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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 poor median OS of 5–10 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 non-immune-based approaches for this entity.

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TP53; myelodysplastic; syndrome; acute myeloid leukemia

Introduction

TP53 is a tumor suppressor gene which encodes for a 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 sub-optimal responses to conventional therapies across multiple cancer types.(1) Response to cytotoxic chemotherapy is highly dependent on the presence of an 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 dismal median survival of less than 5–10 months, irrespective of therapies employed.(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 review we summarize the key biologic implications of *TP53* mutations, their prognostic relevance to MDS and AML, outcomes with currently approved therapies, and discuss current and future directions for drug development for *TP53*-mutated AML/MDS.

TP53 mutation and cancer

TP53 is 20kb gene located on chromosome 17p13.1 which codes for at least 15 different isoforms and has two paralogs p63 and p73 with similar structure 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).(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, 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 gain-of-function.(1,11,12) Majority of the *TP53* hot-spot mutations lead to loss of function causing 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, etc., and those involved in DNA damage response, e.g., CHK2, MSH6.(10) However, the gain-of-function hypothesis has

been challenged by elegant work demonstrating a dominant negative effect of missense *TP53* mutations leading to 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 co-mutational 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 non-hotspot mutations and out of those around 30% of the mutations, e.g., those involving E180 and R181, while tumorigenic, behave very differently from p53-null and hotspot mutations.(15) These partial loss-of-function mutant p53 retain 10–50% of transcriptional activity compared to 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, e.g., *RB1, VHL*, etc. 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 (TLR) mediated apoptosis, and increasing PD-L1 expression.(17) However, mutant p53 also favorably modulates the immune response by increasing NF-κB activity, tumor-associated macrophage (TAM) infiltration, eliciting B-cell response, and activating T-cells, effects which 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 impact cytokine production, immune synapse formation between antigen-presenting cells (APC) and T cells, and T cell fate.(18–20) With these diverse effects on various components of both the adaptive and innate immune system, p53 is increasingly being recognized as a ‘guardian of immune integrity’.(21)

TP53 mutation in MDS and AML

Clonal hematopoiesis is noted in 2% to 6% in the blood of patients with cancer, including clonal *TP53* variants which could represent a precursor lesion in diverse malignancies.(22,23) *TP53* abnormalities occur in nearly 5–10% of patients with *de novo* MDS and AML.(24–26) This frequency is much lower than several other solid tumors, e.g., uterine carcinosarcoma, esophageal adenocarcinoma and lung squamous cell cancers where *TP53* alterations are noted in more than 80% cases. However, the frequency in AML/MDS goes up to 20–40% in older patients or those with therapy-related myeloid malignancies.(6,27) The frequency of *TP53* abnormalities further increases to 70–80% in patients with complex karyotype, and in patients with loss of chromosome 17/17p, 5/5q, and 7/7q.(28,29) Therapy for a previous cancer, including radiation or chemotherapy do not directly induce *TP53* mutations. Rather, pre-existing progenitors carrying mutant *TP53* and 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) While over 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 range from partial loss-of-function, complete loss-of-function, or gain-of-function, resulting in diverse functional consequences.(1,26,27) Among *TP53*-mutated MDS, 'multi-hit' 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* mutant, particularly multi-hit, 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 10–19% (MDS/AML) or AML with mutated *TP53* if blasts are 20% to recognize this highly adverse-risk myeloid pathology.(32–35)

