Preliminary Results from a Phase 2 Proof of Concept Trial of Tipifarnib in Tumors with HRAS mutations

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Background: HRAS is a proto-oncogene that is mutated in head and neck, bladder, thyroid, and salivary gland tumors, among others. While discovered over 40 years ago, no specific therapies have yet been developed targeting mutant HRAS. Tipifarnib is a potent and highly selective inhibitor of farnesyltransferase, a critical enzyme requisite for HRAS activation. Over 5,000 patients (pts) have been treated with tipifarnib; although responses have been documented in several tumor indications, the mechanisms of response are still poorly understood. Tipifarnib has demonstrated robust activity in HRAS mutant patient derived xenograft (PDX) models of head and neck squamous cell carcinoma (HNSCC) and squamous non-small cell lung cancer that are resistant to standard therapies. This Phase 2 study (NCT02383927) was conducted to test the hypothesis that inhibition of mutant HRAS oncogenic activity with tipifarnib could translate to objective responses in HNSCC pts driven by the HRAS oncogene.

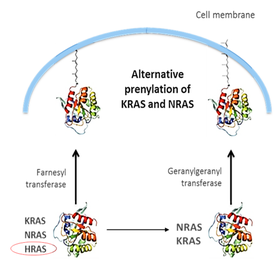
Methods: The study was originally designed to enroll pts into 2 single-arm study cohorts: Cohort 1 (thyroid cancer) and Cohort 2 (other solid tumors), each one with a 2-stage design (11+7 evaluable pts) to determine overall response rate (ORR) as the primary objective. This design has 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.087. Two objective responses were needed to be observed in the first stage for each cohort to proceed to stage 2. The study is considered positive if at least 4 responses are observed in one of the 2 cohorts (N=18 each, stages 1 and 2 combined). The prespecified activity goal for the first stage of accrual in Cohort 2 was met and based on data observed in the first stage of this Cohort, ongoing enrollment to the second stage of Cohort 2 was limited to HRAS mutant HNSCC. For enrollment, pts must have an HRAS mutant, locally advanced/unresectable and/or metastatic solid tumor malignancy and RECIST v1.1 measurable disease. Tipifarnib is given at 900 mg orally twice daily on days 1-7 and 15-21 of 28-day cycles. Response assessments are conducted every 8 weeks.

Results: As of August 30, 2017, 28 pts have been enrolled. Tipifarnib was generally well tolerated with myelosuppression, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue constituting the most common adverse events (≥30% of pts, all grades). Twenty four pts are currently evaluable for efficacy: 10 in Cohort 1 and 14 in Cohort 2. Stage 1 enrollment continues in Cohort 1. The primary objective was met for Cohort 2 prior to completing full enrollment, with 4 confirmed responses observed out of 14 evaluable pts. Notably, of the 6 pts in Cohort 2 with HNSCC currently evaluable for efficacy, 4 (67%) achieved a confirmed partial response. Three of these pts remain on treatment in cycles 3, 5, and 19, and one subject discontinued at Cycle 21. Two (33%) pts had disease stabilization as best response (4 cycles, ongoing and 7 cycles). Importantly, 4 of these pts were refractory to prior therapies, including regimens containing immunotherapy (pembrolizumab, nivolumab) or cetuximab +/- chemotherapy. None of the 6 HNSCC patients experienced an objective partial response on their last prior therapy.

Conclusions: These data suggest that HRAS mutant HNSCC pts may be refractory to standard therapies but can derive prolonged clinical benefit from tipifarnib treatment. Based on the encouraging activity of tipifarnib in pts with HNSCC with HRAS mutations, enrollment continues in this cohort.

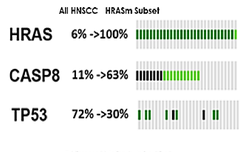
HRAS is Uniquely Dependent on Farnesylation

- **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.



Casey et al. Solski et al. 1989 Proc Natl Acad Sci USA 86:8323-27

HRAS Mutations Define a Unique Molecular Subset of HNSCC

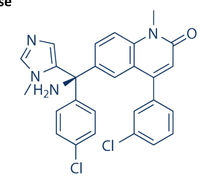


- *HRAS* mutations in HNSCC may result from carcinogenic exposure (e.g. tobacco) and are observed in ~5% of cases at initial diagnosis [1-2] .
- An additional 15% of cases may develop during 1L therapy, in subjects treated with cetuximab [3] .
- The *HRAS* mutant subset of HNSCC is characterized by low rate of genetic alterations, frequent CASP8 inactivation, and infrequent of TP53 mutation [4].
- It is thought that HRAS/CASP8 alteration converge on NF-kB inducing tumor cell growth and survival [4].

