# Preliminary results from a phase 2 proof of concept trial of tipifarnib in tumors with HRAS mutations

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KURA ONCOLOGY

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# Disclosures

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- Koltan
- Kura Oncology
- Merck
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- AstraZeneca
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- Eisai
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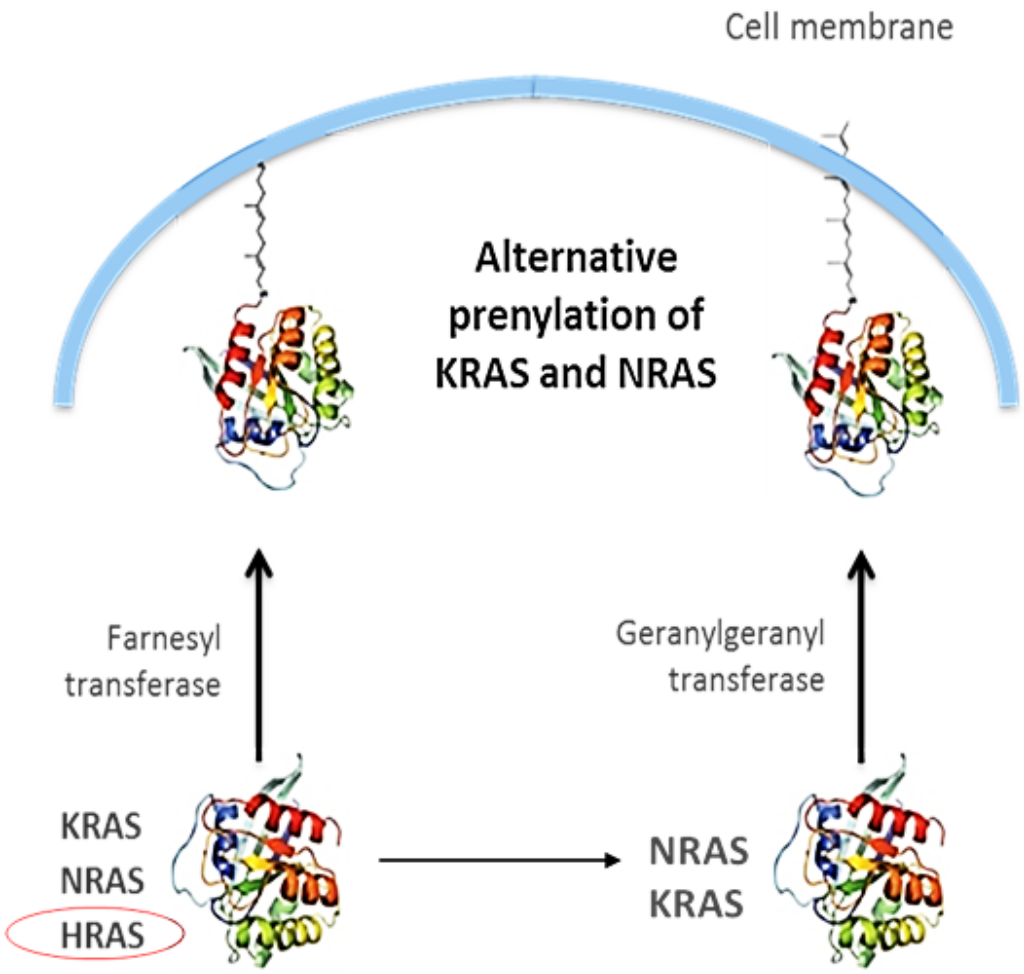
- Genzyme
- Regeneron
- Sun Pharmaceuticals

Travel/Meeting Expenses: Kura Oncology

Off-label use of drugs will be discussed.

# Mutant HRAS Oncogene Activity 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.




**CENTRAL HYPOTHESIS:**

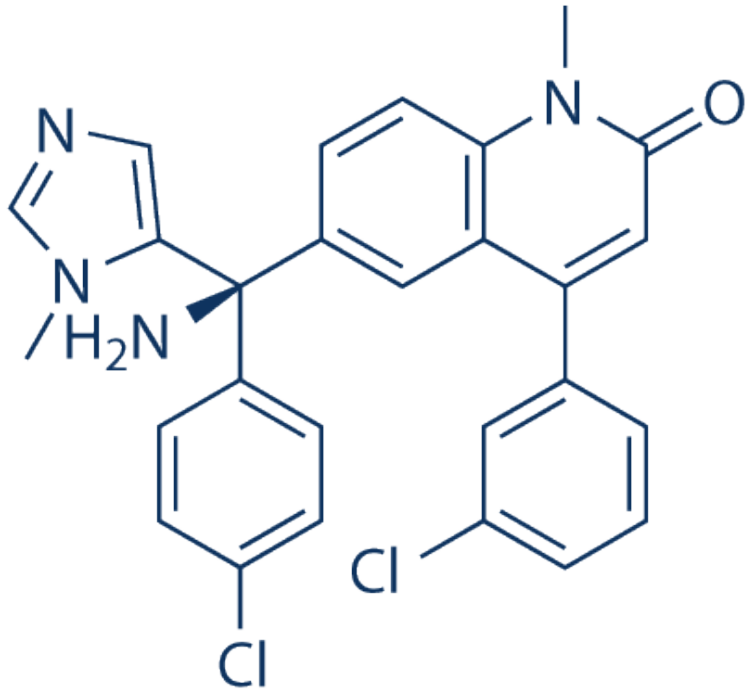
**HRAS driven malignancies are uniquely susceptible to FTI therapy.**



