HNSCC OVEREXPRESSING WILD-TYPE HRAS ARE SENSITIVE TO COMBINED TIPIFARNIB AND ALPELISIB TREATMENT

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Tipifarnib, a farnesyltransferase inhibitor, has shown single agent clinical activity in a highly-selected population of HNSCC driven by mutations in HRAS. The interplay between HRAS and PIK3CA oncogenic mutations in HNSCC is partially farnesylation-dependent, suggesting that dual inhibition of PIK3CA signaling and farnesyltransferase activity could be a novel approach for targeted therapy. We have previously shown that combining tipifarnib and the PIK3CA inhibitor alpelisib results in synergistic cell killing and anti-tumor activity in HNSCC models with pathogenic alterations in HRAS and PIK3CA (Malik et al., Cancer Res. 2022, 82:12, Abstract 1120). The preclinical data and high prevalence (>45%) of HRAS- and PIK3CA-dependent tumors provided the strong rationale to open KURRENT-HN, a Phase 1/2 open label dose escalation study combining tipifarnib and alpelisib in patients with R/M HNSCC and PIK3CA mutations/amplification and/or HRAS overexpression.

Fig 1: The tipifarnib and alpelisib combo is a potent inhibitor of mTOR and RSK signaling in PIK3CA- and HRAS-dependent cells

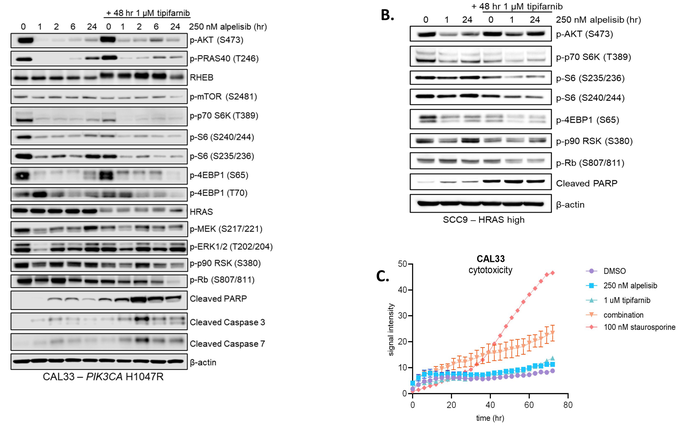
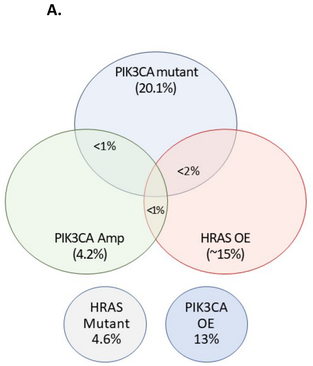


Figure 1: Tipifarnib blunts mTOR and RSK reactivation following alpelisib treatment and induces cell cycle arrest and apoptosis in *PIK3CA*-mutant and HRAS-overexpressing (OE) cell lines. (A, B): Immunoblot of signaling proteins in *PIK3CA* mutant CAL33 cells **(A)** and HRAS-high SCC9 cells **(B)** treated with alpelisib plus or minus tipifarnib. **(C):** Late apoptosis/necrosis (loss of membrane integrity, nuclei exposure) over time in CAL33 cells treated with alpelisib or tipifarnib monotherapy or the combination for 72 hours measured via Incucyte live cell imaging. Data are means +/- SD of three biological replicates.

Fig 2: Actionable HRAS and PIK3CA alterations in HNSCC



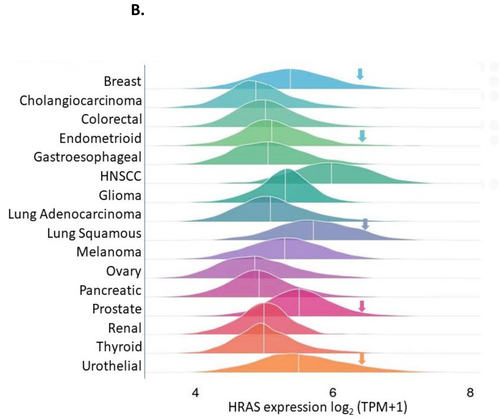


Figure 2: Comprehensive genomic profiling using Tempus XT reveals HRAS- and/or PIK3CA-dependence in HNSCC. (A): Venn diagram of PIK3CA alterations and HRAS overexpression (OE) in 1,119 HNSCC tumors. HRAS expression ≥1 standard deviation above the mean was defined as HRAS OE. **(B):** Mean HRAS expression was highest in HNSCC, with other tumors such as breast, endometrioid, lung squamous, prostate, and urothelial containing a subset with high HRAS expression (arrows), possibly associated with squamous histology.

