TYRA

Targeting acquired resistance in oncology with purpose-built drugs

November 2022

Disclaimers

Forward-looking statements and market data

We caution you that this presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation, including statements regarding the potential to develop purpose-built therapies that overcome tumor resistance and improve outcomes for patients and address unmet needs; and the potential to accelerate development of TYRA-300 with the SURF301 study are forward-looking statements. In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplates,” “believes,” “estimates,” “predicts,” “potential” or “continue” or the negative of these terms or other similar expressions. The inclusion of forward-looking statements should not be regarded as a representation by us that any of our plans will be achieved. Actual results may differ from those set forth in this presentation due to the risks and uncertainties inherent in our business, including, without limitation: we are early in our development efforts, have not tested any of our product candidates in clinical trials and the approach we are taking to discover and develop drugs based on our SNÅP platform is novel and unproven and it may never lead to product candidates that are successful in clinical development or approved products of commercial value; potential delays in the commencement, enrollment, and completion of preclinical studies and clinical trials; our dependence on third parties in connection with manufacturing, research and preclinical testing; an accelerated development or approval pathway may not be available for TYRA-300 or other product candidates and any such pathway may not lead to a faster development process; unexpected adverse side effects or inadequate efficacy of our product candidates that may limit their development, regulatory approval, and/or commercialization; results from preclinical studies or early clinical trials not necessarily being predictive of future results; our ability to maintain undisrupted business operations due to the COVID-19 pandemic, including delaying or disrupting our preclinical studies and clinical trials, manufacturing, and supply chain; regulatory developments in the United States and foreign countries; and other risks described in our prior filings with the Securities and Exchange Commission (SEC), including under the heading “Risk Factors” in our annual report on Form 10-K and any subsequent filings with the SEC. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof, and we undertake no obligation to update such statements to reflect events that occur or circumstances that exist after the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

This presentation also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions, and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk. These and other factors could cause results to differ materially from those expressed in the estimates made by the independent parties and by us.

Why invest in TYRA?

What we do

Next gen product candidates

- Acquired drug resistance
- Improved tolerability

How we do it

SNAP CHEMISTRY DESIGN

What we're developing

FGFR3−selective inhibitor, FGFR1/2/3, achondroplasia and other FGFR-3 related skeletal dysplasias, FGFR4-related cancers, and RET

NASDAQ:	TYRA
CASH:*	$263.2M
Common Stock O/S:*	42.6M
Fully diluted:*	53.6M

*Sept. 30, 2022

TYRA

Introduction to Urothelial Cancer

Opportunity for next-gen FGFR3 inhibitors

Our differentiated FGFR3 Inhibitor

Overview of SURF-301

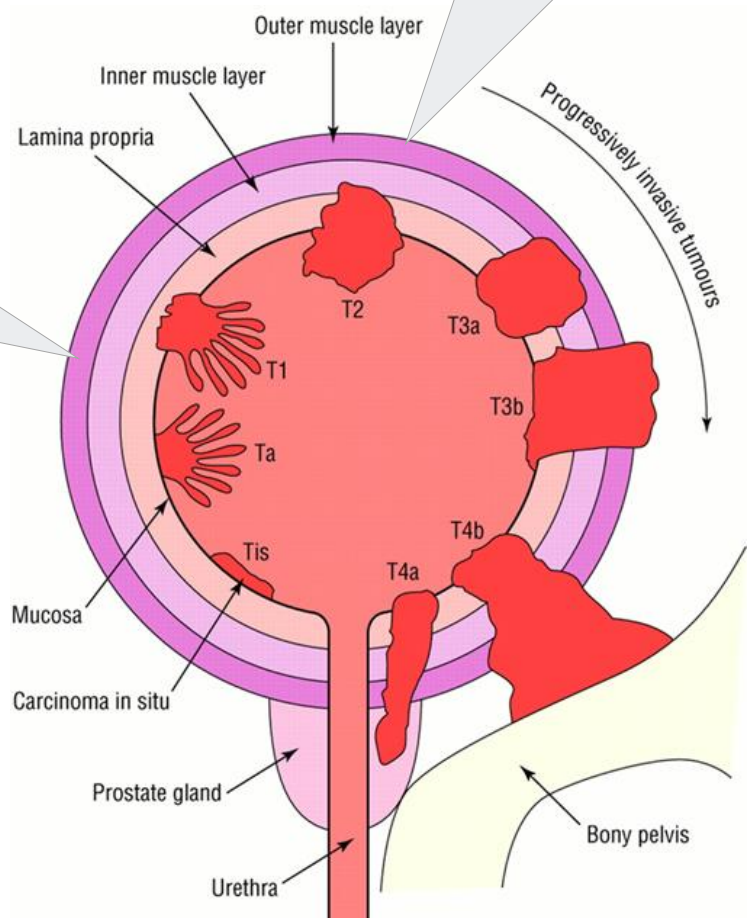
Dr Jonathan Rosenberg

Chief of the Genitourinary Medical Oncology Service,
Division of Solid Tumor Oncology and the Enno W. Ercklentz Chair
at Memorial Sloan Kettering Cancer Center

FGFR3 is mutated across the spectrum of disease states in urothelial cancer

Muscle invasive and metastatic tumors:
~12-20% harbor FGFR3 mutations or fusions

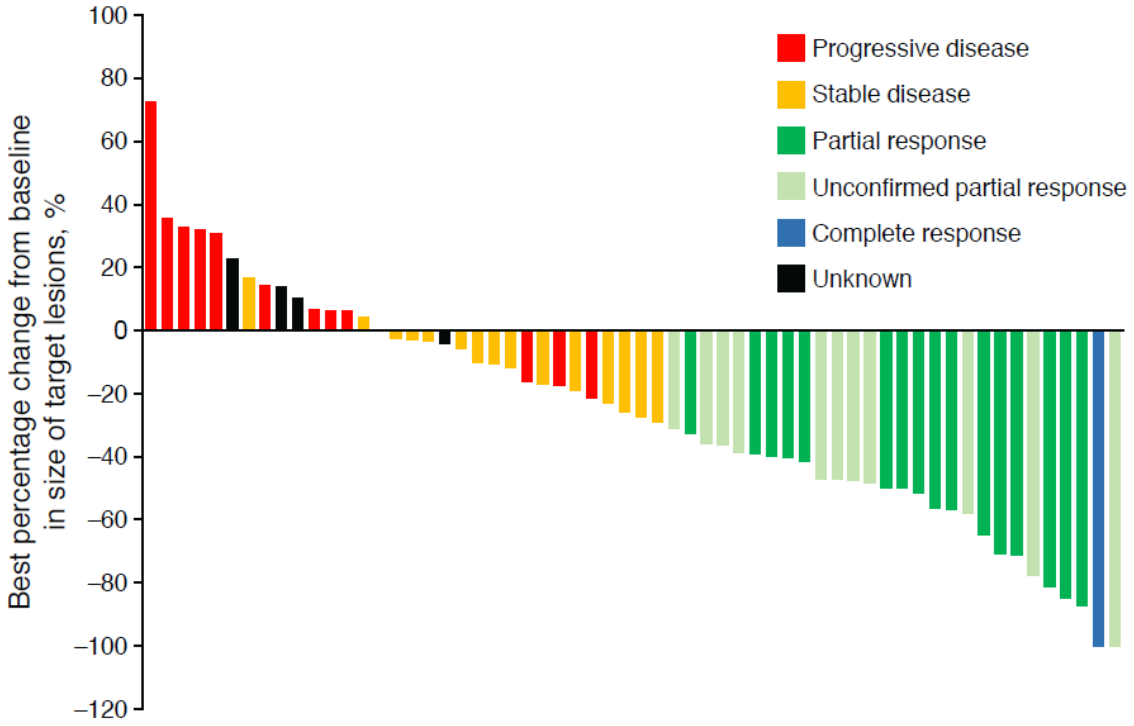
Ta tumors:
Up to 70% harbor FGFR3 mutations
Frequently recurrent