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

# Tipifarnib: First-in-class FTI

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

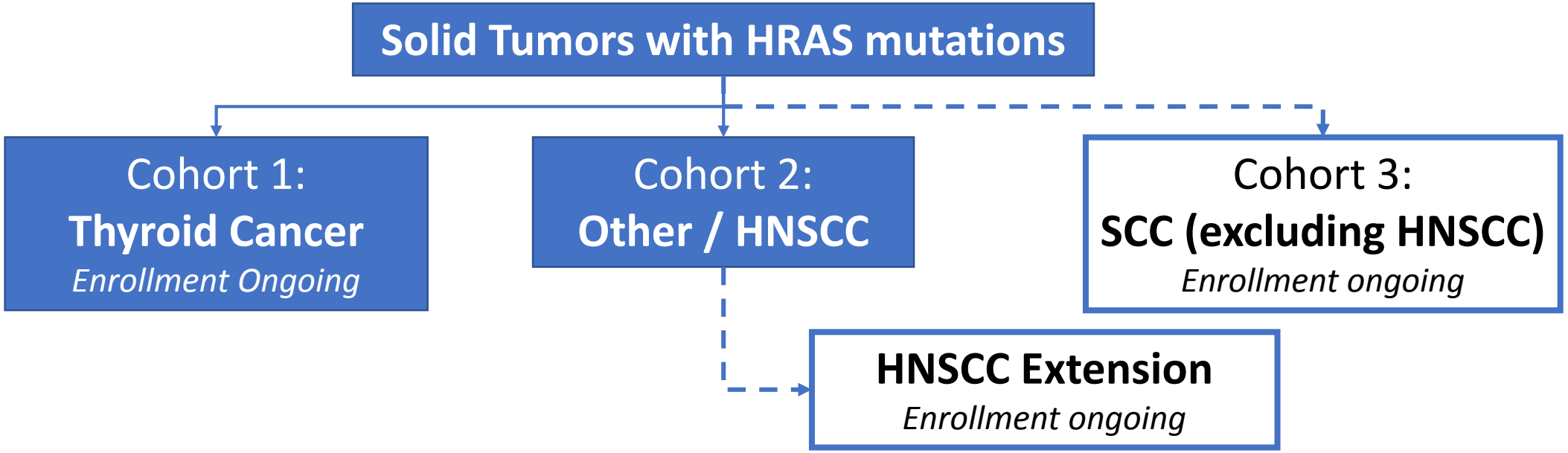



**Tipifarnib**
(in-licensed by Kura Oncology from Janssen)



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

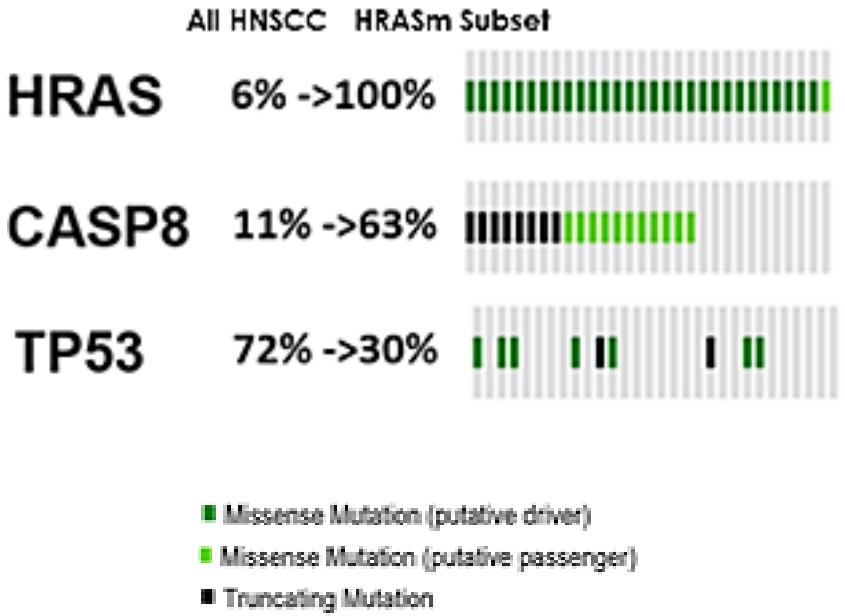
Primary Objective: ORR

Design: Simon 2-stage (11+7 pts)

