Best Practice & Research Clinical Haematology 32 (2019) 134–144

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Current status and new treatment approaches in *TP53* mutated AML

Anthony M. Hunter[a,b], David A. Sallman[a,*]

[a] *Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA*
[b] *University of South Florida, Morsani College of Medicine, Tampa, FL, USA*

ARTICLE INFO

Keywords:
Acute myeloid leukemia (AML)
TP53
therapy-related acute myeloid leukemia (t-AML)

ABSTRACT

Mutations in the essential tumor suppressor gene, *TP53,* are observed in only 5–10% of acute myeloid leukemia (AML) cases, but are highly associated with therapy-related AML and cases with complex karyotype. The mutational status of *TP53* is a critical prognostic indicator, with dismal outcomes consistently observed across studies. Response rates to traditional cytotoxic chemotherapy are poor and long-term survival after allogeneic hematopoietic stem cell transplant is rare. Therapy with hypomethylating agents has resulted in a modest improvement in outcomes over intensive chemotherapy, but durable responses are seldom observed. In view of the intrinsic resistance to standard chemotherapies conferred by mutations in *TP53,* novel treatment approaches are required. In this review, we examine the current treatment landscape in *TP53* mutated AML and discuss emerging therapeutic approaches currently under clinical investigation.

1. Introduction

Advancements in genomic techniques such as next generation sequencing (NGS) have dramatically enhanced our knowledge of the underlying genetic alterations in acute myeloid leukemia (AML) [1,2]. Elucidation of the prognostic significance of these recurrently mutated genes has paved the way for genomics-based classification and risk stratification systems [1,3–5]. Furthermore, with the recent expansion of available treatment options and development of molecularly targeted therapies, this genomic information now plays a central role in treatment selection. Mutations in the *TP53* gene have garnered particular importance in prognostication and treatment selection in AML due to their association with inferior responses to standard treatment options and uniformly poor outcomes [1,5–14].

The most widely mutated gene across all human malignancies, mutations in *TP53* are seen in nearly half of all tumors [15,16]. Located on chromosome 17p13.1, the *TP53* gene encodes a 393 amino acid phosphoprotein, p53, which functions as a transcription factor with vital tumor suppressor functionality [17,18]. It contains several important functional domains including the N-terminal transactivation domain, which interacts with the negative regulator MDM2, a proline-rich SH3 domain, a DNA-binding domain, a tetramerization domain and the C-terminal regulatory domain [19]. Upon activation by cellular stressors such as DNA damage, oncogene activation and ribonucleotide depletion it regulates expression of an array of target genes involved in DNA repair, differentiation, cell-cycle arrest and induction of apoptosis [15,18–20]. Notably, p53 plays a crucial role in mediating the apoptotic response to cytotoxic chemotherapy, with mutant p53 conferring an inherent resistance to DNA damaging agents commonly utilized as anti-cancer therapy, including traditional therapies utilized in AML for decades [21–24]. This substantiates the poor outcomes seen

* Corresponding author. Moffitt Cancer Center, FOB 3rd floor, 12902 USF Magnolia Drive, Tampa, FL, 33612, USA.
E-mail address: David.Sallman@moffitt.org (D.A. Sallman).

https://doi.org/10.1016/j.beha.2019.05.004
Received 14 March 2019; Accepted 8 May 2019

Table 1
Efficacy of standard treatment options in *TP53* mutated AML.

Therapeutic Class	Agent	Indications	Complete Response Rates	Survival	References
Intensive Chemotherapy	Anthracycline and cytarabine based combination therapy (e.g. "7 + 3")	Frontline induction therapy or salvage therapy in AML	20–40%	mOS of 4–9 months	[6–10,13,46,47]
	CPX-351 (liposomal daunorubicin and cytarabine)	Induction therapy in secondary and t-AML	28% (vs. 45% in WT patients)	mOS of ~9 months	[50]
Hypomethylating agents	Azacitidine	Frontline or R/R AML	20–30%	mOS of 7.2 months (vs. 2.4 months with CCR)	[40,61]
	Decitabine	Frontline or R/R AML	20–30%	mOS 6–12 months	[61–63]
Antibody-drug conjugate	Gemtuzumab ozogamicin	Frontline treatment in combination with induction therapy or single agent in R/R AML	No benefit over induction chemotherapy alone	5-year OS of 9.1% (vs. 7.9% with induction alone) in adverse-risk cytogenetic group	[48]

AML, acute myeloid leukemia; mOS, median overall survival; t-AML, therapy-related acute myeloid leukemia; WT, wild type; R/R, relapsed and/or refractory; CCR, conventional care regimen.

Table 2
Emerging therapies in *TP53* mutated AML currently under investigation.

Therapeutic class	Agent	Novel features	Clinical Setting	Phase of Development	Reported Results	NCT no.	Reference
Bcl-2 inhibitor	Venetoclax	Inhibitor of the anti-apoptotic protein Bcl-2	Frontline treatment in elderly or medically unfit pts with AML; in combination with HMA or LDAC	Received accelerated approval from FDA on 11/21/18	Overall Outcomes: CR/CRi in 67%, mOS of 17.5 months *TP53* mutant Outcomes: CR/CRi in 47%, mOS of 7.2 months	Numerous ongoing trials investigating multiple combinations and treatment settings	[79]
HDAC inhibitor	Multiple agents	Epigenetic regulation and mutant p53 degradation	De novo or R/R AML and high-risk MDS (as combination therapy); post allo-HSCT maintenance	Phase 3	CR in ~15–40% in combination with HMA (no clear improvement over HMA monotherapy)	NCT03151408	[82–86]
HSP90 inhibitor	Ganetespib (STA-9090)	Inhibitor of heat shock protein 90; degradation of mutant p53	Older adults with AML; in combination with LDAC	Phase 2/3	CR in 18% vs. 16% in control ($p = 0.6$); 2-yr OS of 19% vs. 12% ($p = 0.5$)	None currently enrolling	[96]
Statins	Atorvastatin	HMG-CoA Reductase inhibitor; degradation of mutant p53	*TP53* mutant Relapsed AML and solid tumors	Pilot Trial	Not reported	NCT03560882	No results reported from clinical study
TP53 reactivators	APR-246	Restores WT *TP53* conformation and function	*TP53* mutated MDS, in combination with aza	Phase 3	*TP53* mutant Outcomes: CR in 82% (9/11), mOS and mPFS NR	NCT03745716	[105–107]
Checkpoint Inhibitors	Nivolumab	anti-PD-1 monoclonal antibody	Under investigation in multiple settings, alone or in combination with HMA, chemotherapy and/or ipilimumab	Phase 3	CR/CRi in 22% in R/R AML in combination with aza	Multiple trials currently ongoing	[112,114–119]
	Ipilimumab	anti-CTLA-4 monoclonal antibody	Multiple clinical settings, alone or in combination	Phase 2	Single agent: CR of 33% in R/R AML (4/12 pts)	Multiple trials currently ongoing	[113,114,116]
Bispecific antibodies	Flotetuzumab (MGD006)	CD123xCD3 DART antibody	R/R AML and high-risk MDS	Phase 1	CR/CRi in 19% (5/27 pts)	NCT02152956	[122]
	AMG 330	CD33xCD3 BiTE antibody	R/R AML	Phase 1	2 CR and 2 CRi (in 35 pt at 12 dose cohorts)	NCT02520427	[123]
CAR T-cell Therapy	CYAD-01	NKG2D receptor expressing CAR T-cells	R/R AML	Phase 1	CRi/CRh in 42% (3/7 pts) treated with multiple infusions	NCT03018405	[125,126]
	CART-33	CD33 directed CAR T-Cells	R/R AML	Phase 1	Blast reduction in only reported patient	NCT01864902 (additional CD33 CAR-T trials ongoing)	[127]
	MB-102	CD123 directed CAR T-Cells	R/R AML and BPDCN	Phase 1	2 CR, 1 MLFS in the AML cohort (6 pts)	NCT02159495 (additional CD123 CAR-T trials ongoing)	[129,130]
	ICG144	CLL1-CD33 compound CAR T-Cells	R/R high-risk myeloid neoplasms	Phase 1	MRD neg. CR reported in a single pediatric patient	NCT03795779	[131]

Bcl-2, B-Cell Lymphoma 2; pts, patients; HMA, hypomethylating agent; LDAC, low dose cytarabine; AML, acute myeloid leukemia; FDA, Food and Drug Administration; CR, complete response; CRi, complete response with incomplete hematologic recovery; mOS, median overall survival; HDAC, histone deacetylase; R/R, relapsed and/or refractory; MDS, myelodysplastic syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplant; HSP90, heat shock protein 90; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; WT, wild type; aza; azacitidine; mPFS, median progression-free survival; NR, not reached; nivo, nivolumab; DART, Dual-affinity Re-targeting; BiTE, Bi-specific T-cell engager; CAR, chimeric antigen receptor; NKG2D, Natural Killer Group 2D; CRh, complete response with partial hematologic recovery; BPDCN, blastic plasmacytoid dendritic cell neoplasm; MLFS, morphologic leukemia-free state; MRD, minimal residual disease.

in *TP53* mutated AML and highlights the importance of novel therapies with pharmacologic activity that does not rely on this pathway. Herein, we will review the role of *TP53* mutations in the treatment of AML and highlight emerging therapies with the potential to improve outcomes in this challenging molecular subgroup (Tables 1 and 2).

