FURTHER (FURMO-002): A Global, Randomized Study of Firmonertinib at Two Dose Levels in TKI-Naïve, Advanced NSCLC with EGFR PACC Mutations

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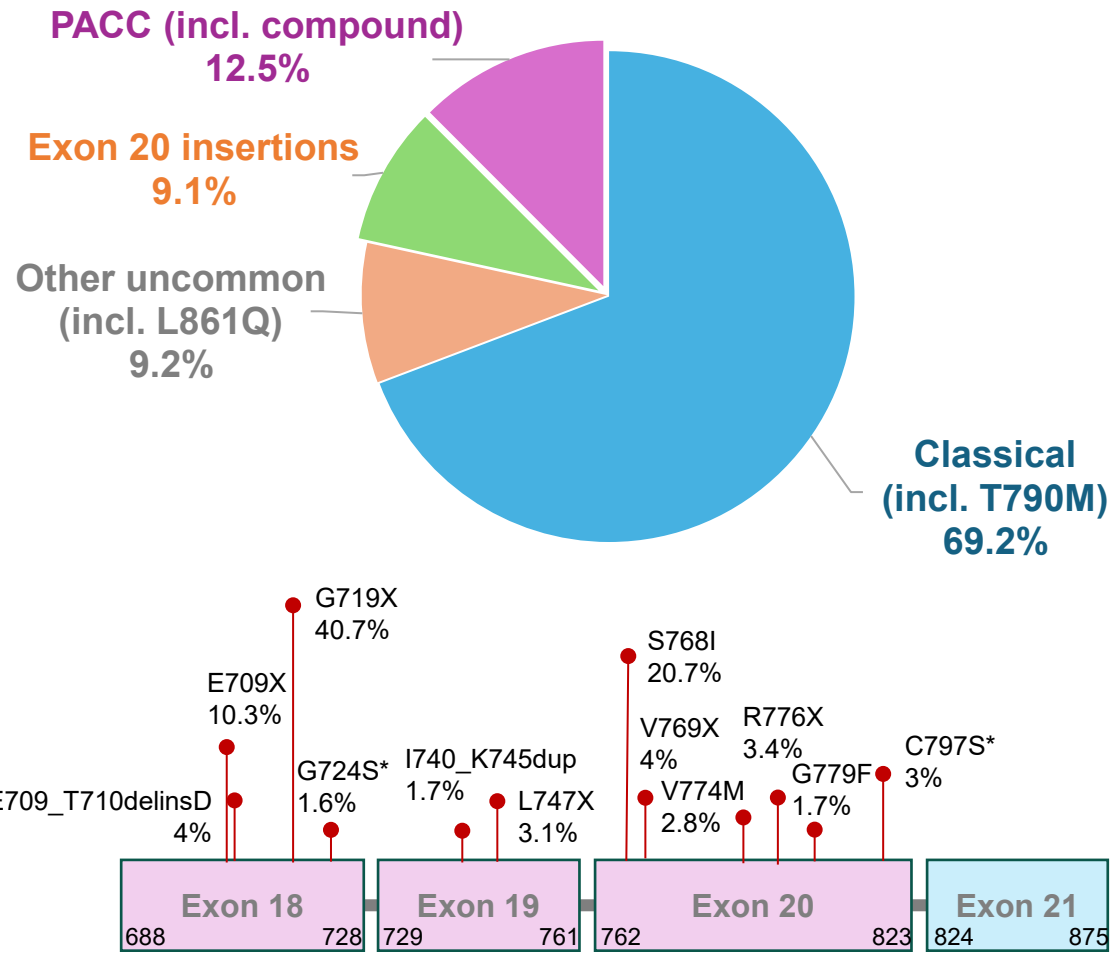
Background: EGFR PACC Mutations



The most common (> 1% among PACC) EGFR PACC mutations are shown.
*G724S and C797S mutations have been reported as resistance mutations to osimertinib.

- EGFR P-loop and αC-helix compressing (PACC) mutations accounts for ~12.5% of all EGFR mutations[1,2] located primarily in exons 18-20
- PACC mutations are similar to Exon 20 insertion mutations in narrowing the drug-binding pocket to affect TKI activity[1]
- PACC mutations can exist as single PACC mutations or compound mutations with other PACC or EGFR mutations[1,2]
- Real-world evidence (RWE) indicates that there is no broadly utilized standard of care treatment for 1L PACC mutant patients[3]

[1]Robichaux et al,, Nature, 2021. [2]Nilsson et al, AACR Annual Meeting, Abstract #1964, 2024 [3]Arrivent data on file. Based on analysis of Tempus RWE US database using LENS software

Background: Firmonertinib

- Firmonertinib (previously known as furmonertinib) is an oral, highly CNS-penetrant EGFR inhibitor with broad activity and selectivity across EGFR mutations.
- Firmonertinib was approved in China for first-line, advanced NSCLC with EGFR Ex19del/L858R in June 2022 and previously treated advanced NSCLC with EGFR T790M mutations in March 2021.

