TPS6104

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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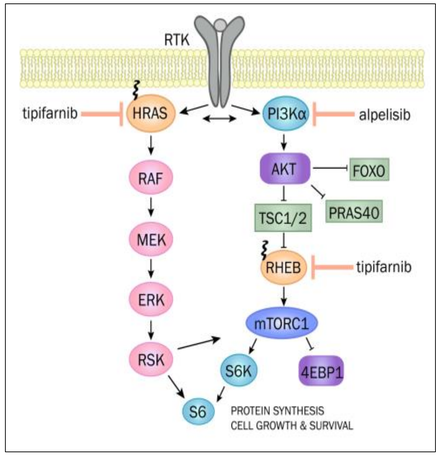
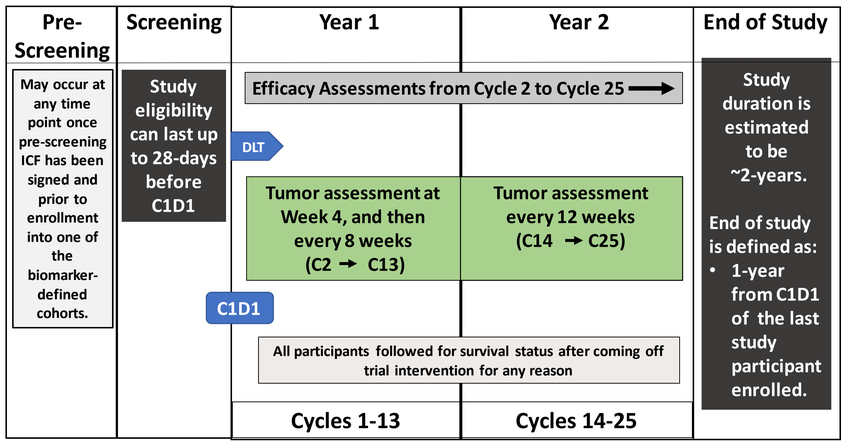
Background

- HRAS mutation/overexpression and *PIK3CA* mutations and/or amplifications occur in up to 50% of head and neck squamous cell carcinoma (HNSCC)[1].
- HRAS preferentially activates PI3K 5-fold more efficiently than KRAS[2].
- Furthermore, mutant HRAS requires PI3K for oncogenic activity[3], while PI3K requires RAS to drive tumor biology [4].
- 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



Abbreviations: Cx = Cycle x; CxDy = Cycle x Day y; DLT = Dose-limiting toxicity; ICF= Informed consent form

Total Enrollment, N=40

Cohort 1 (N=20)	Cohort 2 (N=20)
Tumors with *PIK3CA* mutations/amplifications*	Tumors with HRAS overexpression**

*Local or central NGS; **Central IHC

Initial Dose Regimen*

Simultaneous Dosing: 28 Day Cycle			
Week 1	**Week 2**	**Week 3**	**Week 4**
600 mg (300 mg BID) **Tipifarnib**	Rest	600 mg (300 mg BID) **Tipifarnib**	Rest
200 mg QAM **Alpelisib**	200 mg QAM **Alpelisib**	200 mg QAM **Alpelisib**	200 mg QAM **Alpelisib**

Abbreviations: BID = twice daily; QAM = once each morning *Doses may be escalated. Alpelisib: 250, 300 mg; Tipifarnib: 900, 1200 mg, total daily doses

The Optimal Biologically Active Dose (OBAD) will be determined using an adaptive dose escalation design (based on Bayesian logistic regression model) while maintaining a dose limiting toxicity (DLT) rate <33%.

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 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1

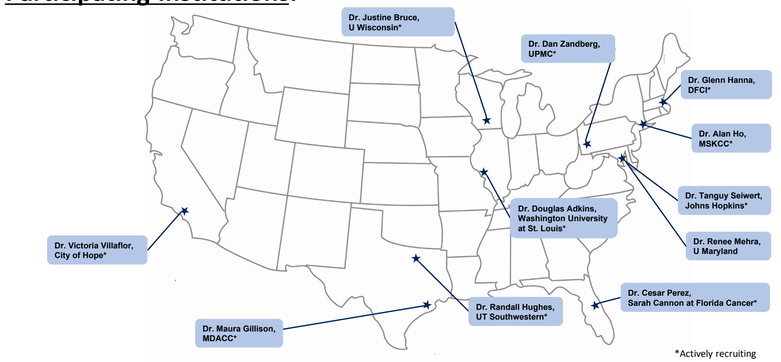
Primary Objective:

- 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:



*Actively recruiting

Current Enrollment Status:

PIK3CA Cohort	HRAS Cohort
Opened for enrollment October 2021	Opened for enrollment April 2022
First participant dosed December 2021	

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ClinicalTrials.gov identifier: NCT04997902

REFERENCES

[1]TCGA Data

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[3]Gupta S, Ramjaun AR, Haiko P, Wang Y, et al. Binding of ras to phosphoinositide 3-kinase p110alpha is required for ras-driven tumorigenesis in mice. Cell. 2007.129: 957-68.

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