Preliminary results from a phase 2 proof of concept trial of tipifarnib in tumors with HRAS mutations

Alan Ho¹, Nicole Chau², Deborah J. Wong³, Maria E. Cabanillas⁴, Jessica Bauman⁵, Marcia S. Brose⁶, Keith Bible⁷, Valentina Boni⁸, Irene Brana⁹, Charles Ferte¹⁰, Caroline Even¹⁰, Francis Burrows¹¹, Linda Kessler¹¹, Vishnu Mishra¹¹, Kelly Magnuson¹¹, Catherine Scholz¹¹ and Antonio Gualberto¹¹

¹ Memorial Sloan Kettering Cancer Center, New York, NY USA, ² Dana-Farber Cancer Institute, Boston, MA USA, ³ UCLA Medical Center, Santa Monica, CA USA, ⁴ The University of Texas MD Anderson Cancer Center, Houston, TX, USA, ⁵ Fox Chase Cancer Center, Philadelphia, PA, USA, ⁶ Abramson Cancer Center at the University of Pennsylvania School of Medicine, Philadelphia, PA USA, ⁷ Mayo Clinic, Rochester, MN, USA, ⁸ START Madrid-CIOCC, Madrid, Spain, ⁹ Vall D’Hebron Institute of Oncology, Barcelona, Spain, ¹⁰ Gustave Roussy, Villejuif, France, ¹¹ Kura Oncology, San Diego, CA, USA
Off-label use of drugs will be discussed.
Mutant HRAS Oncogene Activity is Uniquely Dependent on Farnesylation

- RAS superfamily (KRAS/NRAS/HRAS) members require the covalent addition of a hydrophobic group to their C-terminal tail (known as “prenylation”) for membrane localization and downstream signaling.

- **Farnesyltransferase (FT)** catalyzes the attachment of farnesyl groups to RAS proteins and other cell signaling proteins.

- NRAS and KRAS are susceptible to redundant forms of prenylation, but HRAS can only be farnesylated.

**CENTRAL HYPOTHESIS:**
HRAS driven malignancies are uniquely susceptible to FTI therapy.
Tipifarnib: First-in-class FTI

- Potent/highly selective inhibitor of farnesyltransferase (FT) that competitively binds to the CAAX motif\(^1\).
- Previously studied in > 5,000 patients (70+ studies).
- Prior trials without genetic selection yielded insufficient clinical activity to support registration, though anecdotal evidence of single agent durable responses had been reported.
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

\(^1\) End et al. 2001 Cancer Res 61:131-37
Phase 2 Trial in HRAS Mutant Solid Tumors

Solid Tumors with HRAS mutations

Cohort 1: Thyroid Cancer
Enrollment Ongoing

Cohort 2: Other / HNSCC

Cohort 3: SCC (excluding HNSCC)
Enrollment ongoing

HNSCC Extension
Enrollment ongoing

Key Eligibility:
– No curative therapy available
– HRAS mutation
– Measurable disease (RECIST v1.1)
– ECOG PS 0 – 1

Primary Objective: ORR
Design: Simon 2-stage (11+7 pts)
Hypothesis: 10% (H0) vs 30% (H1) ORR, a=0.05, 80% power (4 responses needed)

Tipifarnib 900 mg po bid on Days 1 – 7 and 15 – 21 of 28-day treatment cycles
HRAS Mutations Define a Unique Molecular HNSCC Subset

- The HRAS mutant subset of HNSCC is characterized by low rate of genetic alterations, frequent CASP8 inactivation, and infrequent of TP53 mutation\(^1\).

- It is thought that HRAS/CASP8 alteration converge on NF-κB to induce tumor cell growth and survival\(^1\).

- HRAS mutations in HNSCC are observed in ~5% of cases at initial diagnosis\(^2\).

- An additional 15% of cases may develop during 1L therapy, in subjects treated with cetuximab\(^3\).

