original reports abstract

Eprenetapopt (APR-246) and Azacitidine in *TP53*-Mutant Myelodysplastic Syndromes

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PURPOSE Approximately 20% of patients with *TP53*-mutant myelodysplastic syndromes (MDS) achieve complete remission (CR) with hypomethylating agents. Eprenetapopt (APR-246) is a novel, first-in-class, small molecule that restores wild-type p53 functions in *TP53*-mutant cells.

METHODS This was a phase Ib/II study to determine the safety, recommended phase II dose, and efficacy of eprenetapopt administered in combination with azacitidine in patients with *TP53*-mutant MDS or acute myeloid leukemia (AML) with 20%-30% marrow blasts (ClinicalTrials.gov identifier: NCT03072043).

RESULTS Fifty-five patients (40 MDS, 11 AML, and four MDS/myeloproliferative neoplasms) with at least one *TP53* mutation were treated. The overall response rate was 71% with 44% achieving CR. Of patients with MDS, 73% (n = 29) responded with 50% (n = 20) achieving CR and 58% (23/40) a cytogenetic response. The overall response rate and CR rate for patients with AML was 64% (n = 7) and 36% (n = 4), respectively. Patients with only *TP53* mutations by next-generation sequencing had higher rates of CR (69% *v* 25%; $P = .006$). Responding patients had significant reductions in *TP53* variant allele frequency and p53 expression by immunohistochemistry, with 21 (38%) achieving complete molecular remission (variant allele frequency < 5%). Median overall survival was 10.8 months with significant improvement in responding versus nonresponding patients by landmark analysis (14.6 *v* 7.5 months; $P = .0005$). Overall, 19/55 (35%) patients underwent allogeneic hematopoietic stem-cell transplant, with a median overall survival of 14.7 months. Adverse events were similar to those reported for azacitidine or eprenetapopt monotherapy, with the most common grade ≥ 3 adverse events being febrile neutropenia (33%), leukopenia (29%), and neutropenia (29%).

CONCLUSION Combination treatment with eprenetapopt and azacitidine is well-tolerated yielding high rates of clinical response and molecular remissions in patients with *TP53*-mutant MDS and oligoblastic AML.

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INTRODUCTION

TP53 gene mutations are detected in approximately 10%-20% of patients with de novo myelodysplastic syndromes (MDS)[1-4] or acute myeloid leukemia (AML)[5,6] and 30%-40% of patients with therapy-related disease.[7] Treatment outcomes for patients with *TP53* mutations are poor with available therapies.[8-12] Hypomethylating agents (HMAs), such as azacitidine and decitabine, yield statistically similar complete remission (CR) rates of approximately 15%-20% in patients with either *TP53*-mutant or wild-type MDS.[12-14] However, remissions in *TP53*-mutant patients are brief with a median overall survival (OS) ranging from 5 to 12 months,[8,9,12,13,15-17] reflecting the significant unmet medical need for novel, targeted therapies for patients with *TP53*-mutant MDS and AML. The *TP53* mutation burden (ie, high variant allele frequency [VAF], concurrent complex karyotype, and/or multihit state) is integrally linked to inferior survival with median OS of 6-8 months.[8-10,12] Increased HMA duration, such as 10-day decitabine, initially suggested improved outcomes in a limited number of patients with *TP53*-mutant myeloid malignancies (patients with MDS; n = 9),[18] but there was no improvement in CR or OS in a prospective randomized study comparing 10-day versus 5-day decitabine in AML, and this treatment schedule has not been widely adopted.[19,20]

Eprenetapopt (APR-246) is a novel, first-in-class, small molecule that selectively induces apoptosis in *TP53*-mutant cancer cells. Eprenetapopt is a prodrug that, under physiological conditions, is spontaneously converted to methylene quinuclidinone, a Michael acceptor that covalently binds to cysteine residues in mutant p53, leading to thermodynamic stabilization of the p53 protein and shifting the equilibrium toward a functional conformation.[21] In addition, eprenetapopt

ASSOCIATED CONTENT

Data Supplement
Protocol

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

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CONTEXT

Key Objective

To evaluate if it is possible to improve outcomes for patients with *TP53*-mutant myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia, who have a complete remission rate of < 20% with standard-of-care azacitidine therapy.

Knowledge Generated

Eprenetapopt (APR-246) is a first-in-class mutant p53 reactivator and the combination of azacitidine and eprenetapopt was well-tolerated in patients with *TP53*-mutant MDS or acute myeloid leukemia, with an adverse event profile similar to azacitidine and eprenetapopt monotherapies. Azacitidine and eprenetapopt resulted in a 71% overall response rate and 44% complete remission rate in the intention-to-treat population (50% for patients with MDS) with a median overall survival of 10.8 months, comparing favorably with single-agent azacitidine.

