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Preliminary safety and anti-tumor activity of TYRA-300, a highly selective FGFR3 inhibitor, in participants with advanced solid tumors with activating *FGFR3* mutations/fusions (SURF301)

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ABSTRACT 500 LBA

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DISCLOSURES

I have the following potential conflicts of interest to report:

Research Funding	Amgen, Astellas, AstraZeneca, Bayer, BMS, Genentech, Ipsen, Janssen, Pfizer, Movember, MSD
Honoraria	Amgen, Astellas, AstraZeneca, Bayer, BMS, Ipsen, Janssen, Merck, MSD, Pfizer, Sanofi, Tolmar
Consulting / Advisory	Amgen, Astellas, AstraZeneca, Bayer, BMS, Ipsen, IQVIA, Janssen, Merck, MSD, Novartis, Pfizer, Roche, Sanofi, Tolmar

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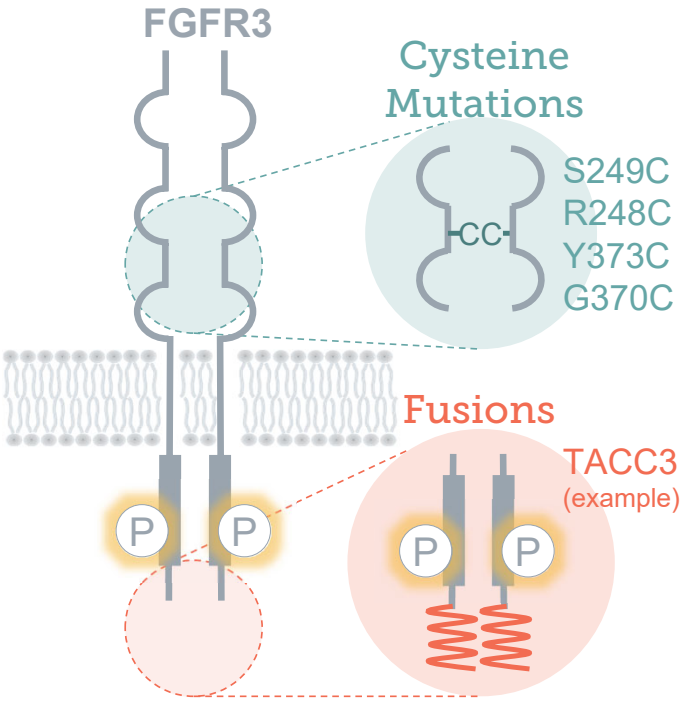
FGFR3 activating alterations occur in 10–20% of mUC[1]



Erdafitinib[2]

Pan-FGFR inhibitor approved for locally advanced or mUC with susceptible *FGFR3* alterations that progressed after ≥1 prior therapy.[2,#]

OS 12.1mo*

ORR 35.3%

(n=135)

Other FGFRi

The FGFR1/2/3 inhibitors pemigatinib and infigratinib were previously evaluated in mUC, but are not approved for this indication.[3,4]

*Pemi. ORR 23%***

Infi. ORR 25.4%

Available FGFRi are associated with significant toxicities, which limit their clinical utility.[1,3,4]

Abbreviations: DoR, duration of response; FGFR, fibroblast growth factor receptor; FGFRi, FGFR inhibitor; Infi, Infigratinib; mUC, metastatic urothelial cancer; OS, overall survival; ORR, objective response rate; Pemi, Pemigatinib.

[1]Loriot Y, et al. N Engl J Med. 2023. [2]Erdafitinib tablets, for oral use. Prescribing information 01/2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s007s008s009lbl.pdf. Accessed 06 October 2024. [3]Necci A, et al. Annals of Oncology, 2024. [4]Lyou Y, et al. Clin Genitourin. Cancer, 2022. #Erdafitinib is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations whose disease has progressed on or after at least one line of prior systemic therapy. *HR for death vs. chemotherapy=0.64 (95% CI, 0.47 – 0.88, p=0.005), Study BLC3001' **ORR reported for intermittent dosing.

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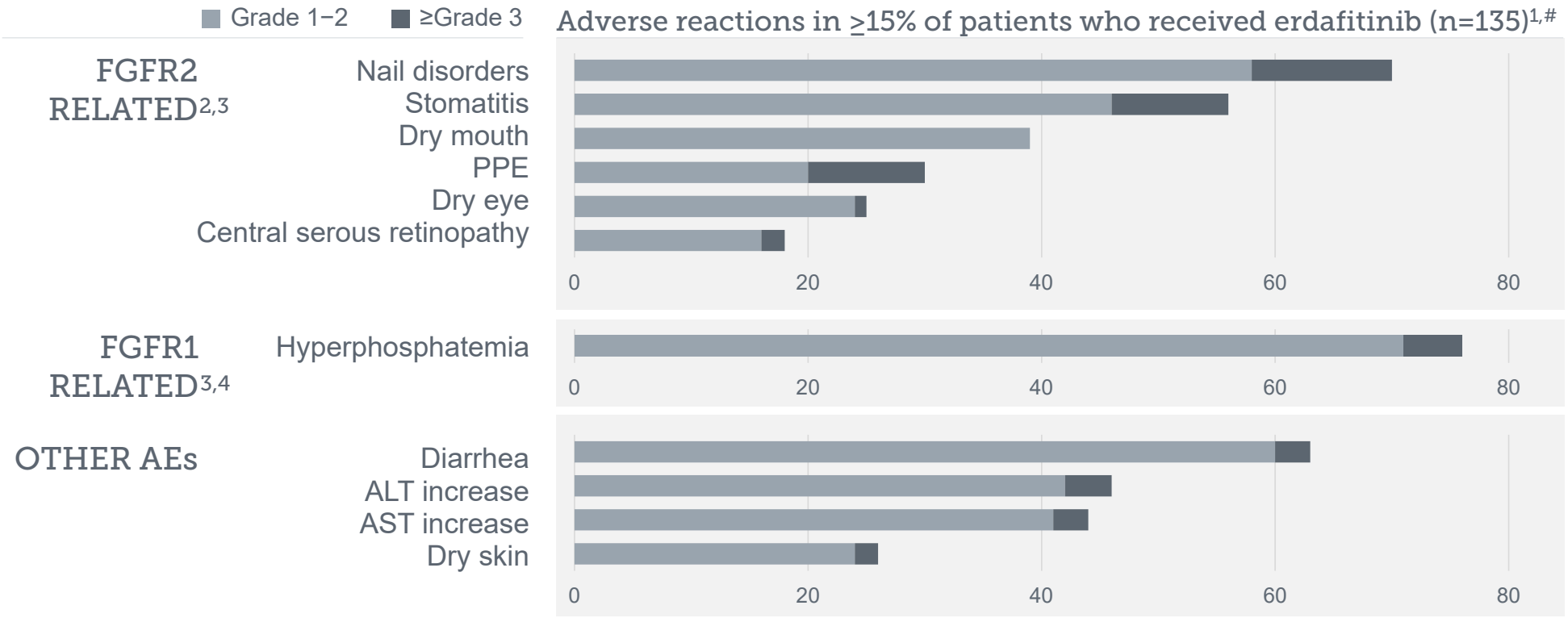
Pan FGFR inhibition is associated with key on-target toxicities