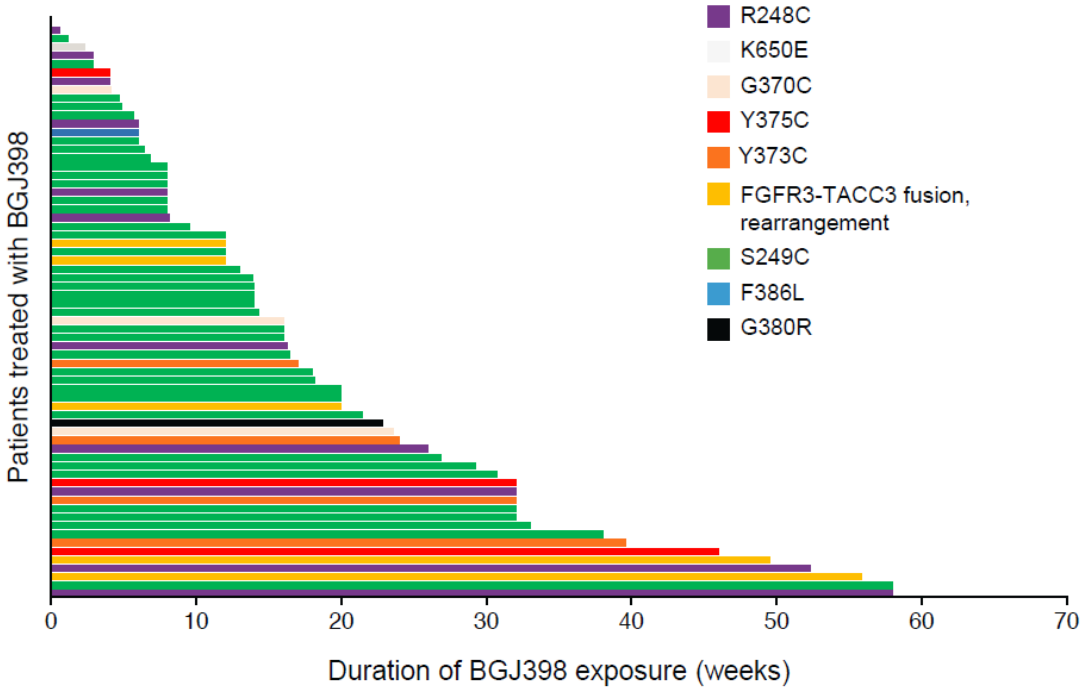


Upper tract urothelial cancer has high rates of FGFR3 mutation:
92% low grade tumors
60% high grade tumors

Moss et al. *European Urology* 2017. 72:641-9

FGFR inhibition in refractory bladder cancer: infigratinib anti-tumor activity

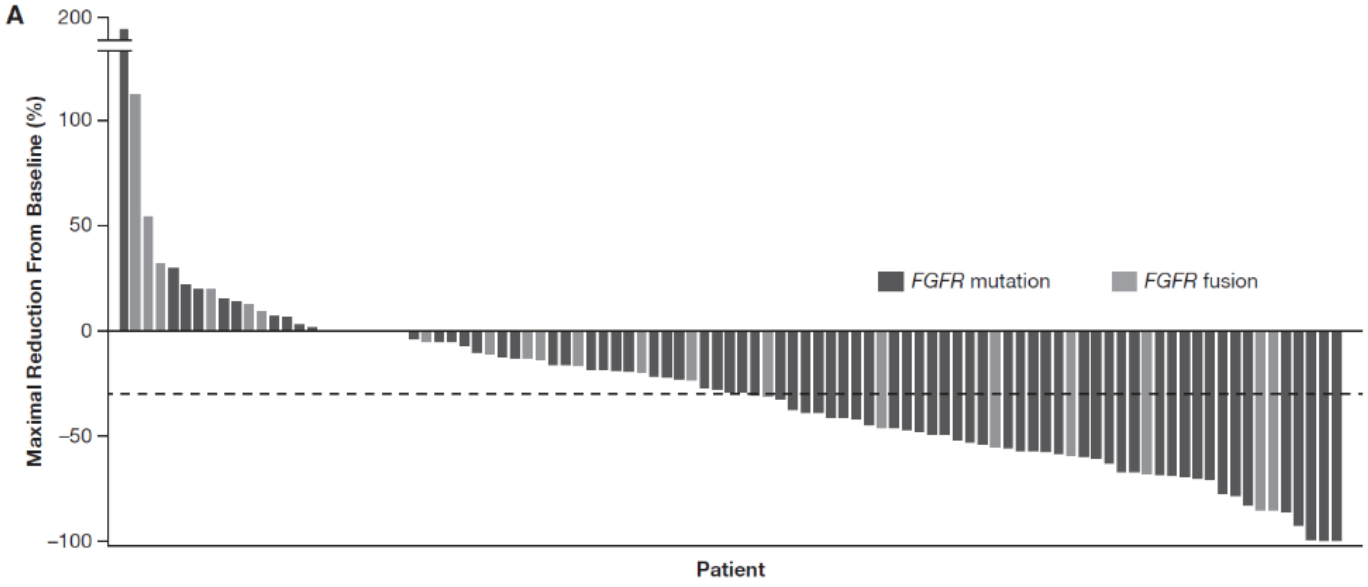


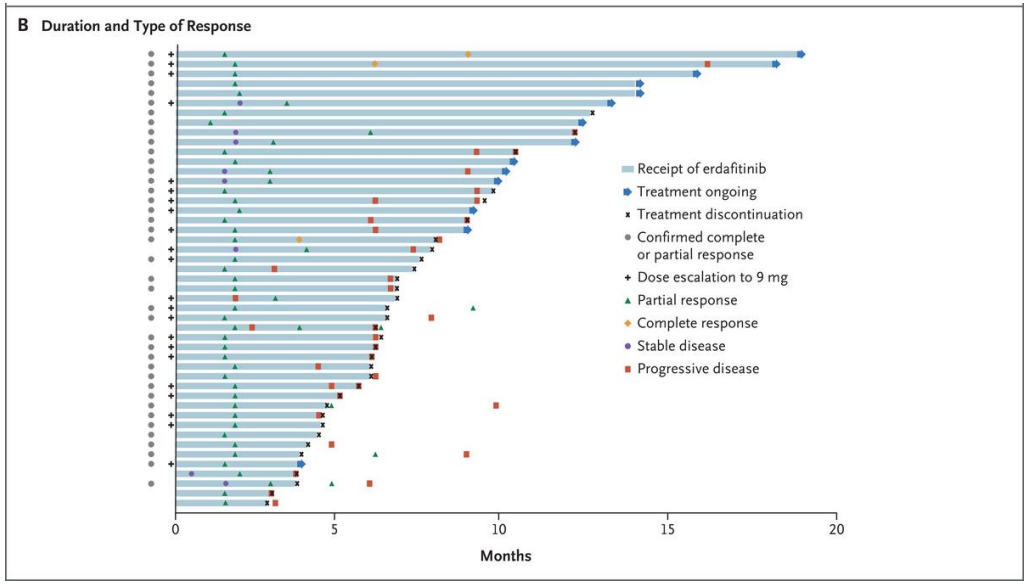


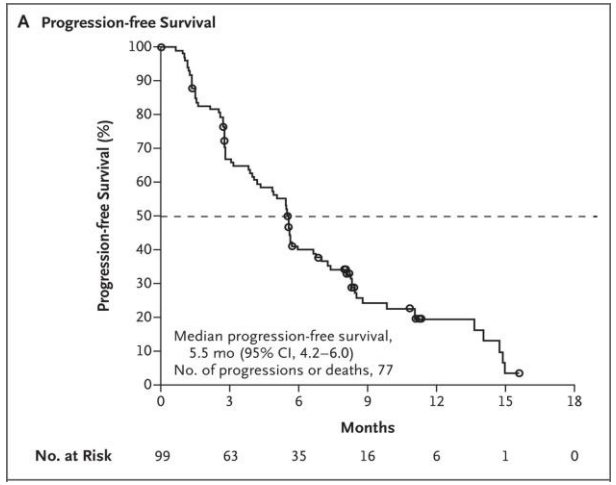
ORR 25.4%

Pal, Rosenberg, et. al. Cancer Discovery 2018

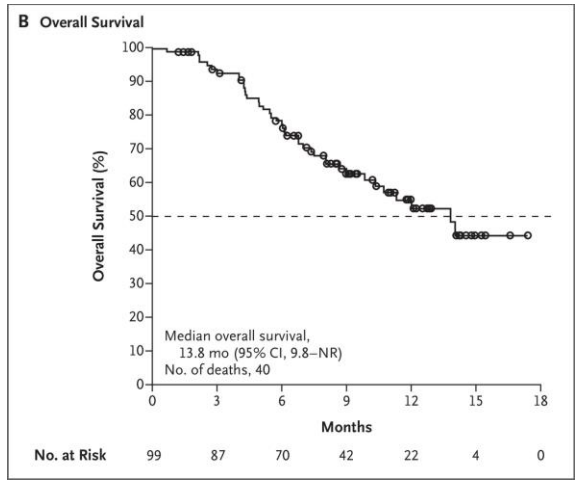
Erdafitinib: BLC2001 showed ORR 40%, FDA approved for pre-treated patients







