MUNICH 2018 ESMO congress

Memorial Sloan Kettering Cancer Center

# PRELIMINARY RESULTS FROM A PHASE 2 PROOF OF CONCEPT TRIAL OF TIPIFARNIB IN SQUAMOUS CELL CARCINOMAS (SCCS) WITH HRAS MUTATIONS


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# DISCLOSURE SLIDE

Advisory Boards/Consulting: **Kura Oncology (travel/lodging/conference fees only)**, Regeneron, Eisai, Ayala, TRM Oncology, Sun Pharmaceuticals, Merck, Sanofi Aventis, BMS, Genentech, Genzyme, Novartis, Janssen (travel only), AstraZeneca, Hai-II, Guidepoint Global Advisors (no payment received), Ignyta (travel/lodging/conference fees only)

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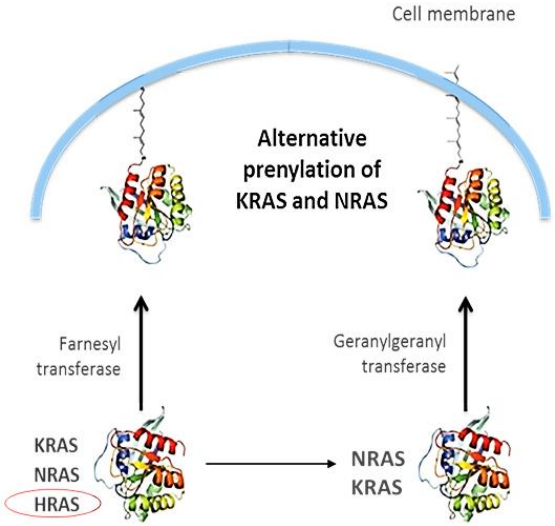
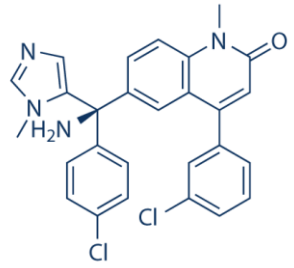
Leadership Roles: International Thyroid Oncology Group (board member, correlative science committee co-chair, member of the protocol committee), International Rare Cancer Initiative (co-chair of head/neck section), NCI Rare Tumors Task Force (HNSC member), NCI Head and Neck Steering Committee (member), National Comprehensive Cancer Network (investigator steering committee member, non-melanoma skin guidelines committee member), Alliance for Clinical Trials (Experimental Therapeutics Committee member), MSKCC Investigational New Drug Committee (chair)

Other: Advised **Kura Oncology** on tipifarnib development (as Principal Investigator)

# Mutant HRAS Oncogene Activity is Uniquely Dependent on Farnesylation

- Members of the **RAS superfamily (KRAS / NRAS / HRAS)** require covalent addition of a hydrophobic group to their C-terminal tail ("prenylation") for membrane localization and downstream signaling.
- **Farnesyltransferase (FT)** enzyme catalyzes the attachment of farnesyl groups to RAS proteins and other cell signaling proteins.
- NRAS and KRAS are susceptible to alternate forms of prenylation, but HRAS can only be farnesylated.
- **Hypothesis**: Tumors driven by HRAS mutations may be highly sensitive to tipifarnib, a potent and selective FTI



