CT253

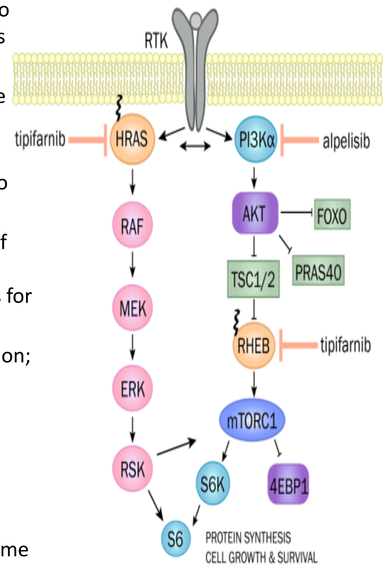
A Phase 1/2 trial to evaluate the safety and antitumor activity of tipifarnib and alpelisib for patients with HRAS-overexpressing and/or PIK3CA-mutated/amplified recurrent/metastatic head and neck squamous cell carcinoma (The KURRENT Trial)

Glenn J. Hanna[1], Cesar A. Perez[2], Alan Ho[3], Maura Gillison[4], Douglas Adkins[5], Ashley Dayoub[6], Andrew Saunders[6], Mollie Leoni[6], Stephen Dale[6], Kun Nie[6], Alex Dmitrienko[7]

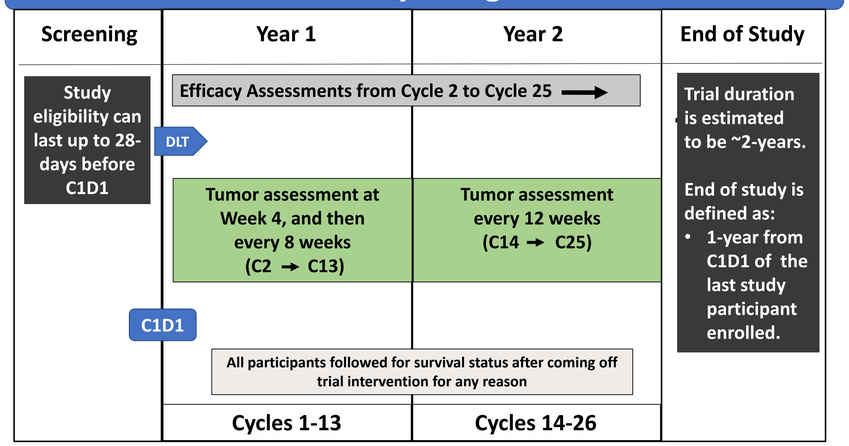
[1] Dana-Farber Cancer Institute, Boston, MA USA , [2] Sarah Cannon at Florida Center, Orlando, FL USA , [3] Memorial Sloan Kettering Cancer Center, New York, NY USA , [4] MD Anderson Cancer Center, Houston, TX, USA, [5]Washington University, St. Louis, MO, USA , [6] Kura Oncology, Inc., Boston, MA USA, [7] Mediana, LLC, USA

BACKGROUND

- HRAS mutation/overexpression and PIK3CA mutations and/or amplifications occur in up to 50% of mutations in 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; enhanced activity observed in both HRAS mutant/overexpressed and PIK3CA mutant/amplified populations 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 (an inhibitor of PI3Ka) and assess early antitumor activity in adult patients with HNSCC.



Study Design



Abbreviations: Cx = Cycle x; CxDy = Cycle x Day y; DLT = dose-limiting toxicity

Total Enrollment, N=40

Cohort 1 (N=20): Tumors with PI3KCA mutations/amplifications*

Cohort 2 (N=20): 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 R/M setting
- Tumors with HRAS 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 histologies
- 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

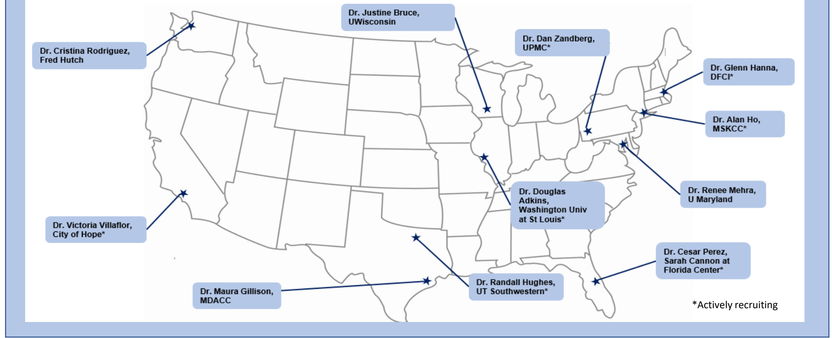
Primary Objective:

- Determine the recommended dose and regimen
- Evaluate the safety and tolerability of tipifarnib and alpelisib in combination

Secondary Objectives:

- Overall response rate (ORR) and disease control rate (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 Sites:



Status: The trial opened for enrollment in October 2021 and is currently enrolling.

Study Contacts: Phone: 617-588-3755
E-mail: KO-TIP-013@kuraoncology.com

ClinicalTrials.gov identifier: NCT04997902

REFERENCES

[1]TCGA Data

[2]Yan J, Roy S, Apolloni A, Lane A, et al. Ras isoforms vary in their ability to activate Raf-1 and phosphoinositide 3-kinase. J Biol Chem. 1998. 273: 24052-6.

[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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