hemato

MDPI

Review

The Current Understanding of and Treatment Paradigm for Newly-Diagnosed *TP53*-Mutated Acute Myeloid Leukemia

Rory M. Shallis [1], Maximilian Stahl [2], Jan Philipp Bewersdorf [3] and Amer M. Zeidan [1,*]

[1] Section of Hematology, Department of Internal Medicine, Yale University School of Medicine and Yale Cancer Center, 333 Cedar Street, New Haven, CT 06510, USA; rory.shallis@yale.edu
[2] Department of Medical Oncology, Adult Leukemia Program, Dana-Farber Cancer Institute, Boston, MA 02115, USA; Maximilian_Stahl@DFCI.HARVARD.EDU
[3] Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA; BewersdJ@mskcc.org
* Correspondence: amer.zeidan@yale.edu

Abstract: About 10% of newly diagnosed and 20–30% of therapy-related acute myeloid leukemia (AML) harbors a *TP53* mutation (*mTP53*-AML). Unfortunately, this biological subset predicts one of the worst prognoses among patients with AML, specifically a median overall survival of about 7 months with fewer than 10% of patients eventually cured of disease. Although remission rates appear to be increased with venetoclax-based, less-intensive regimens when compared with contemporary, intensive chemotherapy (55–65% vs. 40%), survival appears to be no different between the two approaches. Attempts to discern whether or not the prognosis of *mTP53*-AML is universally poor have centered around the study of concurrent cytogenetic risk and predicted *TP53* allelic state, measurable residual disease status and the impact of conditioning intensity for patients proceeding to allogeneic hematopoietic stem cell transplantation. We discuss these considerations in this review and offer the current treatment approach to *TP53*-mutated AML.

Keywords: acute myeloid leukemia; AML; leukemia; p53; *TP53*

Citation: Shallis, R.M.; Stahl, M.; Bewersdorf, J.P.; Zeidan, A.M. The Current Understanding of and Treatment Paradigm for Newly-Diagnosed *TP53*-Mutated Acute Myeloid Leukemia. *Hemato* **2021**, *2*, 748–763. https://doi.org/10.3390/hemato2040051

Academic Editors: Ugo Testa and Roland B. Walter

Received: 26 October 2021
Accepted: 1 December 2021
Published: 9 December 2021

1. Introduction

The *TP53* gene, located on chromosome 17p13.1, encodes the transcription factor and tumor suppressor p53 whose cellular levels increase in response to deoxyribonucleic acid (DNA) damage among other cellular stressors; the consequent transcription of numerous p53 target genes, including those responsible for DNA damage repair, cell cycling and differentiation, induces cell cycle arrest and apoptosis [1]. Consequently, loss-of-function of this critical regulator via mutation and/or deletion threatens both cellular integrity and susceptibility to therapies targeted against cells harboring the abnormality. The plurality of mutations observed across all human tumor types are those within *TP53* (approximately 40%) [2]. Approximately 10% of all new cases of AML are characterized by the presence of a *TP53* mutation (*mTP53*-AML) [2–4]. Therapy-related AML is particularly enriched for this molecular subgroup of disease with *TP53* mutations found in up to 25-35% of cases [5–7].

Given the critical importance and pleotropism of *TP53* mutations and relatively unfavorable prognosis of most patients with AML, it is predictable that *mTP53*-AML is an informative example of why poor-risk disease is aptly named so. The presence of a *TP53* mutation within AML has consistently predicted, irrespective of other relevant covariates like cytogenetic risk, a poor prognosis [8,9]. The median overall survival (OS) of patients with *mTP53*-AML is approximately 7 months when treated with standard-of-care therapies many of which will be discussed in this review [10–12]. Additionally, fewer than 10% of patients with *mTP53*-AML remain alive three years following allogeneic hematopoietic stem cell transplantation (alloHCT) performed while in complete remission (CR) [11,13–15].

In this review we review the evolution of *mTP53*-AML management to its current form and also briefly discuss the novel treatment options that hold promise in light of these currently dismal outcomes.

2. Associated Factors and Important Considerations

Several factors associate with the presence of *TP53* mutations in AML and bear relevance in appraising clinical studies or formulating a treatment plan for *mTP53*-AML. The only consistent patient-specific factor predicting a higher rate of *TP53* mutated disease among patients with *mTP53*-AML appears to be age with patients with *mTP53*-AML being older than their *TP53* wild type counterparts [8,16,17].

Disease-specific factors are more readily associated with the likelihood of detecting a *TP53* mutation within AML. Interestingly, *mTP53*-AML appears to be associated with a lower burden of marrow blasts at diagnosis when compared with *TP53* wild-type disease [13,16,17]. One-third of therapy-related AML (t-AML) harbors a *TP53* mutation, which is detected in only 5–10% of patients with *de novo* disease [18–20]. In apparent contrast, the rate of *TP53* mutations in AML with myelodysplasia-related changes (AML-MRC) may not be higher than that observed in de novo AML [6,16]. These observations are likely better explained by disease biology rather than histologic or historical factors, which are likely indirect surrogates. For instance, t-AML is more likely to be characterized by complex karyotype [21], defined as $\geq$3 acquired chromosomal aberrations, which might explain why the latter is more commonly seen in *mTP53*-AML (80-90%) [17,22]. Conversely, about 50–60% of AML with a complex karyotype will have a detectable *TP53* mutation [8,17,22,23]. A higher rate of complex karyotype has been associated with increasing *TP53* variant allele frequency (VAF) [16].

mTP53-AML is also enriched for monosomal karyotype, defined as $\geq$2 autosomal monosomies or a single monosomy along with one other chromosomal abnormality, when compared with *TP53* wild type disease (87% vs. 55%, $p < 0.0001$) [17]. Individual cytogenetic aberrations, using conventional cytogenetic and microarray techniques, are reported with greater frequency in *mTP53*-AML including monosomy 17/abnormal 17p [8], monosomy 7 [17], monosomy 5 [8,17], in addition to monosomy 3 (71% vs. 29%, $p = 0.008$) [8], monosomy 12 (63% vs. 37%, $p = 0.02$) [17], monosomy 20 (28% vs. 13%, $p= 0.02$) [17], +11/+11q (33% vs. 10%, $p = 0.0002$) [17], +13/+13q (16% vs. 4%, $p = 0.02$) [17], and +19/+19q (13% vs. 4%, $p = 0.04$) [17].

In contrast to the frequent cytogenetic abnormalities that are associated with mutated *TP53,* consistent co-mutations are not identified. In fact, *mTP53*-AML is noted to have statistically-significant decreased frequency of *NPM1* (2–3%) and *FLT3* mutations (2–7%) when compared with patients with *TP53* wild type AML in which 30% of cases have these mutations, arguably the most commonly observed in AML [8,13,16,17,24]. The reasons for this lack of association are incompletely understood.

Several multivariable analyses after adjusting for age, performance status and other relevant disease- and patient-specific factors have demonstrated that even among patients with AML harboring poor-risk cytogenetics, the presence of a *TP53* mutation predicts worse OS [8,9]. Similarly, among patients with *mTP53*-AML, the presence of high-risk cytogenetics like complex or monosomal karyotype have worse OS than patients with non-high risk cytogenetics [16,25–27]. These observations have turned recent attention to *TP53* allelic state in AML as patients with mono-allelic loss of *TP53* in the pathobiologically similar disease myelodysplastic syndrome may have a prognosis similar to that with wild type *TP53*; bi-allelic loss of *TP53* (predicted by a concurrent *TP53* point mutation, deletion or copy neutral loss of heterozygosity) appears to drive the poor prognosis seen with the disease as a whole [28]. However, current techniques and resources do not allow consistent or expedient detection of these aberrations, which are often cryptic.

Retrospective analyses have shown that the burden of detectable *TP53* appears to impact outcomes, specifically that a higher *mTP53* variant allelic fraction (VAF) is predictive of a worse median OS [25,29]. This may be related to the observation that a higher

mTP53 VAF is associated a higher rate of complex karyotype [16], which is more likely (approximately 70% of cases) to be associated with bi-allelic *TP53* alteration predicting complete loss of TP53 protein function [17]. In an attempt to dichotomize a continuous variable, some groups identified specific VAF "cutoffs" to refine prognostic estimates. A *mTP53* VAF > 40% predicts worse median OS when compared with a VAF ≤ 40% in patients treated for *mTP53*-AML (hazard ratio [HR] = 1.61, 95% confidence interval [CI]:1.17–2.21; $p = 0.003$) [25], suggesting that this VAF cutoff should be accounted for in efficacy analyses [25]. However, the impact of *mTP53* VAF may depend upon the intensity of remission induction therapy. One of the largest retrospective analyses of 202 patients with *mTP53* found that a *mTP53* VAF cutoff of 40% was only predictive in intensively-treated patients and not those treated less-intensively [25]. Conversely, other studies have shown no association at all between *mTP53* VAF and median OS [16,24].

3. Intensive Therapy and Its Limitations

Intensive induction therapy has represented the standard-of-care for patients appropriate to receive it, is typically constituted by cytarabine and an anthracycline and has largely been agnostic of disease subgroups defined by cytogenetic or molecular abnormalities. Subgroup analyses of both retrospective and prospective studies have demonstrated the rates of CR of *mTP53*-AML to cytarabine + anthracycline intensive range from 28% to 34% [6,8,17,30]. Although some analyses have reported CR rates as high as 48% [16], a consistent statistically-significant difference in the rate of CR is observed between patients with *mTP53*-AML and AML with wild-type *TP53* for whom the rate of CR is estimated to be 50–85% [8,16,17,30]. Furthermore, patients with *mTP53*-AML are observed to have a statistically-significant higher rate of primary induction failure/refractory disease when compared with their counterparts with *TP53* wild-type disease (approximately 50% vs. 15–35%) (Table 1) [17,30].

Table 1. Summary of experience with intensive therapy for *TP53*-mutated acute myeloid leukemia.

