original reports

Eprenetapopt Plus Azacitidine in *TP53*-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM)

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abstract

PURPOSE *TP53*-mutated (*TP53m*) myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) have very poor outcome irrespective of the treatment received, including 40% responses (20% complete remission [CR]) with azacitidine (AZA) alone, short response duration, and a median overall survival (OS) of approximately 6 months. Eprenetapopt (APR-246), a novel first-in-class drug, leads to p53 protein reconformation and reactivates its proapoptotic and cell-cycle arrest functions.

PATIENTS AND METHODS This phase II study assessed the safety and efficacy of eprenetapopt in combination with AZA in untreated high or very high International Prognostic Scoring System-R *TP53m* MDS and AML patients.

RESULTS Fifty-two *TP53m* patients (34 MDS, 18 AML [including seven with more than 30% blasts]) were enrolled. In MDS, we observed an overall response rate (ORR) of 62%, including 47% CR, with a median duration of response at 10.4 months. In AML, the ORR was 33% including 17% CR (27% and 0% CR in AML with less than and more than 30% marrow blasts, respectively). Seventy-three percent of responders achieved *TP53* next-generation sequencing negativity (ie, variant allele frequency $< 5\%$). The main treatment-related adverse events were febrile neutropenia (36%) and neurologic adverse events (40%), the latter correlating with a lower glomerular filtration rate at treatment onset ($P < .01$) and higher age ($P = .05$), and resolving with temporary drug interruption without recurrence after adequate eprenetapopt dose reduction. With a median follow-up of 9.7 months, median OS was 12.1 months in MDS, and 13.9 and 3.0 months in AML with less than and more than 30% marrow blasts, respectively.

CONCLUSION In this very high-risk population of *TP53m* MDS and AML patients, eprenetapopt combined with AZA was safe and showed potentially higher ORR and CR rate, and longer OS than reported with AZA alone.

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ASSOCIATED CONTENT

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Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

TP53 mutations are seen in 5%-10% tof de novo myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) and in 25%-40% of therapy-related MDS and AML.[1,2] They are also observed in 50% of patients with complex karyotype and 20% of lower-risk MDS with isolated deletion 5q, with the former generally having biallelic mutation, whereas the latter generally having monoallelic mutation.[3] Treatment outcome with currently available therapies is poor, especially in patients with complex karyotype or when *TP53* mutation is biallelic.[4,5] The hypomethylating agents azacitidine (AZA) and decitabine (DAC), and intensive chemotherapy, yield poor and very short responses in these patients, with complete remission (CR) rates of 15%-20% and a median overall survival (OS) around 6 months.[3,6-8] A high risk of relapse is also observed after allogeneic stem cell transplantation (allo-SCT), particularly in patients with *TP53* mutation with complex karyotype, thus limiting improvements in OS.[9]

Eprenetapopt (APR-246) is a novel, first-in-class, small molecule that targets *TP53*-mutant cancer cells. Eprenetapopt is a prodrug that is spontaneously converted to methylene quinuclidinone, a Michael acceptor that covalently binds to Cys residues in mutant p53, leading to thermodynamic stabilization of

CONTEXT

Key Objective

TP53-mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) have very poor outcome irrespective of the treatment received, including 40% responses (20% complete remission [CR] with azacitidine [AZA] alone), short response duration, and a median overall survival (OS) of approximately 6 months. This phase II study assessed the safety and efficacy of eprenetapopt in combination with AZA in untreated patients with high or very high International Prognostic Scoring System-R *TP53*-mutated MDS and AML.

Knowledge Generated

Fifty-two patients (34 MDS and 18 AML) were enrolled. In MDS, we observed an overall response rate (ORR) of 62% (including 47% CR), and in AML, an ORR of 33% (including 17% CR). Median OS was 12.1 months in MDS and 10.4 months in AML.

Relevance

Eprenetapopt combined with AZA was safe and showed potentially higher ORR and CR rate, and longer OS than reported with AZA alone.

p53 protein by shifting the equilibrium toward the wild-type conformation and restoring protein function.[10] The excretion mechanism is renal, and a relationship of APR-246 clearance to creatinine clearance was previously reported.[11] Plasma protein binding is low, and albumin binding is not expected to be relevant to estimate effective drug levels. In addition, the metabolizing enzymes for APR-246 have not yet been identified, but oxidation seems to play a minor role in APR-246 elimination, and clinically relevant drug-drug interactions with CYP inhibitors are unlikely (unpublished data).