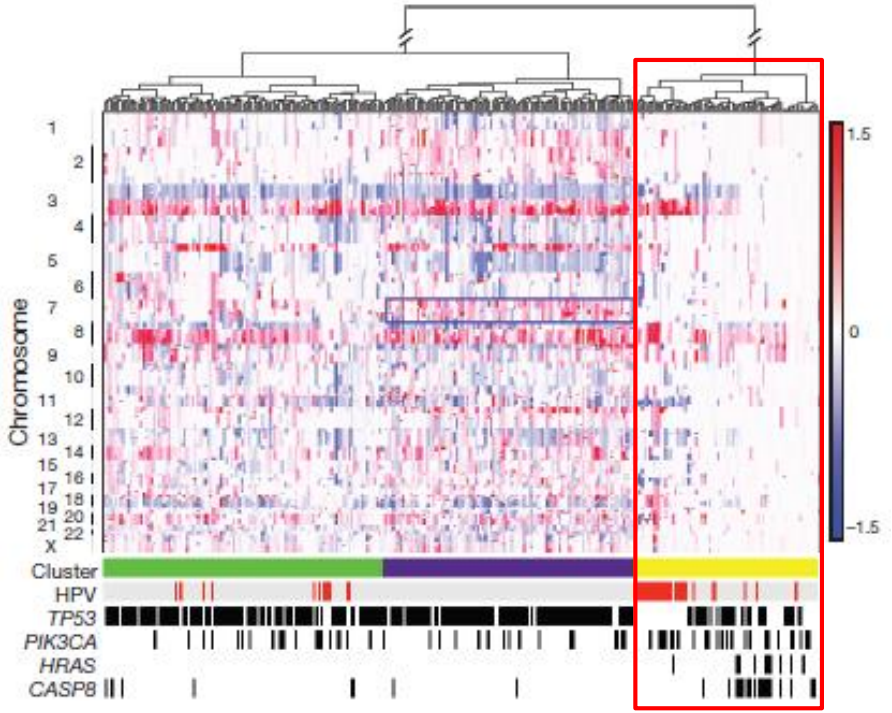




Tipifarnib



Casey, P.J. *et al.* 1989 *Proc. Natl. Acad. Sci.* USA 86:8323-27.

# HRAS Mutations are part of a Unique Molecular Subset of HNSCC



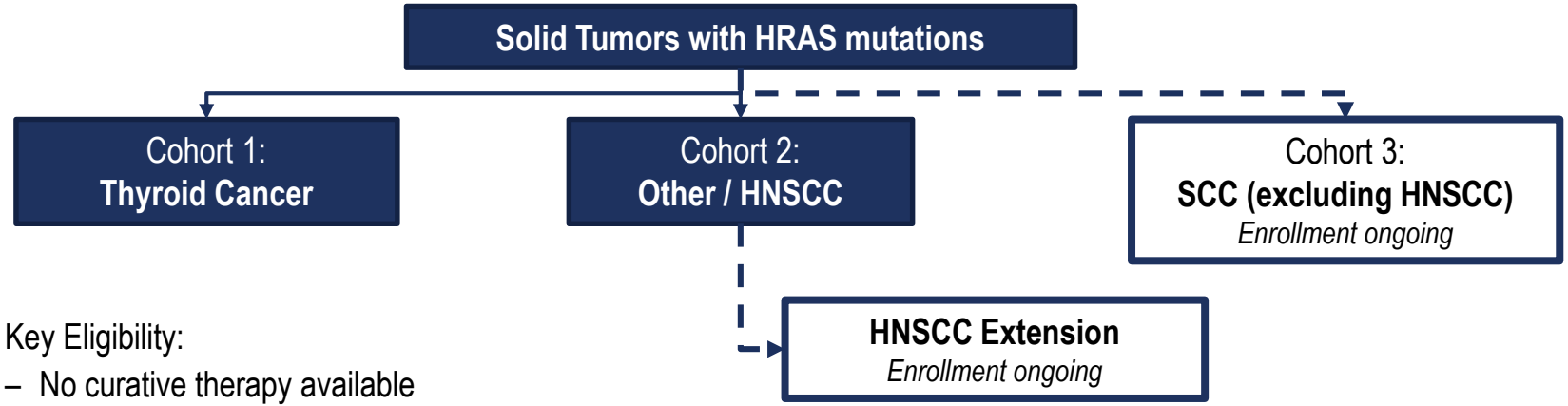

HRAS mutations are observed in a distinct molecular subset of HNSCC[1] characterized by:

- Reduced copy number alterations
- Inactivating caspase 8 mutations
- p53 WT



[1]Cancer Genome Atlas Network 2015. *Nature* 517:576-82. Reproduced with permission