Regimen	Response Rates	Early Mortality *	Outcomes	AlloHCT Rate	Reference(s)
Cytarabine + anthracycline (7 + 3)	CR: 28–48% CR/CRi: 33–66%	11–21%	Median EFS: 1.6–5.7 months 3-year EFS: 1-6% Median OS: 5.1–6.5 months 3-year OS: 3–8%	31–58%	[6,8,16,17,30,31]
CPX-351	CR: 29% CR/CRi: 11–41%	6%	Median EFS: 1.0–8.1 months Median OS: 4.5–8.5 months	13%	[6,31,32]

Abbreviations: AlloHCT, allogeneic hematopoietic stem cell transplantation; CR, complete remission; CRi, complete remission with incomplete count recovery; EFS, event-free survival; OS, overall survival. * defined as death occurring up to 60 days from start of induction.

A randomized, multi-center, phase 3 trial compared CPX-351, the liposomal combination of cytarabine and daunorubicin, to a standard combination of cytarabine and daunorubicin (7 + 3) in older patients with newly-diagnosed AML-MRC or t-AML [31]. CPX-351 demonstrated superior rates of CR (38% vs. 26%, $p = 0.036$) [31]. Furthermore, CPX-351 was associated with superior median OS (9.6 vs. 5.9 months, $p = 0.005$) with more CPX-351-treated patients proceeding to alloHCT in first CR (20% vs. 12%) and an overall comparable safety profile [31]. Based on these data CPX-351 was approved by the Food and Drug Administration (FDA) for the treatment of patients with newly-diagnosed t-AML or AML-MRC. However, similar to the inferior rates of CR/CRi and survival for *mTP53*-AML patients treated with standard 7 + 3 induction, subsequent analyses demonstrated only a 29% CR/CRi rate for patients with *mTP53*-AML treated with CPX-351, in comparison to 66% for patients with *TP53* wild-type disease ($p = 0.0353$) [6,11]. Real-world, multivariable analyses have also reaffirmed the lower response rates of *mTP53*-AML to CPX-351 (CR/CRi 41% vs. 66%, $p = 0.04$) [33]. Furthermore, *post hoc* analyses of the original phase 3 trial have shown that CPX-351 appears to be less effective in its ability to induce CR/CRi for patients with *mTP53*-AML when compared with those treated with classical 7 + 3 induction, although this was not statistically significant (29% vs. 40%; odds ratio [OR] = 0.62, 95% CI: 0.20–1.87) [6]. Real-world analyses have demonstrated similar results (Table 1) [32].

Improved rates of remission do not necessarily correlate adequately with outcomes, however, when specifically evaluating the *mTP53*-AML sub-population. The median OS of patients with *mTP53*-AML treated with CPX-351 on the original phase 3 trial was similar to those treated with 7 + 3 (4.5 vs. 5.1 months; HR = 1.19, 95% CI: 0.70–2.05) [6]. This is likely due to the fact that the remission durations and event-free survival (EFS) were similar between both arms and limited salvage options for this particular disease subset; however, a lesser proportion of patients treated with CPX-351 eventually proceeded to alloHCT (13% vs. 31%) [6].

The limited expectations with intensive therapy for *mTP53*-AML must be rectified with its expected toxicity. Patients who receive intensive therapy accept an appreciable risk of toxicity as well as treatment-related early death with the latter typically defined as that occurring within the first 30 days of therapy. No large, high-quality estimates of intensive therapy-attributable early mortality of patients with *mTP53*-AML exist, but disease biology is unlikely to influence this risk. The early mortality for all patients treated with CPX-351 on the phase 3 trial was 5.9%, increasing to 13.7% up to 60 days out and this compared favorably with 7 + 3-treated patients (10.6% and 21.2%, respectively), but did not reach statistical significance ($p = 0.149$ and $p = 0.97$, respectively) [31]. Real-world analyses of patients with newly-diagnosed AML treated with intensive induction have estimated a higher early mortality rate of approximately 15% and this increases to about 25% when evaluating older patients (age $\geq$65 years), who as previously discussed are more likely to have *mTP53*-AML [34]. The early mortality rate of intensively-treated older patients remains up to 25–30% when analyzing those treated in the largest clinical trials, which typically enroll less frail and more "fit" patients [35–41]. Age is an imperfect surrogate for intensive therapy appropriateness but often associates with decreased end-organ reserve and decreased performance status [42,43]. The latter correlates with higher post-intensive therapy early mortality with an ECOG PS of 3–4 predicting rates of approximately 50–60% [36,44–47]. This must be taken into account when formulating a treatment plan for the patient with *mTP53*-AML.

4. The Evolution of Less-Intensive Therapy for *mTP53*-AML

All patients with AML, irrespective of age, should be considered for disease-directed therapy. However, the previously discussed risks that associate with increased chronological age make less-intensive induction therapy a more attractive option for the older and comorbidity-burdened patient. This may be even more so when considering the relatively unattractive risk:benefit ratio associated with intensive therapy for *mTP53*-AML.

4.1. Hypomethylating Agent Monotherapy

The hypomethylating agents (HMAs) azacitidine (AZA) and decitabine (DEC), since their availability in the mid-2000s, were the standard of care for the treatment of patients with AML who were inappropriate for intensive therapy [48]. A pre-specified sensitivity analysis of the data from the randomized phase 3 AZA-AML-001 trial found that AZA 75 mg/m^2 daily for 7 days improved the median OS of patients diagnosed with AML at age $\geq$ 65 years when compared with a "conventional care regimen (CCR)" comprised of either low-dose cytarabine (LDAC), intensive induction therapy or best supportive care (12.1 vs. 6.9 months; HR = 0.76, 95% CI: 0.60–0.96; $p = 0.019$) [49,50]. DEC was shown in a randomized, phase 3 trial to non-significantly increase median OS in a similar population of patients when compared with supportive care or LDAC (7.7 vs. 5.0 months, $p = 0.108$) [51]. As AZA-AML-001 was a positive study and included a more externally valid comparator group, AZA had generally been considered the optimal HMA for the treatment of the patient with AML and inappropriate for intensive therapy. However, this study was not designed to evaluate differences in outcome between patients treated with AZA and a specific "CCR." Furthermore, the majority of patients in the "CCR" arm received low-dose cytarabine monotherapy, an arguably ineffective therapy. Large, high-quality, population-based analyses and randomized trials, however, have found no

difference in outcomes between AZA- and DEC-treated patients without accounting for *TP53* status [52,53]. The CR/CRi rate of *mTP53*-AML to AZA is reported to be as low as 0% in randomized prospective trials [15], but as high as 40% in retrospective, single-center studies [13]. Subsequent analyses restricted to patients with *mTP53*-AML treated on AZA-AML-001 revealed that, as expected given the low rates and duration of remission, these patients have outcomes inferior to patients with *TP53* wild-type disease, specifically a median OS of 7.2 months (vs. 12.0 months) for AZA-treated patients (Table 2) [54].

Table 2. Summary of experience with less-intensive therapy for *TP53*-mutated acute myeloid leukemia.

Regimen	Response rates	Early Mortality *	Outcomes	Reference(s)
AZA 75 mg/m^2 daily × 7 days	CR: 40% CR/CRi: 0–40%	6%	Median OS: 7.2 mo	[13,15,54]
DEC 20 mg/m^2 daily × 5 days	CR/CRi: 29%	16–21%	Median OS: 2.1–5.5 mo	[51,55–57]
DEC 20 mg/m^2 daily × 10 days	CR: 31% CR/CRi: 38–47%	2–25%	Median EFS: 5.7 mo Median OS: 4.9–7.3 mo	[55,56,58,59]
AZA 75 mg/m^2 daily × 7 days + venetoclax	CR/CRi: 47–67%	3–7%	Median EFS: 5.6 mo Median OS: 7.2 mo	[10,15,60]
DEC 20 mg/m^2 daily × 5 days + venetoclax	CR/CRi: 47–50%	3–7%	Median EFS: 5.6 mo Median OS: 7.2 mo	[10,60]
DEC 20 mg/m^2 daily × 10 days + venetoclax	CR/CRi: 50–69%	11–26%	Median EFS: 3.4–5.7 mo Median OS: 5.2–6.9 mo	[24,60,61]

Abbreviations: AZA, azacitidine; CR, complete remission; CRi, complete remission with incomplete count recovery; DEC, decitabine; EFS, event-free survival; mo, months; OS, overall survival. * defined as death occurring up to 60 days from start of therapy.

DEC is traditionally administered at 20 mg/m^2 on a 5-day schedule (DEC5), but may have improved activity when extended to a 10-day schedule (DEC10). A retrospective study by Welch, et al. reported a 100% CR/CRi rate with DEC10 for *mTP53*-AML in addition to robust, albeit incomplete, mutation clearance and survival rates that seemed to remit to those observed in intermediate-risk AML populations [59]. However, other studies of DEC10 have not duplicated that striking response rate, affirmed the minority of patients with mutation clearance, and comparative studies of DEC10 or DEC5 for *mTP53*-AML have reported no differences in response rates between the two groups [51,55–58]. The only randomized, prospective study comparing DEC10 to DEC5 reported a numerically higher rate of CR/CRi (47% vs. 29%, $p = 0.40$) and better median OS for patients with *mTP53*-AML treated with DEC10 (8.5 vs. 5.5 months, $p = 0.55$), however these differences were not statistically significant [62]. The risk of neutropenic fever and infection appeared to be higher in the DEC10 group [62]. It should be noted that the pre-treatment median *mTP53* VAF was higher in the DEC10 arm (50.3% vs. 23.1%) and specifically above the 40% "cut-off" that has been identified as being of prognostic significance in the previously mentioned retrospective analyses; similarly the median *mTP53* VAF of patients in the DEC5 arm was below the ascribed VAF with negative prognostic implications [25,55]. Given this shortcomings, the question whether or not DEC10 is more effective than DEC5 for *mTP53*-AML remains unanswered.