2. *TP53* mutations in MDS and AML

Despite the frequency of *TP53* mutations observed in human cancers, they are seen in only 5–10% of AML cases [1,2,25]. Patients tend to be older, with lower white blood cell counts (WBC), lower platelet counts and lower bone marrow (BM) blast percentage and share significant clinical phenotype overlap with *TP53* mutant myelodysplastic syndrome (MDS) patients [6,10,26]. As BM blast % distinction between MDS/AML represents an arbitrary cutoff, significant data support that *TP53* mutant MDS and AML represent a homogeneous disease entity. As an example, Lindsley and colleagues were able to identify *TP53* mutant AML as a genetic ontogeny distinct from de novo or secondary-type mutant AML [26]. *TP53* mutations are highly correlated with a complex karyotype and are seen in 70–80% of such cases, particularly in those with a monosomal karyotype or loss of 5/5q, 7/7q or 17/17p [8,10,12,27,28]. Both *TP53* mutations and complex karyotype independently predict inferior overall survival (OS), with the most dismal prognosis seen when these co-occur [1]. However, in the largest cohort of complex karyotype MDS, *TP53* mutation represented the strongest covariate for inferior OS in multivariable analysis, with complexity only being predictive in patients with 5 or more cytogenetic abnormalities [28]. *TP53* mutations are seen with increased frequency in patients with MDS and AML with isolated 5q deletion [28–30]. Additionally, they are enriched in cases of therapy-related AML (t-AML), where they are observed with a frequency of 25–40% [9,31,32]. Interestingly, in cases of t-AML it has been shown that cytotoxic chemotherapy does not necessarily directly induce these mutations, but rather mutations present in very low frequencies prior to chemotherapy undergo preferential expansion after treatment [33]. Additionally, *TP53* mutant MDS/AML have a paucity of other driver mutations, further highlighting the critical role of *TP53* in these disease subsets [26,28,34].

Though all classes of mutations have been observed, the majority of variants are missense alterations occurring in the DNA-binding domain (encoded by exons 5–8) with a predilection for arginine residues and noted mutational “hot spots” such as R175H, Y220C, R248Q and R273C [6,19,35,36]. Mutations in other functional domains have unique effects on p53 protein function, however, their clinical implications in AML are not well understood at this time [37,38]. *TP53* is the sole mutated gene identified in up to 75% of patients, while patients with co-occurring mutations have a decreased incidence of mutations in a number of AML-associated genes including *FLT3, NPM1, IDH1, IDH2, DNMT3A, WT1, RUNX1* and *RAS* [2,6,28,34,39]. The median variant allele frequency (VAF) has been observed to be the highest of all recurrently mutated genes in AML at nearly 50%, with a higher VAF shown to be predictive of inferior survival in MDS and AML patients [14,34,40].

Detection of increased levels of p53 protein by immunohistochemical (IHC) techniques has been shown to accurately correlate with *TP53* gene mutation by sequencing analysis, as well as clinical features seen in *TP53* mutated AML including complex karyotype, higher-risk disease and inferior OS [41–43]. However, with the decreasing cost and widespread availability of NGS at most centers, molecular profiling with targeted gene panels should now be considered standard of care in AML. Such methods have proven accurate and effective in detecting mutations in clinically relevant genes in AML, including *TP53,* and have been shown to improve upon risk stratification over conventional cytogenetics alone [44,45]. This has led to the incorporation of relevant gene mutations into standard risk stratification models, with *TP53* a notable inclusion into adverse-risk groups [1,3].

3. Outcomes with standard treatment approaches

3.1. Cytotoxic chemotherapy

Induction chemotherapy with cytotoxic agents, including anthracyclines and cytarabine, has been considered the standard of care in medically fit patients with AML for decades. While this may produce favorable results, particularly in younger patients and those with favorable-risk disease, *TP53* mutations are a strong predictor of inferior responses, with complete response (CR) rates in the range of 20–40% (Table 1) [6,8,10,46]. An array of studies have unequivocally demonstrated that such treatment is associated with dismal outcomes in *TP53* mutated patients, with increased relapse rates and a median OS in the range of 4–9 months [6–10,13,46,47]. Yet, patients who do not receive chemotherapy fare even worse, revealing the aggressive biology of the disease and suggesting that *TP53* mutation alone is not a reason to forgo treatment [13].

Gemtuzumab ozogamicin has been added to induction chemotherapy in attempt to improve outcomes, with a large meta-analysis of five randomized clinical trials demonstrating reduced rates of relapse and improved 5-year survival rates [48]. However, subgroup analysis identified no benefit in patients with adverse-risk cytogenetics, a cytogenetic group that is highly enriched in *TP53* mutations. CPX-351, a dual-drug liposomal encapsulation of cytarabine and daunorubicin, recently received FDA approval after a phase 3 study demonstrated improved CR rates (47.7% vs. 33.3%) and OS (9.56 vs.5.95 months) compared with “7 + 3” induction in patients with t-AML or secondary AML [49]. Subsequent evaluation of genomic predictors has identified *TP53* mutation as a predictor of significantly inferior response rates with this therapy, though this has not been compared directly to other induction regimens in this molecular subgroup [50].

3.2. Hypomethylating agents

The hypomethylating agents (HMA) azacitidine and decitabine are the preferred frontline treatment for elderly patients with AML

and those deemed not medically fit to receive induction chemotherapy. They function as cytidine nucleoside analogues that have been shown to incorporate into DNA (as well as RNA in the case of azacitidine) leading to inhibition of DNA methyltransferases, global DNA hypomethylation and induction of DNA damage [51,52]. The use of azacitidine in AML is supported by the randomized, prospective AZA-AML-001 trial, as well as subgroup analysis from the pivotal AZA-001 trial in high risk MDS, which demonstrated favorable OS (10.4 vs. 6.5 months) compared to conventional care regimens (best supportive care, low-dose cytarabine or 7 + 3 induction) [53,54]. A phase 3 trial of decitabine has also demonstrated improved CR rates (17.8% vs. 7.8%) and OS (7.7 vs. 5.0 months, statistically significant only after an unplanned survival analysis with prolonged follow up) compared to supportive care or low-dose cytarabine, supporting its use in older patients with newly diagnosed AML [55].

Further clinical inquiry in *TP53* mutated patients has suggested that these agents may produce superior results compared to standard therapies (Table 1), which is supported by pre-clinical work demonstrating increased sensitivity of *TP53* mutated cells to HMA [56,57]. Several studies have demonstrated that adverse-risk cytogenetics groups including complex and monosomal karyotypes, known to have a high prevalence of *TP53* mutations, do not negatively impact OS or response rates with HMA [40,58–60]. In a post-hoc analysis of the AZA-AML-001 study, *TP53* mutations only exhibited an inferior impact on OS in the conventional care treatment group, with *TP53* mutated patients treated with azacitidine demonstrating a median OS of 7.2 months compared to 2.4 months in the conventional care group ($p = 0.09$) [40]. A recent retrospective analysis demonstrated similar treatment outcomes between azacitidine and decitabine in patients with *TP53* mutated MDS and AML and also demonstrated an improvement in OS in those with *TP53* clonal clearance after HMA treatment (defined by VAF < 5%) [61]. A prospective, single-institution trial evaluated somatic mutations and their correlation to responses with a 10-day decitabine regimen and found that *TP53* mutated patients had increased response rates (100% blast clearance ($n = 21$), although CR in only 19% of patients ($n = 4$)) compared to wild-type patients (blast clearance in 41% ($n = 32$) and CR in 14% ($n = 14$)) and demonstrated rapid clearance of their *TP53* mutations (though in all cases remained detectable at low levels) [62]. Additionally, *TP53* mutations were not associated with inferior OS, as is typically observed in this molecular cohort (12.7 months compared to 15.4 in wild-type patients, $p = 0.79$). However, in larger cohorts, CR rates to HMA in this molecular subgroup range from 20 to 30% and a median OS of 6–12 months with no difference noted between azacitidine and decitabine [61,63].