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2. Sathyan et al. 2007. Modern Path 20, 1141-8
Tipifarnib in HRAS Mutant HNSCC and Skin SCC Patients

Preliminary data as of 04 October 2017

Patient 005-005 (tracheal)
- Cetuximab, Carboplatin, Paclitaxel, RT
- ~6 mos, SD
- C21

Patient 001-005 (nasopharyngeal)
- Pembrolizumab
- ~2 mos, SD

Patient 005-012 (laryngeal)
- Pembrolizumab, RT
- PD

Patient 005-007 (oral cavity)
- Cetuximab
- PD

Patient 005-009 (oral cavity)
- Cetuximab, Paclitaxel
- PD

Patient 012-001 (oral cavity)
- Nivolumab + Lirilumab
- Nivolumab + Lirilumab
- SD C6

Patient 011-001 (metastatic from primary ear)
- Carboplatin, RT
- ~1 mo, PR
- SD C2
- C6

Tipifarnib

Cetuximab, Carboplatin, Paclitaxel, RT

Pembrolizumab

Pembrolizumab, RT

Cetuximab

Cetuximab

Nivolumab + Lirilumab

Carboplatin, RT

Preliminary data as of 04 October 2017
Durable Response on Tipifarnib after Cetuximab/Chemo/RT

76 yo man with metastatic tracheal SCC
HPV/p16 (-), no tobacco/ETOH
HRAS Q22K (observed in Costello’s Syndrome) and CDKN2A deletion (p14, p16)
Tipifarnib Response in Nasopharyngeal Ca s/p Immunotherapy

Patient 001-005 (nasopharynx)  

Cisplatin  
Pembrolizumab  
Tipifarnib  
Cycle 7  

59 yo female with nasopharynx SCC with HRAS G12D

Baseline  
Cycle 2, 40% reduction  
Cycle 6, 49% reduction

Images provided by Dr. Nicole Chau
Symptom Improvement and Stable Disease in Cutaneous SCC

81 yo male with right ear SCC and history of aggressive disease.
- HRAS G12D, TP53 R110P and R248W mutations.
- Disease stabilization and dramatic reduction in pain medication with tipifarnib treatment.

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<th>Date</th>
<th>Pain Medication</th>
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<td>5/May/2017</td>
<td>Fentanyl patch 100 mcg/h Transmucosal fentanyl 200 mcg for breakthrough pain</td>
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<tr>
<td>16/May/2017</td>
<td>Methadone 5 mg Q 8 hours Transmucosal fentanyl 200 mcg for breakthrough pain</td>
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<td>5/Jul/2017</td>
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Images provided by Dr. Irene Braña
Tipifarnib Regression of Widely Metastatic Laryngeal SCC

55 yo male with metastatic laryngeal SCC (mediastinal LNs, muscle, adrenal gland, lung, bone)
80 pk-years, no current ETOH
HRAS G13V, TP53 R248Q

Patient 05-012 (Laryngeal)

Baseline

Cycle 2, 22% reduction
Tipifarnib Response and Resolution of Disfiguring Skin Lesions s/p Immunotherapy Failure

69 yo man with recurrent oral cavity SCC.
No tobacco/ETOH
HRAS G12S, TP53 R248Q

Initial PR (40% tumor reduction) on Cycle 1 Day 15 (7 days tipifarnib + 7 days rest); 56% size reduction at Cycle 3

Images provided by Dr. Caroline Even and Dr. Charles Ferte
Significant Tumor Size Reduction and Durable Responses Observed in HRASm HNSCC Patients Treated with Tipifarnib

-41% Tracheal 005-005
-30% Oral Cavity 005-009
-49% Nasopharyngeal 001-005
-56% Oral Cavity 012-001
-8.4% Oral Cavity 005-007

-22% Laryngeal 005-012

4 confirmed PRs in 6 (67%) HRAS mutant HNSCC patients treated with Tipifarnib
Conclusions

• First clinical evidence that mutant HRAS is a targetable oncogene.

• Phase 2 proof-of-concept of tipifarnib efficacy for recurrent/metastatic HNSCC carrying HRAS mutations.
  – Confirmed PRs in 4 of 6 HNSCC patients (67%, 22-95% 95% CI)
  – Rapid and durable responses (2 responses >1 year)
  – Activity in disease resistant to chemotherapy, cetuximab and immunotherapy
  – Resolution of disfiguring lesions
  – Decrease in pain and use of pain medication (cutaneous SCC)

• AEs observed are consistent with the known safety profile of tipifarnib
  – ≥ Gr 3 TEAEs included myelosuppression (neutropenia, 31%, anemia 19%, thrombocytopenia 15%), GI disturbances (15%), and increased creatinine (11%) (N=27, overall study).
  – 2 HNSCC required dose reductions for Gr 2 peripheral neuropathy at Cycle 1 and Cycle 10.
  – 3/27 (11%) patients (0/6 HNSCC) discontinued for reasons other than disease progression [(Gr 3 GI (1); Gr 3 Renal (2)]
Acknowledgements

• Patients, their families and caregivers
• Study Investigators and their study teams
• Kura Oncology