[1]Adapted from: Erdafitinib tablets, for oral use. Prescribing information 01/2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s007s008s009lbl.pdf. Accessed 06 October 2024. [2]Lacouture ME et al. Oncologist. 2021. [3]Subbiah V, Verstovsek S. Cell Rep Med. 2023. [4]Kommalapati A, et al. Cancers. 2021. [#]Study BLC3001

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Adverse reactions requiring dosage modifications of erdafitinib

Adverse reactions resulting in dose adjustments in patients who received erdafitinib (n=135)[1,#]

INTERRUPTION 72%

Nail disorders	22
Stomatitis	19
Eye disorders	16
PPE	15
Diarrhea	10
Hyperphosphatemia	7
Increased AST	6
Increased ALT	5

REDUCTION 69%

Nail disorders	27
Stomatitis	19
Eye disorders	17
PPE	12
Diarrhea	7
Dry mouth	4.4
Hyperphosphatemia	4.4

DISCONTINUATION 14%

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPE, palmar-plantar erythrodysesthesia syndrome
[1]Adapted from: Erdafitinib tablets, for oral use. Prescribing information 01/2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212018s007s008s009lbl.pdf. Accessed 06 October 2024.
[#]Study BLC3001. Adverse reactions leading to dosage interruptions or reductions of erdafitinib in >4% of patients.

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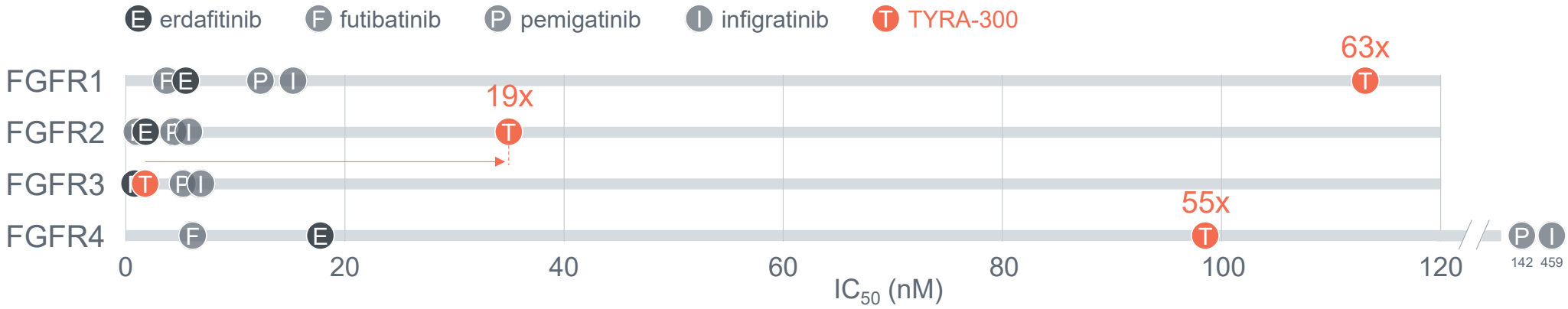
TYRA-300 is a first-in-class, highly selective FGFR3 inhibitor

Selectivity observed for TYRA-300 vs. other FGFR inhibitors: *in vitro* Ba/F3 Cellular IC_{50} (nM)[1]



	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

Ba/F3 cell lines were transduced with recombinant kinase fusions and assayed for cell viability (48 hr treatment).
All experiments conducted under identical conditions, tested in duplicate.
Abbreviations: IC50; half-maximal inhibitory concentration.

[1]Starrett J, Allen E, Balcer A, et al. Annals of Oncology, Volume 33, S751. Data on File.

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SURF301: FIH study of TYRA-300 in mUC and other solid tumors

SURF301

Dose Escalation

Phase 1 Part A i3+3 design

- Advanced solid tumors (must have exhausted all standard therapies)
- ECOG 0–1
- Prior FGFRi allowed

TYRA-300 was dosed daily in 28-day cycles until disease progression or unacceptable toxicity.

QD (mg)

n= 4	120
n= 5	90
n= 3	60
n= 3	40
n= 1	20
n= 1	10

Dose Expansions

Phase 1 Part B

- Advanced solid tumors with activating *FGFR3* alterations; focus on mUC
- ECOG 0 – 1
- Prior FGFRi allowed[1]

QD (mg)

	120
n= 10	90
n= 7	60
n= 7	40

BID (mg)

60
50
40

Endpoints

Primary

- Incidence of DLTs / AEs
- Other safety parameters[2]

Secondary

- PK parameters
- ORR, DOR, DCR, TTR, PFS

Abbreviations: AE, adverse event; BID, twice daily; DLT, dose-limiting toxicity; DCR, disease control rate; DOR, duration of response; FIH, first-in-human; i3+3; interval 3+3; mUC, metastatic urothelial cancer; ORR, overall response rate; PK, pharmacokinetics; PFS, progression-free survival; QD, once daily; TTR, time to response;. [1]Requires the presence of acquired on-target gatekeeper resistance mutations. [2]Laboratory parameters, ECG, vital signs, and physical examinations. SURF301 NCT05544552.

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Part A & B QD data from ongoing Phase 1 portion

SURF301

Dose Escalation

Phase 1 Part A i3+3 design

- Advanced solid tumors (must have exhausted all standard therapies)
- ECOG 0–1
- Prior FGFRi allowed

TYRA-300 was dosed daily in 28-day cycles until disease progression or unacceptable toxicity.

QD (mg)

n= 4	120
n= 5	90
n= 3	60
n= 3	40
n= 1	20
n= 1	10

Dose Expansions

Phase 1 Part B

- Advanced solid tumors with activating *FGFR3* alterations; focus on mUC
- ECOG 0 – 1
- Prior FGFRi allowed[1]

QD (mg)		BID (mg)
	120	60
n= 10	90	50
n= 7	60	40
n= 7	40	

Endpoints

Primary

- Incidence of DLTs / AEs
- Other safety parameters[2]

Secondary

- PK parameters
- ORR, DOR, DCR, TTR, PFS

Abbreviations: AE, adverse event; BID, twice daily; DLT, dose-limiting toxicity; DCR, disease control rate; DOR, duration of response; FIH, first-in-human; i3+3; interval 3+3; mUC, metastatic urothelial cancer; ORR, overall response rate; PK, pharmacokinetics; PFS, progression-free survival; QD, once daily; TTR, time to response;. [1]Requires the presence of acquired on-target gatekeeper resistance mutations. [2]Laboratory parameters, ECG, vital signs, and physical examinations. SURF301 NCT05544552.