Multi-hit *TP53*-mutated MDS/AML often represents a distinct stem-cell disorder with a paucity of co-mutations in other myeloid malignancy-related genes, with co-mutations occurring in less than 25% cases.(36) This is consistent with *TP53* mutations being early truncal events in the MDS/AML pathogenesis in such cases and consequently multi-hit *TP53* mutations or bi-allelic defects evolve to become dominant clones conferring resistance to current standard therapies and consequently carry worse prognosis.(26) Mono-allelic *TP53* mutations (33%) on the other hand frequently have co-mutations in other genes, most commonly *TET2* (29%), *SF3B1* (27%), *ASXL1* (16%), and *DNMT3A* (16%), and are likely to be late sub-clonal events with varying impacts on outcomes.(26) As accurate multi-hit analysis requires determination of the allelic state by loss of heterozygosity mapping, clinically available conventional and cytogenetic techniques currently do not capture all bi-allelic patients. However, a reasonable determination of multi-hit state can be made if there is 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 LOH variants.(26) Nuclear p53 accumulation assessed by immunohistochemistry 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 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 correlate 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, frameshift and nonsense alterations 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 have either a concomitant *TP53* mutation and *TP53* copy number loss, or when multiple *TP53* mutations are 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 haplo-insufficient tumor suppressors that may further enhance the oncogenic potential of mutant *TP53* via p53 independent mechanisms.(41) Experimental CRISPR/Cas9 genome modelling 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 where 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 (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 which 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 impact 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 quiescence of HSCs, preservation of genomic stability, and reduction of reactive oxygen species. Loss or dysfunction of p53 leads to enhanced self-renewal of HSCs, and with other supporting oncogenic aberrations can lead to their transformation into leukemia stem cells (LSC).(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 multi-hit *TP53*-mutated MDS/AML.(46,48,49) Haploinsufficiency of genes located on chromosome 5q, e.g., *CSNK1A1*, *EGR1*, *APC*, cooperate with loss of or mutations in *TP53* to confer survival advantage in hematopoietic stem cells.(50,51) Degradation of the remaining CK1α leading to an increased p53-mediated apoptosis is the key mechanism of benefit with lenalidomide in MDS with del(5q).(52) Expansion of pre-existing 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 multi-hit *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/AML have an enrichment of immunoinhibitory checkpoints including PD-L1 on HSCs, TIM3 on myeloid derived suppressor cells, and LAG3 and TIGIT on bulk bone marrow blasts.(20,58,59) Furthermore, *TP53*-mutated MDS/AML have an immune-dampened microenvironment with up-regulation of *FoxP3* transcription, an increase in $ICOS^{high}$ (activated) regulatory T-cells, PD-1^{low} myeloid derived suppressor cells (MDSC), and a decrease in $OX40^{+}$ cytotoxic T-cells, $ICOS^{+}$ and 4-$1BB^{+}$ natural killer cells, as well as a marked impairment of CD3-CD28 stimulated T-cells to secrete immune effector Th1 cytokines (polyfunctionality).(20,58,60) IFN-γ signaling is well recognized as a major driver of response to immune checkpoint inhibition in solid tumors. While studies in *TP53*-mutated AML show that IFN-γ signaling may be a biomarker of response to CD3 × CD123 dual-affinity receptor targeting (DART) antibody flotetuzumab , there is debate about whether the increased IFN-γ signal is a reflection of T-cell fitness in the tumor microenvironment, or a sequela of increased inflammation in response to cell death causing a heightened IFN-gamma production.(20,60) While bulk RNA analysis of bone marrow has shown high IFN-γ signaling pretherapy in *TP53*-mutated AML responders to flotetuzumab, single-cell CD3-CD28 stimulated T-cell cytokine profiling has suggested decreased IFN-γ and Th1 cytokine secretion by T cells in newly diagnosed and relapsed/refractory *TP53*-mutated AML.(20,60) In addition, *TP53*-mutated AML also showed upregulation of proinflammatory Th17 genes, NF-κB, PI3K-AKT signaling and other markers of immune senescence. One could postulate that this may not only impact their response to standard therapies but also potentially abrogate development of a robust graft-vs-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*^{mut} MDS and AML

HMAs are the current standard approach for newly diagnosed HR-MDS and in *TP53*-mutated MDS patients offer an overall response rate (ORR) of 17–77% (encompassing CR, mCR, PR, HI), with IWG complete remission (CR) in 10–25%, and median OS of 8.2–12.4 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 median OS of 4.1–7.7 months with HMA therapy (Table 1).(29,45) In a large cohort of MDS and oligoblastic AML who underwent sequential genomic testing during

HMA therapy, *TP53* mutation was a strong negative predictor with 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 outcome to HMA therapy, particularly in patients that were bridged to allogeneic stem cell transplantation (allo-SCT; HR 0.28; p=0.001).(44)

