TYRA-300 Demonstrates Significant Increases in Growth and Bone Length in a Mouse Model of FGFR3-Related Skeletal Dysplasia

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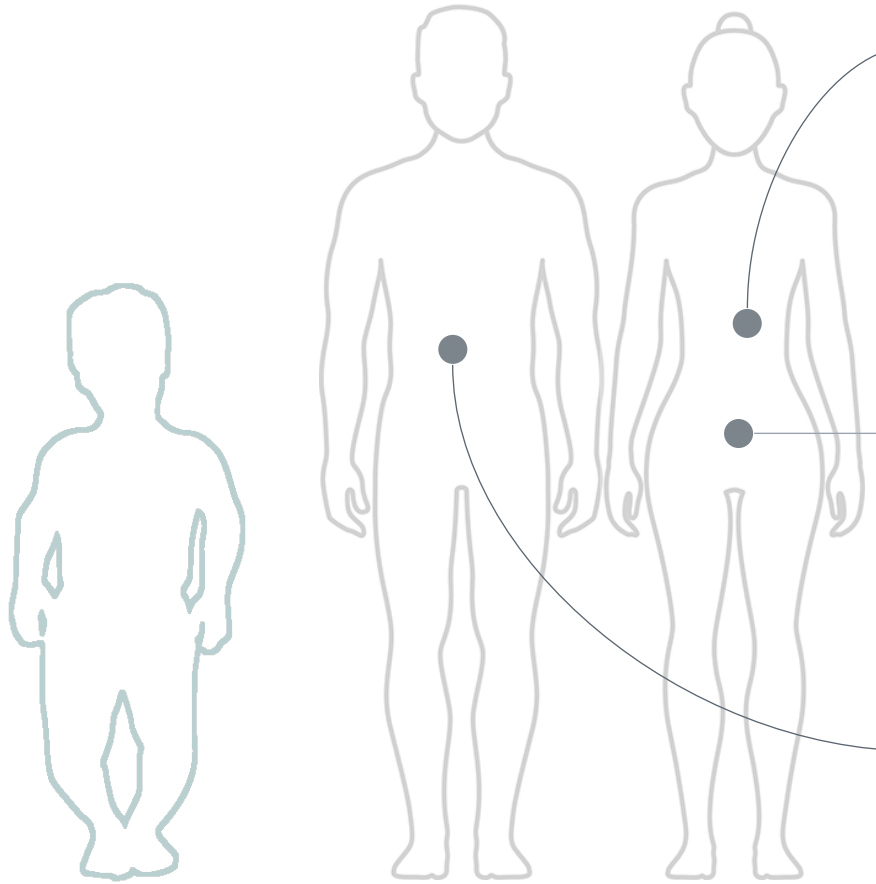
FGFR alterations are implicated in many clinical conditions

ACHONDROPLASIA (ACH)
~99% FGFR3
~3,000/yr (US)

OTHER FGFR3-RELATED SKELETAL DYSPLASIAS
~40,000/yr (US)



HEPATOCELLULAR CARCINOMA (HCC)
~30% FGF19 (FGFR4/3 ligand)
~9,000/yr (US)

UROTHELIAL CARCINOMA (UC)
~50% FGFR3
~40,000/yr (US)

INTRAHEPATIC CHOLANGIOCARCINOMA (ICC)
~10–20% FGFR2
~1,700/yr (US)

Note: oncology figures represent 2022 US incidence across all stages of the disease; skeletal dysplasias represent 2022 US pediatric prevalence

ACH can result in serious clinical complications

ACH is the most common cause of disproportionate short stature

MECHANISM

FGFR3 G380R gain of function mutation accounts for over 99% of ACH[1,2]

FGFR3 inhibits chondrocyte proliferation and differentiation, resulting in decreased longitudinal bone growth[3]

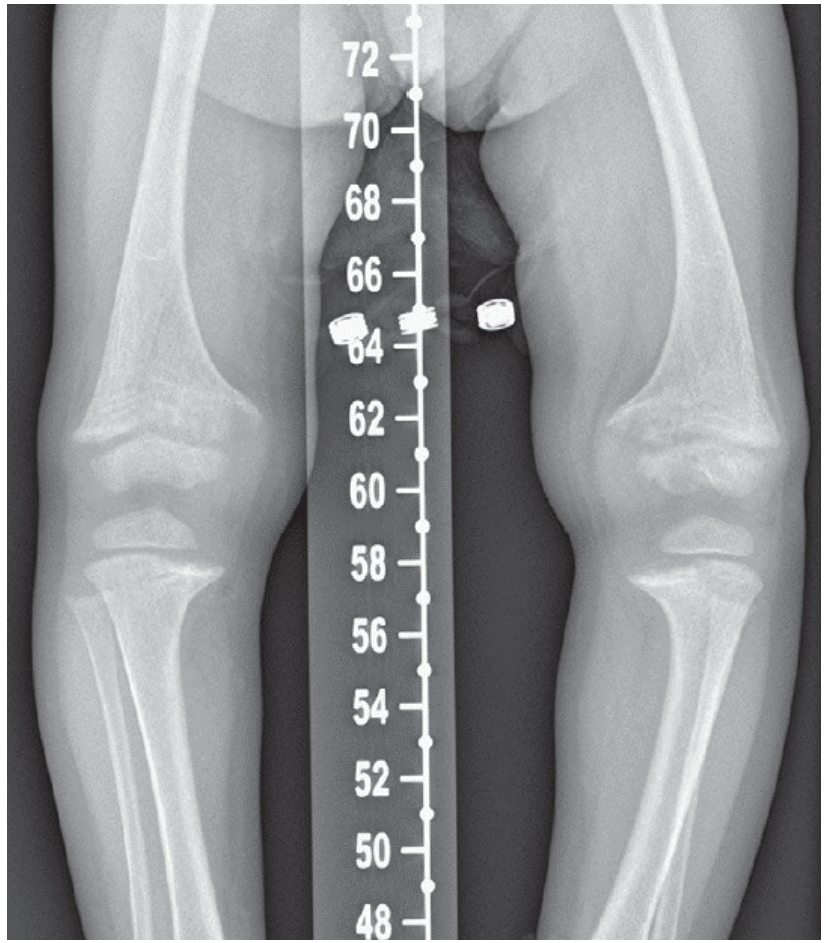
COMPLICATIONS

Infants can face serious complications related to critical foramen magnum stenosis[4,5]

Additionally: ENT, orthopedic and spinal surgeries

1. Bellus et al., 1995; 2. Rousseau et al., 1994; 3. Ornitz and Legeai-Mallet, 2017; 4. Hecht et al., 1987; 5. Pauli et al., 2019