Relevance

Together, these data support the ongoing pivotal phase III, multicenter, randomized study of eprenetapopt in combination with azacitidine versus azacitidine alone in patients with *TP53*-mutant MDS (ClinicalTrials.gov identifier: NCT03745716).

increases oxidative stress by depletion of glutathione and inhibition of thioredoxin reductase, leading to accumulation of reactive oxygen species and further promoting tumor cell death.[22,23] Eprenetapopt has synergistic cytotoxicity when combined with azacitidine in *TP53*-mutant MDS and AML cell lines, primary patient specimens, and in vivo models.[24] In a phase I study including patients with AML, eprenetapopt monotherapy demonstrated clinical activity with corresponding activation of p53-dependent pathways.[25,26] In January 2020, the US Food and Drug Administration granted breakthrough therapy designation for the treatment of patients with *TP53*-mutant MDS with the combination of eprenetapopt and azacitidine. Here, we report the safety and efficacy findings from the phase Ib/II trial evaluating combined treatment with eprenetapopt and azacitidine in patients with *TP53*-mutant myeloid malignancies.

METHODS

Study Design

This was a phase Ib/II open-label, multicenter, dose-escalation and dose-expansion study. The initial dose-escalation phase employed a standard 3 + 3 design to evaluate eprenetapopt in combination with azacitidine. Dose-limiting toxicities (DLTs) were evaluated to establish the recommended phase II dose (RP2D). Eprenetapopt was administered as a 6-hour intravenous infusion on days 1-4 of each 28-day cycle. Azacitidine was administered at the standard dose of 75 mg/m^2 (seven consecutive days, days 4-10 or 2 + 5 [ie, days 4-5 and 8-12]) as a subcutaneous injection or an intravenous infusion (Data Supplement, online only). In the dose-escalation phase, 12 patients initially received eprenetapopt monotherapy (lead-in phase) over the same schedule on days −14 to −11 (prior to the start of combination therapy) at three dose levels (50, 75, and 100 mg/kg/d lean body mass [LBM]). As no DLTs occurred in the phase Ib study, eprenetapopt was subsequently given at a fixed dose of 4,500 mg/patient/d in phase II (100 mg/kg/d LBM equivalent on the basis of population pharmacokinetic modeling). The phase II portion of the study used a Simon's two-stage minimax design (Data Supplement). Disease assessments were undertaken after the lead-in phase (day −10) and then every three cycles. The study Protocol (online only) was approved by the institutional review boards of the participating sites. Written informed consent was provided by all the patients before screening and enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

Patients

Patients age ≥ 18 years with an Eastern Cooperative Oncology Group performance status of 0-2 and adequate renal and hepatic function and who had HMA-naive MDS, MDS/myeloproliferative neoplasm (MDS/MPN) overlap syndrome, chronic myelomonocytic leukemia, or oligoblastic AML (20%-30% blasts) and were classified as higher risk as defined by the revised International Prognostic Scoring System (ie, intermediate, high, or very high) were eligible for inclusion. All patients were required to have a *TP53* mutation identified on the basis of local next-generation sequencing (NGS) testing.

Study Assessments

The primary end point of the phase II study was CR as defined by the 2006 International Working Group criteria.[27] Key predefined secondary end points included overall response rate (ORR), duration of response, and OS. In addition, p53 reactivation (lead-in phase only), *TP53* clonal suppression (measurable residual disease [MRD]) via high-sensitivity NGS analyses, and biomarkers of response including p53 protein expression and presence of co-occurring non-*TP53* mutations were evaluated (Data Supplement).

Statistical Analysis

The intention-to-treat (ITT) and safety populations included all patients who received at least one dose of eprenetapopt. All patients who completed at least one treatment cycle of eprenetapopt and azacitidine and had at least one post-treatment clinical response assessment were included in the response-evaluable population. Duration of response was calculated from the date of first response to the date of progression or death and was not censored at the date of allogeneic hematopoietic stem-cell transplant (HSCT). OS was calculated from the date of initiation of therapy to death or last follow-up and was evaluated using the Kaplan-Meier method. Log-rank test was used to compare the survival curves between the patient groups of interest. Landmark analyses were used for survival comparisons in responding versus nonresponding patients. The Cox proportional hazards model was used to evaluate the impact of HSCT as a time-dependent covariate. Fisher's exact and paired *t*-tests were used for comparative analyses. Biomarker and subgroup analyses were performed as exploratory end points (Data Supplement). A P value $< .05$ was considered statistically significant.

RESULTS

Baseline Patient Characteristics and Disposition

Patients were enrolled between May 2017 and February 2019, and the data cutoff was November 15, 2019, at which point all patients had been enrolled for ≥ 6 months. A total of 55 patients received eprenetapopt in combination with azacitidine (12 in the dose-escalation phase [including six patients treated at RP2D] and 43 patients in the phase II dose-expansion phase). Baseline demographics and clinical characteristics are shown in Table 1 and a heat map containing individual patient molecular and cytogenetic characteristics is provided in Figure 1A. Most patients had significant adverse molecular and genetic features (89% complex karyotype and/or multihit [ie, > 1 *TP53* mutation or deletion 17p/-17]). *TP53* was the dominant clone, that is, only mutation or mutation with highest VAF, in 89% of patients. The median number of *TP53* mutations was one (range, 1-3), with 17 (31%) patients having > 1 *TP53* mutation, and median VAF in peripheral blood was 21%. Fifty-three (96%) patients had at least one mutation in the DNA-binding domain, including 48 (87%) with a missense