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Baseline demographics and disease history characteristics

n=41		
MEDIAN AGE	(range 34–84)	66 (yrs)
		n (%)
SEX AT BIRTH	Male	30 (73)
ECOG PS	0	14 (34)
	1	27 (66)
FGFR3 ALTERATION	Mutation	17 (41)
	Fusion	15 (37)
	None	10 (24)

		n (%)
TUMOR TYPE	mUC	25 (61)
	Lung	3 (7)
	Head and Neck	4 (10)
	Other	9 (22)
PRIOR LINES OF THERAPY	0	5 (12)
	1	7 (17)
	2	11 (27)
	≥3	18 (44)

76%

of mUC patients had ≥3 prior lines of therapy

Abbreviations: mUC, metastatic urothelial cancer
Safety analysis set, n=41

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Preliminary data suggest TYRA-300 is generally well tolerated

n=41	Any Grade	≥ Grade 3
Any TRAEs, n (%)	32 (78)	8 (20)
TRAEs in >10% of participants, n(%)		
ALT increase#	10 (24)	2 (5)
Diarrhea*	9 (22)	1 (2)
Dry mouth	9 (22)	
AST increase	8 (20)	1 (2)
Dry skin	6 (15)	
Fatigue	5 (12)	

#Drug-related discontinuation, Grade 3 ALT elevation 90 mg QD; *DLT, Grade 3 diarrhea 90 mg QD
Abbreviations: TRAE, treatment-related adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DLT, dose-limiting toxicity; SAE, serious adverse event
Safety analysis set, n=41

1 DLT — 90 mg QD, Gr. 3 diarrhea*

1 Drug-related discontinuation — 90 mg QD, Gr. 3 ALT elevation#

4 SAEs — Related to TYRA-300

0 ≥Grade 4 SAE — No drug-related events leading to death

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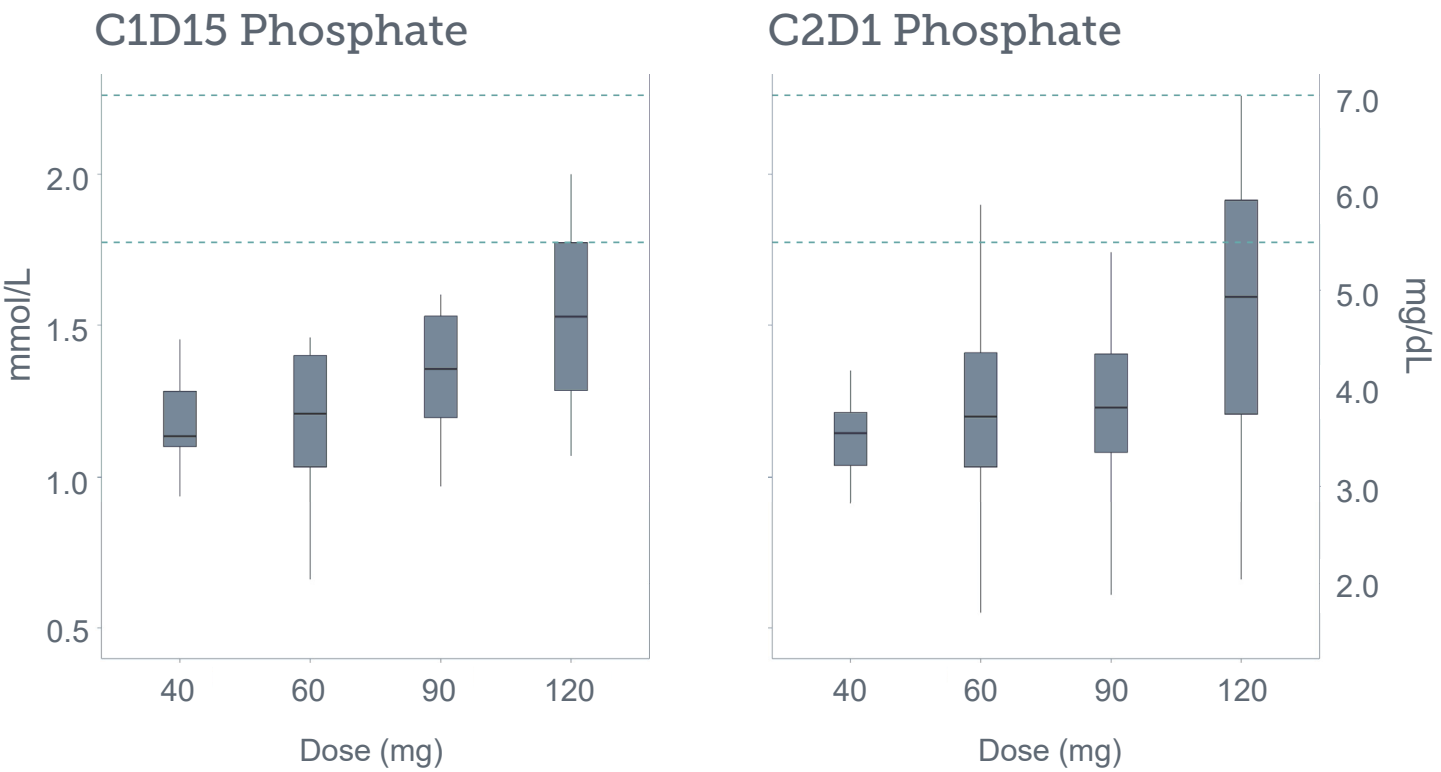
There was no phosphorus elevation >7.0 mg/dL across all doses



Phosphate binder was used to manage treatment-related hyperphosphatemia in one patient (90 mg QD).