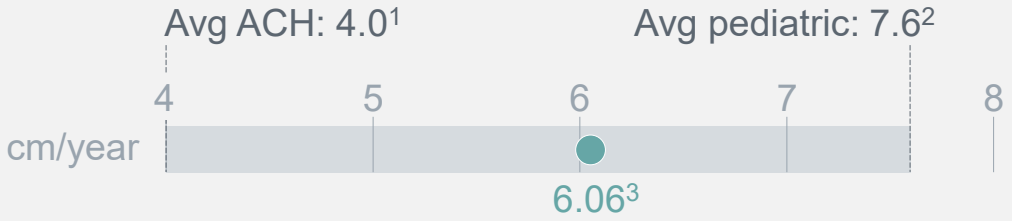
There is a strong need for an oral therapy selective for FGFR3



Vosoritide
(CNP analog)

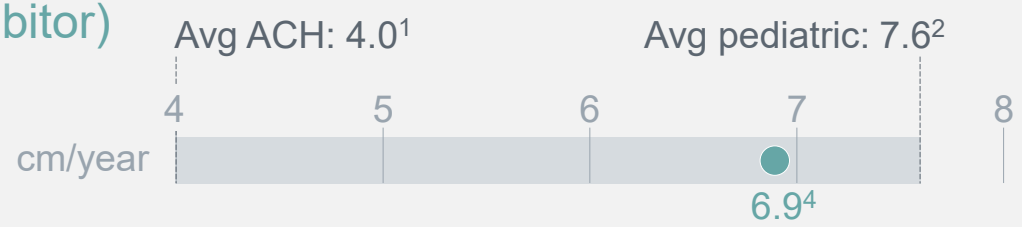
Daily injection,
US FDA-approved

Annual Height Velocity (AHV)



Infigratinib
(Pan-FGFR1/2/3 inhibitor)

Oral, Phase 2 trial



1. Savarirayan, 2021 (5 to 14yrs); 2. Merck Manuals (12mo to 10yrs); 3. Phase 2 Cohort 3 Data, VOXOGO Label, Savarirayan, 2021; 4. Cohort 5 0.250mg/kg daily, Savarirayan, 2023 (ENDO)

Pan-FGFR inhibitors' lack of selectivity limits dosing in oncology

FGFR1: HYPERPHOSPHATEMIA

PAN-FGFR INHIBITORS	% PATIENTS AFFECTED
pemigatinib	60%
futibatinib	88%
erdafitinib	76%
infigratinib	82%

