TYRA-300 pharmacokinetic and pharmacodynamic analysis in SURF301 demonstrates PD activity and selectivity over FGFR1

Yohann Loriot[1], Allison Zhang[2], Aaron Hansen[3], Charlene Mantia[4], Valentina Boni[5], Andrew Weickhardt[6], Evan Y. Yu[7], Marie Robert[8], Gopa Iyer[9], Andrew Murtha[10], Sherry Owens[11], Ben Suttle[12], Gillian Vandekerkhove[10], Alexander Wyatt[10], Guy Gammon[11], Timothy Burn[11], Ben Tran[13]

BACKGROUND

Activating *FGFR3* gene alterations are present in up to 20% of advanced/metastatic urothelial cancers (mUC). While FGFR+ mUC is responsive to treatment with FGFR inhibitors, the lack of FGFR isoform specificity in current pan-FGFR inhibitors leads to on-target FGFR1/2/4 toxicity. In particular, hyperphosphatemia (FGFR1 inhibition), ocular toxicities (FGFR2 inhibition), stomatitis (FGFR2 inhibition), and skin and nail toxicity (FGFR2 inhibition).

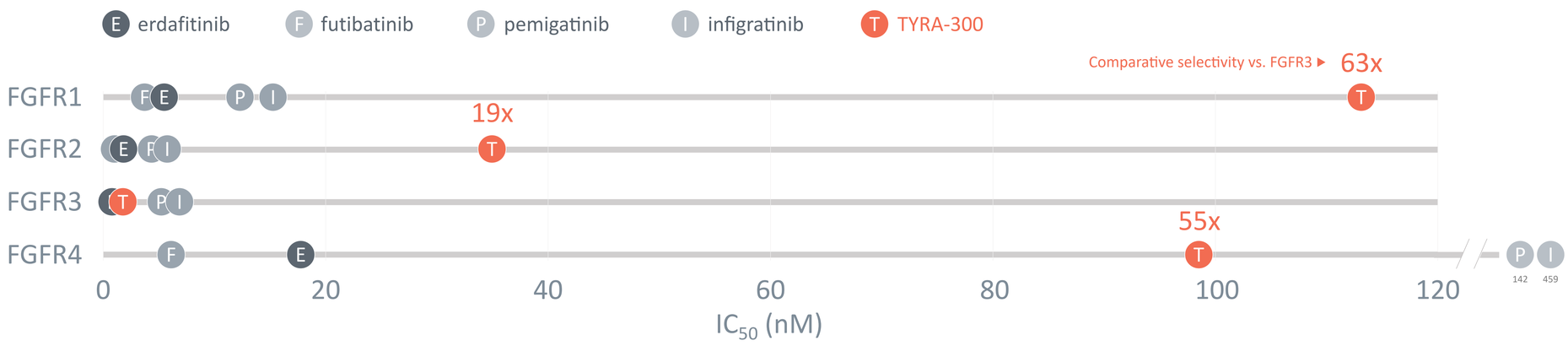
Additionally, loss of activity to current generation FGFR inhibitors has been demonstrated in the clinic due to development of on-target resistance mutations (e.g., FGFR3 V555M/L gatekeeper). TYRA-300 was designed to be more selective for FGFR3 as well as target FGFR3 gatekeeper mutations.[1] TYRA-300 is in development for the treatment of *FGFR3* gene alteration positive mUC and other solid tumors (SURF301 - NCT05544552).