4.2. The Addition of Venetoclax

AML BCL-2 overexpression likely mediates apoptotic evasion and has been clinically associated with chemoresistance and ultimately poor survival [63,64]. Venetoclax, an oral, small molecule inhibitor of BCL-2 initially demonstrated robust leukemic cell kill in AML cell lines [65]. An initial non-comparative study of the combination of venetoclax with either AZA or DEC5 reported a CR rate of 37% (and CR/CRi rate of 67%) in the intention-to-treat population sufficient in 2018 to garner an FDA approval for the treatment of older or frail patients inappropriate for intensive therapy [10]. In sub-group analysis of patients with *mTP53*, the combination was associated with a CR/CRi rate of 47%, median duration of response of 5.6 months (95% CI: 1.2–9.4 months) and a median OS of 7.2 months (95% CI: 3.7 months-not reached) [10]. The subsequent confirmatory VIALE-A trial, which compared AZA monotherapy to AZA + venetoclax combination therapy in patients with newly diagnosed AML, demonstrated that AZA + venetoclax significantly prolonged the

median OS in older patients with AML (median age 76 years, range 49-91 years) when compared with azacitidine monotherapy (14.7 vs. 9.6 months, $p < 0.001$)(Table 2) [15].

The presence of *TP53* mutation predicts resistance, both primary and adaptive, to venetoclax-based therapy [60,66,67]. Although VIALE-A demonstrated a statistically-significant improved rate of CR/CRi with AZA + venetoclax combination therapy for *mTP53*-AML when compared with AZA monotherapy (55% vs. 0%, $p < 0.001$), an unplanned subgroup analysis of these 52 patients found no improvement in OS (HR = 0.76, 95% CI: 0.40–1.45) [15]. Retrospective analyses have also tempered enthusiasm for the addition of venetoclax to AZA for this specific patient population. Among patients with *mTP53*-AML and poor-risk cytogenetics, although associated with a higher rate of CR (20% vs. 11%), the addition of venetoclax to AZA does not appear to impact median OS (5.1 vs. 4.8 months). Recent real-world analyses have also demonstrated no survival advantage with venetoclax combination therapy over AZA monotherapy for patients with *mTP53*-AML and poor-risk cytogenetics, which are found in the majority of such patients, as previously discussed [68].

Given the equivocal "benefit" imparted by AZA + Ven for the treatment of *mTP53*-AML and the debate regarding the most favorable DEC monotherapy dosing schedule, the combination of DEC10 + venetoclax has been studied. A single-center, single-arm phase 2 trial of DEC10 + venetoclax in 118 patients, including 35 with *mTP53*-AML, reported 57% rate of CR/CRi among patients with *mTP53*-AML (vs. 77% for *TP53* wild-type disease, $p = 0.29$) with 29% being measurable residual disease (MRD)-negative by flow cytometric analysis (MFC) [24]. However, median remission duration and OS was only 3.5 months and 5.2 months, respectively [24]. Additionally, when compared with the historical rates reported with DEC10 monotherapy, and despite a higher CR/CRi rate, DEC10 + venetoclax offered no apparent improvement in rate of MRD-negativity, time to remission, RFS or OS (Table 2) [24,55]. However, similar to AZA or DEC5, it is unclear if the addition of venetoclax to DEC10 imparts any true benefit relating to the depth, duration of remission and consequently overall outcome.

5. Allogeneic Hematopoietic Stem Cell Transplantation

Patients with poor/adverse risk AML are generally recommended to be considered for alloHCT as part of their consolidation strategy [69]. The exceedingly poor outcomes overall observed for patients with *mTP53*-AML when paired with the non-trivial risks associated with alloHCT call into question the unequivocal recommendation for consolidative alloHCT for this specific disease subset. However, a high-quality appraisal of the benefit associated with alloHCT have been hampered by the relatively uncommon rate of *mTP53*-AML among all AML and concerns regarding equipoise in conducting a randomized trial.

Earlier retrospective studies have been limited by a small number of patients with *mTP53*-AML proceeding to alloHCT, lack of dedicated subset analyses or the use of imperfect surrogates for loss of *TP53* such as patients with chromosome 17p abnormalities [12,14,60,70,71]. Relatively large retrospective analyses of patients with disease harboring chromosome 17p abnormalities predicted to negatively impact *TP53* function and proceeding to alloHCT have informatively shown two- or three-year OS rates that are as low as 10–15% with nearly all relapses occurring within six months post-alloHCT [70,71]. Some studies specifically evaluating patients with *mTP53*-AML have shown favorable outcomes at one-year post-alloHCT [12,60]. Other studies with slightly longer follow-up have demonstrated two-year rates of survival that essentially approximate 0% [8,54]. Comparative analyses attempting to describe any potential benefit to alloHCT are likewise limited, but a multivariable analysis of a retrospective cohort of 174 patients with *mTP53*-AML found that patients able to proceed to alloHCT in first remission had more favorable OS than their non-transplanted counterparts (HR = 0.28, 95% CI: 0.15–0.53; $p = 0.001$) [27].

The largest retrospective study of *mTP53*-AML to date reported on 98 patients, 18 of whom (55%) underwent alloHCT [16]. A significant improvement in EFS was noted for patients undergoing alloHCT when compared with those undergoing only chemo-

consolidation or autologous stem cell transplantation (HR = 0.25, 95% CI: 0.11–0.58; $p = 0.001$) [16]. However, this is very likely confounded by selection bias. Although the poor median OS observed for patients with *mTP53*-AML may be attributed to the minority of patients proceeding to a seemingly definitive consolidative modality like alloHCT, post-alloHCT outcomes still remain poor. Retrospective studies offering more granular descriptions of *mTP53*-AML populations proceeding to alloHCT have still demonstrated a median EFS or progression-free (PFS) survival of 5.0–7.5 months, even in studies with most patients receiving myeloablative conditioning [14,72]. Post-alloHCT relapse of *mTP53*-AML appears to herald forthcoming death as EFS approximates OS in this circumstance at approximately 8–10 months [14,72]. Only 5–10% of patients are alive at two years post-alloHCT (Table 3) [14,60,73].

Table 3. Summary of experience with allogeneic hematopoietic stem cell transplantation for *TP53*-mutated acute myeloid leukemia.

Study	AlloHCT Period	N	Median Age (years)	Disease Risk	MAC	Outcomes	Reference
Najima, et al.	2005–2018	21	51 (R: 21–71)	86% complex KT 67% monosomal KT 62% *TP53* VAF >60%	70%	2-year OS: 9.5% 2-year CIR: 52% 2-year NRM: 38% Patients with *TP53* VAF >60% had worse 2-year OS than those with VAF ≤60% (0 vs. 25%; $p = 0.20$)	[73]
Ciurea, et al.	2011–2017	83	60 (R: 18–75)	99% "poor risk" cytogenetics	71%	Median PFS: 5 months Median OS: 8 months 1-year PFS: 25% (95% CI: 16–35%) 1-year NRM: 20% 1-year OS: 35% (95% CI: 25–46%) HCT-CI >4, KPS ≤80% and disease not in CR1/CR2 at time of alloHCT associated with inferior survival in multivariable analysis	[72]
Middeke, et al.	1996–2009	40	55 (R: 25–66)	49% complex KT 26% monosomal KT	30%	Median EFS: 7.5 months Median OS: 10.0 months CIR: 60% (95% CI: 44–76%) NRM: 33% (95% CI: 18–47%) 2-year OS: 5% Concurrent chromosome 17p abnormality predicted worse OS (8.0 vs. 13.3 months)	[14]

Abbreviations: AlloHCT, allogeneic hematopoietic stem cell transplantation; CIR, cumulative incidence of relapse; EFS, event-free survival; KT, karyotype; NRM, non-relapse mortality; MAC, myeloablative conditioning; OS, overall survival; PFS, progression-free survival; R, range; VAF, variant allele frequency.

The study of particular subgroups of patients within those diagnosed with *mTP53*-AML are likely to be important in identifying those truly benefitting from alloHCT. Patient-specific factors like age appear to impact the post-alloHCT outcomes of patients with *mTP53*-AML with some data suggesting a benefit with alloHCT for patient younger than 60 years at time of diagnosis [13,74]; one study reported no difference in outcomes for patients age ≥ 60 years and a striking difference in one-year OS based on this age cut-off (75% vs. 29%, $p = 0.012$), although the analysis was limited to 6 patients and may be confounded by selection bias [13]. Age, however, as previously-mentioned is likely just a reflection of fitness and comorbidity burden. A hematopoietic cell transplant-comorbidity index (HCT-CI) ≥ 4 and a Karnofsky Performance Status ≤ 80% at time of alloHCT predicts worse OS for patients with *mTP53*-AML [72]. These factors are also likely to influence the likelihood of a provider offering myeloablative conditioning, which is generally believed to increase the likelihood of cure [74,75]. Although studies with statistical comparisons are limited, patients with *mTP53*-AML clearly appear to have a higher rate of post-alloHCT relapse when compared with those receiving reduced-intensity/non-myeloablative conditioning [74]. This apparent difference needs to be rectified with the observed higher rate of alloHCT-related mortality [74].

Disease-specific features like cytogenetic status have been evaluated in this specific setting and appear to have prognostic impact. Post-alloHCT relapse rates among patients with *mTP53*-AML appear to be higher for those with poor-risk cytogenetics compared with those with intermediate cytogenetic risk [14,74]. *mTP53*-AML with complex karyotype predicts an inferior prognosis when compared with the absence of complex karyotype

($p = 0.04$), suggesting that patients with *mTP53*-AML and complex karyotype might not derive benefit from alloHCT; the presence of concurrent chromosome 17p abnormality, specifically, and thus likely bi-allelic loss, predicts worse post-alloHCT survival (8.0 vs. 13.3 months) [14,74]. Similarly indicative of bi-allelic *TP53* loss, patients with a pre-alloHCT *TP53* VAF > 60% are found to have a lesser chance at longer-term survival than their counterparts with a *TP53* VAF $\leq$ 60% (2-year OS 0% vs. 25%; $p = 0.20$)(Table 3) [73]. Overall, the benefit of alloHCT for patients with *mTP53*-AML appears to be modest at best, but some sub-populations may benefit.

6. Formulating a Treatment Plan

Patients with newly diagnosed AML with poor-risk features including t-AML are shown to have a lower likelihood of receiving leukemia-directed therapy and this appears to be irrespective of age [76–78]. As no evidence suggests that *mTP53*-AML is more likely to present with acute disease-related complications that preclude appropriate consideration for therapy, a perceived unfavorable risk:benefit of therapy for a nearly incurable, aggressive disease may be responsible.