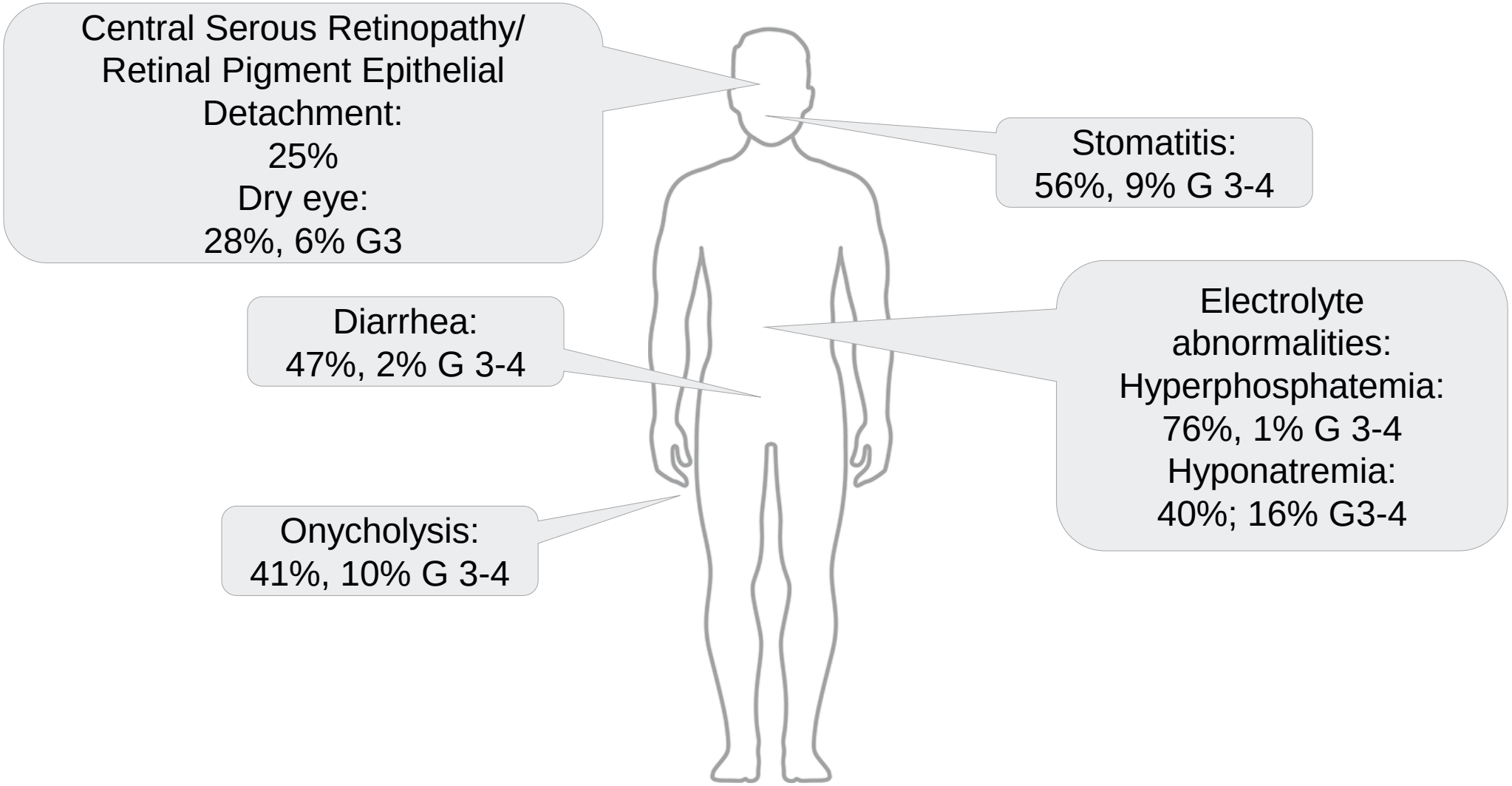
PFS 5.5 months



OS 13.8 months

Y Loriot et al. N Engl J Med 2019;381:338-348.

Pan FGFR inhibition leads to many side effects related to FGFR1, 2, 4 inhibition



Erdafitinib prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212018s000lbl.pdf

Infigratinib showed antitumor activity in a marker lesion study of patients with recurrent high-grade papillary NMIBC

Pt	FGFR3 Alteration	Treatment Duration	Response	Disease-Free Interval	Dose Reductions	Treatment Discontinuation Reasons
1	FGFR3-TACC3 fusion	11 wks	CR	6 mo (LG Ta)	C2, C3: 100 mg	Nail pain (Gr 1), Blurred vision (Gr 1)
2	K650E	6 wks	CR	12 mo (LG Ta)	None	LFT elevation (Gr 3)
3	S249C	4 wks	Indeterminate	15+ mo (ongoing)	None	Ectopic mineralization (Gr 2)
4	S249C	16 wks	CR	8+ mo (ongoing)	C3: 100 mg C4: 75 mg	Nail infection (Gr 2), Mucositis (Gr 1)

Three of four patients (75%) had CRs at 7-week evaluation, but treatment was discontinued secondary to toxicities in all subjects

GU ASCO, February 2020: https://meetinglibrary.asco.org/record/183915/abstract

TYRA

Introduction to Urothelial Cancer

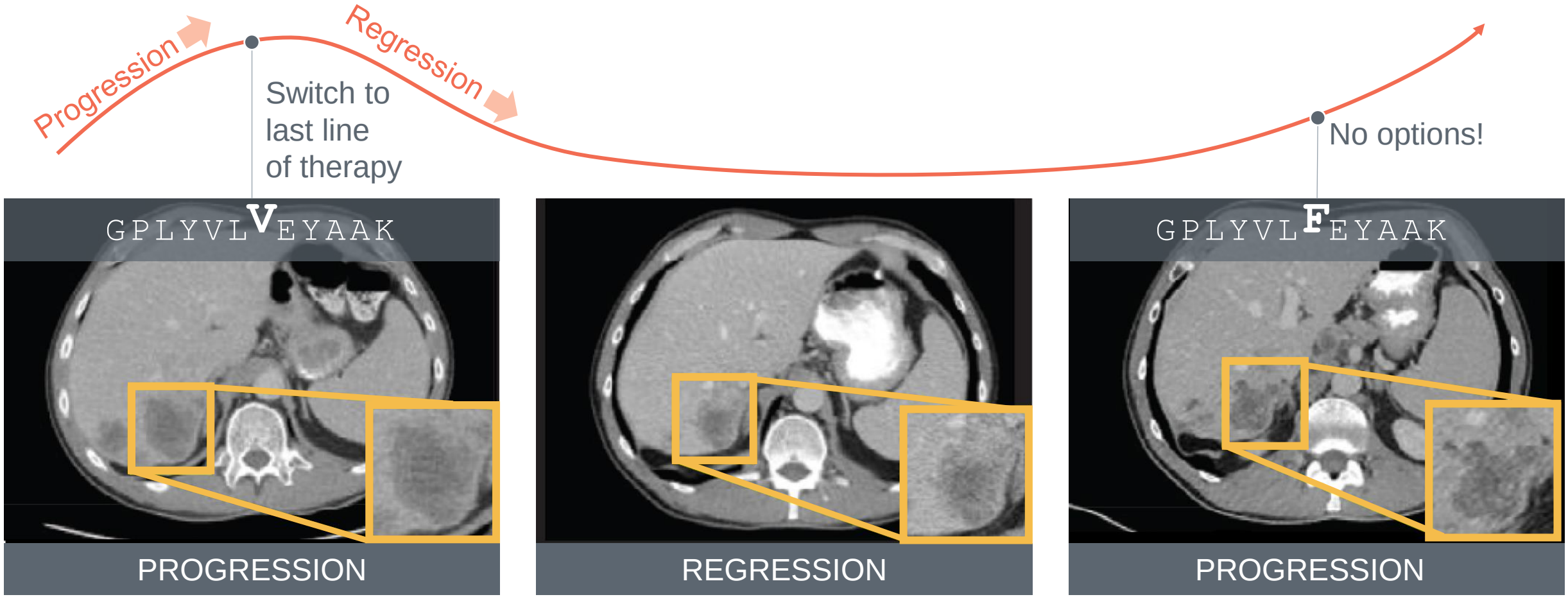
Opportunity for next-gen FGFR3 inhibitors