METHODS

Eligible adults with advanced malignancies with/without *FGFR3* alterations received oral TYRA-300 in continuous 28-day cycles. Dose escalation (10mg -120mg QD) allowed any FGF/FGFR pathway alteration. Dose expansion (40-90mg QD) required FGFR3 alterations. The current analysis included 41 patients from the QD cohorts. Steady-state PK was assessed at C1D15. Phosphate levels were assessed as part of laboratory chemistries. PD and ctDNA analysis

were performed on available plasma samples collected at Baseline, C1D15 and C2D1. Changes in plasma proteins were determined using the Olink® platform (Waltham, MA). On treatment Olink® data was compared to baseline with a paired T-Test using the 60-120 mg QD participants and a cut-off of $P < 0.01$ and an absolute fold-change of 1.5. Changes in ctDNA fraction were assessed in a subset of patients with available ctDNA samples (n=19) using a custom deep targeted sequencing approach.[2]

Selectivity observed for TYRA-300 vs. approved FGFR inhibitors: *in vitro* Ba/F3 Cellular IC_{50}

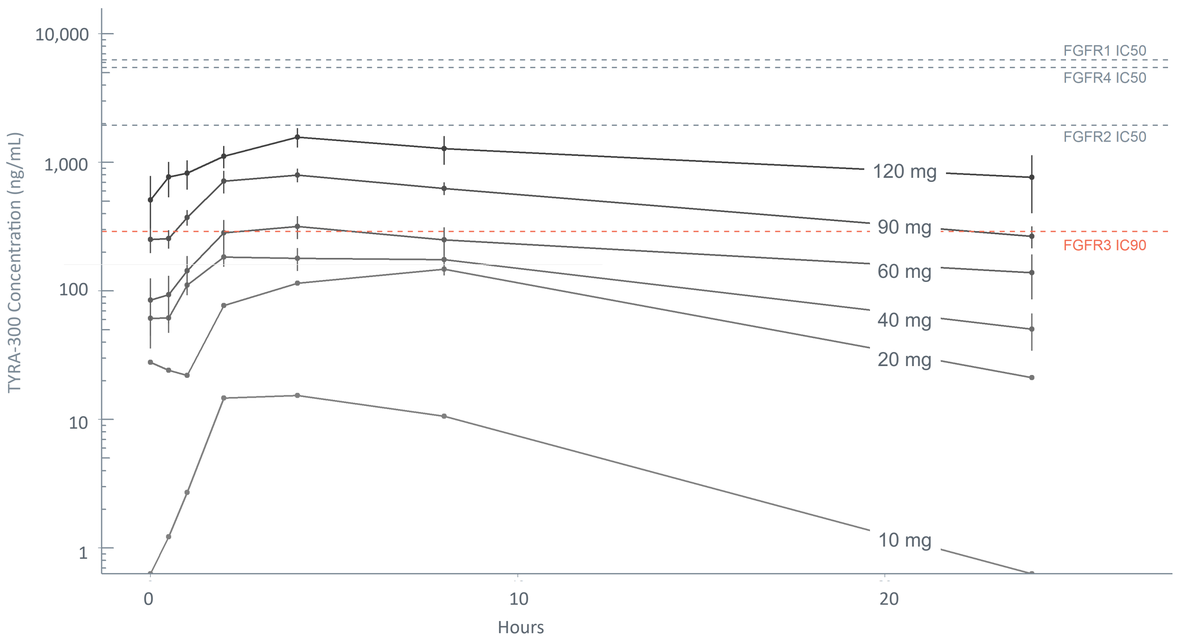


Comparative selectivity of approved FGFR inhibitors vs FGFR3

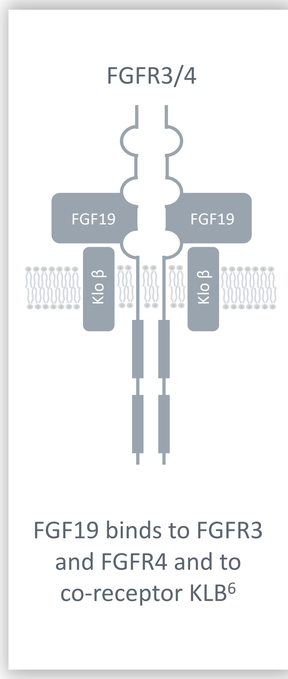
	E	F	P	I
FGFR1	4.2x	4.9x	2.4x	2.2x
FGFR2	1.4x	1.3x	0.8x	0.8x
FGFR4	14x	7.6x	27x	67x

