TAT 2017

15th International Congress on
Targeted Anticancer Therapies

Preliminary evidence of clinical activity with tipifarnib in squamous cell carcinomas of the head & neck (SCCHN) with HRAS mutations

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Alan Ho MD PhD

1.	Kura Oncology	Research Support
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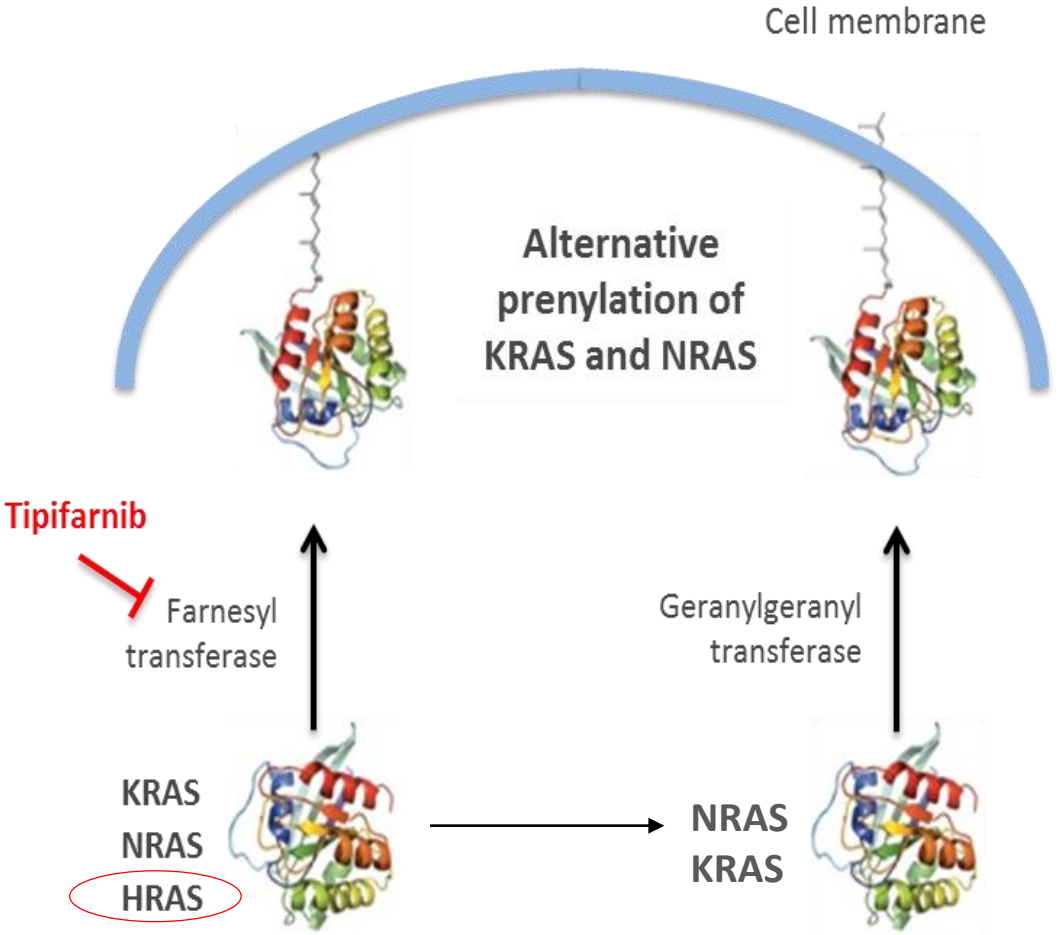
Farnesyltransferase inhibitors (FTIs): Targeting HRAS

- The **RAS superfamily (KRAS/NRAS/HRAS)** require the covalent addition of a hydrophobic group to the 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, <u>but HRAS is uniquely dependent upon farnesylation alone</u>.



CENTRAL HYPOTHESIS: HRAS driven malignancies are uniquely susceptible anti-tumor effects FTI therapy.

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

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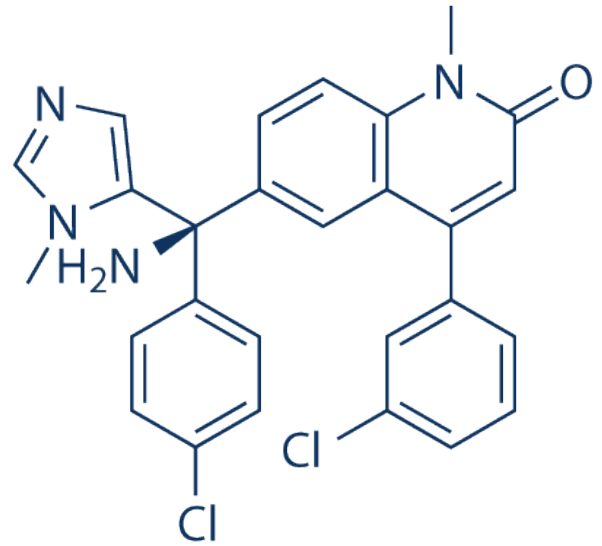
Tipifarnib: First-in-class FTI