NMPA
CHINA

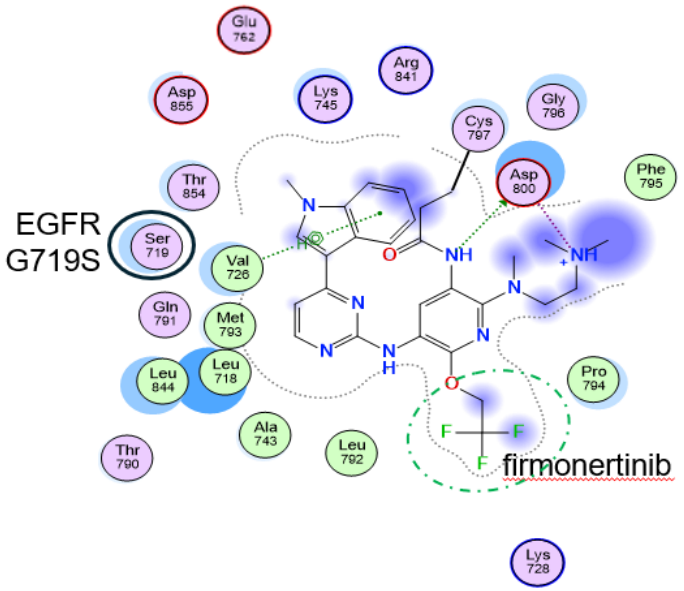
- In the FAVOUR Ph1b study in NSCLC patients with EGFR Exon 20 insertion mutations, a confirmed ORR 78.6% and median duration of response of 15.2 months was observed in treatment-naïve patients treated with firmonertinib at the 240mg QD accompanied with an acceptable safety profile[1].
- Firmonertinib received FDA Breakthrough Therapy Designation (BTD) for first-line, advanced NSCLC with EGFR Exon 20 insertion mutations on October 2023.

