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*Review*

# *TP53* Mutant Acute Myeloid Leukemia: The Immune and Metabolic Perspective

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**Abstract:** *TP53* mutated/deleted acute myeloid leukemia (AML) stands out as one of the poorest prognosis forms of acute leukemia with a median overall survival not reaching one year in most cases, even in selected cases when allogenic stem-cell transplantation is performed. This aggressive behavior relies on intrinsic chemoresistance of blast cells and on high rates of relapse. New insights into the biology of the disease have shown strong linkage between *TP53* mutant AML, altered metabolic features and immunoregulation uncovering new scenarios and leading to possibilities beyond current treatment approaches. Furthermore, new targeted therapies acting on misfolded/dysfunctional p53 protein are under current investigation with the aim to improve outcomes. In this review, we sought to offer an insight into *TP53* mutant AML current biology and treatment approaches, with a special focus on leukemia-associated immune and metabolic changes.

**Keywords:** acute myeloid leukemia; *TP53* mutation; metabolism; immunotherapy



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## 1. Introduction

P53 is a key protein in tumor suppression encoded by the *TP53* gene located on chromosome 17, its mutation being found in more than 50% of human cancers [1]. P53 exerts its effects by promoting apoptosis, cell cycle arrest, DNA repair and multiple events including senescence, autophagy and ferroptosis [2]. Another hallmark of p53 mutated cancer is reprogramming of several metabolic pathways, including glycolysis, TCA (tricarboxylic acid cycle), purine and pyrimidine biosynthesis, fatty acid metabolism and iron metabolism [3]. In addition, recent data have highlighted a role for altered p53 function in promoting the induction of immunosuppressive pathways within the tumor microenvironment (TME) [4], thus leading to immuno-escaping of malignant cells and facilitating disease progression.

In acute myeloid leukemia (AML), p53 mutations occur in 5 to 10% of de novo AML patients. The frequency dramatically increases in older patients (about 25% in patients >65 years), therapy-related AML and AML with myelodysplasia (MDS)-related changes, reaching about 30–35% of cases, while in complex-karyotype AML the *TP53* mutation rate rockets up to 70% of cases [5]. Deletion of chromosome 17p involving the 17p13.1 region is considered a p53 mutation and relates to inferior overall survival (OS) and higher relapse rates even in non-complex karyotype cases [6]. Of notice, *TP53* mutated AML is frequently associated with complex karyotypes, chromotrypsis and deletions of chromosomes 5, 7 and 17, especially when a bi-allelic *TP53* mutation is found [7]. As for concurrent mutations, *TP53* mutations in AML blasts do not include typical molecular mutations found in acute myeloid leukemia with wild type *TP53*, with a lower prevalence of NPM1, RAS and FLT3 mutations [8,9].

*TP53* mutations are predominantly represented by missense mutations in DNA binding domain (exons 5–8) and mainly involving arginine residues [8]. R248Q, R175H, G245S, R248W, R249S, R273H, R273S and R282W, the so-called "hotspot mutations", account for

approximately 28% of all p53 mutations [10]. In fewer cases, mutational events can the affect amino-terminal (AT) region and oligomerization domain (OD). Mutations in the *TP53* gene can lead to diverse mutated protein phenotypes, including LOF (loss of function) variants, GOF (gain of function) variants altering efficacy of pro-apoptotic p63 and p73 proteins [11] and dominant negative (DN) variants, which selectively inhibit normal functions of wild-type variant. As shown in The Cancer and Genome Atlas (TCGA) study, missense mutations often prolong mutated p53 half-life [12].

## 2. Prognostic Aspects

Similarly to most tumors, including hematological malignancies, the presence of *TP53* mutations in AML blast cells is widely associated with chemoresistance, especially in patients treated with anthracyclines and cytarabine [13], which confers a negative prognostic value. In a seminal work on AML, Papaemmanuil et al. studied 1540 AML patients using a 111-gene myeloid panel, identifying 14 mutational patterns with different prognostic value. The group with *TP53* mutations and/or chromosomal aneuploidies was associated with a dismal prognosis [8]. The estimated median overall survival in *TP53* mutated AML is around 4 to 6 months with a 2-year OS less than 10% [9]. Allogenic hematopoietic stem cell transplantation (HSCT) is the treatment of choice in high-risk leukemias including *TP53* mutated AML, especially when the first complete remission (CR1) is achieved. Nonetheless, the *TP53* mutant AML outcomes post-HSCT are only slightly improved due to the strikingly high relapse rate, reaching a 2-year relapse rate (RR) of 61% in a cohort of patients with AML and abnormalities of chromosome 17p [14].

Based on these findings, in the latest European Leukemia Net (ELN) 2022 guidelines, the presence of a pathogenic *TP53* mutation (at a variant allele fraction of at least 10%, with or without loss of the wild-type TP53 allele) defines the new entity AML with mutated *TP53* [15], which confers to patients a very adverse prognosis. More generally, a novel panel of driver mutations, such as the ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1 and/or ZRSR2 mutations, have entered the risk classification. These mutations are highly associated with AML following prior MDS or MDS/MPN and confer an adverse prognosis even if they occur in de novo AML. Remarkably, a hierarchical prognostic classification was introduced, placing from most to less adverse. In that, AML with mutated TP53 constitutes the entity with the most adverse prognosis as compared to "AML with myelodysplasia-related gene mutations" and "AML with myelodysplasia-related cytogenetic abnormalities".