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

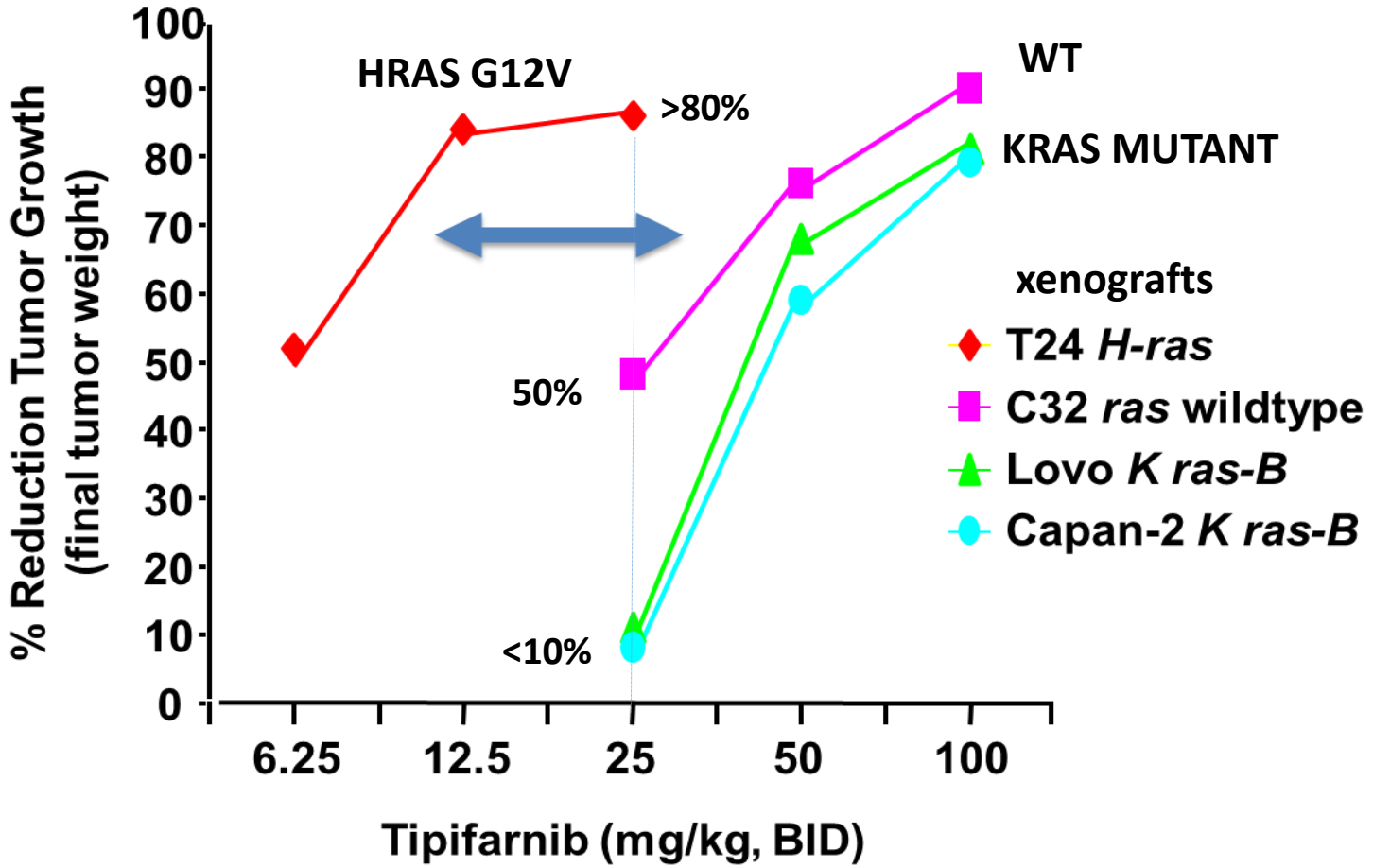
Tipifarnib AEs (472 solid tumors pts): Myelosuppression (neutropenia 25%, anemia 31%, thrombocytopenia 19%); non-hem >25%: fatigue (41%) and GI unspecific (nausea 47%, anorexia 33%, diarrhea 32%, vomiting 32%).