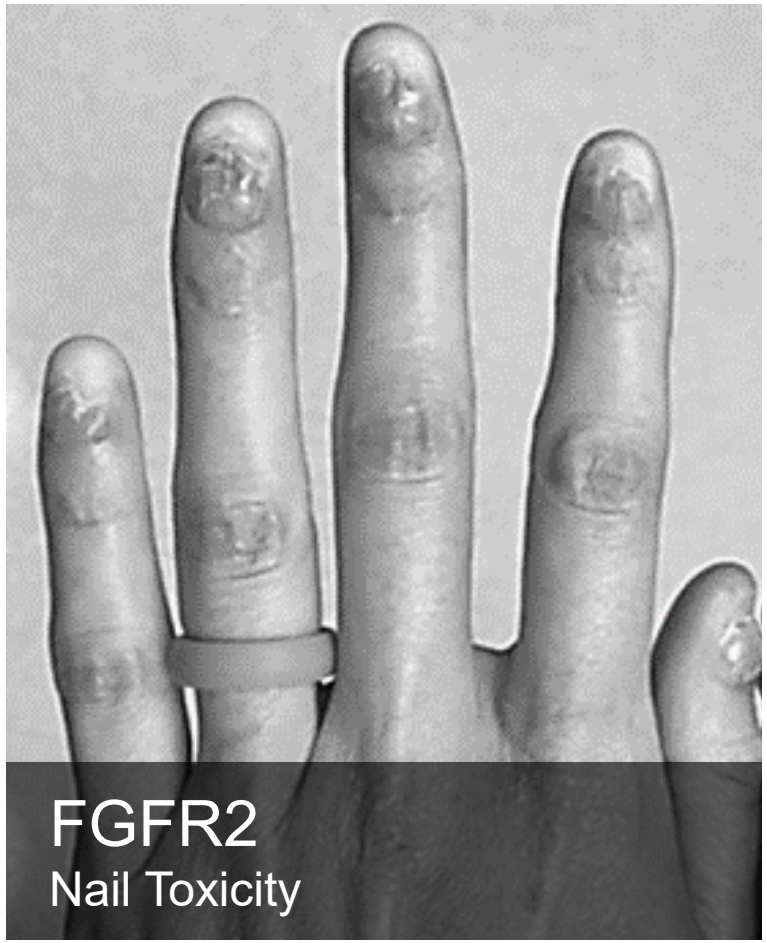
FGFR1
Hyperphosphatemia

Source: product labels and websites

Pan-FGFR inhibitors' lack of selectivity limits dosing in oncology

OTHER TOXICITIES

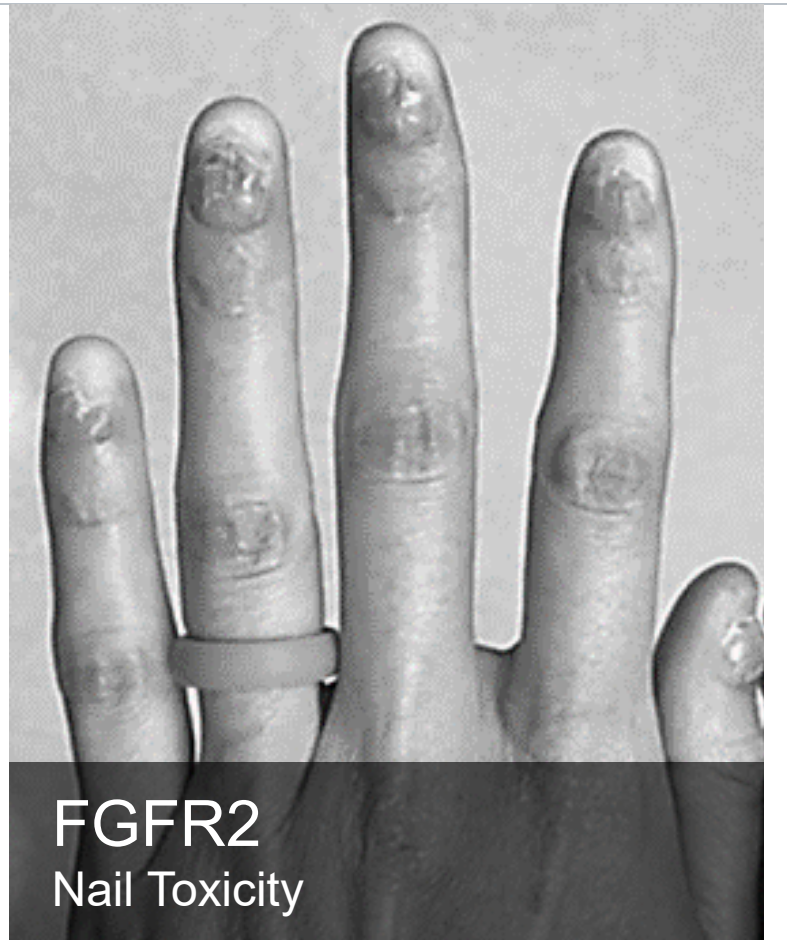
FGFR1
Hyperphosphatemia



FGFR2
Nail Toxicity

Pan-FGFR inhibitors' lack of selectivity limits dosing in oncology

FGFR1
Hyperphosphatemia

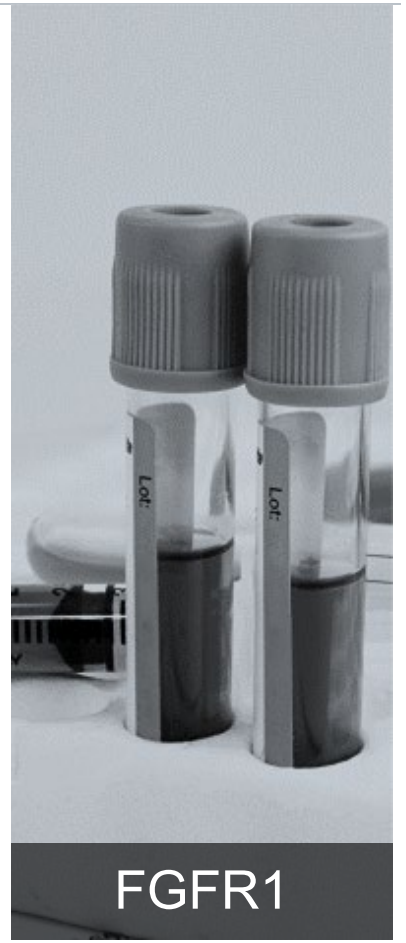


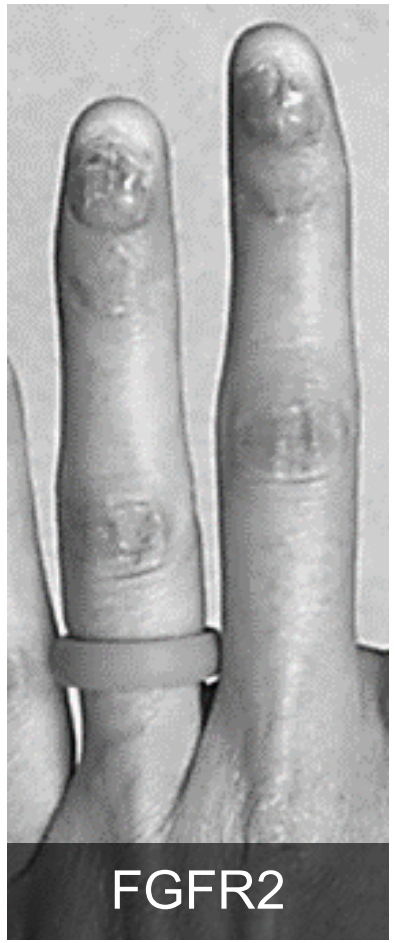
FGFR2
Nail Toxicity

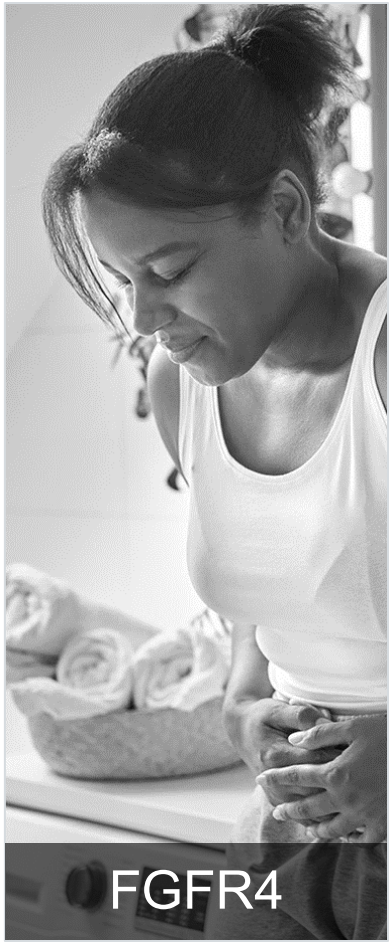
FGFR4
Diarrhea

Side effects lead to dose reduction or discontinuation in oncology

PAN-FGFR INHIBITOR	% PATIENTS DOSE REDUCTION/ DISCONTINUATION
pemigatinib	23%
futibatinib	63%
erdafitinib	66%
infigratinib	75%