TABLE 1. Baseline Characteristics in Intention-to-Treat Population

Characteristic	All Patients (N = 55)	MDS (n = 40)	AML (n = 11)	MDS/MPN (n = 4)
Female	29 (53)	17 (43)	8 (73)	4 (100)
Age, years, median (range)	66 (34-85)	66 (34-80)	68 (47-85)	57 (41-79)
Age category				
< 65 years	23 (42)	17 (43)	4 (36)	2 (50)
≥ 65 years	32 (58)	23 (58)	7 (64)	2 (50)
ECOG PS at screening				
0	17 (31)	15 (38)	2 (18)	0
1	34 (62)	22 (55)	8 (73)	4 (100)
2	4 (7)	3 (8)	1 (9)	0
Disease risk				
IPSS-R: intermediate	4 (7)	4 (10)	0	0
IPSS-R: high	14 (25)	8 (20)	3 (27)	3 (75)
IPSS-R: very high	37 (67)	28 (70)	8 (73)	1 (25)
Therapy-related disease	18 (33)	14 (35)	4 (36)	0
Complex karyotype	46 (84)	36 (90)	8 (73)	2 (50)
Transfusion-dependent	38 (69)	27 (68)	8 (73)	3 (75)
TP53 mutations	55 (100)	40 (100)	11 (100)	4 (100)
Mutations per patient, median (range)	1 (1-3)	1 (1-3)	2 (1-2)	2 (2)
p53 IHC ≥ 10%	42 (76)	33 (83)	6 (55)	3 (75)
TP53 VAF %, median (range)	21 (0.5-72)	20 (1-72)	15 (0.5-50)	44 (5-47)
Other somatic mutations	21 (38)	15 (38)	5 (45)	1 (25)

NOTE. Data are n (%) unless otherwise stated.

Abbreviations: AML, acute myeloid leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; IPSS-R, revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic syndromes/myeloproliferative neoplasms; VAF, variant allele frequency.

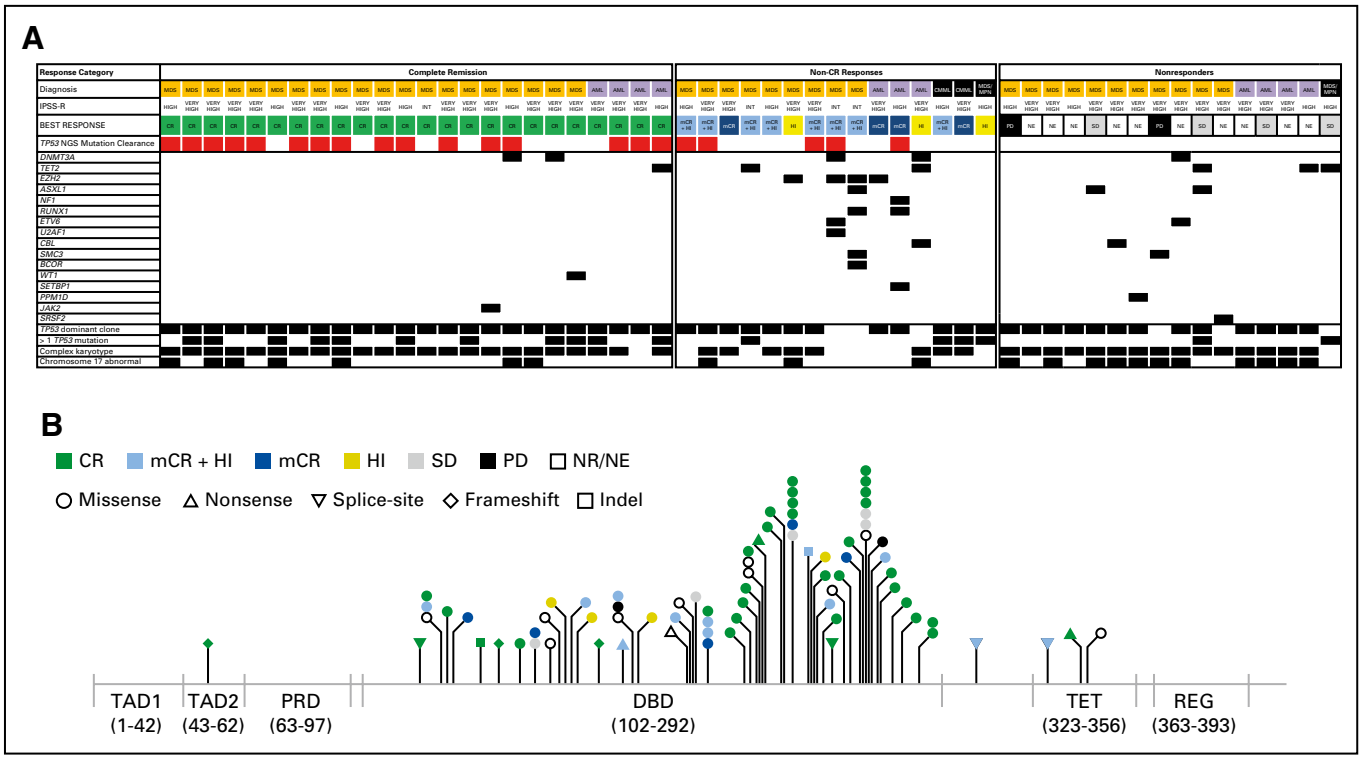

FIG 1. (A) Heat map of individual patient baseline risk characteristics including molecular and genetic features and best response to treatment, and (B) matchstick plot of *TP53* mutation types and locations by best response. AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; DBD, DNA-binding domain; HI, hematologic improvement; INT, intermediate; IPSS-R, revised International Prognostic Scoring System; mCR, marrow complete remission; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic syndromes/myeloproliferative neoplasms; NE, not evaluable; NR, not reported; ORR, overall response rate; PD, progressive disease; PRD, proline-rich domain; REG, C-terminal regulatory domain; SD, stable disease; TAD, transactivation domain; TET, tetramerization domain.

