Phase I/II study of TYRA-300 in mUC and other solid tumors with activating *FGFR3* alterations (SURF301)

Aaron Hansen[2], Alison Zhang[1], Charlene Mantia[3], Andrew Weickhardt[4], Valentina Boni[5], Evan Yu[6], Marie Robert[7], Shilpa Gupta[8], Gopa Iyer[9], Michael Millward[10], Rafael Morales-Barrera[11], Christopher Hoimes[12], Jordan Berlin[13], Andrew Hill[14], Fabricio Racca[15], Damien Pouessel[16], Kriti Mittal[17], Christine Lihou[18], Yohann Loriot[19], Ben Tran[20]

TRIALS IN PROGRESS

Abstract ID TPS904

BACKGROUND

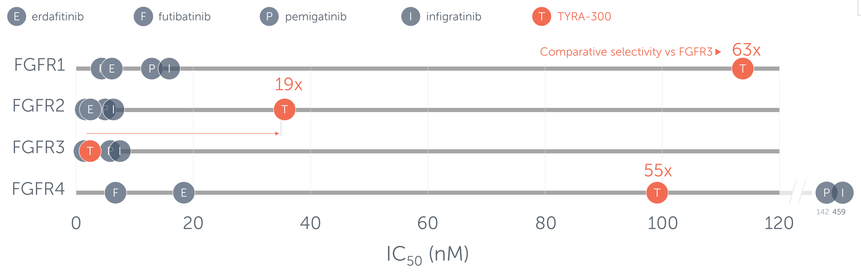
Activating *FGFR3* gene alterations have been identified in up to 20% of metastatic urothelial cancers (mUC)[1]. Currently available FGFR inhibitors in mUC lack isoform specificity for FGFR3, which can lead to off-target toxicities driven by FGFR1 (hyperphosphatemia), FGFR2 (stomatitis, ocular toxicity, and skin and nail toxicities), and FGFR4 (GI disturbances)[2,3,4]. TYRA-300 has been designed to be more selective for FGFR3 over FGFR1/2/4 to minimize off-target toxicity and to avoid interactions with known FGFR3 gatekeeper mutations. TYRA-300 is in development for the treatment of FGFR3+ mUC and other advanced solid tumors (NCT05544552).

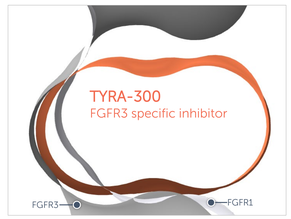
SURF301

STUDY DESIGN, OBJECTIVES, and KEY ELIGIBILITY

PRE-CLINICAL RATIONALE

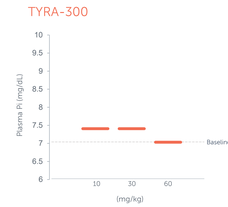
Selectivity observed for TYRA-300 vs. approved or late-stage clinical compounds: *in vitro* Ba/F3 Cellular IC_{50} (nM)[5]

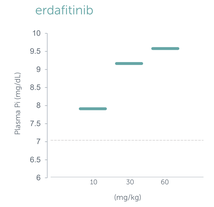




CRYSTALLOGRAPHY

Lack of isoform specificity by currently available FGFR inhibitors limits dosing and treatment duration. Through a series of high-resolution crystal structures using Tyra Biosciences' SNAP platform, TYRA-300 was designed to selectively target FGFR3[5].

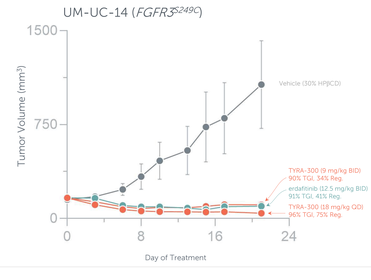




In vivo, single-dose studies of TYRA-300 or erdafitinib in a rat model indicate that TYRA-300 did not impact plasma phosphate levels[5,6].

IN VIVO POTENCY

Tumor growth inhibition studies in UM-UC-14 ($FGFR3^{S249C}$) xenograft models treated with TYRA-300 or erdafitinib[5,6].



