A Phase 1/2 trial to evaluate the safety and antitumor activity of tipifarnib and alpelisib for patients with HRAS-overexpressing and/or PIK3CA-mutated/amplified recurrent/metastatic head and neck squamous cell carcinoma (The KURRENT-HN Trial)

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**Background**
- HRAS mutation/overexpression and PIK3CA mutations/amplifications occur in up to 50% of head and neck squamous cell carcinoma (HNSCC).
- HRAS preferentially activates PI3K more efficiently than KRAS2.
- Furthermore, mutant HRAS requires PI3K for oncogenic activity4, while PI3K requires RAS to drive tumor biology6.
- Thus, understanding the interdependencies of key cellular pathways may be particularly important in designing combination regimens for HNSCC.
- Preclinical data is supportive of the combination of tipifarnib and alpelisib; enhanced activity observed in both HRAS mutant/overexpressed and PIK3CA mutant/amplified in xenograft models of HNSCC.
- This Phase 1/2, open-label, 2-drug dose escalation trial will evaluate the safety of the combination of tipifarnib (a potent, selective inhibitor of farnesyltransferase, a critical enzyme required for HRAS activity)2 and alpelisib (a PI3Ka inhibitor and degrader) to assess early antitumor activity in adult patients with HNSCC.

**Study Design**

**Pre-Screening**
- May occur at any time prior to any pre-screening visit and prior to enrollment into one of the dose-escalation defined cohorts.

**Study Eligibility**
- Can last up to 28 days before C1D1.

**Year 1**
- DLT
- Tumor assessment at Week 4, and then every 8 weeks (C2 → C13).

**Year 2**
- DLT
- Tumor assessment every 12 weeks (C14 → C25).

**End of Study**
- Study duration is estimated to be ~2 years.

- End of study is defined as: 1 year from C1D1 of the last study participant enrolled.

- All participants followed for survival status after coming off trial intervention for any reason.

**Cycles 1-13**
- Cycles 1-13

**Cycles 14-25**
- Cycles 14-25

**Efficacy Assessments from Cycle 2 to Cycle 25**

**Key Inclusion Criteria**
- Age ≥18 years
- Histologically confirmed HNSCC not amenable to local therapy with curative intent
- Documented treatment failure from at least one prior therapy in the recurrent/metastatic setting
- Tumors with HRAS protein overexpression and/or PIK3CA mutation and/or amplification
- Measurable disease by RECIST v1.1

**Key Exclusion Criteria**
- Salivary gland, thyroid, (primary) cutaneous squamous or non-squamous histology
- Prior treatment (at least 1 full treatment cycle) with a FTI, PI3K, mTOR, or AKT inhibitor
- Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to Cycle 1 Day 1
- Intolerable Grade 2 or Grade 3 neurotoxicity or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1

**Primary Objective:**
- Determine the recommended dose and regimen
- Evaluate the safety and tolerability of tipifarnib and alpelisib in combination

**Secondary Objectives:**
- ORR and DCR
- Pharmacokinetics of tipifarnib and alpelisib in combination
- Anti-tumor activity in terms of PFS and rate of PFS at 6-months
- Estimate the OS and rate of OS at 12 months

**Participating Institutions:**

**Current Enrollment Status:**

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ClinicalTrials.gov identifier: NCT04997902

**REFERENCES**