Some important issues are still a matter for debate. In particular, there is conflicting evidence about a possible prognostic significance of the variant allele frequency (VAF) and the *TP53* allelic status (mono or biallelic) in *TP53* mutated AML. In particular, recent studies suggest that a pivotal role in prognosis is held by variant allele frequency (defined as the ratio between the number of mutant copies of the gene and mutant plus wild type copies of the gene). In a retrospective study, 202 patients with de novo AML and a median age of 70 years were stratified according to VAF and previously received therapy. Results showed that outcomes of *TP53* mutated AML were driven by VAF and that this association was treatment-dependent [16]. Specifically, a *TP53* VAF threshold of 40% was predictive of a statistically significant difference in OS (median OS of 6.9 months if <40% versus median OS of 5.5 months if >40%). Therapy response rates were shown to be dependent on *TP53* mutant VAF as well, especially when cytarabine-based regimens were used (median OS of 7.3 months if <40% and median OS of 4.7 months if >40%), pointing out the chemoresistance of high VAF mutant TP53 clones. Moreover, the threshold of 40% VAF plus a single-hit *TP53* mutation was predictive for survival after HSCT. The role of multi-hit *TP53* mutations is indeed very important in affecting prognosis, as shown by Bernard et al. in the context of myelodysplastic syndrome as a distinct adverse outcome category together with FLT3-ITD mutations and MLL partial tandem duplications. These three categories were associated with inferior OS and higher AML transformation rates [17]. In contrast to these pieces of evidence, Grob and colleagues recently analyzed a large cohort of *TP53* mutated AML and

MDS-EB focusing on different features, including *TP53* mutant allelic status (mono- or biallelic), the number of *TP53* mutations, mutant *TP53* clone size, concurrent mutations, cytogenetics and molecular measurable residual disease (MRD) [18]. The *TP53* mutation was found in 10.5% of a cohort of 2200 AML/MDS-EB patients. Most common co-mutations were DNMT3A, TET2, ASXL1, RUNX1 and SRSF2. Most importantly, this study pointed out that no survival differences emerged between the two groups (AML/MDS) and this difference was irrespective of the molecular features mentioned above. Taken together, the prognostic impact of *TP53* VAF in the AML setting is controversial. For this reason, AML and MDS-EB with mutant *TP53*, independently from molecular specifics or 20% BM blasts threshold, should be considered a single, extremely aggressive entity with adverse outcomes [15,18].

## 3. Therapeutic Approach: Circumventing the Intrinsic Chemoresistance Related to TP53 Mutations: Immunological and Metabolic Strategies

To circumvent the intrinsic chemoresistance related to *TP53* mutations in AML, in recent years a variety of novel approaches have been evaluated and are under active clinical investigation. Here, we summarize some of these approaches, moving from the preclinical rationale and then analyzing the most recent clinical evidence (Figure 1).

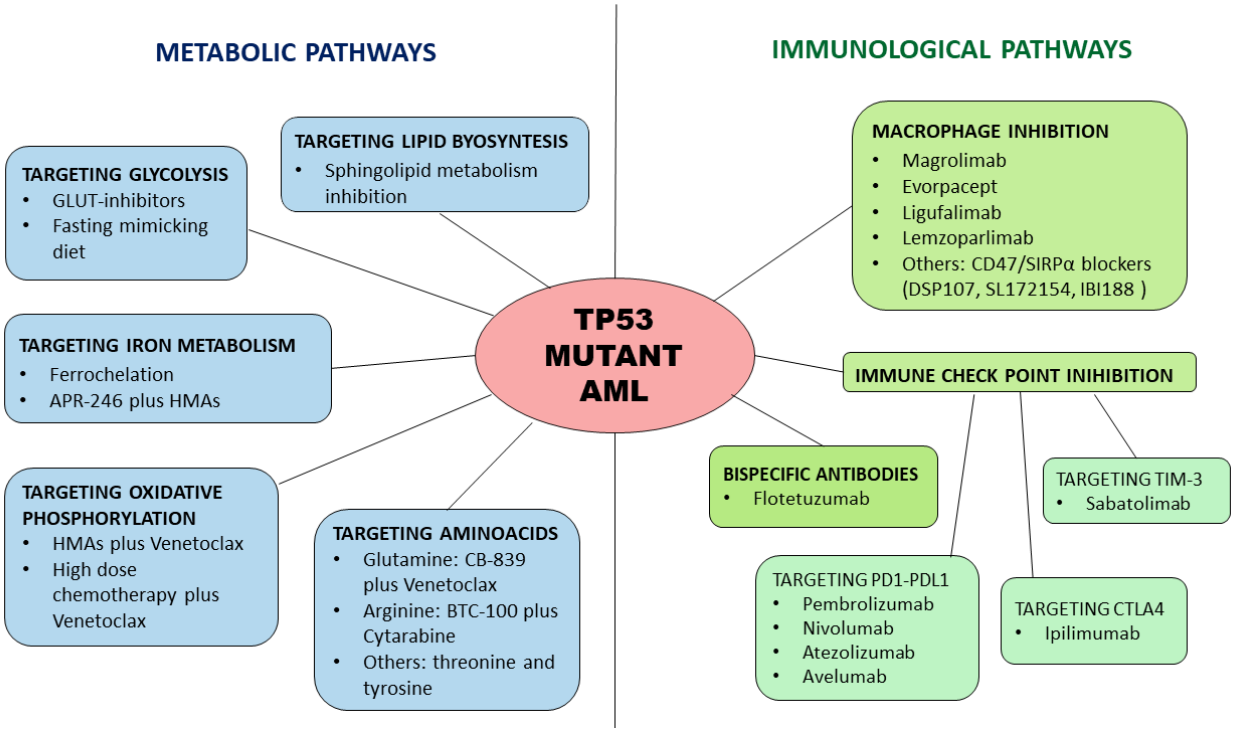


**Figure 1.** New strategies and approaches under clinical investigation targeting metabolic and immunological pathways for patients with TP53 mutant AML.

