TYRA-300: FGFR3-selective and gatekeeper agnostic

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Poster # 462P

Background

There is an unmet clinical need for next generation therapies with improved efficacy and tolerability for patients with metastatic urothelial carcinoma.

~15% of metastatic urothelial cancers harbor mutations or fusions in FGFR3[1].

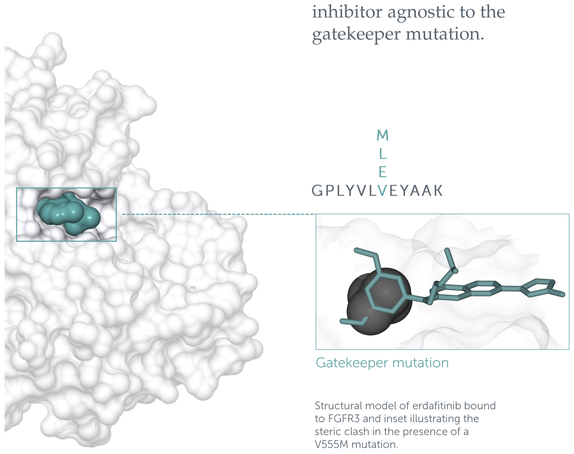
Erdafitinib is a pan-FGFR inhibitor that is FDA approved for the treatment of FGFR3- and FGFR2-altered metastatic urothelial carcinoma.

Resistance to FGFR targeted therapies can be mediated by an acquired gatekeeper mutation[2].

No approved therapies are available for tumors harboring the FGFR3 gatekeeper mutation.

Currently available pan-FGFR inhibitors induce hyperphosphatemia in patients due to FGFR1 inhibition, which is dose limiting and often results in dose reduction[3].

TYRA-300 is an FGFR3-selective inhibitor agnostic to the gatekeeper mutation.



Structural model of erdafitinib bound to FGFR3 and inset illustrating the steric clash in the presence of a V555M mutation.

Results

FGFR3 V555M/L/E gatekeeper mutations confer resistance to erdafitinib.

MUTATION TYPE	SUBSTIT.	FREQ
Gatekeeper	V555M	30
	V555L	10
	V555E	9
DFG Latch	L608V	1
Activation loop	K650V	1
None identified		14

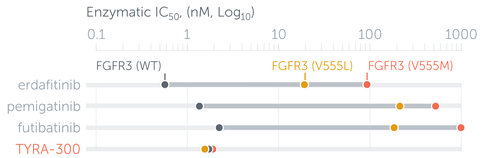
N=65

Ba/F3 FGFR3::BAIAP2L1 cells were treated with ENU for 24 hours, then treated with 50-1000 nM erdafitinib. Surviving clones were expanded then sequenced for the presence of acquired mutations in FGFR3.

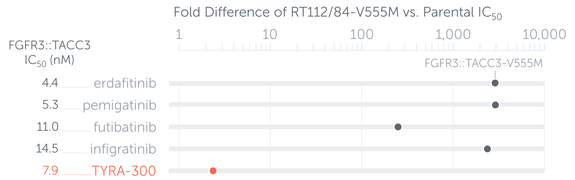
Results

IN VITRO POTENCY

TYRA-300 maintains potency against gatekeeper mutants V555M/L in enzymatic assays.