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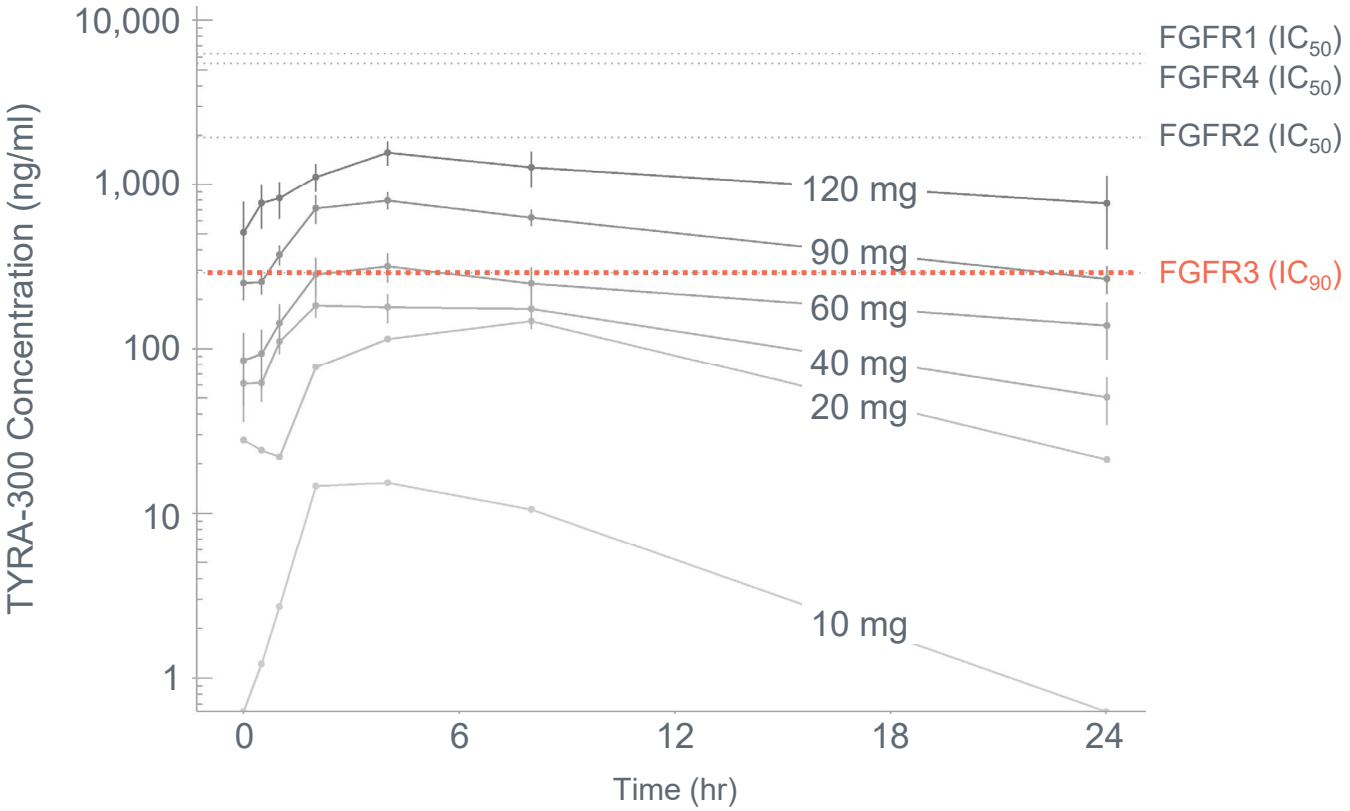
Exposure at ≥90 mg exceeded FGFR3 IC_{90} target coverage



Dose (mg)	N (C1D15)	AUC (ng*h/mL)	
120	3	23,578	2.5x
90	13	10,300	2.4x
60	8	4,360	2.5x
40	10	2,270	
20	1	1,830	
10	1	91.5	

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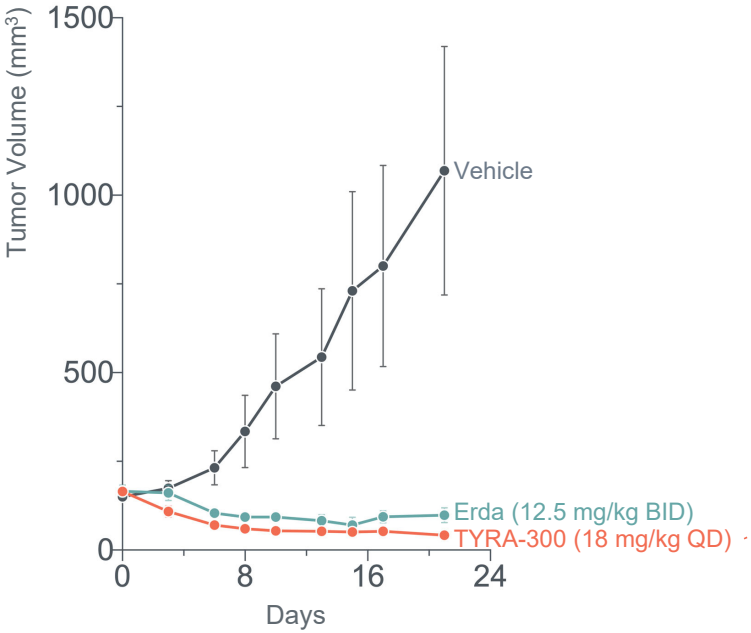
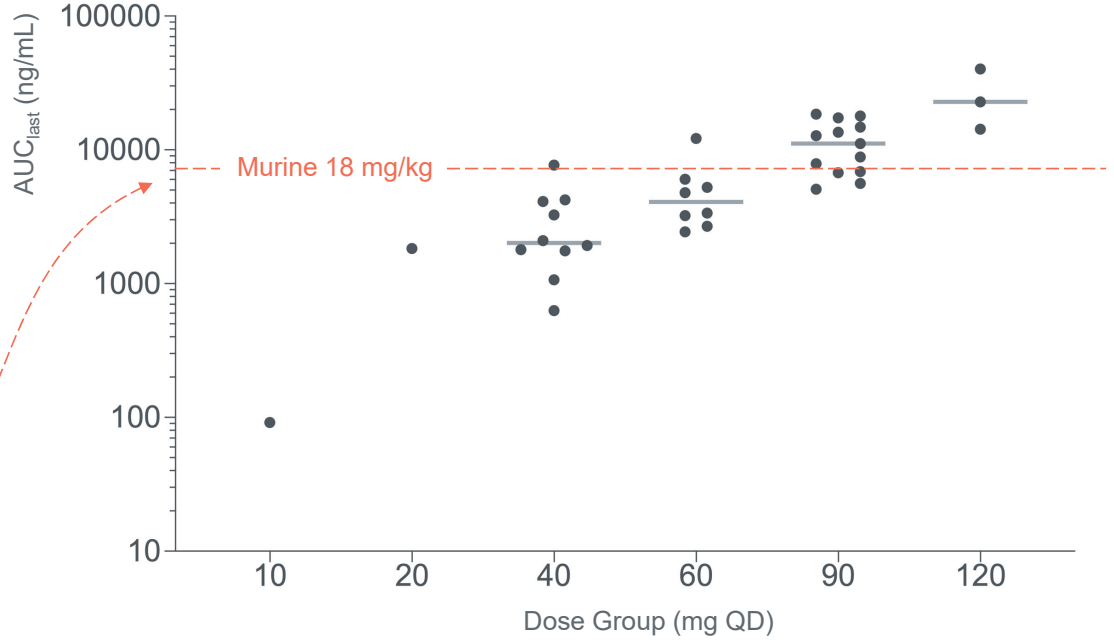
Predicted exposure was achieved in human doses ≥90 mg QD

FGFR3+ UM-UC-14 Xenograft



Individual Steady State AUCs in Patients



Data on File.