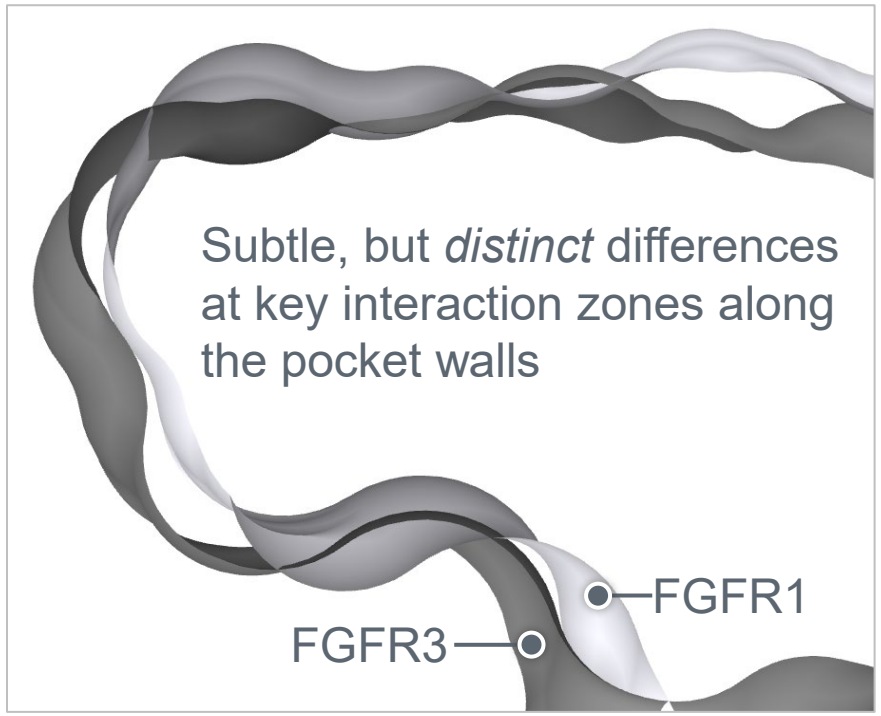




Source: product labels and websites

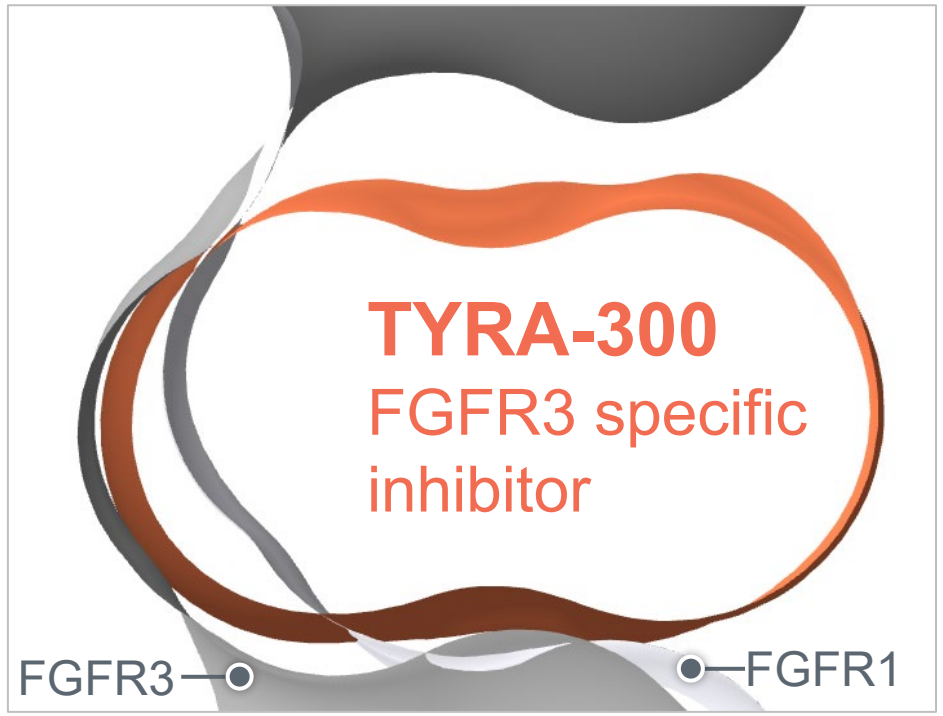
The challenge: FGFR family active sites are nearly identical

FGFR isoform selectivity



MOLECULAR MODEL

dozens of high-resolution crystal structures



CRYSTALLOGRAPHY

3.0Å cross-sections

TYRA-300 is more selective for FGFR3 than pan-FGFR inhibitors

TYRA-300 selectivity vs. approved or late-stage clinical compounds: Ba/F3 Cellular IC_{50} (nM)

	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR1	5.5	3.9	12.3	15.3	113.0
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

TYRA-300 is active against the human FGFR3 mutation, G380R

The FGFR3 G380R mutation accounts for >99% of ACH

NanoBRET™ binding assay IC_{50} (nM)

	infigratinib	TYRA-300
FGFR3 Wild Type	24	21
FGFR3 G380R	22	21

TYRA-300 increased bone growth in the Fgfr3$^{Y367C/+}$ mouse model

17.9%

Increase in naso-anal length*

*p<0.0001

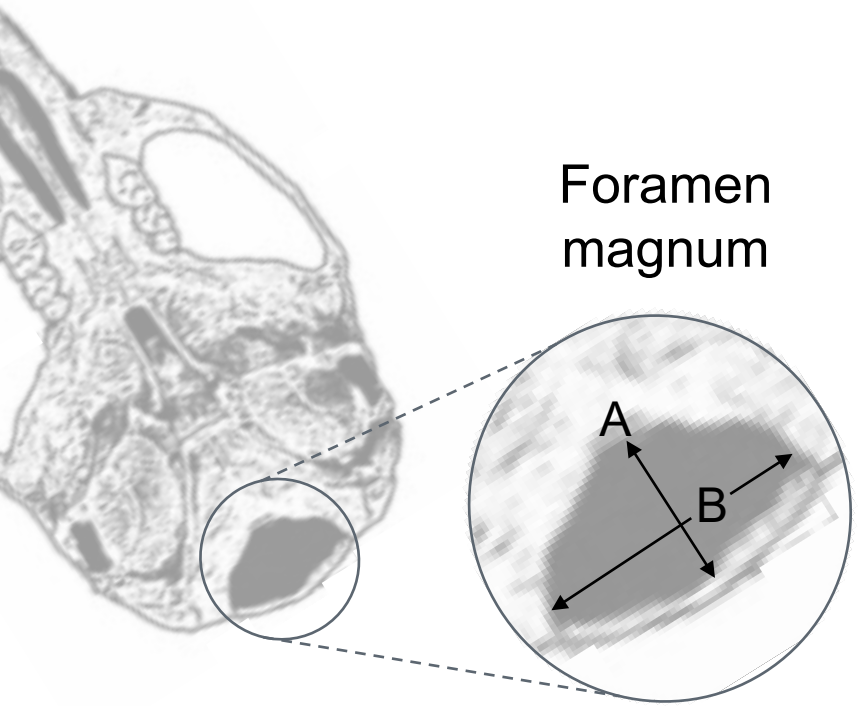
	Dose (mg/kg/day)	Femur	Tibia	L4-L6
TYRA-300	1.2[1]	22.6%*	33.0%*	23.5%*
infigratinib	2.0[2]	20.9%	32.6%	12.1%
infigratinib	0.5[3]	10.4%	16.8%	N/R