Tipifarnib
(in-licensed by Kura Oncology from Janssen)

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

HRAS Mutant Tumors: Tipifarnib Susceptibility



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

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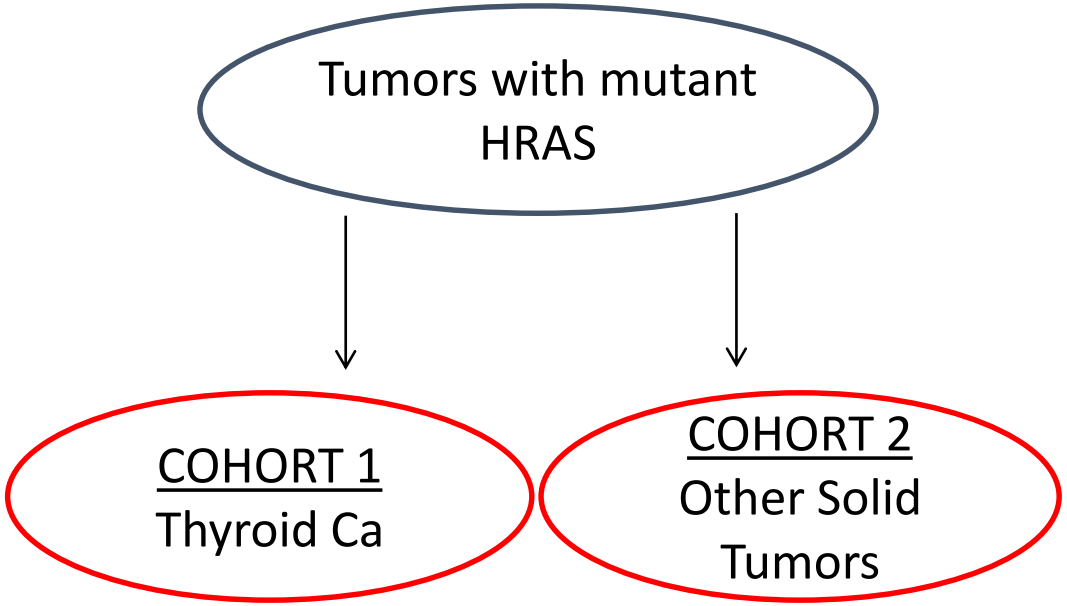
Phase II Design to Evaluate Tipifarnib in *HRAS* Mutant Cancers



Primary Objective
Objective Response Rate

Secondary Objectives:
PFS and DOR
Safety/tolerability

Tipifarnib: 900 mg bid daily on Days 1 – 7 and 15 – 21 in 28-day cycles

Simon two-stage design for ORR (each cohort):

Stage I: Need 2 CR/PRs in the first 11 patients

Stage II: If Stage I criteria met, enroll 7 patients

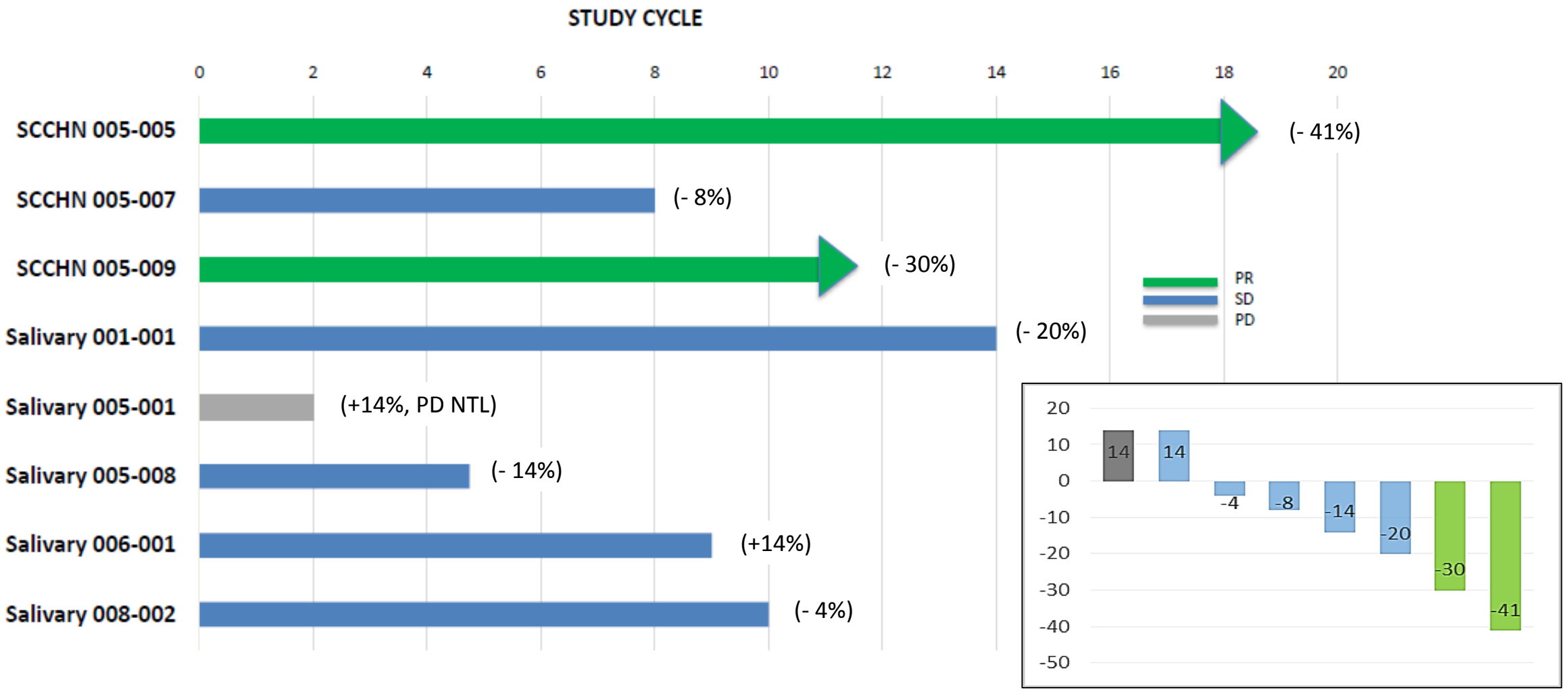
(For 10% (H0) vs 30% (H1) ORR, targeting ≥4 CR/PRs out of 18)

