Preliminary results from an open-label, phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CMML)

Mrinal M. Patnaik[1], David A. Sallman[2], Mikkael A. Sekeres[3], Selina Luger[4], Rafael Bejar[5], Gabriela Hobbs[6], Amy DeZern[7], James Bolognese[8], Mary Traynor[9], Vishnu Mishra[10], David Wages[9], Antonio Gualberto[9], Catherine Scholz[9] and Eric Padron[2]

[1]Mayo Clinic, Rochester, MN, USA , [2]H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA, [3]Cleveland Clinic, Cleveland, OH USA, [4]Abramson Cancer Center at the University of Pennsylvania School of Medicine, Philadelphia, PA USA, [5]UC San Diego Moores Cancer Center, La Jolla, CA, USA, [6]Massachusetts General Hospital, Boston, MA, USA, [7]Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD, USA, [8]Cytel, Cambridge, MA, USA, [9]Kura Oncology, Inc., Cambridge, MA USA, [10]Kura Oncology, Inc., San Diego, CA, USA

BACKGROUND

Tipifarnib:

- **Potent and highly selective inhibitor of farnesyl transferase (FT)**
  - All RAS isoforms (KRAS/NRAS/HRAS) are FT substrates. HRAS is uniquely dependent upon farnesylation alone. NRAS and KRAS are susceptible to redundant forms of prenylation and may lead to resistance to FT inhibition.
  - Oncogenic RAS pathway mutations (NRAS, KRAS, CBL and PTPN11) are seen in approximately 30% of CMML patients[a] (pts) and are associated with a proliferative phenotype.
- Previous trials without genetic selection yielded insufficient clinical activity to support registration, though evidence of single agent activity had been reported.
  - In a prior study, 26/82 intermediate-high risk pts (32%) responded to tipifarnib, including 8 pts with CMML-1 and 9 with CMML-2 (WHO Classification): 12 (15%) complete responses (CRs) and 14 (17%) hematologic improvements; 37 (45%) had stable disease (modified International Working Group criteria, 2006). In poor-risk CMML-2 (n = 9), tipifarnib yielded a 22% CR rate, with an overall median survival of 11.9 months (95% CI, 7.1-17.1)[b].
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

METHODS

Phase 2 study designed to investigate the antitumor activity of tipifarnib in 20 evaluable pts with CMML (aged ≥ 18 yrs and ECOG PS 0-1) and retrospectively stratified based on KRAS/NRAS mutational status.

Study Design

- Tipifarnib 900 mg orally twice daily on Days 1 – 7 and 15 – 21 in 28-day cycles
- **Primary endpoint:** Overall response rate (ORR) per Myelodysplastic/Myeloproliferative International Working Group (MDS/MPN IWG) criteria[c] with the probability that the TRUE underlying ORR rate exceeds historical control rate 0.1 computed via Bayesian methodology.
- **Secondary endpoints:** safety and tolerability, duration of response (DOR) and progression free survival (PFS).
- **Biomarkers:** serial next-generation sequencing, gene expression profiling of pre- and on-treatment bone marrow samples by RNASeq and flow cytometry based monocyte and immune cell subsets analyses

Clinical trial information: NCT02807272

RESULTS

Results based on preliminary data as of 07 November 2017.

PATIENT DISPOSITION

Total Treated	n (%)	24 (100)
CMML-1	n (%)	17 (70.8)
CMML-2	n (%)	7 (29.2)
Prior Lines of Therapy	Median (Range)	1 (0 – 3)
Total Discontinuations	n (%)	13 (54.2)
Reasons for Discontinuation:		
Adverse Event	n (%)	4 (17)
PI Decision	n (%)	2 (8.3)
Progressive Disease	n (%)	6 (25)
Withdrawal of Consent	n (%)	2 (8.3)
Total Efficacy Evaluable	n	16[†]
RAS wildtype (wt)	n (%)	9 (56)
RAS mutant (mut)	n (%)	7 (44)

[†]5 pts (3 KRAS mut, 2 RAS wt) discontinued prior to first response assessment; 3 pts (2 RAS wt, 1 RAS unknown) have not reached first response assessment