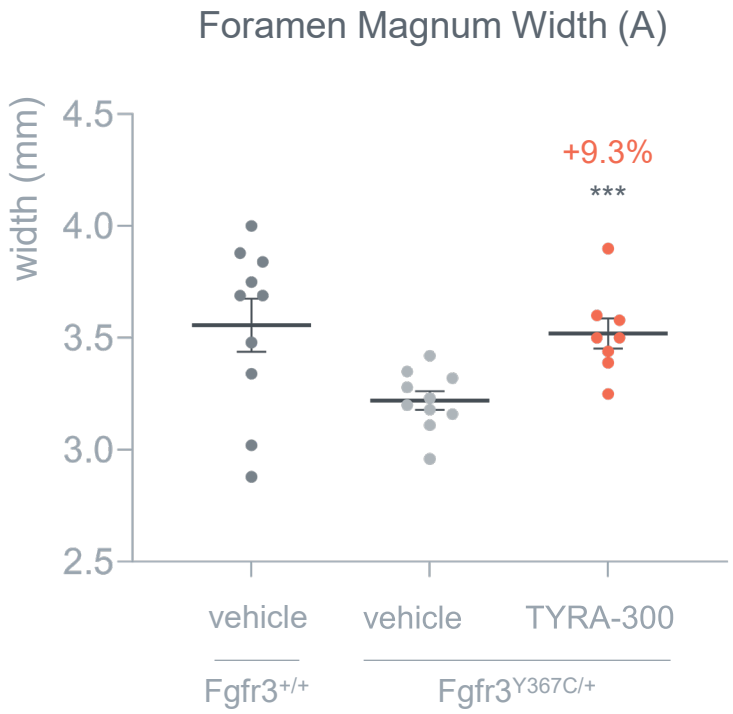
*p<0.0001

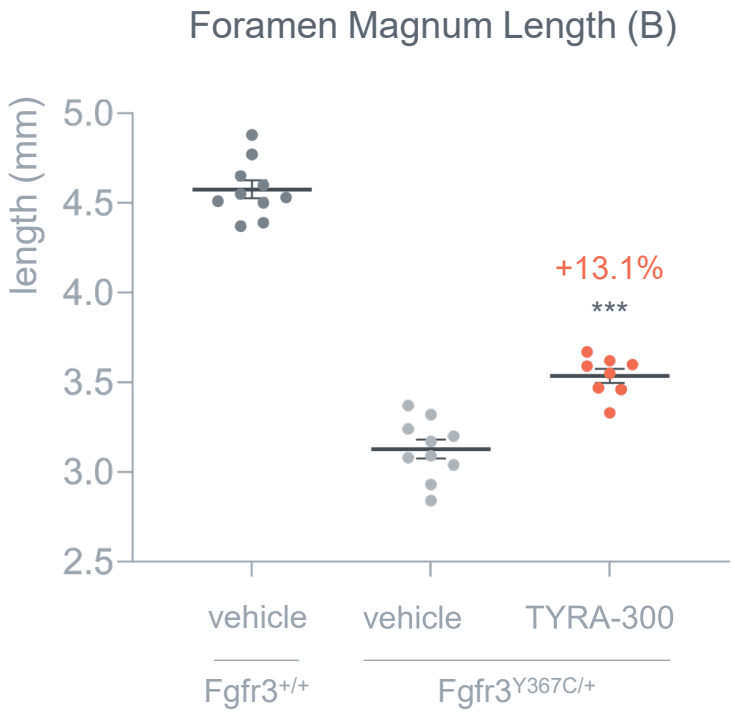
Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; data reflects separate experiments for TYRA-300 and infigratinib

1. 15 days subQ starting at day one; n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from dataset when molecular analysis showed chimeric incorporation of mutation;
2. Data from Komra-Ebri et al 2016 (Legeai-Mallet lab);
3. Demuynck, 2019; 0.667mg/kg human equivalent dose for 2.058 mg/kg; 0.167mg/kg human equivalent dose for 0.514mg/kg; infigratinib human recommended phase 2 dose for ACH is 0.25mg/kg

TYRA-300 improved the shape of the foramen magnum



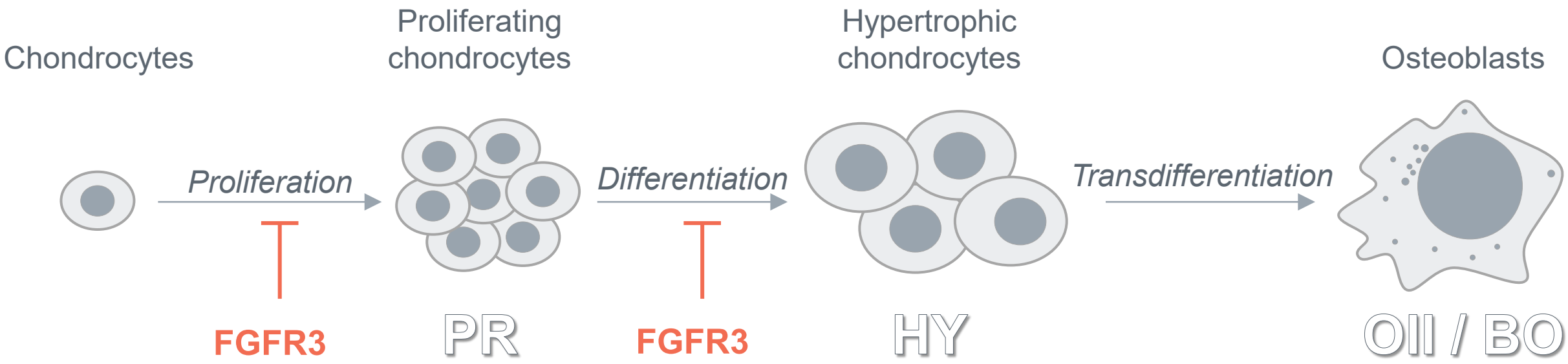




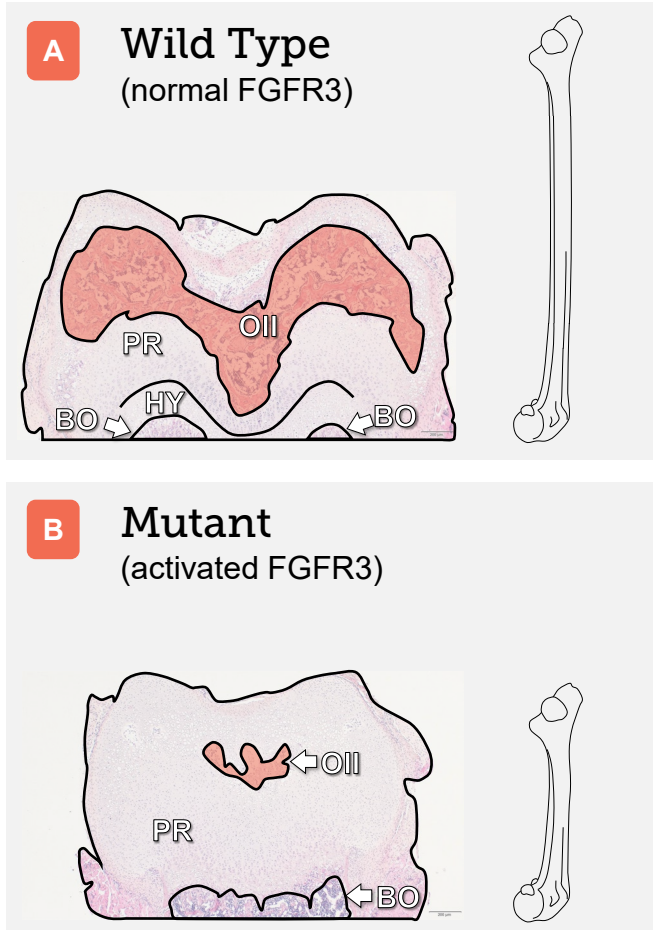
Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France; Daily subcutaneous injection of TYRA-300 at 1.2 mg/kg/day for 15 days starting at Day 1; n=8 for TYRA-300 and n=10 for vehicle, after excluding three mice from dataset when molecular analysis showed chimeric incorporation of mutation.

