonstrated an ORR of 14% to 62% with a median OS of 2.1 to 8.1 months. The rates of response with the 5-day versus 10-day regimen of decitabine were similar (29% vs. 47%, $P = 0.40$) in a single-institution randomized study (6, 63–66). Intensive chemotherapy-based approaches offered similar outcomes with an ORR of 47% to 55% and a median OS of 6.8 to 10.1 months, often with more toxicities, longer hospital stays, and prolonged myelosuppresion (6, 63, 64, 67). Baseline *TP53* VAF was prognostic for response to cytarabine-based regimens with VAF >40% associated with an inferior CR and CR with incomplete hematologic recovery (CRi) rate of 35% and median OS of 4.7 months compared with a CR/CRi rate of 79% and median OS of 7.3 months in patients with TP53 VAF ≤40% (47). *TP53* VAF, however, did not seem to affect response rates and median OS in the context of HMA-based regimens for AML, unlike the trend observed in *TP53*-mutated MDS with HMA (47).

TP53 mutations confer resistance to venetoclax-based regimens in AML through alterations in mitochondrial homeostasis by inhibiting mitochondrial stress response and increasing oxidative phosphorylation (68). Leukemia cells with *TP53* loss have an increased threshold for BAX/BAK activation, and although this can be suppressed initially by venetoclax, over time they are able to escape BCL-2 inhibition due to competitive advantage (49). HMA with venetoclax did show encouraging responses in first-line, *TP53*-mutated, poor cytogenetic risk AML, with a CR/CRi rate of 41% (CR rate of 20%) versus a CR/CRi rate of 17% (CR rate of 11%) with HMA alone, as noted in subset analysis from the phase IB study of HMA with venetoclax and the VIALE-A trial (46, 48, 69–71). However, the median OS in older/unfit patients with AML treated with venetoclax and HMA was 6.5 months, which was similar to the 6.7 months with HMA alone. Given prior data suggesting 10-day decitabine may have a specific benefit in *TP53*-mutated AML, one study combining decitabine for 10 days with venetoclax showed a CR/CRi rate of 57% (CR rate 37%) but a median OS of only 5.2 months (46). A high 60-day mortality rate of 26% was observed with decitabine plus venetoclax, mainly due to refractory disease, and contributed to poor long-term OS. Nonetheless, venetoclax may still have a role in combination with novel therapies in *TP53*-mutated AML, harnessing independent mechanisms of synergy. Combined inhibition of BCL-2 and MCL1 as well as blockade of extrinsic and intrinsic apoptotic pathways may also offer a novel approach that preclinically appears to be effective against *TP53*-mutated AML (49, 72).

ROLE OF ALLO-SCT IN *TP53*-MUTATED AML

Multiple analyses have shown that patients with *TP53*-mutated AML/MDS harbor an 80% to 90% higher risk of relapse and death after allo-SCT compared with *TP53* wild-type patients (25, 73, 74). A majority of these relapses and death following allo-SCT occur in patients with concomitant chromosome 17 abnormality or complex karyotype, leading to multihit disease (75). However, among patients with *TP53*-mutated AML, allo-SCT in first remission (CR1) can reduce the risk of relapse by up to 80% and risk of death by up to 70% (47). However, only a minority of patients with *TP53*-mutated AML, regardless of age or fitness, are able to proceed to allo-SCT in CR1, ranging from 0 to 33% across different published series, with lower response rates, poor count recovery, increased rates of early mortality, and early relapse being the predominant barriers to allo-SCT in this population (46, 47, 66). A case could be made for limiting allo-SCT only in *TP53*-mutated patients with AML who achieve at least a morphologic remission (i.e., <5% marrow blasts), as outcomes in patients not in morphologic remission before allo-SCT are poor in general and even more inferior in *TP53*-mutated patients. Clearance of *TP53* mutation prior to allo-SCT has been shown to be a favorable prognostic marker, and patients who achieve *TP53* mutation clearance or <5% by next-generation sequencing should be strongly considered for transition to allo-SCT in otherwise suitable candidates (76).

