A Multicenter, Open-label, First-in-Human Study of TYRA-200 in Advanced Intrahepatic Cholangiocarcinoma and Other Solid Tumors with Activating *FGFR2* Gene Alterations

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TRIALS IN PROGRESS

Abstract ID TPS646

BACKGROUND

Activating alterations in the *FGFR2* gene are observed in approximately 15 – 20% of intrahepatic cholangiocarcinoma (ICC) cases[1]. *FGFR2* alterations have also been reported in other advanced cancers, such as endometrial (12%), gastric (4%), and non-small cell lung cancer (4%), among others[2]. Approved FGFR inhibitors have demonstrated clinical benefit in locally advanced or metastatic ICC harboring oncogenic *FGFR2* fusions or other rearrangements[3,4,5]. However, acquired resistance mutations limit their clinical activity and duration of responses[6].

TYRA-200 is an orally bioavailable FGFR1/2/3 inhibitor designed to specifically address these clinically observed acquired resistance alterations in *FGFR2*. TYRA-200 was designed to have an adaptable binding mode to accommodate significant changes in the shape of the ATP binding pocket caused by these mutations and has demonstrated similar potency in preclinical assays and animal models against both wild-type and resistant FGFR2 targets. TYRA-200 is currently being investigated in participants with advanced ICC and other solid tumors with activating *FGFR2* gene alterations in the active, ongoing SURF201 clinical trial (NCT06160752).

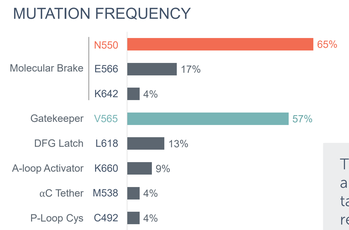
SURF201

STUDY DESIGN, OBJECTIVES, and KEY ELIGIBILITY

SURF201 is a phase 1, open-label, first-in-human study designed to evaluate TYRA-200 in participants with advanced ICC and other solid tumors with alterations in the FGF/FGFR pathway. The study is currently actively recruiting (NCT06160752).

UNMET NEED

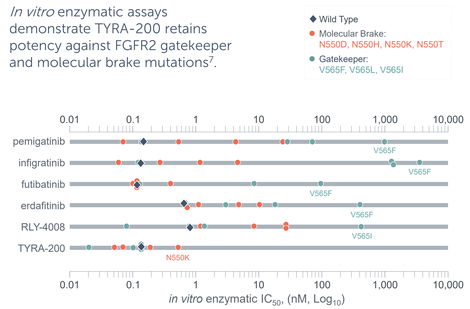
Patients with *FGFR2*+ ICC treated with currently available FGFRi can develop polyclonal acquired resistance mutations[6].



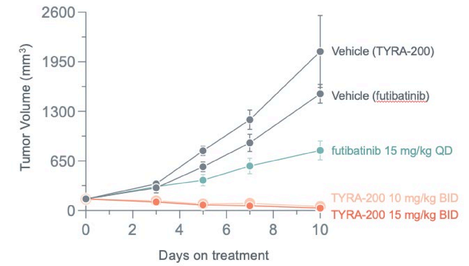
There are currently no approved therapies that target all common resistance mutations.

PRE-CLINICAL RATIONALE

In vitro enzymatic assays demonstrate TYRA-200 retains potency against FGFR2 gatekeeper and molecular brake mutations[7].



Xenograft model of Ba/F3 cells harboring the *FGFR2* gatekeeper mutation V565F treated with TYRA-200 or the pan-FGFRi futibatinib[7].



DESIGN

Dose Escalation

Phase 1 Part A

Advanced solid tumors with *FGFI FGFR* alterations

Interval 3+3

Target toxicity rate[a]
0.3 (0.25 – 0.33)

Starting dose
5 mg QD

Intra-patient dose escalation allowed

[a]Target toxicity rate for the highest dose level tested based on i3+3 dose escalation design[8].

Dose Expansion

Phase 1 Part B

Advanced ICC with activating *FGFR2* alterations and kinase domain mutation(s) that confer resistance to a prior FGFRi

Select doses will be further explored in expansion cohorts

DOSE B1

DOSE B2

TYRA-200 is administered orally in 28-day cycles until disease progression, death, unacceptable toxicity, withdrawal of consent for treatment, withdrawal from the study at the discretion of the investigator, or study termination.

OBJECTIVES

Primary

- Safety and tolerability

Secondary

- PK and preliminary anti-tumor activity

Exploratory

- Biomarkers of FGFR target engagement, toxicity, tumor response, and resistance to TYRA-200

ENDPOINTS

- Incidence of DLTs, AEs, and clinically meaningful changes in safety parameters
- ORR, DOR, DCR, and TTR
- Serum phosphorous, ctDNA, and other known FGF/FGFR pathway plasma pharmacodynamic biomarkers

KEY INCLUSION

Part A

- Adults ≥ 18 years old.
- ECOG 0 – 1
- Advanced solid tumor with FGF/FGFR pathway alteration
- Evaluable/measurable disease per RECIST v1.1.
- Any number of prior therapies, including FGFRi

Part B

- Adults ≥ 18 years old
- ECOG 0 – 1
- Measurable disease per RECIST v1.1
- Have received ≥1 prior FGFRi
- Histologically confirmed ICC with a previously identified *FGFR2* activating gene alteration, *AND*
- Presence of an *FGFR2* kinase domain mutation

KEY EXCLUSION

- Serum phosphate >ULN at screening
- Ocular conditions that may increase risk of developing ocular toxicity
- History of or current uncontrolled cardiovascular disease
- Active and/or symptomatic, or untreated brain metastases
- Females who are pregnant, breastfeeding, or plan to become pregnant, or males who plan to conceive a child
- Discontinued a prior FGFRi due to hepatotoxicity ≥Gr. 3 or any Gr. 4 AE
- Primary progression on a prior FGFRi, defined as PD within <6 mo. with no tumor response and no evidence of an *FGFR2* resistance mutation (Part B only)

STUDY LOCATIONS

University of California San Francisco
San Francisco, CA

University of Texas MD Anderson Cancer Center
Houston, TX

The Ohio State University
Columbus, OH

Massachusetts General Hospital
Boston, MA

Sponsor contact information
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The authors would like to acknowledge all patients, caregivers, and all study staff on this ongoing clinical trial. Additionally, the authors would like to thank Eric Allen, Dan Bensen, Guy Gammon, and Grace Indyk for their contributions.

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