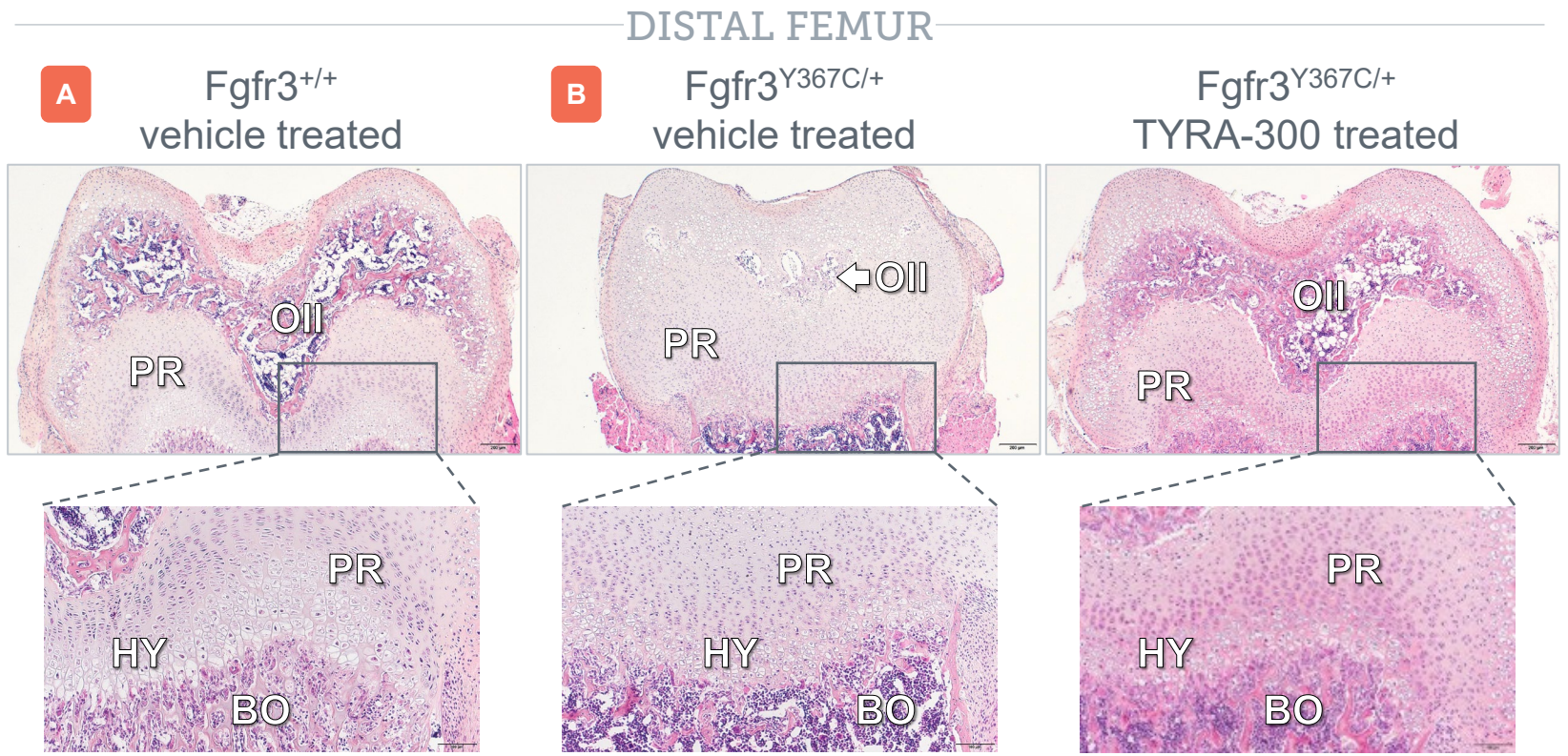
Mann Whitney test vs. vehicle
*** $p < 0.001$

FGFR3 regulates chondrocyte proliferation and differentiation



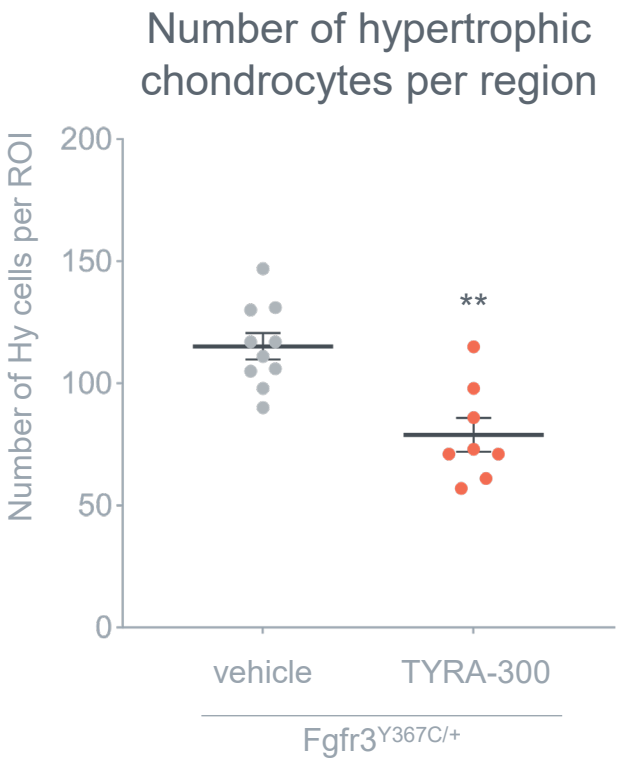
TYRA-300 restored the architecture of the growth plate