Recently presented work demonstrated similar outcomes in patients treated with 5-day compared to 10-day decitabine regimens, including in patients with *TP53* mutations (median OS of 5.5 months with 5-day regimen and 4.9 months with 10-day regimen) [64]. With this growing body of evidence, and the pharmacologic rationale that these therapies do not rely on cytotoxic pathways to which *TP53* mutations confer inherent resistance, HMAs have emerged as the standard frontline treatment option in *TP53* mutated AML, regardless of age or fitness.

3.3. Allogeneic hematopoietic stem cell transplant

Post-remission therapy in AML varies by risk stratification as well as patient characteristics. While favorable-risk disease may be cured with chemotherapy alone, the vast majority of patients with intermediate and adverse-risk disease will relapse and allogeneic hematopoietic stem cell transplant (allo-HSCT) is routinely recommended for medically fit patients in these risk groups [3]. Current risk-stratification systems classify *TP53* mutations as an adverse-risk feature and these patients will invariably relapse with currently approved therapies [1,3]. However, the role of allo-HSCT in *TP53* mutated patients is debated due to dismal long-term outcomes.

A number of studies have evaluated molecular predictors of outcomes in patients with MDS and AML undergoing allo-HSCT, with mutations in *TP53* consistently identified as the strongest predictor of inferior outcomes, outweighing all other genetic or clinical characteristics [65–70]. Notably, *TP53* is the only gene uniformly identified across these large cohorts to predict for inferior OS. The three-year survival statistics reported in these studies was in the range of 10–20%, with several studies reporting no long-term survivors beyond 5–10 years. The majority of deaths were due to relapse, frequently occurring early after transplant (40% at 6 months and 50% at 100 days in two of these studies), but no increase in non-relapse mortality was observed. While this has led to some centers foregoing allo-HSCT in all *TP53* mutated patients, it should still be considered on a case-by-case basis after a detailed discussion with the patient, as a minority of patients may still experience long-term survival which would be unattainable with standard therapies [71].

Optimizing outcomes with allo-HSCT may be achievable with proper patient selection, appropriate remission-induction strategies and consideration of post-transplant maintenance therapies. Welch et al. demonstrated that after initial treatment with 10-day decitabine, of all evaluated variables, consolidation with allo-HSCT had the greatest impact on overall survival [62]. This was not negatively impacted by *TP53* mutation status, suggesting that use of HMA prior to transplant may help to abrogate the poor outcomes typically seen in this cohort. Furthermore, we have identified that patients with clonal suppression of mutant *TP53* after HMA therapy who proceeded to transplant had improved OS (16.3 vs. 8.9 months), suggesting a potentially valuable strategy in identifying patients who may receive the most benefit [61]. The use of post-transplant maintenance therapies has been proposed as a method to curb relapse rates, though data to recommend this in routine practice is insufficient at this time. Several studies evaluating post-transplant HMA's have suggested that these can safely be administered, with the potential for reducing relapse rates [72–74]. However, Oran and colleagues recently presented data on a randomized azacitidine vs no intervention maintenance trial which was negative for an improvement of RFS in all subgroups [75]. Notably, this trial was closed early secondary to slow accrual and also challenged by many patients not receiving the planned 12 cycles of treatment. Additionally, there was no subgroup analyses presented in regards to *TP53* mutation status, and thus further investigation is needed in this patient population which has a substantially higher relapse risk. Histone Deacetylase (HDAC) inhibitors have also been evaluated in this setting with favorable outcomes compared to historical populations although no randomized evidence is available to date [76].

4. Emerging treatment options & therapies under investigation

In view of the lack of durable responses and generally dismal outcomes seen with currently approved treatment options in this molecular subgroup, enrollment into clinical trials evaluating novel therapeutics should be considered in all patients. Considering the innate resistance to cytotoxic agents conferred by mutations in *TP53*, therapies with activity that relies on distinct cellular pathways and processes are most promising. Broadly, these can be categorized into targeted therapies and immunotherapies, which will be discussed in further detail and are summarized in Table 2.

4.1. Targeted therapies

The past several years has seen a surge in new drug approvals in AML. While targeted therapies against *FLT3, IDH1* and *IDH2* have little value in *TP53* mutated AML, the recently approved drug venetoclax holds some promise in this setting. Venetoclax is a selective inhibitor of the protein Bcl-2, an anti-apoptotic protein which plays a role in the survival of leukemic blasts [77,78]. Approval was based on a multicenter, phase 1b dose-escalation and expansion study showing promising activity in elderly patients unfit for induction chemotherapy, with 67% of patients achieving CR/CRi and a median OS of 17.5 months [79]. Notably, 25% of the study population had mutations in *TP53,* and, while these patients had inferior outcomes compared to the study population as a whole, they exhibited a reasonable CR/CRi rate of 47%, though median OS remained poor at 7.2 months. Given the small sample size, further study is warranted in this population, particularly in novel combination.

HDAC inhibitors are a class of drugs that function as epigenetic regulators by reducing histone deacetylation leading to altered expression of genes involved in cell cycle arrest, differentiation and apoptosis. They have also been shown to promote degradation of mutant p53 and pre-clinical work has suggested that they may present a promising strategy in patients with mutations in *TP53* [80,81]. Yet, despite strong pre-clinical rationale, several HDAC inhibitors have been evaluated in phase 1 and 2 studies in MDS and AML demonstrating increased toxicity without a significant improvement in outcomes [82–86]. However, early drug discontinuation due to toxicity and pleiotropic drug effects may contribute to these results and study remains ongoing, with more selective HDAC inhibitors having a potential role [87,88].

Directly or indirectly targeting mutant p53 is a novel approach that is particularly intriguing given its specificity against the underlying biology of the disease. This has been explored through several approaches including targeting pathways with synthetic lethality, increasing degradation of mutant p53 and restoring mutant p53 protein function. Regulators of the G2/M checkpoint and several kinase signaling pathways have demonstrated synthetic lethality in cell models, though the clinical applicability in AML is unknown at this time [36,89–93]. HSP90 inhibitors have been shown to increase degradation of mutant *TP53,* however, clinical trials in myeloid diseases have not produced favorable results [94–96]. Statins, widely used for their cholesterol-lowering properties, have been shown to induce degradation of abnormal p53 protein, inhibit tumor growth in *TP53* mutated tumor cells and work synergistically with chemotherapeutic agents, representing a possible novel agent that could be added to conventional and investigational therapies [97–99]. In further support of this therapy, recent elegant investigations have shown that the mevalonate pathway is selectively vulnerable in tumors lacking p53 [100].

A number of compounds have been developed that restore wild-type p53 conformation and function, many of which target specific missense mutations [36]. The most promising agent in this class to date, which has reached clinical study, is the methylated PRIMA-1 analogue APR-246. This small molecule functions to restore wild-type p53 conformation and activity (not specific to a particular variant), resulting in caspase activation and selective induction of apoptosis in *TP53* mutated cancer cells, while also demonstrating synergy with traditional chemotherapeutic agents [101–103]. APR-246 spontaneously releases the active drug species, methylene quinuclidinone (MQ), which forms a covalent bond with cysteine residues in p53, leading to thermodynamic stabilization of the p53 protein [104]. This event shifts the dynamic equilibrium away from the unfolded/misfolded state and toward the wild-type p53 conformation. APR-246 is currently being evaluated in multiple malignancies, with initial single-agent phase 1 testing in hematologic malignancies demonstrating tolerability and both biologic effects and clinical responses [105,106]. Preliminary results of a phase 1b/2 trial of APR-246 in combination with azacitidine in MDS and AML were recently reported, demonstrating tolerability of this regimen and promising clinical activity with a CR rate of 82% and deep molecular remissions [107]. This trial is ongoing and a multi-center, phase 3 trial recently opened for recruitment (NCT03745716).