Clinicaltrials.gov NCT02383927

Tipifarnib in *HRAS* Mutant Squamous Cell Carcinomas of the Head and Neck (SCCHN)

- Cohort 1 (*HRAS* mutant thyroid carcinomas) still enrolling to the Stage I.
- Cohort 2 enrollment to Stage I has been completed (n=11):
  - *HRAS* mutant SCCHN (3): 2 cPRs and 1 SD (~7 mos)
  - *HRAS* mutant salivary gland tumors (5): 3 SDs > 6 months
- Cohort 2 has advanced to Stage II, and only enrolling *HRAS* mutant SCCHN to further explore this signal.
- Tipifarnib was generally well tolerated with AEs consistent with the known safety profile.

KO-TIP-001 Best Response and Status



001-001: epithelial-myoepithelial ca; 005-001: mucoepidermoid ca; 005-008: Poorly differentiated adenoca; 006-001: Salivary duct ca; 008-002: Oncocytic ca

SD: Sum of Diameters; PD NTL: Progression of Disease at Non-Target Lesions

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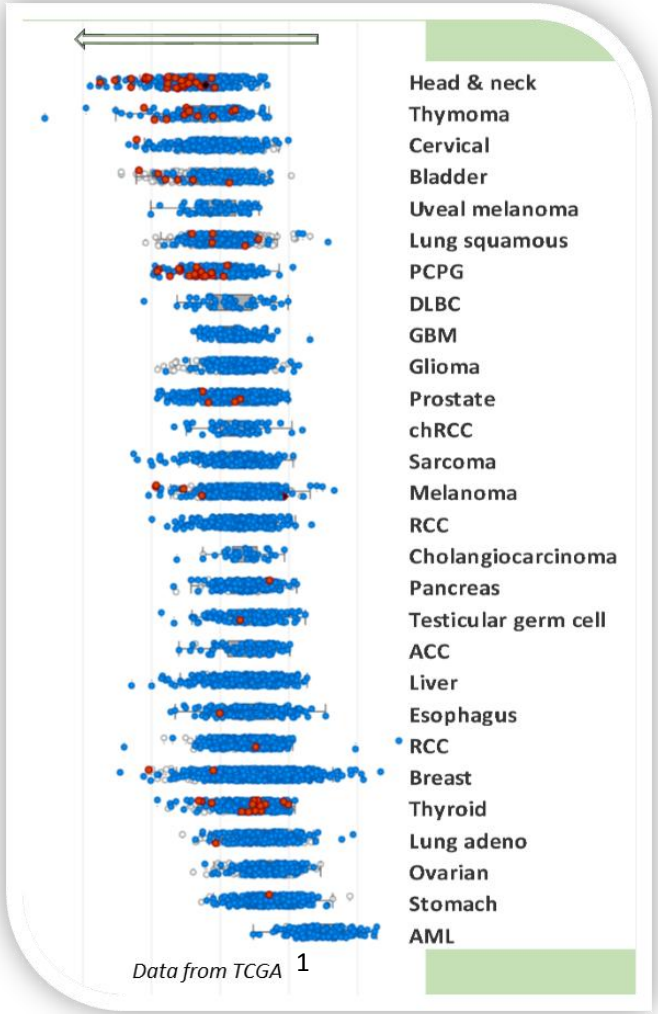
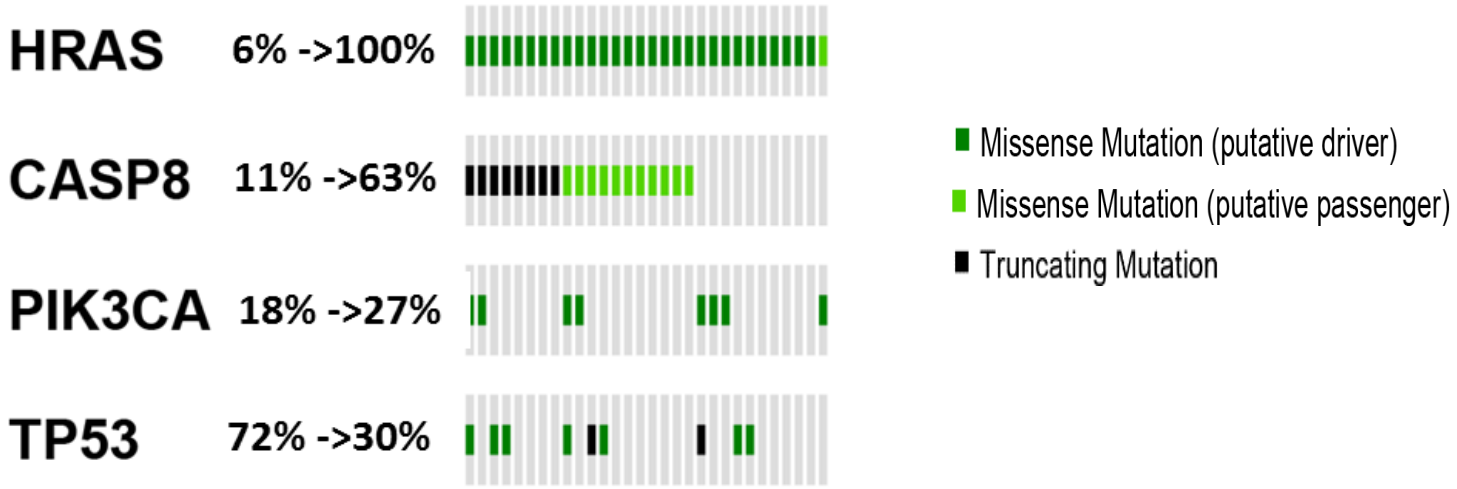
HRAS Mutations Define a Unique SCCHN Molecular Subset





- SCCHN express high levels of *HRAS*[2].
- *HRAS* mutant SCCHN (~6% at initial diagnosis) characterized by frequent CASP8 mutations and low rate of TP53 mutation[3].
- *HRAS* mutation may result from carcinogenesis (e.g. tobacco exposure)[4].

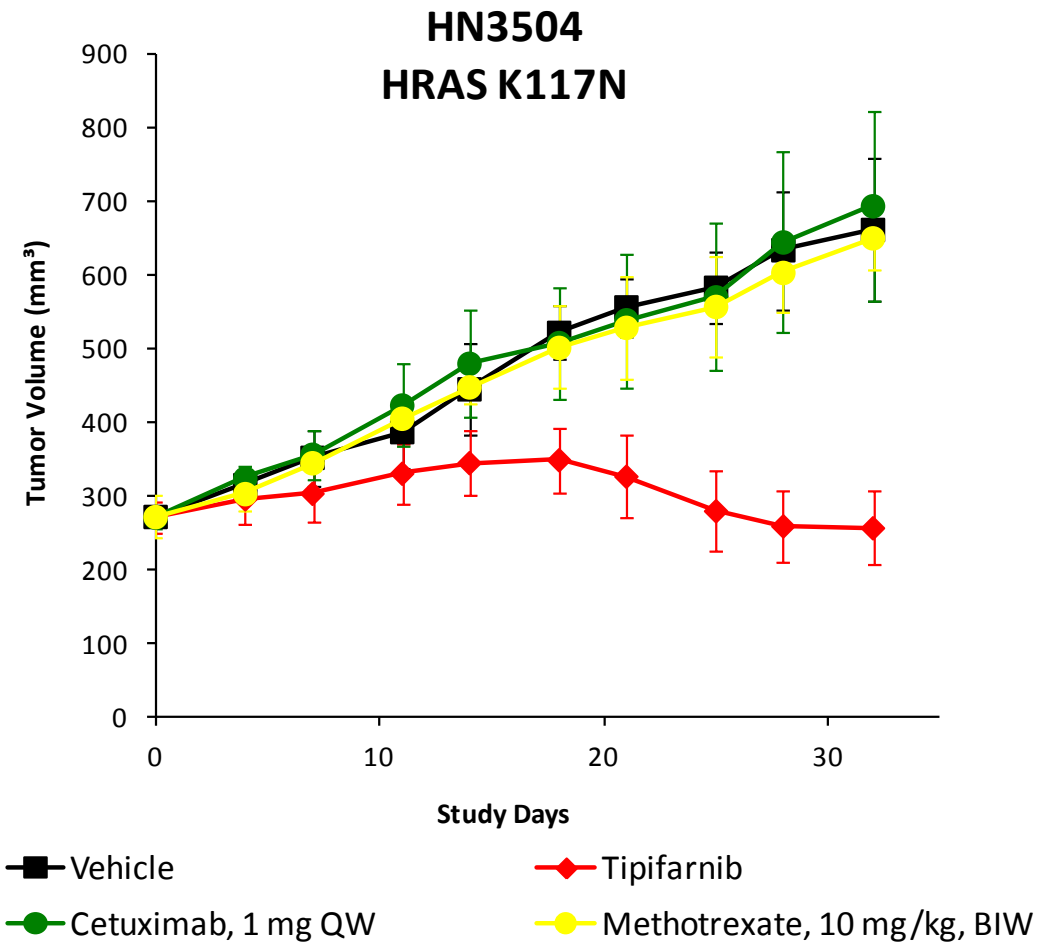
1. TCGA data. Gao et al. 2013. Sci Signal 6:pl1; Cerami et al 2012. Cancer Discov. 2:401-4
2. Cancer Genome Atlas Network 2015. Nature 517:576-82.
3. Cancer Genome Atlas Research Network 2012. Nature 489:519-25
4. Sathyan et al. 2007. Modern Path 20, 1141-8