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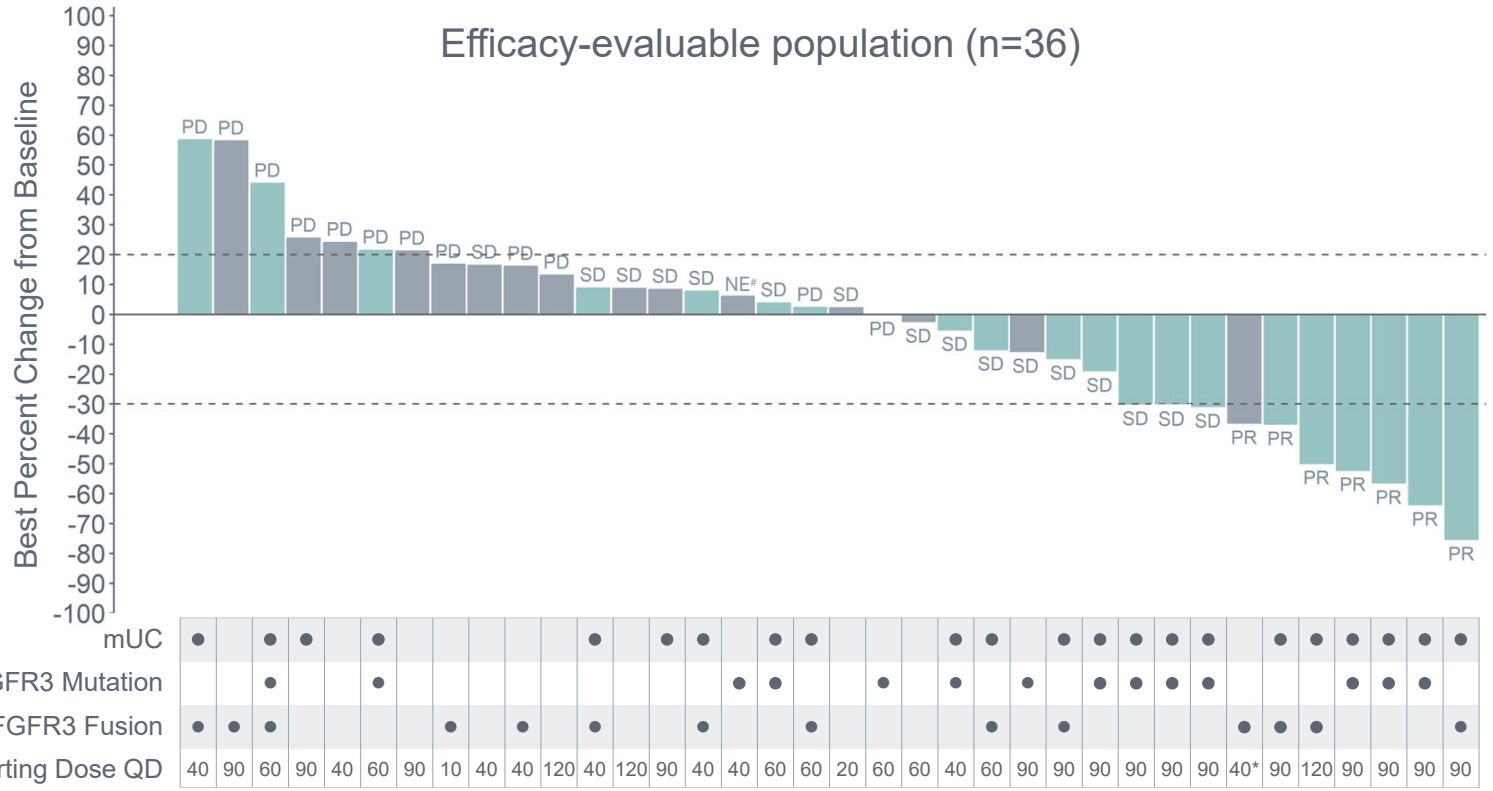
Radiographic response assessment in all evaluable patients



Abbreviations: BOR, best overall response; NE, non-evaluable; PR, partial response; SD, stable disease; PD, progressive disease. BOR by investigator-assessed by RECIST v1.1. Only confirmed PRs reported. #Participant discontinued due to non-compliance. *Dose-escalation from 40 mg QD to 60 mg QD prior to response

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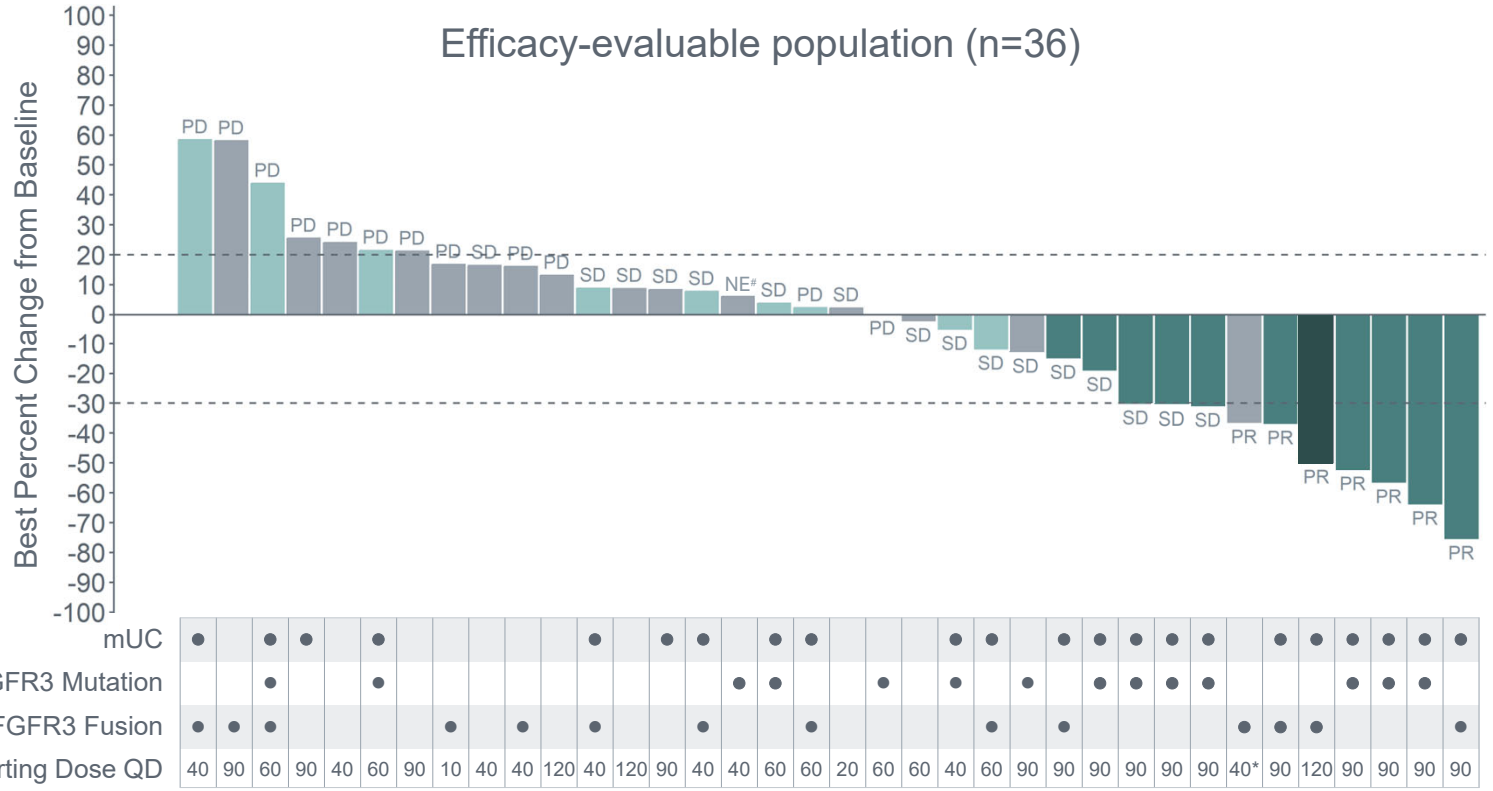
Anti-tumor activity observed in all *FGFR3*+ mUC ≥90 mg QD