### *3.1. The Metabolic Perspective and Novel Approaches*

Recent studies have shed new light on the metabolic profile of AML cells. In particular, it is now well-established that the core leukemic cell population differs from leukemic stem cell (LSC) in the bioenergetics program, with the latter mainly relying on oxidative phosphorylation (OXPHOS) rather than on anaerobic glycolysis. OXPHOS can be sustained by amino acid (AA) metabolism in AML LSC, with cysteine and glutamine being two of the most important AAs involved in the process [19]. Along with the effects mediated by p53 in regulating crucial functions of AML cells, recent data revealed that p53 also has a crucial role in metabolic reprogramming for bioenergetics. Wild-type p53 itself acts by regulating and promoting the tricarboxylic acid (TCA) cycle, for instance by enhancing cytochrome c oxidase assembly (SCO2) expression to maintain cytochrome c oxidase com-

plex and increasing Parkin levels in cells, which increases pyruvate dehydrogenase E1α1 (PDHA1), a critical component of the pyruvate dehydrogenase complex [20]. Therefore, p53 gain of function (GOF) mutants could act sustaining OXPHOS in LSCs. In that, *TP53* mutations have been associated with a distinct metabolic profile, which may serve as the identification of novel therapeutic approaches and strategies. Mutant p53 promotes anaerobic glycolysis via downregulation of glucose transporters (GLUTs) [21] and upregulation of important enzymes, such as hexokinase 2 (HK2) and protein mammalian target of rapamycin complex 1 (MTORC1) [22]. Moreover, mutant p53 acts on lipid biosynthesis via sterol regulatory element-binding transcription factor 1 (SREBP1/2) upregulation [23] and enhances nucleotide biosynthesis via activation of transcription factor Protein C-ETS2 (ETS2) [24]. Recently, by examining the intracellular AML metabolome on a large cohort of patients, Simonetti et al. revealed three distinct AML clusters, correlating with distinct molecular features, including NPM1-mutated (mut), chromatin/spliceosome-mut and *TP53*-mut/aneuploid AML [25]. In particular, the *TP53*-mut/aneuploid AML cluster showed intermediate threonine and tyrosine levels and high citrate in the serum compared to the other two clusters. Moreover, *TP53* mutant patients displayed a different metabolic pattern with regard to the metabolites composition of biofluids (serum and urine) as compared with controls. Specifically, in *TP53* mutant AML patients, lower levels of threonine and glucose were detected in serum along with altered levels of glutamine, reflecting increased cellular uptake and expensive bioenergetic requirements by blast cells in this AML subtype. Additional evidence supporting the effect of *TP53* mutations on AML cell metabolic reprogramming comes from one study by Lo Presti et al. [26]. In this study, evidence of metabolic changes was evidenced in AML samples with differences regarding FAB subtypes, IDH 1/2 mutational status, chemosensitivity versus chemoresistance and high-risk versus low-risk ELN subtypes. Surprisingly, in the adverse risk subgroup (including only one *TP53* mutated patient) and in the chemoresistant patients' subgroup, the same metabolites were overexpressed, including phospholipids and glutathione (GSH) levels, a molecule strongly affecting blast drug resistance and relapse rate [27].

Iron metabolism requires a special mention in the context of the *TP53* mutated AML metabolism. Besides its crucial role for vital processes, iron overload is associated with increased cancer risk [28]. P53 acts as a key regulator of iron metabolism through different pathways, such as hepcidin upregulation and, more importantly, ferredoxin reductase (FDXR) induction [29]. Iron metabolism vice versa regulates p53 functions, with iron excess being able to downregulate p53 protein levels and activity [30]. A master role in the iron metabolism-p53 axis is ferroptosis, an iron-mediated caspase-independent type of cell death that relies on p53 and ferredoxin reductase (FDXR) interaction [31]. P53 has been demonstrated to induce ferroptosis through repression of the cystine/glutamate transporter (SLC7A11) gene, which encodes for a cysteine/glutamate antiporter [32]. SLC7A11 downregulation by p53 impairs cysteine import, thus leading to cell death via glutathione levels' drop and ROS levels' increase. In that, mutant *TP53* blasts may have an impaired capacity of adapting to this defense mechanism. Accordingly, adverse-risk leukemias display high levels of GSH and low levels of ROS, which promote cell growth and survival. Furthermore, overexpression of transferrin receptor protein 1 (TFRC), a ubiquitously expressed high-affinity transferrin-binding receptor (CD71), was demonstrated in AML cells, thus corroborating the hypothesis of a higher iron consumption by AML blasts [33]. Even though evidence is still weak, based on these findings, it sounds reasonable that *TP53* mutated AML blasts have an altered iron metabolism and thus could be targeted by new therapeutic approaches.

Moving from this background, some recent approaches have sought to target the metabolic reprogramming of AML cells, especially LSCs, as one of the emerging mechanisms of chemoresistance and relapse in *TP53* mutant AML [34]. Here, we provide a summary of the therapeutic strategies and approaches aimed at exploiting the metabolic perspective for the clinical management of *TP53* mutant AML.