Eprenetapopt monotherapy showed efficacy in a phase I study including patients with AML. *In vitro* synergy was demonstrated with AZA in SKM1 *TP53*-mutated (*TP53m*) cell line. *In vivo* synergy was also observed in mice transplanted with the SKM1 *TP53m* cell line, and ex vivo synergistic effect was confirmed in bone marrow samples of *TP53m* MDS and AML patients.[12]

Here, we report the safety and efficacy of eprenetapopt combined with AZA in *TP53m* MDS and AML patients in a phase II clinical trial.

PATIENTS AND METHODS

Study Design

This was a phase II open-label multicenter study, whose design was similar to that of a US phase II study (ClinicalTrials.gov identifier: NCT03072043),[13] except that our study also included AML with more than 30% blasts, and allowed maintenance therapy with eprenetapopt and AZA for up to 1 year after allo-SCT. Eprenetapopt was administered by 6-hour intravenous infusion daily at a fixed dose of 4,500 mg on days 1-4 of each 28-day cycle. AZA was administered at the standard dose of 75 mg/m^2 subcutaneous injection daily on days 4-10 of each 28-day cycle. In patients consolidated with allo-SCT, maintenance treatment was administered with reduced doses of AZA (36 mg/m^2 daily on days 1-5) and eprenetapopt at a fixed dose of 3,700 mg on days 1-4 of each 28-day cycle. The protocol provided for dose adjustments depending on adverse events (AEs) and management guidelines for neurologic AEs, including use of chlorpromazine and temporary interruption and/or dose reduction of eprenetapopt. The initial fixed starting dose of eprenetapopt was 4,500 mg, and the dose was reduced in 500-mg increments (500 mg down for DL-1 and 1,000 mg for DL-2) for neurologic AEs, if needed.

The clinical trial was approved by a French research ethics committee (Comité de Protection des Personnes Ile de France IV) and by the French National competent authority (Agence National de Securité du Médicament). Written informed consent was provided by all patients before screening and enrollment. The study was conducted in accordance with the Declaration of Helsinki and registered in ClinicalTrials.gov (identifier: NCT03588078).

Patients

Patients ≥18 years of age with an Eastern Cooperative Oncology Group performance status of 0-2 and adequate renal and hepatic function, who had de novo MDS or chronic myelomonocytic leukemia classified as intermediate, high, or very high using International Prognostic Scoring System (IPSS)-R, or AML including low blast count AML (ie, with less than 30% marrow blasts) and AML with more than 30% of blasts were included. All patients were hypomethylating agent-naive and were not previously allografted. All patients had at least one *TP53* mutation identified based on local next-generation sequencing testing with central review. Therapy-related MDS and AML were eligible if they had at least 1-year disease-free survival from prior malignancy. Prior treatment with growth factors, lenalidomide, and/or hydroxyurea was permitted. All inclusion and exclusion criteria are listed in the Appendix (online only).

Study Assessments

The primary end point of the study was response based on intention to treat and in evaluable patients, using IWG

2006 criteria for MDS and IWG 2003 criteria for AML.[14,15] Secondary end points were safety using National Cancer Institute-Common Terminology Criteria for Adverse Events 4.03 criteria, OS, response duration, AML progression rate, and correlation between *TP53* variant allele frequency (VAF) and response. Responses, in MDS, included CR, marrow CR (mCR), partial remission (PR), and stable disease (SD) with hematologic improvement (SD with HI). Responses, in AML, included CR and CR with incomplete count recovery (CRi). Progression, in AML, was defined by a 50% increase of baseline blast percentage, as defined by ELN 2017.[16] Minimal residual disease (MRD) was evaluated by detection of *TP53* mutation (Appendix).

Statistical Analysis

It is described in detail in the supplemental data.

The intention-to-treat (ITT) population included all patients enrolled in this study. The evaluable population per protocol included all patients receiving at least three cycles of treatment and who had a bone marrow assessment after the third cycle. Treatment-emergent AEs were evaluated according to National Cancer Institute-Common Terminology Criteria for Adverse Events 4.03 criteria. Statistical analyses were performed on both the ITT and the evaluable population.

RESULTS

Baseline Patient Characteristics

Patients were enrolled between September 2018 and July 2019, and the data cutoff was April 1, 2020, with all patients enrolled for ≥ 9 months. As mentioned in the protocol, more than six patients achieved CR in the first 24 patients and allowed to continue until a total of 52 patients treated with eprenetapopt combined with AZA. As described below, although this patient number led to accrual of only 39 evaluable patients, ie, less than the planned 45 evaluable patients, the study eventually did meet the threshold of observing more than 14 CR in the evaluable population.