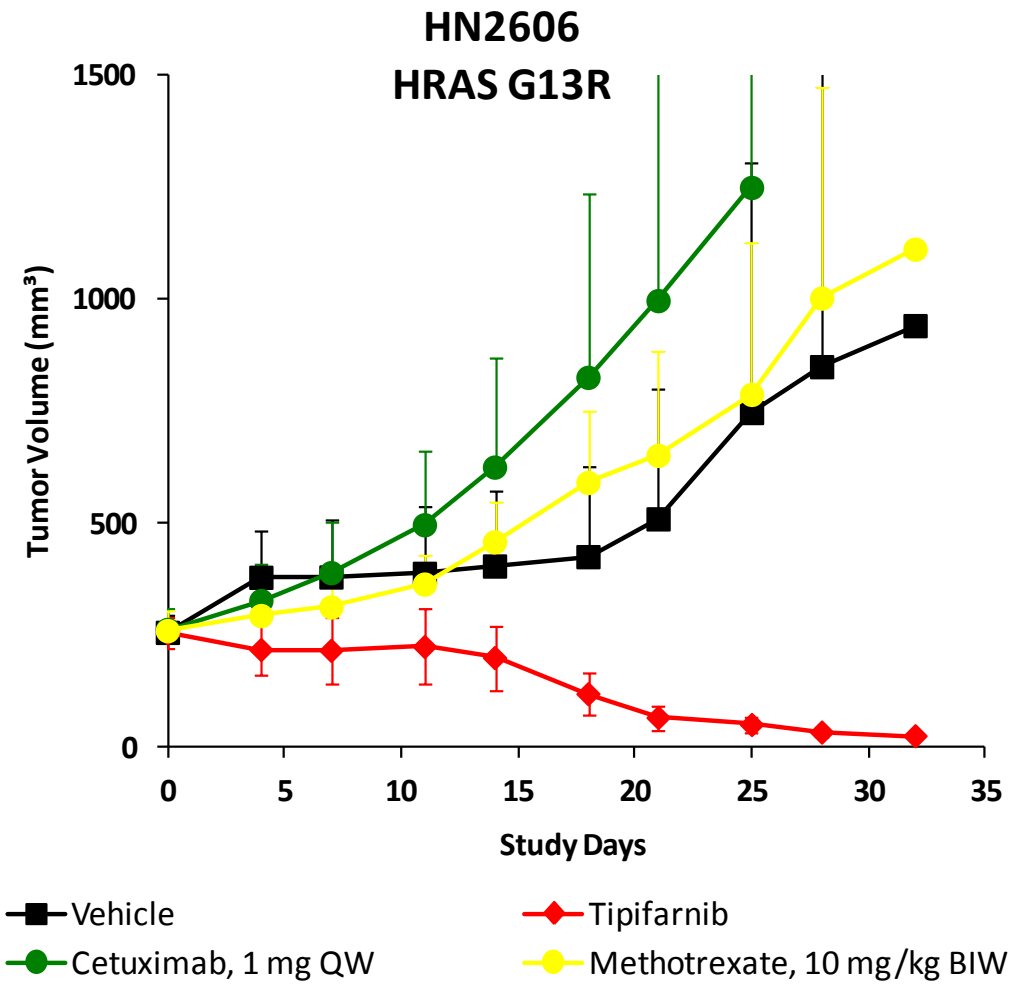
Emergence of *RAS* Mutations Is Associated with Acquired Cetuximab Resistance in SCCHN Patients