Although augmented reduced-intensity conditioning with fludarabine/amsacrine/cytarabine-busulphan has not been shown to improve outcomes over a fludarabine-based reduced-intensity conditioning regimen, a myeloablative conditioning regimen has been shown to improve survival over reduced-intensity conditioning in patients with AML with measurable residual disease (MRD; refs. 77, 78). Even with allo-SCT in *TP53*-mutated MDS and AML, the risk of relapse remains very significant and long-term survival remains low at less than 20% (28, 29). Nevertheless, allo-SCT still appears to offer the best chances of improving outcomes and achieving long-term survival in appropriately selected patients, with up-front noncytotoxic strategies to attain remissions without severe toxicities, early transition to allo-SCT in suitable candidates, close peritransplant monitoring for *TP53*-mutated clones, and the use of rational maintenance therapies after transplant to improve outcomes in *TP53*-mutated patients (75). To this end, novel mutant p53–directed therapies such

Table 1. Currently available therapies and selected emerging therapies for *TP53*-mutated AML and MDS

Agent/regimen	Study phase	Population	*TP53*-mutated pts	Response	CR rate	Median OS (months)	Reference
AML							
Azacitidine or decitabine	II; retrospective	ND AML	22	CR/CRi 22%–38%	13%–22%	2.1–7.3	(63–66)
Venetoclax + azacitidine or 5-day decitabine	Ib/II, III	ND AML	36, 54	CR/CRi 47%, 41%	NR, 20%	4.9–7.2	(70, 71)
Venetoclax + 10-day decitabine	II; *post hoc*	ND AML	26	ORR 77%	48%	5.4	(126)
Magrolimab + azacitidine	Ib	ND AML	72	CR/CRi 49%	33%	10.8	(82, 127)
Magrolimab + venetoclax + azacitidine	Ib/II	ND AML	14	ORR 86%	64%	NR	(84)
Eprenetapopt + azacitidine	Ib/II	ND AML	18	ORR 33%	17%	10.4	(97)
Sabatolimab + HMA	Ib	ND AML	5	CR/CRi 40%	20%	DOR 6.4	(107)
SGN-CD33A ± HMA	I/II	ND AML	7	CR/CRi 86%	NR	NA	(128)
Nivolumab + intensive chemotherapy	*Post hoc*	ND AML	4	ORR 50%	NA	NA	(67)
Intensive chemotherapy	Retrospective	ND AML	Various	ORR 47%–55%	45%–55%	6.8–8.8	(6, 64)
Low-intensity chemotherapy	Retrospective	ND AML	Various	ORR 14%–50%	36%	6.7–9.0	(6, 63, 64)
Flotetuzumab	I/II	R/R AML	15	ORR 60%	47%	4.0	(90)
Nivolumab + azacitidine	II	R/R AML	26	ORR 23%	NA	NA	(110)
Venetoclax + 10-day decitabine	II; *post hoc*	R/R AML	24	ORR 46%	19%	4.5	(126)
MDS							
Azacitidine or decitabine	*Post hoc*	MDS	Various	ORR 39%–100%	1%–32%	9.4–12.4	(61, 64)
Eprenetapopt + azacitidine	Ib/II	MDS	40	ORR 73%	50%	10.8	(96)
Sabatolimab + HMA	Ib	MDS	14	ORR 71%	29%	OS NR (DOR 21.5)	(107)
Magrolimab + azacitidine	IB	MDS	25	ORR 68%	40%	16.3	(83)

Abbreviations: CRi, CR with incomplete hematologic recovery; DOR, duration of response; NA, not applicable; ND, newly diagnosed; NR, not reported; ORR, overall response rate, defined as sum of all responses per the IWG criteria or European LeukemiaNet (ELN2017) criteria; pts, patients.

as eprenetapopt in combination with azacitidine have shown promising results as maintenance therapy after allo-SCT. In patients with *TP53*-mutated AML/MDS following allo-SCT, this combination showed a median relapse-free survival of 14.5 months and a median OS of 20.6 months, which compared favorably with historical expectations (79).

EMERGING STRATEGIES FOR *TP53*-MUTATED MDS AND AML

Recent progress in immunotherapeutics and mutant p53–directed approaches offer the hope of potentially improving outcomes in these patients (Fig. 2; ref. 80). In this section,