mutation in the DNA-binding domain. A lollipop plot of all variants is shown in Figure 1B. Co-occurring somatic mutations were found in 38% of patients, of which *TET2* (11%) and *DNMT3A* (9%) were the most common (Data Supplement).

The median age of the cohort was 66 years, and 53% were female. The majority of patients had MDS (73%) and 93% had high or very high revised International Prognostic Scoring System. Most patients (69%) were transfusion-dependent at baseline. No patients progressed during the first two cycles of treatment. The disposition of all patients is shown in the Data Supplement. At the time of the data cutoff date, three (5%) patients were continuing study treatment and 22 (40%) had discontinued study treatment to proceed to HSCT. The median time to HSCT was 5.6 months (range, 1.7-9.7 months). Ten (18%) patients were in post-transplant follow-up at the time of data cutoff, and 13 (24%) discontinued treatment because of progressive disease. The rates of discontinuation were similar for patients with MDS and AML. The median treatment duration was 5.2 months (range, 0.4-16.8 months).

Safety

In the dose-escalation phase, no DLTs were observed in 12 patients across the three eprenetapopt dose levels (six were treated with eprenetapopt 100 mg/kg/d LBM) during the eprenetapopt monotherapy phase or in combination with azacitidine. During the eprenetapopt monotherapy lead-in, adverse events (AEs) of any grade that were reported in ≥ 3 patients included nausea (n = 4), peripheral sensory neuropathy (n = 4), and dizziness (n = 3) (Data Supplement). In addition, grade 3 and 4 AEs are listed in the Data Supplement, and AEs assessed related to eprenetapopt treatment (most were grade 1 or 2) are listed in the Data Supplement. All neurologic AEs were fully reversible upon treatment with prochlorperazine and/or temporary eprenetapopt treatment interruption. The RP2D of eprenetapopt with azacitidine was 100 mg/kg/d LBM, equivalent to 4,500 mg/d fixed dosing by population pharmacokinetics.

The most commonly reported AEs (> 20%) of any grade in patients receiving eprenetapopt and azacitidine are summarized in Table 2. Of these, dizziness (36%), peripheral sensory neuropathy (31%), ataxia (24%), and tremor (20%) were the most frequently reported neurologic events, occurring during the infusion phase and resolving thereafter (Data Supplement). Among the 15 (27%) patients with recurrent neurologic AEs, the initial occurrence was reported in cycle 1, and 14 of 15 patients had a recurrence of the same neurologic AE in subsequent cycles. No recurrent

TABLE 2. AEs of Any Grade Occurring in ≥ 20% of Patients and Grade ≥ 3 (intention-to-treat population)

Patients With Treatment-Emergent AEs	Any Grade	Grade ≥ 3
Nausea	35 (64)	0
Vomiting	25 (45)	1 (2)
Fatigue	24 (44)	0
Constipation	23 (42)	0
Edema	21 (38)	2 (4)
Dizziness	20 (36)	1 (2)
Diarrhea	18 (33)	1 (2)
Febrile neutropenia	18 (33)	18 (33)
Peripheral sensory neuropathy	17 (31)	0
Leukopenia	17 (31)	16 (29)
Dyspnea	16 (29)	1 (2)
Headache	16 (29)	0
Lung infection	16 (29)	14 (25)
Neutropenia	16 (29)	16 (29)
Thrombocytopenia	16 (29)	14 (25)
Cough	15 (27)	1 (2)
Pruritis	14 (25)	0
Anorexia	13 (24)	0
Ataxia or unsteady gait	13 (24)	2 (4)
Fever	12 (22)	1 (2)
Alanine aminotransferase increased	11 (20)	1 (2)
Mucositis oral	11 (20)	0 (0)
Tremor	11 (20)	1 (2)

NOTE. Data are n (%).
Abbreviation: AE, adverse event.

neurologic AEs worsened to grade ≥ 3. The most commonly reported grade ≥ 3 AEs were febrile neutropenia (33%), leukopenia (29%), neutropenia (29%), thrombocytopenia (25%), and lung infection (25%) with < 5% of grade ≥ 3 AEs considered possibly related to eprenetapopt treatment. Three patients had eprenetapopt dose reductions for nausea: two by one dose level and one by two dose levels. No patients had dose reductions because of neurologic AEs. Three patients (5%) discontinued treatment because of AEs: grade 4 sepsis (1), baseline grade 3 creatinine elevation that did not resolve (1), and pneumonia requiring > 28-day dose delay (1), none were treatment-related. The most common serious AEs were febrile neutropenia (25%), lung infection (20%), respiratory failure (7%), and sepsis (7%). By day 30, one (2%) patient had died because of pneumonia and by day 60, two additional patients (5%) had died because of pneumonia and sepsis, respectively, none were treatment-related.