# Phase 2 Trial in HRAS Mutant Solid Tumors

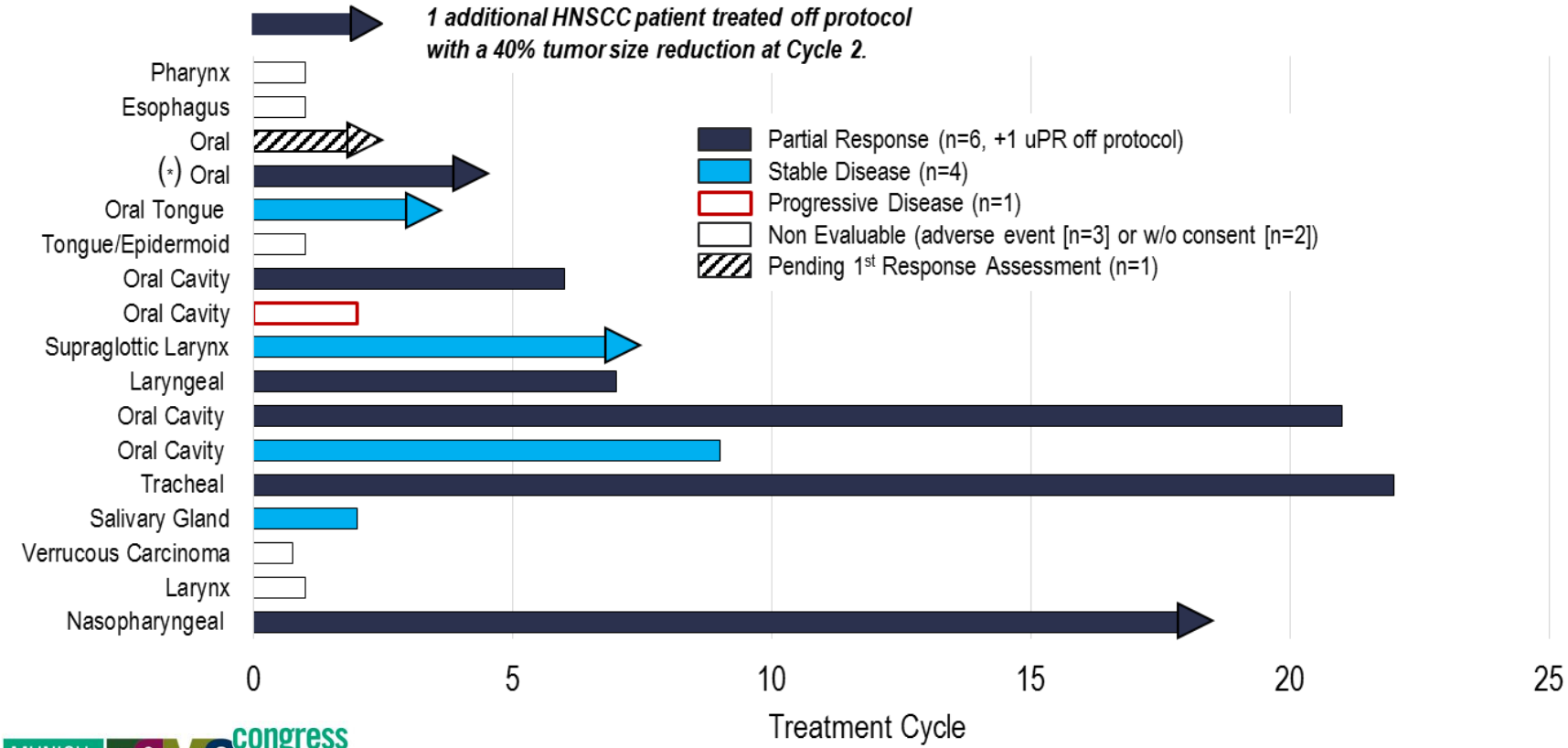



- Key Eligibility:
  - No curative therapy available
  - HRAS mutation
  - Measurable disease (RECIST v1.1)
  - ECOG PS 0 – 1
- Initial dose regimen: Tipifarnib 900 mg po bid on Days 1 – 7 and 15 – 21 of 28-day treatment cycles
- Primary Objective: ORR
- Cohort 1 and 2 Design: Simon 2-stage (11+7 pts)
- Hypothesis: 10% (H0) vs 30% (H1) ORR, a=0.05, 80% power (4 responses needed)