Our differentiated FGFR3 Inhibitor

Overview of SURF-301

We need next gen drugs in targeted oncology

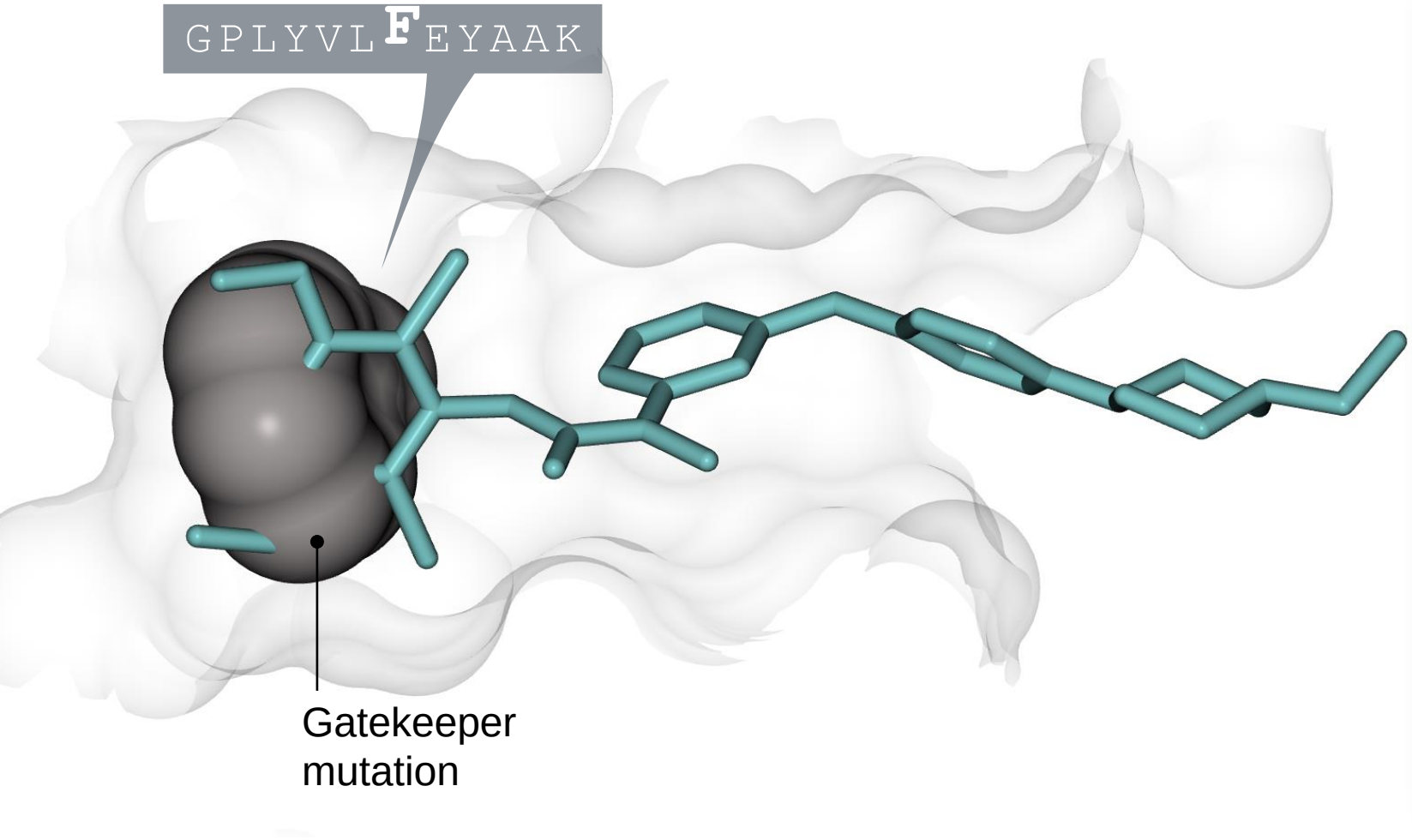
FGFR2 Example

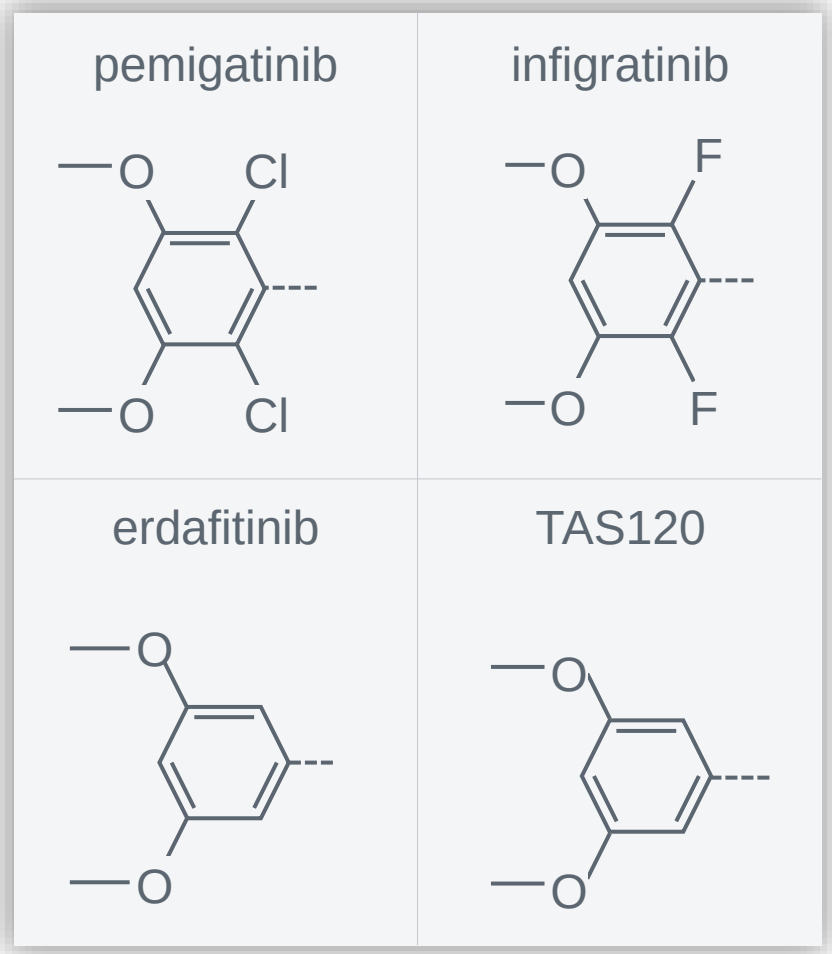


Goyal et. al., Cancer Discov. 2017 Mar;7(3):252-263

Sequence and structure inform what is driving resistance

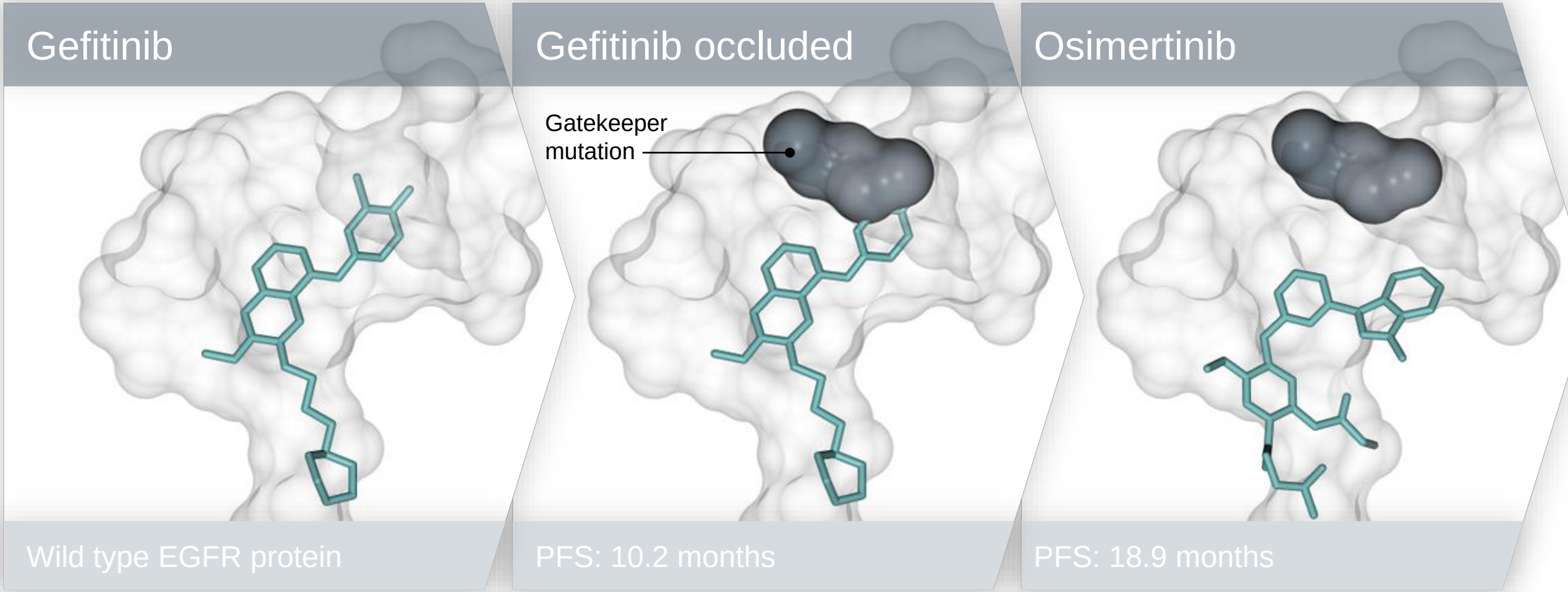
FGFR2 Example



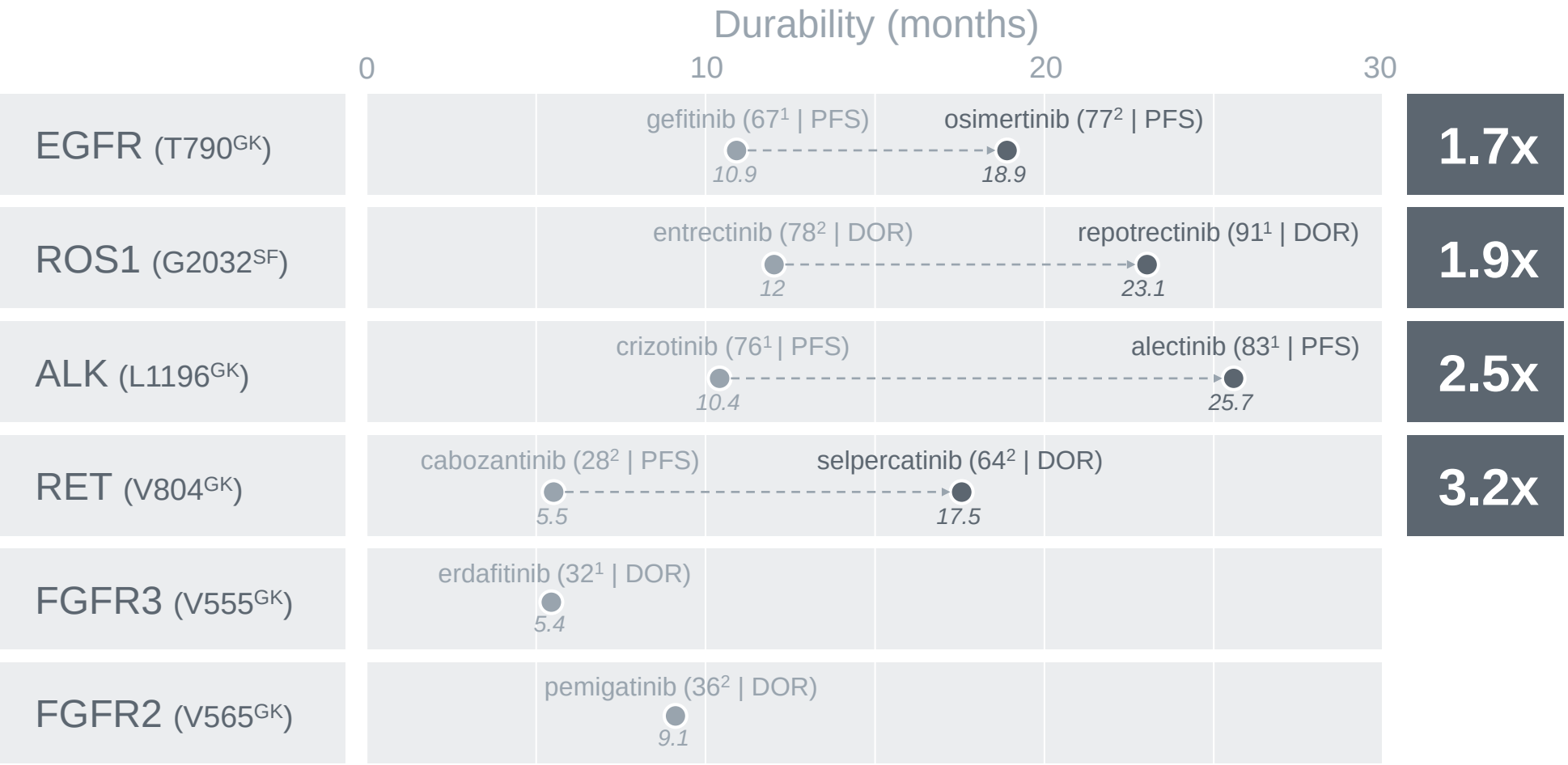


Structural insights provide a rational path to address recurrence

EGFR Example



