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

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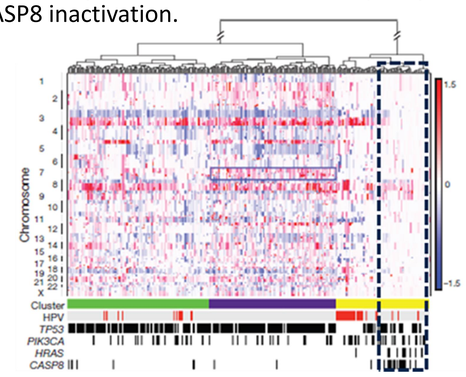
BACKGROUND

Tipifarnib: Potent and highly selective inhibitor of farnesyl transferase (FT)

- All RAS isoforms (KRAS/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.



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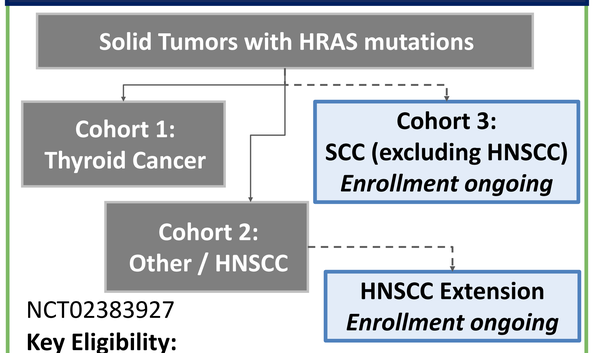
Acquired HRAS Mutations Develop during 1st Line Therapy[1]

- Results suggest discovery of a ~15% rate of de novo HRAS mutation following cetuximab

[1] Braig *et al.*, *Oncotarget* 7:42988-42995, 2016

METHODS



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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)

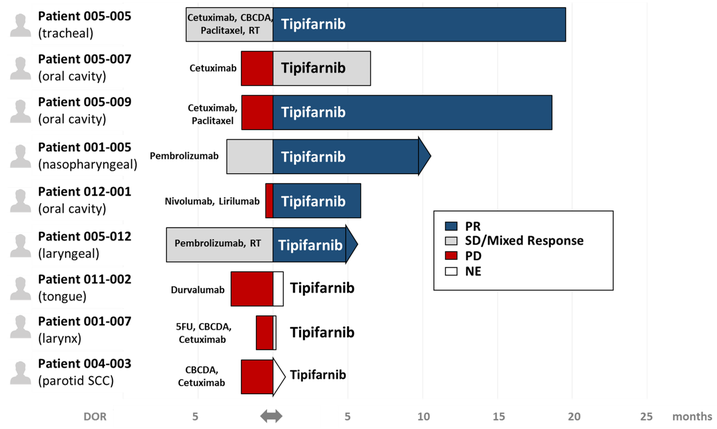
Hypothesis: 10% (H0) vs 30% (H1) ORR, a=0.05, 80% power (4 responses needed)

Tipifarnib: 900 mg po bid on Days 1 – 7 and Days 15 – 21 of 28-day treatment cycles

For patient referral or clinical trial information: medicalaffairs@kuraoncology.com

RESULTS

HRAS mutant HNSCC patients received limited/no benefit from prior therapies, including chemotherapy, cetuximab and immunotherapy



PR: partial response, SD: stable disease, PD: progressive disease, NE: not evaluable, CBCDA: carboplatin, RT: radiotherapy, 5FU: fluorouracil

Results based on preliminary data as of 08 February 2018.

Patient Disposition

Total HRASm HNSCC Treated	n (%)	9 (100)
Larynx	n	2
Oral Cavity	n	4
Pharynx (Nasopharyngeal)	n	1
Other: Trachea, Parotid	n	2
Prior Lines of Therapy	Median (Range)	2 (1 – 4)
Age, yrs	Median (Range)	58 (20 – 76)
Total Discontinuations	n (%)	6 (67)
Progressive Disease	n (%)	4 (44)
Withdrawal of Consent	n (%)	1 (11)
Early Death, unrelated	n (%)	1 (11)
Total Efficacy Evaluable	n	6
Not evaluable by RECIST†	n	3

†011-002 (early death, unrelated); 001-007 (consent withdrawal); 004-003 (too early for disease assessment)

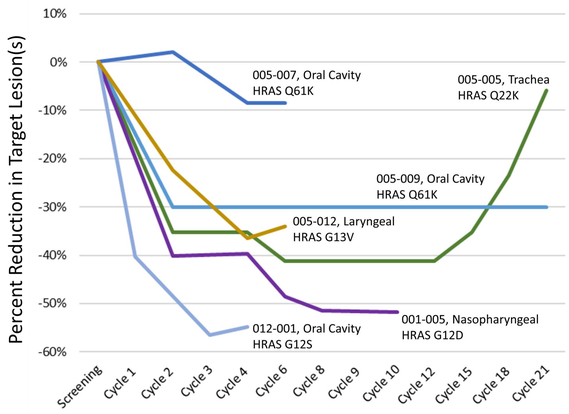
Overall Response Rate (ORR)	**83% (36-99.6%, 95%CI)**	
Overall Best Response		
Confirmed Partial Response	**n (%)**	**5 (83)**
Stable Disease	**n (%)**	**1 (17)**
Progressive Disease	**n (%)**	**0 (0)**