In *TP53*-mutated AML, frontline therapy with low-intensity chemotherapies, e.g., HMAs or low-dose cytarabine-based regimens demonstrated an ORR of 14–62% with a median OS of 2.1–8.1 months. The rates of response with the 5-day vs 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 47–55% and median OS of 6.8–10.1 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 impact 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 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 frontline *TP53*-mutated poor cytogenetic risk AML with a CR/CRi rate of 41% (CR rate of 20%) versus 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 VIALE-A trial.(46,48,69–71) However, the median OS in older/unfit patients with AML with venetoclax and HMA was 6.5 months which was similar to the 6.7 months with HMA alone. Given prior data suggesting decitabine 10 days may have a specific benefit in *TP53*-mutated AML, one study combining decitabine 10 days with venetoclax showing a CR/CRi rate of 57% (CR rate 37%) but with 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 the 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 MCL-1, and 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 Allogeneic Stem Cell Transplant in *TP53* mutated AML

Multiple analyses have shown that patients with *TP53* mutated AML/MDS harbor a 80 to 90% higher risk of relapse and death after allo-SCT compared to *TP53* wild-type patients.(25,73,74) Majority of these relapses and death following allo-SCT occur in patients with concomitant chromosome 17 abnormality or complex karyotype, leading to ‘multi-hit’

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 0–33% 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.(46,47,47,66) 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)

While augmented reduced intensity conditioning with fludarabine/amsacrine/cytarabine-busulphan has not been shown to improve outcomes over fludarabine-based reduced intensity conditioning regimen, myeloablative conditioning regimen has been shown to improve survival over reduced intensity conditioning in patients with AML with measurable residual disease (MRD).(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, in the consensus opinion of the authors, allo-SCT still appears to offer the best chances of improving outcomes and achieving long term survival in appropriately selected patients, with upfront non- cytotoxic strategies to attain remissions without severe toxicities, early transition to allo-SCT in suitable candidates, close peri-transplant monitoring for *TP53* mutated clones, and the use of rational maintenance therapies post-transplant to improve outcomes in *TP53* mutated patients.(75) To this end novel mutant p53 directed therapies such 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 median OS of 20.6 months which compared favorably to historical expectations.(79)

Emerging strategies for *TP53*^{mut} MDS and AML

Recent progress in immunotherapeutics and mutant p53-directed approaches offer the hope of potentially improving outcomes in these patients (Fig. 2).(80) In this section 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 anti-phagocytic protein which 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 pro-phagocytic 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 a leukemia stem-cell (LSC) marker and targeting CD47 can potentially eliminate LSCs while sparing normal hematopoietic stem cells. Pre-clinical studies showed synergism between azacitidine and magrolimab in an AML cell lines and this combination was tested in a phase 1b trial which 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 with *TP53*-mutated AML treated on this trial (n=72), azacitidine with magrolimab showed an ORR of 49% (n=35/72) and CR rate of 33% (n=24/72).(82) The median duration of response was 8.7 months, and the median OS was 10.8 months.(82) In the 4 patients with *TP53*-mutated MDS enrolled, the combination led to a response in 3 of 4 patients and a complete cytogenetic response in all patients.(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%, MRD negative rate of 55%, and robust clearance of *TP53*-mutated clones in 8 of 9 CR/CRi patients (VAF sensitivity 1%).(84) Other anti-CD47 targeted therapies in phase 1/2 clinical trials include lemzoparlimab, TTI-621, TTI-622, ALX148, SL-172154 (SIRPα-Fc-CD40L) and others with many agents have *TP53* mutant specific cohorts.(85)

Flotetuzumab

CD123 serves as the receptor for interleukin-3, 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% patients with AML and overexpression on AML blasts is associated with inferior outcomes.(87,88) Flotetuzumab is a CD123×CD3ε dual-affinity retargeting (DART) molecule which mediated T-cell activation and proliferation, resulting in eradication of CD123-expressing primary AML blasts *in vitro* and *in vivo*.(86,89) Flotetuzumab was evaluated in a phase 1/2 study in R/R AML, enriched for patients with AML with primary induction failure or early relapse (within 6 months of response).(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 duration of response of 2–5 months in non-transplanted patients

CD123 expression did not correlate with response or cytokine release syndrome with flotetuzumab. Transcriptomic analysis suggested that an IFN-γ 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*, *PD1* and inflammatory chemokines correlated with response along with *CD8B* and *IFNG*.(20,90) Vibecotamab (XmAb14045) is another CD123×CD3 bi-specific T cell engager (BiTE) which showed a modest ORR of 14% (n=7/51) in R/R AML.(91) Multiple CD33-directed BiTEs are currently in dose-escalation phase and have yielded modest responses in R/R AML. There are several other bi-specific antibody platforms targeting

CD123, CD33, CD135, CLEC12A, as well novel NK-cell-directed bi-specific killer cell engager (BiKE) and tri-specific killer cell engagers (TriKE) in early clinical development and if effective and safe may be interesting to evaluate for *TP53*^{mut} AML given their potentially mutation agnostic mechanism of actions.

