

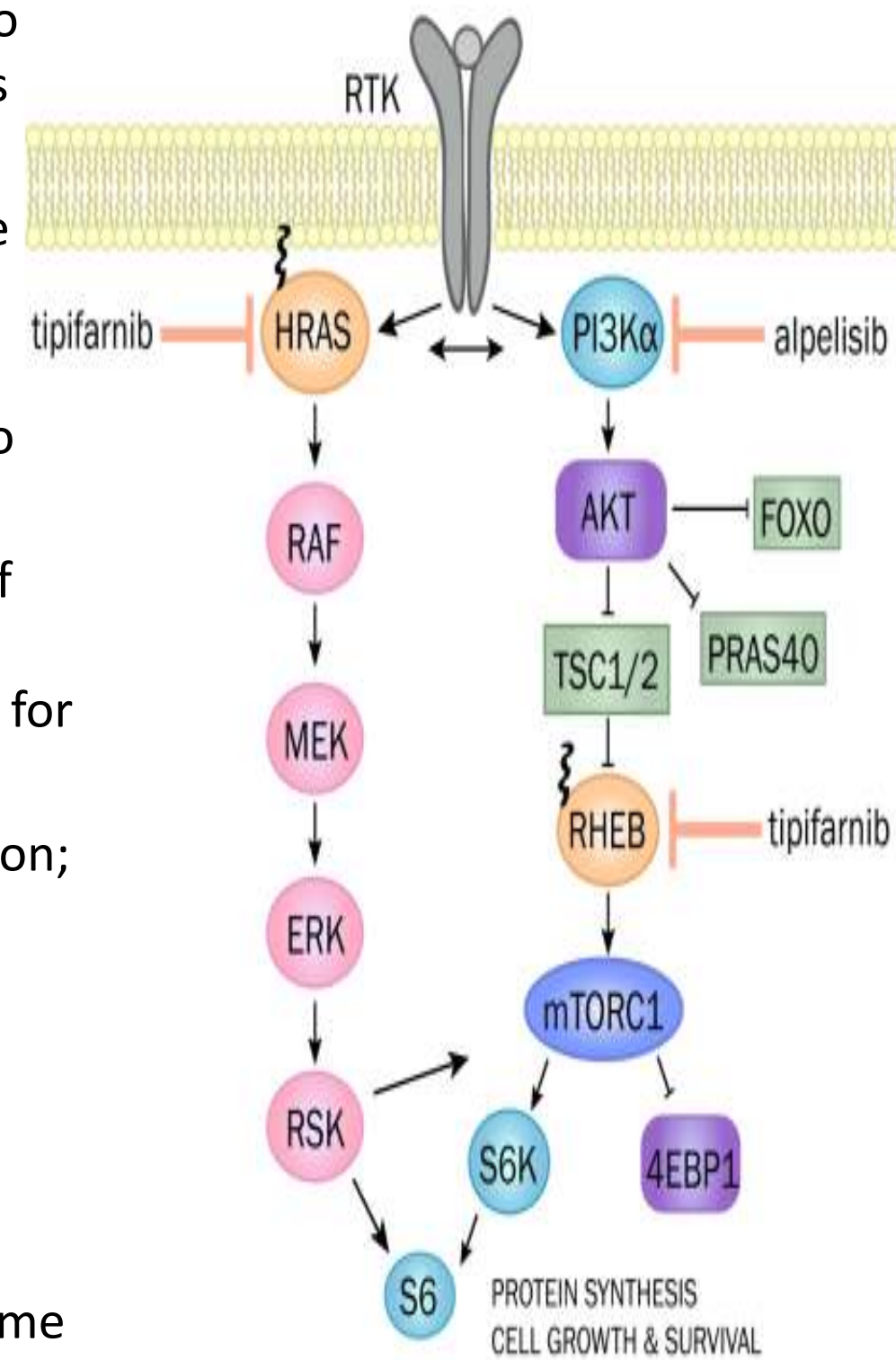
A Phase 1/2 trial to evaluate the safety and antitumor activity of tipifarnib and alpelisib for patients with HRAS-overexpressing and/or PIK3CA-mutated/amplified recurrent/metastatic head and neck squamous cell carcinoma (The KURRENT Trial)

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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 KRAS².
- Furthermore, mutant HRAS requires PI3K for oncogenic activity³, while PI3K requires RAS to drive tumor biology⁴.
- 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 activity²) and alpelisib (an inhibitor of PI3K α) and assess early antitumor activity in adult patients with HNSCC.