At the cutoff date, 12 (23%) patients were continuing on study treatment and four (8%) had received allogeneic SCT, two of whom started post-transplant maintenance treatment. Early discontinuation, before cycle 3 bone marrow evaluation, was observed in 13 (25%) patients and was related to severe infection (n = 6), progression (n = 4, who all had AML at inclusion, including two with more than 30% blasts at baseline), multiorgan dysfunction (n = 2), and consent withdrawal (n = 1). The median treatment duration was 8.6 months (range, 0.3-17.3 months). Baseline demographic and clinical characteristics are shown in Table 1. Thirty-four patients had MDS and 18 had AML. Using conventional cytogenetics, 80% of the patients had complex karyotype. 17p deletion was cytogenetically detectable in only in 25% of the patients but was probably often overlooked in those patients with complex karyotypes, as fluorescent in situ hybridization analysis of 17p was not assessed in most cases. The median number of *TP53* point mutations was 1 (range, 1-3), with 25% of patients having two or more *TP53* point mutations. The *TP53m* clone was dominant (ie, with VAF greater than that of the other mutated clones) in 83% of the patients. Median baseline *TP53m* VAF was 20% (range, 0.1-83%), and 10 (19%) had a baseline VAF > 50%. Forty-nine (94%) patients had at least one mutation in the DNA-binding domain (including 44 [90%] with a missense mutation) (Fig 1). Based on having either > 1 *TP53* point mutation, *TP53m* VAF > 50%, or *TP53* mutation plus cytogenetically detectable 17p deletion, including potential loss of heterozygosity, 21 (40%) patients were estimated to have biallelic mutation. Co-occurring somatic mutations were found in 48% of patients and are shown in Figure 3.

Efficacy

Intention-to-treat population. Fifty-two patients received combination therapy (ITT cohort). In MDS, the overall response rate (ORR) was 62%, including 47% CR, 6% mCR, and 9% SD with HI. In AML, the ORR was 33%, including 17% CR and 10% CRi. The ORR was 45% for low blast count AML (including 27% CR) and 14% for AML with more than 30% blasts (with no CR) (Table 2). When combining AML and MDS, the ORR was 52%, including 37% CR.

In MDS, median duration of overall duration response and CR was 10.4 (2.8-16.8+) and 11.4 (6.5-16.8+) months, respectively. In AML, median duration of overall duration response and CR was 12.7 (6.0-17.3+) and 14.0 (11.3-17.3+) months, respectively. When combining AML and MDS, median duration of overall response and CR was 11.3 (95% CI, 2.8 to 17.3+) and 11.7 (95% CI, 6.5 to 17.3+) months, respectively, with no significant difference between MDS, low blast AML, and AML with more 30% of blasts. When combining MDS and AML to have sufficient patient numbers, presence of biallelic *TP53* mutation and presence of comutations had no impact on the ORR and CR rate (Appendix Fig A1, online only).

Evaluable population per protocol. Only 39 patients received at least three cycles of combination treatment and had a bone marrow evaluation after 3 cycles, and were considered evaluable. Although accruing fewer than 45 evaluable patients, the study did meet the threshold of observing 19 CR, ie, more than 14 CR in the evaluable population. In MDS, the ORR was 75%, including 57% CR, 7% mCR, and 11% SD with HI. In AML, the ORR was 55%, including 36% CR and 18% CRi. The ORR was 55% for low blast count AML (including 50% CR) and 50% for AML with more than 30% blasts (with no CR) (Appendix). When combining AML and MDS, the ORR was 69%, including 19% CR.

In MDS, median duration of overall duration response and CR was 10.4 (2.8-16.8+) and 11.4 (6.5-16.8+) months, respectively. In AML, median duration of overall duration response and CR was 12.7 (6.0-17.3+) and 14.0 (11.3-17.3+) months, respectively. When combining AML and

TABLE 1. Baseline Demographics and Clinical Characteristics

Characteristic	All Patients N = 52	MDS n = 34	AML n = 18
Age (median), years	74 (44-87)	74 (46-87)	72 (44-83)
M/F	27/25	15/19	12/6
ECOG	0 (0-2)	0 (0-2)	0 (0-2)
WHO classification			
MDS-ULD	1 (2%)	1 (3%)	
MDS-RS-MLD	1 (2%)	1 (3%)	
MDS-MLD	5 (10%)	5 (15%)	
MDS-EB1	10 (19%)	10 (29%)	
MDS-EB2	15 (29%)	15 (44%)	
AML 20%-30% marrow blasts	11 (21%)		11 (61%)
AML > 30% marrow blasts	7 (13%)		7 (39%)
Cytogenetic risk			
Complex karyotype	45 (87%)	29 (85%)	16 (89%)
Monosomal karyotype	36 (69%)	27 (79%)	9 (50%)
IPSS-R (for MDS)			
Very low	0	0	
Low	0	0	
Intermediate	4 (8%)	4 (12%)	
High	5 (10%)	5 (15%)	
Very high	25 (48%)	25 (74%)	
ELN classification (for AML)			
Favorable	0		0
Intermediate	0		0
Unfavorable	18 (35%)		18 (100%)
TP53 mutation			
Median number	1 (1-3)	1 (1-3)	1 (1-2)
Biallelic mutation[a]	21 (40%)	11 (32%)	10 (56%)
Median VAF	23 (0.1-83)	20 (0.1-83)	25 (1.3-81)

Abbreviations: AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndrome; M/F, male/female; MLD, multilineage dysplasia; ULD, unilineage dysplasia; VAF, variant allele frequency.