RESULTS

Cycle 1 Day 15 Steady State Plasma PK

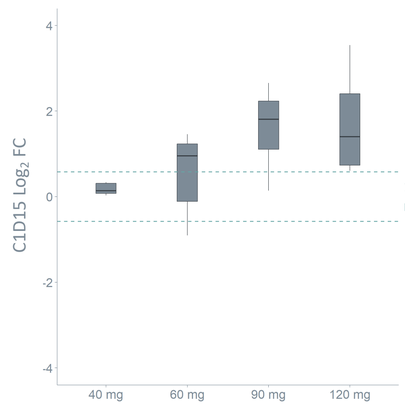


Greater than dose proportional exposure observed. FGFR1-4 target exposures are based on protein binding adjusted Ba/F3 cellular assays. Doses ≥ 90 mg exceeded the FGFR3 IC90 target coverage that resulted in tumor regressions in an FGFR3 p.S249C mUC xenograft model.[1] (Error bars are Mean ± SEM).

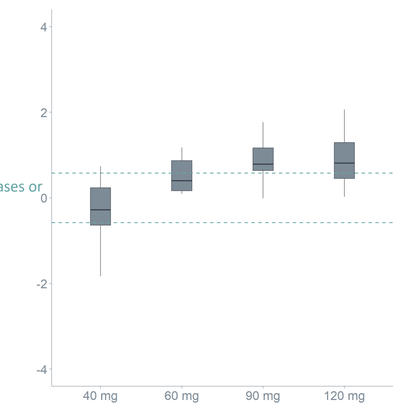


FGF19 binds to FGFR3 and FGFR4 and to co-receptor KLB[6]

FGF19

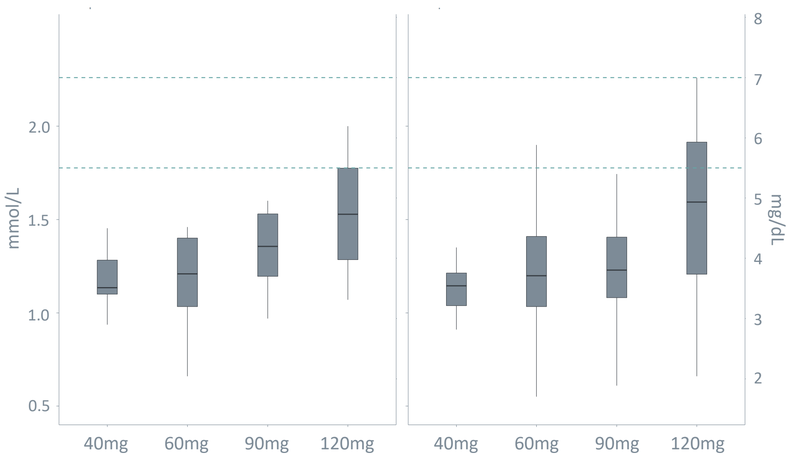


KLB



FGF19 and KLB increased as potential compensatory mechanism to FGFR3 inhibition. No differences in response based on tumor type or FGFR3 status, consistent endogenous and not tumor derived response. Confirmation of FGFR3 dependence ongoing with FGFR4 PD analysis.