Precedent shows next gen drugs extend progression free survival

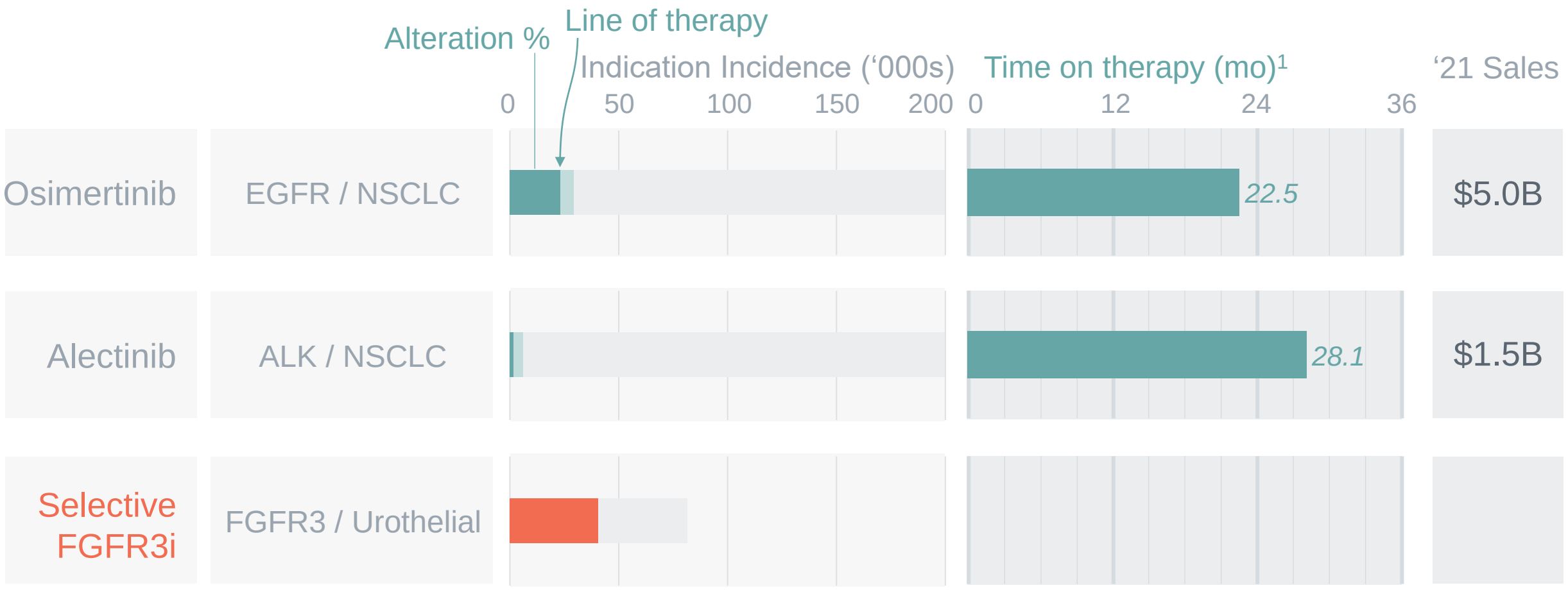


GK: Gatekeeper
SF: Solvent Front
PFS: Progression Free Survival
DOR: Duration of Response

1. Objective Response Rate (%)
2. Overall Response Rate (%)

Information provided in the table above is for illustrative purposes only and is not a head-to-head comparison. Differences exist between study or trial designs and subject characteristics, and caution should be exercised when comparing data across studies.