Given the almost universal poor prognosis and limited data to support an unequivocal frontline therapy, we ultimately recommend that patients with newly-diagnosed *mTP53*-AML be treated in the context of a clinical trial.

6.1. Clinical Trials

Fortunately, an increasing understanding of the mechanisms of *TP53*-associated chemoresistance as well as the cellular and marrow microenvironment features with which *mTP53*-AML is associated has offered promise for more effective therapies.

APR-246 or eprenetapopt is a molecule theorized to restore p53 protein to its wild-type conformation and in ex vivo experiments was shown to abrogate the chemoresistance of *mTP53*-AML to conventional chemotherapies as well as upregulate p53 protein levels [79–81]. An intention-to-treat analysis of the patients with oligoblastic *mTP53*-AML studied in a phase 2 study of APR-246 + AZA combination therapy demonstrated a median OS of 10.8 months [82]. An updated analysis with median follow-up exceeding two years also found that patients achieving CR/partial remission (PR) with *TP53* mutational clearance prior to alloHCT had a median OS that was not reached [83]. A trial studying a triplet combination of APR-246 with AZA + venetoclax is ongoing (NCT04214860).

The targeting of CD47, or the transmembrane protein that interacts with macrophage-expressed signal-regulatory protein alpha, to increase macrophage-mediated phagocytosis of malignant cells has also shown promise for the treatment of *mTP53*-AML [84,85]. This is an enthusiastic area of clinical research as the surface of leukemic hematopoietic stem/progenitor cells (HSPCs) from primary AML patient blood and marrow samples overexpress CD47, thus promoting evasion from immunosurveillance, which in murine models is shown to be restored with anti-CD47 therapy [86–88]. The anti-CD47 monoclonal antibody magrolimab was associated with a favorable toxicity profile and a median OS of 12.9 months, the longest reported, in patients with *mTP53*-AML [89]. A phase 3 trial comparing magrolimab + AZA to AZA monotherapy (NCT04313881) as well as a phase 1b/2 trial of AZA + venetoclax + magrolimab triplet therapy (NCT04435691) are ongoing. Early results of the latter study demonstrate a 100% rate of CR/CRi in seven evaluable patients with newly-diagnosed *mTP53*-AML with a 57% rate of MFC-MRD-negativity; data the proportion of patients with *mTP53*-AML proceeding to alloHCT and long-term outcomes are eagerly awaited [90].

Other emerging therapies have provided optimism beyond mutant p53 protein refolding/reactivating or anti-CD47 therapies. The NEDD8-activating enzyme inhibitor pevonedistat led to four of five patients with newly-diagnosed *mTP53*-AML achieving CR/PR and a majority responding for >10 cycles at last follow-up [91]. Triplet therapy with pevonedistat and AZA + venetoclax led to CR/CRi/morphologic leukemia-free state in six out of eight patients (75%) with newly-diagnosed oligoblastic *mTP53*-AML, although

median OS at last data cutoff was only minimally better than that expected with current therapies at 8.9 months [27]. Furthermore, the *mTP53*-AML marrow immune microenvironment appears to be one in an immunosuppressive state. HSPCs and leukemic blasts isolated from patients with *mTP53*-AML are found to overexpress the negative immune checkpoint regulators PD-L1 and TIM-3, thus hampering the T-cell-mediated anti-AML response [92–97]. Indeed, the *mTP53*-AML marrow is characterized by lesser infiltration by CD8+ cytotoxic T-cells, natural killer cells and helper T-cells as well as an expansion of regulatory T-cells, which promotes immune evasion [97]. Anti-PD-L1 or anti-TIM-3 therapies, either as monotherapy or in combination with standard-of-care backbones, to modulate this immunosuppressive state have been studied in unselected patients with activity in *mTP53*-AML to be determined by unplanned subset analyses (NCT02775903, NCT04150029, NCT04266301, NCT03946670, NCT03066648 and NCT03940352). Newer preclinical data also demonstrate that the combined inhibition of BCL-2 as well as the anti-apoptotic BH3 protein MCL-1 may abrogate the resistance imparted by *TP53* mutations harbored by AML and thus support the development and study of dual BCL-2/MCL-1 inhibitor therapy for *mTP53*-AML [98]. A more granular discussion on these ongoing research efforts is beyond the scope of this review.

It is our hope that ongoing and emerging therapies eventually establish a more effective standard of care for these patients. However, if a clinical trial is not available, providers are left to devise a treatment plan using current standard therapies and interpret the nuances of the data supporting them.

6.2. Intensive vs. Less-Intensive Induction

The poor outcomes observed among patients with *mTP53*-AML may be irrespective of therapy intensity. There have been no prospective, randomized trials comparing intensive with non-intensive therapies for patients with *mTP53*-AML and thus it is only feasible to use indirect comparisons using historical data at present. As previously-discussed, older patients with *mTP53*-AML treated with classical induction therapy including CPX-351 are predicted to only have a CR/CRi rate of 30–40% and median OS of only about 6–7 months [6,11,33,99]. Less-intensive options such as HMA + venetoclax are associated with CR/CRi rates of about 55–65% in *mTP53*-AML and this favorably, although indirectly, compares with intensive therapy [10,15,61]. The largest retrospective analysis of patients with *mTP53*-AML (n = 174) recently demonstrated no difference in the survival between patients treated with AZA + Ven when compared with other therapies like CPX-351 or 7+3 as well as no difference between patients treated with CPX-351 vs. other therapies [27]. However, one recent multivariable analysis of 95 patients with *mTP53*-AML demonstrated that patients treated with CPX-351 fared better than those treated with AZA + venetoclax when evaluating relapse-free survival (RFS)(HR = 0.37, 95% CI: 0.14–0.96; $p = 0.04$) and OS (OR = 0.41, 95% CI: 0.22–0.74; $p = 0.003$) [100]. The authors duly note that the survival advantage attributed to CPX-351 may be confounded by bias including the higher rate of alloHCT in CPX-351-treated patients likely indicating these patients were more fit with less comorbidity.

The uncertainty in whether efficacy differs based on therapy intensity implores providers to consider whether differences in toxicity or quality of life (QoL) exist between these two approaches. Like the efficacy evaluation, the absence of prospective, comparative trials limits the strength of any conclusion regarding toxicity/QoL. Indirectly, the 3–7% 30-day mortality rate associated with HMA + venetoclax approximately in older patients compares favorably to the 6–11% associated with modern intensive induction in similar populations [10,15,31]. The toxicity profiles between the two modalities are slightly different, as venetoclax combination therapies are typically continuous and may be associated with more protracted myelosuppression when indirectly compared with cyclic, but finite intensive therapy. Although early mortality may be no different for patients treated with AZA + venetoclax and CPX-351, the rate of febrile neutropenia and microbiologically-proven infection as well as length of stay appear to be higher for patients

treated with CPX-351 [101]. QoL is another important consideration when evaluating the most appropriate remission induction therapy for a disease with a poor prognosis and therapies that are almost universally associated with at least some toxicity. Differences in QoL measures between patients treated intensively and with less-intensive therapies such as venetoclax combinations are lacking and cannot guide decision-making at the moment.

It is unclear if AZA + venetoclax represents a meaningful advance as patients with *mTP53*-AML garner only a 5–7 month median OS when treated with this therapy, illustrating the discordance between initial response and event-based outcomes for this subset of patients. Given the similarly poor OS observed for patients treated with AZA monotherapy and AZA + venetoclax therapy and the higher rate of protracted and deep myelosuppression associated with the latter, the older patient with *mTP53*-AML who is inappropriate to receive intensive therapy and alloHCT can be reasonably considered for HMA monotherapy. Deciding upon an induction strategy for the younger, intensive therapy appropriate patient may be more nuanced and requires accounting for the presence of concurrent high-risk features like concurrent monosomal/complex karyotype, *TP53* VAF or mono- vs. bi-allelic *TP53* loss as best predicted by current techniques. The more favorable survival observed for patients with *mTP53*-AML with *TP53* VAF $\leq$ 40% and without additional high-risk cytogenetic features [16,25,26] may warrant more consideration for intensive induction, perhaps favoring 7 + 3 over CPX-351, for the younger patient with such disease and who is appropriate to receive intensive therapy including alloHCT with myeloablative conditioning.

6.3. Allogeneic Hematopoietic Stem Cell Transplantation

Beyond remission induction, the benefits of alloHCT in the treatment of *mTP53*-AML, as previously discussed, remain unanswered. The previously discussed available data, albeit limited, might suggest that patients in first remission who are *able* to proceed to alloHCT should do so. This consolidative strategy should be more strongly considered for the younger patient without disease harboring complex karyotype or predicted bi-allelic *TP53* inactivation who can achieve MRD-negative remission and ultimately receive myeloablative conditioning. Patients with MFC-MRD positivity entering alloHCT may be accepting an exceedingly high rate of post-alloHCT relapse for the expected alloHCT-related mortality risk with reduced-intensity/non-myeloablative condition as opposed to myeloablative conditioning. However, the decision must always be individualized with appropriate patient input regarding goals of treatment/care after review of what is known of the current nature and treatment of this disease. Post-remission, less-intensive therapy to deepen the response for patients in CR or convert MRD-positive to MRD-negative disease prior to alloHCT may be considered, but is not a practice guided by strong evidence. The role of post-alloHCT maintenance therapy is similarly unknown. Prospective, randomized studies are needed and are fortunately being planned to answer these questions.

7. Conclusions

The management of *mTP53*-AML represents one of the most critical areas of need within myeloid oncology with a slim minority of patients likely cured of disease. Although intensive therapies have traditionally been the backbone of remission induction for AML including *mTP53*-AML, the advent of novel and targeted therapies have offered some promise in the ability to induce similar if not better rates of remission with lesser toxicity and treatment-related mortality. Despite this apparent progress, improvements in survival have not yet been realized. Additional novel therapies and perhaps combinations of novel agents with other novel agents are needed to help rectify the disconnect observed between improved rates of remission and prolonged survival for patients with *mTP53*-AML. For these reasons, we recommend frontline clinical trial for patients with newly-diagnosed *mTP53*-AML. The benefits of alloHCT in the management of *mTP53*-AML are unclear and require a more nuanced accounting for relevant covariates like allelic state, MRD status, conditioning intensity among others. For these reasons, dedicated clinical trials for patients

with *mTP53*-AML are needed and should be the preferred option for the newly diagnosed patient with this terrible disease.

