Phase 2 Results of APR-246 and Azacitidine (AZA) in Patients with *TP53* mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML)

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Introduction:

TP53 gene mutations (m*TP53*), found in up to 20% of MDS or AML pts and 30-40% of therapy-related (TR) MDS/AML cases, represent a distinct molecular cohort with poor outcomes. Hypomethylating agents (HMA) are the standard of care with CR rates of ~20% and median OS of 7-8 months. APR-246 is a novel, first-in-class small molecule that selectively induces apoptosis in m*TP53* cancer cells via thermodynamic stabilization of the p53 protein and shifting equilibrium toward the wild-type conformation. We previously reported the Phase 1b results of APR-246+AZA with no DLTs, transcriptional activation of p53 targets and high response rates, identifying a Phase 2 (P2) dose of 4500mg days 1-4 (Sallman et al., ASH 2018). We report herein the planned, completed phase 2 results.

Methods*:*

This is a multicenter Phase 1b/2 trial of APR-246+AZA in HMA-naïve m*TP53* higher risk MDS, MDS/MPN and oligoblastic AML (≤ 30% blasts) pts (NCT03072043). P2 pts received APR-246 4500mg IV (days 1-4) + AZA 75 mg/m^2 SC/IV x 7 days (days 4-10 or 4-5 and 8-12) in 28 day cycles. Primary objective was CR rate by International Working Group (IWG) 2006 criteria. Secondary objectives included ORR, OS, outcome following allogeneic hematopoietic stem cell transplant (allo-HSCT), and both next generation sequencing (NGS) and p53 immunohistochemistry (IHC) to monitor clonal suppression and remission depth as prognostic covariates. For minimal residual disease (MRD) analysis, a custom target-capture NGS assay was developed using unique molecular Identifiers for error correction with a 0.1% limit of detection.

Results:

As of July 15, 2019, 55 pts were enrolled (6 P1; 49 P2) with a median age 66 years (34-85; 47% male). By WHO, 40 pts had MDS, 11 AML-MRC and 4 CMML/MDS-MPN; 85% had complex cytogenetics and 33% TR-MDS/AML. All pts had higher risk disease by IPSS-R (7% Intermediate, 24% High, 69% Very High). Fifty pts (91%) had a *TP53* missense mutation in the DNA binding domain with multiple mutations in 18 (33%), and median variant allele frequency (VAF) of 25%. In 34 pts (62%), *TP53* was the sole mutation. Median time on treatment is 154 days (11-392) with 8 pts ongoing. Eighteen pts (33%; 40% of evaluable pts) discontinued study treatment to proceed to allo-HSCT. Treatment (Tx)-related AEs in ≥ 20% of pts included nausea/vomiting (58%), dizziness (31%), constipation (24%), neuropathy (22%), leukopenia (22%) and thrombocytopenia (20%; all G1/G2 except cytopenias (G3/G4). Tx-related febrile neutropenia and anemia occurred in 9% and 5% of pts with no other G3/G4 event in >1 pt. Thirty and 60 day mortality was 2% (n=1) and 6% (n=3), respectively.

At data cutoff, 45pts were response evaluable with a median follow up of 10.5 months (Fig 1A). ORR by IWG was 87% (39/45) with 24 CR (53%), 8 marrow CR (mCR)+HI (18%), 3 HI alone (7%), and 4 with mCR (9%). Of 6 non-responders, 4 had stable disease and 2 pts had progressive disease.

Median time to response was 2.1 months (0.1-5.4) and median duration of response of 6.5 months. CR rate for MDS was 61% (20/33), 50% for AML (4/8) and 0% for MDS/MPN (0/4) with an 88% ORR rate for MDS/AML and 75% for MDS/MPN. An isolated m*TP53* was predictive for a higher CR rate (69% vs 25%; *P*=.006) with a trend for higher ORR (93% vs 75%; *P*=.17). Additionally, pts with $\geq$10% p53 IHC^{+} BM-MNC was a covariate associated with higher CR rate (66% vs 13%; *P*=.01). Complete and partial cytogenetic response occurred in 41% (n=18) and 18% (n=8) of pts, respectively. On serial *TP53* NGS using a VAF cutoff of 5%, 39% (n=21) of patients achieved NGS negativity, which was associated with improved OS (12.8 vs 9.2 months; *P*=.02). In NGS^{-} pts, the median MRD VAF at maximum clearance was 0.63% (0.0%-5%) with 5 pts (11%) MRD negative. By intention-to-treat analysis, median OS was 11.6 months (95% CI 9.2-14) with significantly longer OS in responding pts (12.8 vs 3.9 months; *P*<.0001). Pts undergoing allo-HSCT had improved median OS (16.1 [95% CI 11.6-NE] vs 9.2 [95% CI 6.3-13.7] months), with a 1-year OS of 66% vs 29% in pts who were not transplanted (*P*=.002; Fig 1B). All NGS^{-} pts prior to allo-HSCT remain alive at date cutoff.