# Patient Disposition

| | | HNSCC | Other SCC |
|---|---|---|---|
| Total Treated | n (%) | 17 (100) | 6 (100) |
| Oral Cavity, including tongue | n | 8 | -- |
| Other HNSCC | n | 9 | -- |
| Non-HNSCC | n | -- | 6 |
| Prior Lines of Therapy | Median (Range) | 2 (1 – 5) | 1 (1 – 2) |
| Age, yrs | Median (Range) | 59 (20 – 76) | 63 (49 – 81) |
| Treatment Discontinuations | n (%) | 12 (76) | 3 (50) |
| Progressive Disease | n (%) | 5 (38) | 1 (17) |
| Symptomatic Deterioration | n (%) | 1 (8) | -- |
| Withdrawal of Consent | n (%) | 2 (15) | -- |
| Adverse Event | n (%) | 3 (23) | 2 (33) |
| Death, unrelated | n (%) | 1 (8) | -- |
| Total Efficacy Evaluable | n | 11 | 2 |
| Pending 1st Efficacy Response Assessment | n | 1 | 2 |
| Not evaluable by RECIST | n | 5 | 2 |

# HNSCC Patients (n=17 on study, +1 pt treated off protocol)

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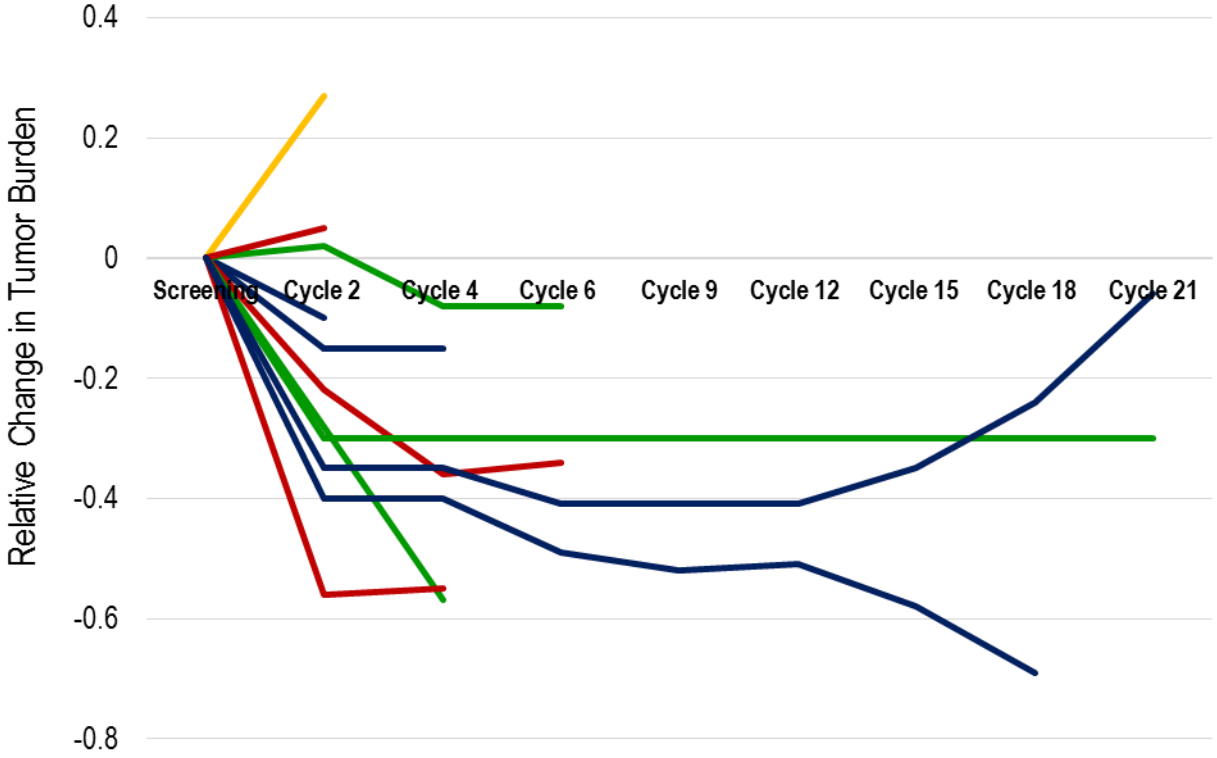
Preliminary Results as of 9/7/2018