- *FGFR3*+ mUC 120 mg
- *FGFR3*+ mUC 90 mg
- *FGFR3*+ mUC <90 mg
- Others

Abbreviations: BOR, best overall response; NE, non-evaluable; PR, partial response; SD, stable disease; PD, progressive disease. BOR by investigator-assessed by RECIST v1.1. Only confirmed PRs reported. #Participant discontinued due to non-compliance. *Dose-escalation from 40 mg QD to 60 mg QD prior to response

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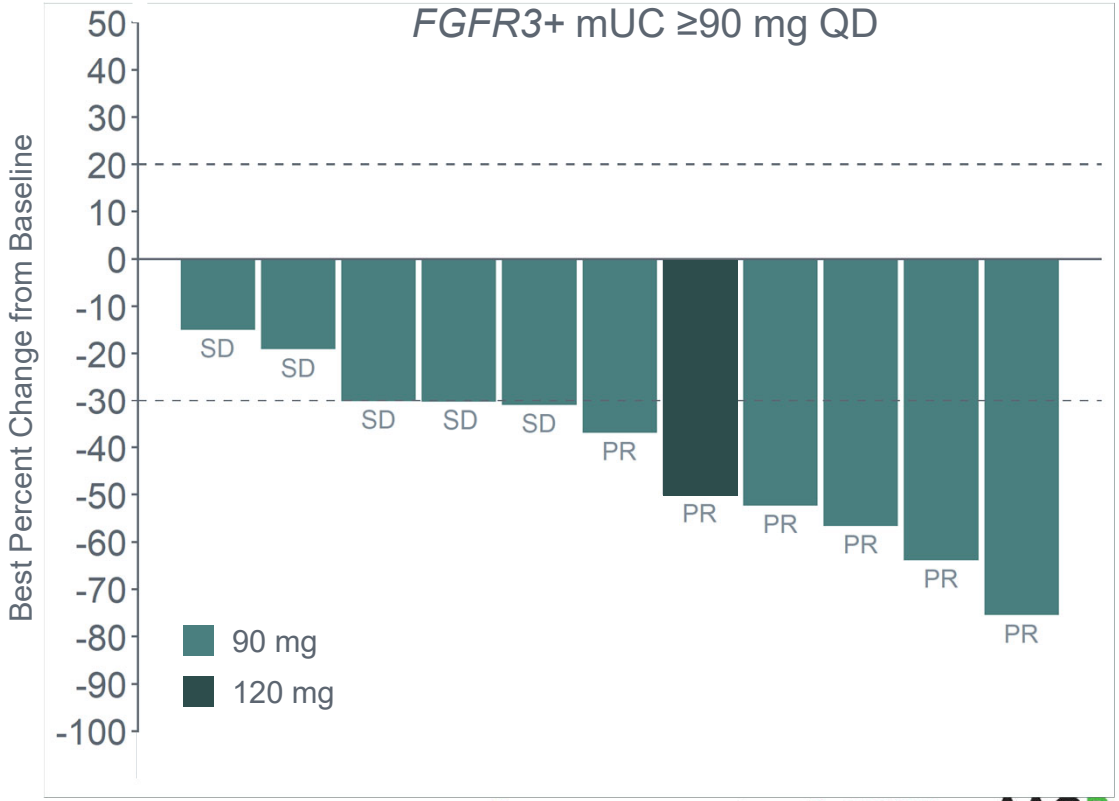
Anti-tumor activity observed in all *FGFR3*+ mUC ≥90 mg QD

Investigator-assessed radiographic BOR by RECIST v1.1 (n=11)

6 confirmed PRs at ≥90 mg QD (n=11)

- 5 confirmed PRs at 90 mg QD (n=10)
- 1 confirmed PR at 120 mg QD (n=1)

100% Disease Control Rate



Abbreviations: BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease.
Only confirmed PRs reported.
Disease Control Rate: CR+PR+SD

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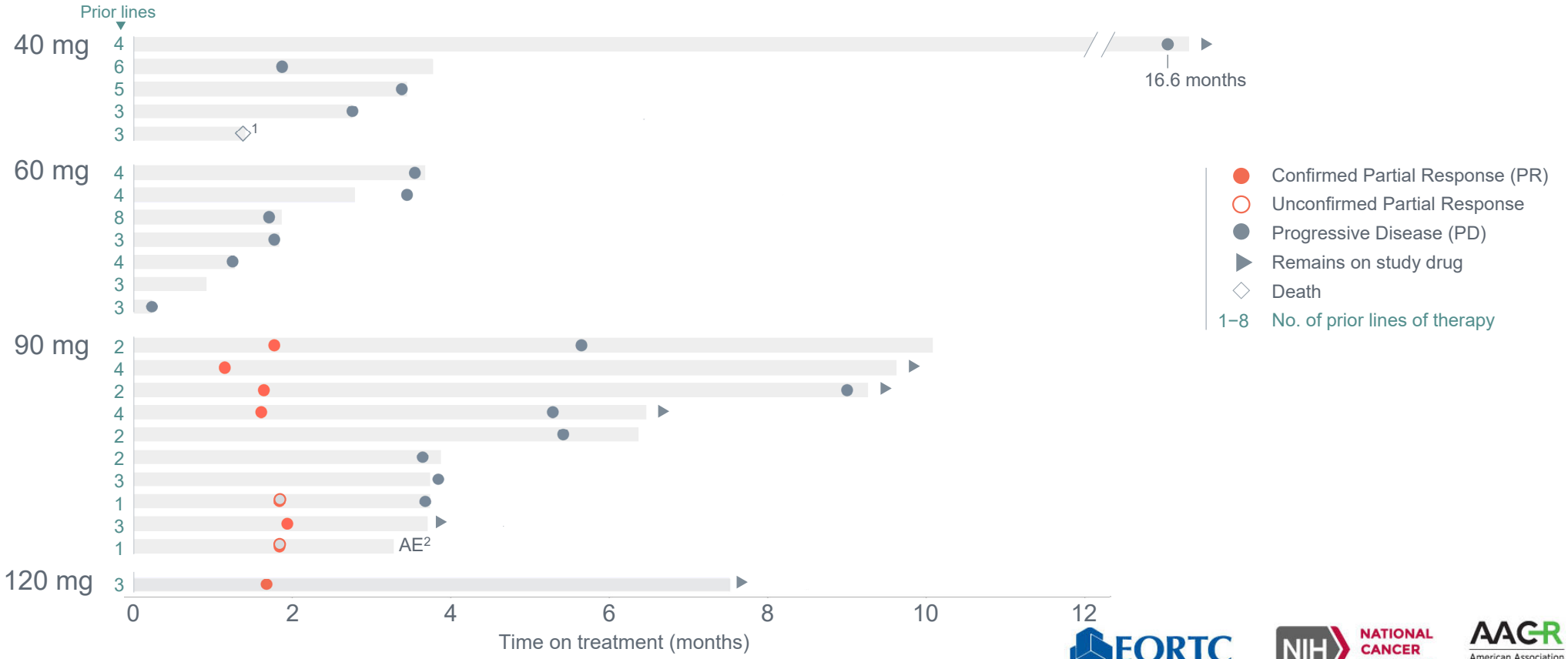
Overview: time on treatment for target population, *FGFR3*+ mUC