Efficacy

ITT population. Fifty-five patients received combination therapy (ITT cohort); of these, 40 patients had MDS. The ORR was 71%, and the CR rate was 44% (Table 3). By disease subtype, the ORR was 73% for patients with MDS and 64% for those with AML, and the CR rate was 50% for patients with MDS and 36% for those with AML. The median times to ORR and CR were 2.1 months (95% CI, 0.1 to 5.4) and 3.1 months (95% CI, 2.5 to 6.1), respectively. Of the 39 patients who responded, 35 (90%) experienced hematologic improvement by International Working Group criteria. For the 12 patients treated in the dose-escalation phase, after 4 days of eprenetapopt monotherapy, one patient achieved a marrow complete remission (mCR; bone marrow blasts decrease from 18.5% to 0.5% with partial cytogenetic response) and ultimately CR following eprenetapopt and azacitidine therapy.

Response-evaluable population. Individual responses for the 45 patients in the response-evaluable cohort are shown in Figure 2A. The ORR for the overall cohort was 87%: 88% each for patients with MDS (n = 29) and AML (n = 7) (Data Supplement). The overall CR rate was 53%: 61% for patients with MDS and 50% for patients with AML. Cytogenetic responses were observed in 59% of patients (18% partial and 41% complete), with responses highest in the MDS population (70%; 24% partial and 46% complete). The median durations of ORR and CR were 8.0 and 7.3 months, respectively, with no difference between MDS and AML.

Survival

At a median follow-up time of 10.5 months, the median OS in the ITT population was 10.8 months (95% CI, 8.1 to 13.4; Fig 3A), which was similar between the MDS (10.4 months; 95% CI, 7.6 to 13.3) and AML disease cohorts (10.8 months; 95% CI, 5.1 to 16.5). A landmark analysis of responders and nonresponders at 4 months demonstrated significantly longer median OS in responding patients (14.6 months; 95% CI, 12.4 to 16.8) versus 7.5 months in nonresponding patients (95% CI, 6.1 to 8.7 months; hazard ratio, 0.23; P = .0005; Fig 3B). Patients achieving CR and non-CR responses had significantly improved OS compared with nonresponding patients in landmark analysis at 4 months (P = .001; Fig 3C), although the median OS between CR and non-CR responding patients was not significantly different (12.8 [95% CI, 10.8 to 14.7] *v* 14.7 [95% CI, 8.4 to 21.1] months; P = .63). The median OS for patients who were bridged to HSCT was 14.7 months (95% CI, 8.6 to 20.9). HSCT was modeled as a time-dependent covariate in the Cox proportional hazards model, which showed that HSCT was not significantly associated with survival (hazard ratio, 1.01; P = .98). However, patients receiving ≥ 4 cycles of combination therapy prior to HSCT had significantly improved OS compared with those with < 4 cycles (16.1 months; 95% CI, 10.4 to not reported [NR] *v* 9.3 months; 95% CI, 8 to NR months, respectively; P = .01; Data Supplement). The median OS was not reached for patients with *TP53* VAF clearance to < 5% (n = 6) prior to HSCT versus 14.7 months (95% CI,

TABLE 3. Hematological Responses in All Patients and by Disease Type (intention-to-treat population)

Response	All Patients (N = 55)	MDS (n = 40)	AML (n = 11)	MDS/MPN (n = 4)
ORR (95% CI)[a]	39 (71) [57 to 82]	29 (73) [56 to 85]	7 (64) [31 to 89]	3 (75)[b]
Time to first response, months, median (range)	2.1 (0.1-5.4)	1.9 (0.1-5.4)	2.3 (1.2-3.0)	2.7 (2.0-2.9)
Duration of response, months, median [95% CI][c]	8.0 [6.5 to 11.2]	8.4 [6.5 to 13.2]	7.5 [4.2 to NE]	7.4 [NE to NE]
Best response by IWG, n (%)				
CR	24 (44)	20 (50)	4 (36)	0 (0)
PR	0 (0)	0 (0)	0 (0)	0 (0)
mCR + HI	8 (15)	7 (18)	0 (0)	1 (25)
mCR	4 (7)	1 (3)	2 (18)	1 (25)
HI	3 (5)	1 (3)	1 (9)	1 (25)
SD	4 (7)	2 (6)	1 (9)	1 (25)
NE	10 (18)	7 (18)	3 (27)	0 (0)
PD	2 (4)	2 (4)	0 (0)	0 (0)
CR (95% CI)	24 (44) [30 to 58]	20 (50) [34 to 66]	4 (36) [11 to 69]	0 (0)
Time to CR, months, median (range)	3.1 (2.5-6.1)	3.1 (2.5-6.1)	3.2 (2.8-3.5)	NA
Duration of CR, months, median (95% CI)	7.3 [5.8 to NE]	7.3 [5.8 to NE]	7.0 [3.3 to NE]	NA
Cytogenetic response (95% CI)	26 (47) [34 to 61]	23 (58) [41 to 73]	3 (27) [6 to 61]	0[d]
Partial	8 (15) [7 to 27]	8 (20) [9 to 36]	0 (0) [NE]	
Complete	18 (33) [21 to 47]	15 (38) [23 to 54]	3 (27) [6 to 61]	
TP53				
NGS-negative	21 (38)	17 (43)	4 (36)	0
Serial IHC ≤ 5%	26 (47)	19 (48)	6 (55)	NA

NOTE. Data are n (%) unless otherwise stated.

