Farnesyl Transferase Inhibitors- Evolution from Targeting HRAS to Overcoming Adaptive Resistance to Targeted Therapies

Shivani Malik

5th RAS-Targeted Drug Development Summit
September 26-28, 2023
Disclosures

- Employee of Kura Oncology, Inc.
FTIs and the RAS Family of Oncogenes

- Tipifarnib—first-in-class FTI, originally developed to target KRAS
- Upon farnesyl transferase inhibition, KRAS and NRAS become geranylgeranylated
- HRAS is an obligate farnesylation target—it lacks the geranylgeranylation rescue pathway
Tipifarnib Demonstrates Durable Anti-Tumor Activity in Patients with Recurrent or Metastatic HRAS-Mutant HNSCC

Patients with high variant allele frequency (VAF, ≥20%) mHRAS HNSCC

Red, PR; blue, SD; green, not evaluable for efficacy; diamond, patient initiated treatment at 600 mg twice a day; cross, patient withdrew consent; arrow in bar, start of response; arrow, active treatment. Numbers at the end of the bars represent VAF for each patient.

Efficacy—evaluable patients with HRAS mutant variant allele frequency (VAF) ≥ 20% and serum albumin ≥ 3.5 g/dL, or HRAS VAF ≥ 35%

One patient treated off-protocol through compassionate use

Ho et al. ASCO 2020 #6504 (preliminary exploratory data as of 9/30/19)

Tipifarnib: n = 20; median PFS = 5.6 months
Last prior therapy: n = 19; median PFS = 3.6 months
Cox regression: n = 0.0012

Median OS (months) 95% CI
HNSCC with high VAF, including additional patient (N=18) 15.4 7.0 46.4

Ho et al. ASCO 2020 #6504 (preliminary exploratory data as of 9/30/19)
Can FTIs Be Clinically Effective in a Broader HNSCC Population?

Comprehensive genomic profiling using Tempus XT reveals HRAS- and/or PIK3CA-dependence in HNSCC

HRAS-PIK3CA crosstalk in HNSCC - Tipifarnib blocks hyperactivated growth factor signaling at multiple nodes, including HRAS and RHEB
Combined Tipifarnib and Alpelisib Inhibits mTOR Reactivation for the Entire Dosing Interval

RHEB, An Obligately Farnesylated Protein, is a Key FTI Target

Tipifarnib blocks localization of RHEB to the lysosomes

RHEB depletion enhances mTOR inhibition when combined with alpelisib in PIK3CA mutant HNSCC cells

<table>
<thead>
<tr>
<th>WCL</th>
<th>lysosomes</th>
<th>1 μM tipifarnib (48 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>+</td>
<td>RHEB</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>LAMP1</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>β-tubulin</td>
</tr>
</tbody>
</table>

**CAL33 – PIK3CA H1047R**

siControl

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

siRHEB

<table>
<thead>
<tr>
<th>0</th>
<th>1</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

250 nM alpelisib (hr)

<table>
<thead>
<tr>
<th>RHEB</th>
<th>p-AKT (S473)</th>
<th>p-p70 S6K (T389)</th>
<th>p-S6 (S235/236)</th>
<th>p-S6 (S240/244)</th>
<th>p-4EBP1 (S65)</th>
<th>β-actin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**CAL33 – PIK3CA H1047R**

Durable Clinical Response Observed in Patient with PIK3CA-dependent HNSCC

- **35yo, male, nonsmoker, HPV16 positive**
- SCC of tonsil Stage III cT4N2M0; PD-L1 CPS = 60
- Prior Treatments
  - CDDP/rad for 1 mo (Nov-Dec2019), BOR UNK
  - Cemiplimab/ISA101b (Jun-Nov2021), BOR PD
- **PIK3CA R88Q mutation** (44%) and HRAS OE (3+ staining in 100% of tumor cells) by IHC from May 2021 biopsy
  - DL1 tipifarnib, DL2 alpelisib; completed 6 cycles
- G1/2 TRAE, G3 lipase elevation; presented clinical benefit and improvement in respiratory symptoms
  - 81% reduction in target lesions after 1 cycle of treatment
  - 84% reduction in target lesions after 3 cycles (BOR)
- Continued on-study for >27 weeks maintaining QoL

Soifer H et al, ENA 2022 PB041; Data cut as of 14Sep2022; Preliminary raw data
Mechanism-Based Combinations Needed to Fully Realize the Potential of Breakthrough KRAS$^{G12C}$ Inhibitors

pERK inhibition by KRAS$^{G12C}$ inhibitors hyperactivates RTK signaling leading to ERK-RSK and/or mTOR-S6 pathway activation

cell growth and survival
• FTIs represent an attractive therapeutic and commercial opportunity in oncology with compelling options in combination with other targeted therapies
• KO-2806 is a potent next-generation FTI designed to improve upon potency, pharmacokinetic and physicochemical properties of earlier FTI drug candidates
• IND application cleared by FDA; on track to initiate Phase 1 study of KO-2806 in 2H 2023
Combination of KO-2806 and adagrasib has superior antitumor effect compared with adagrasib monotherapy

Adagrasib - 100mg/kg, QD
***. p<0.001
KO-2806 Deepens Signaling Inhibition by Adagrasib in KRAS$^{G12C}$-Mutant NSCLC Tumor Spheroids: Inhibition of MAPK Signaling

100 nM adagrasib (hr)