1. Death unrelated to study drug (Respiratory Syncytial Virus)
2. AE, adverse event

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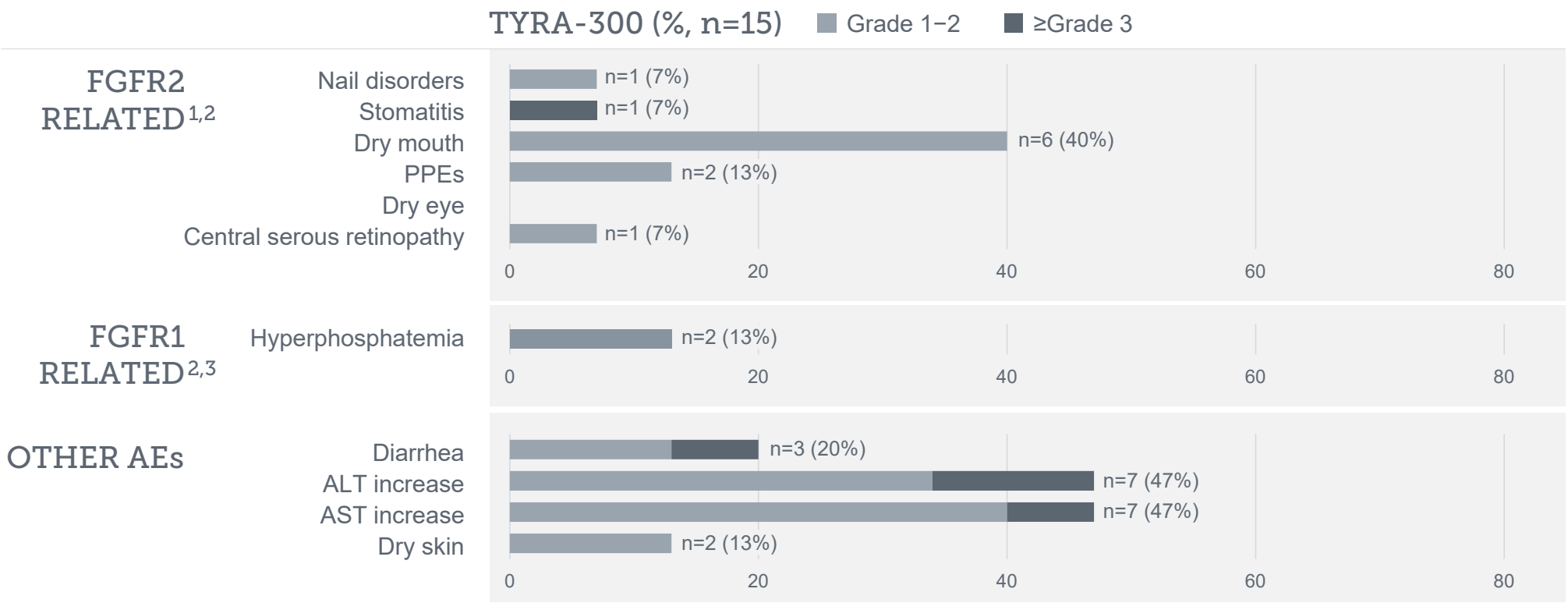
FGFR2- or FGFR1-associated TRAEs at 90 mg QD



90 mg QD: Dose reductions, n = 4; Discontinuation, n = 1
Results are preliminary based on the emerging data from the ongoing Phase 1 portion of the SURF301 study

[1]Lacouture ME, et al. Oncologist. 2021. [2]Subbiah V, Verstovsek S. Cell Rep Med. 2023. [3]Kommalapati A, et al. Cancers. 2021.

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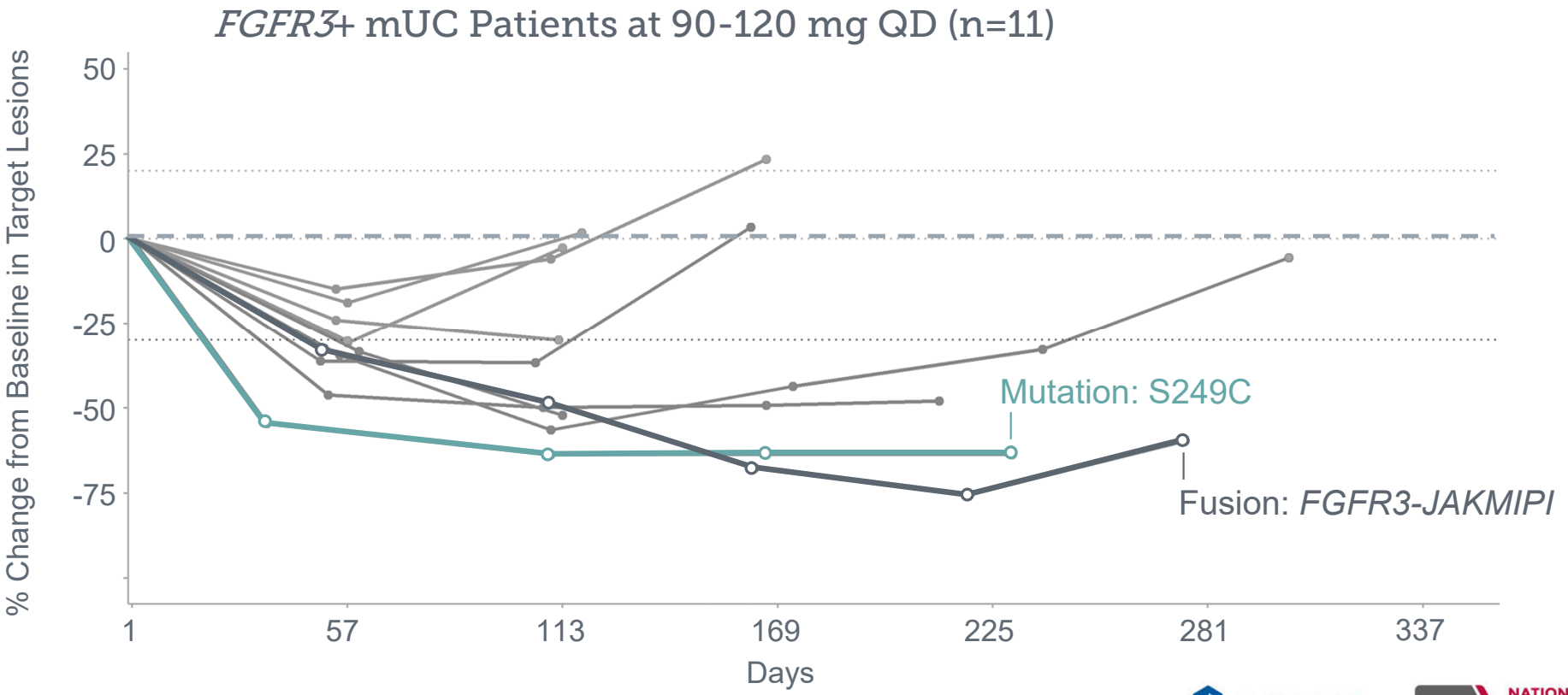
Radiographic regression seen at first imaging