4.2. Immunotherapeutic approaches

Immunotherapy, a form of cancer treatment which seeks to harness the innate ability of the immune system to detect and eliminate malignant cells, has gained widespread notoriety in the field oncology. Though its use in AML has lagged behind most cancers, it is actively being explored given its noted success in other tumor types. Given the unique mechanism in contrast to currently available treatments, this presents a potentially promising avenue in *TP53* mutated AML.

Checkpoint inhibitors function to block inhibitory co-receptors on T-cells, such as PD-1 and CLTA-4, which play a role in immune evasion by cancer cells. Increased expression of these receptors and their ligands have been observed on leukemic blasts and marrow infiltrating T-cells, with further upregulation seen after treatment with HMAs [108–110]. This suggests a possible resistance mechanism to HMA therapy and provides rationale for combination therapy. Notably, increased expression of PD-L1 has been identified in blasts and hematopoietic stem cells in *TP53* mutant patients in comparison to wild-type patients [108,111]. A recent phase 2 study of nivolumab in combination with azacitidine in relapsed/refractory (R/R) AML demonstrated acceptable toxicity and an overall response rate (ORR) of 33%, though increased response rates were seen in HMA-naïve patients and those with increased BM and

peripheral blood T-cells by flow cytometry [112]. *TP53* mutations were present in 23% of patients and mutation status was not predictive of response. Single-agent ipilimumab was evaluated in patients with relapse after allo-HSCT and demonstrated feasibility with clinical responses seen [113]. Preliminary data from trials evaluating checkpoint inhibitors in combination with HMAs, in combination with induction chemotherapy and as post-remission maintenance treatment in MDS and AML patients have recently been presented demonstrating tolerability and promising early efficacy data, with numerous trials ongoing [114–119].

Bispecific antibodies (termed Bi-specific T-Cell Engager, BiTE or Dual-affinity Re-Targeting, DART) and cellular therapies, including chimeric antigen receptor (CAR) T-cell therapy, represent additional immunotherapeutic approaches which have made significant gains in lymphoid malignancies. Both therapies require a specific target antigen which has made their implementation in AML more difficult due to less restrictive expression and greater variability in AML antigens compared to B-Cell malignancies, though a number of candidate targets are under investigation [120,121]. Preliminary phase 1 data was recently presented for Flotetuzumab, a CD123xCD3 DART, and AMG 330, a CD33xCD3 BiTE, with safety and anti-leukemic activity noted in R/R AML patients [122,123]. To date, there have not been analyses on molecular predictors of response with bispecific therapies.

The first documented objective clinical response to CAR T-cell therapy in an AML patient was reported with CYAD-01, an NKG2D receptor-based construct [124]. Subsequently, data from two phase 1 trials with this product have been reported. While one trial reported no objective responses with a single infusion of the cellular product, preliminary data from a second trial utilizing multiple infusions demonstrated promising anti-leukemic activity, with an ORR of 42% [125,126]. Reports of *in vivo* anti-leukemic activity with CD33-directed and LeY antigen-directed CAR T-cells have also been published [127,128]. Preliminary data for CD123-directed CAR T-cells and a CLL1-CD33 compound CAR-T cell have also been presented with promising activity noted [129–131].

5. Summary

Mutations in *TP53,* though less common than in most solid tumors, are a recurrently observed molecular alteration in AML. Mutations result in impaired function of p53 protein leading to impaired apoptosis and cellular immortality, providing malignant cells with an innate resistance to traditional chemotherapeutic agents. Outcomes in this subgroup are dismal, particularly with intensive induction chemotherapies typically considered as frontline treatment in AML. Initial therapy with HMAs is associated with favorable response rates and reduction in *TP53* clone, but durable responses are not typically seen. Allo-HSCT remains an option in appropriately selected patients, though long-term survival is uncommon. Given these results, all patients should be considered for enrollment into clinical trials. Novel therapies that have shown promising results in early clinical study include agents that directly target mutant p53 and immunotherapeutic strategies, though further evaluation is needed.

Practice Points

- *TP53* mutations are observed in 5–10% of AML cases and play a vital role in risk stratification and treatment selection due to their association with uniformly poor outcomes.
- Inferior responses to traditional cytotoxic therapies have led to the emergence of hypomethylating agents as the standard frontline treatment option, with a modest improvement in outcomes.
- Though long-term survival after allogeneic hematopoietic stem cell transplant is uncommon, it remains an option for appropriately selected patients.

Research Agenda

- The management of *TP53* mutated AML remains challenging and enrollment in clinical trials should be encouraged to foster development of novel therapies.
- Novel agents that directly target mutant p53 have shown promise, but require further study in larger, randomized clinical trials.
- Immunotherapeutic approaches are being widely explored in AML and warrant further investigation in this molecular subgroup.
- Dynamic monitoring of the mutant clone through the use of sequential molecular profiling may have an emerging role in adapting therapy and requires further inquiry.

Acknowledgements

David A. Sallman: Research Funding from Celgene and Jazz
Anthony Hunter: conflict of interest - none.

References

[1] Papaemmanuil E, Gerstung M, Bullinger L, Gaidzik VI, Paschka P, Roberts ND, et al. Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 2016;374(23):2209–21. https://doi.org/10.1056/NEJMoa1516192.