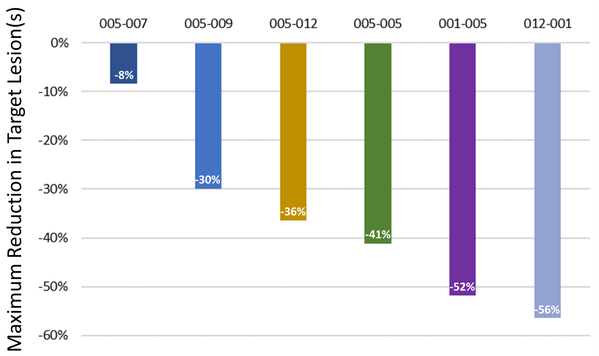
Safety & Tolerability

Tipifarnib was generally well-tolerated.

- AEs 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 Gr 2 peripheral neuropathy at Cycle 1 and Cycle 10. 1 HNSCC patient initiated treatment at 600 mg.

Reduction in target lesions observed in HRASm HNSCC pts treated with Tipifarnib

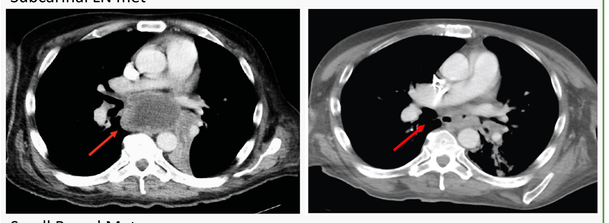




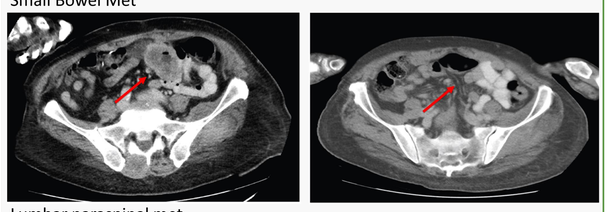
Tipifarnib Regression of Widely Metastatic Laryngeal SCC

- 55 yo male with metastatic laryngeal SCC (005-012, mediastinal LNs, muscle, adrenal gland, lung, bone)
- Prior therapies: cetuximab + carboplatin + paclitaxel and pembrolizumab + RT
- Molecular status: HRAS G13V, TP53 R248Q

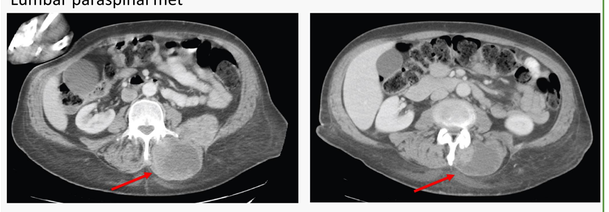
Subcarinal LN met



Small Bowel Met



Lumbar paraspinal met

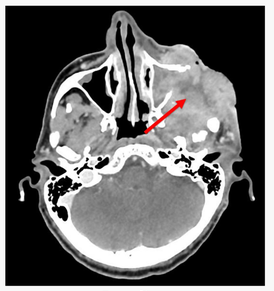


Baseline | Cycle 6, 34% reduction

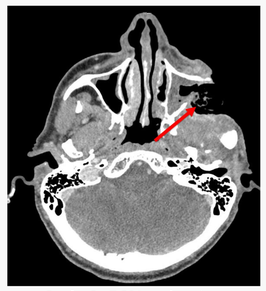
Tipifarnib Response and Resolution of Disfiguring Skin Lesions s/p Immunotherapy Failure

- 69 yo man with recurrent oral cavity SCC (012-001)
- Prior therapies: TPEx (Docetaxel, CDDP, Cetuximab), nivolumab + lirilumab
- Molecular status: HRAS G12S, TP53 R248Q

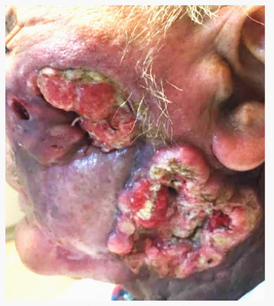
Initial PR (40% tumor reduction) on Cycle 1 Day 15 (7 days tipifarnib + 7 days rest); 56% size reduction at Cycle 3



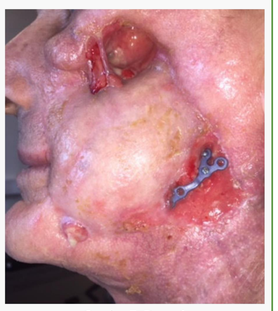
Baseline



Cycle 3, 56% reduction



Cycle 1 Day 1



Cycle 5 Day 1

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