Total Enrollment, N=40

Cohort 1 (N=20)

Cohort 2 (N=20)

Tumors with PI3CA 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 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

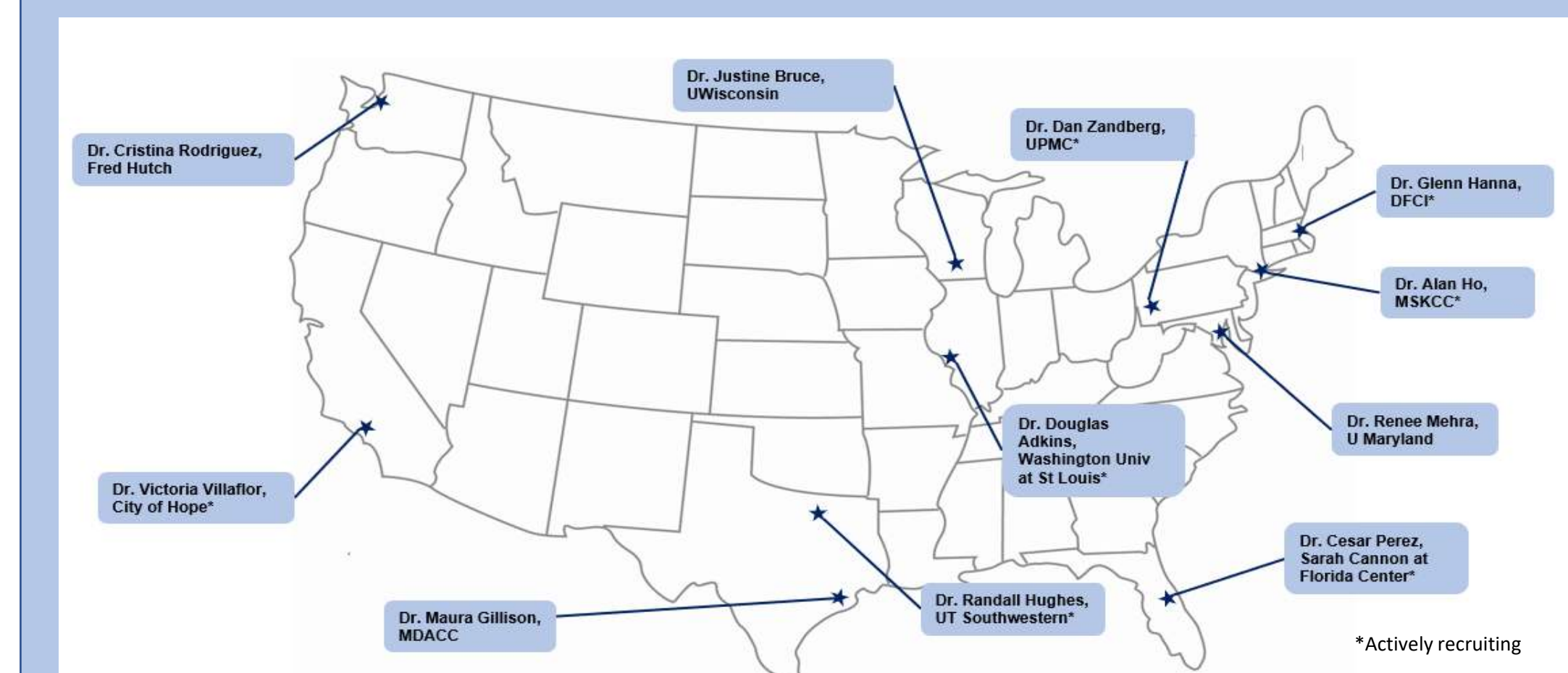
Primary Objective:

- 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.

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ClinicalTrials.gov identifier: NCT04997902

REFERENCES

- TCGA Data
- 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.
- 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.
- Zhao L, Vogt PK. Class I PI3K in oncogenic cellular transformation. Oncogene. 2008. 27: 5486-96.

Study Design

Screening	Year 1	Year 2	End of Study
Study eligibility can last up to 28-days before C1D1	Efficacy Assessments from Cycle 2 to Cycle 25 →		Trial duration is estimated to be ~2-years. End of study is defined as: • 1-year from C1D1 of the last study participant enrolled.
DLT	Tumor assessment at Week 4, and then every 8 weeks (C2 → C13)	Tumor assessment every 12 weeks (C14 → C25)	
C1D1	All participants followed for survival status after coming off trial intervention for any reason		
	Cycles 1-13	Cycles 14-26	

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