Based on Investigator Assessment; RECIST v1.1

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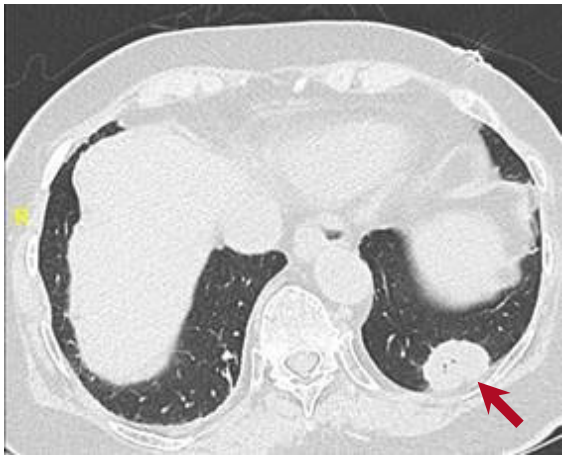
Case study: mUC with an activating *FGFR3*^{S249C} mutation

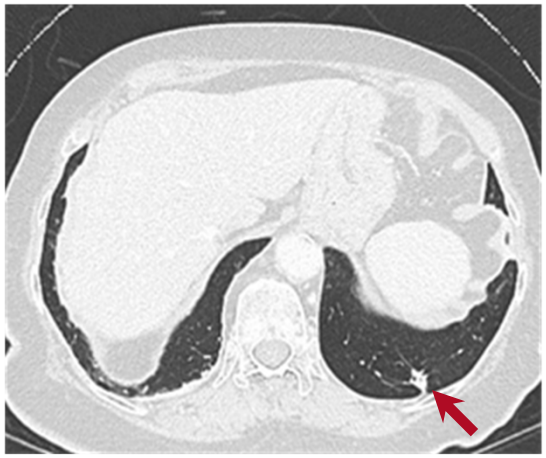
Age/sex:	84-year-old female
# prior lines tx:	4
Target lesions:	Lung
NTL:	Lung, bone
BOR:	-64% (cPR)
Treatment:	90 mg QD, 11 mo.*

LUNG TARGET LESION

SEPT 25, 2023 — *4mo* ▸ — JAN 15, 2024



Baseline



Confirmed PR

* Treatment ongoing at time of data cut

BOR, Best Overall Response; cPR, Confirmed Partial Response; NTL, Non-Target Lesion; tx, Therapy

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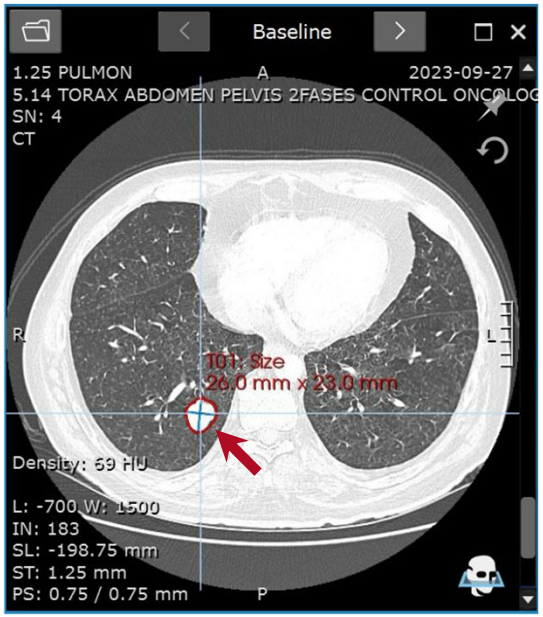
Case study: mUC with an activating *FGFR3-JAKMIPI* fusion

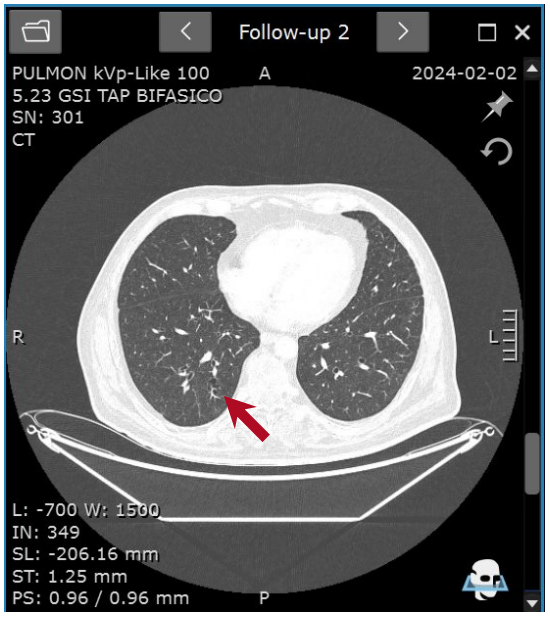
Age/sex:	64-year-old male
# prior lines tx:	2
Target lesions:	Lung (x2), LN (x2)
NTL:	Lung (x2) and LN (x2)
BOR:	-75% (cPR)
Treatment:	90 mg QD, 11 mo.*

LUNG TARGET LESION

SEPT 27, 2023 — *4mo* ▸ — FEB 2, 2024



Baseline



Confirmed PR

* Treatment ongoing at time of data cut

BOR, Best Overall Response; cPR, Confirmed Partial Response; NTL, Non-Target Lesion; tx, Therapy

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Preliminary data are encouraging as SURF301 continues

1. Preliminary data from SURF301 suggest TYRA-300 to be generally well tolerated, with infrequent FGFR2- and FGFR1-associated toxicities.

2. TYRA-300 plasma concentrations indicate adequate target coverage at ≥90 mg QD; further pharmacokinetic characterization is ongoing.

3. Preliminary anti-tumor activity of TYRA-300 in heavily pre-treated patients is encouraging, especially at doses ≥90 mg QD.

Phase 1 is ongoing and the MTD was not reached; the optimal dose is yet to be determined. Emerging profile warrants continued development in mUC.

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