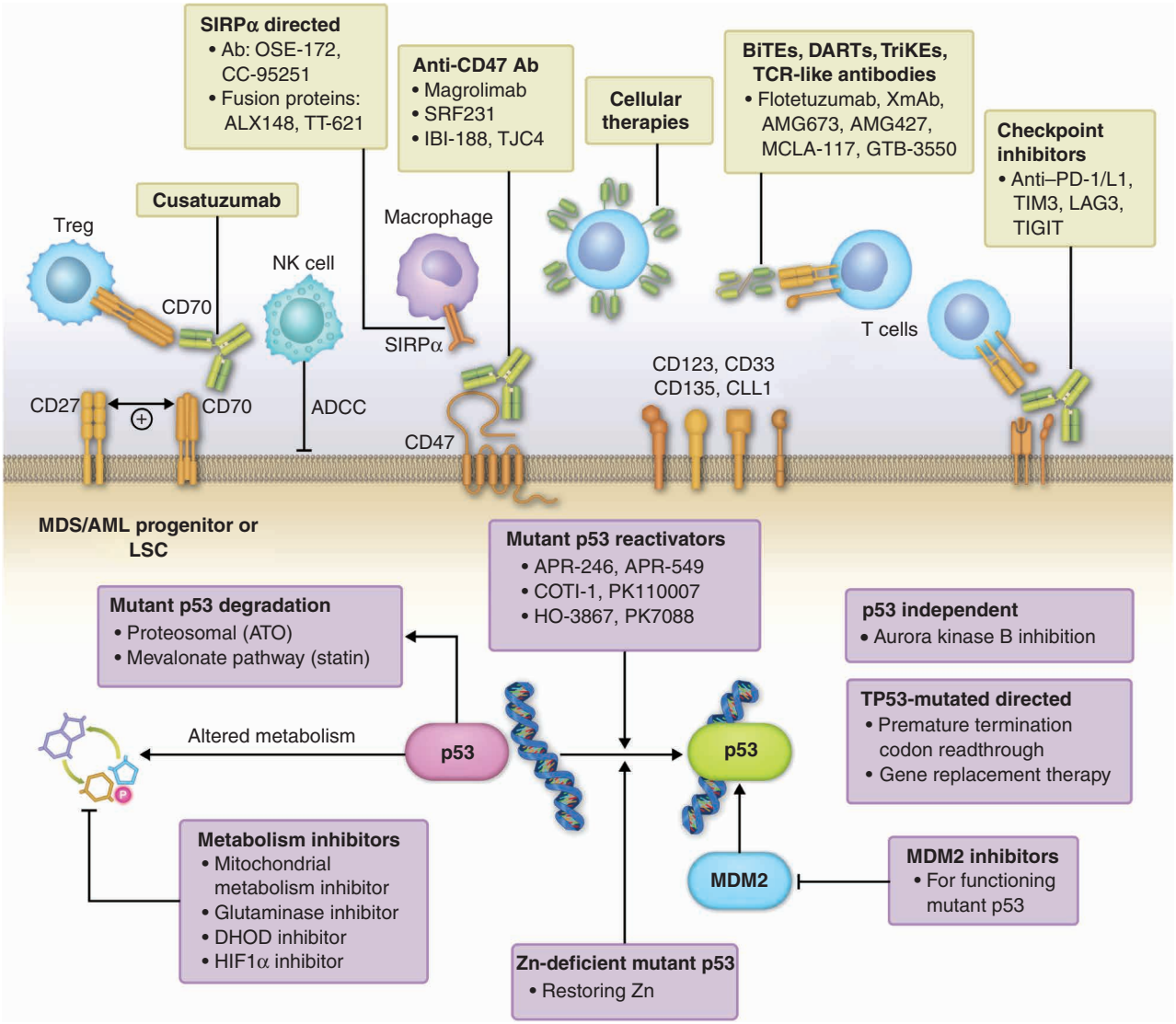

Figure 2. Novel therapies for *TP53*-mutated MDS and AML. Cell-extrinsic immunotherapeutic approaches include targeting cell-surface markers including LSC markers, macrophage and T-cell checkpoints, bispecific engagers, and adoptive cellular therapies including unmodified and chimeric antigen receptor–modified cells. Cell-intrinsic approaches include mutant p53 reactivators, mutant p53 degraders, metabolism-targeting agents, GSPT1 degraders, and others. Ab, antibody; ADCC, antibody-dependent cell-mediated cytotoxicity; BiTE, bispecific T-cell engager; NK, natural killer; TCR, T-cell receptor; Treg, regulatory T cell; TriKE, trispecific killer cell engager.

we discuss emerging data with four promising agents in this space, namely, magrolimab, flotetuzumab, sabatolimab, and eprenetapopt, and have briefly described other emerging strategies with potential for the field of *TP53*-mutated MDS/AML (Table 2).