[a]Defined as either > 1 *TP53* point mutation, mutated *TP53* VAF > 50%, or *TP53* mutation plus cytogenetically detectable 17p deletion.

MDS, median duration of overall responses and CR was 11.3 (95% CI, 2.8 to 17.3+) and 11.7 (95% CI, 6.5 to 17.3+) months, respectively, with no significant difference between MDS, low blast AML, and AML with more 30% of blasts (ORR, 95% CI, 10.4 *v* 14.0 *v*11.5 months and CR, 95% CI, 11.4 *v* 14.0 months *v* not evaluable, respectively).

Safety

All AEs are reported in Table 3. AEs observed in ≥ 20% were febrile neutropenia (37%) and neurologic (40%). Hematologic toxicities appeared similar to those reported for AZA monotherapy. Neurologic AEs reached grade 3 in only three patients (one acute confusion and two ataxia). Occurrence of neurologic AEs was correlated with lower glomerular filtration rate at treatment onset ($P < .01$) and higher age ($P = .003$, Appendix Fig A2, online only). Neurologic toxicity was fully reversible within 5 days of drug discontinuation and showed no recurrence after dose reduction (one dose reduction [n = 13] and two dose reductions [n = 4]). Nine (69%) of the 13 patients who required one dose reduction, and two (50%) of the four patients who required two dose reductions responded, including six and one CR, respectively. Only one early discontinuation was because of eprenetapopt-related neurologic AE, and occurred in a patient with antibiotic-related renal failure. The 30-day and 60-day mortality was 0% and 8%, respectively.

Survival

At a median follow-up time of 9.7 months, median OS was 12.1 months for MDS and 10.4 months for AML without

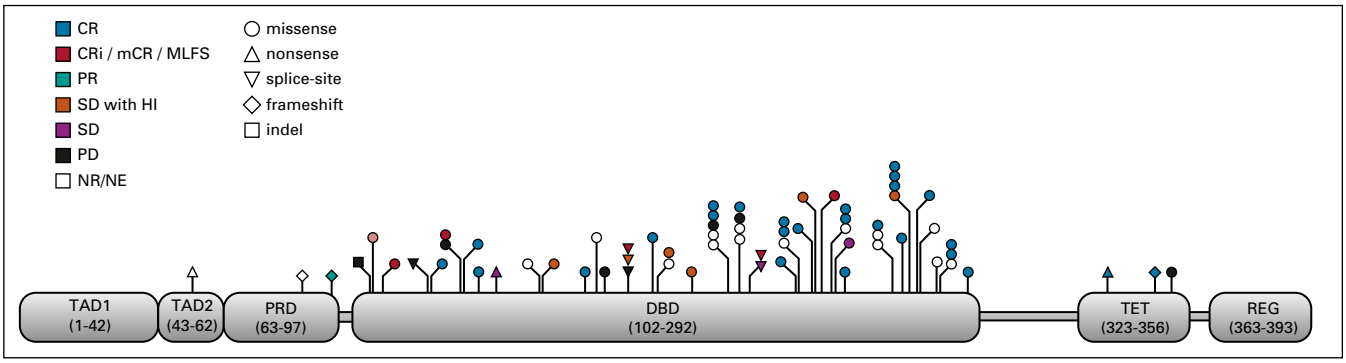

FIG 1. Spectrum of *TP53* mutations in all patients (N = 52) at baseline. CR, complete remission; CRi, CR with incomplete count recovery; DBD, DNA binding domain; HI, hematologic improvement; mCR, marrow CR; NE, not evaluable; PR, partial remission; PRD, proline-rich domain; REG, C-terminal regulatory domain; SD, stable disease; TAD, transactivation domain; TET, tetramerization domain.

significant difference between the two populations (P = .92). Nevertheless, we observed a trend for shorter OS in AML with more than 30% blasts versus MDS and low blast count AML: median 3.0 versus 12.1 versus 13.9 months, respectively (P = .34, Fig 2B). Median OS in the ITT population was 12.1 months (95% CI, 8.1 to 13.4 months; Fig 2A). Median OS was 13.7 months (95% CI, 11.7 to 15.7 months) in patients who received at least three treatment cycles (Fig 2C).