HER3
p-MEK1/2 (S217/221)
p-ERK1/2 (T202/204)
p-p90 RSK (S380)
p-AKT (S473)
RHEB
p-mTOR (S2481)
p-mTOR (S2448)
p-p70 S6K (T389)
p-S6 (S235/236)
p-S6 (S240/244)
p-4EBP1 (T37/46)
p-4EBP1 (S65)
p-Rb (S807/811)
Cleaved PARP
Cleaved caspase 3
β-actin

MAPK inhibition

Cell cycle arrest & apoptosis
KO-2806 Deepens Signaling Inhibition by Adagrasib in KRAS\textsuperscript{G12C}-Mutant NSCLC Tumor Spheroids: Strong Inhibition of mTOR Signaling

<table>
<thead>
<tr>
<th>+72 hr 1\textmu M KO-2806</th>
<th>0</th>
<th>6</th>
<th>24</th>
<th>48</th>
<th>0</th>
<th>6</th>
<th>24</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER3</td>
<td>![HER3 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-MEK1/2 (S217/221)</td>
<td>![p-MEK1/2 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-ERK1/2 (T202/204)</td>
<td>![p-ERK1/2 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-p90 RSK (S380)</td>
<td>![p-p90 RSK Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-AKT (S473)</td>
<td>![p-AKT Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHEB</td>
<td>![RHEB Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-mTOR (S2481)</td>
<td>![p-mTOR S2481 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-mTOR (S2448)</td>
<td>![p-mTOR S2448 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-p70 S6K (T389)</td>
<td>![p-p70 S6K Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-S6 (S235/236)</td>
<td>![p-S6 S235/236 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-S6 (S240/244)</td>
<td>![p-S6 S240/244 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-4EBP1 (T37/46)</td>
<td>![p-4EBP1 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-4EBP1 (S65)</td>
<td>![p-4EBP1 S65 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-Rb (S807/811)</td>
<td>![p-Rb Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleaved PARP</td>
<td>![Cleaved PARP Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cleaved caspase 3</td>
<td>![Cleaved caspase 3 Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-actin</td>
<td>![β-actin Image]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

100 nM adagrasib (hr)

mTOR inhibition

Cell cycle arrest & apoptosis
KO-2806 Deepens Signaling Inhibition by Adagrasib in KRAS$^{G12C}$-Mutant NSCLC Tumor Spheroids: HER3 Inhibition
KO-2806 Deepens Signaling Inhibition by Adagrasib in KRAS^{G12C}-Mutant NSCLC Tumor Spheroids: Induction of Cell Cycle Arrest and Apoptosis
KO-2806-Adagrasib Combination Reduces mTOR and RSK Activation, Increases Apoptosis and Blocks Proliferation in vivo
KO-2806-Adagrasib Combination Increases the Depth of Response Compared to Adagrasib Monotherapy

Adagrasib - 100mg/kg, QD

Response calls based on mRECIST
PD-Progressive disease
SD-Stable disease
PR-Partial response
KO-2806-Adagrasib Combination Increases the Duration of Response Compared to Adagrasib Monotherapy

NCI-H2030

\((K\text{RAS}^{G^{12C}})\) NSCLC CDX

**stop dosing**

\[ \begin{align*}
\text{Tumor Volume (mm}^3) & \quad \text{Treatment Days} \\
0 & \quad 0 \quad 5 \quad 10 \quad 15 \quad 20 \quad 25 \quad 30 \quad 35 \quad 40 \quad 45 \quad 50 \\
0 & \quad 500 \quad 1000 \quad 1500 \quad 2000 \quad 2500 \quad 3000 \\
\end{align*} \]

*** \( p < 0.001 \)

NCI-H2030

\((K\text{RAS}^{G^{12C}})\) NSCLC CDX

Change in tumor volume (%)

Day46 vs Day0

Vehicle
KO-2806
Adagrasib
KO-2806+Adagrasib
Summary

• FTIs have the promise to enhance antitumor activity of targeted therapies in solid tumors
  • FTIs in combination with KRAS\textsuperscript{G12C} inhibitors drive tumor regressions and durable responses in preclinical NSCLC models
  • First demonstration of a durable clinical response with combination of FTI tipifarnib with alpelisib in patient with PIK3CA-mutant HNSCC

• FTIs are efficacious and tolerable and work by blocking oncogenic signaling at multiple nodes to enhance antitumor efficacy in combinations
  • FTIs potently inhibit adaptive mTORC1 signaling (S6K and 4EBP1) when combined with appropriate partner drugs in biomarker-defined tumors.
  • In addition to mTOR, FTIs target additional key oncogenic nodes in the adaptive response to KRAS inhibitors, including upstream RTK signaling and HRAS
  • FTIs are likely to exhibit less on-target toxicity compared to both mTOR kinase inhibitors and rapalogs by sparing mTORC2
Acknowledgements

The patients and their families

Kura Oncology
Translational Research group

Francis Burrows
Hetika Vora Patel
Stacia Chan
Alison Smith
Linda Kessler
Lyn Gatchalian
Yahu Liu
Asako McCloskey
Quinn Reilley
Betsy Gonzalez

Patel H et al. The next generation farnesyltransferase inhibitor, KO-2806, blocks oncogenic signaling at multiple nodes to enhance the antitumor efficacy of KRAS$^{G12C}$ inhibitor adagrasib in KRAS$^{G12C}$ NSCLC (B025)

Smith A et al. The next-generation farnesyltransferase inhibitor KO-2806 constrains compensatory signaling reactivation to deepen responses to KRAS$^{G12D}$ inhibition (B023)

Gatchalian J et al. KO-2806, a next-generation farnesyltransferase inhibitor, potentiates the antitumor activity of cabozantinib in RCC (B024)