Eprenetapopt

Eprenetapopt (APR246) is a first-in-class agent which 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 mechanism 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/MPN.(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%).(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 median OS not reached. In the overall AML, MDS, MPN population, immunohistochemistry of bone marrow mononuclear cells showing more than 10% staining for p53 was associated with higher CR rate (66% vs 13%, p=.01).(96) Reduction of mutant *TP53* VAF below 0.1% was associated with improved OS (NR vs. 10.7 months, p=.05).(97) However, in a randomized trial in newly diagnosed patients with *TP53*-mutated MDS azacitidine with eprenetapopt vs azacitidine with placebo did not meet the primary endpoint in spite of a numerically improved CR rate (33% vs 22%, p=0.13).(99,100) Preliminary results of a triple combination of eprenetapopt, venetoclax with azacitidine in previously untreated *TP53*-mutated AML (n=30) showed 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 pre-clinical development. Mutant specific p53 activators, e.g., PC14586 for p.Y220C are currently under investigation for solid tumors (NCT04585750).(102)

Sabatolimab

Potential for immunotherapeutic agents to act in 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 have led to an increasing interest in evaluating other immunotherapies in *TP53*-mutant AML/MDS. The T-cell immunoglobulin and mucin domain-3 (TIM-3) is another checkpoint which forms a part of a co-inhibitory receptor module expressed on exhausted T cells and is preferentially over-expressed on MDS/AML LSCs.(103)(104) TIM-3 is involved in an autocrine signaling loop via galectin-9 which promotes LSC renewal and antibodies blocking TIM-3 could therefore selective eradicate AML LSCs via CDC, ADCC, and ADCP.(105,106) Sabatolimab (MBG453) is a humanized, high-affinity, IgG4 targeting TIM-3 being evaluated in solid tumors and hematological malignancies. A phase Ib trial evaluated sabatolimab with HMA in newly diagnosed patients with high-risk (HR) MDS by

IPSS-R (n=53) or AML unfit for intensive therapy (n=48).(107) The adverse event profile of the combination was consistent with that of HMA alone with few, and mostly lower grade, immune related AEs noted. In patients with HR-MDS this combination demonstrated an ORR of 57% (CR rate 20%) and median duration of response (DOR) of 17.1 months. Among patients with newly diagnosed AML, this combination yielded a CR/CRi rate of 30%, CR rate of 25% and median DOR of 12.6 months. Specifically, in patients with HR-MDS with adverse risk mutations *TP53, RUNX1*, *ASXL1*, CR/mCR rate was 43% and median DOR was encouraging at 21.5 months in 10/14 responders. In patients with newly diagnosed *TP53*-mutant AML the CR/CRi was 40% with median DOR of 6.4 months.

Other Immunotherapeutic Approaches

SIRPα-directed therapies

SIRPα-directed therapies to the macrophage ligand: SIRPα offer another approach to disrupt the CD47-SIRPα immune checkpoint and modulate myeloid derived suppressor cells. 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, CC-95251, and SIRPα fusion proteins, e.g., ALX148, TT-621, are currently in phase 1 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

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% patients (n=5/12) with relapsed AML post 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 14–36% patients. The median OS was 6.3–10.5 months with ORR of 23% in *TP53*-mutated R/R AML in these PD-1 based combinations.(109,110) In the frontline setting nivolumab with idarubicin and cytarabine yielded CR/CRi 50% in patients with *TP53*-mutated AML (n=4/8).(67) Unfortunately no significant improvement in CR/CRi rates or in OS in frontline higher risk MDS (n=84) or frontline older/unfit AML (n=129) was noted in a randomized frontline phase II study of azacitidine with or without anti-PD-L1 antibody durvalumab resulting in tempered enthusiasm and uncertain future for PD1/PD-L1/CTLA4-based therapies in myeloid malignancies.(111,112)