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

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

# HRAS Mutations Define a Unique Molecular HNSCC Subset

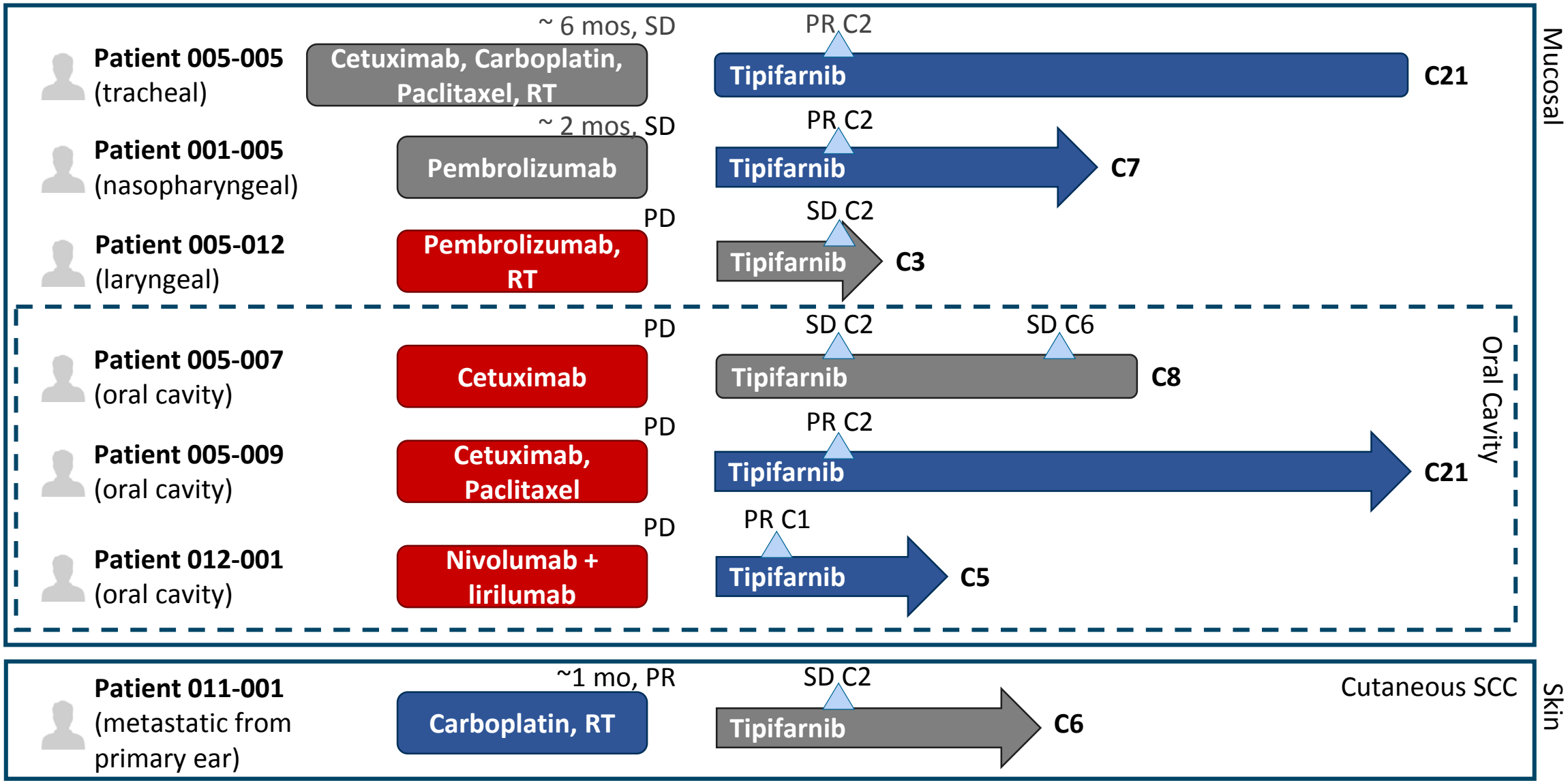



- The *HRAS* mutant subset of HNSCC is characterized by low rate of genetic alterations, frequent CASP8 inactivation, and infrequent of TP53 mutation[1].
- It is thought that HRAS/CASP8 alteration converge on NF-kB to induce tumor cell growth and survival[1].
- *HRAS* mutations in HNSCC are observed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


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 in HRAS Mutant HNSCC and Skin SCC Patients