1. Cerami et al 2012. Cancer Discov. 2:401-4
2. Sathyan et al. 2007. Modern Path 20, 1141-8
3. Braig et al., Oncotarget 7:42988-42995, 2016
4. Cancer Genome Atlas Network 2015. Nature 517:576-82.

Tipifarnib: First-in-class FTI

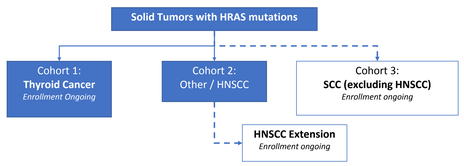
- Potent/highly selective inhibitor of **farnesyltransferase (FT)** that competitively binds to this enzyme CAAX motif binding site [1].
- Previously studied in > 5,000 patients (70+ studies).
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).
- Prior trials without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



Tipifarnib
(in-licensed by Kura Oncology from Janssen)

1. End et al. 2001 Cancer Res 61:131-37

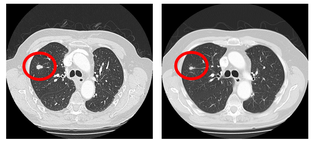
Phase 2 Trial in HRAS Mutant Solid Tumors



- 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, α=0.05, 80% power (4 responses needed)
- Tipifarnib 900 mg po bid on Days 1 – 7 and 15 – 21 of 28-day treatment cycles

Durable Response Post Cetuximab/Chemo/RT

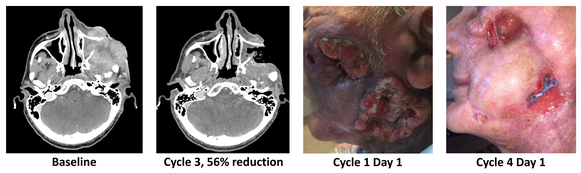
- 76 yo man with metastatic tracheal SCC
- HPV/p16 (-), no tobacco/ETOH; HRAS Q22K and CDKN2A deletion (p14, p16)



Baseline | Cycle 4 Day 22

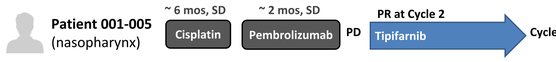
Major Response and Resolution of Disfiguring Skin Lesions Post Nivolumab Failure

- Rapid progression on combination of nivolumab + lirilumab
- Initial PR (40% tumor reduction) on Cycle 1 Day 15 (7 days tipifarnib + 7 days rest); 56% size reduction at Cycle 3

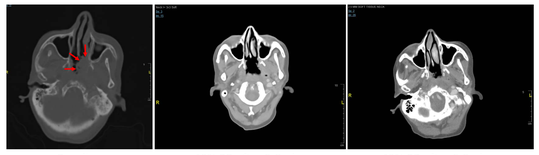


Baseline | Cycle 3, 56% reduction | Cycle 1 Day 1 | Cycle 4 Day 1

Major Response in Nasopharyngeal Ca Post Pembrolizumab Failure



- 59 yo female with nasopharynx SCC with HRAS G12D

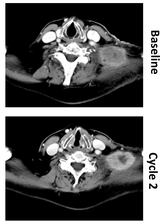


Baseline | 40% PR after 2 Cycles | 49% PR after 6 Cycles

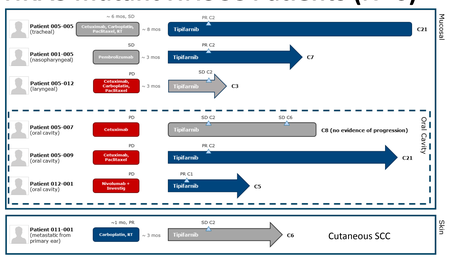
Symptomatic Improvement and Stable Disease in Cutaneous SCC

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

Date	Pain Medication
5/May/2017	Fentanyl patch 100 mcg/h Transmucosal fentanyl 200 mcg for breakthrough pain
16/May/2017	Methadone 5 mg Q 8 hours Transmucosal fentanyl 200 mcg for breakthrough pain
24/May/2017	**C1D1 Tipifarnib – grade 2 pain**
28/May/2017	Pain grade 1. No breakthrough medication needed
5/Jul/2017	Fentanyl patch 50 mcg/h



HRAS mutant HNSCC Patients (N=6)



Summary

- First clinical evidence that mutant HRAS is a targetable oncogene
- Phase 2 proof-of-concept study for tipifarnib in the treatment of recurrent or metastatic HNSCC that carries 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
- AEs consistent with the known safety profile of tipifarnib
  - Severe toxicities included myelosuppression (neutropenia, 30%, anemia 22%, thrombocytopenia 15%), GI disturbances (15%), and increased creatinine (12%) (N=27, overall study)
  - 1/27 patients discontinued due to adverse events

Acknowledgements

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