[2] Cancer Genome Atlas Research N, Ley TJ, Miller C, Ding L, Raphael BJ, Mungall AJ, et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. N Engl J Med 2013;368(22):2059–74. https://doi.org/10.1056/NEJMoa1301689.
[3] Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–47. https://doi.org/10.1182/blood-2016-08-733196.
[4] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–405. https://doi.org/10.1182/blood-2016-03-643544.
[5] Grossmann V, Schnittger S, Kohlmann A, Eder C, Roller A, Dicker F, et al. A novel hierarchical prognostic model of AML solely based on molecular mutations. Blood 2012;120(15):2963–72. https://doi.org/10.1182/blood-2012-03-419622.
[6] Kadia TM, Jain P, Ravandi F, Garcia-Manero G, Andreef M, Takahashi K, et al. TP53 mutations in newly diagnosed acute myeloid leukemia: clinicomolecular characteristics, response to therapy, and outcomes. Cancer 2016;122(22):3484–91. https://doi.org/10.1002/cncr.30203.
[7] Ohgami RS, Ma L, Merker JD, Gotlib JR, Schrijver I, Zehnder JL, et al. Next-generation sequencing of acute myeloid leukemia identifies the significance of TP53, U2AF1, ASXL1, and TET2 mutations. Mod Pathol 2015;28(5):706–14. https://doi.org/10.1038/modpathol.2014.160.
[8] Bowen D, Groves MJ, Burnett AK, Patel Y, Allen C, Green C, et al. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. Leukemia 2009;23(1):203–6. https://doi.org/10.1038/leu.2008.173.
[9] Christiansen DH, Andersen MK, Pedersen-Bjergaard J. Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 2001;19(5):1405–13. https://doi.org/10.1200/JCO.2001.19.5.1405.
[10] Rucker FG, Schlenk RF, Bullinger L, Kayser S, Teleanu V, Kett H, et al. TP53 alterations in acute myeloid leukemia with complex karyotype correlate with specific copy number alterations, monosomal karyotype, and dismal outcome. Blood 2012;119(9):2114–21. https://doi.org/10.1182/blood-2011-08-375758.
[11] Devillier R, Mansat-De Mas V, Gelsi-Boyer V, Demur C, Murati A, Corre J, et al. Role of ASXL1 and TP53 mutations in the molecular classification and prognosis of acute myeloid leukemias with myelodysplasia-related changes. Oncotarget 2015;6(10):8388–96. https://doi.org/10.18632/oncotarget.3460.
[12] Haferlach C, Dicker F, Herholz H, Schnittger S, Kern W, Haferlach T. Mutations of the TP53 gene in acute myeloid leukemia are strongly associated with a complex aberrant karyotype. Leukemia 2008;22(8):1539–41. https://doi.org/10.1038/leu.2008.143.
[13] Yanada M, Yamamoto Y, Iba S, Okamoto A, Inaguma Y, Tokuda M, et al. TP53 mutations in older adults with acute myeloid leukemia. Int J Hematol 2016;103(4):429–35. https://doi.org/10.1007/s12185-016-1942-1.
[14] Metzeler KH, Herold T, Rothenberg-Thurley M, Amler S, Sauerland MC, Gorlich D, et al. Spectrum and prognostic relevance of driver gene mutations in acute myeloid leukemia. Blood 2016;128(5):686–98. https://doi.org/10.1182/blood-2016-01-693879.
[15] Vousden KH, Lu X. Live or let die: the cell's response to p53. Nat Rev Canc 2002;2(8):594–604. https://doi.org/10.1038/nrc864.
[16] Vogelstein B, Lane D, Levine AJ. Surfing the p53 network. Nature 2000;408(6810):307–10. https://doi.org/10.1038/35042675.
[17] Chang F, Syrjanen S, Syrjanen K. Implications of the p53 tumor-suppressor gene in clinical oncology. J Clin Oncol 1995;13(4):1009–22. https://doi.org/10.1200/JCO.1995.13.4.1009.
[18] Levine AJ. p53, the cellular gatekeeper for growth and division. Cell 1997;88(3):323–31.
[19] Bode AM, Dong Z. Post-translational modification of p53 in tumorigenesis. Nat Rev Canc 2004;4(10):793–805. https://doi.org/10.1038/nrc1455.
[20] Harris SL, Levine AJ. The p53 pathway: positive and negative feedback loops. Oncogene 2005;24(17):2899–908. https://doi.org/10.1038/sj.onc.1208615.
[21] Lowe SW, Bodis S, McClatchey A, Remington L, Ruley HE, Fisher DE, et al. p53 status and the efficacy of cancer therapy in vivo. Science 1994;266(5186):807–10.
[22] Eliopoulos AG, Kerr DJ, Herod J, Hodgkins L, Krajewski S, Reed JC, et al. The control of apoptosis and drug resistance in ovarian cancer: influence of p53 and Bcl-2. Oncogene 1995;11(7):1217–28.
[23] Hamada M, Fujiwara T, Hizuta A, Gochi A, Naomoto Y, Takakura N, et al. The p53 gene is a potent determinant of chemosensitivity and radiosensitivity in gastric and colorectal cancers. J Cancer Res Clin Oncol 1996;122(6):360–5.
[24] Li R, Sutphin PD, Schwartz D, Matas D, Almog N, Wolkowicz R, et al. Mutant p53 protein expression interferes with p53-independent apoptotic pathways. Oncogene 1998;16(25):3269–77. https://doi.org/10.1038/sj.onc.1201867.
[25] Fenaux P, Preudhomme C, Quiquandon I, Jonveaux P, Lai JL, Vanrumbeke M, et al. Mutations of the P53 gene in acute myeloid leukaemia. Br J Haematol 1992;80(2):178–83.
[26] Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 2015;125(9):1367–76. https://doi.org/10.1182/blood-2014-11-610543.
[27] Schoch C, Kern W, Kohlmann A, Hiddemann W, Schnittger S, Haferlach T. Acute myeloid leukemia with a complex aberrant karyotype is a distinct biological entity characterized by genomic imbalances and a specific gene expression profile. Genes Chromosomes Cancer 2005;43(3):227–38. https://doi.org/10.1002/gcc.20193.
[28] Haase D, Stevenson KE, Neuberg D, Maciejewski JP, Nazha A, Sekeres MA, et al. TP53 mutation status divides myelodysplastic syndromes with complex karyotypes into distinct prognostic subgroups. Leukemia 2019. https://doi.org/10.1038/s41375-018-0351-2.
[29] Sebaa A, Ades L, Baran-Marzack F, Mozziconacci MJ, Penther D, Dobbelstein S, et al. Incidence of 17p deletions and TP53 mutation in myelodysplastic syndrome and acute myeloid leukemia with 5q deletion. Genes Chromosomes Cancer 2012;51(12):1086–92. https://doi.org/10.1002/gcc.21993.
[30] Kulasekararaj AG, Smith AE, Mian SA, Mohamedali AM, Krishnamurthy P, Lea NC, et al. TP53 mutations in myelodysplastic syndrome are strongly correlated with aberrations of chromosome 5, and correlate with adverse prognosis. Br J Haematol 2013;160(5):660–72. https://doi.org/10.1111/bjh.12203.
[31] Ok CY, Patel KP, Garcia-Manero G, Routbort MJ, Peng J, Tang G, et al. TP53 mutation characteristics in therapy-related myelodysplastic syndromes and acute myeloid leukemia is similar to de novo diseases. J Hematol Oncol 2015;8:45. https://doi.org/10.1186/s13045-015-0139-z.
[32] Pedersen-Bjergaard J, Andersen MK, Andersen MT, Christiansen DH. Genetics of therapy-related myelodysplasia and acute myeloid leukemia. Leukemia 2008;22(2):240–8. https://doi.org/10.1038/sj.leu.2405078.
[33] Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 2015;518(7540):552–5. https://doi.org/10.1038/nature13968.
[34] Sallman DA, Komrokji R, Vaupel C, Cluzeau T, Geyer SM, McGraw KL, et al. Impact of TP53 mutation variant allele frequency on phenotype and outcomes in myelodysplastic syndromes. Leukemia 2016;30(3):666–73. https://doi.org/10.1038/leu.2015.304.
[35] Terada K, Yamaguchi H, Ueki T, Usuki K, Kobayashi Y, Tajika K, et al. Full-length mutation search of the TP53 gene in acute myeloid leukemia has increased significance as a prognostic factor. Ann Hematol 2018;97(1):51–61. https://doi.org/10.1007/s00277-017-3143-2.
[36] Zhao D, Tahaney WM, Mazumdar A, Savage MI, Brown PH. Molecularly targeted therapies for p53-mutant cancers. Cell Mol Life Sci 2017;74(22):4171–87. https://doi.org/10.1007/s00018-017-2575-0.
[37] Sabapathy K, Lane DP. Therapeutic targeting of p53: all mutants are equal, but some mutants are more equal than others. Nat Rev Clin Oncol 2018;15(1):13–30. https://doi.org/10.1038/nrclinonc.2017.151.
[38] Kim MP, Zhang Y, Lozano G. Mutant p53: multiple mechanisms define biologic activity in cancer. Front Oncol 2015;5:249. https://doi.org/10.3389/fonc.2015.00249.
[39] Kuykendall A, Duployez N, Boissel N, Lancet JE, Welch JS. Acute myeloid leukemia: the good, the bad, and the ugly. Am Soc Clin Oncol Educ Book 2018;38:555–73. https://doi.org/10.1200/EDBK_199519.
[40] Dohner H, Dolnik A, Tang L, Seymour JF, Minden MD, Stone RM, et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. Leukemia 2018;32(12):2546–57. https://doi.org/10.1038/s41375-018-0257-z.
[41] McGraw KL, Nguyen J, Komrokji RS, Sallman D, Al Ali NH, Padron E, et al. Immunohistochemical pattern of p53 is a measure of TP53 mutation burden and adverse clinical outcome in myelodysplastic syndromes and secondary acute myeloid leukemia. Haematologica 2016;101(8):e320–3. https://doi.org/10.3324/haematol.2016.143214.
[42] Fernandez-Pol S, Ma L, Ohgami RS, Arber DA. Immunohistochemistry for p53 is a useful tool to identify cases of acute myeloid leukemia with myelodysplasia-