*Preliminary data as of 04 October 2017*



# Durable Response on Tipifarnib after Cetuximab/Chemo/RT



**Patient 005-005**
(tracheal tumor)

~ 6 mos, SD

**Cetuximab, Carboplatin, Paclitaxel, RT**

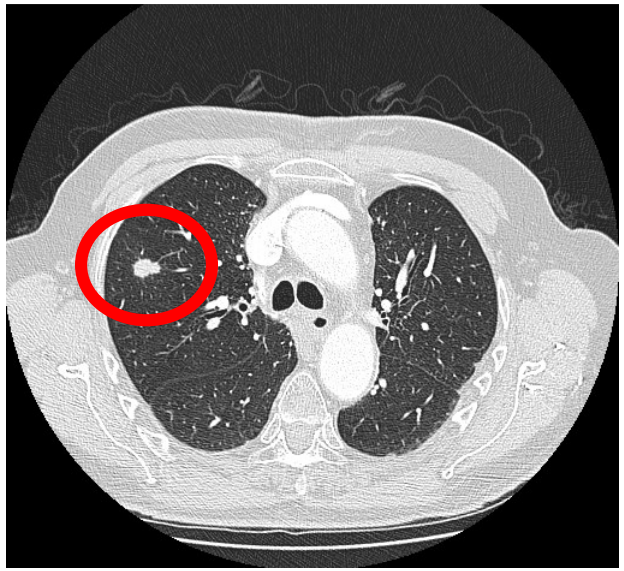
~ 8 mos

**PR at Cycle 2**

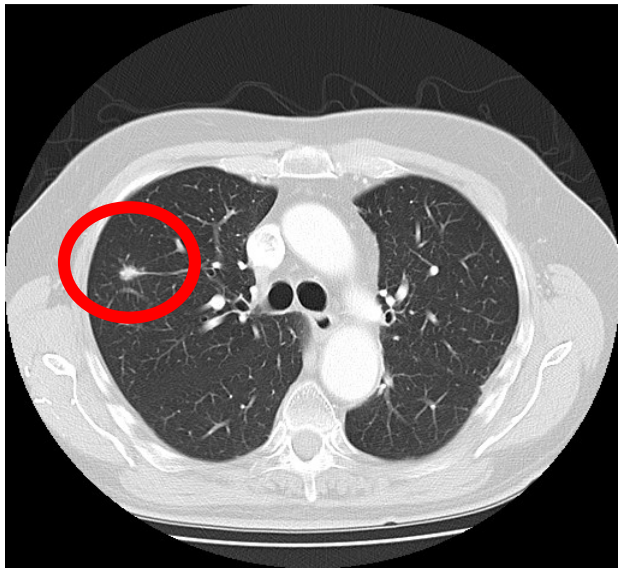
**Tipifarnib**

**Off Therapy**
**Cycle 21 for POD**

76 yo man with metastatic tracheal SCC
HPV/p16 (-), no tobacco/ETOH
HRAS Q22K (observed in Costello's Syndrome) and CDKN2A deletion (p14, p16)