- 2/46 (4.3%) SCCHN tumors possessed an *HRAS* mutation.
- 20 SCCHN pts receiving cetuximab plus platinum/5-fluoruracil had ctDNA collected/analyzed during and after therapy.
  - 6/13 (46%) patients with on-treatment disease progression acquired *RAS* mutations, half of which were *HRAS* mutations (3/13, 23%).
  - No *RAS* mutations were found in the remaining 7 patients without progression on therapy.
  - Emergence of *RAS* mutations associated significantly with progression on cetuximab-based treatment (Chi-square *P*=0.032).

Braig et al., Oncotarget 7:42988-42995, 2016.

HRAS Mutant SCCHN PDXs are Sensitive to Tipifarnib and Resistant to Cetuximab and Chemotherapy





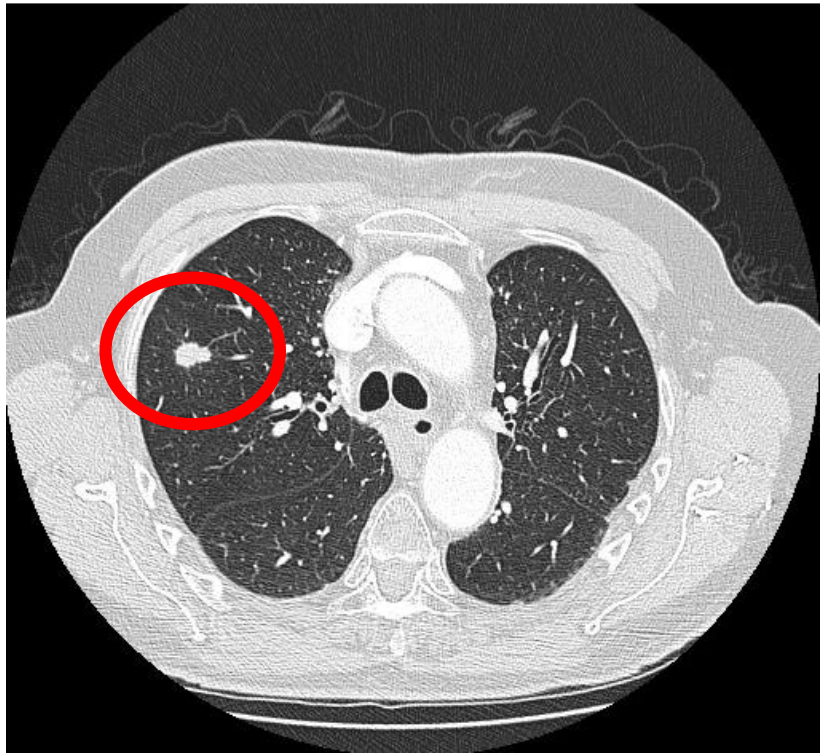
Kura Oncology Data

Patient 005-005

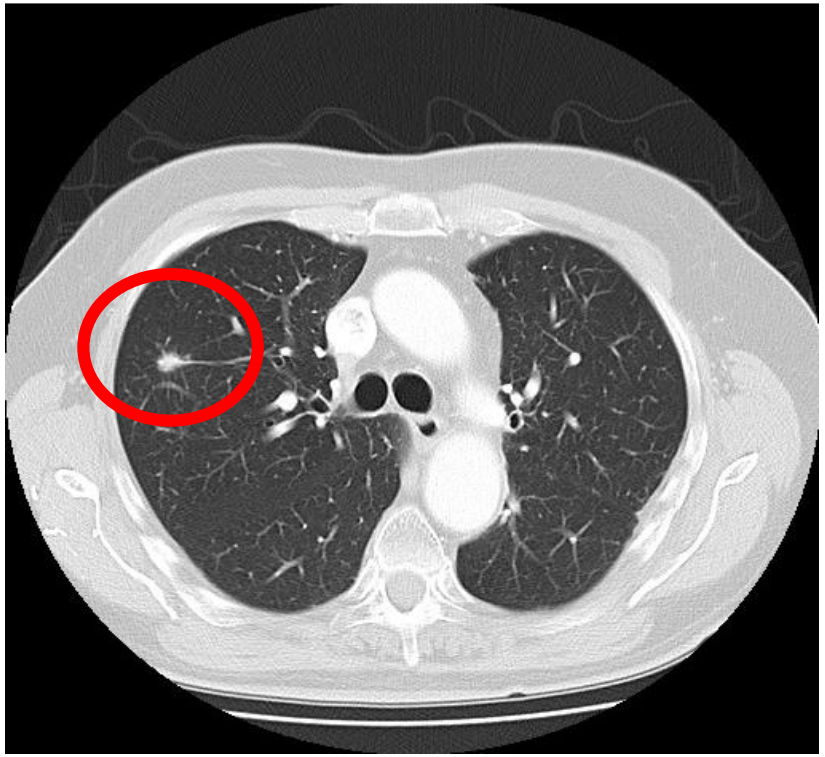
- Elderly white male with a metastatic SCCHN (primary tracheal tumor and prior history of nasal SCC)
  - Received 2 cycles of paclitaxel, carboplatin and cetuximab with a mixed response
  - Further treatment with paclitaxel and cetuximab followed by cetuximab and radiation
- Non hotspot *HRAS Q22K* (WT for *TP53*, *CASP8*, *PIK3CA*)
  - Observed in Costello syndrome (tumor predisposition syndrome due to germline HRAS mutations) [1]
  - Equivalent *KRAS Q22K* mutation known to be tumor-related[2,3]
- Partial Response at C2D22 (confirmed at C4), on tipifarnib for >1 year (currently in C19)