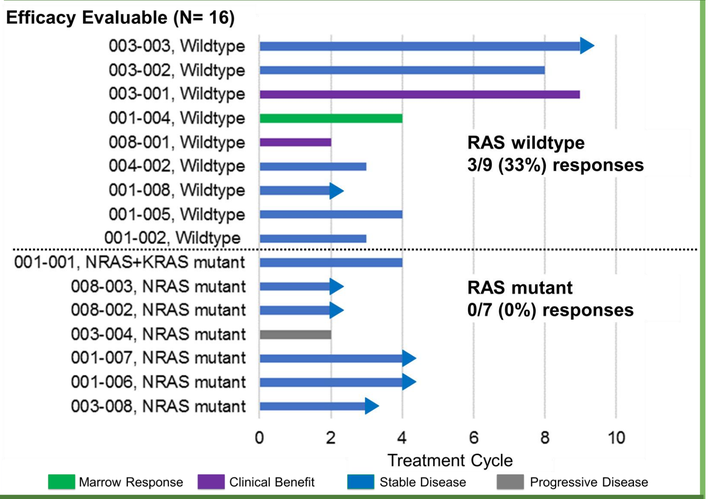
SAFETY & TOLERABILITY

- Toxicities were consistent with the known safety profile of tipifarnib.
- Grade ≥ 3 drug-related TEAEs occurring in ≥ 10% of pts were hematology related: thrombocytopenia (38%), anemia (24%), neutropenia (14%) and leukopenia (17%). Additionally, one Gr 4 tumor lysis syndrome and one possible Gr 4 acute hepatitis were observed.
- Myelosuppression was manageable with treatment interruption, dose reductions and/or transfusion support.
- Starting dose was reduced from 1200 mg to 900 mg twice daily on days 1-7 and 15 -21 of 28-day treatment cycles due to frequent myelosuppression and azotemia.

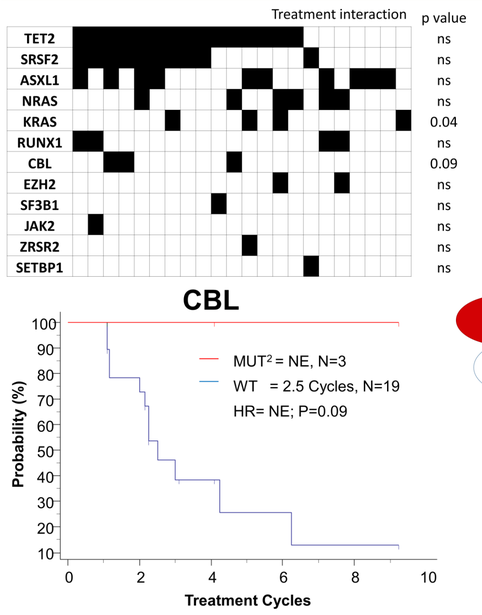
PRIMARY ENDPOINT MET, ORR 33% IN RAS WT

- 2 Stratums:
  - Pts with tumor KRAS and NRAS wild type status
  - Pts with either tumor KRAS mutant, NRAS mutant or double mutant status.
- Bayesian Design:
  - Trial success criteria was defined as >80% probability that the TRUE underlying ORR rate is > 0.1, given the observed results of the trial (with and without informative prior N=10 with ORR=0.2).
  - ORR = CR + CytoCR + PR + MR + CB
- **Primary Endpoint achieved for the RAS wildtype stratum with at least 96% probability**
  - Informative Prior (per protocol analysis): 99% probability of success (PoS)
  - Uninformed Prior: 96% PoS

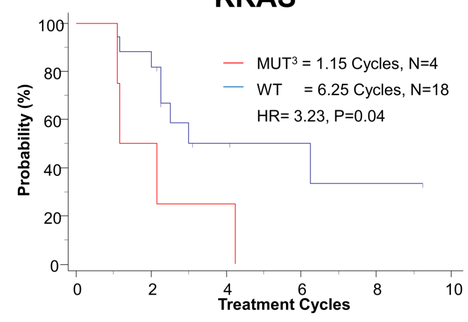
BEST RESPONSE AND TIME ON STUDY



RAS PATHWAY MUTATIONS MAY AFFECT TREATMENT DURATION[1]



- The presence of activating KRAS mutations translated to poor prognosis.
- Both KRAS hot spots and exon 4 mutations appeared equally deleterious.
- Loss of the KRAS mutant clones (1%, 2%) was observed in one pt who remained 4 cycles on study.
- No significant effect observed with NRAS; however, NRAS clone expansion was observed in 2 pts.
- A trend for better prognosis was observed in pts with inactivating CBL mutations.



1. 22 treated pts with CMML mutation data (Pathogenic SNVs, Genoptix)
2. (001-006) E479fs, C384Y, C404Y; allele frequency 7-15%. (003-001) C384Y; 36%. (003-010) C404Y; 84%
3. (001-001) A146T, A146V; allele frequency 1-2%. (003-007) G12S; 43%. (004-001) Q61H; 44%. (007-001) K117; 18%

CONCLUSIONS

- **The primary endpoint of the study was met with an ORR of 33% in CMML patients whose tumors are RAS wildtype. These preliminary data may support further study of tipifarnib for the treatment of CMML.**
- **Tipifarnib was generally well-tolerated. Most common treatment-related AEs (grade ≥ 3) were myelosuppression, including thrombocytopenia, anemia, neutropenia and leukopenia.**

REFERENCES

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Corresponding author:
Eric.Padron@moffitt.org