**Baseline**



**Cycle 4, 35% reduction**

# Tipifarnib Response in Nasopharyngeal Ca s/p Immunotherapy



**Patient 001-005**
(nasopharynx)

~ 6 mos, SD

**Cisplatin**

~ 2 mos, SD

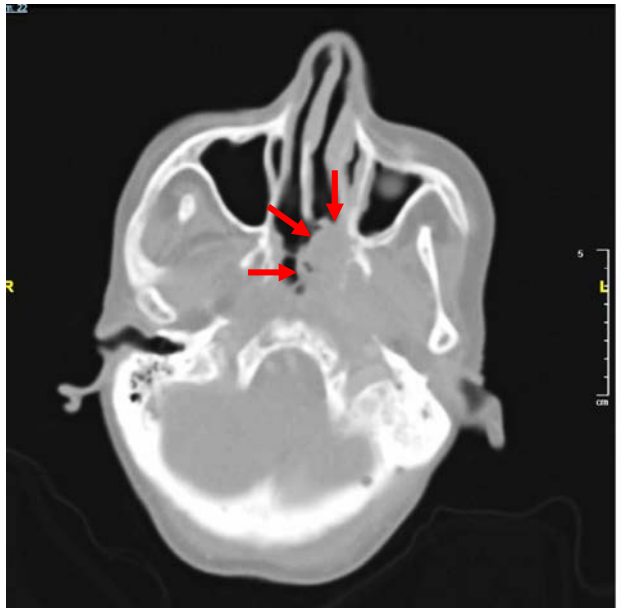
**Pembrolizumab**

**PR at Cycle 2**

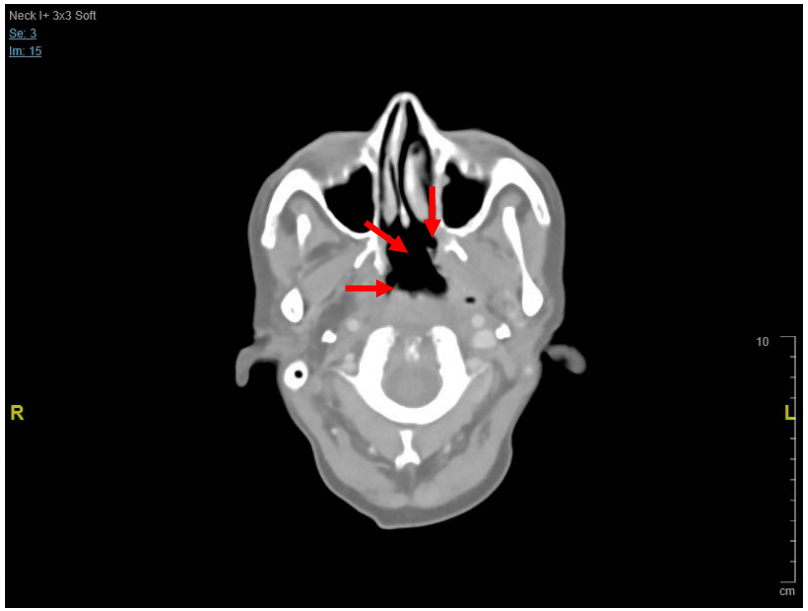
**Tipifarnib**

**Cycle 7**

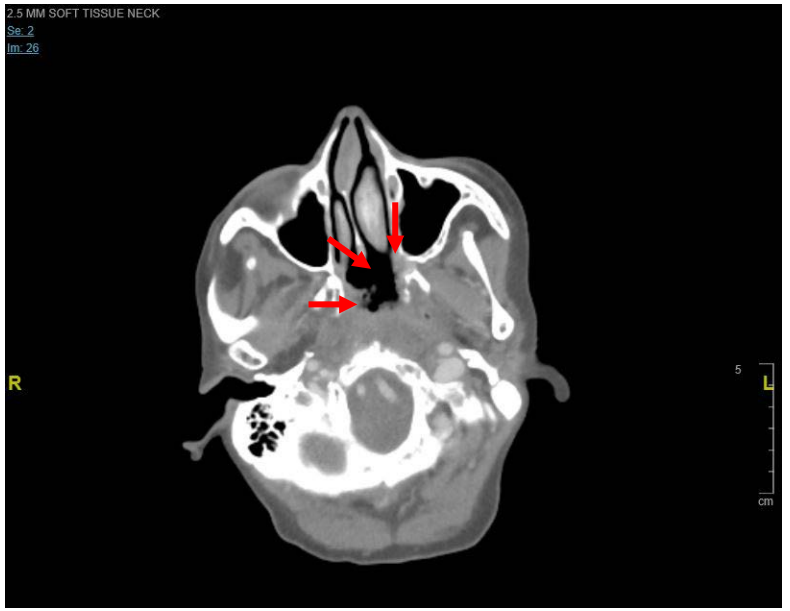
59 yo female with nasopharynx SCC with HRAS G12D



**Baseline**




**Cycle 2, 40% reduction**




**Cycle 6, 49% reduction**

*Images provided by Dr. Nicole Chau*

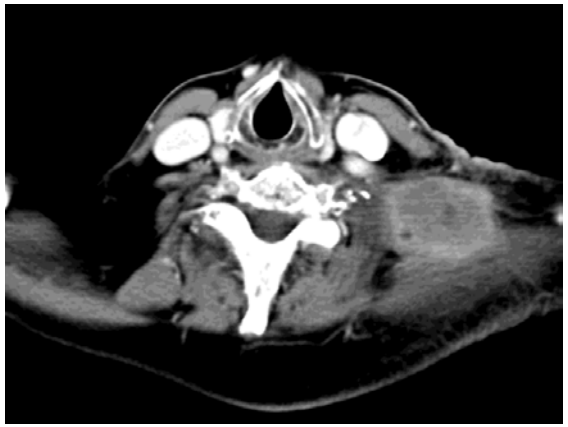
# Symptom Improvement and Stable Disease in Cutaneous SCC



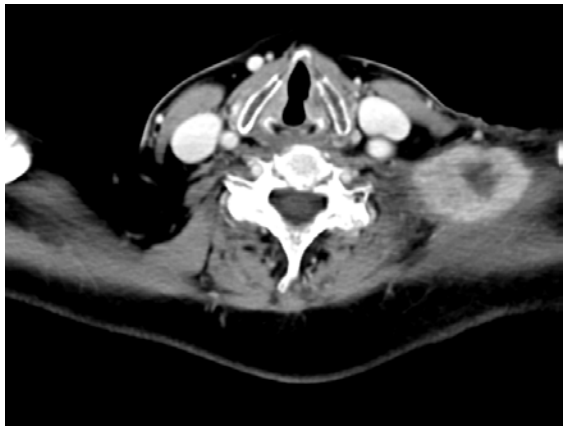
**Patient 011-001**
(metastatic from ear primary)

~1 mo, PR
**Carboplatin, RT**
~ 3 mos
**SD at Cycle 2**
**Tipifarnib**
**Cycle 6**

**Baseline**



**Cycle 2**



81 yo male with right ear SCC and history of aggressive disease.