Abbreviations: AML, acute myeloid leukemia; CR, complete remission; HI, hematologic improvement; IHC, immunohistochemistry; IWG, International Working Group; mCR, marrow complete remission; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic syndromes/myeloproliferative neoplasms; NA, not applicable; NE, not evaluable; NGS, next-generation sequencing; ORR, overall response rate; PD, progressive disease; PR, partial remission; SD, stable disease.

[a]Two-sided 95% CIs are based upon Clopper-Pearson.

[b]CI data not provided because of low patient number

[c]Duration of response values reflect the median, min, and max values for response duration at the data cutoff date. Some patients had not progressed or died at this time. As such, these statistics represent the minimum duration of response.

[d]Only one patient had a serial cytogenetic assessment and had no response, two patients had no serial cytogenetic assessment (one not conducted and one no metaphases), and the other one was baseline normal and thus is not applicable.

10.1 to NR) in patients without clearance (n = 12), although this was not statistically significant in this limited data set (P = .56; Data Supplement).

Biomarkers

Evaluation of response biomarkers showed that patients with an isolated *TP53* mutation, that is, absence of a mutation in any other gene by NGS, had a higher rate of CR than those with co-occurring mutations (69% *v* 25%; P = .006). Additionally, p53 protein accumulation, defined as ≥ 10% p53 immunohistochemistry (IHC)$^+$ bone marrow (BM) mononuclear cells at baseline, was associated with CR (66% *v* 13%; P = .01). NGS for *TP53* mutations using a VAF cutoff of 5% showed that 21 (38%) patients achieved NGS negativity. *TP53* VAF clearance was significantly associated with CR (P < .0001; Fig 2B) with a trend for clearance in patients with non-CR responses (P = .061). There was no change in *TP53* VAF clearance in patients without a response (P = .87). Additionally, patients who achieved a CR had significantly lower *TP53* VAF (maximum reduction at disease assessment) than those who achieved a non-CR response (P < .001). The median MRD VAF at maximum clearance was 0.63% (range, 0%-5%) with 2 (4%) patients having undetectable MRD. Similarly, p53 protein clearance on the basis of IHC was significantly associated with CR (P < .0001; Fig 2C) with mild reductions in non-CR responders (P = .066) and nonresponding patients (P = .052) (Data Supplement).

DISCUSSION

The presence of a *TP53* gene mutation in patients with MDS or AML confers a poor prognosis, highlighting the urgent need for novel, effective therapy in this molecularly