Magrolimab

CD47 is an integrin-associated antiphagocytic protein that is overexpressed in cancer cells and correlates with poor outcomes in AML. It binds to the signal receptor protein-α (SIRPα) on macrophages and dendritic cells and enables immune evasion by inhibiting prophagocytic receptors like complement receptor 3, Fc receptors, and SLAMF7 from initiating phagocytosis (81). Magrolimab (Hu5F9-G4) is a first-in-class humanized IgG4 monoclonal antibody against CD47 and prompts cancer cell phagocytosis by macrophages through disruption of the CD47–SIRPα inhibitory checkpoint, thereby blocking the "don't eat me signal." CD47 is also an LSC marker, and targeting CD47 can potentially eliminate LSCs while sparing normal HSCs. Preclinical studies showed synergism between azacitidine and magrolimab in AML cell lines, and this combination was tested in a phase Ib trial that enrolled older/unfit patients with newly diagnosed AML ineligible for induction therapy and newly diagnosed intermediate- to high-risk MDS. Among older/unfit patients with *TP53*-mutated AML treated on this trial ($n = 72$), azacitidine with magrolimab showed an ORR of 49% ($n = 35/72$) and a CR rate of 33% ($n = 24/72$; ref. 82). The median duration of response (DOR) was 8.7 months, and the median OS was 10.8 months (82). In 25 patients with *TP53*-mutated

Table 2. Ongoing clinical trials of interest for *TP53*-mutated MDS and AML

AML	Phase	Disease	Identifier
Magrolimab + azacitidine vs. venetoclax + azacitidine OR intensive chemotherapy (ENHANCE-2)	III	ND *TP53*-mutated AML only	NCT04778397
Azacitidine + venetoclax ± magrolimab (ENHANCE-3)	III	ND AML (including *TP53*-mutated)	NCT05079230
Magrolimab + venetoclax + azacitidine	I/II	ND and R/R AML	NCT04435691
Multiarm study: -Magrolimab + venetoclax + azacitidine -Magrolimab + MEC -Magrolimab + CC486	I/II	ND, R/R, and postinduction maintenance AML	NCT04778410
Decitabine + cytarabine + arsenic trioxide	II	ND AML	NCT03381781
Sabatolimab + venetoclax + azacitidine		ND AML	NCT04150029
APR-246 + venetoclax + azacitidine	I	ND AML	NCT04214860
CC-90009 + venetoclax + azacitidine		ND and R/R AML	NCT04336982
Gamma-delta T cells	I	MRD-positive AML	NCT05001451
NK cells	I	R/R AML	NCT04220684 NCT04023071 NCT04623944
AML/MDS			
CAR-T cells targeting CD123, CD33, CD135, CLL1-CD33, NKG2D receptor, Lewis Y	I	R/R AML, high-risk myeloid neoplasms	NCT03018405 NCT01864902 NCT02159495 NCT03795779
APR-246 + azacitidine	II	Posttransplant AML, MDS maintenance	NCT03931291
Magrolimab + azacitidine	I/II	ND and R/R AML, ND and R/R MDS	NCT03248479
MDS			
APR-246 ± azacitidine	III	ND *TP53*-mutated MDS only	NCT03745716
Magrolimab ± azacitidine (ENHANCE-1)	III	ND HR-MDS	NCT04313881
Sabatolimab, hypomethylating agent (STIMULUS)	II, III	ND HR-MDS, CMML	NCT03946670 NCT04266301
APR-548 + azacitidine	I	ND MDS	NCT04638309

Abbreviations: CAR, chimeric antigen receptor; CMML, chronic myelomonocytic leukemia; ND, newly diagnosed; NK, natural killer.

MDS enrolled, the combination led to an ORR of 68%, a CR rate of 40%, and a median OS of 16.3 months (83). Magrolimab with venetoclax and azacitidine was evaluated in patients with newly diagnosed *TP53*-mutated AML ($n = 14$), with an ORR of 86% with a CR rate of 64%, an MRD-negative rate of 55%, and robust clearance of *TP53*-mutated clones in eight of nine CR/CRi patients (VAF sensitivity 1%; ref. 84). Other anti-CD47–targeted therapies in phase I/II clinical trials include lemzoparlimab, TTI-621, TTI-622, ALX148, SL-172154 (SIRPα-Fc-CD40L), etc., with many trials having cohorts for patients with *TP53* mutations (85).

