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Final results of a phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CMML) and other myelodysplastic /myeloproliferative neoplasms (MDS/MPN)

Mrinal M. Patnaik[1*], Mikkael A. Sekeres[2], Amy DeZern[3], Selina Luger[4], Lisa Sproat[5], Rafael Bejar[6], Gabriela Hobbs[7], Gail J. Roboz[8], Mollie Leoni[9], Bridget Martell[9] and Eric Padron[10]

[1]Mayo Clinic, Rochester, MN, USA , [2]University of Miami, FL, USA , [3]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA, [4]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA, [5]Mayo Clinic, Phoenix, AZ, USA, [6]UC San Diego Moores Cancer Center, La Jolla, CA, USA, [7]Massachusetts General Hospital, Boston, MA, USA, [8]Weill Cornell Medicine, New York, NY, USA, [9]Kura Oncology, Boston, MA, USA, [10]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA

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
  - CXCR4 and CXCR2 are involved in bone marrow homing of myeloid cells
    - CXCL12/CXCR4 pathway is a potential target of FT inhibitors based upon work in T Cell Lymphomas[3]
- 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[4]
- Initial findings suggested tipifarnib may have greater activity in patients with RAS wild-type (wt) CMML, while activity in MDS/MPN with high CXCR4/CXCR2 may be predictive of activity[5]

METHODS

A phase 2 study (NCT02807272) evaluating the efficacy and safety of tipifarnib in patients with CMML and other MDS/MPN

Enrollment based on Key Eligibility Criteria → **Tipifarnib Treatment (N=44)**
400 mg orally, BID on days 1-21 of 28-day treatment cycles

Primary Objective:
Objective response rate (ORR) per MDS/MPN IWG criteria
- CMML: KRAS/NRAS wt
- MDS/MPN: high and low CXCR4/CXCR2

Key Secondary Objectives:
Adverse event (AE) profile according to NCI CTCAE v 4.03
PFS and OS at 1 year
Duration of response

Study sponsored by Kura Oncology

**Conflict of interest disclosure: advisory board for Kura Oncology*

RESULTS

Demographics

- For CMML patients, 26 (70.3%) were CMML-1 and 11 (29.7%) were CMML-2
- The most common prior anti-cancer therapies for patients with CMML were azacytidine (22%), hydrea (11%), and hydroxyurea (11%)
- The most common prior anti-cancer therapies for patients with MDS/MPN were decitabine (29%) and hydroxyurea (29%)

Patients	CMML (N=37)	MDS/MPN (N=7)
Median Age, y (min, max)	71 (57, 80)	69 (64, 76)
Gender, n (%)		
Male	22 (59%)	3 (43%)
Female	15 (41%)	4 (57%)
Race, n (%)		
White	31 (84%)	7 (100%)
Black or African American	3 (8%)	0 (0%)
Asian	2 (5%)	0 (0%)
Other	1 (3%)	0 (0%)
Any prior anti-cancer therapy		
Yes	23 (62%)	4 (57%)
No	14 (38%)	3 (43%)
Baseline EOG performance status		
0	6 (16%)	2 (29%)
1	29 (78%)	5 (71%)
2	2 (5%)	0 (0%)

Safety

- All patients had at least one treatment related AE
- Fifteen (34%) patients had at least one serious treatment related AE
- Seven (16%) patients discontinued tipifarnib due to treatment related AEs
- No treatment-related deaths occurred

Most Common Treatment-related AEs (≥20%) for CMML or MDS/MPN	CMML (N=37)	MDS/MPN (N=7)	Total (N=44)
Platelet count decreased	21 (57%)	3 (43%)	24 (55%)
Anemia	20 (54%)	3 (43%)	23 (52%)
Nausea	17 (46%)	5 (71%)	22 (50%)
Diarrhea	17 (46%)	1 (14%)	18 (41%)
Fatigue	13 (35%)	4 (57%)	17 (39%)
Neutrophil count decreased	13 (35%)	1 (14%)	14 (32%)
Blood creatinine increased	12 (32%)	1 (14%)	13 (30%)
Decreased appetite	10 (27%)	2 (29%)	12 (27%)
White blood cell count decreased	8 (22%)	3 (43%)	11 (25%)
Lymphocyte count decreased	5 (14%)	2 (29%)	7 (16%)
Hypokalemia	4 (11%)	2 (29%)	6 (14%)
Gastroesophageal reflux disease	0 (0%)	2 (29%)	2 (5%)

Efficacy

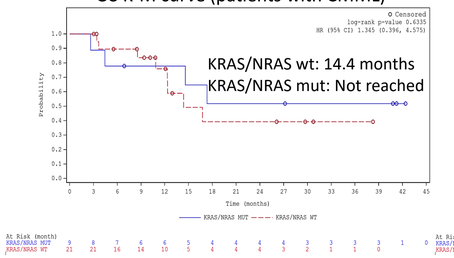
- For patients with CMML, ORR regardless of KRAS/NRAS mutational status was 21.9% (7/32); 14.3% (3/21) in KRAS/NRAS wt and 33.3% (3/9) in KRAS/NRAS mutant (mut). Duration of response was 14.6 months for KRAS/NRAS wt , and not reached for KRAS/NRAS mut.
- For patients with MDS/MPN, ORR was 25.0% including both high and low CXCR4/CXCR2 levels

Best Response (CMML)	KRAS/NRAS Wt (N=21)	KRAS/NRAS Mut (N=9)	KRAS/NRAS Missing (N=2)	Total (N=32)
Complete cytogenetic remission	0 (0%)	1 (11.1%)	0 (0%)	1 (3.1%)
Marrow response	2 (9.5%)	1 (11.1%)	0 (0%)	3 (9.4%)
Clinical benefit^	1 (4.8%)	1 (11.1%)	1 (50.0%)	3 (9.4%)
Stable disease	15 (71.4%)	5 (55.6%)	1 (50.0%)	21 (65.6%)
Progressive disease	3 (14.3%)	1 (11.1%)	0 (0%)	4 (12.5%)
Objective response rate	3 (14.3%)	3 (33.3%)	1 (50.0%)	7 (21.9%)

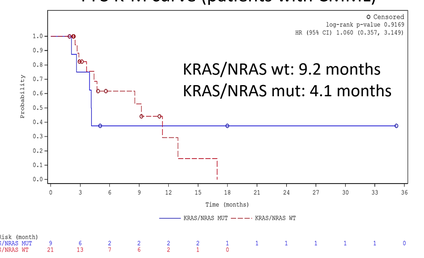
^symptom assessment was not performed

Best Response (MDS/MPN)	CXCR4/CXCR2 High (N=1)	CXCR4/CXCR2 Low (N=3)	Total (N=4)
Partial remission	0 (0%)	1 (33.3%)	1 (25.0%)
Stable disease	1 (100%)	1 (33.3%)	2 (50.0%)
Progressive disease	0 (0%)	1 (33.3%)	1 (25.0%)
Objective response rate	0 (0%)	1 (33.3%)	1 (25.0%)

OS K-M curve (patients with CMML)



PFS K-M curve (patients with CMML)



(Sample size too small to display the OS and PFS curves for patients with MDS/MPN)

CONCLUSIONS

- Overall, data from this phase 2 study showed tipifarnib was reasonably well-tolerated.
- Modest efficacy was demonstrated in a difficult-to-treat population with limited therapeutic options.
- Although small numbers, the initial hypotheses surrounding KRAS/NRAS mutational status and CXCR4/CXCR2 levels were not supported.

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