Conclusions:

APR-246+AZA is a well-tolerated combination with high response rates in m*TP53* MDS/AML. Response durations are promising accompanied by a high fraction of cytogenetic and deep molecular remissions leading to encouraging outcomes post-HSCT. These data support the ongoing, randomized phase 3 study of APR-246+AZA versus AZA alone in m*TP53* MDS (NCT03745716).

APR-246 Combined with Azacitidine (AZA) in *TP53* Mutated Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). a Phase 2 Study By the Groupe Francophone Des Myélodysplasies (GFM)

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Introduction:

TP53 mutated (*TP53m*) MDS and AML have very poor outcome irrespective of the treatment received, including 40% responses (20% CR) with azacitidine (AZA) with short response duration and a median overall survival (OS) of about 8 months (Bejar, Blood 2014). APR-246 is a prodrug spontaneously converted to methylene quinuclidinone (MQ), a Michael acceptor that binds covalently to cysteines in mutant p53, leading to protein reconformation that reactivates its pro apoptotic and cell cycle arrest functions. The combination of AZA and APR 246 showed promising results in a phase Ib study in *TP53m* MDS (Sallman, ASH 2018). We report interim results of a GFM phase 2 study of AZA+ APR-246 in *TP53m* MDS and AML, conducted in parallel with a similar US MDS consortium study.

Patients and Methods:

The study included hypomethylating agent (HMA) naïve and not previously allografted intermediate, high or very high IPSS-R *TP53m* MDS and AML adult patients. Patients received APR-246 4500 mg IV /d (6 hour infusions) (days 1-4) followed by AZA 75 mg/m²/d (days 4-10) in 28 day cycles. Response (primary endpoint, assessed by IWG 2006 for MDS and ELN criteria for AML) was evaluated after 3 and 6 cycles in the intent to treat (ITT) population, ie all patients who had received any protocol treatment, and in patients who had at least a blood and bone marrow evaluation after cycle 3 (evaluable population). Allo-SCT, when possible, was proposed after 3 to 6 cycles, and treatment with reduced APR 246 and AZA doses could be continued after allo-SCT.

Results:

53 patients were enrolled between Sept 2018 and July 2019 in 7 GFM centers, with a median age of 73 years (range 44-87), and M/F: 28/25. 34 patients had MDS (including 74% very high IPSS-R) and 19 had AML. IPSS-R cytogenetic risk was very poor in 30/34 MDS, and unfavorable in 18/19 AML, complex in 89% of the patients. Median baseline mutated *TP53* VAF was 21% (range 3-76).

Nineteen of the 53 patients had been included at least 7 months before date of analysis (25 July 2019), had received protocol treatment and were thus potentially evaluable for response after 6 treatment cycles (ITT population). One of them died after only one cycle from an unrelated cause (cerebral ischemic stroke), and 2 during the third cycle (from bleeding and sepsis, respectively). In the remaining 16 patients (evaluable population per protocol), the response rate was 75% including 9 (56%) CR, 3 (19%) marrow CR or stable disease with hematological improvement (HI), and 4 treatment resistance. In the ITT population, the response rate was 63%, including 47% CR, and 16% stable or marrow CR+ HI. Among CR patients, complete cytogenetic CR and negative NGS for TP53 mutation (VAF cutoff of 2%) were achieved in 7/9 (78%) and 8/8 (100%), respectively. So far, 1 patient has undergone allo-SCT.

All 53 patients had received at least one treatment cycle, and no increased myelosuppression, compared with AZA alone, was apparent. Treatment related AEs observed in ≥ 20% of patients

were febrile neutropenia in 19 (36%) and neurological AEs in 21 (40%) of the patients. The latter, reviewed with a neurological team, were mainly grade 1 or 2 and consisted of ataxia (n=13), sometimes associated with cognitive impairment (n=4), suggesting a cerebellar origin. Other patients experienced acute confusion (n=4), isolated dizziness (n=3) and facial paresthesia (n=1). Neurological AEs reached grade III in 3 cases (1 acute confusion, 2 ataxia). Occurrence of neurological AEs was correlated with lower glomerular filtration rate at treatment onset ($p<0.01$) and higher age ($p=0.05$). Neurological symptoms spontaneously regressed within 5 days of drug discontinuation (after a median of 1 day). They did not recur in the following cycles after per protocol APR 246 dose reductions.

Conclusion:

In this very high-risk elderly population of *TP53m* MDS and AML, generally with complex karyotype, a promising 56% CR rate at 6 cycles was reached in the evaluable population with AZA+ APR 246 combination, with deep molecular remission in all CR patients. We observed manageable neurologic AEs, mainly in elderly patients with reduced renal function, who therefore require close monitoring and dose reduction if necessary. An update regarding safety and efficacy in the 53 patients, including survival data, will be available at the meeting. A phase III international trial comparing AZA alone and AZA+ APR 246 in *TP53m* MDS is ongoing.