Flotetuzumab

CD123 serves as the receptor for IL3, and its downstream signaling promotes hematopoietic progenitor cell proliferation through activation of the PI3K/MAPK pathway and upregulation of antiapoptotic proteins (86). CD123 is differentially expressed in about 90% of patients with AML, and overexpression on AML blasts is associated with inferior outcomes (87, 88). Flotetuzumab is a CD123 × CD3ε DART molecule that mediates T-cell activation and proliferation, resulting in the eradication of CD123-expressing primary AML blasts *in vitro* and *in vivo* (86, 89). Flotetuzumab was evaluated in a phase I/II study in R/R AML, enriched for patients with AML with primary induction failure or early relapse (within 6 months of response; ref. 90). Among patients with *TP53*-mutated R/R AML, the ORR was 47% ($n = 7/15$) with an encouraging median OS of 10.3 months in responding patients (20). The relatively short durability of response outside of patients who were bridged quickly to allo-SCT remains a challenge with a DOR of 2 to 5 months in nontransplanted patients.

CD123 expression did not correlate with response or cytokine release syndrome with flotetuzumab. Transcriptomic analysis suggested that an IFNγ-enriched, immune-infiltrated tumor microenvironment predicted response to flotetuzumab, and an immunosuppressed tumor microenvironment could be rejuvenated by flotetuzumab through T cell–driven mechanisms (90). Specifically among *TP53*-mutated patients, higher bulk RNA expression of *FOXP3, PD-1*, and inflammatory chemokines correlated with a response along with *CD8B* and *IFNG* (20, 90). Vibecotamab (XmAb14045) is another CD123 × CD3 bispecific T-cell engager (BiTE) that showed a modest ORR of 14% ($n = 7/51$) in R/R AML (91). Multiple CD33-directed BiTEs are currently in the dose-escalation phase and have yielded modest responses in R/R AML. There are several other bispecific antibody platforms targeting CD123, CD33, CD135, CLEC12A, as well as novel natural killer (NK) cell–directed bispecific engager and trispecific engagers in early clinical development and if found to be effective and safe may be interesting to evaluate for *TP53*-mutated AML given their potential mutation-agnostic mechanism of actions.

Eprenetapopt

Eprenetapopt (APR-246) is a first-in-class agent that binds covalently to cysteine residues in the core DNA domain of mutant p53 and is postulated to cause refolding and restoration of an active wild type–like conformation and function of p53 (16). Other proposed mechanisms of this class of agents include induction of cell death via reactive oxygen species, ferroptosis, depletion of deoxyribonucleotides, and triggering of unfolded protein responses through depletion of antioxidants (92–95). Two studies evaluated eprenetapopt with azacitidine in newly diagnosed adults with HMA-naïve low- to high-risk MDS, AML, and MDS/myeloproliferative neoplasm (MPN; refs. 96, 97). In a pooled analysis of the two trials, significantly higher rates of CR were noted in patients with isolated *TP53* mutations (CR rate of 52% vs. 30%), and in patients with biallelic *TP53* mutation or complex karyotype (CR rate of 49% vs. 8%; ref. 98). Additionally, patients with complete or partial remission and/or clearing *TP53* mutation (VAF sensitivity 1%) and proceeding to allo-SCT had favorable outcomes with the median OS not reached. In the overall AML, MDS, MPN population, IHC of bone marrow mononuclear cells showing more than 10% staining for p53 was associated with a higher CR rate (66% vs. 13%, $P = 0.01$; ref. 96). Reduction of mutant *TP53* VAF below 0.1% was associated with improved OS (not reached vs. 10.7 months, $P = 0.05$; ref. 97). However, in a randomized trial in newly diagnosed patients with *TP53*-mutated MDS, azacitidine with eprenetapopt versus azacitidine with placebo did not meet the primary endpoint in spite of a numerically improved CR rate (33% vs. 22%, $P = 0.13$; refs. 99, 100). Preliminary results of a triple combination of eprenetapopt in combination with venetoclax and azacitidine in previously untreated *TP53*-mutated AML ($n = 30$) showed a CR/CRi rate of 53% and a CR rate of 37%, and accrual is ongoing (101). A next-generation oral p53 reactivator, APR-548, is currently under preclinical development. Mutant-specific p53 activators, such as PC14586 for p.Y220C, are currently under investigation for solid tumors (NCT04585750; ref. 102).