Cellular therapy

Cellular therapy approaches have been challenging to develop due to the hostile milieu of the bone marrow niche in AML.(80) CAR-T 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% 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 6/8 patients without any grade 3/4 cytokine release syndrome or immune effector cell-associated neurotoxicity syndrome.(114)

While CLL1 is not expressed in hematopoietic stem cells, its expression on granulocytes and monocytes led to associated neutropenia which only resolved after eradication of CLL1 CAR-T cells. Novel approaches to safely improve CAR-T cell efficacy through targeting multiple antigens with novel gating strategies, enhancing fitness and in vivo persistence, overcoming immunosuppressive microenvironment, and developing allogeneic CAR-based approaches will hopefully lead to better cellular therapies for AML.(115) Development of T-cell receptor (TCR)-like antibodies against mutant p53 and potential for engineering similar adoptive T-cell approaches are in early pre-clinical 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-vs-host disease. In a phase 1 trial of FT516/538 (an induced pluripotent stem cell derived high-affinity, non-cleavable CD16 expressing NK cell) in 12 patients with R/R AML with a median of 3 prior lines of therapy, the ORR was 42% with durable remissions in 2 patients lasting >6 months without subsequent interventions after NK infsuions.(118) If successful such strategies may find an important role in traditionally difficult to treat molecular and cytogenetic subsets such as *TP53*, *RUNX1*, inv3q and other subsets of AML/MDS. Such approaches may be especially attractive in patients with low-burden disease, MRD+ disease or potentially as a maintenance post-AML-therapy or post 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 clinic for AML/MDS include gamma-delta T-cells, invariant NKT cells are currently in pre-clinical development (NCT04754100).(119–121)

Other Non-immunologic Approaches

COTI-2

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 gynecological malignancies (NCT02433626).(122) Other similar mutant p53 reactivators including PK110007, HO-3867, PK7088, etc. are in various stages of development.

Other miscellaneous approaches

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(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 integration of allo-SCT as a part of the continuum of therapy (total therapy approach as pioneered by our multiple myeloma colleagues) may be needed to harness novel dependencies and synthetic lethality to improve response durability and survival *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 both on the tumor and the immune micro-environment, 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 VEN are showing encouraging efficacy that need to be confirmed in randomized registration studies. If successful, new questions will emerge regarding predictive biomarkers, time and role of alloSCT, 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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Conflict of Interests

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PV: Stock and Other Ownership Interests - OxStem; Honoraria - Abbvie; Celgene; Daiichi Sankyo; Jazz Pharmaceuticals; Pfizer; Research Funding - Celgene; Forty-Seven; Patents, Royalties, Other Intellectual Property - Patent for flow cytometric detection of leukaemic stem cells.

RM: is on the Board of Directors of CircBio Inc., the Advisory Boards of Kodikaz Therapeutic Solutions Inc. and Syros Pharmaceuticals, and is an inventor on a number of patents related to CD47 cancer immunotherapy licensed to Gilead Sciences, Inc. R.M. receives research support from CircBio Inc. and Gilead Sciences, Inc.. R.M. is a co-founder and equity holder of CircBio Inc., Pheast Therapeutics, and MyeloGene Inc.

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Statement of significance

Emerging data on the impact of co-mutations and associated cytogenetic aberrations, *TP53* allelic burden, immunobiology, and tumor microenvironment of *TP53*-mutated MDS and AML are further unraveling the complexity of *TP53*-mutated AML and MDS. 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 non-immune strategies for treatment of this entity. It is hoped that these novel rationally designed therapies and combinations will improve the outcomes in this area of significant unmet need.