- 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<br>Transmucosal fentanyl 200 mcg for breakthrough pain |
| 16/May/2017 | Methadone 5 mg Q 8 hours<br>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 |

*Images provided by Dr. Irene Braña*

# Tipifarnib Regression of Widely Metastatic Laryngeal SCC



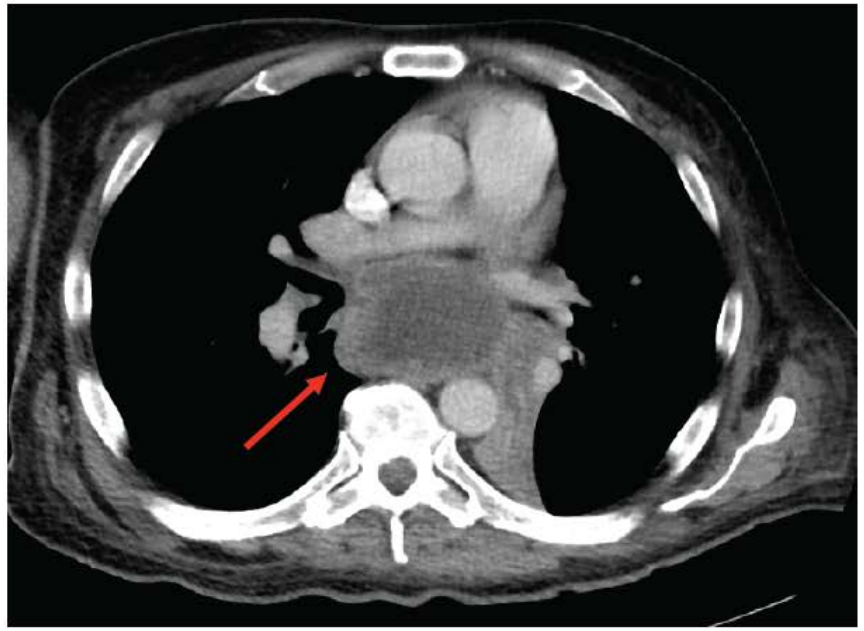
**Patient 05-012**
(Laryngeal)

~2 mo, PD
**Cetuximab + Paclitaxel**

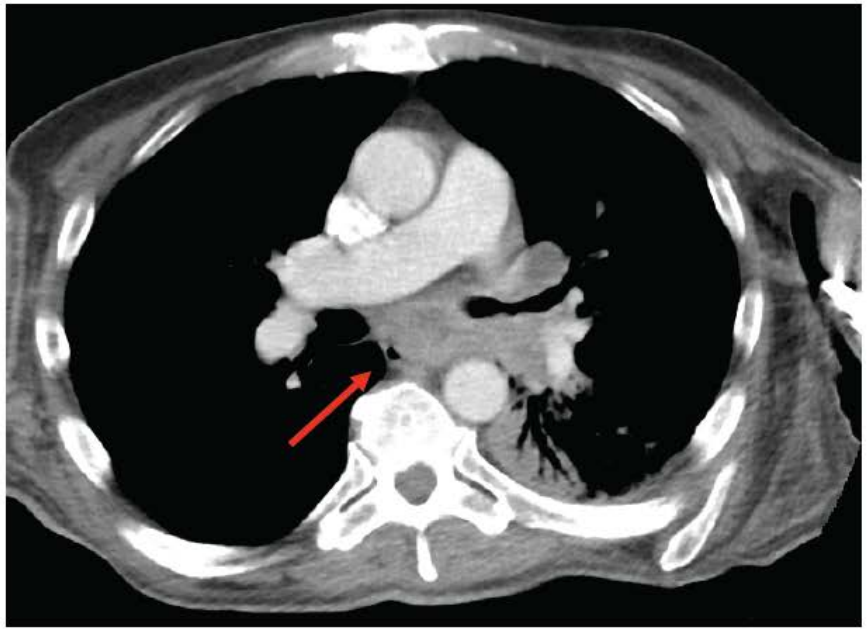
~8 mo, PD
**Pembrolizumab + palliative RT**

**SD at Cycle 2**
**Tipifarnib**
**Cycle 3**

55 yo male with metastatic laryngeal SCC (mediastinal LNs, muscle, adrenal gland, lung, bone)
80 pk-years, no current ETOH
HRAS G13V, TP53 R248Q