When combining MDS and AML to have sufficient patient numbers, using a landmark analysis analyzing survival according to response, OS was significantly longer in responders (median 15.6 months, 95% CI, 13.0 to 18.1 months) than in nonresponders (median, 3.8 months, 95% CI, 2.8 to 4.9 months, $P < .0001$) (Fig 2D). In responders, there was no significant difference in OS between CR and non-CR patients (median 13.9 months *v* not reached, P = .37).

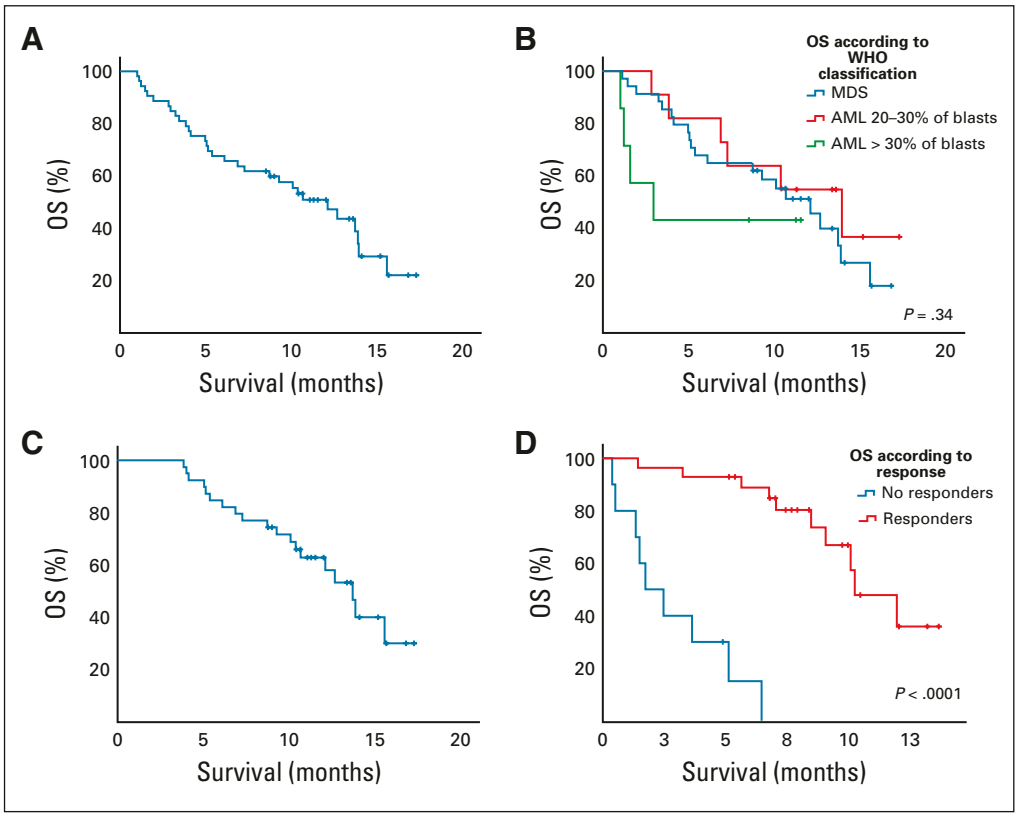

FIG 2. OS (A) in the overall population, (B) in MDS and AML, (C) in patients who received at least three cycles, and (D) in responders versus nonresponders. AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; OS, overall survival.

TABLE 2. Responses in the Intent-to-Treat Population in MDS, Low Blast Count AML, and AML With More Than 30% of Blasts

Response	MDS n = 34	AML 20%-30% n = 11	AML > 30% n = 7	All Population N = 52
ORR[a]	62%		14%	
CR	47%	27%	0%	
CRi	[a]	18%	14%	
mCR[b]	6%	[a]	[a]	
PR	0%	[a]	[a]	
SD with HI	9%	[a]	[a]	
Duration of response (median, 95% CI)	10.4 (2.8 to 16.8)	14% (6.0 to 17.3)	11.5	11.3 (2.8 to 17.3)
Duration of CR (median, 95% CI)	11.4 (6.5 to 16.8)	14.0 (11.3 to 17.3)	NE	11.7 (6.5 to 17.3)

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; HI, hematologic improvement; mCR, marrow CR; MDS, myelodysplastic syndrome; NE, not evaluable; ORR, overall response rate; PR, partial remission; SD, stable disease.

[a]ORR included CR, mCR, PR, and SD with HI for MDS. ORR included only CR and CRi for AML.

[b]mCR was only used for MDS.