3.1.1. Venetoclax-Based Regimens

BCL-2 inhibitors have shown activity on the AML cell metabolic profile, probably due to LSCs upregulation of BCL-2 and low-ROS state, mainly associated with the CD34+/CD38− stem/progenitor cell subset [35]. Numerous studies suggest that venetoclax, a well-known BCL-2 inhibitor, has a role in this process. Of note, a renowned effect and possible mechanisms underlying venetoclax activity have been correlated to its capacity to induce apoptosis in a p53-indipendent manner [36]. In addition, Pollyea et al. demonstrated that the efficacy of BCL2 inhibitors could be related to their metabolic effects on the LSC compartment and tumor microenvironment (TME) [37]. Indeed, after a venetoclax-based regimen, analysis on LSCs from treated patients showed a drastic oxygen consumption rate, Krebs cycle products and glutathione levels reduction, which is known to interfere with normal LSCs' metabolism. Based on this rationale, venetoclax has been investigated in combination with hyomethylating agents (HMAs) and chemotherapy. In the setting of *TP53* mutant AML, the rationale for combining venetoclax with HMAs relies on the early clinical results with HMAs alone, demonstrating a remarkable activity when used at higher dosage in the subset of *TP53* mutated AML. In particular, Welch et al. proposed a 10-day schedule with Decitabine, reporting 100% ORR in a *TP53* mutated AML/MDS cohort versus 41% ORR in a *TP53* wild-type group. A response rate of 67% was reported in patients with adverse cytogenetics versus 34% in those with intermediate/favorable cytogenetics [38]. Reasons for such an exceptional sensitivity of the *TP53* mutated clone to decitabine, such as a specific mutation epigenetic priming pattern, remain unknown. Besides these encouraging data, supported by a robust clearance of leukemia-associated mutations, namely *TP53* and *SF3B1*, nearly all patients treated tested positive for *TP53* and concurrent mutations, highlighting emergence of a resistant subclone or persistence of the original one. In the pivotal study by Di Nardo et al. [39], a different approach was used, adding venetoclax to azacitidine in patients unfit for intensive chemotherapy. In spite of the excellent results for the IDH1/2 and NPM1 subgroups, in the *TP53* mutated subgroup, composite remission rates are globally unsatisfactory, reaching 55.3% with a 23% molecular response in CR patients. In a further study enrolling R/R *TP53* mutated patients and including patients with relapse after prior HSCT, the CR + CRi rate was around 38% with HMA and venetoclax [40]. Pollyea et al. [41] evaluated CR rates, duration of response (DoR) and OS in the Phase III study (NCT02993523) and Phase Ib study (NCT02203773) by focusing on patients harboring poor-risk cytogenetics with or without the *TP53* mutation. These studies showed that patients with poor-risk cytogenetics and $TP53^{mut}$ receiving venetoclax and azacitidine had higher RR but comparable DoR and OS than patients treated with azacitidine alone. On the contrary, patients with poor-risk cytogenetics and $TP53^{wt}$ treated with venetoclax and azacitidine had better RR, DoR and OS compared with patients receiving azacitidine alone. Taken together, these studies suggest that, in spite of the strong and abovementioned rationale, the addition of venetoclax to HMAs is not likely to provide a clear benefit in the presence of the *TP53* mutation. On the contrary, recent data indicate that in the setting of fit-to-chemotherapy AML patients, the combination of venetoclax with intensive chemotherapy may provide very promising results, also in the setting of high-risk AML, including AML with mutant *TP53*. In particular, in a trial by Di Nardo et al. [42], venetoclax plus the FLAG-IDA regimen produced ORR and MRD negativity rates higher than 90% (composite CR 89%) in 45 newly diagnosed patients, with 60% of the patients' cohort receiving HSCT. Ten patients, including three with newly diagnosed (ND) AML and seven with R/R-AML, had *TP53* mutations at baseline. Sixty percent attained a CR (ND-AML, 3/3; R/R-AML, 3/7), including 4 with MRD negative CR by flow-cytometry. Median DOR and OS in ND-AML were 3.4 and 9 months, respectively. In R/R-AML, median DOR and OS were 3.2 and 7 months. Of interest, the *TP53* mutation persisted in all four patients with MRD negativity, highlighting how *TP53* is not a reliable marker for MRD monitoring [18].

#### 3.1.2. Novel Drugs and Compounds

A potential strategy for the near future is the combination of specific metabolic-targeting drugs with current and well-established therapies. For example, by acting on glutamine metabolism through inhibition of GLS1, CB-839 has shown synergistic effects with venetoclax [43]. Of note, a remarkable drop in arginine concentrations, which suggests a biologic relevance in metabolic cell reprogramming, was obtained with pegylated recombinant arginase, BCT-100, in combination with cytarabine. Nonetheless, the study exploring this therapeutic option did not include *TP53* mutated patients [44]. A recent drug under investigation in the setting of *TP53* mutated MDS/AML is Eprenetapopt (APR-246). This compound works by inducing mutant p53 refolding and reactivation but also promoting blasts p53 independent cell death through ferroptosis [45]. Indeed, APR-246 causes a decrease in GSH content, resulting in an increase in ROS and in lipid peroxides, which in turn lead to AML cell death by ferroptosis. Notably, this result has been shown to be irrespective of *TP53* mutational status and its action seems to synergize with glycine and serine dietary restriction [46]. A trial [47] enrolling MDS/AML/MPN patients with mutant *TP53* showed that the overall response rate and CR rate for patients with AML was 64% (n = 7) and 36% (n = 4), respectively, combining azacitidine and APR-246. A preliminary analysis of another ongoing clinical trial [48], which combines APR-246 with azacitidine and venetoclax, has shown an ORR of 64% and a CR rate of 39% with a median OS of 8.8 months. Azacitidine plus APR-246 is also being evaluated in a trial in the post-HSCT setting (NCT03931291). Another possible promising compound in the *TP53* mutated AML scenario is COTI-2. This novel molecule acts on mutant p53 protein refolding and, similarly to APR-246, it targets in a p53 independent manner AMPK and mTOR pathways contributing to malignant cells' DNA damage and consequent death [49]. COTI-2 based clinical trials in *TP53* mutated AML are eagerly awaited.

In summary, *TP53* mutant AML is characterized by multiple metabolic pathways, making it difficult to find a single, successful, therapeutic intervention. Venetoclax has become a main backbone for therapies targeting metabolism. In this scenario, potential future approaches may include the use of innovative and experimental metabolic strategies, such as fasting mimicking diet (FMA), selective GLUT's inhibition [50], sphingolipid metabolism inhibition [51], amino acids metabolism inhibitors and iron overload control. To this aim, specific clinical trials are highly warranted.