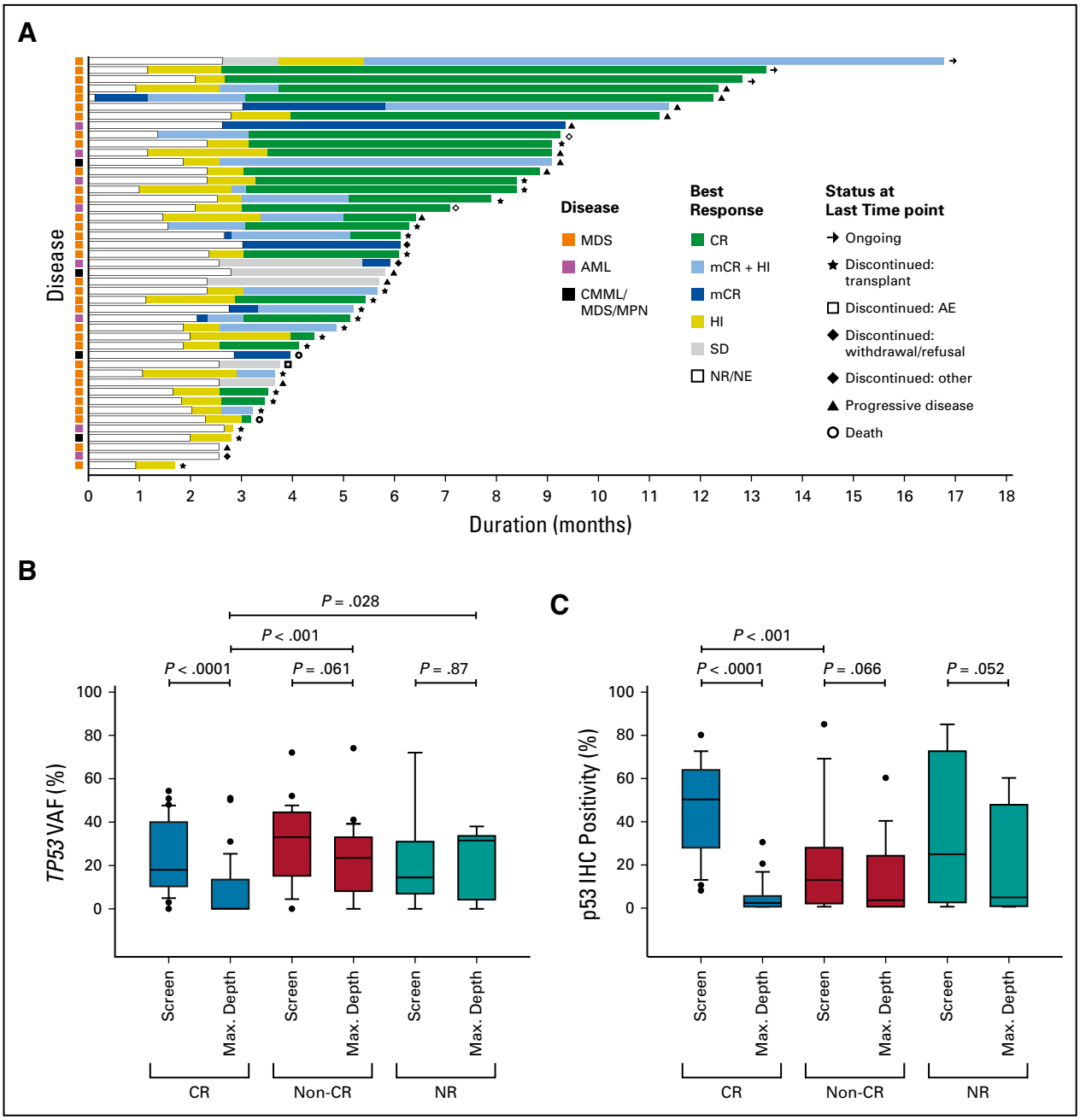

FIG 2. (A) Treatment response and duration for all 45 response-evaluable patients, (B) *TP53* variant allele frequency by best response, and (C) serial p53 IHC positivity by best response. AE, adverse event; AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; CR, complete remission; HI, hematologic improvement; IHC, immunohistochemistry; mCR, marrow complete remission; MDS, myelodysplastic syndromes; MDS/MPN, myelodysplastic syndromes/myeloproliferative neoplasms; NE, not evaluable; NR, not reported; SD, stable disease; VAF, variant allele frequency.

defined subgroup. Patients enrolled to this study comprised very high-risk patients with *TP53*-mutant myeloid malignancies, the majority of whom (91%) had more than one *TP53* mutation, complex cytogenetics, and/or abnormalities in chromosome 17, thus representing a molecular subset with the poorest of outcomes.[8-10,12,28] In this study, treatment with eprenetapopt and azacitidine yielded a high rate of CR (44%, 50% in MDS), which is substantially higher than previously reported for single-agent HMAs in patients with MDS, including those with *TP53* mutations.[9,13,14,29,30] In addition, the majority (90%) of responding patients experienced hematologic improvement with a high degree of cytogenetic clearance (59%) and molecular remission (47% with *TP53* VAF $<$ 5%; 4% undetectable MRD), which is notable given recent data supporting improved OS in patients with *TP53* VAF clearance