When combining MDS and AML to have sufficient patient numbers, presence of biallelic *TP53* mutation or presence of comutations had no impact on OS. Four patients received allogeneic SCT, two of whom started maintenance treatment, precluding analysis of the impact of transplant. No relapse has so far been observed after allogeneic SCT. Sixty-eight percent of the patients who died had progressed before death. Forty one percent of patients with MDS progressed in AML during treatment. Analysis of the molecular profile at relapse is underway by pooling data from the US and French trials, to determine whether the frequency of *TP53* mutant disease at relapse is negatively selected or not, akin to the lower frequency of FLT3-mutant AML often observed at relapse among patients exposed to an FLT3 inhibitor in combination with chemotherapy.

Correlation Between *TP53* VAF and Response

When combining MDS and AML to have sufficient patient numbers, 22 (73%) of the responders achieved *TP53* VAF levels below the 5% threshold, and nine (30%) *TP53* VAF levels below the 0.1% threshold. Eighteen of the 22 patients with no detectable mutant *TP53* at the 5% threshold were already negative at the first response assessment after cycle 3, and the remaining four patients after cycle 6. Eight of the nine patients with no detectable mutant *TP53* at the 0.1% threshold were already negative after cycle 3, and the remaining patient after cycle 6. *TP53* VAF decrease was strongly associated with response ($P < .0001$), CR achievement ($P = .002$), and duration of response ($P < .0001$). Achieving *TP53* VAF level below the 5% threshold was associated with significantly longer response duration ($P < .001$) and significantly longer OS (13.9 months *v* 5.0 months, $P < .0001$). Achieving *TP53* VAF level below the 0.1% threshold was also associated with better outcome (median OS not reached *v* 10.7 months, $P = .05$).

DISCUSSION

In this phase II clinical trial evaluating eprenetapopt and AZA in a very high-risk population, we report in MDS an ORR of 62% including 47% CR with a median duration of response at 10.4 months; in AML, the ORR of 33% including 17% CR in the ITT population with a median duration of response of 12.7 months. The ORR was 75% in patients with evaluable MDS and 55% in patients with

TABLE 3. AEs in All Patients

AE	All Grades	Grade 3 or 4
Hematologic AEs		
Febrile neutropenia	19 (37%)	19 (37%)
Neurologic AEs	21 (40%)	3 (6%)
Ataxia	13 (25%)	2 (4%)
Cognitive impairment	4 (8%)	0
Acute confusion	4 (8%)	1 (2%)
Isolated dizziness	3 (6%)	0
Facial paresthesia	1 (2%)	0

Abbreviation: AE, adverse event.

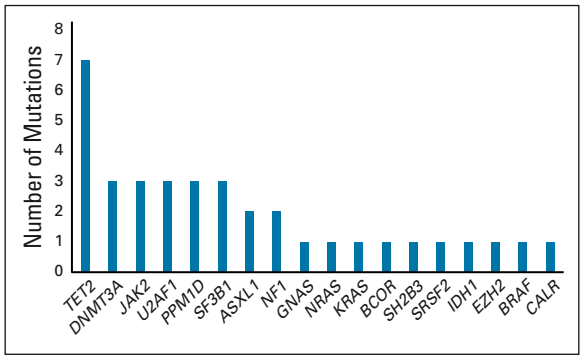

FIG 3. Co-occurring somatic mutations.

evaluable AML (ie, who received at least 3 cycles). ORR was 55% in patients with low blast count AML. Outcome was poorer in AML with > 30% marrow blasts, but similar in MDS and low blast count AML.

Patients with *TP53m* MDS and AML have a poor prognosis, with poor and very short responses to all available treatments, and a median OS of about 6 months when treated with AZA alone in previous studies (median 7, 9, 8, and 4 months, respectively, in four large series where patient characteristics, including median Eastern Cooperative Oncology Group, were similar to those of this study).[3,8,10,17] Recently, the combination of AZA and venetoclax demonstrated improved OS over AZA alone in patients with AML not eligible for intensive chemotherapy.[18,19] In *TP53m* patients, however, although the combination was significantly associated with an increased CR/CRi rate (55.3% *v* 0% for AZA alone), it failed to improve OS. DiNardo et al[20] reported, in AML, three patterns of resistance to venetoclax including *TP53* mutations. In another study, a 10-day schedule of DAC showed a CR rate of 100% in 21 *TP53m* MDS or AML patients, with a median OS of 12.7 months, similar to that seen in *TP53* wild-type patients.[21] However, those results were not reproduced in a randomized phase II clinical trial comparing 5-day and 10-day schedules of DAC in patients with AML. In that study, with the 10-day schedule, the CR rate and median OS in the *TP53m* patients were 47% and 5.5 months, respectively.[22]

Responding patients had a deep molecular response with 73% achieving *TP53* VAF levels below the 5% threshold, and 30% achieving *TP53* VAF levels below the 0.1% threshold. *TP53* VAF levels, using both sensitivity thresholds of 5% and 0.1%, were associated with a significant longer duration of response ($P < .001$) and a significant better OS.