### *3.2. The Immunological Perspective and Novel Approaches*

Possible reasons for the *TP53* mutant AML dismal outcomes may rely on the perturbation of the bone marrow (BM) immune landscape induced by malignant cells. Recent data have revealed a peculiar association between *TP53* mutant AML and specific alterations of immune cell subsets within the leukemia microenvironment. In particular, *TP53* mutant HSCs have a higher expression of the immune-checkpoint molecule Programmed cell death ligand 1 (PD-L1), a higher expression of the oncogene MYC, which is paralleled by the downregulation of MYC negative regulator, miR-34a, a well-known p53 target and a key element in preventing T cell exhaustion [52,53]. The authors found that in the TME of *TP53* mutant myeloid neoplasms, including AML and high-risk MDS, there is a reduced frequency of $OX40^{+}$ cytotoxic and helper T cells compared with controls and a remarkably higher number of $ICOS^{high}/PDL\text{-}1^{-}$ regulatory T-cells (Tregs) and $PDL\text{-}1^{-}$ myeloid derived suppressor cells (MDSCs). Furthermore, an increased level of $ICOS^{high}/PDL\text{-}1^{-}$ Treg cells was an independent covariate for inferior overall survival in the total cohort of patients, showing how changes in immune regulation may profoundly affect chemosensitivity and survival outcomes. Interestingly, MYC overexpression in *TP53* mutated AML cells leads to upregulation of PDL-1 but also of CD47, a well-known "don't eat me" molecule. Our group has recently investigated the mechanisms underlying the high expression of Tregs in the AML BM microenvironment and we found that the release of interferon (IFN)y by AML cells positively correlates with a higher BM suppressive Tregs frequency and is associated with poor overall survival. AML cells were demonstrated to be the main source of IFNy,

revealing a unique feature of AML in which IFNy production is more likely the result of an intrinsic dysregulation of leukemia cells rather than the consequence of inflammatory BM changes. Furthermore, IFNy$^{high}$ AML cells modified mesenchymal stromal cell (MSC) transcriptome by upregulating IFNy-dependent genes related to Treg induction, including indoleamine 2,3-dioxygenase 1 (IDO1), an IFNy-inducible mediator that catalyzes the rate-limiting step in tryptophan metabolism along the kynurenine pathway. AML blasts can produce IDO1 and ROS, which induce differentiation towards Tregs, facilitating disease progression [54,55]. IDO1 acts by suppressing local CD8$^+$ T effector cells and natural killer cells, and induces CD4$^+$ Tregs (iTreg) and MDSC [56]. In tumors, IDO1 is negatively controlled by the BIN1 tumor suppressor, which in turn is regulated by the RBM25 splicing factor, generating a dominant-negative BIN1 isoform that is unable to repress MYC activity. Of note, our group recently found that abnormalities in immune genes, which are part of a novel IDO1-based immune signature, capable to prognostically stratify AML patients and to predict survival [57], also positively correlate with *TP53* mutational status, thus corroborating the tight link between *TP53*-related cell-intrinsic abnormalities and microenvironment modifications of the immune landscape [58]. Considering this rationale, different immunotherapy strategies are being proposed and under clinical investigation as a new immunological approach for *TP53* mutant AML.

#### 3.2.1. Macrophage Inhibition

Magrolimab: In a Phase Ib study combining azacytidine and magrolimab, an anti-CD47 antibody unlocking macrophage phagocytosis of malignant cells by acting on the CD47/SIRPα axis, favorable outcomes were observed in both *TP53*-mutant (40% CR, median OS 16.3 months) and wild-type patients with high-risk MDS (31% CR, median OS NR) [59]. In the subgroup of patients with *TP53* mutant AML, ORR was 71% (15/21) with 67% (14/21) of patients achieving CR/CRi. Median overall survival for *TP53*-mutant and wild-type AML patients was 12.9 and 18.9 months, respectively. Such promising results have led to the ongoing randomized Phase 3 ENHANCE-2 trial comparing magrolimab plus azacitidine to venetoclax plus azacitidine or 7 + 3 chemotherapy in untreated *TP53*-mutant AML (NCT04778397) [60]. The rationale for this study relies on the synergistic effect of azacitidine with magrolimab [61]. In addition, magrolimab was shown to circumvent resistance in venetoclax-resistant cancer cells and *TP53* mutant cells in preclinical models [62]. In consideration of this, a trial is evaluating the safety and early efficacy of the triplet azacitidine, venetoclax plus magrolimab in three subgroups: frontline, venetoclax-naïve R/R AML, and venetoclax-exposed R/R AML. The frontline cohort included 17 patients ineligible for intensive chemotherapy or patients with adverse-risk karyotype and/or *TP53*$^{mut}$ regardless of age/fitness. Among these, eight patients (47%) were TP53$^{mut}$. Preliminary results indicate that CR/CRi rates for each subgroup are 94% (newly diagnosed), 63% (venetoclax-naïve R/R AML), and 27% (venetoclax-exposed R/R AML), respectively, In particular, seven of eight newly diagnosed TP53$^{mut}$ patients were evaluable with a CR/CRi in 100%, CR in 86% and MRD negativity by MFC in 57% of patients, highlighting the clinical activity of this triplet regimen [63].