DESIGN

PH 1

TWO PART
i3+3 design

Dose Escalation

Part A

Participants with advanced solid tumors who have exhausted all available therapies

QD Dosing

10 mg
20 mg
40 mg
60 mg
90 mg
100 mg
110 mg
120 mg

Dose Expansions

Part B

QD Dosing
Advanced solid tumors *FGFR3+*

40 mg
60 mg
90 mg
100 mg
110 mg
120 mg

BID Dosing
Advanced mUC *FGFR3+*

40 mg
50 mg

PH 2

Participants diagnosed with mUC or other advanced solid tumors harboring activating *FGFR3* gene alterations

Cohorts

1. FGFR inhibitor-exposed mUC with activating *FGFR3* alterations
2. FGFR inhibitor naïve mUC with activating *FGFR3* alterations
3. Other advanced solid tumors with activating *FGFR3* alterations

ASSESSMENT REQUIREMENTS

	Admin	Safety	Labs	Disease Assessments	PK & PD
Baseline (-28 to -1 days)	●	●	●		
Cycle 1 (28-day cycles)		●	●		● (C1D1, C1D15)
Cycle 2+		●	●	● (q2 cycles up to C12; q3 cycles from C13+)	● (C2D1, C2D15, C3D1, C5D1, C7D1)
EOT		●	●	●	
Safety F/U		●	●		
Survival F/U	●				

KEY INCLUSION

PHASE 1 (PARTS A AND B)

- Adults ≥ 18 years old.
- ECOG performance status 0-1
- Solid tumor with focus on mUC (Part B)
- Evaluable/measurable disease per RECIST v1.1.
- Documented *FGFR3* mutation/fusion (Part B).
- Any # of prior therapies, including FGFRi
- Adequate organ and bone marrow function

PHASE 2

- Adults ≥ 18 years old.
- ECOG performance status of 0-2.
- Measurable disease per RECIST v1.1.
- Histologically confirmed mUC (Cohorts 1 & 2)
- Adequate organ and bone marrow function
- Any number of prior therapies
- Prior FGFRi treatment with documented *FGFR3* gatekeeper mutation (Cohort 1 only)

KEY EXCLUSION

- Serum phosphate > ULN at screening
- Ocular conditions that may increase risk of developing ocular toxicity
- History of or current uncontrolled cardiovascular disease
- Brain metastasis that is active and/or symptomatic or untreated
- GI disorder that may affect administration/absorption of TYRA-300.
- Females who are pregnant, breastfeeding, or plan to become pregnant, or males who plan to conceive a child while enrolled

OBJECTIVES

PRIMARY

- Determine optimal dose, MTD, and RP2D(s) (Phase 1)
- Evaluate preliminary anti-tumor activity (Phase 2)

SECONDARY

- Assess safety and tolerability (Phase 1&2)
- Characterize pharmacokinetic profile (Phase 1)

EXPLORATORY

- Identify potential biomarkers (Phase 1 & 2)
- Estimate overall survival (Phase 2)

ENDPOINTS

- Incidence of DLTs/AEs
- Overall response rate (ORR)
- Changes in labs, ECG, VS, PE
- PK parameters
- DOR, DCR>12 weeks, TTR (Phase 1 Part B, Phase 2) and PFS (Phase 2)
- ctDNA, serum proteomics, exosomes
- OS

REFERENCES & ACKNOWLEDGEMENTS

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AUTHOR AFFILIATIONS

1. Princess Alexandra Hospital & University of Queensland, Woolongaba, QLD, Australia; 2. Macquarie University Health Sciences Centre, Macquarie Park, NSW, Australia; 3. Dana-Farber Cancer Institute, Boston, MA, USA; 4. Olivia Newton-John Cancer and Wellness Centre, Austin Health, Melbourne, VIC, Australia; 5. NEXT Madrid, Hospital Quironsalud, Madrid, Spain; 6. Fred Hutchinson Cancer Center and University of Washington, Seattle, WA, USA; 7. Institut de Cancerologie de l'Ouest, Saint Hebran, France; 8. Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; 9. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 10. Linear Clinical Research, Nedlands, WA, Australia; 11. Vall d'Hebron Institute of Oncology (VHIO). Vall d'Hebron University Hospital, Barcelona, Spain; 12. Department of Medicine, Medical Oncology, Duke Cancer Institute, Duke University School of Medicine, Durham, NC, USA; 13. Vanderbilt Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; 14. Tasman Oncology, Southport, QLD; 15. NEXT Barcelona, Hospital Quironsalud, Barcelona, Spain; 16. Claudius Regaud Institute, Toloune University Cancer Center (IUCT) Oncopole, Toloune, France; 17. University of Massachusetts Medical School, Worcester, MA, USA; 18. Tyra Biosciences, Inc, Carlsbad, CA, USA; 19. Institut de Cancerologie Gustave Roussy, Villejuif, France; 20. Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.

Sponsor contact information
TyraClinicalTrials@tyra.bio
Tyra Biosciences, Inc.
Carlsbad, CA, USA