* Response confirmed on 10/15/2018

# HNSCC Patients – Response By Prior Therapy




- Responses independent of prior therapies
- No evidence of PR on last prior therapy

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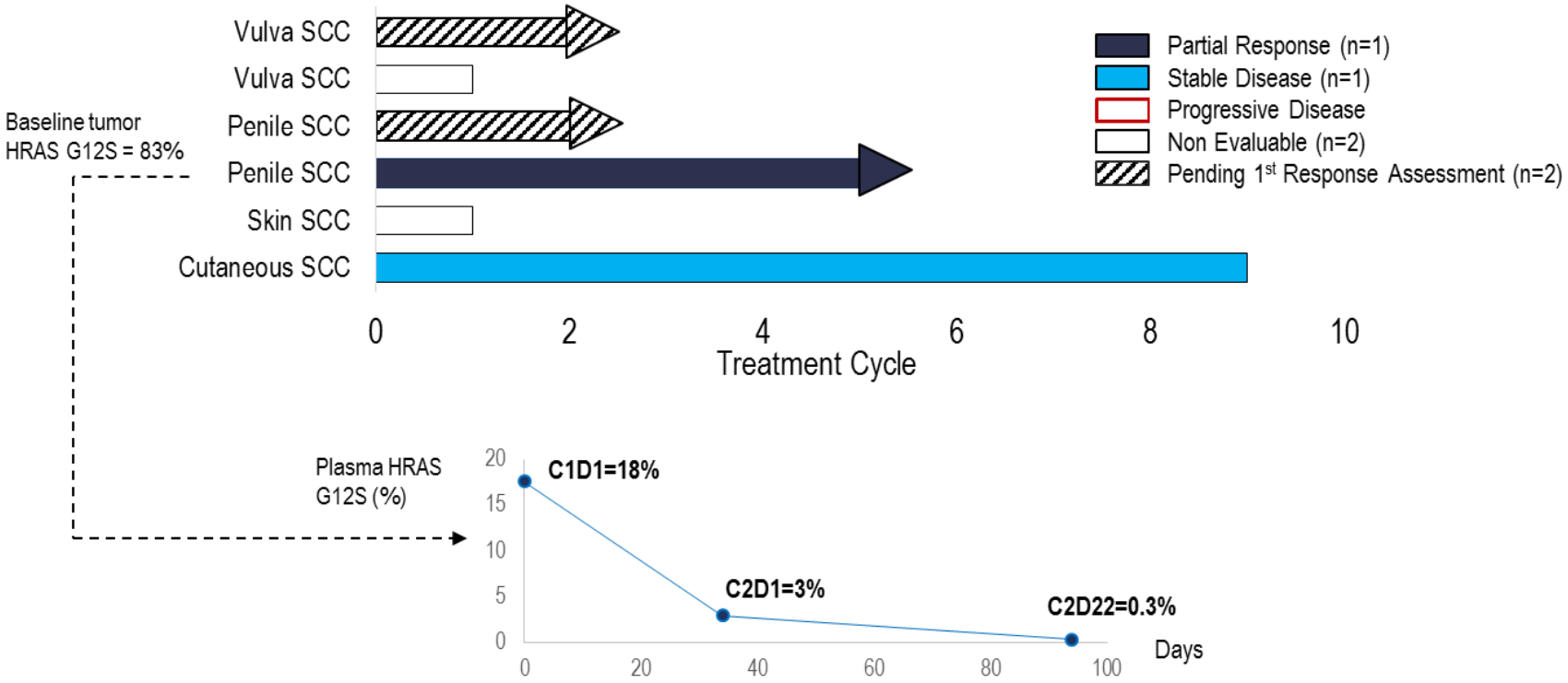
# Other SCC Patients (n=6)