Outsized opportunity for FGFR3-selective inhibitors in urothelial



Source: SEER, ACS, Project Genie; Company filings; GlobalData; Wu et al., 2020; Mok et al, 2020; Kacew et al, 2020; Matulewicz, 2020; Rizzo, 2022; Necchi, 2020
1. Median duration of exposure for earliest line study

FGFR3-selective inhibitors could address needs in earlier stages

	LEAD TX OPTION	UNMET NEED
Intermediate Risk NMIBC	Intravesical Chemo	30% recur ≤1yr
High Risk NMIBC	Intravesical BCG	25% recur ≤1yr
BCG Resistant NMIBC	Immunotherapy	30-50% recur to mUC
MIBC	Neo/adjuvant chemo	
1L mUC	Chemo or PD1 [+ ADC]	Tolerability
2L / 3L mUC	Erda or ADC	
Erdafitinib Resistant	ADC or palliative	Resistance mutations

UROLOGY
CYSTECTOMY
ONCOLOGY

Source: Matulewicz, 2020; Mari et al, 2018

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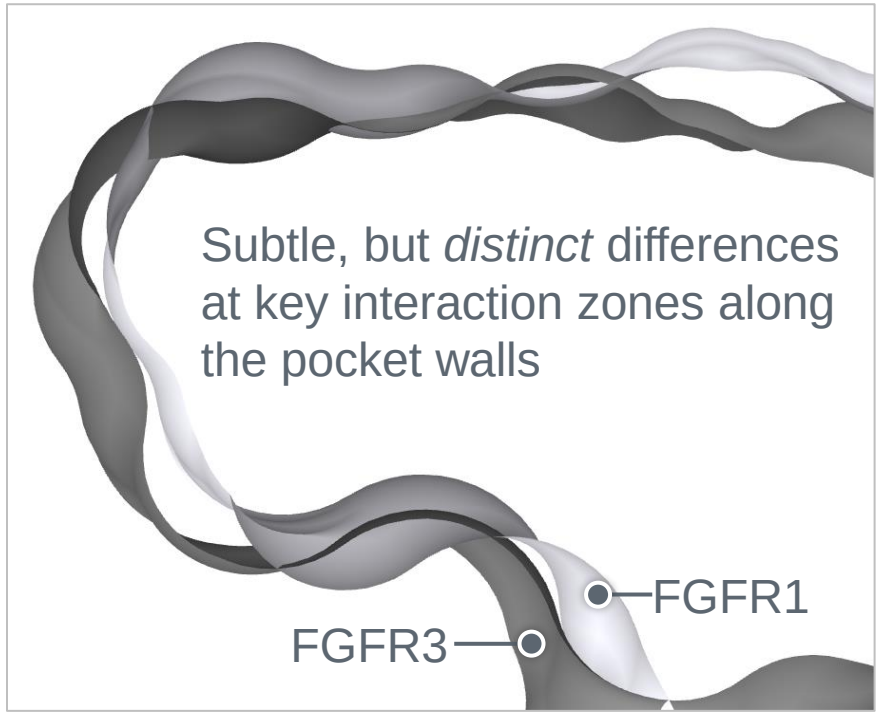
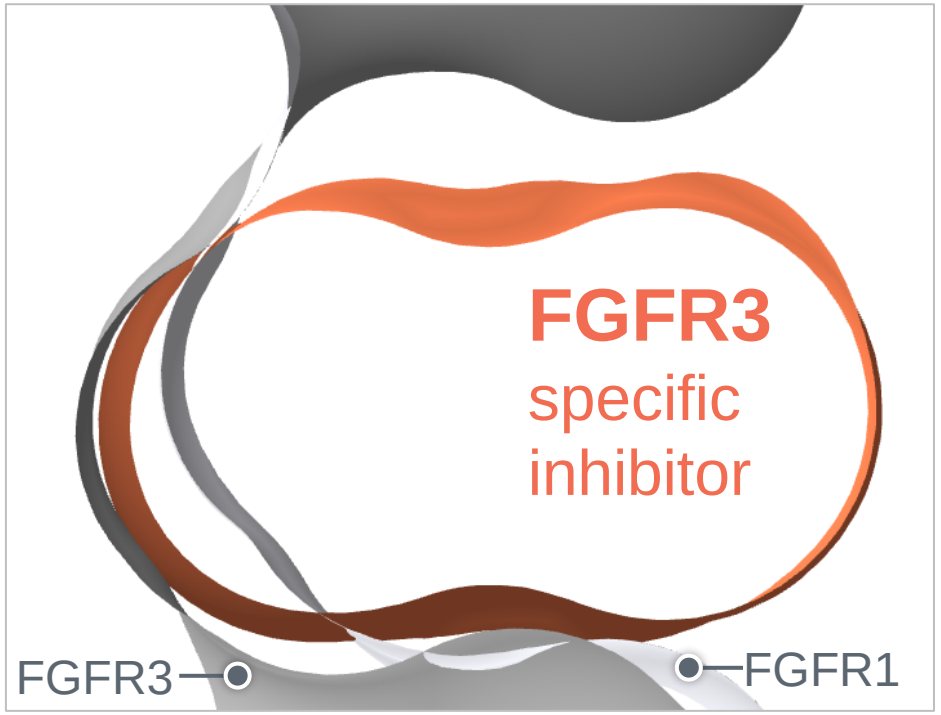
We designed TYRA-300 to be FGFR3 selective

FGFR isoform selectivity



MOLECULAR MODEL

dozens of high-resolution crystal structures



CRYSTALLOGRAPHY

3.0Å cross-sections

TYRA-300 has shown selectivity for FGFR3 over other isoforms

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
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

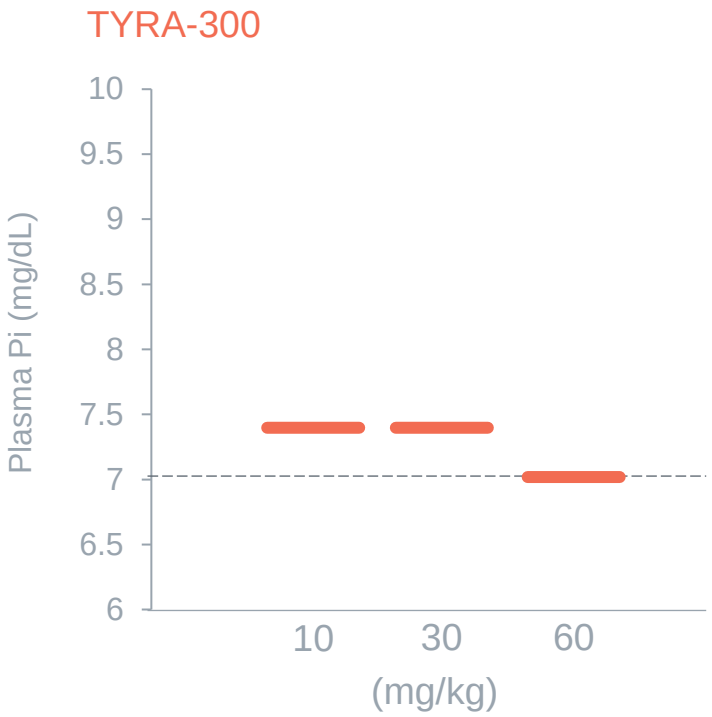
Fold Selectivity for FGFR3

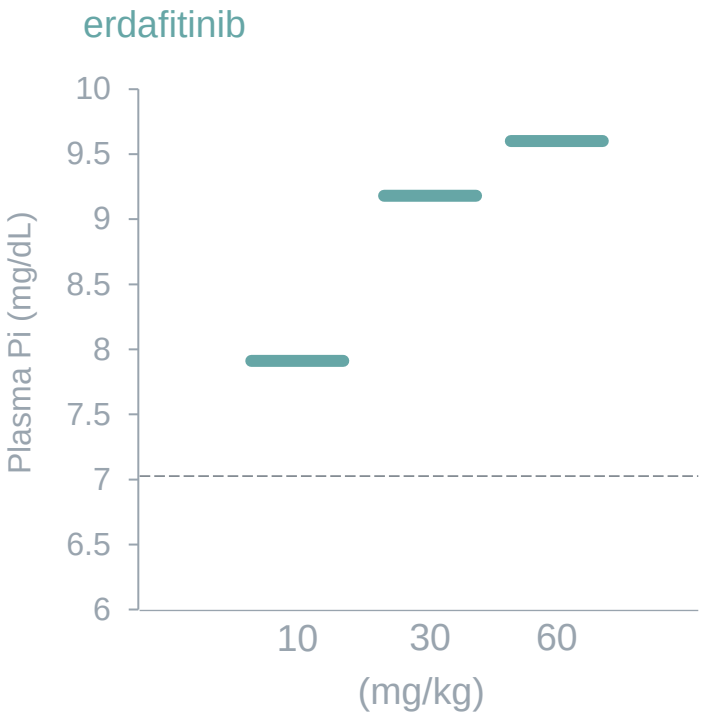
FGFR1	4.2x	4.9x	2.4x	2.2x	63x
FGFR2	1.4x	1.3x	0.8x	0.8x	19x
FGFR4	14x	7.6x	27x	67x	55x