**Baseline**



**Cycle 2, 22% reduction**

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

**Patient 012-001**
(oral cavity)

PD

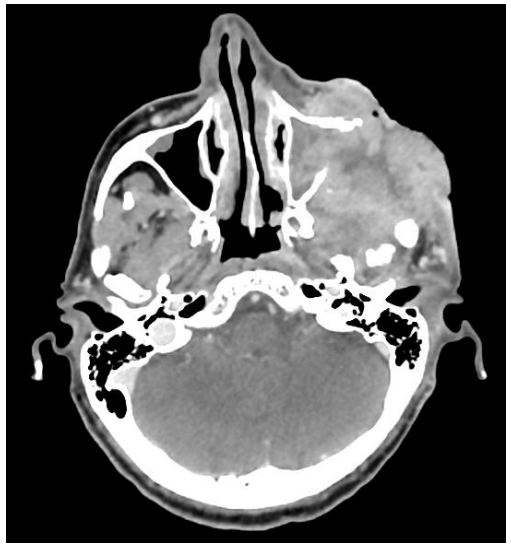
**Nivolumab + Investigational IO**

**PR at Cycle 1**

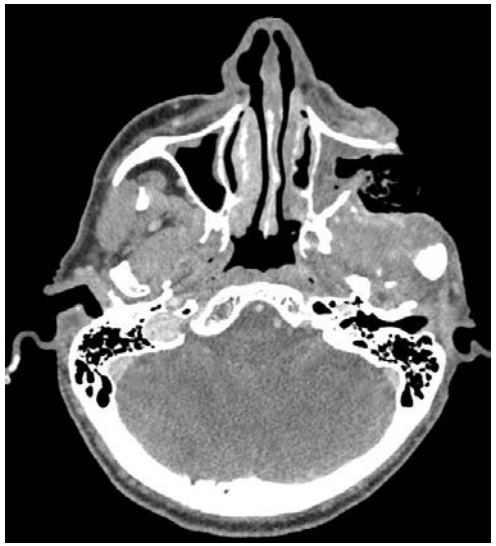
**Tipifarnib** → **Cycle 5**

69 yo man with recurrent oral cavity SCC.
No tobacco/ETOH
*HRAS G12S, TP53 R248Q*

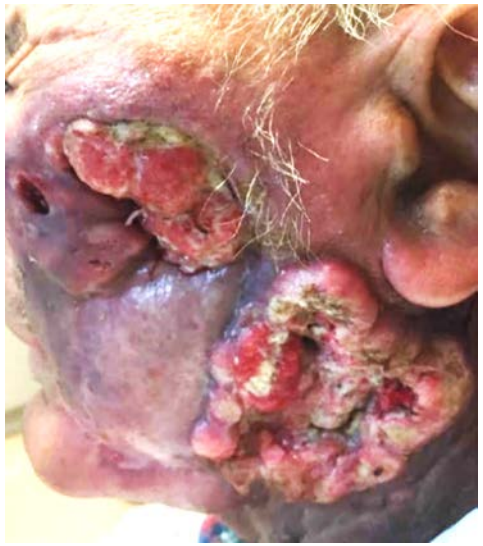
Initial PR (40% tumor reduction) on Cycle 1 Day 15 (7 days tipifarnib + 7 days rest); 56% size reduction at Cycle 3