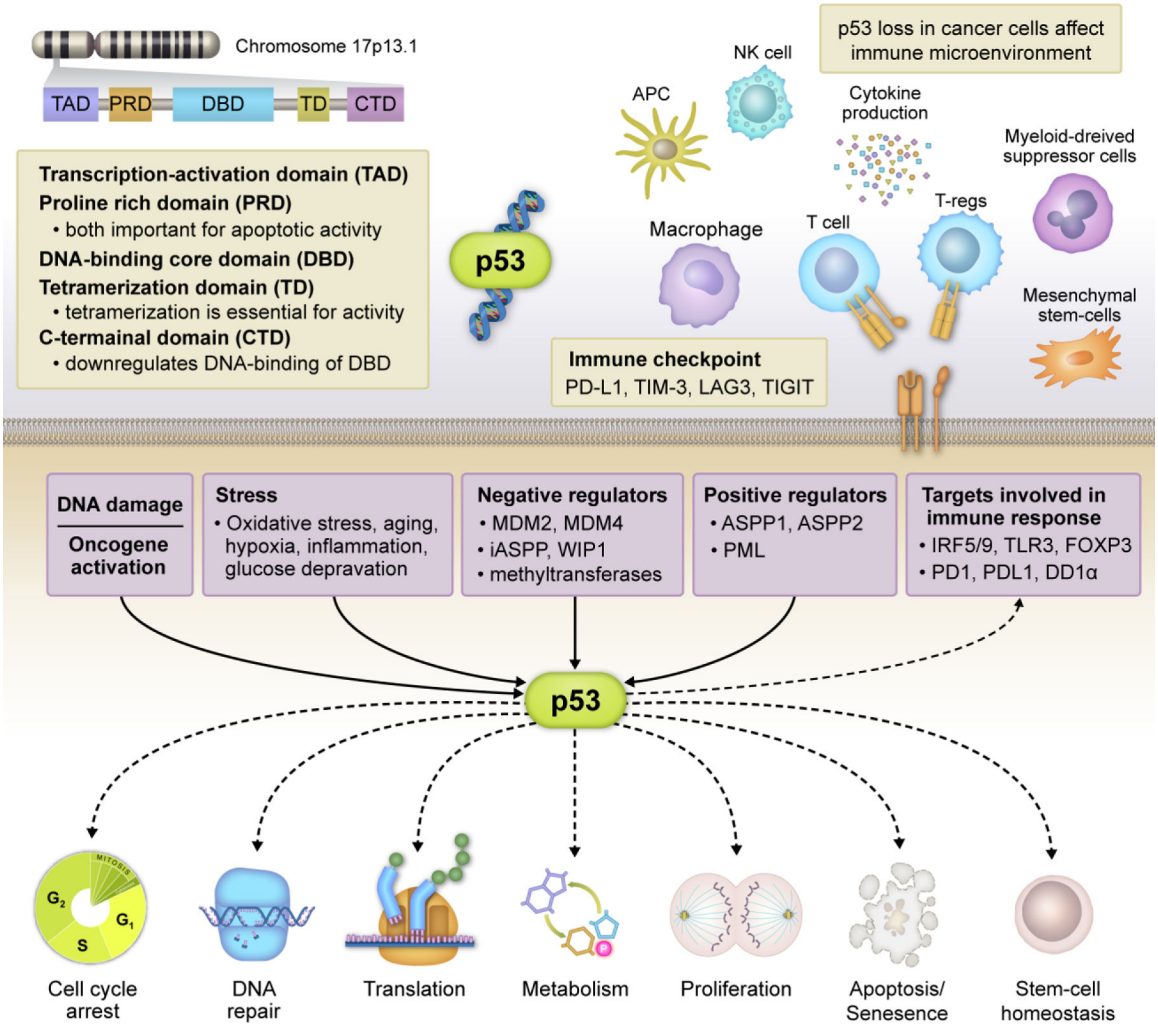

Fig. 1.

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 direct effect on several immunological targets.