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

TYRA-300 did not elevate phosphate relative to erdafitinib

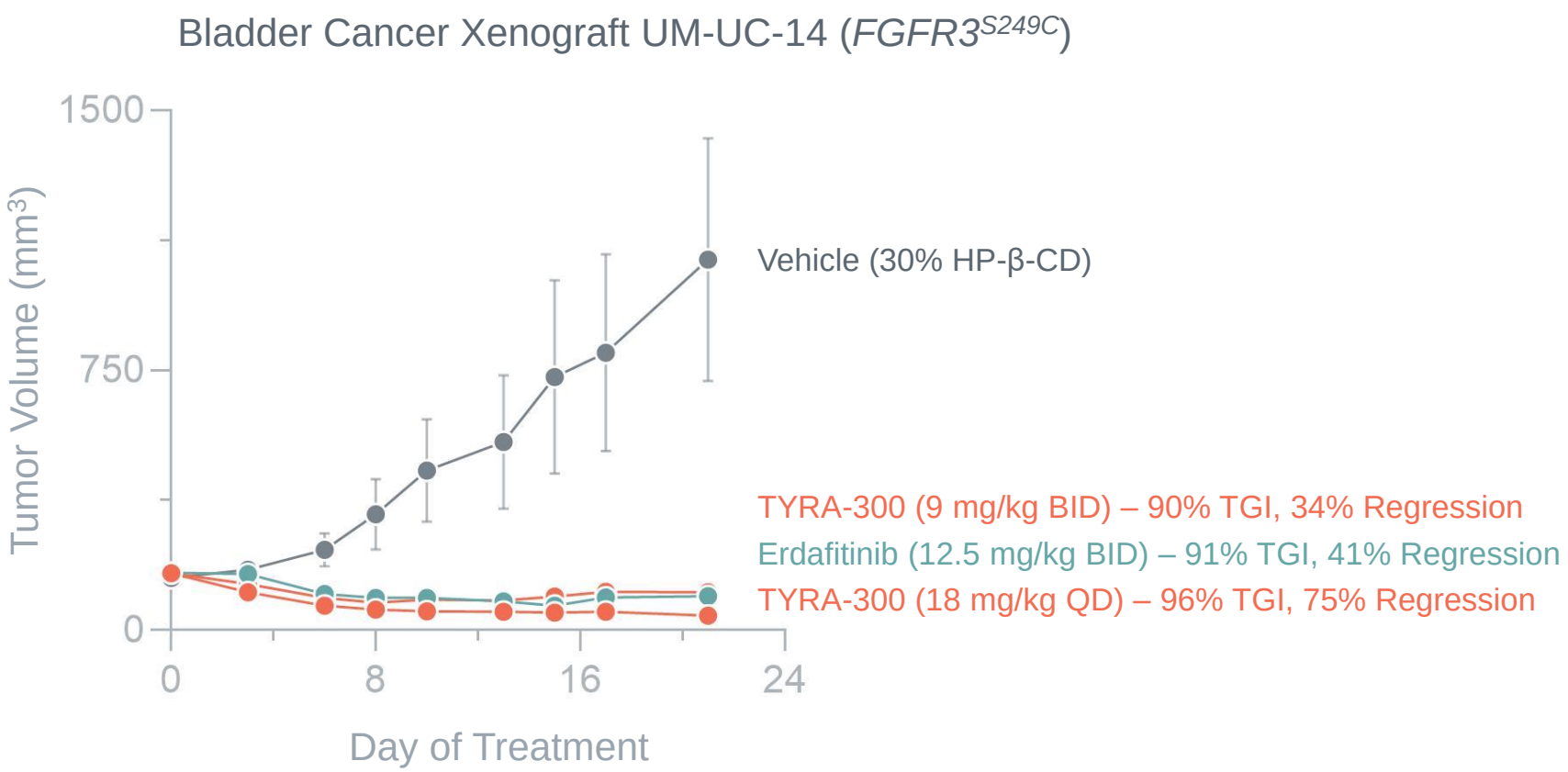
Rat plasma phosphate at 24 hours after single dose[1]





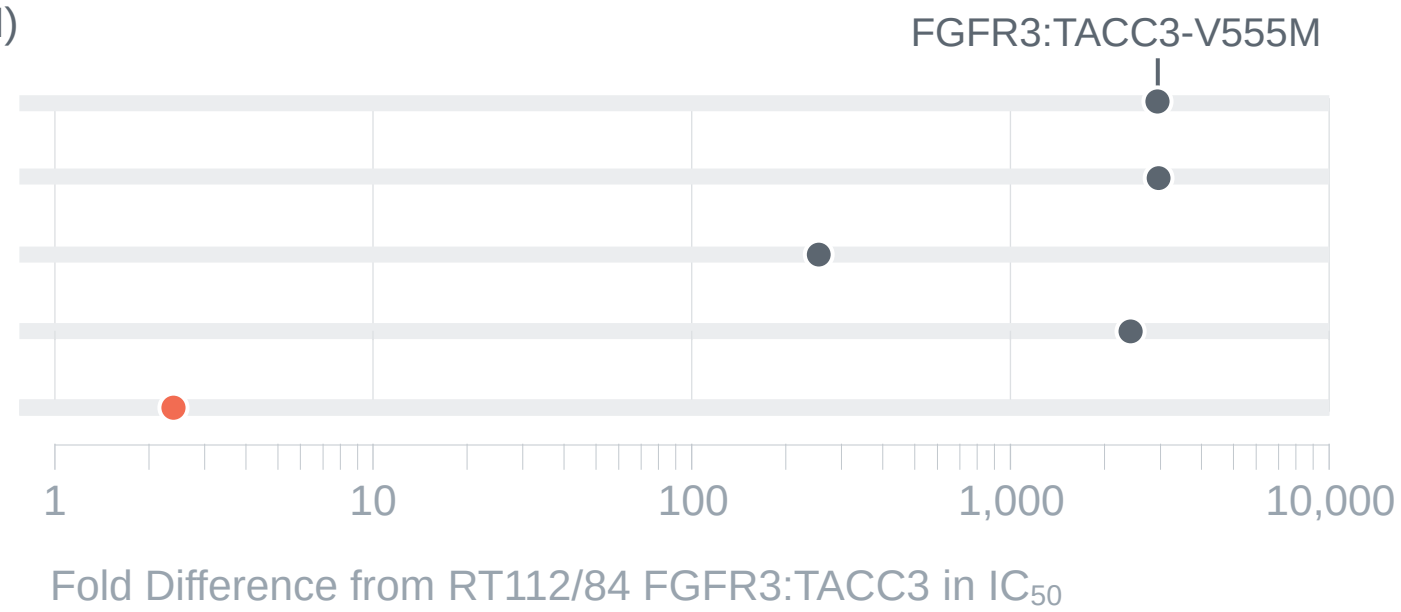
1. N=4 per group, pooled rat plasma; dotted line = pre-dose phosphate value of 3 dose groups

TYRA-300 is active *in vivo* in bladder cancer models



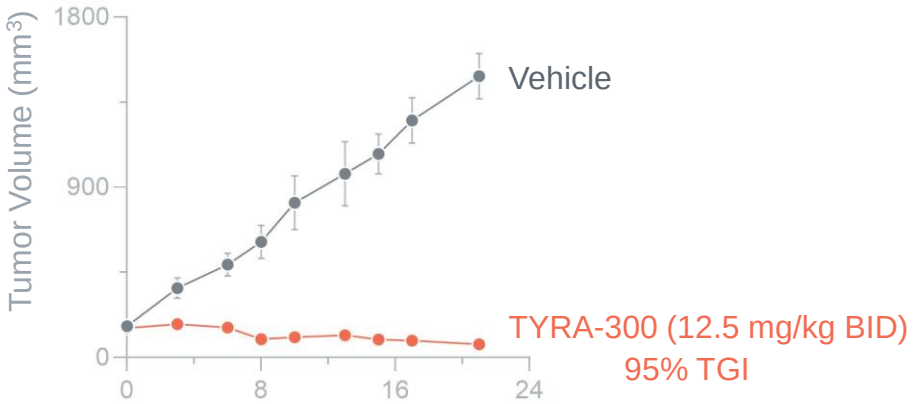
TYRA-300 retains potency in a FGFR3:TACC3-V555M cell line

	FGFR3:TACC3 RT112/84 IC_{50} (nM)
erdafitinib	4.4
pemigatinib	5.3
futibatinib	11.0
infigratinib	14.5
TYRA-300	7.9

