Preliminary results from an open-label, phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CMML) and other myelodysplastic/myeloproliferative neoplasias (MDS/MPNs)

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BACKGROUND

- Tipifarnib is a potent and highly selective farnesyl transferase (FT) inhibitor
  - All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates[1,2]
    - HRAS is uniquely dependent on farnesylation for membrane localization and signaling activation
    - NRAS and KRAS can use redundant forms of prenylation (geranylgeranylation and farnesylation), which may lead to resistance to FT inhibition
  - Oncogenic RAS pathway mutations (*NRAS*, *KRAS*, *CBL*, and *PTPN11*) are seen in approximately 30% of patients with chronic myelomonocytic leukemia (CMML) and are associated with a proliferative phenotype[3]
    - Previous trials of tipifarnib in myelodysplastic syndrome (MDS) without genetic selection yielded insufficient clinical activity to support registration, although evidence of single-agent activity was reported[4]
    - Tipifarnib had a manageable safety profile as single-agent therapy (<25% treatment discontinuation)
  - Initial findings suggested tipifarnib may have greater activity in patients with RAS wild-type (wt) CMML
    - A 2017 study met the primary endpoint, with objective responses observed in 3/9 evaluable patients with RAS wt CMML[5]
    - Protocol was amended to include additional cohorts of patients with MDS/myeloproliferative neoplasms (MPNs)

AIMS

- To report preliminary efficacy, safety and relevant genomic data from a Phase 2 study of tipifarnib in patients with CMML and MDS/MPN

METHODS

- This Phase 2 study was designed to investigate the antitumor activity of tipifarnib in patients with MDS/MPN and CMML. Patients must be ≥18 years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 – 2.
- Study design
  - **Cohorts**: MDS/MPN and CMML
  - Tipifarnib 400 mg orally twice daily on Days 1 – 21 of 28-day treatment cycles; dosing was selected based on two previous AML studies that showed optimal benefit/risk at selected dose
  - **Primary endpoint:** To assess objective response rate (ORR), based on MDS/MPN International Working Group criteria,[6] in KRAS/NRAS wt and mutant populations of patients with CMML
- Clinical trial information: NCT02807272

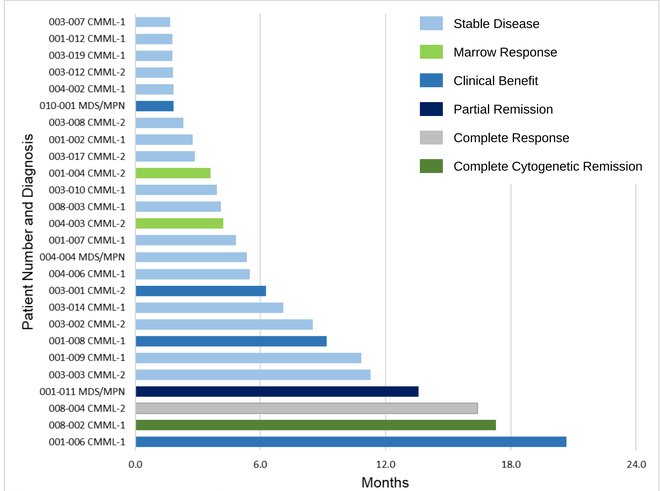
RESULTS

TABLE 1. PATIENT DISPOSITION
RESULTS BASED ON PRELIMINARY DATA AS OF 20 JANUARY 2020

	Total
Patients enrolled, n	42
Patients treated (per protocol), n (%)	39 (100)
CMML	33 (84.6)
CMML-1	23/33 (69.7)
CMML-2	10/33 (30.3)
MDS/MPN	6 (15.4)
Prior lines of therapy, n (%)	
Hypomethylating agent	18 (46.1)
Experimental therapy	15 (38.5)
Hydroxyurea	8 (20.5)
Stem cell transplant	2 (5.1)
No prior therapy	14 (35.9)
RAS wild-type (wt), n (%)	31 (79.5)
RAS mutant (mut), n (%)	8 (20.5)
Baseline ECOG performance status n, (%)	
0	8 (20.5)
1	29 (74.4)
2	2 (5.1)

CMML, chronic myelomonocytic leukemia; ECOG, Eastern Cooperative Oncology Group; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm.

Figure 1. Best Response and Duration of Response for Patients With CMML or MDS/MPN



CMML, chronic myelomonocytic leukemia; MDS/MPN, myelodysplastic syndrome/myeloproliferative neoplasm.

RESULTS (CONT.)

Tipifarnib Activity in Patients with CMML and MDS/MPN Neoplasms

- Of the 42 patients enrolled, the majority were ≥65, and 59% were male
- Patients received a median of 1 prior therapeutic intervention (range 0-6); 46.1% (18/39) received a prior hypomethylating agent
- Among the 32 efficacy-evaluable patients, 9 (28.1%) objective responses were seen (1 complete response [CR], 1 complete cytogenetic remission [cCR], 1 partial remission [PR], 2 marrow response [MR], 4 clinical benefit [CB])
- Objective responses were similar between the KRAS/NRAS wt and KRAS/NRAS mutant populations, with ORRs of 23.8% (5/21) and 25% (3/12), respectively

- **Figure 1** demonstrates:
  - 38.5% (10/26) of patients with a best response of at least stable disease (SD) were on treatment for >6 months
  - 65.4% (17/26) had a best response of stable disease (SD)
  - Higher risk CMML-2 patients had a more favorable response to tipifarnib than CMML-1 patients
    - Among the 9 CMML-2 responses were 1 CR, 2 MR, and 1 CB, whereas among the 14 CMML-1 responses were 1 cCR and 2 CB

Safety and Tolerability

- All patients had ≥1 treatment-emergent adverse event (TEAE)
  - 38 (97.4%) had ≥1 study drug-related TEAE
  - 14 (35.9%) had ≥1 study drug-related serious adverse event (SAE)
  - There were no study drug-related deaths
- Toxicities were consistent with the known safety profile of tipifarnib
- Grade ≥3 drug-related TEAEs occurring in ≥10% of pts were hematological-related events (thrombocytopenia, neutropenia, anemia), gastrointestinal disturbances (nausea, vomiting, diarrhea) and fatigue
- 28.6% discontinued due to an adverse event (AE; **Table 2**)

RESULTS (CONT.)

TABLE 2. REASONS FOR TREATMENT DISCONTINUATION

	Per-protocol set (n=39)
Total discontinuations	36
Reasons for discontinuation, n (%)	
Progressive disease	15 (42.9)
AE	10 (28.6)
Withdrew consent	7 (20.0)
Other	2 (5.7)
Death	1 (2.9)
PI decision	1 (2.9)

AE, adverse event.

CONCLUSIONS

- In this ongoing Phase 2 trial, tipifarnib demonstrated modest antitumor activity in CMML and other MDS/MPN overlap neoplasms
  - 38.5% of patients who responded to tipifarnib were on therapy for 6 months or longer
  - Tipifarnib was generally well tolerated and had a manageable safety profile
- Tipifarnib responses do not appear to be dependent on KRAS/NRAS mutational status
- Tipifarnib may provide a treatment alternative for a population of patients with limited options, providing disease stabilization, and may serve as a bridge to transplant

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