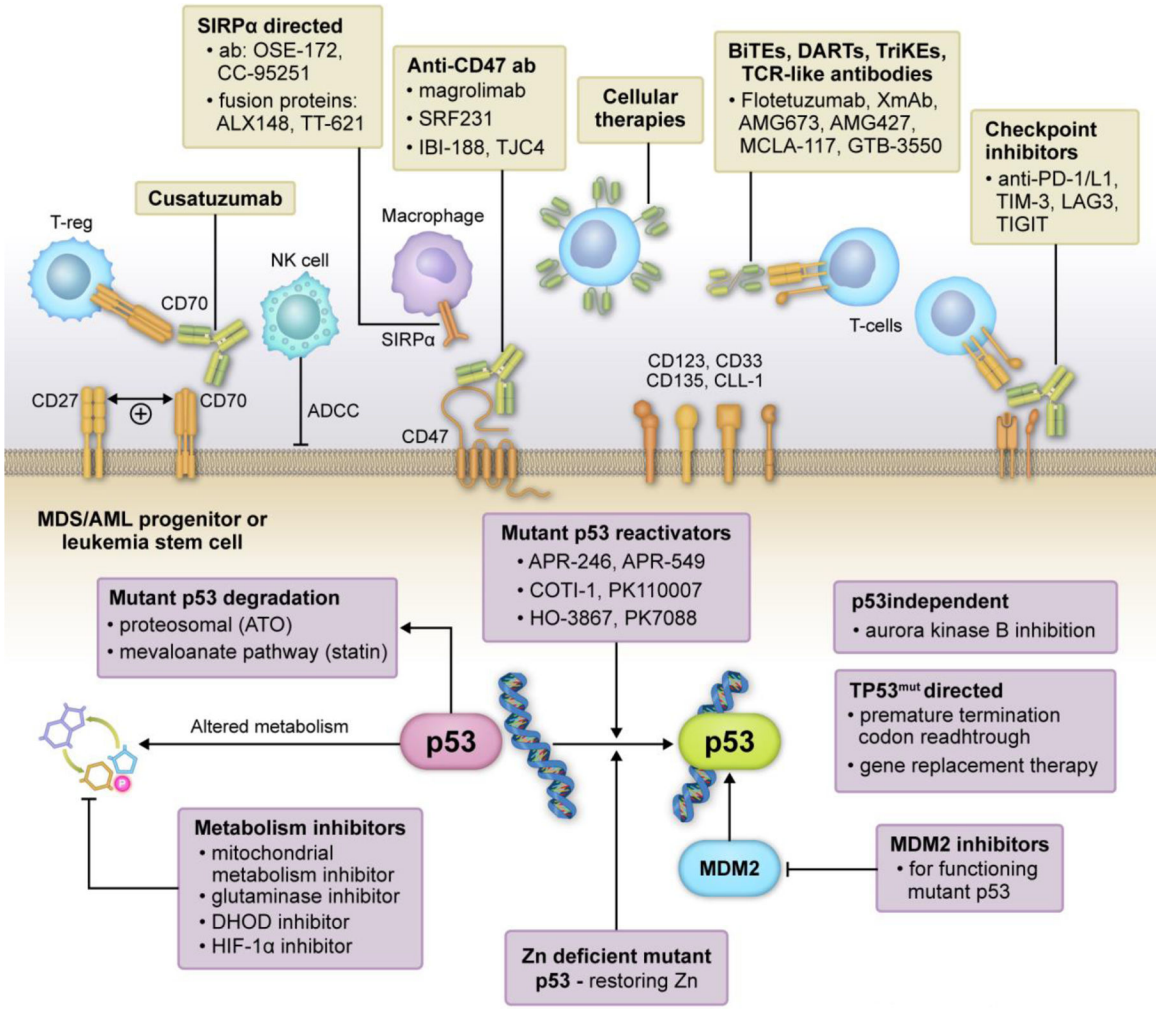

Fig. 2.

Novel therapies for *TP53*-mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). Cell extrinsic immunotherapeutic approaches include targeting cell surface markers including leukemia stem cell markers, negative regulatory macrophage and T cell checkpoints, bispecific engagers, adoptive cellular therapies including unmodified and chimeric antigen receptor modified cells. Cell intrinsic approaches include mutant p53 reactivators, mutant p53 degraders, metabolism targeting agents, and others.

Table 1.