Finally, the eprenetapopt plus AZA combination was generally well tolerated, with relatively frequent but reversible neurologic side effects that appeared more prevalent in elderly patients and/or those with renal failure, as already reported.[11] Neurologic AEs were managed using supportive measures, including rare use of chlorpromazine, and with temporary interruption or dose reductions of eprenetapopt, if needed, and their precise mechanism is being explored. Given the potential relationship with impaired renal function, eprenetapopt should potentially be contraindicated or used with extreme precautions in patients with serum creatinine > 2 upper limit normal. Close monitoring of the renal function should be performed, especially in elderly patients, in patients with serum creatinine between normal and ≤2 upper limit normal, and those receiving concomitant potentially nephrotoxic agents.

In conclusion, the addition of eprenetapopt to AZA appeared to compare favorably with AZA alone in *TP53m* MDS or AML, and our results are consistent with results from a US phase I or II of eprenetapopt and AZA in *TP53m* MDS and low blast count AML showing an ORR of 71% with 44% achieving CR in the ITT population.[23] Those data support the ongoing international phase III, multicenter, randomized study of eprenetapopt in combination with AZA versus AZA alone in patients with *TP53*-mutant MDS (ClinicalTrials.gov identifier: NCT03745716). The combination of AZA and eprenetapopt will have to be compared, in patients with AML, with the AZA and venetoclax combination. A phase I, multicenter, study of eprenetapopt in combination with AZA and venetoclax in patients with AML with *TP53*-mutant AML is also ongoing (ClinicalTrials.gov identifier: NCT04214860).

In January 2020, based on our current results and results from the US phase I or II trial of eprenetapopt and AZA, the Food and Drug Administration granted breakthrough therapy designation for the treatment of patients with *TP53*-mutant MDS with the combination of eprenetapopt and AZA.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Eprenetapopt Plus Azacitidine in *TP53*-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia: A Phase II Study by the Groupe Francophone des Myélodysplasies (GFM)

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APPENDIX

SUPPLEMENTAL PATIENTS AND METHODS

Study Design

Bone marrow aspiration was performed at baseline and every three cycles until progression or relapse. Adverse events were declared using the National Cancer Institute Common Terminology Criteria for AEs version 4.03 criteria and managed by standard of care.

Study Assessments

Minimal residual disease was evaluated by detection of TP53 mutation using (1) a classical next-generation sequencing (NGS) method with a 5% sensitivity (Genoptix, Carlsbad, CA) and (2) a high-sensitivity NGS method (human serum albumin panel from Genoptix, Carlsbad, CA) with a sensitivity of 0.1%.

Statistical Analysis

To determine the sample size, we used a Simon mini-max two-stage design, considering a proportion of patients achieving complete remission [CR] $\leq$ 20% with azacitidine alone versus the alternative hypothesis $\geq$ 40% with the combination treatment. Using a type I error 0.05 and a type II error rate of 0.10, it was computed that 24 patients should be enrolled at the first stage, with at least six patients achieving CR to continue to stage II. Then, 21 additional patients were required for a total of 45, with at least 14 CR to conclude there was sufficient evidence to support further study of APR-246 in combination with azacitidine in phase III. We decided to enroll 52 patients to take into account possible nonevaluable patients. Continuous variables were described using medians [interquartile ranges] (minimum; maximum) and qualitative variables were described using counts and percentages. Mann-Spearman correlation and Mann-Whitney test were used for continuous variables. The median follow-up time was calculated as the median time from initiation of treatment to last follow-up. Duration of response was estimated as the time between response and either loss of response, progression, or death. Kaplan-Meier estimates of the median duration of response were computed with 95% CI. Overall survival was calculated from the date of treatment initiation to date of death or last follow-up and was not censored at date of allogeneic stem cell transplantation. Survival curves were estimated using the Kaplan-Meier method and were compared by the logrank test. To compare survival curves according to response, and *TP53* NGS variant allele frequency levels, a landmark analysis was performed at 109 days, corresponding to the maximum time of response evaluation.