Evorpacept (ALX148): Evorpacept is a next-generation CD47 blocker. The CD47 binding domain of evorpacept is an affinity-enhanced extracellular domain of SIRPα, and its engineered Fc domain fails to provide the pro-phagocytic signal, while still maintaining an antibody-like pharmacokinetic half-life for the molecule. There are several ongoing Phase I/II trials of evorpacept in combination with chemotherapy and/or target agents in both solid and hematologic malignancies. In particular, two trials that combine evorpacept with azacitidine in high-risk MDS (ASPEN-02; NCT04417517) and with azacitidine plus venetoclax in R/R AML (ASPEN-05; NCT04755244) are ongoing. The Phase I dose escalation part has been completed and Phase II will evaluate the pharmacological combination early efficacy. Ligufalimab (AK117): Ligufalimab is a humanized IgG4 antibody against CD47. An open label, Phase Ib/II study in AML patients is currently ongoing. The purpose

of this study is to evaluate the safety and early efficacy of AK117 plus azacitidine in patients with intermediate-high risk AML with CRc as primary end point (NCT04980885).

Lemzoparlimab (TJC4): Lemzoparlimab is a differentiated human IgG4 antibody targeting a distinct epitope of CD47, which enables a unique red blood cell sparing property while retaining strong anti-tumor activity. A Phase Ib open label, dose escalation trial (NCT04912063) is evaluating the safety and dose-limiting toxicities of lemzoparlimab in combination with azacitidine and venetoclax for patients with treatment-naïve AML and with adverse cytogenetic/molecular risk not suitable for induction therapy and for treatment-naïve high-risk MDS patients [64]. In addition, lemzoparlimab is being evaluated in monotherapy and in combination with azacitidine in patients with AML or MDS in a Phase I/II trial (NCT04202003).

Others: Other CD47/SIRP$\alpha$ blockers, such as DSP107, SL172154 and IBI188, are now in study in association with azacitidine alone or azacitidine plus venetoclax in several Phase I trials for newly diagnosed AML patients.

#### 3.2.2. Immune Checkpoint Inhibition

Preclinical and biological data indicate a specificity of immune dysregulation in the TME of *TP53* mutant AML. These findings clearly point at using immune checkpoint inhibitors in the setting of *TP53* mutant AML. The targeting of several immune checkpoint receptors is under active clinical investigation. Here, we provide a brief summary of the results of recently published and ongoing clinical studies with a specific focus on *TP53* mutant AML patients.

(a) Targeting PD1

PD1 (programmed death protein 1) is an immunosuppressive receptor located on the surface of T cells. Its ligand, PD-L1, is expressed by different cell types such as epithelial cells, endothelial cells, macrophages, dendritic cells and tumor cells, including AML cells. The physiological function of the PD-1/PD-L1 pathway is to modulate the immune response, downregulating the immune system and promoting self-tolerance. To date, it is well-known that in many neoplasms, both solid and hematological, tumor cells overexpress PD-L1, preventing their own destruction by the immune system. In recent years many drugs targeting and blocking this pathway have been developed. These therapies have been tested in several settings, showing encouraging results.

Nivolumab: In a recent study, nivolumab was used in combination with azacitidine in 70 R/R AML patients, of whom 45 had been previously exposed to HMAs and 16 of whom were *TP53* mutated [65]. The ORR was 33%, with a median OS of 6.3 months. Higher responses were documented among HMA-naïve patients (ORR rate: 52%), while only three *TP53* mutated patients showed a response. Nivolumab has been also used in combination with chemotherapy in young patients, who were candidates to allogeneic HSCT. As for the *TP53* mutant AML patients, the rationale for combining nivolumab with chemotherapy relies on the high probability that these patients reach allogeneic HSCT with a significant proportion of residual cells, carrying high expression of PD-L1, which is likely to hamper and mitigate the GVL effect [66]. Based on this rationale, a Phase 1/2 study combining nivolumab with frontline idarubicin and cytarabine induction regimen was conducted in 44 patients with AML and high-risk MDS, of whom 8 were *TP53* mutated [67]. At a median follow-up of 17 months, the median event-free survival was not reached and median OS was 18 months, with 43% of patients achieving a response and proceeding to HSCT. The GVHD grade 3–4 rate was 26%, a rate of occurrence not precluding this strategy in frontline setting in high-risk leukemias. In the entire cohort, the CR/CRi rate was 78%, of which 79% had negative MRD. A comparison of characteristics between overall responders and non-responders showed that non-responders tended to have more *TP53* mutations and more secondary and therapy-related AML. Notably, there was no difference in the OS between responders who continued on therapy beyond remission and those bridged to allo-SCT, suggesting the potential ability of nivolumab to restore anti-tumor immune surveillance and eradicate MRD [68]. Based on this, a pilot Phase

II clinical trial studying the efficacy and safety of nivolumab as maintenance therapy in AML was conducted in patients with high-risk AML in remission not being considered for allogeneic HSCT. While the study demonstrated the safety and feasibility of maintenance nivolumab for patients with high-risk AML, it showed a modest effect in eradicating MRD and extending remissions as a single agent, suggesting potential mechanisms of resistance to nivolumab as monotherapy [69]. In that and based on the finding that the association of azacitidine plus nivolumab can lead to the upregulation of CTLA4 on bone marrow CD8 cells, thus resulting in a reduced anti-leukemia immune response [65], a triplet combination of azacitidine + nivolumab + ipilimumab is being evaluated with the aim of contrasting PD-1 mediated resistance. A Phase II study that aims to investigate the side effects and best dose of nivolumab and azacitidine with or without ipilimumab is ongoing for AML patients who have not responded to previous treatment or have relapsed or are newly diagnosed (NCT02397720). Results about R/R population were recently reported. The study enrolled 59 R/R AML patients treated with azacitidine + nivolumab and in a second cohort 36 R/R AML patients treated with Azacitidine + Nivolumab + ipilimumab. The median age of cohort 2 was 67 years, secondary AML was 50%, ELN adverse cytogenetics were 67%, *TP53* mutated AML was 36%, and 67% of patients were previously treated with HMA-based therapies. All 36 pts were evaluable. Per ELN 2017, CR/CRi was reported in 19% and PR in 3%. Fourteen percent of patients had durable stable disease and sixty-four percent were non-responders. Converse to azacitidine + nivolumab, responders did not have a higher frequency of pre-therapy BM CD8+ T cells infiltration, but did have progressive BM CD8+ T cells infiltration on therapy, compared with non-responders, demonstrating that ipilimumab, differently from nivolumab, may be able to mobilize peripheral T-cells to the BM. The median OS with azacitidine + ipilimumab + nivolumab versus azacitidine + nivolumab versus contemporary HMA-controls in R/R AML, were 7.6, 5.9, and 4.6 months, respectively. The 1-year OS in R/R AML patients who received azacitidine +nivolumab +ipilimumab was 25% and the median OS with azacitidine + ipilimumab + nivolumab was comparable to the median OS of 6–8 months reported with HMA plus venetoclax salvage in numerous studies and only modestly improved over azacitidine + nivolumab [70].