Preliminary Results as of 9/7/2018

# Tipifarnib Regression of Widely Metastatic Laryngeal SCC

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

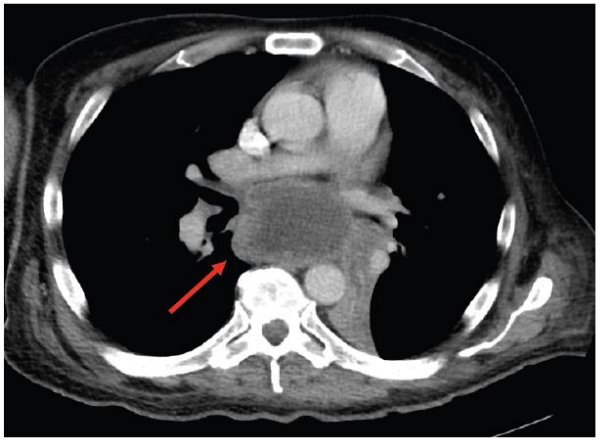


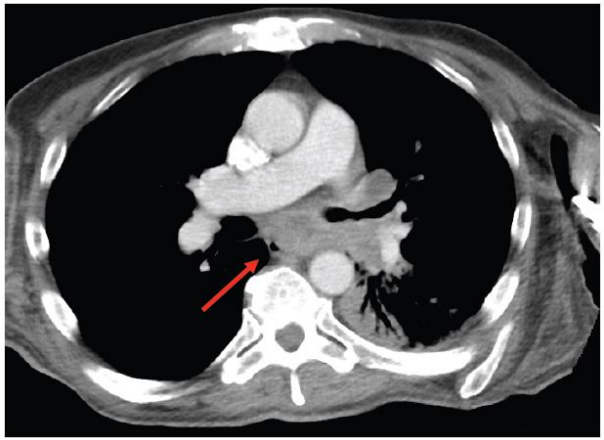
**Patient 05-012**
(Laryngeal)