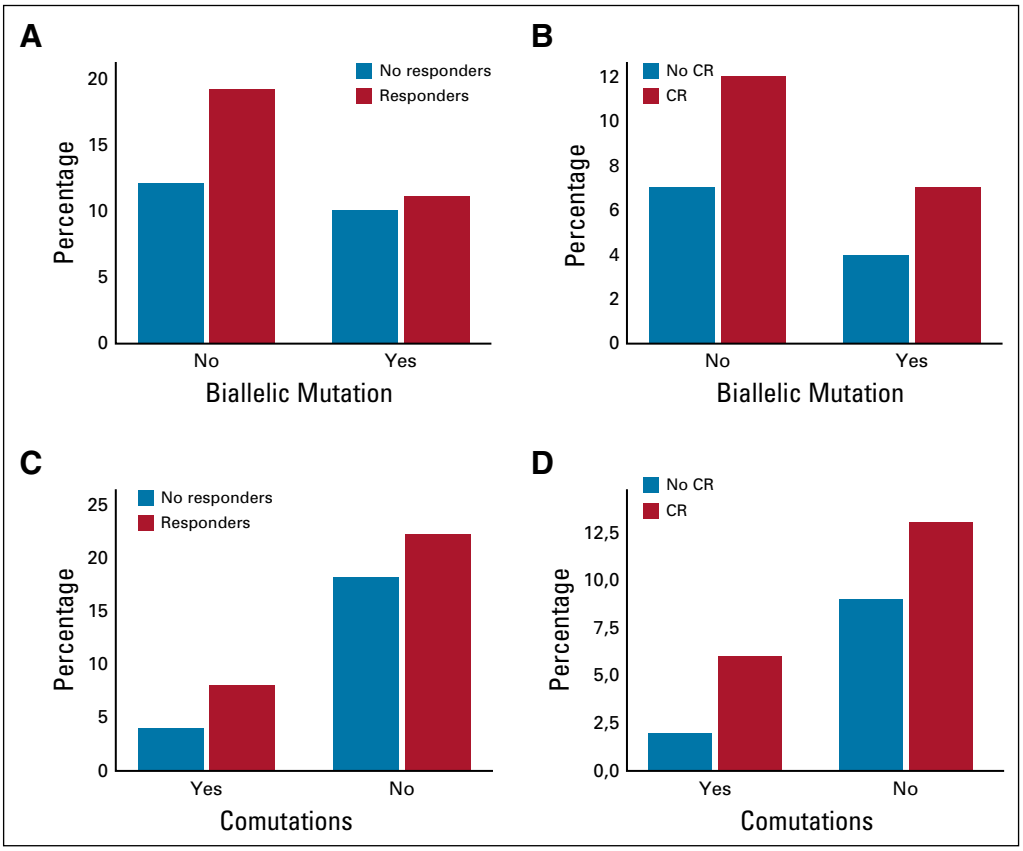

FIG A1. Correlation between response and presence or absence of comutation or biallelic mutation. Correlation between CR and presence or absence of comutation or biallelic mutation. CR, complete remission.

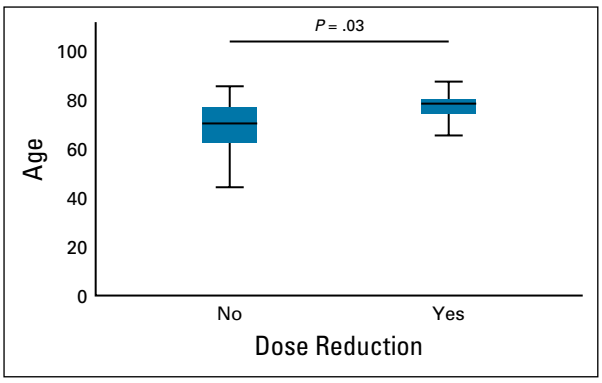

FIG A2. Correlation between dose reduction and age.

TABLE A1. Responses in the Evaluable Population in MDS, Low Blast Count AML, and AML With More Than 30% of Blasts

Parameter	MDS (n = 28)	AML 20%-30% (n = 9)	AML > 30% (n = 2)	All Population (N = 39)
ORR[a]	75%	55%	50%	69%
CR	57%	33%	0%	49%
CRi	[a]	22%	50%	13%
mCR[b]	7%	[a]	[a]	
PR	0%	[a]	[a]	
SD with HI	11%	[a]	[a]	
Duration of response (median, 95% CI)	10.4 (2.8 to 16.8)	14.0 (6.0 to 17.3)	11.5	11.3 (2.8 to 17.3)
Duration of CR (median, 95% CI)	11.4 (6.5 to 16.8)	14.0 (11.3 to 17.3)	NE	11.7 (6.5 to 17.3)

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; CRi, CR with incomplete count recovery; mCR, marrow CR; MDS, myelodysplastic syndrome; NE, not evaluable; ORR, overall response rate; PR, partial remission; SD with HI, stable disease with hematologic improvement.

[a]ORR included CR, mCR, PR, and SD with HI for MDS. ORR included only CR and CRi for AML.

[b]mCR was used only for MDS.