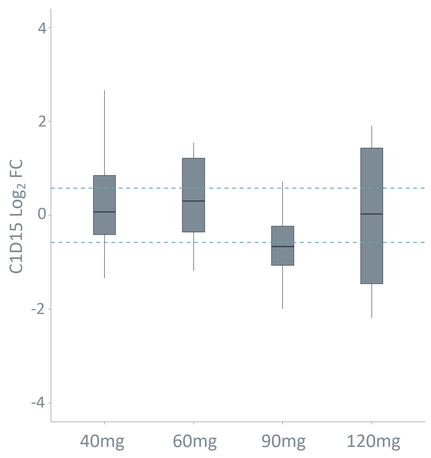
C1D15 Phosphate



C2D1 Phosphate

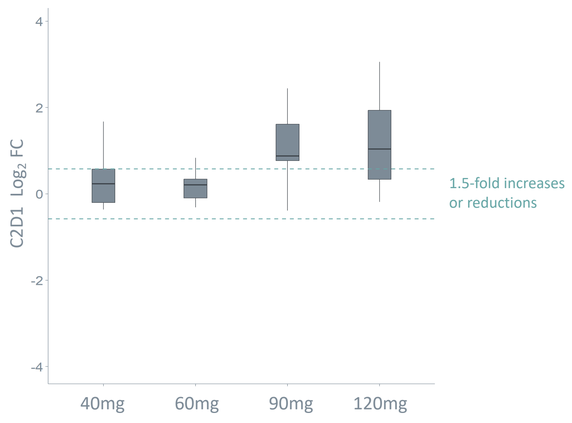
No hyperphosphatemia was observed at levels > 7 mg/dL across all doses with 7 mg/dL being the level requiring intervention for currently approved panFGFR inhibitors.[3-5]

C1D15 FGF21



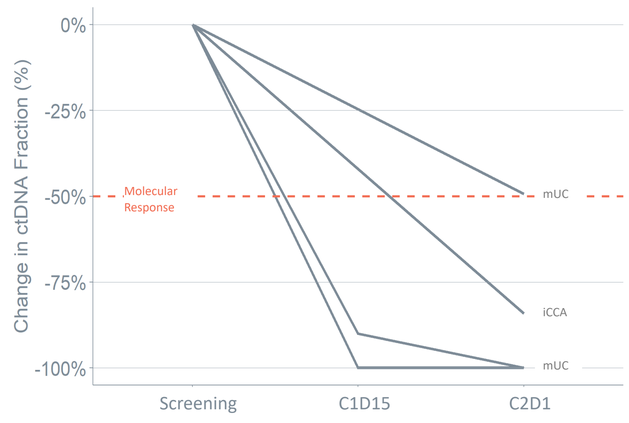
No compensatory increase in FGF21 (FGFR1 ligand) consistent with selectivity against FGFR1. Dotted green lines denote 1.5-fold absolute fold change.

COL9A1



Compromised Collagen 2a1 and 9a1 secretion causes overactive FGFR3 signaling in Slc26a2 deficient chondrocytes[7] linking collagen secretion to FGFR3.

ctDNA



Decreases in ctDNA observed for participants with FGF/FGFR3 altered tumors treated with 90 mg QD . A molecular response was defined as a >50% decrease.[8]

CONCLUSIONS

In the ongoing SURF301 study, TYRA-300 had demonstrated exposures above the IC_{90} for FGFR3 inhibition that are below the IC_{50} for FGFR1/2/4. TYRA-300 led to changes in FGFR3 PD markers, a low incidence of hyperphosphatemia and decreases in plasma ctDNA fractions for all four participants with available samples.

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AUTHOR AFFILIATIONS

1. Institut de Cancerologie Gustave Roussy, Villejuif, France
2. Macquarie University Health Sciences Centre, Macquarie Park, NSW, Australia.
3. Princess Alexandra Hospital & University of Queensland, Woolongaba, QLD, Australia.
4. Harvard Medical School, Boston, MA, USA.
5. NEXT Madrid, Hospital Quironsalud, Madrid, Spain.
6. Olivia Newton-John Cancer and Wellness Centre, Austin Health, Melbourne, VIC, Australia
7. Fred Huthinson Cancer Center and University of Washington, Seattle, WA, USA
8. Institut de Cancerologie de l'Ouest, Saint Hebran, France.
9. Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA.
10. Vancouver Prostate Centre, Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
11. Tyra Biosciences, Inc, Carlsbad, CA, USA.
12. qPharmetra, 506 Grant Forest Lane. Cary , North Carolina 27519, USA
13. Department of Medical Oncology, Sir Peter MacCallum Cancer Centre, Melbourne, VIC, Australia.

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