Author Contributions: R.M.S., M.S., J.P.B., and A.M.Z. conceptualized and wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: The research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: A.M.Z. received research funding (institutional) from Celgene/BMS, Abbvie, Astex, Pfizer, Medimmune/AstraZeneca, Boehringer-Ingelheim, Trovagene, Incyte, Takeda, Novartis, Aprea, and ADC Therapeutics. A.M.Z participated in advisory boards, and/or had a consultancy with and received honoraria from AbbVie, Otsuka, Pfizer, Celgene/BMS, Jazz, Incyte, Agios, Boehringer-Ingelheim, Novartis, Acceleron, Astellas, Daiichi Sankyo, Cardinal Health, Taiho, Seattle Genetics, BeyondSpring, Trovagene, Takeda, Ionis, Amgen, Janssen, Epizyme, Syndax, and Tyme. A.M.Z received travel support for meetings from Pfizer, Novartis, and Trovagene. R.M.S. had equity ownership in Curis. None of these relationships were related to the development of this manuscript. All other others had no conflicts of interest to disclose.

References

1. Bykov, V.J.N.; Eriksson, S.E.; Bianchi, J.; Wiman, K.G. Targeting mutant p53 for efficient cancer therapy. *Nat. Rev. Cancer* **2018**, *18*, 89–102. [CrossRef] [PubMed]
2. Kandoth, C.; McLellan, M.D.; Vandin, F.; Ye, K.; Niu, B.; Lu, C.; Xie, M.; Zhang, Q.; McMichael, J.F.; Wyczalkowski, M.A.; et al. Mutational landscape and significance across 12 major cancer types. *Nature* **2013**, *502*, 333–339. [CrossRef]
3. Papaemmanuil, E.; Gerstung, M.; Bullinger, L.; Gaidzik, V.I.; Paschka, P.; Roberts, N.D.; Potter, N.E.; Heuser, M.; Thol, F.; Bolli, N.; et al. Genomic Classification and Prognosis in Acute Myeloid Leukemia. *N. Engl. J. Med.* **2016**, *374*, 2209–2221. [CrossRef]
4. The Cancer Genome Atlas Research Network; Ley, T.J.; Miller, C.; Ding, L.; Raphael, B.J.; Mungall, A.J.; Robertson, A.; Hoadley, K.; Triche, T.J., Jr.; Laird, P.W.; et al. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N. Engl. J. Med.* **2013**, *368*, 2059–2074. [CrossRef]
5. Lindsley, R.C.; Mar, B.G.; Mazzola, E.; Grauman, P.V.; Shareef, S.; Allen, S.L.; Pigneux, A.; Wetzler, M.; Stuart, R.K.; Erba, H.P.; et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. *Blood* **2015**, *125*, 1367–1376. [CrossRef] [PubMed]
6. Lindsley, R.C.; Gibson, C.J.; Murdock, H.M.; Stone, R.M.; Cortes, J.E.; Uy, G.L.; Lin, T.L.; Ritchie, E.K.; Prebet, T.; Ryan, R.J.; et al. Genetic Characteristics and Outcomes By Mutation Status in a Phase 3 Study of CPX-351 Versus 7+3 in Older Adults with Newly Diagnosed, High-Risk/Secondary Acute Myeloid Leukemia (AML). *Blood* **2019**, *134*, 15. [CrossRef]
7. Wong, T.N.; Ramsingh, G.; Young, A.L.; Miller, C.A.; Touma, W.; Welch, J.S.; Lamprecht, T.L.; Shen, D.; Hundal, J.; Fulton, R.S.; et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. *Nature* **2015**, *518*, 552–555. [CrossRef] [PubMed]
8. Bowen, D.; Groves, M.J.; Burnett, A.K.; Patel, Y.; Allen, C.; Green, C.; Gale, R.E.; Hills, R.; Linch, D.C. TP53 gene mutation is frequent in patients with acute myeloid leukemia and complex karyotype, and is associated with very poor prognosis. *Leukemia* **2009**, *23*, 203–206. [CrossRef] [PubMed]
9. Itzykson, R.A.; Fournier, E.; Berthon, C.; Rollig, C.; Braun, T.; Marceau-Renaut, A.; Pautas, C.; Nibourel, O.; Lemasle, E.; Micol, J.B.; et al. Genetic Identification of AML Patients Older than 60 years Achieving Long-term Survival with Intensive Chemotherapy. *Blood* **2021**, *138*, 507–519. [CrossRef]
10. DiNardo, C.D.; Pratz, K.; Pullarkat, V.; Jonas, B.A.; Arellano, M.; Becker, P.S.; Frankfurt, O.; Konopleva, M.; Wei, A.H.; Kantarjian, H.M.; et al. Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. *Blood* **2019**, *133*, 7–17. [CrossRef] [PubMed]
11. Goldberg, A.D.; Talati, C.; Desai, P.; Famulare, C.; Devlin, S.M.; Farnoud, N.; Sallman, D.A.; Lancet, J.E.; Roboz, G.J.; Sweet, K.L.; et al. TP53 Mutations Predict Poorer Responses to CPX-351 in Acute Myeloid Leukemia. *Blood* **2018**, *132*, 1433. [CrossRef]
12. Bewersdorf, J.P.; Shallis, R.M.; Gowda, L.; Wei, W.; Hager, K.; Isufi, I.; Kim, T.K.; Pillai, M.M.; Seropian, S.; Podoltsev, N.A.; et al. Clinical outcomes and characteristics of patients with TP53-mutated acute myeloid leukemia or myelodysplastic syndromes: A single center experience. *Leuk. Lymphoma* **2020**, *61*, 2180–2190. [CrossRef] [PubMed]
13. Kadia, T.M.; Jain, P.; Ravandi, F.; Garcia-Manero, G.; Andreef, M.; Takahashi, K.; Borthakur, G.; Jabbour, E.; Konopleva, M.; Daver, N.G.; et al. TP53 mutations in newly diagnosed acute myeloid leukemia: Clinicomolecular characteristics, response to therapy, and outcomes. *Cancer* **2016**, *122*, 3484–3491. [CrossRef] [PubMed]