Pembrolizumab: pembrolizumab was used in conjunction with high-dose cytarabine in 37 RR AML patients with a CR/CRi rate of 38% and with 24% of patients proceeding to HSCT [71]. No grade > 3 GVHD cases were reported post-HSCT. Of note, two out of five (40%) treated patients with *TP53* mutations achieved CR. Pembrolizumab was also tested in combination with azacitidine in 29 newly diagnosed older AML [72] patients in a multi-center Phase II study (NCT02845297). In that, 64% of patients had poor-risk cytogenetics and 23% had *TP53* mutation. The study shows promising results. Among 17 evaluable patients, 47% of them achieved CR/CRi, 12% PR, 12% hematologic improvement and 24% stable disease for at least six cycles. With a median follow-up of 19 months, the median OS was 13.1 months for the whole cohort and not reached for patients in CR/CRi/PR. The median DFS for patients in CR/CRi was 16.6 months. In terms of safety, 18% of patients had G2 and 14% had G3–4 immune related adverse events (IRAEs), which were managed with steroids and supportive care in the majority of cases.

Atezolizumab: atezolizumab is a human immunoglobulin 1 (IgG1) anti PD-L1. It was tested in a Phase 1 b study evaluating the safety and pharmacology when administered in combination with guadecitabine in 16 AML patients with a median age of 73 years and with disease progression or failure to achieve complete or partial response after intensive cytotoxic therapy or treatment naïve, but unfit for induction chemotherapy. Patients with intermediate- or adverse-risk cytogenetic and molecular alterations were also included (NCT02892318). Fourteen of the sixteen patients (87.5%) died during the trial period due to disease progression (8/14) or AEs (6/14). The combination showed limited clinical activity and an overall unfavorable benefit-risk profile at the investigated dose [73].

Avelumab: avelumab is an anti-PD-L1 monoclonal antibody, which was tested in 19 R/R AML patients during a Phase Ib/II trial in association with azacitidine. All patients had adverse-risk disease based on ELN 2017 risk categories and *TP53* was the most common

mutation. The ORR was 10.5%, and the median OS of the entire population was 4.8 months, the same as *TP53* mutated patients, showing good tolerance but only limited activity [74].

(b) Targeting CTLA-4

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) is a co-inhibitory receptor expressed predominantly on T cells that binds ligands with greater affinity, resulting in inhibition of T-cell activation. Preclinical studies with murine models have shown that CTLA-4 ligand expression is upregulated in AML cell lines similar to upregulation of PD-L1, thus increasing the resistance of such cells to lysis by cytotoxic T cells [75].

Ipilimumab: Ipilimumab is a recombinant, human immunoglobulin 1 (IgG1) kappa immunoglobulin that binds and inhibits CTLA-4. It was investigated in a Phase 1/1b trial enrolling 28 patients with post-HSCT relapsed hematologic cancer including AML with extramedullary involvement [76]. Durable complete responses were observed in 5 out of 14 patients at the higher dose of ipilimumab (10 mg/Kg), with a documented decrease in activation of Tregs and an increase in effector T cells in the peripheral blood. A Phase 1 trial that aims to determine the safety and benefit of nivolumab, ipilimumab or the combination of nivolumab with ipilimumab given after allogeneic HSCT for patients with intermediate- and high-risk AML/MDS is currently ongoing (NCT02846376). Outside the setting of post-transplantation, one Phase 1 clinical trial testing ipilimumab monotherapy in the setting of relapsed/refractory AML is enrolling (01757639). HMAs can augment the immune response against cancer through multiple mechanisms, including improved antigen uptake by macrophages and dendritic cells, improved recognition of neo-epitopes over the MHC I and T cell receptor, and increased susceptibility of tumor cells to immune-mediated cytotoxicity [77]. Based on this rationale, a Phase I, multicenter trial (CTEP 10026) of decitabine plus ipilimumab in patients with R/R MDS/AML with (Arm A) and without (Arm B) prior HCT, including *TP53* mutated patients is ongoing [78]. Very preliminary results have been reported, indicating that approximately 50% of patients develop grade 1–2 IRAEs, comprising late-onset acute (grade 3, 1 patient) or chronic GHVD. All IRAEs were managed though steroids' administration, except for the grade 3 steroid-refractory acute GVHD, which was complicated by fatal septic shock. Eight of sixteen evaluable AML/MDS patients showed objective responses (3 CR, 2 CRi and 3 marrow CR), and the median OS was 18.3 months (95% CI: 11.7–NA) [79].