Fig 3: Validation of an immunohistochemistry assay to select patients with HRAS overexpression

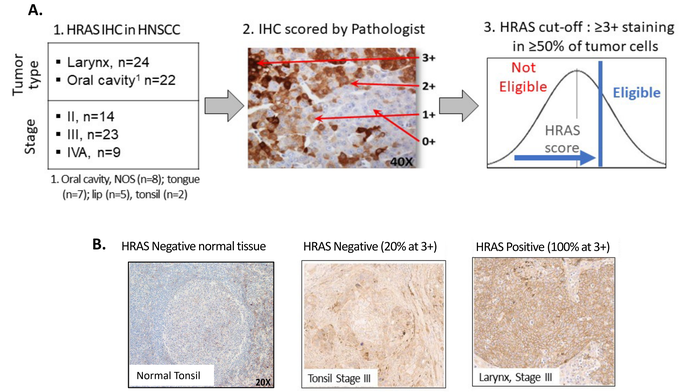
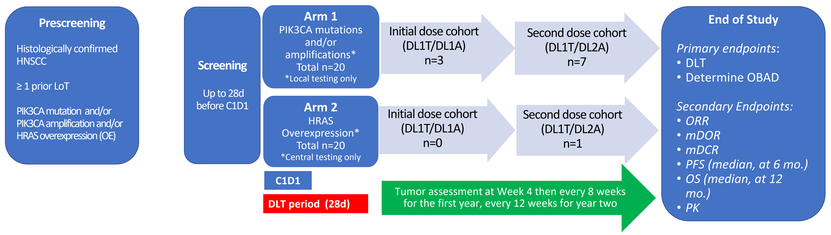


Figure 3: Validation of a CAP/CLIA IHC laboratory developed test to screen HNSCC patients for HRAS overexpression. (A): Forty-six HNSCC tumors were stained with an HRAS-specific antibody and scored by a BC-Pathologist. Specimens in which ≥50% of tumor cells showed ≥3+ HRAS staining were defined as positive for overexpression (OE). **(B):** HRAS IHC staining in normal tonsil (negative, 100% at 0+), HNSCC-Tonsil (Negative, 20% at 3+), and HNSCC-Larynx (100% at 3+)

Fig 4: KURRENT-HN Phase 1/2 open label tipifarnib + alpelisib



Potential Dosing*		
Dose Level	**Tipifarnib (T)**	**Alpelisib (A)**
3	DL3T	DL3A
2	DL2T	DL2A**
1	DL1T**	DL1A
-1	DL-1T	DL-1A

Initial Dosing Regimen—Simultaneous Dosing: 28 Day Cycle			
Week 1	**Week 2**	**Week 3**	**Week 4**
DL1T **Tipifarnib**	Rest	DL1T **Tipifarnib**	Rest
DL1A **Alpelisib**	DL1A **Alpelisib**	DL1A **Alpelisib**	DL1A **Alpelisib**

Abbreviations: DCR= disease control rate; DL= dose level; DLT= dose limiting toxicity; DOR= duration of response; LoT= line of therapy; OBAD= optimal biologically active dose, ORR= overall response rate; OS=overall survival; PFS= progression free survival; PK= pharmacokinetics

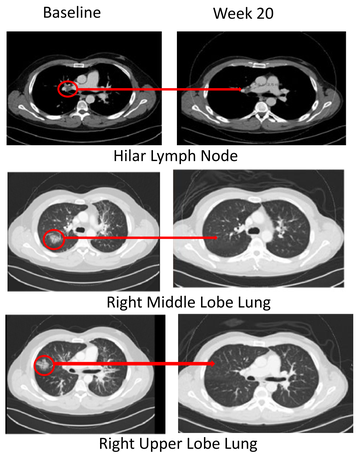
*Dose escalations or de-escalations are determined by the BLRM (Bayesian Logistic Regression Model) in addition to the clinical data which are reviewed and discussed with the SMC (Safety Monitoring Committee).
**Current dose cohort.

Fig 5: Patient on study

- 35y, male, nonsmoker, HPV16 positive
- SCC of tonsil Stage III cT4N2M0; PD-L1 CPS = 60

- Prior Treatments
  - CDDP/rad for 1 mo (Nov-Dec2019), BOR UNK
  - Cemiplimab/ISA101b (Jun-Nov2021), BOR PD
- PIK3CA R88Q mutation (44%) and HRAS OE (3+ staining in 100% of tumor cells) by IHC from May 2021 biopsy
- DL1 tipifarnib, DL2 alpelisib; completed 6 cycles
- G1/2 TRAE, G3 lipase elevation; presented clinical benefit and improvement in respiratory symptoms
- 81% reduction in target lesions after 1 cycle of treatment
- 84% reduction in target lesions after 3 cycles (BOR)
- Continues on-study for >27 weeks maintaining QoL

Data cut as of 14Sep2022; Preliminary raw data.



6: Overall safety summary

- No DLTs have been reported
  - Manageable safety; most treatment related AEs (TRAEs) are G1/2
  - G3+ alpelisib related AE/SAEs: hyperglycemia* (2), GGT increase (1), elevated lipase (1)
  - G3+ alpelisib and tipifarnib related AE/SAEs: acute kidney injury* (1), headache (1), facial pain (1), fatigue (1), nausea (1)

*SAEs

7: Conclusions

- Preclinical data provides a biologic rationale that precision combination therapies may achieve meaningful clinical responses in HRAS- and PIK3CA-dependent HNSCC.
- These data expand the potential benefit of targeted therapy to ~45% of HNSCC tumors that harbor an actionable HRAS and/or PIK3CA mutation or overexpression.
- Preliminary safety and efficacy data from KURRENT-HN is encouraging and TRAE have been consistent with known safety profile of each drug and are manageable.