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.

6: Overall safety summary

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

- Preliminary safety and efficacy data from KURRENT-HN is encouraging and TRAEs are generally manageable.
- 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 TRAEs are generally manageable.