Tipifarnib is Highly Active in HRAS-mutant Lung Squamous Cell Carcinoma Tumor Models

Linda Kessler1, Catherine Scholz2, Antonio Gualberto2, Yi Liu1 and Francis Burrows1

1Kura Oncology, Inc., San Diego, CA, USA, 2Kura Oncology, Inc., Cambridge, MA, USA

BACKGROUND
- Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FT) that catalyzes the post-translational attachment of farnesyl groups to proteins that require localization to the inner cell membrane. Although all RAS isoforms (KRAS/NRAS/HRAS) are FT substrates, HRAS is exclusively dependent upon farnesylation for membrane localization and signaling activation, making HRAS mutant tumors uniquely susceptible to tipifarnib-mediated inhibition of FT.
- HRAS is the most commonly mutated RAS species in both lung squamous cell carcinoma (LSCC) and head and neck squamous cell carcinoma (HNSCC), observed in approximately 2% and 5% of cases, respectively (TCGA, Nature 2012 and 2015).
- Recent evidence supports the clinical utility of tipifarnib for treatment of HRAS-mutant LSCC as well as in HNSCC and illustrates the potential for tipifarnib in the treatment of HRAS-mutant LSCC.

GENOMIC PROFILING OF SQAMOUS TUMORS HAS REVEALED IMPORTANT SIMILARITIES BETWEEN LUNG SQUAMOUS CELL CARCINOMA (LSCC) AND HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC).

- Gene signatures have been described that correlate common molecular characteristics across squamous cell carcinomas including head and neck, lung, cutaneous, gastrointestinal and gynecologic cancers.3


Cluster analysis of 12 pathologically defined cancer types using DNA methylation, RNA expression, copy number, RPPA and miRNA shows strong correlation between LSCC and HNSCC tissue types

Comparison TCGA data for most frequently mutated genes in LSCC and HNSCC shows correlation in mutation frequency

TP53
KMT2C
CDKN2A
FAF1
PIK3CA
NOTCH1
RB1
CASP8
HRAS
HLA-A

Lung squamous cell carcinoma (LSCC)

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Solid Tumors with HRAS mutations

Cohort 1: Thyroid Cancer
Cohort 2: SCC (excluding HNSCC)
Cohort 3: Other / HNSCC
HNSCC Extension Enrollment ongoing

CONCLUSIONS
- Treatment of HRAS-mutant LSCC PDX models induces tumor regressions, which is similar to the activity of tipifarnib observed in HRAS-mutant HNSCC PDX models.
- Clinical activity, including durable partial responses have been observed in patients with HRAS-mutant HNSCC in the ongoing RUN-HN trial.
- These data demonstrate that HRAS is a targetable mutation in LSCC as well as in HNSCC and illustrate the potential for tipifarnib in the treatment of additional HRAS-mutant squamous cell carcinomas.

Poster #4917, AACR Annual Meeting April 14-18th, 2018

Tipifarnib is active in model resistant to cetuximab

Cetuximab vehicle

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