related changes that are TP53 mutated, have complex karyotype, and have poor prognosis. Mod Pathol 2017;30(3):382–92. https://doi.org/10.1038/modpathol.2016.206.
[43] Murnyak B, Hortobagyi T. Immunohistochemical correlates of TP53 somatic mutations in cancer. Oncotarget 2016;7(40):64910–20. https://doi.org/10.18632/oncotarget.11912.
[44] Lin PH, Li HY, Fan SC, Yuan TH, Chen M, Hsu YH, et al. A targeted next-generation sequencing in the molecular risk stratification of adult acute myeloid leukemia: implications for clinical practice. Canc Med 2017;6(2):349–60. https://doi.org/10.1002/cam4.969.
[45] Au CH, Wa A, Ho DN, Chan TL, Ma ES. Clinical evaluation of panel testing by next-generation sequencing (NGS) for gene mutations in myeloid neoplasms. Diagn Pathol 2016;11:11. https://doi.org/10.1186/s13000-016-0456-8.
[46] Hou HA, Chou WC, Kuo YY, Liu CY, Lin LI, Tseng MH, et al. TP53 mutations in de novo acute myeloid leukemia patients: longitudinal follow-ups show the mutation is stable during disease evolution. Blood Canc J 2015;5:e331. https://doi.org/10.1038/bcj.2015.59.
[47] Seifert H, Mohr B, Thiede C, Oelschlagel U, Schakel U, Illmer T, et al. The prognostic impact of 17p (p53) deletion in 2272 adults with acute myeloid leukemia. Leukemia 2009;23(4):656–63. https://doi.org/10.1038/leu.2008.375.
[48] Hills RK, Castaigne S, Appelbaum FR, Delaunay J, Petersdorf S, Othus M, et al. Addition of gemtuzumab ozogamicin to induction chemotherapy in adult patients with acute myeloid leukaemia: a meta-analysis of individual patient data from randomised controlled trials. Lancet Oncol 2014;15(9):986–96. https://doi.org/10.1016/S1470-2045(14)70281-5.
[49] Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol 2018;36(26):2684–92. https://doi.org/10.1200/JCO.2017.77.6112.
[50] Aaron D, Goldberg M, Chetasi Talati, Desai Pinkal, Christopher Famulare, Devlin Sean M, Farnoud Noushin, et al. TP53 mutations predict poorer responses to CPX-351 in acute myeloid leukemia. American society of hematology annual meeting; 2018 12/2018; San Diego, CA. 2018.
[51] Hollenbach PW, Nguyen AN, Brady H, Williams M, Ning Y, Richard N, et al. A comparison of azacitidine and decitabine activities in acute myeloid leukemia cell lines. PLoS One 2010;5(2):e9001https://doi.org/10.1371/journal.pone.0009001.
[52] Christman JK. 5-Azacytidine and 5-aza-2'-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 2002;21(35):5483–95. https://doi.org/10.1038/sj.onc.1205699.
[53] Dombret H, Seymour JF, Butrym A, Wierzbowska A, Selleslag D, Jang JH, et al. International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with > 30% blasts. Blood 2015;126(3):291–9. https://doi.org/10.1182/blood-2015-01-621664.
[54] Fenaux P, Mufti GJ, Hellstrom-Lindberg E, Santini V, Gattermann N, Germing U, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol 2010;28(4):562–9. https://doi.org/10.1200/JCO.2009.23.8329.
[55] Kantarjian HM, Thomas XG, Dmoszynska A, Wierzbowska A, Mazur G, Mayer J, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol 2012;30(21):2670–7. https://doi.org/10.1200/JCO.2011.38.9429.
[56] Nieto M, Samper E, Fraga MF, Gonzalez de Buitrago G, Esteller M, Serrano M. The absence of p53 is critical for the induction of apoptosis by 5-aza-2'-deoxycytidine. Oncogene 2004;23(3):735–43. https://doi.org/10.1038/sj.onc.1207175.
[57] Yi L, Sun Y, Levine A. Selected drugs that inhibit DNA methylation can preferentially kill p53 deficient cells. Oncotarget 2014;5(19):8924–36. https://doi.org/10.18632/oncotarget.2441.
[58] Cashen AF, Schiller GJ, O'Donnell MR, DiPersio JF. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. J Clin Oncol 2010;28(4):556–61. https://doi.org/10.1200/JCO.2009.23.9178.
[59] Blum W, Garzon R, Klisovic RB, Schwind S, Walker A, Geyer S, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. Proc Natl Acad Sci U S A 2010;107(16):7473–8. https://doi.org/10.1073/pnas.1002650107.
[60] Lubbert M, Ruter BH, Claus R, Schmoor C, Schmid M, Germing U, et al. A multicenter phase II trial of decitabine as first-line treatment for older patients with acute myeloid leukemia judged unfit for induction chemotherapy. Haematologica 2012;97(3):393–401. https://doi.org/10.3324/haematol.2011.048231.
[61] Sallman NHAA David A, Yun Seongseok, Padron Eric, Song Jinming, Hussaini Mohammad, Talati Chetasi, et al. Clonal suppression of TP53 mutant MDS and oligoblastic AML with hypomethylating agent therapy improves overall survival. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[62] Welch JS, Petti AA, Miller CA, Fronick CC, O'Laughlin M, Fulton RS, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med 2016;375(21):2023–36. https://doi.org/10.1056/NEJMoa1605949.
[63] Montalban-Bravo G, Takahashi K, Garcia-Manero G. Decitabine in TP53-mutated AML. N Engl J Med 2017;376(8):796–7. https://doi.org/10.1056/NEJMc1616062.
[64] Five-day versus ten-day schedules of decitabine in older patients with newly diagnosed acute myeloid leukemia: results of a randomized phase II study. In: Nicholas J Short M, Kanarjian Hagop M, Loghavi Sanam, Huang Xeulin, Qiao Wei, Borthakur Gautam, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[65] Della Porta MG, Galli A, Bacigalupo A, Zibellini S, Bernardi M, Rizzo E, et al. Clinical effects of driver somatic mutations on the outcomes of patients with myelodysplastic syndromes treated with allogeneic hematopoietic stem-cell transplantation. J Clin Oncol 2016;34(30):3627–37. https://doi.org/10.1200/JCO.2016.67.3616.
[66] Bejar R, Stevenson KE, Caughey B, Lindsley RC, Mar BG, Stojanov P, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol 2014;32(25):2691–8. https://doi.org/10.1200/JCO.2013.52.3381.
[67] Qin T, Wu S, Zhao H, Xu K, Fu H, Cheng Z, et al. Molecular predictors of post-transplant survival in acute myeloid leukemia. Blood Canc J 2017;7(12):641. https://doi.org/10.1038/s41408-017-0027-6.
[68] Yoshizato T, Nannya Y, Atsuta Y, Shiozawa Y, Iijima-Yamashita Y, Yoshida K, et al. Genetic abnormalities in myelodysplasia and secondary acute myeloid leukemia: impact on outcome of stem cell transplantation. Blood 2017;129(17):2347–58. https://doi.org/10.1182/blood-2016-12-754796.
[69] Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 2017;376(6):536–47. https://doi.org/10.1056/NEJMoa1611604.
[70] Middeke JM, Herold S, Rucker-Braun E, Berdel WE, Stelljes M, Kaufmann M, et al. TP53 mutation in patients with high-risk acute myeloid leukaemia treated with allogeneic haematopoietic stem cell transplantation. Br J Haematol 2016;172(6):914–22. https://doi.org/10.1111/bjh.13912.
[71] Cutler C. Transplantation for therapy-related, TP53-mutated myelodysplastic syndrome - not because we can, but because we should. Haematologica 2017;102(12):1970–1. https://doi.org/10.3324/haematol.2017.181180.
[72] de Lima M, Giralt S, Thall PF, de Padua Silva L, Jones RB, Komanduri K, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. Cancer 2010;116(23):5420–31. https://doi.org/10.1002/cncr.25500.
[73] Pusic I, Choi J, Fiala MA, Gao F, Holt M, Cashen AF, et al. Maintenance therapy with decitabine after allogeneic stem cell transplantation for acute myelogenous leukemia and myelodysplastic syndrome. Biol Blood Marrow Transplant 2015;21(10):1761–9. https://doi.org/10.1016/j.bbmt.2015.05.026.
[74] Craddock C, Jilani N, Siddique S, Yap C, Khan J, Nagra S, et al. Tolerability and clinical activity of post-transplantation azacitidine in patients allografted for acute myeloid leukemia treated on the RICAZA trial. Biol Blood Marrow Transplant 2016;22(2):385–90. https://doi.org/10.1016/j.bbmt.2015.09.004.
[75] Maintenance with 5-azacytidine for acute myeloid leukemia and myelodysplastic syndrome patients. In: Betul Oran M, de Lima Marcos, Garcia-Manero Guillermo, Thall Peter F, Lin Ruitao, Alousi Amin M, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[76] Bug G, Burchert A, Wagner EM, Kroger N, Berg T, Guller S, et al. Phase I/II study of the deacetylase inhibitor panobinostat after allogeneic stem cell transplantation in patients with high-risk MDS or AML (PANOBEST trial). Leukemia 2017;31(11):2523–5. https://doi.org/10.1038/leu.2017.242.
[77] Pan R, Hogdal LJ, Benito JM, Bucci D, Han L, Borthakur G, et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. Cancer Discov 2014;4(3):362–75. https://doi.org/10.1158/2159-8290.CD-13-0609.