1. van der Burgt et al. J Med Genet. 2007 ; 44: 459–62.
2. Metro et al. Ecancermedicalscience. 2015; 9: 559.
3. Azzato et al. Anticancer Research 2015 ;35 no. 5 3007-12

005-005: Partial Response

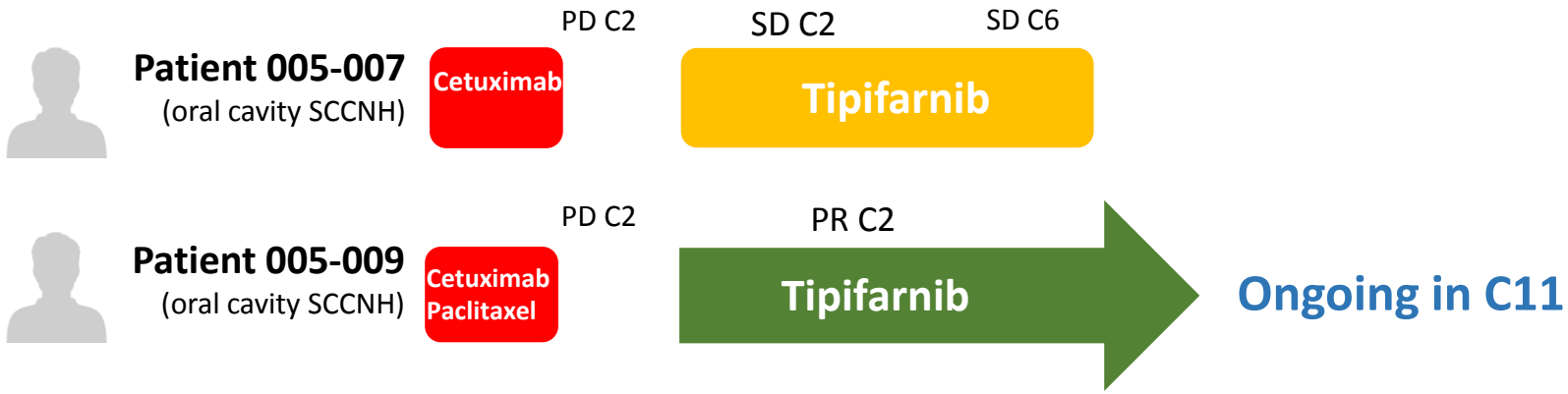


08/17/2015
(Baseline)



12/22/2015
(Cycle 4 Day 22)

Patients 005-007 and 005-009



Patients 005-007 and 005-009 are two male subjects with advanced oral cavity SCCHN tumors that carry the *HRAS* hotspot mutation Q61K.

- Patient 005-007 tumor: 16 additional mutations, including a *MAPK1 E322K* mutation (WT for *CASP8/TP53/PIK3CA*). Medical history included diagnosis of *dyskeratosis congenita*.
- Patient 005-009 tumor: *TP53* mutant; WT for *CASP8* and *PIK3CA*.
- Both patients failed cetuximab either as monotherapy (005-007) or in combination with chemotherapy (005-009) (PD at cycle 2).

Summary

- *HRAS* mutant SCCHN represents a biologically and clinically distinct subset of disease.
- Acquired resistance to cetuximab in *RAS* WT SCCHN may be related to emergence of RAS mutations.
- A subset of *HRAS* mutant SCCHN may be sensitive to tipifarnib, potentially representing a therapeutic alternative to EGFR targeting.
- Expansion of the phase II trial to recruit *HRAS* mutant SCCHN will seek to verify the potential tipifarnib signal in this disease subset.

Acknowledgements

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