14. Middeke, J.M.; Herold, S.; Rucker-Braun, E.; Berdel, W.E.; Stelljes, M.; Kaufmann, M.; Schafer-Eckart, K.; Baldus, C.D.; Stuhlmann, R.; Ho, A.D.; et al. TP53 mutation in patients with high-risk acute myeloid leukaemia treated with allogeneic haematopoietic stem cell transplantation. *Br. J. Haematol.* **2016**, *172*, 914–922. [CrossRef]
15. DiNardo, C.D.; Jonas, B.A.; Pullarkat, V.; Thirman, M.J.; Garcia, J.S.; Wei, A.H.; Konopleva, M.; Dohner, H.; Letai, A.; Fenaux, P.; et al. Azacitidine and Venetoclax in Previously Untreated Acute Myeloid Leukemia. *N. Engl. J. Med.* **2020**, *383*, 617–629. [CrossRef]
16. Prochazka, K.T.; Pregartner, G.; Rucker, F.G.; Heitzer, E.; Pabst, G.; Wolfler, A.; Zebisch, A.; Berghold, A.; Dohner, K.; Sill, H. Clinical implications of subclonal TP53 mutations in acute myeloid leukemia. *Haematologica* **2019**, *104*, 516–523. [CrossRef] [PubMed]
17. Rucker, F.G.; Schlenk, R.F.; Bullinger, L.; Kayser, S.; Teleanu, V.; Kett, H.; Habdank, M.; Kugler, C.M.; Holzmann, K.; Gaidzik, V.I.; 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*, 2114–2121. [CrossRef] [PubMed]
18. Ok, C.Y.; Patel, K.P.; Garcia-Manero, G.; Routbort, M.J.; Fu, B.; Tang, G.; Goswami, M.; Singh, R.; Kanagal-Shamanna, R.; Pierce, S.A.; et al. Mutational profiling of therapy-related myelodysplastic syndromes and acute myeloid leukemia by next generation sequencing, a comparison with de novo diseases. *Leuk. Res.* **2015**, *39*, 348–354. [CrossRef] [PubMed]
19. Schoch, C.; Kern, W.; Schnittger, S.; Hiddemann, W.; Haferlach, T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): An analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. *Leukemia* **2004**, *18*, 120–125. [CrossRef] [PubMed]
20. Pedersen-Bjergaard, J.; Andersen, M.K.; Andersen, M.T.; Christiansen, D.H. Genetics of therapy-related myelodysplasia and acute myeloid leukemia. *Leukemia* **2008**, *22*, 240–248. [CrossRef]
21. Kayser, S.; Dohner, K.; Krauter, J.; Kohne, C.H.; Horst, H.A.; Held, G.; von Lilienfeld-Toal, M.; Wilhelm, S.; Kundgen, A.; Gotze, K.; et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. *Blood* **2011**, *117*, 2137–2145. [CrossRef]
22. 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 Chromosom. Cancer* **2005**, *43*, 227–238. [CrossRef]
23. Leung, G.M.K.; Zhang, C.; Ng, N.K.L.; Yang, N.; Lam, S.S.Y.; Au, C.H.; Chan, T.L.; Ma, E.S.K.; Tsui, S.P.; Ip, H.W.; et al. Distinct mutation spectrum, clinical outcome and therapeutic responses of typical complex/monosomy karyotype acute myeloid leukemia carrying TP53 mutations. *Am. J. Hematol.* **2019**, *94*, 650–657. [CrossRef]
24. Kim, K.; Maiti, A.; Loghavi, S.; Pourebrahim, R.; Kadia, T.M.; Rausch, C.R.; Furudate, K.; Daver, N.G.; Alvarado, Y.; Ohanian, M.; et al. Outcomes of TP53-mutant acute myeloid leukemia with decitabine and venetoclax. *Cancer* **2021**, *127*, 3772–3781. [CrossRef]
25. Short, N.J.; Montalban-Bravo, G.; Hwang, H.; Ning, J.; Franquiz, M.J.; Kanagal-Shamanna, R.; Patel, K.P.; DiNardo, C.D.; Ravandi, F.; Garcia-Manero, G.; et al. Prognostic and therapeutic impacts of mutant TP53 variant allelic frequency in newly diagnosed acute myeloid leukemia. *Blood Adv.* **2020**, *4*, 5681–5689. [CrossRef]
26. Venugopal, S.; Shoukier, M.; Konopleva, M.; Dinardo, C.D.; Ravandi, F.; Short, N.J.; Andreeff, M.; Borthakur, G.; Daver, N.; Pemmaraju, N.; et al. Outcomes in patients with newly diagnosed TP53-mutated acute myeloid leukemia with or without venetoclax-based therapy. *Cancer* **2021**, *127*, 3541–3551. [CrossRef]
27. Short, N.J.; Montalban-Bravo, G.; Alvarado, Y.; Konopleva, M.; Jabbour, E.J.; Garcia-Manero, G.; Yilmaz, M.; Jain, N.; Borthakur, G.; DiNardo, C.D.; et al. Azacitidine, Venetoclax and Pevonedistat As Frontline Therapy for Patients with Secondary Acute Myeloid Leukemia Who Are Unfit for Intensive Chemotherapy: Results from a Phase I/II Study. In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.
28. Bernard, E.; Nannya, Y.; Hasserjian, R.P.; Devlin, S.M.; Tuechler, H.; Medina-Martinez, J.S.; Yoshizato, T.; Shiozawa, Y.; Saiki, R.; Malcovati, L.; et al. Implications of TP53 allelic state for genome stability, clinical presentation and outcomes in myelodysplastic syndromes. *Nat. Med.* **2020**, *26*, 1549–1556. [CrossRef]
29. Sasaki, K.; Kanagal-Shamanna, R.; Montalban-Bravo, G.; Assi, R.; Jabbour, E.; Ravandi, F.; Kadia, T.; Pierce, S.; Takahashi, K.; Nogueras Gonzalez, G.; et al. Impact of the variant allele frequency of ASXL1, DNMT3A, JAK2, TET2, TP53, and NPM1 on the outcomes of patients with newly diagnosed acute myeloid leukemia. *Cancer* **2020**, *126*, 765–774. [CrossRef]
30. Hou, H.A.; Chou, W.C.; Kuo, Y.Y.; Liu, C.Y.; Lin, L.I.; Tseng, M.H.; Chiang, Y.C.; Liu, M.C.; Liu, C.W.; Tang, J.L.; et al. TP53 mutations in de novo acute myeloid leukemia patients: Longitudinal follow-ups show the mutation is stable during disease evolution. *Blood Cancer J.* **2015**, *5*, e331. [CrossRef]
31. Lancet, J.E.; Uy, G.L.; Cortes, J.E.; Newell, L.F.; Lin, T.L.; Ritchie, E.K.; Stuart, R.K.; Strickland, S.A.; Hogge, D.; Solomon, S.R.; 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*, 2684–2692. [CrossRef]
32. Madarang, E.; Lykon, J.; Nguyen, N.; Watts, J.M.; Bradley, T.J.; Chandhok, N.S. Real World Outcomes of Liposomal Daunorubicin and Cytarabine Versus 7+3 in Patients with Secondary Acute Myeloid Leukemia. *Blood* **2020**, *136*, 5–6. [CrossRef]
33. Chiche, E.; Rahme, R.; Bertoli, S.; Dumas, P.Y.; Micol, J.B.; Hicheri, Y.; Pasquier, F.; Peterlin, P.; Chevallier, P.; Thomas, X.; et al. Real-life experience with CPX-351 and impact on the outcome of high-risk AML patients: A multicentric French cohort. *Blood Adv.* **2021**, *5*, 176–184. [CrossRef]

34. Zeidan, A.M.; Podoltsev, N.A.; Wang, X.; Zhang, C.; Bewersdorf, J.P.; Shallis, R.M.; Huntington, S.F.; Neparidze, N.; Giri, S.; Gore, S.D.; et al. Patterns of care and clinical outcomes with cytarabine-anthracycline induction chemotherapy for AML patients in the United States. *Blood Adv.* **2020**, *4*, 1615–1623. [CrossRef]
35. Kantarjian, H.; Ravandi, F.; O'Brien, S.; Cortes, J.; Faderl, S.; Garcia-Manero, G.; Jabbour, E.; Wierda, W.; Kadia, T.; Pierce, S.; et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood* **2010**, *116*, 4422–4429. [CrossRef]
36. Kantarjian, H.; O'Brien, S.; Cortes, J.; Giles, F.; Faderl, S.; Jabbour, E.; Garcia-Manero, G.; Wierda, W.; Pierce, S.; Shan, J.; et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: Predictive prognostic models for outcome. *Cancer* **2006**, *106*, 1090–1098. [CrossRef]
37. Klepin, H.D.; Geiger, A.M.; Tooze, J.A.; Kritchevsky, S.B.; Williamson, J.D.; Pardee, T.S.; Ellis, L.R.; Powell, B.L. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* **2013**, *121*, 4287–4294. [CrossRef]
38. Lowenberg, B.; Ossenkoppele, G.J.; van Putten, W.; Schouten, H.C.; Graux, C.; Ferrant, A.; Sonneveld, P.; Maertens, J.; Jongen-Lavrencic, M.; von Lilienfeld-Toal, M.; et al. High-dose daunorubicin in older patients with acute myeloid leukemia. *N. Engl. J. Med.* **2009**, *361*, 1235–1248. [CrossRef]
39. Burnett, A.K.; Milligan, D.; Goldstone, A.; Prentice, A.; McMullin, M.F.; Dennis, M.; Sellwood, E.; Pallis, M.; Russell, N.; Hills, R.K.; et al. The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: The results of the LRF AML14 trial. *Br. J. Haematol.* **2009**, *145*, 318–332. [CrossRef]
40. Goldstone, A.H.; Burnett, A.K.; Wheatley, K.; Smith, A.G.; Hutchinson, R.M.; Clark, R.E.; Medical Research Council Adult Leukemia Working Party. Attempts to improve treatment outcomes in acute myeloid leukemia (AML) in older patients: The results of the United Kingdom Medical Research Council AML11 trial. *Blood* **2001**, *98*, 1302–1311. [CrossRef]
41. Buchner, T.; Berdel, W.E.; Haferlach, C.; Haferlach, T.; Schnittger, S.; Muller-Tidow, C.; Braess, J.; Spiekermann, K.; Kienast, J.; Staib, P.; et al. Age-related risk profile and chemotherapy dose response in acute myeloid leukemia: A study by the German Acute Myeloid Leukemia Cooperative Group. *J. Clin. Oncol.* **2009**, *27*, 61–69. [CrossRef]
42. Shallis, R.M.; Boddu, P.C.; Bewersdorf, J.P.; Zeidan, A.M. The golden age for patients in their golden years: The progressive upheaval of age and the treatment of newly-diagnosed acute myeloid leukemia. *Blood Rev.* **2020**, *40*, 100639. [CrossRef]
43. Shallis, R.M.; Wang, R.; Davidoff, A.; Ma, X.; Zeidan, A.M. Epidemiology of acute myeloid leukemia: Recent progress and enduring challenges. *Blood Rev.* **2019**, *36*, 70–87. [CrossRef] [PubMed]
44. Juliusson, G. Older patients with acute myeloid leukemia benefit from intensive chemotherapy: An update from the Swedish Acute Leukemia Registry. *Clin. Lymphoma Myeloma Leuk.* **2011**, *11* (Suppl. S1), S54–S59. [CrossRef]
45. Juliusson, G.; Antunovic, P.; Derolf, A.; Lehmann, S.; Mollgard, L.; Stockelberg, D.; Tidefelt, U.; Wahlin, A.; Hoglund, M. Age and acute myeloid leukemia: Real world data on decision to treat and outcomes from the Swedish Acute Leukemia Registry. *Blood* **2009**, *113*, 4179–4187. [CrossRef]
46. Walter, R.B.; Othus, M.; Borthakur, G.; Ravandi, F.; Cortes, J.E.; Pierce, S.A.; Appelbaum, F.R.; Kantarjian, H.A.; Estey, E.H. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: A novel paradigm for treatment assignment. *J. Clin. Oncol.* **2011**, *29*, 4417–4423. [CrossRef]
47. Appelbaum, F.R.; Gundacker, H.; Head, D.R.; Slovak, M.L.; Willman, C.L.; Godwin, J.E.; Anderson, J.E.; Petersdorf, S.H. Age and acute myeloid leukemia. *Blood* **2006**, *107*, 3481–3485. [CrossRef] [PubMed]
48. Oran, B.; Weisdorf, D.J. Survival for older patients with acute myeloid leukemia: A population-based study. *Haematologica* **2012**, *97*, 1916–1924. [CrossRef] [PubMed]
49. Fenaux, P.; Mufti, G.J.; Hellstrom-Lindberg, E.; Santini, V.; Gattermann, N.; Germing, U.; Sanz, G.; List, A.F.; Gore, S.; Seymour, J.F.; 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*, 562–569. [CrossRef]
50. Dombret, H.; Seymour, J.F.; Butrym, A.; Wierzbowska, A.; Selleslag, D.; Jang, J.H.; Kumar, R.; Cavenagh, J.; Schuh, A.C.; Candoni, A.; 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*, 291–299. [CrossRef]
51. Kantarjian, H.M.; Thomas, X.G.; Dmoszynska, A.; Wierzbowska, A.; Mazur, G.; Mayer, J.; Gau, J.P.; Chou, W.C.; Buckstein, R.; Cermak, 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*, 2670–2677. [CrossRef] [PubMed]
52. Zeidan, A.M.; Wang, R.; Wang, X.; Shallis, R.M.; Podoltsev, N.A.; Bewersdorf, J.P.; Huntington, S.F.; Neparidze, N.; Giri, S.; Gore, S.D.; et al. Clinical outcomes of older patients with AML receiving hypomethylating agents: A large population-based study in the United States. *Blood Adv.* **2020**, *4*, 2192–2201. [CrossRef] [PubMed]
53. Zeidan, A.M.; Fenaux, P.; Gobbi, M.; Mayer, J.; Roboz, G.J.; Krauter, J.; Robak, T.; Kantarjian, H.M.; Novak, J.; Jedrzejczak, W.W.; et al. Comparative results of azacitidine and decitabine from a large prospective phase 3 study in treatment naive acute myeloid leukemia (TN-AML) not eligible for intensive therapy. In Proceedings of the European Hematology Association 2020 Meeting, Hamburg, Germany, 11–14 June 2020.