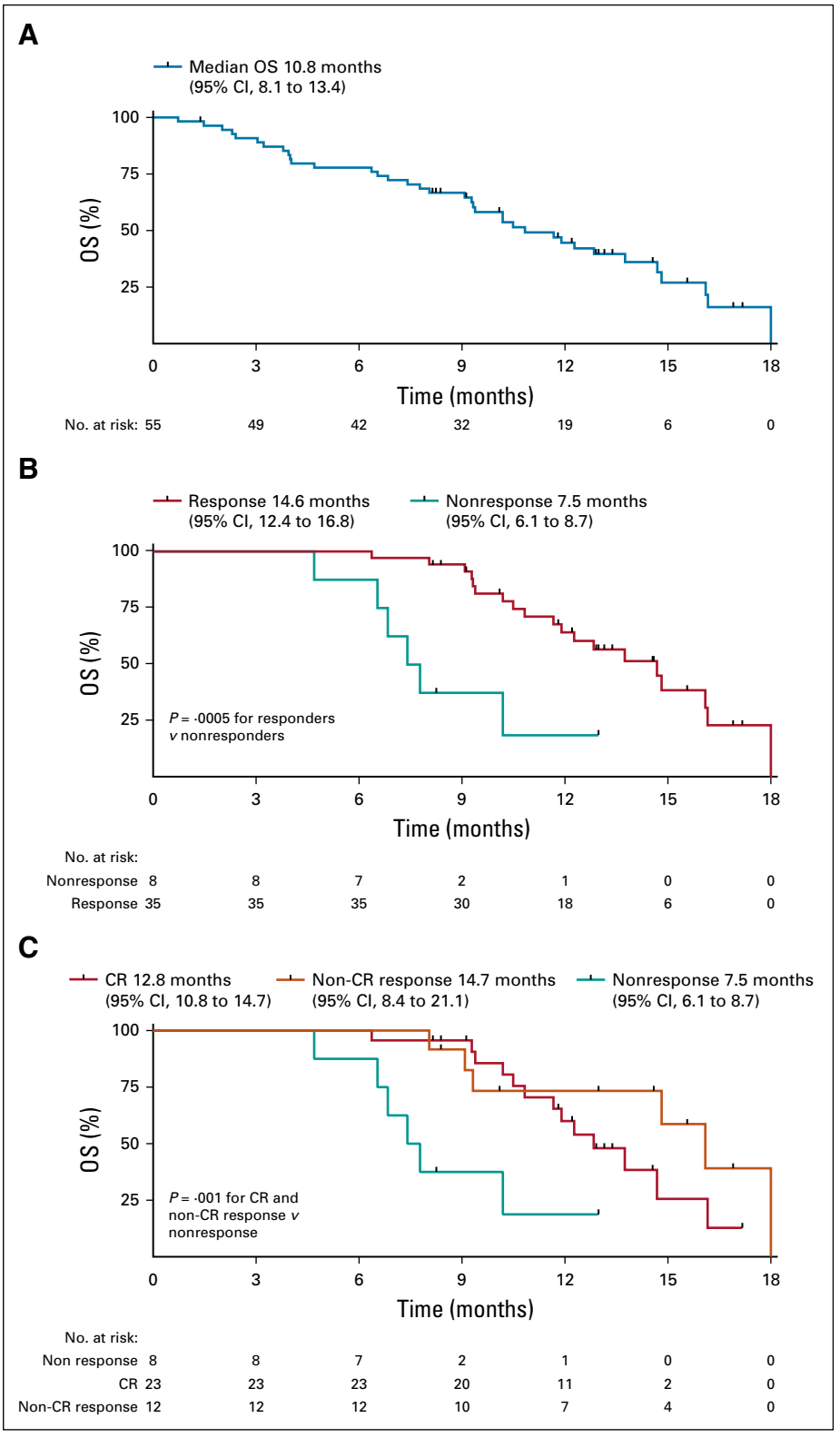

FIG 3. Kaplan-Meier curves for OS (A) in intention-to-treat population, (B) in patients with response versus no response by landmark analysis at 4 months, and (C) in patients with CR and non-CR response versus no response by landmark analysis at 4 months. CR, complete remission; OS, overall survival.

to < 5%, which is rare in patients treated with azacitidine monotherapy.[16,31]

Predefined biomarker analyses identified subgroups with higher rates of response to treatment. Consistent with the mechanism by which eprenetapopt restores wild-type function to the misfolded mutant p53 protein, patients with insufficient p53 levels on baseline BM biopsies (< 10% p53 IHC$^+$ BM mononuclear cells) had significantly lower rates of CR than those who were p53-positive (13% *v* 66%, respectively). Notably, there was only one patient on study who had an isolated nonsense or frameshift mutation where an absence of p53 protein was confirmed by IHC, and this patient did not respond to treatment. Patients with mutant *TP53* without other somatic gene mutations had the highest CR rates (69% *v* 25%). Notably, 100% of CR patients had *TP53* in the dominant clone.

The median OS was 10.8 months in the ITT cohort. Median OS was significantly longer in responding patients than nonresponders by landmark analysis (14.6 *v* 7.5 months; $P = .0005$). These findings compare favourably to historical outcomes with HMA treatment, including azacitidine or low-dose cytarabine administered with venetoclax where median OS was 7.2 and 3.7 months, respectively.[32,33] Combination of azacitidine with other novel agents such as magrolimab and pevonedistat are in development for *TP53*-mutant MDS or AML[34,35] and if warranted on the basis of promising data could be studied in novel combinatorial approaches to further improve outcomes in this patient population.

Historically, the proportion of patients with MDS who proceed to HSCT is < 10%.[36] Among the 19 (35%) patients who proceeded to HSCT in our study, the median OS of 14.7 months was encouraging. As patients experienced a deepening of cytogenetic and molecular responses over time, a longer duration of azacitidine and eprenetapopt prior to HSCT may be important to reduce the risk for relapse. Indeed, our study showed that median OS was significantly longer in patients who received at least four cycles of treatment.

The combination of eprenetapopt and azacitidine was well-tolerated and displayed a similar safety profile to that reported for eprenetapopt and azacitidine monotherapies. The majority of grade ≥ 3 AEs were hematologic with similar frequencies to those reported in a phase III study of azacitidine.[14] Furthermore, AEs with eprenetapopt monotherapy were transient and infusion-related neurologic events, which were generally grade ≤ 2 and similar to those reported previously.[25] Importantly, no treatment-related AEs led to permanent discontinuation of eprenetapopt. Moreover, the mortality rate with the combination was very low (one death within 30 days), which may relate to the more rapid time to response with the eprenetapopt combination.

In conclusion, eprenetapopt in combination with azacitidine is well-tolerated and yields high remission rates in patients with *TP53*-mutant MDS and AML. Consistent with these data, results from a phase II study of eprenetapopt and azacitidine by the Groupe Francophone des Myélodysplasies (ClinicalTrials.gov identifier: NCT03588078) showed comparable response rates.[37] Together, these data support the ongoing pivotal phase III, multicenter, randomized study of eprenetapopt in combination with azacitidine versus azacitidine alone in patients with *TP53*-mutant MDS (ClinicalTrials.gov identifier: NCT03745716).

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DATA SHARING STATEMENT

Data and clinical protocols are available from the corresponding author David Sallman (david.sallman@moffit.org). Details of the study are also available at www.clinicaltrials.gov/ct2/show/NCT03072043.

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Eprenetapopt (APR-246) and Azacitidine in *TP53*-Mutant Myelodysplastic Syndromes

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