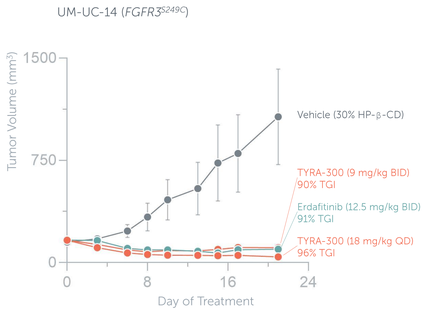


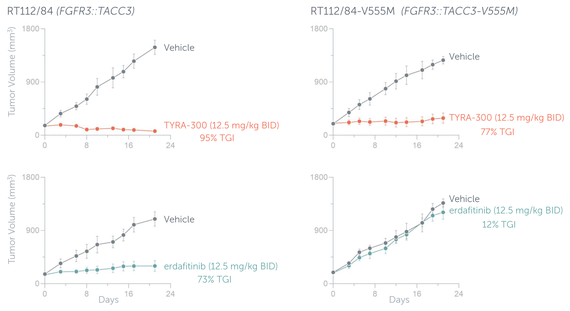
TYRA-300 is potent in a CRISPR-engineered gatekeeper-mutant cell line.



IN VIVO POTENCY

In vivo tumor efficacy in FGFR3 activating mutant, fusion, and gatekeeper-mutant bladder cancer xenograft models.





Mice were inoculated with either UM-UC-14 (left), RT112/84 (middle), or RT112/84-V555M (right) cells then dosed orally with vehicle, TYRA-300, or erdafitinib.

SELECTIVITY

TYRA-300 shows significant selectivity for FGFR3 over other FGFR isoforms.

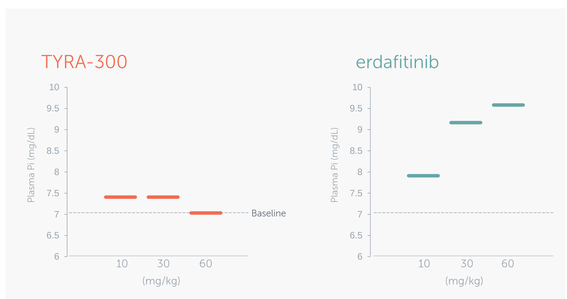
TYRA-300 vs. Ba/F3 Cellular IC50 (nM)

	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR1	5.5	3.9	12.3	15.3	113
FGFR2	1.8	1.0	4.3	5.8	34.9
FGFR3	1.3	0.8	5.2	6.9	1.8
FGFR4	17.7	6.1	142	459	98.4
Fold Selectivity for FGFR3					
FGFR1	4.2x	4.9x	2.4x	2.2x	63x
FGFR2	1.4x	1.3x	0.8x	0.8x	19x
FGFR4	14x	7.6x	27x	67x	55x

Significantly greater FGFR3 selectivity

TYRA-300 does not substantially elevate phosphate levels in rats.

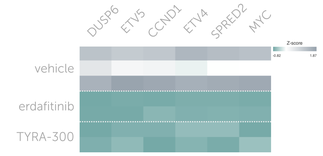
Rat plasma phosphate from 4 pooled mice at 24 hours after a single dose.

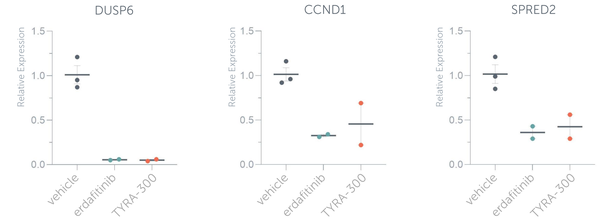


Results

RNA sequencing identified potential ***in vivo*** biomarkers for TYRA-300 FGFR3 activity.

Mice with UM-UC-14 xenograft tumors were treated with vehicle, erdafitinib (25 mg/kg QD), or TYRA-300 (18 mg/kg QD) for 3 days. Tumors were collected 6 hours after the final dose for RNA sequencing analysis (heatmap) and confirmatory qRT-PCR analysis (plots).





Conclusions

TYRA-300 retains potency in the presence of a gatekeeper resistance mutation ***in vitro*** and ***in vivo***.

TYRA-300 is selective for FGFR3, and thus may limit toxicities observed with pan-FGFR inhibitors.

Biomarkers of ***in vivo*** response to TYRA-300 were identified by RNA sequencing.

TYRA-300 is currently being studied in metastatic urothelial cancer and other advanced solid tumors.

References

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