Preliminary Results from a Phase 2 Trial of Tipifarnib in HRAS mutant Head & Neck Squamous Cell Carcinomas (HNSCC).

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BACKGROUND
Tipifarnib: Potent and highly selective inhibitor of farnesyl transferase (FT)
- All RAS isoforms (K Ras/NRAS/HRAS) are FT substrates.
- HRAS is uniquely dependent upon farnesylation alone.
- NRAS and KRAS are susceptible to redundant forms of prenylation and may lead to resistance to FT inhibition.

HRAS MUTATIONS ARE OBSERVED IN AN UNIQUE MOLECULAR SUBSET OF HNSCC
HRAS mutations (~5% of tumors at diagnosis) are present in a distinctive molecular subset of HNSCC, characterized by: 1) low rate of genetic alterations, 2) less frequent TP53 mutation and 3) frequent CASP8 inactivation.

METHODS

Acquired HRAS Mutations Develop during 1st Line Therapy
- Results suggest discovery of a >15% rate of de novo HRAS mutation following cetuximab

RESULTS

PTEN is lost in 82% of HNSCC patients with HRAS mutations (~5% of tumors at diagnosis) are present in a distinctive molecular subset of HNSCC, characterized by: 1) low rate of genetic alterations, 2) less frequent TP53 mutation and 3) frequent CASP8 inactivation.

Tipifarnib was generally well-tolerated.
- AE observed are consistent with the known safety profile of tipifarnib.
- Most common treatment-related AEs (grade ≥ 3) were anemia (33.3%), nausea (22.2%), neutropenia, vomiting and decreased appetite (11.1% each).
- 2 HNSCC patients required dose reductions for grade 2 peripheral neuropathy at Cycle 1 and Cycle 10. 1 HNSCC patient initiated treatment at 600 mg.


CONCLUSIONS
First clinical evidence that mutant HRAS is a targetable oncogene.
- Responses observed in patients with hotspot and non-hotspot mutations.
- Phase 2 proof-of-concept of tipifarnib efficacy for recurrent / metastatic HNSCC carrying HRAS mutations.
- Confirmed PRs in 5 of 6 HNSCC patients (83%, 36-99.6% 95% CI).
- Rapid and durable responses (2 responses > 1.5 year).
- Activity in disease resistant to chemotherapy, cetuximab and immunotherapy.
- Resolution of disfiguring lesions.

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