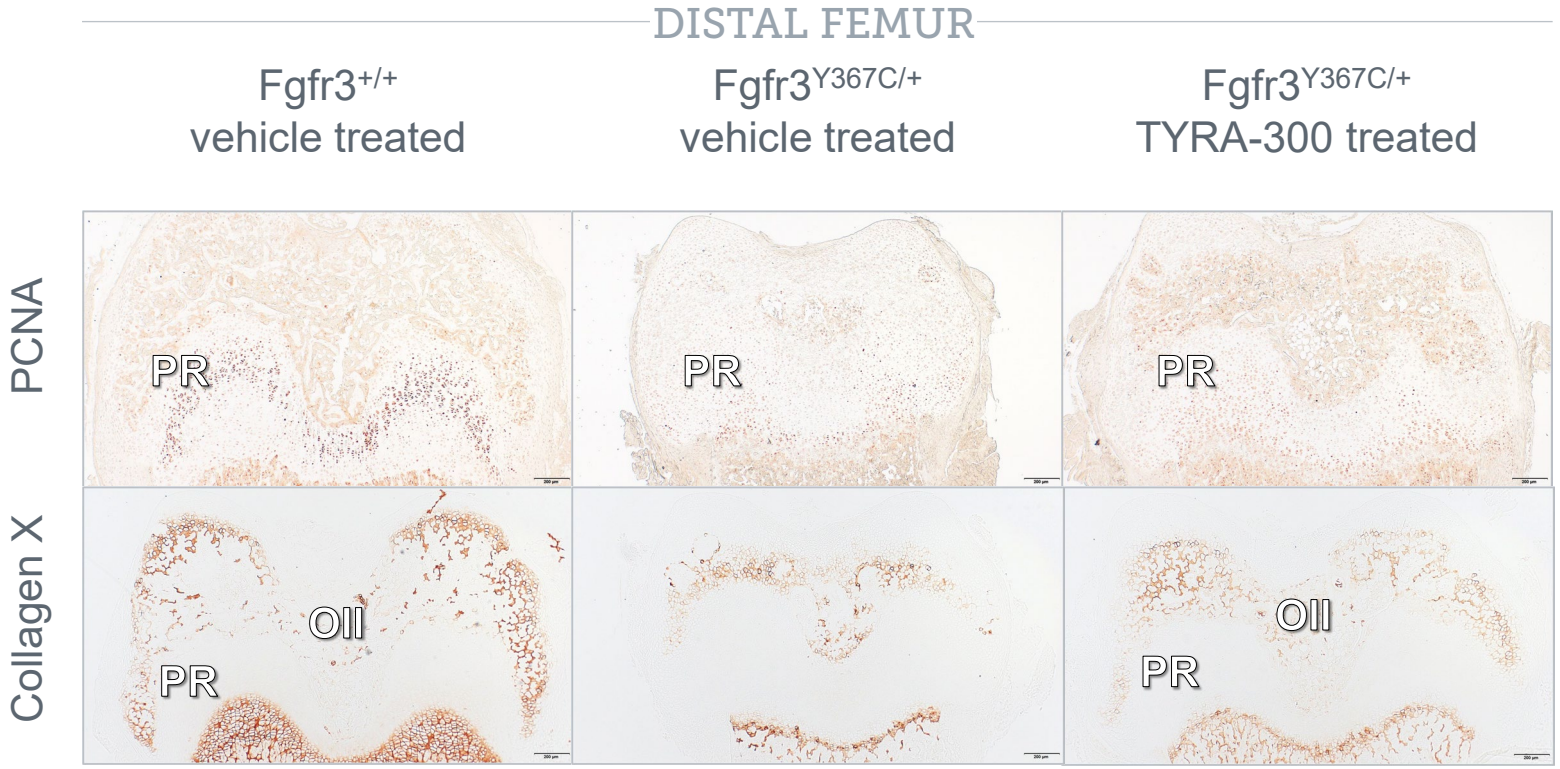


Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France
Hematoxylin and eosin stains of distal femurs. PR: proliferating chondrocytes, OII: secondary ossification center, HY: hypertrophic chondrocytes, BO: bone

TYRA-300 increased chondrocyte proliferation and differentiation



Mann Whitney test vs. vehicle
** p < 0.01



Experiment conducted in the lab of Laurence Legeai-Mallet at Imagine Institute in Paris, France
Immunohistochemical staining of distal femurs. PR: proliferating chondrocytes, OII, secondary ossification center; PCNA: proliferating cell nuclear antigen

Here are our key pre-clinical conclusions about TYRA-300

1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2.
3.
4.
5.

Fold Selectivity for FGFR3

	Infigratinib	TYRA
FGFR1	2.2x	63x
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1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2. Exhibited equal binding against the FGFR3 G380R mutant and wild-type FGFR3 (NanoBRETTM assay)
3.
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	TYRA-300
FGFR3 Wild Type	21
FGFR3 G380R	21

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3. Increased bone length of the appendicular and axial skeleton in the Fgfr3Y367C/+ mouse model
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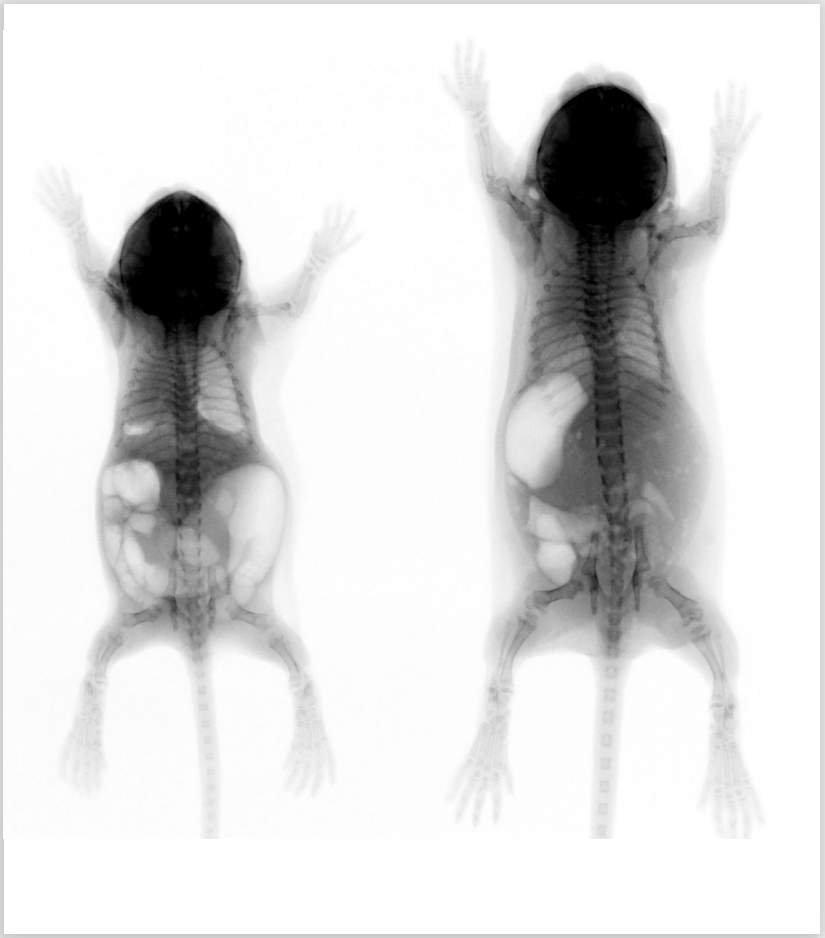

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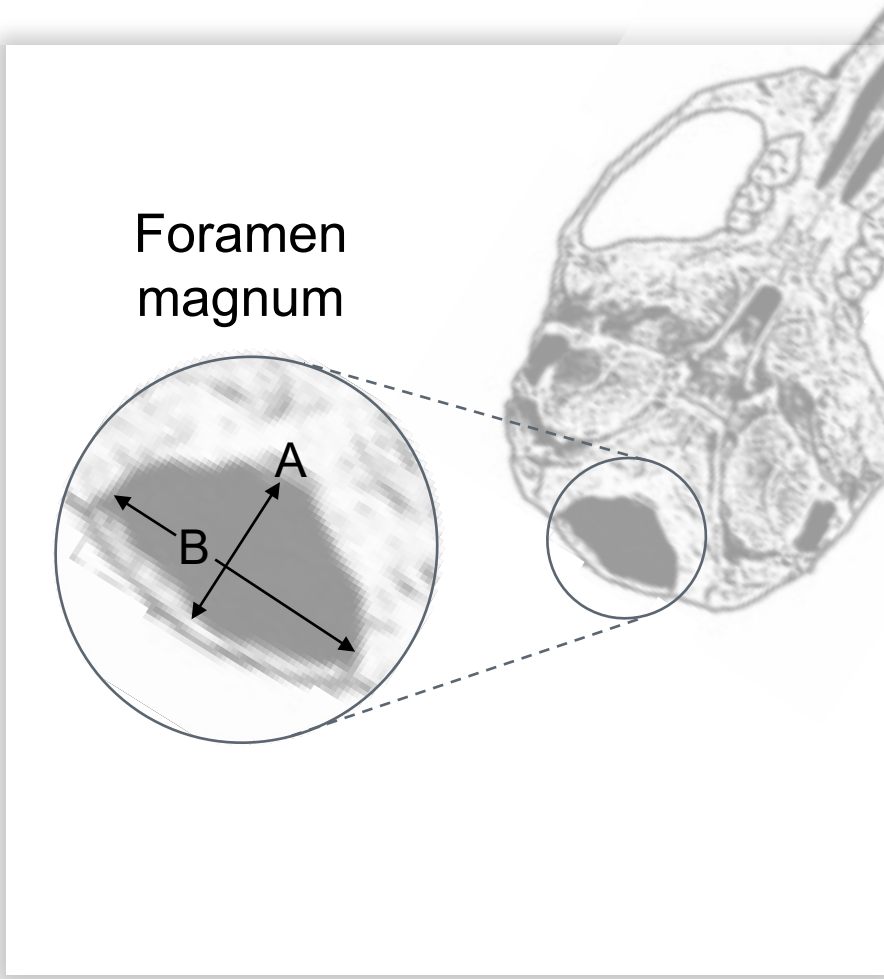
5.