54. Dohner, H.; Dolnik, A.; Tang, L.; Seymour, J.F.; Minden, M.D.; Stone, R.M.; Del Castillo, T.B.; Al-Ali, H.K.; Santini, V.; Vyas, P.; et al. Cytogenetics and gene mutations influence survival in older patients with acute myeloid leukemia treated with azacitidine or conventional care. *Leukemia* **2018**, *32*, 2546–2557. [CrossRef]
55. Short, N.J.; Kantarjian, H.M.; Loghavi, S.; Huang, X.; Qiao, W.; Borthakur, G.; Kadia, T.M.; Daver, N.; Ohanian, M.; Dinardo, C.D.; et al. Treatment with a 5-day versus a 10-day schedule of decitabine in older patients with newly diagnosed acute myeloid leukaemia: A randomised phase 2 trial. *Lancet Haematol.* **2019**, *6*, e29–e37. [CrossRef]
56. Boddu, P.; Kantarjian, H.; Ravandi, F.; Garcia-Manero, G.; Borthakur, G.; Andreeff, M.; Jabbour, E.J.; Benton, C.B.; DiNardo, C.D.; Konopleva, M.; et al. Outcomes with lower intensity therapy in TP53-mutated acute myeloid leukemia. *Leuk. Lymphoma.* **2018**, *59*, 2238–2241. [CrossRef] [PubMed]
57. Cashen, A.F.; Schiller, G.J.; O'Donnell, M.R.; DiPersio, J.F. Multicenter, phase II study of decitabine for the first-line treatment of older patients with acute myeloid leukemia. *J. Clin. Oncol.* **2010**, *28*, 556–561. [CrossRef] [PubMed]
58. Blum, W.; Garzon, R.; Klisovic, R.B.; Schwind, S.; Walker, A.; Geyer, S.; Liu, S.; Havelange, V.; Becker, H.; Schaaf, L.; 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. USA* **2010**, *107*, 7473–7478. [CrossRef] [PubMed]
59. Welch, J.S.; Petti, A.A.; Miller, C.A.; Fronick, C.C.; O'Laughlin, M.; Fulton, R.S.; Wilson, R.K.; Baty, J.D.; Duncavage, E.J.; Tandon, B.; et al. TP53 and Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndromes. *N. Engl. J. Med.* **2016**, *375*, 2023–2036. [CrossRef] [PubMed]
60. Aldoss, I.; Zhang, J.; Pillai, R.; Shouse, G.; Sanchez, J.F.; Mei, M.; Nakamura, R.; Stein, A.S.; Forman, S.J.; Marcucci, G.; et al. Venetoclax and hypomethylating agents in TP53-mutated acute myeloid leukaemia. *Br. J. Haematol.* **2019**, *187*, e45–e48. [CrossRef]
61. DiNardo, C.D.; Maiti, A.; Rausch, C.R.; Pemmaraju, N.; Naqvi, K.; Daver, N.G.; Kadia, T.M.; Borthakur, G.; Ohanian, M.; Alvarado, Y.; et al. 10-day decitabine with venetoclax for newly diagnosed intensive chemotherapy ineligible, and relapsed or refractory acute myeloid leukaemia: A single-centre, phase 2 trial. *Lancet Haematol.* **2020**, *7*, e724–e736. [CrossRef]
62. Short, N.J.; Kantarjian, H.M.; Loghavi, S.; Huang, X.; Qiao, W.; Borthakur, G.; Kadia, T.M.; Daver, N.G.; Ohanian, M.N.; DiNardo, C.D.; et al. Five-Day Versus Ten-Day Schedules of Decitabine in Older Patients with Newly Diagnosed Acute Myeloid Leukemia: Results of a Randomized Phase II Study. *Blood* **2018**, *132*, 84. [CrossRef]
63. Lauria, F.; Raspadori, D.; Rondelli, D.; Ventura, M.A.; Fiacchini, M.; Visani, G.; Forconi, F.; Tura, S. High bcl-2 expression in acute myeloid leukemia cells correlates with CD34 positivity and complete remission rate. *Leukemia* **1997**, *11*, 2075–2078. [CrossRef]
64. Del Poeta, G.; Venditti, A.; Del Principe, M.I.; Maurillo, L.; Buccisano, F.; Tamburini, A.; Cox, M.C.; Franchi, A.; Bruno, A.; Mazzone, C.; et al. Amount of spontaneous apoptosis detected by Bax/Bcl-2 ratio predicts outcome in acute myeloid leukemia (AML). *Blood* **2003**, *101*, 2125–2131. [CrossRef]
65. Pan, R.; Hogdal, L.J.; Benito, J.M.; Bucci, D.; Han, L.; Borthakur, G.; Cortes, J.; DeAngelo, D.J.; Debose, L.; Mu, H.; et al. Selective BCL-2 inhibition by ABT-199 causes on-target cell death in acute myeloid leukemia. *Cancer Discov.* **2014**, *4*, 362–375. [CrossRef]
66. DiNardo, C.D.; Tiong, I.S.; Quaglieri, A.; MacRaild, S.; Loghavi, S.; Brown, F.C.; Thijssen, R.; Pomilio, G.; Ivey, A.; Salmon, J.M.; et al. Molecular patterns of response and treatment failure after frontline venetoclax combinations in older patients with AML. *Blood* **2020**, *135*, 791–803. [CrossRef]
67. Nechiporuk, T.; Kurtz, S.E.; Nikolova, O.; Liu, T.; Jones, C.L.; D'Alessandro, A.; Culp-Hill, R.; d'Almeida, A.; Joshi, S.K.; Rosenberg, M.; et al. The TP53 Apoptotic Network Is a Primary Mediator of Resistance to BCL2 Inhibition in AML Cells. *Cancer Discov.* **2019**, *9*, 910–925. [CrossRef]
68. Pollyea, D.A.; Pratz, K.W.; Wei, A.H.; Pullarkat, V.A.; Jonas, B.A.; Recher, C.; Babu, S.; Schuh, A.C.; Dail, M.; Sun, Y.; et al. Outcomes in Patients with Poor-Risk Cytogenetics with or without TP53 Mutations Treated with Venetoclax Combined with Hypomethylating Agents. In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.
69. Tallman, M.S.; Altman, J.K.; Appelbaum, F.R.; Bhatt, V.R.; Bixby, D.; De Lima, M. Acute Myeloid Leukemia, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.* **2021**. Available online: https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (accessed on 4 October 2021).
70. Middeke, J.M.; Beelen, D.; Stadler, M.; Gohring, G.; Schlegelberger, B.; Baurmann, H.; Bug, G.; Bellos, F.; Mohr, B.; Buchholz, S.; et al. Outcome of high-risk acute myeloid leukemia after allogeneic hematopoietic cell transplantation: Negative impact of abnl(17p) and -5/5q. *Blood* **2012**, *120*, 2521–2528. [CrossRef] [PubMed]
71. Middeke, J.M.; Fang, M.; Cornelissen, J.J.; Mohr, B.; Appelbaum, F.R.; Stadler, M.; Sanz, J.; Baurmann, H.; Bug, G.; Schafer-Eckart, K.; et al. Outcome of patients with abnl(17p) acute myeloid leukemia after allogeneic hematopoietic stem cell transplantation. *Blood* **2014**, *123*, 2960–2967. [CrossRef]
72. Ciurea, S.O.; Chilkulwar, A.; Saliba, R.M.; Chen, J.; Rondon, G.; Patel, K.P.; Khogeer, H.; Shah, A.R.; Randolph, B.V.; Perez, J.M.R.; et al. Prognostic factors influencing survival after allogeneic transplantation for AML/MDS patients with TP53 mutations. *Blood* **2018**, *131*, 2989–2992. [CrossRef] [PubMed]
73. Najima, Y.; Sadato, D.; Harada, Y.; Oboki, K.; Hirama, C.; Toya, T.; Doki, N.; Haraguchi, K.; Yoshifuji, K.; Akiyama, M.; et al. Prognostic impact of TP53 mutation, monosomal karyotype, and prior myeloid disorder in nonremission acute myeloid leukemia at allo-HSCT. *Bone Marrow Transplant.* **2021**, *56*, 334–346. [CrossRef]
74. Hourigan, C.S.; Dillon, L.W.; Gui, G.; Logan, B.R.; Fei, M.; Ghannam, J.; Li, Y.; Licon, A.; Alyea, E.P.; Bashey, A.; et al. Impact of Conditioning Intensity of Allogeneic Transplantation for Acute Myeloid Leukemia With Genomic Evidence of Residual Disease. *J. Clin. Oncol.* **2020**, *38*, 1273–1283. [CrossRef] [PubMed]