[78] Vo TT, Ryan J, Carrasco R, Neuberg D, Rossi DJ, Stone RM, et al. Relative mitochondrial priming of myeloblasts and normal HSCs determines chemotherapeutic success in AML. Cell 2012;151(2):344–55. https://doi.org/10.1016/j.cell.2012.08.038.
[79] DiNardo CD, Pratz K, Pullarkat V, Jonas BA, Arellano M, Becker PS, et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 2019;133(1):7–17. https://doi.org/10.1182/blood-2018-08-868752.
[80] Nishioka C, Ikezoe T, Yang J, Udaka K, Yokoyama A. Simultaneous inhibition of DNA methyltransferase and histone deacetylase induces p53-independent apoptosis via down-regulation of Mcl-1 in acute myelogenous leukemia cells. Leuk Res 2011;35(7):932–9. https://doi.org/10.1016/j.leukres.2011.04.004.
[81] Li D, Marchenko ND, Moll UM. SAHA shows preferential cytotoxicity in mutant p53 cancer cells by destabilizing mutant p53 through inhibition of the HDAC6-Hsp90 chaperone axis. Cell Death Differ 2011;18(12):1904–13. https://doi.org/10.1038/cdd.2011.71.
[82] Craddock CF, Houlton AE, Quek LS, Ferguson P, Gbandi E, Roberts C, et al. Outcome of azacitidine therapy in acute myeloid leukemia is not improved by concurrent vorinostat therapy but is predicted by a diagnostic molecular signature. Clin Cancer Res 2017;23(21):6430–40. https://doi.org/10.1158/1078-0432.CCR-17-1423.
[83] Bewersdorf JP, Shallis R, Stahl M, Zeidan AM. Epigenetic therapy combinations in acute myeloid leukemia: what are the options? Ther Adv Hematol 2019;10. https://doi.org/10.1177/2040620718816698. 2040620718816698.
[84] Prebet T, Sun Z, Ketterling RP, Zeidan A, Greenberg P, Herman J, et al. Azacitidine with or without Entinostat for the treatment of therapy-related myeloid neoplasm: further results of the E1905 North American Leukemia Intergroup study. Br J Haematol 2016;172(3):384–91. https://doi.org/10.1111/bjh.13832.
[85] Issa JP, Garcia-Manero G, Huang X, Cortes J, Ravandi F, Jabbour E, et al. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. Cancer 2015;121(4):556–61. https://doi.org/10.1002/cncr.29085.
[86] Kirschbaum M, Gojo I, Goldberg SL, Bredeson C, Kujawski LA, Yang A, et al. A phase 1 clinical trial of vorinostat in combination with decitabine in patients with acute myeloid leukaemia or myelodysplastic syndrome. Br J Haematol 2014;167(2):185–93. https://doi.org/10.1111/bjh.13016.
[87] Min C, Moore N, Shearstone JR, Quayle SN, Huang P, van Duzer JH, et al. Selective inhibitors of histone deacetylases 1 and 2 synergize with azacitidine in acute myeloid leukemia. PLoS One 2017;12(1):e0169128https://doi.org/10.1371/journal.pone.0169128.
[88] Ungerstedt JS. Epigenetic modifiers in myeloid malignancies: the role of histone deacetylase inhibitors. Int J Mol Sci 2018;19(10). https://doi.org/10.3390/ijms19103091.
[89] Origanti S, Cai SR, Munir AZ, White LS, Piwnica-Worms H. Synthetic lethality of Chk1 inhibition combined with p53 and/or p21 loss during a DNA damage response in normal and tumor cells. Oncogene 2013;32(5):577–88. https://doi.org/10.1038/onc.2012.84.
[90] Toledo LI, Murga M, Zur R, Soria R, Rodriguez A, Martinez S, et al. A cell-based screen identifies ATR inhibitors with synthetic lethal properties for cancer-associated mutations. Nat Struct Mol Biol 2011;18(6):721–7. https://doi.org/10.1038/nsmb.2076.
[91] Ma CX, Cai S, Li S, Ryan CE, Guo Z, Schaiff WT, et al. Targeting Chk1 in p53-deficient triple-negative breast cancer is therapeutically beneficial in human-in-mouse tumor models. J Clin Investig 2012;122(4):1541–52. https://doi.org/10.1172/JCI58765.
[92] Baldwin A, Grueneberg DA, Hellner K, Sawyer J, Grace M, Li W, et al. Kinase requirements in human cells: V. Synthetic lethal interactions between p53 and the protein kinases SGK2 and PAK3. Proc Natl Acad Sci U S A 2010;107(28):12463–8. https://doi.org/10.1073/pnas.1007462107.
[93] Gyorffy B, Bottai G, Lehmann-Che J, Keri G, Orfi L, Iwamoto T, et al. TP53 mutation-correlated genes predict the risk of tumor relapse and identify MPS1 as a potential therapeutic kinase in TP53-mutated breast cancers. Mol Oncol 2014;8(3):508–19. https://doi.org/10.1016/j.molonc.2013.12.018.
[94] Li D, Marchenko ND, Schulz R, Fischer V, Velasco-Hernandez T, Talos F, et al. Functional inactivation of endogenous MDM2 and CHIP by HSP90 causes aberrant stabilization of mutant p53 in human cancer cells. Mol Cancer Res 2011;9(5):577–88. https://doi.org/10.1158/1541-7786.MCR-10-0534.
[95] Alexandrova EM, Yallowitz AR, Li D, Xu S, Schulz R, Proia DA, et al. Improving survival by exploiting tumour dependence on stabilized mutant p53 for treatment. Nature 2015;523(7560):352–6. https://doi.org/10.1038/nature14430.
[96] Dennis Michael, Hills RK, Thomas Ian, Gupta Sunil, Panoskaltsis Nicki, Copland Mhairi, et al. A randomised assessment of ganetespib combined with low dose ara-C versus low dose ara-C in older patients with acute myeloid Leukaimia: results of the LI-1 trial. Americal society of hematology annual meeting; 2016; San Diego, CA. 2016.
[97] Parrales A, Ranjan A, Iyer SV, Padhye S, Weir SJ, Roy A, et al. DNAJA1 controls the fate of misfolded mutant p53 through the mevalonate pathway. Nat Cell Biol 2016;18(11):1233–43. https://doi.org/10.1038/ncb3427.
[98] Martirosyan A, Clendening JW, Goard CA, Penn LZ. Lovastatin induces apoptosis of ovarian cancer cells and synergizes with doxorubicin: potential therapeutic relevance. BMC Canc 2010;10:103. https://doi.org/10.1186/1471-2407-10-103.
[99] Burke LP, Kukoly CA. Statins induce lethal effects in acute myeloblastic leukemia [corrected] cells within 72 hours. Leuk Lymphoma 2008;49(2):322–30. https://doi.org/10.1080/10428190701760011.
[100] Moon SH, Huang CH, Houlihan SL, Regunath K, Freed-Pastor WA, Morris JPt, et al. p53 represses the mevalonate pathway to mediate tumor suppression. Cell 2019;176(3). https://doi.org/10.1016/j.cell.2018.11.011. 564-580 e19.
[101] Perdrix A, Najem A, Saussez S, Awada A, Journe F, Ghanem G, et al. PRIMA-1 and PRIMA-1(met) (APR-246): from mutant/wild type p53 reactivation to unexpected mechanisms underlying their potent anti-tumor effect in combinatorial therapies. Cancers (Basel) 2017;9(12). https://doi.org/10.3390/cancers9120172.
[102] Ali D, Jonsson-Videsater K, Deneberg S, Bengtzen S, Nahi H, Paul C, et al. APR-246 exhibits anti-leukemic activity and synergism with conventional chemotherapeutic drugs in acute myeloid leukemia cells. Eur J Haematol 2011;86(3):206–15. https://doi.org/10.1111/j.1600-0609.2010.01557.x.
[103] Nahi H, Merup M, Lehmann S, Bengtzen S, Mollgard L, Selivanova G, et al. PRIMA-1 induces apoptosis in acute myeloid leukaemia cells with p53 gene deletion. Br J Haematol 2006;132(2):230–6. https://doi.org/10.1111/j.1365-2141.2005.05851.x.
[104] Lambert JM, Gorzov P, Veprintsev DB, Soderqvist M, Segerback D, Bergman J, et al. PRIMA-1 reactivates mutant p53 by covalent binding to the core domain. Cancer Cell 2009;15(5):376–88. https://doi.org/10.1016/j.ccr.2009.03.003.
[105] Lehmann S, Bykov VJ, Ali D, Andren O, Cherif H, Tidefelt U, et al. Targeting p53 in vivo: a first-in-human study with p53-targeting compound APR-246 in refractory hematologic malignancies and prostate cancer. J Clin Oncol 2012;30(29):3633–9. https://doi.org/10.1200/JCO.2011.40.7783.
[106] Deneberg S, Cherif H, Lazarevic V, Andersson PO, von Euler M, Juliusson G, et al. An open-label phase I dose-finding study of APR-246 in hematological malignancies. Blood Canc J 2016;6(7):e447. https://doi.org/10.1038/bcj.2016.60.
[107] Phase 1b/2 combination study of APR-246 and azacitidine (AZA) in patients with TP53 mutant myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). In: Sallman David A, DeZern Amy E, Steensma David P, Sweet Kendra L, Cluzeau Thomas, Sekeres Mikkael, editors. American society of hematology anuual meeting; 2018; San Diego, CA. 2018.
[108] Williams P, Basu S, Garcia-Manero G, Hourigan CS, Oetjen KA, Cortes JE, et al. The distribution of T-cell subsets and the expression of immune checkpoint receptors and ligands in patients with newly diagnosed and relapsed acute myeloid leukemia. Cancer 2018. https://doi.org/10.1002/cncr.31896.
[109] Yang H, Bueso-Ramos C, DiNardo C, Estecio MR, Davanlou M, Geng QR, et al. Expression of PD-L1, PD-L2, PD-1 and CTLA4 in myelodysplastic syndromes is enhanced by treatment with hypomethylating agents. Leukemia 2014;28(6):1280–8. https://doi.org/10.1038/leu.2013.355.
[110] Orskov AD, Treppendahl MB, Skovbo A, Holm MS, Friis LS, Hokland M, et al. Hypomethylation and up-regulation of PD-1 in T cells by azacytidine in MDS/AML patients: a rationale for combined targeting of PD-1 and DNA methylation. Oncotarget 2015;6(11):9612–26. https://doi.org/10.18632/oncotarget.3324.
[111] Sallman DA, Amy M, Komrokji RS, McGraw K, Geyer SM, Eksioglu E, et al. Immune checkpoint profiling of < em > TP53 < /em > mutant and wild-type myeloid malignancies: < em > TP53 < /em > mutations direct immune tolerance via an immunosuppressive phenotype. 2017;130(Suppl 1):423.
[112] Daver N, Garcia-Manero G, Basu S, Boddu PC, Alfayez M, Cortes JE, et al. Efficacy, safety, and biomarkers of response to azacitidine and nivolumab in relapsed/refractory acute myeloid leukemia: a nonrandomized, open-label, phase II study. Cancer Discov 2018. https://doi.org/10.1158/2159-8290.CD-18-0774.
[113] Davids MS, Kim HT, Bachireddy P, Costello C, Liguori R, Savell A, et al. Ipilimumab for patients with relapse after allogeneic transplantation. N Engl J Med 2016;375(2):143–53. https://doi.org/10.1056/NEJMoa1601202.
[114] Double immune checkpoint inhibitor blockade with nivolumab and ipilimumab with or without azacitidine in patients with myelodysplastic syndrome (MDS). In: Garcia-Manero Guillermo, Montalban-Bravo Guillermo, Sasaki Koji, Daver Naval G, Jabbour Elias J, Alvarado Yesid, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.