Sabatolimab

The potential for immunotherapeutic agents to act in a p53-agnostic manner and potentially circumvent some of the p53-associated resistance mechanisms, as well as growing insights into immune microenvironmental remodeling by *TP53*-mutant AML/MDS, has led to an increasing interest in evaluating other immunotherapies in *TP53*-mutant AML/MDS. TIM3 is another checkpoint that forms part of a coinhibitory receptor module expressed on exhausted T cells and is preferentially overexpressed on MDS/AML LSCs (103, 104). TIM3 is involved in an autocrine signaling loop via galectin-9, which promotes LSC renewal, and antibodies blocking TIM3 could therefore selectively eradicate AML LSCs (105, 106). Sabatolimab (MBG453) is a humanized, high-affinity IgG4-targeting TIM3 being evaluated in solid tumors and hematologic malignancies. A phase Ib trial evaluated sabatolimab with HMA in newly diagnosed patients with HR-MDS by the Revised International Prognostic Scoring System (IPSS-R; $n = 53$) or AML unfit for intensive therapy ($n = 48$; ref. 107). The adverse event profile of the combination was consistent with that of HMA alone with few and mostly lower-grade immune-related adverse events noted. In patients with HR-MDS, this combination demonstrated an ORR of 57% (CR rate 20%) and a median DOR of 17.1 months. Among patients with newly diagnosed AML, this combination yielded a CR/CRi rate of 30%, a CR rate of 25%, and a median DOR of 12.6 months. Specifically, in patients with HR-MDS with adverse-risk mutations *TP53, RUNX1*, and *ASXL1*, the CR/mCR rate was 43% and the median DOR was encouraging at 21.5 months in 10 of 14 responders. In patients with newly diagnosed *TP53*-mutant AML, the CR/CRi was 40% with a median DOR of 6.4 months.

OTHER IMMUNOTHERAPEUTIC APPROACHES

SIRPα-directed therapies to the macrophage ligand SIRPα offer another approach to disrupt the CD47–SIRPα immune checkpoint and modulate MDSCs. These agents may potentially mitigate on-target adverse effects of anti-CD47 antibody (e.g., anemia). Such therapies including anti-SIRPα antibodies (e.g., OSE-172 and CC-95251) and SIRPα fusion proteins (e.g., ALX148 and TT-621) are currently in phase I trials, with ALX418 and TTI-621 being evaluated in combination with HMA in MDS and in combination with HMA with venetoclax in AML.

Immune-checkpoint inhibitor–based regimens have overall yielded modest results in MDS/AML so far. The initial report with single-agent ipilimumab yielded a CR in 42% of patients ($n = 5/12$) with relapsed AML after allo-SCT, generating a great deal of excitement for this field in AML and MDS (108). Blockade of PD-1 or PD-1 and CTLA-4 with azacitidine or high-dose cytarabine in all R/R AML yielded modest CR/CRi rates of 14% to 36% in patients. The median OS was 6.3 to 10.5 months, with an ORR of 23% in *TP53*-mutated R/R AML in these PD-1–based combinations (109, 110). In the first-line setting, nivolumab with idarubicin and cytarabine yielded a CR/CRi of 50% in patients with *TP53*-mutated AML ($n = 4/8$; ref. 67). Unfortunately, no significant improvement in CR/CRi rates or in OS in first-line higher-risk MDS ($n = 84$) or first-line older/unfit AML ($n = 129$) was noted in

a randomized, first-line phase II study of azacitidine with or without the anti–PD-L1 antibody durvalumab, resulting in tempered enthusiasm and uncertain future for PD-1/PD-L1/CTLA-4–based therapies in myeloid malignancies (111, 112).

Cellular therapy approaches have been challenging to develop due to the hostile milieu of the bone marrow niche in AML (80). Chimeric antigen receptor (CAR) T-cell therapies directed at myeloid antigens, including CD33, CD38, CD70, CD123, CD135, CD371, CLL1, FLT3, TIM3, LILRB4, NKG2D, Lewis Y, and others, are still in early development, with modest responses ranging from isolated blast count reductions to brief CR/CRi in up to 50% of patients in the dose-escalation cohorts (28, 113). One second-generation CAR-T targeting CLL1 has shown promising outcomes in pediatric AML with CR/CRi in six of eight patients without any grade 3/4 cytokine release syndrome or immune effector cell–associated neurotoxicity syndrome (114). Although CLL1 is not expressed in HSCs, its expression on granulocytes and monocytes led to associated neutropenia, which resolved only after the eradication of CLL1 CAR-T cells. Novel approaches to safely improve CAR-T efficacy through targeting multiple antigens with novel gating strategies, enhancing fitness and *in vivo* persistence, overcoming the immunosuppressive microenvironment, and developing allogeneic CAR-based approaches will hopefully lead to better cellular therapies for AML (115). Development of T-cell receptor–like antibodies against mutant p53 and the potential for engineering similar adoptive T-cell approaches are in early preclinical development (116, 117).