Currently available therapies and selected emerging therapies for *TP53*-mutated acute myeloid leukemia and myelodysplastic syndrome

Agent / Regimen	Study Phase	Population	*TP53*^{mut} pts	Response	CR rate	Median OS (mo.)	Trial identifier
AML							
Azacitidine or decitabine	2, retrospective	ND AML	22	CR/CRi 22–38%	13–22%	2.1–7.3	(63–66)
Venetoclax + azacitidine or 5-day decitabine	1b/2	ND AML	36	CR/CRi 41–72%	20–46%	4.9–7.2	NCT02203773(70,71)
Venetoclax + 10-day decitabine	2; post-hoc	ND AML	26	ORR 77%	48%	5.4	NCT03404193(126)
Magrolimab + azacitidine	1b	ND AML	29	CR/CRi 59%	45%	12.9	NCT03248479(127)
Magrolimab + venetoclax + azacitidine	1b/2	ND AML	14	ORR 86%	64%	NR	NCT04435691(84)
Eprenetapopt + azacitidine	1b/2	ND AML	18	ORR 33%	17%	10.4	NCT03588078(97)
Sabatolimab + HMA	1b	ND AML	5	CR/CRi 40%	20%	DOR 6.4	NCT03066648(107)
SGN-CD33A ± HMA	1/2	ND AML	7	CR/CRi 86%		NA	NCT0192329(128)
Nivolumab + intensive chemotherapy	Post-hoc	ND AML	4	ORR 50%	NA	NA	NCT02464657(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	1/2	R/R AML	15	ORR 60%	47%	4.0	NCT02152956(90)
Nivolumab + azacitidine	2	R/R AML	26	ORR 23%	NA	NA	NCT02397720(110)
Venetoclax + 10-day decitabine	2; post-hoc	R/R AML	24	ORR 46%	19%	4.5	NCT03404193(126)
MDS							
Azacitidine or decitabine	Post-hoc	MDS	various	ORR 39–100%	1–32%	9.4–12.4	NCT01687400(61,64)
Eprenetapopt + azacitidine	1b/2	MDS	40	ORR 73%	50%	10.8	NCT03072043(96)
Sabatolimab + HMA	1b	MDS	14	ORR 71%	29%	OS not reported (DOR 21.5)	NCT03066648(107)

OS = overall survival, ND = newly diagnosed, R/R = relapsed or refractory, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasm, ORR = overall response rate, defined as sum of all responses per the IWG criteria or ELN2017 criteria. CR = complete remission, CRi = CR with incomplete hematologic recovery, mCR = marrow CR, MLFS = morphologic leukemia-free state, DOR = duration of response

Table 2.

Ongoing clinical trials of interest for *TP53*-mutated myelodysplastic syndrome and acute myeloid leukemia

AML	Phase	Disease	Identifier
Magrolimab + Azacitidine vs Venetoclax + Azacitidine OR Intensive Chemotherapy (ENHANCE-2)	3	ND TP53 mutated AML only	NCT04778397
Azacitidine + Venetoclax +/− Magrolimab (ENHANCE-3)	3	ND AML (including TP53)	NCT05079230
Magrolimab + venetoclax + azacitidine	1/2	ND and R/R AML	NCT04435691
Multi-arm study: -Magrolimab + venetoclax + azacitidine -Magrolimab + MEC -Magrolimab + CC486	1/2	ND, R/R, and Post-induction maintenance AML	NCT04778410
Decitabine + cytarabine + arsenic trioxide	2	ND AML	NCT03381781
Sabatolimab + venetoclax + azacitidine		ND AML	NCT04150029
APR-246 + venetoclax + azacitidine	1	ND AML	NCT04214860
CC-90009 + venetoclax + azacitidine		ND and R/R AML	NCT04336982
Gamma delta T cells	1	MRD-positive AML	NCT05001451
NK cells	1	R/R AML	NCT04220684 NCT04023071 NCT04623944
AML/MDS			
CAR-T cells targeting CD123, CD33, CD135, CLL1-CD33, NKG2D receptor, Lewis Y	1	R/R AML, high-risk myeloid neoplasms	NCT03018405NCT01864902 NCT02159495NCT03795779
APR-246 + azacitidine	2	Post-transplant AML, MDS maintenance	NCT03931291
Magrolimab + azacitidine	1/2	ND and R/R AML, ND and R/R MDS	NCT03248479
MDS			
APR-246 ± azacitidine	3	ND TP53 mutated MDS only	NCT03745716
Magrolimab ± azacitidine (ENHANCE-1)	3	ND HR-MDS	NCT04313881
Sabatolimab, hypomethylating agent (STIMULUS)	2,3	ND HR-MDS, CMML	NCT03946670NCT04266301
APR-548 + azacitidine	1	ND MDS	NCT04638309