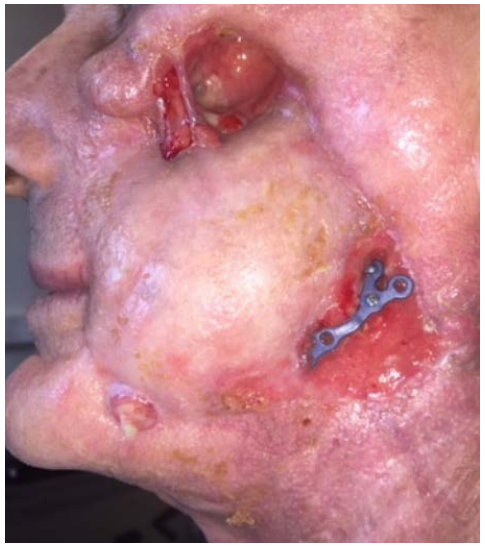
**Baseline**



**Cycle 3, 56% reduction**



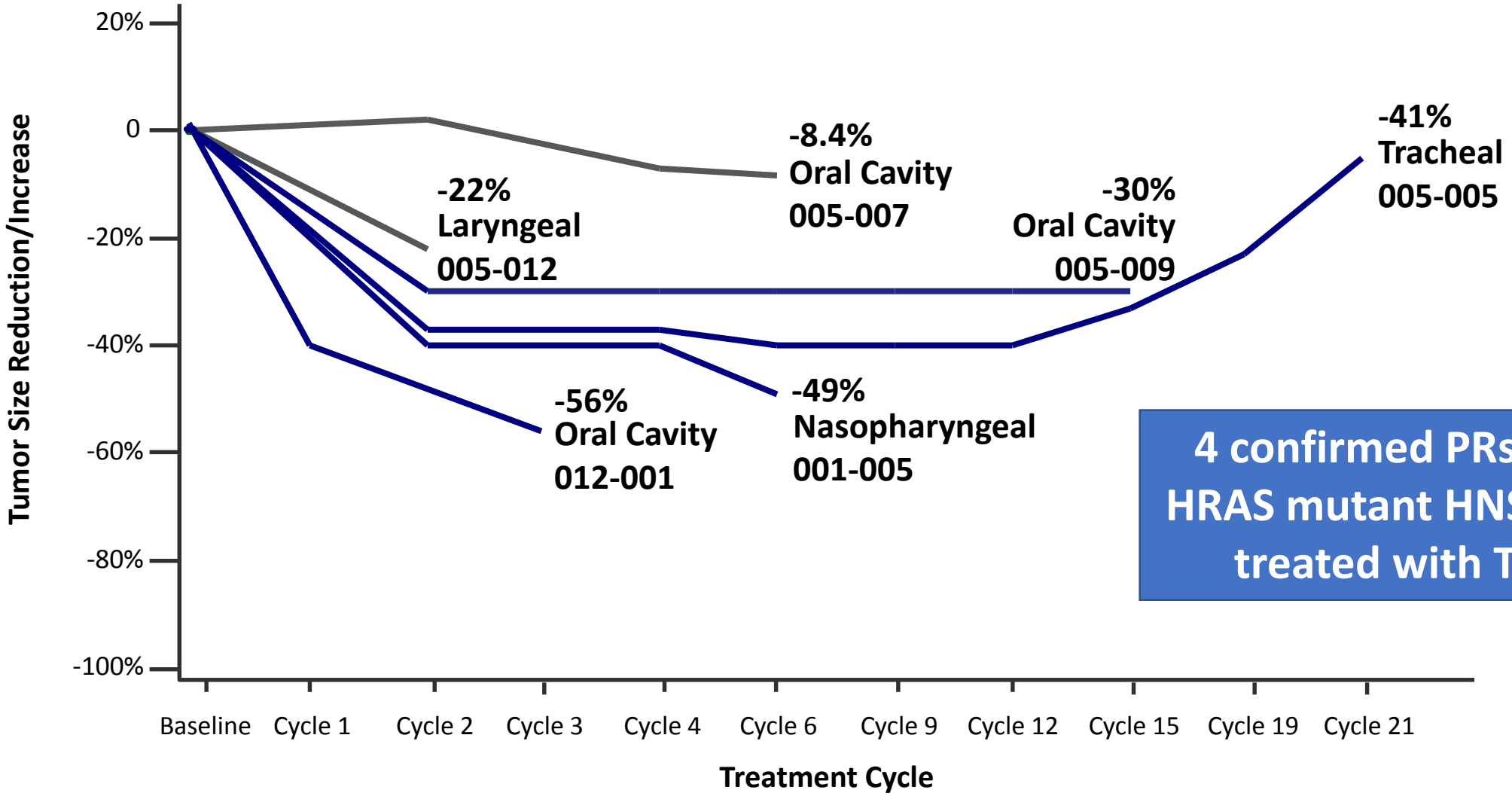
**Cycle 1 Day 1**



**Cycle 4 Day 1**

*Images provided by Dr. Caroline Even and Dr. Charles Ferte*

# Significant Tumor Size Reduction and Durable Responses Observed in HRASm HNSCC Patients Treated with Tipifarnib




**4 confirmed PRs in 6 (67%) HRAS mutant HNSCC patients treated with Tipifarnib**

# Conclusions

- First clinical evidence that mutant HRAS is a targetable oncogene.
- Phase 2 proof-of-concept of tipifarnib efficacy for recurrent/metastatic HNSCC carrying 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 (cutaneous SCC)
- AEs observed are consistent with the known safety profile of tipifarnib
  - ≥ Gr 3 TEAEs included myelosuppression (neutropenia, 31%, anemia 19%, thrombocytopenia 15%), GI disturbances (15%), and increased creatinine (11%) (N=27, overall study).
  - 2 HNSCC required dose reductions for Gr 2 peripheral neuropathy at Cycle 1 and Cycle 10.
  - 3/27 (11%) patients (0/6 HNSCC) discontinued for reasons other than disease progression [(Gr 3 GI (1); Gr 3 Renal (2)]

# Acknowledgements


- Patients, their families and caregivers
- Study Investigators and their study teams
- Kura Oncology