Off-the-shelf modified NK cell–based approaches have shown early promise in R/R AML with no dose-limiting toxicities or cytokine release syndrome, immune effector cell–associated neurotoxicity syndrome, or graft-versus-host disease. In a phase I trial of FT516/538 (an induced pluripotent stem cell–derived high-affinity, noncleavable CD16 expressing NK cell) in 12 patients with R/R AML with a median of three prior lines of therapy, the ORR was 42% with durable remissions in two patients lasting >6 months without subsequent interventions after NK infusions (118). If successful, such strategies may find an important role in traditionally difficult-to-treat molecular and cytogenetic subsets such as *TP53*, *RUNX1*, and inv3q and other subsets of AML/MDS. Such approaches may be especially attractive in patients with low-burden disease, MRD^+ disease, or potentially as maintenance after AML therapy or after allo-SCT in high-risk patients in remission, as these patients are likely to have a more favorable tumor microenvironment potentially not rendered deranged by the presence of high-volume aberrant myeloid cells. Other similar adoptive cellular therapies rapidly entering the clinic for AML/MDS include gamma-delta T cells, and invariant NKT cells are currently in preclinical development (refs. 119–121).

OTHER NONIMMUNOLOGIC APPROACHES

COTI-2 is a thiosemicarbazone compound with effects like eprenetapopt. It binds to mutant p53 and reverses conformation to a wild-type form, thus restoring DNA-binding function and normalizing wild-type p53 target gene expression (16). It can also act independently through inducing DNA damage, causing replication stress, activating AMP-activated protein kinase, and inhibiting the mTOR pathway. It showed acceptable safety in a phase I trial in gynecologic malignancies (NCT02433626; ref. 122). Other similar mutant p53 reactivators including PK110007, HO-3867, and PK7088 are in various stages of development.

Other miscellaneous approaches with potential application to *TP53*-mutated MDS/AML include arsenic trioxide–based approaches to induce proteasomal degradation of mutant p53 (arsenic trioxide has been shown to structurally stabilize p53 mutants and transcriptionally rescue a subset of mutants through a cryptic allosteric site; ref. 123), statin-based approaches to promote mutant p53 degradation via inhibition of the mevalonate pathway, and restoring zinc to zinc-deficient p53 mutants (16, 27, 124, 125). Future approaches directed toward *TP53* mutations may include promotion of premature termination codon readthrough enabling the production of full-length p53 and gene replacement therapies (16, 27).

In addition, rational combinations or sequential approaches of previously mentioned strategies with the integration of allo-SCT as a part of the continuum of therapy may be needed to improve response durability and survival of *TP53*-mutated MDS and AML.

CONCLUSION

Four decades of cumulative discoveries have brought us to what is hopefully the cusp of important breakthroughs in the field of *TP53*-mutated cancers, with many of these efforts culminating in clinical trials being initiated in myeloid malignancies. With the increasing recognition of *TP53*-mutated MDS and AML as distinct stem cell disorders, we are beginning to better understand the diverse genetic and immune landscape of *TP53* alterations, their functional consequences on both the tumor and the immune microenvironment, and the heterogenous nature of *TP53* mutations with varied prognostic consequences. Clearly, it is now well recognized that *TP53*-mutant MDS/AML disease represents a singular entity with poor outcomes necessitating dedicated clinical interventions with the hope of developing and optimizing the first *TP53*-specific agents. Encouraging early results of novel innate and adaptive immunotherapeutic approaches and mutant p53 reactivators in combination with HMA with or without venetoclax are showing encouraging efficacy that needs to be confirmed in randomized registration studies. If successful, new questions will emerge regarding predictive biomarkers, time and role of allo-SCT, resistance mechanisms, side effect management, and optimal combination and sequencing strategies as well as maintenance applications of such novel strategies with the eventual hope of improving survival in this extremely difficult patient population.

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