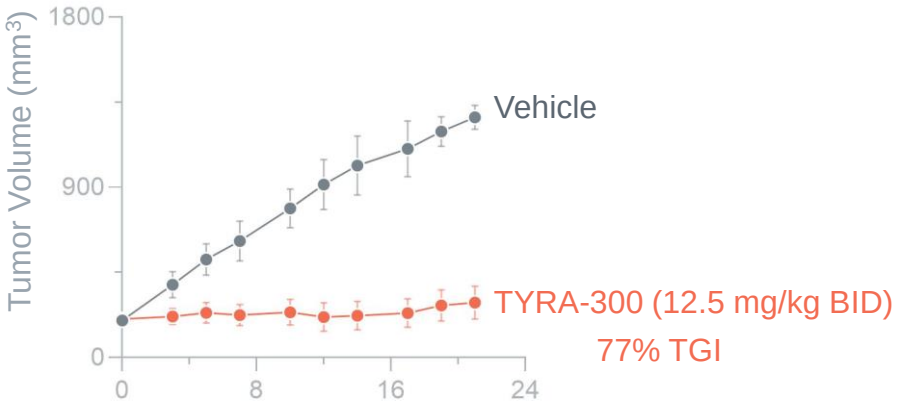


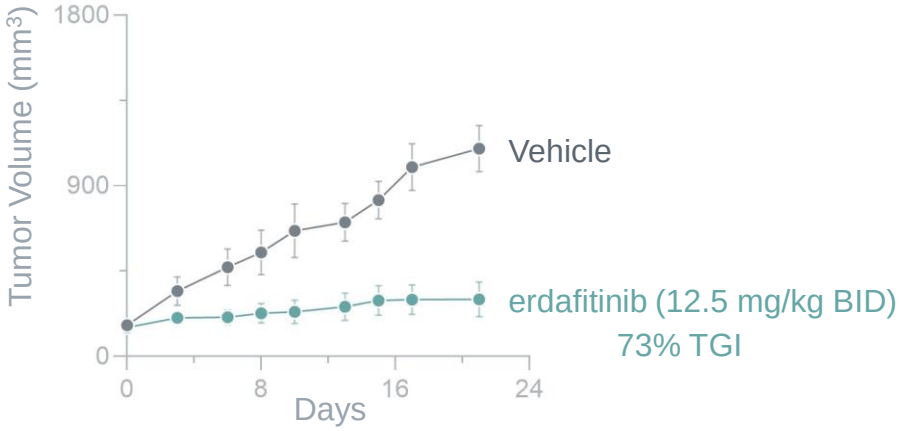
TYRA-300 is active *in vivo* in bladder cancer models

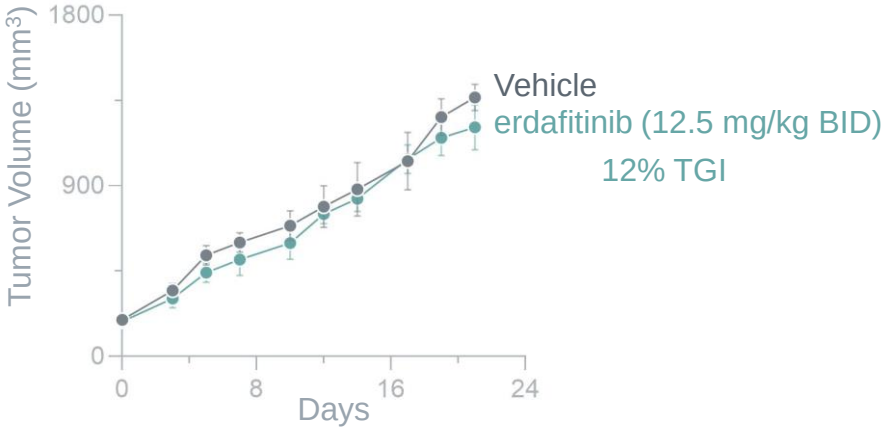
Bladder Cancer Xenograft *FGFR3:TACC3*



Bladder Cancer Xenograft *FGFR3:TACC3-V555M*







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Opportunity for next-gen FGFR3 inhibitors

Our differentiated FGFR3 Inhibitor

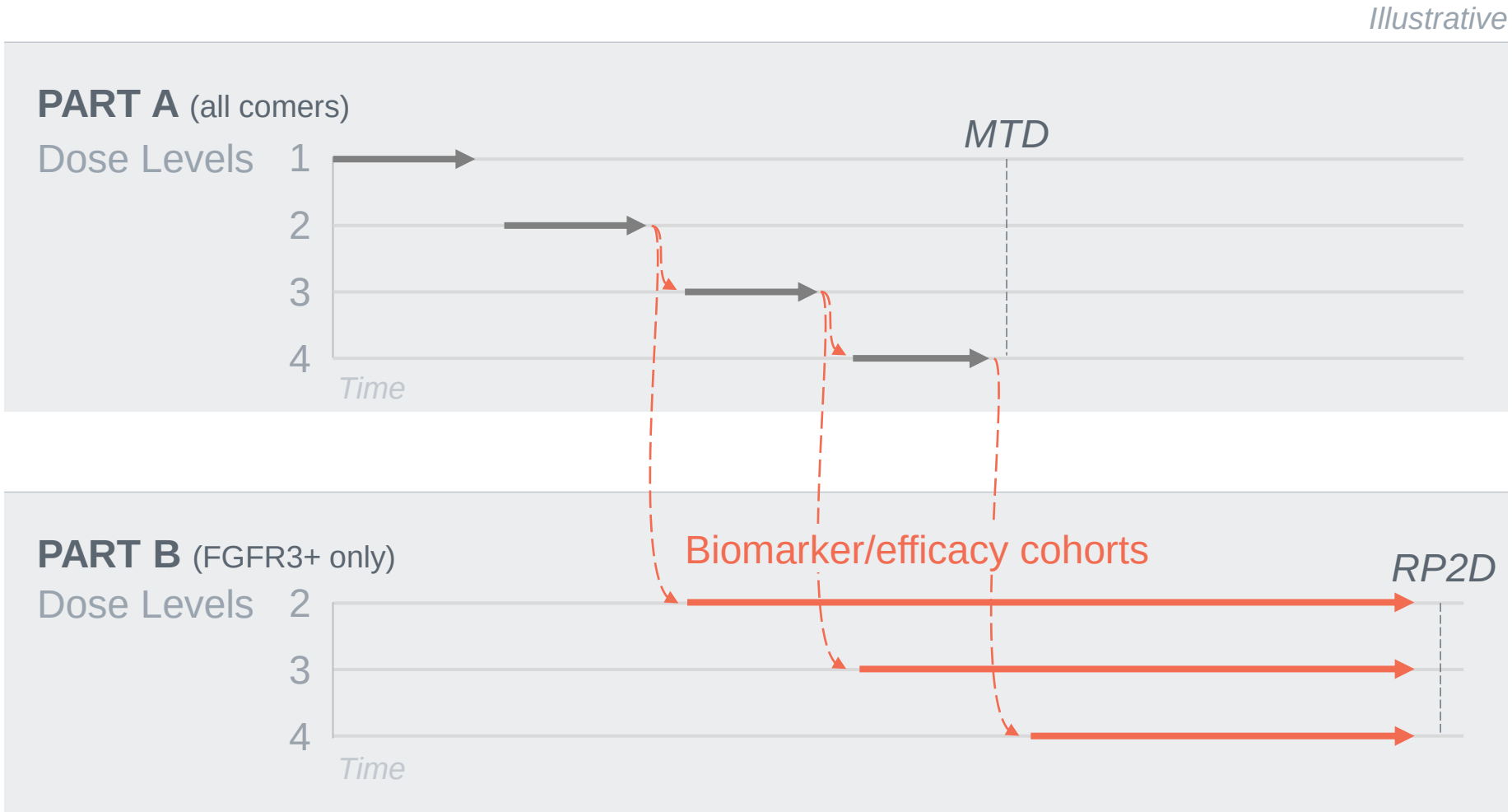
Overview of SURF-301

Phase 1 design determines recommended phase 2 dose (RP2D)

SURF301

Phase 1 Part A:
What is the MTD?

Phase 1 Part B:
What is the optimal dose?



We're building a pipeline of differentiated assets

Program	Resistance alteration	US incidence	Discovery	IND-Enabling	Phase 1	Phase 2	Phase 3	Anticipated Milestone
FGFR3: TYRA-300	V555^{GK}	28-33K			First patient dosed			Complete Phase 1
FGFR1/2/3: TYRA-200	V565^{GK} N550^{MB}	3.5K						File IND YE 2022
FGFR3 (ACH)	G380R[1]	8-22K[2]						Nominate lead candidate
FGFR4	V550^{GK} C552^{CYS}	2K						Nominate lead candidate
RET	V804^{GK} G810^{SF}	2-6K						Nominate lead candidate

SNAP CHEMISTRY DESIGN

ACH: Achondroplasia, GK: Gatekeeper, CYS: Cysteine Mutant, SF: Solvent Front, MB: Molecular Brake

1. Key activating mutation for ACH. 2. Number represents US prevalence rather than incidence