(c) Targeting TIM-3

T-cell immunoglobulin and mucin domain 3 (Tim-3) is a type I trans-membrane glycoprotein expressed on IFNγ-producing T cells, FoxP3+ Tregs and innate immune cells. Binding its receptors, it suppresses immune cells' activation. AML cells overexpress both TIM-3 and some of its ligands, such as galectin-9 creating an autocrine loop that induces a mechanism of self-renewal through activation of a mechanistic target of rapamycin (mTOR) and nuclear factor kappa light chain enhancer of activated B cells (NFkB) pro-survival pathways and β-catenin signaling [80]. Furthermore, TIM-3 overexpression on AML blast cells inhibits CD8+ T-cell recognition and, thus, their destruction. Darwish et al. [81] analyzed the expression of LSC markers (CD34, CLL-1, TIM-3 and BMI-1) using quantitative RT-PCR in BM samples of 40 AML patients, showing that overexpression of TIM-3, CLL-1 and BMI-1 was markedly correlated with poor prognosis in these patients.

Sabatolimab: Based on this rationale, the safety and efficacy of sabatolimab (MBG453), a potential first-in-class immunotherapeutic agent that can target TIM-3 on immune and myeloid cells, are being evaluated in combination with HMAs in patients with AML and high-risk MDS in a Phase Ib ongoing study [82]. The interim analysis of the results revealed CR/CRi in 2 out of 5 patients with *TP53* mutant AML and an ORR of 71% (10 out of 14) in patients with *TP53*-mutated higher-risk MDS. Despite the limits due to the small sample size, the median DoR in this very hard-to-treat population was 21.5 months. These promising data suggest that this combination might be effective for *TP53* mutated AML [83]. On this basis, a Phase II clinical trial of sabatolimab in combination with azacitidine and venetoclax in the setting of newly diagnosed AML patients not suitable for intensive

chemotherapy is ongoing (NCT04150029 STIMULUS-AML1). Safety and tolerability are overall comparable to the reported safety profile of azacitidine plus venetoclax therapy [84]. Interestingly, sabatolimab is being used in combination with other drugs that target the immune microenvironment. In particular, a Phase Ib/II clinical trial evaluating the safety and early efficacy of the combination therapy with sabatolimab and magrolimab with or without azacitidine (NCT05367401) is ongoing in patients with R/R AML. Given the promising results observed with magrolimab plus azacitidine in the setting of *TP53* mutant AML, the clinical results of this trial are awaited.

#### 3.2.3. T-Cell Engagers and Bispecific Antibodies

Immunologic approaches that allow the retargeting of immune effector cells, mostly T cells, against tumor cells, thus providing rapid and robust activation with durable cytotoxic responses, also have been explored in AML. In this scenario, bispecific antibodies (bsAbs), including bispecific T-cell Engagers (BiTEs) and Dual Affinity Retargeting Antibodies (DARTs), deserve consideration, especially for high-risk AML subtypes. In particular, in the setting of *TP53* mutant AML, bispecific DARTs have shown some promising early clinical results [85].

Flotetuzumab: CD123, the low-affinity α subunit of interleukin-3 receptor (IL3RA), is expressed in 60% to 80% of patients with AML. CD123 expression on AML blasts is associated with poor outcomes, thus suggesting a biological relevance and significance for leukemia cell survival. Flotetuzumab is a DART, which links and activates $CD3^+$ cytotoxic lymphocytes against $CD123^+$ myeloid cells. It was investigated in a multicenter Phase 1/2 study enrolling 88 patients with primary induction failure (PIF)/early relapse (ER, within 6 months) and R/R AML [86]. The rate of complete responses was higher in the PIF/ER group (16.7%) with a median OS of 10.3 months, while in the R/R group CR rate was 12%. A comprehensive biological study phase provided the background for the clinical development of flotetuzumab. In particular, in silico analyses showed that CD123 expression correlated positively with ELN risk category and that higher CD123 mRNA predicted PIF and ER in newly diagnosed AML. Moreover, a pivotal study highlighted the different rate of response between AML patients with TME immune infiltration and patients with TME immune cells depletion [87]: The former group appeared to be enriched in IFNγ-related mRNA profiles and showed resistance to cytotoxic chemotherapy but a higher probability of response to flotetuzumab. In the same study, the comparison between *TP53* mutated and wild-type AML patients was carried out showing that tumor inflammation signature, IFN-gamma pathway, chemokines and lymphoid signature scores were higher in *TP53*-mutated AML than complex karyotype AML with wild-type *TP53*. Expression of immune checkpoints (PD-L1 and TIGIT) and immunosuppressive genes such as FOXP3 (expressed by Tregs) was higher in *TP53*-mutated cases. Furthermore, other pathways such as NfKb/JAK-STAT, PI3K-Akt, Hedgehog, Wnt-frizzled were overexpressed in *TP53* mutant AML compared to the wild-type counterpart along with increased expression of immunosuppressive genes such as IFNG, FOXP3, PDL1, CD8A, GZMB and LAG3. Collectively, these findings strongly indicate that *TP53* mutant AML has a strongly immunosuppressed TME, which makes it more sensitive to immunotherapy with flotetuzumab, thus consolidating another therapeutic option for the *TP53* mutated AML subtype [88].

## 4. Concluding Remarks

The BM microenvironment of patients with *TP53* mutant AML has unique characteristics. Moreover, *TP53* mutant AML cells have a peculiar metabolic profile. Through the altered expression of ligands and the release of cytokines and chemokines, AML cells actively modify the surrounding environment, induce immunotolerance and promote their own survival. The intrinsic resistance to conventional chemotherapy related to *TP53* mutations in AML depends on this interdependence between the microenvironment and leukemia cells. The preclinical point of view offers a biological rationale for exploring

new approaches targeting both metabolic and immunological pathways. In recent years, a variety of novel strategies have been evaluated and are under active clinical investigation. Although the studies are still in the initial phase, some results are promising, especially considering the specific subset of patients, whose care remains an unmet medical need.

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