75. Scott, B.L.; Pasquini, M.C.; Logan, B.R.; Wu, J.; Devine, S.M.; Porter, D.L.; Maziarz, R.T.; Warlick, E.D.; Fernandez, H.F.; Alyea, E.P.; et al. Myeloablative Versus Reduced-Intensity Hematopoietic Cell Transplantation for Acute Myeloid Leukemia and Myelodysplastic Syndromes. *J. Clin. Oncol.* **2017**, *35*, 1154–1161. [CrossRef]
76. Bhatt, V.R.; Shostrom, V.; Gundabolu, K.; Armitage, J.O. Utilization of initial chemotherapy for newly diagnosed acute myeloid leukemia in the United States. *Blood Adv.* **2018**, *2*, 1277–1282. [CrossRef]
77. Leone, G.; Mele, L.; Pulsoni, A.; Equitani, F.; Pagano, L. The incidence of secondary leukemias. *Haematologica* **1999**, *84*, 937–945. [PubMed]
78. Yi, C.Y.A.; Kantarjian, H.M.; Garcia-Manero, G.; Wierda, W.G.; Borthakur, G.; Quintas-Cardama, A.; Konopleva, M.; Faderl, S.; Pierce RN, S.A.; Andreef, M.; et al. Comparing Outcomes of Patients with Secondary AML: Treatment-Related MDS/AML, AML Secondary to Myeloproliferative Neoplasms (t-MPN), and AML with Prior Malignancies. *Blood* **2012**, *120*, 3557.
79. Ali, D.; Jonsson-Videsater, K.; Deneberg, S.; Bengtzen, S.; Nahi, H.; Paul, C.; Lehmann, S. APR-246 exhibits anti-leukemic activity and synergism with conventional chemotherapeutic drugs in acute myeloid leukemia cells. *Eur J. Haematol.* **2011**, *86*, 206–215. [CrossRef] [PubMed]
80. Maslah, N.; Salomao, N.; Drevon, L.; Verger, E.; Partouche, N.; Ly, P.; Aubin, P.; Naoui, N.; Schlageter, M.H.; Bally, C.; et al. Synergistic effects of PRIMA-1(Met) (APR-246) and 5-azacitidine in TP53-mutated myelodysplastic syndromes and acute myeloid leukemia. *Haematologica* **2020**, *105*, 1539–1551. [CrossRef]
81. Zhang, Q.; Bykov, V.J.N.; Wiman, K.G.; Zawacka-Pankau, J. APR-246 reactivates mutant p53 by targeting cysteines 124 and 277. *Cell Death Dis.* **2018**, *9*, 439. [CrossRef] [PubMed]
82. Sallman, D.A.; DeZern, A.E.; Garcia-Manero, G.; Steensma, D.P.; Roboz, G.J.; Sekeres, M.A.; Cluzeau, T.; Sweet, K.L.; McLemore, A.; McGraw, K.L.; et al. Eprenetapopt (APR-246) and Azacitidine in TP53-Mutant Myelodysplastic Syndromes. *J. Clin. Oncol.* **2021**, *39*, 1584–1594. [CrossRef]
83. Sallman, D.A.; Komrokji, R.S.; DeZern, A.E.; Sebert, M.; Garcia-Manero, G.; Rahmé, R.; Steensma, D.P.; Che, J.L.; Roboz, G.J.; Madelaine, I.; et al. Long Term Follow-up and Combined Phase 2 Results of Eprenetapopt (APR-246) and Azacitidine (AZA) in Patients with TP53 mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML). In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.
84. Kim, D.; Wang, J.; Willingham, S.B.; Martin, R.; Wernig, G.; Weissman, I.L. Anti-CD47 antibodies promote phagocytosis and inhibit the growth of human myeloma cells. *Leukemia* **2012**, *26*, 2538–2545. [CrossRef]
85. Theocharides, A.P.; Jin, L.; Cheng, P.Y.; Prasolava, T.K.; Malko, A.V.; Ho, J.M.; Poeppl, A.G.; van Rooijen, N.; Minden, M.D.; Danska, J.S.; et al. Disruption of SIRPalpha signaling in macrophages eliminates human acute myeloid leukemia stem cells in xenografts. *J. Exp. Med.* **2012**, *209*, 1883–1899. [CrossRef]
86. Jaiswal, S.; Jamieson, C.H.; Pang, W.W.; Park, C.Y.; Chao, M.P.; Majeti, R.; Traver, D.; van Rooijen, N.; Weissman, I.L. CD47 is upregulated on circulating hematopoietic stem cells and leukemia cells to avoid phagocytosis. *Cell* **2009**, *138*, 271–285. [CrossRef] [PubMed]
87. Majeti, R.; Chao, M.P.; Alizadeh, A.A.; Pang, W.W.; Jaiswal, S.; Gibbs, K.D., Jr.; van Rooijen, N.; Weissman, I.L. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell* **2009**, *138*, 286–299. [CrossRef] [PubMed]
88. Wang, C.; Sun, C.; Li, M.; Xia, B.; Wang, Y.; Zhang, L.; Zhang, Y.; Wang, J.; Sun, F.; Lu, S.; et al. Novel fully human anti-CD47 antibodies stimulate phagocytosis and promote elimination of AML cells. *J. Cell Physiol* **2020**, *236*, 4470–4481. [CrossRef] [PubMed]
89. Sallman, D.A.; Asch, A.S.; Al Malki, M.M.; Lee, D.J.; Donnellan, W.B.; Marcucci, G.; Kambhampati, S.; Daver, N.G.; Garcia-Manero, G.; Komrokji, R.S.; et al. The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination with Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results. *Blood* **2019**, *134*, 569. [CrossRef]
90. Daver, N.; Konopleva, M.; Maiti, A.; Kadia, T.M.; DiNardo, C.D.; Loghavi, S.; Pemmaraju, N.; Jabbour, E.J.; Montalban-Bravo, G.; Tang, G.; et al. Phase I/II Study of Azacitidine (AZA) with Venetoclax (VEN) and Magrolimab (Magro) in Patients (pts) with Newly Diagnosed Older/Unfit or High-Risk Acute Myeloid Leukemia (AML) and Relapsed/Refractory (R/R) AML. In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.
91. Swords, R.T.; Coutre, S.; Maris, M.B.; Zeidner, J.F.; Foran, J.M.; Cruz, J.; Erba, H.P.; Berdeja, J.G.; Tam, W.; Vardhanabhuti, S.; et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood* **2018**, *131*, 1415–1424. [CrossRef]
92. Asayama, T.; Tamura, H.; Ishibashi, M.; Kuribayashi-Hamada, Y.; Onodera-Kondo, A.; Okuyama, N.; Yamada, A.; Shimizu, M.; Moriya, K.; Takahashi, H.; et al. Functional expression of Tim-3 on blasts and clinical impact of its ligand galectin-9 in myelodysplastic syndromes. *Oncotarget* **2017**, *8*, 88904–88917. [CrossRef]
93. Kikushige, Y.; Miyamoto, T.; Yuda, J.; Jabbarzadeh-Tabrizi, S.; Shima, T.; Takayanagi, S.; Niiro, H.; Yurino, A.; Miyawaki, K.; Takenaka, K.; et al. A TIM-3/Gal-9 Autocrine Stimulatory Loop Drives Self-Renewal of Human Myeloid Leukemia Stem Cells and Leukemic Progression. *Cell Stem Cell* **2015**, *17*, 341–352. [CrossRef]
94. Sakuishi, K.; Apetoh, L.; Sullivan, J.M.; Blazar, B.R.; Kuchroo, V.K.; Anderson, A.C. Targeting Tim-3 and PD-1 pathways to reverse T cell exhaustion and restore anti-tumor immunity. *J. Exp. Med.* **2010**, *207*, 2187–2194. [CrossRef]
95. Sakuishi, K.; Jayaraman, P.; Behar, S.M.; Anderson, A.C.; Kuchroo, V.K. Emerging Tim-3 functions in antimicrobial and tumor immunity. *Trends Immunol.* **2011**, *32*, 345–349. [CrossRef]

96. Williams, P.; Basu, S.; Garcia-Manero, G.; Hourigan, C.S.; Oetjen, K.A.; Cortes, J.E.; Ravandi, F.; Jabbour, E.J.; Al-Hamal, Z.; Konopleva, M.; 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* **2019**, *125*, 1470–1481. [CrossRef] [PubMed]
97. Sallman, D.A.; McLemore, A.F.; Aldrich, A.L.; Komrokji, R.S.; McGraw, K.L.; Dhawan, A.; Geyer, S.; Hou, H.A.; Eksioglu, E.A.; Sullivan, A.; et al. TP53 mutations in myelodysplastic syndromes and secondary AML confer an immunosuppressive phenotype. *Blood* **2020**, *136*, 2812–2823. [CrossRef] [PubMed]
98. Thijssen, R.; Diepstraten, S.T.; Moujalled, D.; Chew, E.; Flensburg, C.; Shi, M.X.; Dengler, M.A.; Litalien, V.; MacRaild, S.; Chen, M.; et al. Intact TP-53 function is essential for sustaining durable responses to BH3-mimetic drugs in leukemias. *Blood* **2021**, *137*, 2721–2735. [CrossRef] [PubMed]
99. Chiche, E.; Bertoli, S.; Rahmé, R.; Micol, J.B.; Pasquier, F.; Peterlin, P.; Chevallier, P.; Thomas, X.; Loschi, M.; Genthon, A.; et al. CPX-351 Induces Deep Response and Suppress the Impact of Poor Prognosis Mutations (TP53, ASXL1, RUNX1 and EVI1) Defined By ELN-2017 in t-AML and MRC AML: A Report from a Multicentric French Cohort. *Blood* **2019**, *134*, 1355. [CrossRef]
100. Grenet, J.; Jain, A.G.; Burkart, M.; Waksal, J.; Famulare, C.; Numan, Y.; Stahl, M.; Mckinnell, Z.; Ball, B.; Ma, X.; et al. Outcomes between Liposomal Daunorubicin/Cytarabine (CPX-351) and HMA+Venetoclax As Frontline Therapy in Acute Myeloid Leukemia. In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.
101. Matthews, A.; Perl, A.E.; Luger, S.M.; Babushok, D.V.; Frey, N.V.; Gill, S.; Hexner, E.O.; Martin, M.E.; McCurdy, S.R.; Porter, D.L.; et al. Real World Survival Outcomes of CPX-351 Versus Venetoclax and Azacitadine for Initial Therapy in Adult Acute Myeloid Leukemia. In Proceedings of the American Society of Hematology 2021 Meeting, Atlanta, GA, USA, 11–14 December 2021.