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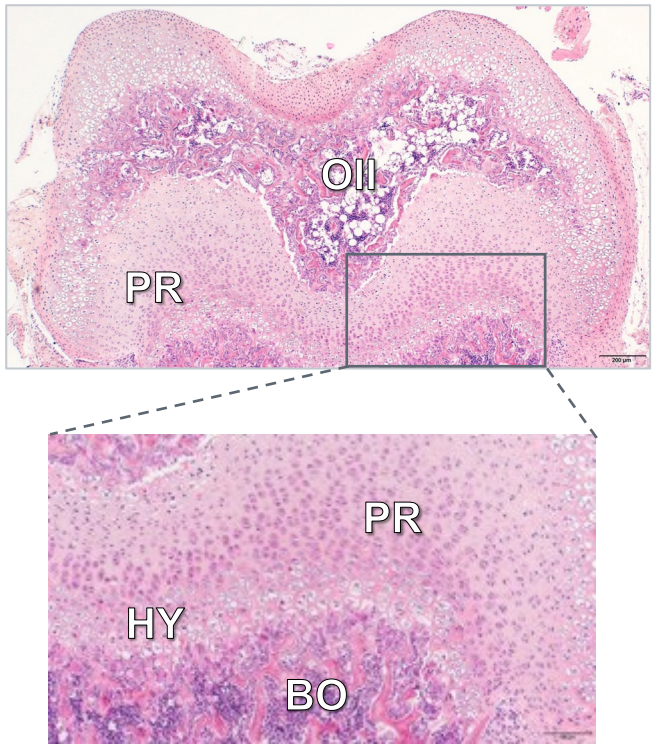
1. Demonstrated significant isoform selectivity for FGFR3 over other FGFR isoforms
2. Exhibited equal binding against the FGFR3 G380R mutant and wild-type FGFR3 (NanoBRET™ assay)
3. Increased bone length of the appendicular and axial skeleton in the $Fgfr3^{Y367C/+}$ mouse model
4. Improved the diameter and shape of the skull and foramen magnum
5. Restored growth plate architecture by improving proliferation and differentiation of chondrocytes

$Fgfr3^{Y367C/+}$
TYRA-300 treated

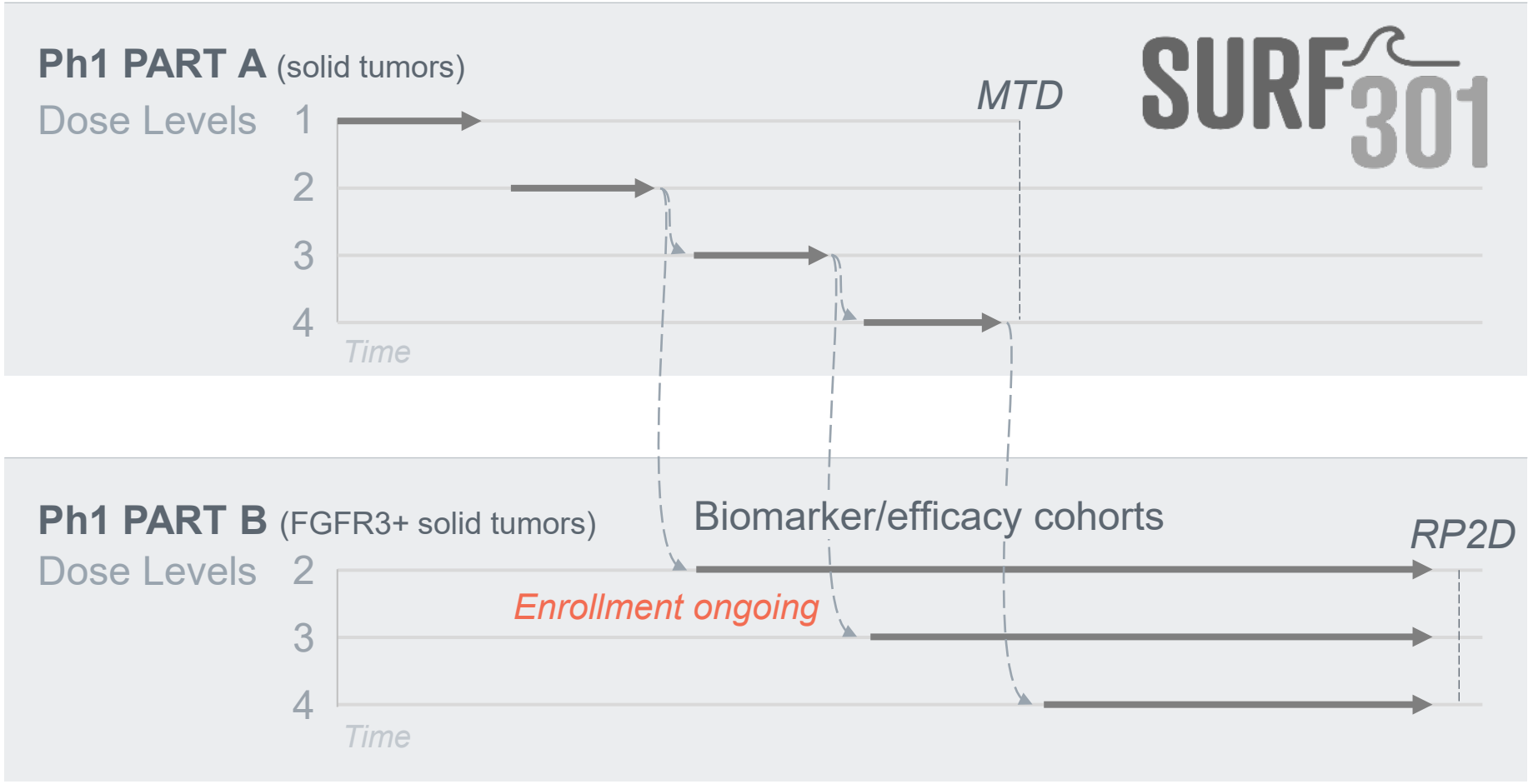


Data from SURF301 will inform our Phase 2 IND for ACH

Illustrative

DOSE SELECTION

DOSE EXPANSION



We greatly appreciate our collaborative Parisian partners!

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