HRAs are proto-oncogenes that are mutated in head and neck, thyroid, and salivary gland tumors, among others. While discovered over 40 years ago, no effective 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. Our Phase 2 trial in patients (pts) with HNSCC has enrolled 28 pts with HRAS mutations, allowing us to study the anti-tumor activities of Tipifarnib that can only be achieved and assessed in this cohort.

**Background:** HRAS is a proto-oncogene that is mutated in head and neck squamous cell carcinoma (HNSCC) and squamous non-small cell lung cancer that are 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 (HNSCC). It is thought that HRAS/CASP8 alteration converge on NF-kB inducing tumor cell death.

**Methods:** The study was designed to enroll pts into single-arm study cohorts: Cohort 1 (head and neck cancer) and Cohort 2 (other solid tumors), each with one 2-cycle (7 days + 7 days rest) design. The proxpected 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 HNSCC that carries HRAS mutations, ascertainment of genetic alterations is available from archived tumor tissue. Cohort 3 will enroll pts with HNSCC who have progressed on prior therapy.

**Results:** As of August 30, 2017, 28 pts have been enrolled. Tipifarnib was generally well tolerated with manageable safety profile as single agent therapy. The study was originally designed to enroll pts into 2 single-arm study cohorts: Cohort 1: Cohort 2: 1. Cerami et al 2012. Cancer Discov. 2:401-423. 2. Manageable safety profile as single agent therapy. Previously studied in > 5,000 patients (70+ studies). Dose: 1,000 mg orally on days 1-7 and 18-21 of a 28-day cycle. 80% of pts have a confirmed partial response at Cycle 2 (12 responses out of 15 evaluable pts). Tipifarnib is given at WHO tolerated oral dose daily from days 1-7 and 18-21 of 28-day cycles. Response assessments are conducted every 28 days.

**Conclusion:** 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.

**Key Points:**

- HRAS superfamily (HRAS/HRAS/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 HRAS proteins and other cell signaling proteins.
- HRAS and HRAS are susceptible to redundant forms of prenylation, but HRAS can only be farnesylated.

**HRAs are Uniquely Dependent on Farnesylation**

**Phase 2 Trial in HRAS Mutant Solid Tumors**

**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 ~10% of cases at initial diagnosis.**
- **An additional 15% of cases may develop during 31 therapy, in subjects treated with cetuximab.**
- **The HRAS mutant subset of HNSCC is characterized by low rate of genetic alterations, frequent C/A transversions, and inactivation of TPS3 mutation.**

**HR Mutations in HNSCC**

**HRAS G12D, TP53 R110P and R248W mutations**

**Durable Response Post Cetuximab/Chemo/RT**

**HRAS mutant HNSCC Patients (N=6)**

**Major Response and Resolution of Disfiguring Skin Lesions Post Nivolumab Failure**

**Symptomatic Improvement and Stable Disease in Cutaneous SCC**

**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 Pfs in 4 of 6 HNSCC patients (63%, 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**
- **Acs consistent with the known safety profile of tipifarnib**
- **Severe toxicities included myelosuppression (neutropenia, 30%, anemia 22%, thrombocytopenia 10%), GI disturbances (15%), and increased creatinine (12%)**

**Acknowledgements**

The authors would like to acknowledge the participating patients, their families and caregivers, study co-investigators and study teams.