[115] Results of a phase 2, open-label study of idarubicin (I), cytarabine (A) and nivolumab (nivo) in patients with newly diagnosed acute myeloid leukemia and high-risk myelodysplastic syndrome (MDS). In: Assi Rita, Kantarjian Hagop M, Daver Naval G, Garcia-Manero Guillermo, Benton Christopher B, Thompson Philip A, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[116] A phase II study of nivolumab or ipilimumab with or without azacitidine for patients with myelodysplastic syndrome (MDS). In: Garcia-Manero Guillermo, Sasaki Koji, Montalban-Bravo Guillermo, Daver Naval G, Jabbour Elias J, Alvarado Yesid, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[117] Nivolumab for relapsed or residual haematological malignancies after allogeneic haematopoietic stem cell transplantation (NIVALLO). In: Wong Eric, Dawson Emily, Davis Joanne, Koldej Rachel, Ludford-Menting Mandy, Lansdown Matthew, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[118] Safety, efficacy, and biomarkers of response to azacitidine (aza) with nivolumab (nivo) and aza with nivo and ipilimumab (ipi) in relapsed/refractory acute myeloid leukemia: a non-randomized, phase 2 study. In: Daver Naval G, Garcia-Manero Guillermo, Basu Sreyashi, Cortes Jorge E, Ravandi Farhad, Kadia Tapan M, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[119] Kadia TM, Cortes JE, Ghorab A, Ravandi F, Jabbour E, Daver NG, et al. Nivolumab (Nivo) maintenance (maint) in high-risk (HR) acute myeloid leukemia (AML) patients. 2018;36(15_suppl):7014. https://doi.org/10.1200/JCO.2018.36.15_suppl.7014.
[120] Hoseini SS, Cheung NK. Acute myeloid leukemia targets for bispecific antibodies. Blood Canc J 2017;7(2):e522. https://doi.org/10.1038/bcj.2017.2.
[121] Tasian SK. Acute myeloid leukemia chimeric antigen receptor T-cell immunotherapy: how far up the road have we traveled? Ther Adv Hematol 2018;9(6):135–48. https://doi.org/10.1177/2040620718774268.
[122] Phase 1 cohort expansion of Flotetuzumab, a CD123xCD3 bispecific dart protein in patients with relapsed/refractory acute myeloid leukemia (AML). In: Uy Geoffrey L, Rettig Michael P, Vey Norbert, Godwin John, Foster Matthew C, Rizzieri David A, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[123] A phase 1 first-in-human study of AMG 300, an anti-CD33 bispecific T-cell engager (BiTE) antibody construct, in relapsed/refractory acute myeloid leukemia (R/R AML). In: Ravandi Farhad, Stein Anthony S, Kantarjian Hagop M, Walter Roland B, Peter Paschka, Jongen-Lavrenic Mojca, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[124] Sallman DA, Brayer J, Sagatys EM, Lonez C, Breman E, Agaugue S, et al. NKG2D-based chimeric antigen receptor therapy induced remission in a relapsed/refractory acute myeloid leukemia patient. Haematologica 2018;103(9):e424–6. https://doi.org/10.3324/haematol.2017.186742.
[125] Baumeister SH, Murad J, Werner L, Daley H, Trebeden-Negre H, Gicobi JK, et al. Phase I trial of autologous CAR T cells targeting NKG2D ligands in patients with AML/MDS and multiple myeloma. Canc Immunol Res 2019;7(1):100–12. https://doi.org/10.1158/2326-6066.CIR-18-0307.
[126] Remissions in relapse/refractory acute myeloid leukemia patients following treatment with NKG2D CAR-T therapy without a prior preconditioning chemotherapy. In: Sallman David A, Kerre Tessa, Poire Xavier, Havelange Violaine, Lewalle Philippe, Davila Marco L, editors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.
[127] Wang QS, Wang Y, Lv HY, Han QW, Fan H, Guo B, et al. Treatment of CD33-directed chimeric antigen receptor-modified T cells in one patient with relapsed and refractory acute myeloid leukemia. Mol Ther 2015;23(1):184–91. https://doi.org/10.1038/mt.2014.164.
[128] Ritchie DS, Neeson PJ, Khot A, Peinert S, Tai T, Tainton K, et al. Persistence and efficacy of second generation CAR T cell against the LeY antigen in acute myeloid leukemia. Mol Ther 2013;21(11):2122–9. https://doi.org/10.1038/mt.2013.154.
[129] Budde L, Song JY, Kim Y, Blanchard S, Wagner J, Stein AS, et al. Remissions of acute myeloid leukemia and blastic plasmacytoid dendritic cell neoplasm following treatment with CD123-specific CAR T cells: a first-in-human clinical trial. 2017;130(Suppl 1):811.
[130] Cummins KD, Frey N, Nelson AM, Schmidt A, Luger S, Isaacs RE, et al. Treating relapsed/refractory (RR) AML with biodegradable anti-CD123 CAR modified T cells. 2017;130(Suppl 1):1359.
[131] First-in-Human CLL1-CD33 compound CAR T cell therapy induces complete remission in patients with refractory acute myeloid leukemia: update on phase 1 clinical trial. In: Fang Liu M, PhDCao Yuanzhen, Kevin Pinz, Ma Yu, Wada Masayuki, PhDeditors. American society of hematology annual meeting; 2018; San Diego, CA. 2018.