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

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

**PR at Cycle 4**
**Tipifarnib**
**Cycle 7**





Cycle 2, 22% reduction
Cycle 4, 36% reduction

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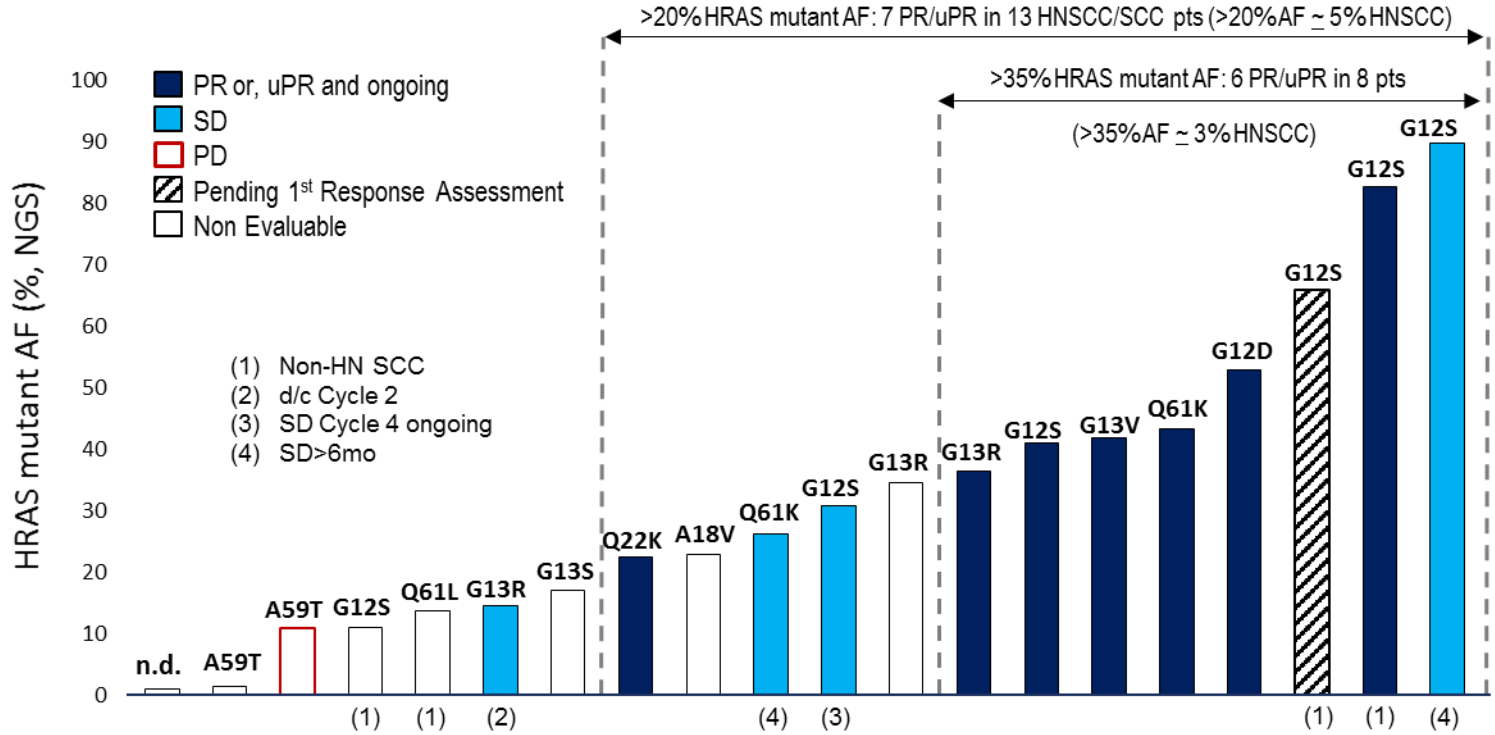
# Association of HRAS Mutant Allele Frequency with Clinical Benefit from Tipifarnib (HNSCC, SCC, n=20)

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Study KO-TIP-001 pts with HN and non-HN SCC tumors with available HRAS mutant allele data (10.17.2018). One additional HNSCC pt was treated off protocol. (Pending AF analysis: 1 HNSCC PR, 1 HNSCC pending 1st scan, 1 SCC pending 1st scan, 1 SCC SD)

# TEAEs

- Dose limiting (Grade ≥3) treatment emergent AEs in HNSCC patients (n=17) included anemia (23%), neutropenia (14%) and GI disturbances (18%).
- Grade 2 creatinine elevations reported in 3 HNSCC patients (18%). Grade 3 hypokalemia observed in 2 HNSCC patients during sponsor's review of safety reports.
- TEAEs were managed by dose delay/dose reduction.
  - Starting dose to be amended to 600 mg bid. Preliminary evidence of activity at 600 mg bid:
    - PR in one subject dosed at a starting dose of 600 mg bid due to frailty
    - Onset of 3 responses after dose reduction to 600 mg bid
    - Two subjects with SD>6 months receiving 600 mg bid
- Guidelines for the management of dehydration and electrolyte imbalance (hypokalemia) to be introduced in the study protocol.

# Conclusions

- Proof-of-concept for tipifarnib activity in recurrent/metastatic HNSCC carrying HRAS mutations.
- Rapid and durable responses.
- Activity in disease resistant to chemotherapy, cetuximab and immunotherapy.
- Association between allele frequency and clinical benefit.
- TEAEs consistent with known safety profile of tipifarnib.
- Preliminary activity in other non-HNSCC SCC patients observed.

# Acknowledgements


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| | | | |
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