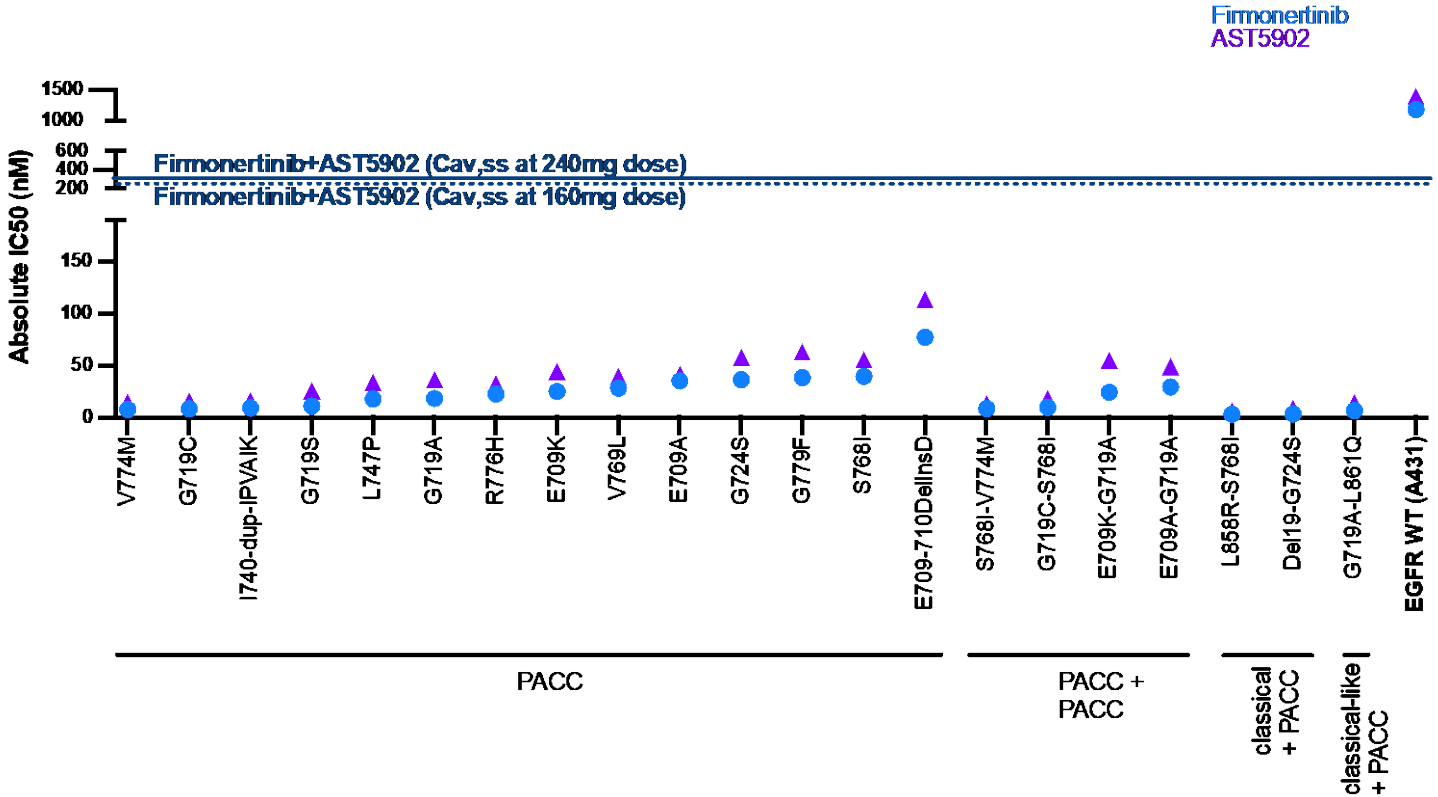
FDA

- Global Phase 3 study (FURVENT) in first-line, advanced NSCLC with EGFR Exon 20 insertion mutations is ongoing.

[1]Han et al., WCLC, 2023.

Preclinically Firmonertinib and its Major Metabolite (AST5902) are Active Against EGFR PACC Mutations





- 2D molecular model of firmonertinib bound to EGFR G719S (PACC) mutant
- Green dotted outline indicates the proximity contour around the tri-fluoroethoxy group, confirming firmonertinib's close contact with the binding pocket and hydrophobic residues of EGFR

- IC50 analysis performed with engineered Ba/F3 cell lines and A431 (EGFR WT) control cells (unpublished data)
- Drug levels based on firmonertinib studies NCT02973763 and NCT03127449

Nilsson et al, AACR Annual Meeting, Abstract #1964, 2024

PACC Cohort in FURTHER Trial with Two Dose Levels (NCT05364073)

Stage 2 Cohort 4 Dose Expansion (PACC Cohort)

Key Eligibility Criteria:

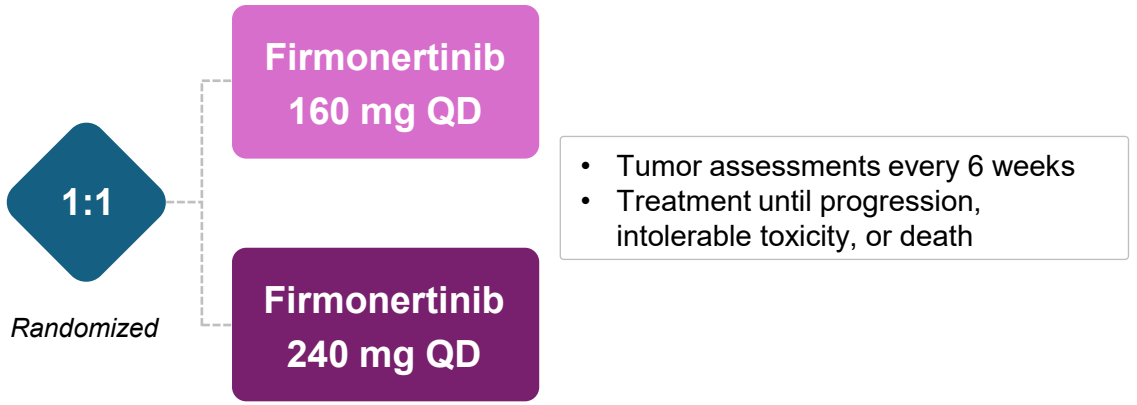
- Locally advanced or metastatic NSCLC with EGFR *PACC* mutations
- No prior EGFR TKI treatment
- Asymptomatic brain metastases without prior radiation therapy allowed

Stratification:

Prior Treatment (Y/N)

Contains G719X or S768I (Y/N)

N=60



Primary endpoints:

Overall Response Rate
ORR (by BICR)

Key secondary endpoints:

Duration of response, CNS ORR, PFS, OS

FURTHER study: Other Stages and Cohorts
Stage 1: Dose escalation/backfill/PK in EGFRmt or HER2 Ex20ins NSCLC
Stage 2, Cohort 1: EGFR Exon 20ins NSCLC with prior treatment (240mg QD)
Stage 2, Cohort 2: HER2 Exon 20ins NSCLC with prior treatment (240mg QD)
Stage 2, Cohort 3: EGFR mutant NSCLC with prior treatment (non-Ex20ins, non-PACC); (240mg QD)

Global study in **40 sites and 10 countries** - Australia, Canada, China, France, Japan, Korea, Netherlands, Spain, UK, USA

PACC Cohort - Demographics and Disease Characteristics

	All PACC Patients		1L PACC Patients	
	160 mg QD N=31	240 mg QD N=29	160 mg QD N=25	240 mg QD N=22
Age (years), median (range)	65.0 (48-86)	68.0 (50-83)	67 (48-86)	67.5 (50-83)
Male / Female, %	32.3 / 67.7	34.5 / 65.5	40.0 / 60.0	36.4 / 63.6
ECOG 0 / 1, %	29.0 / 71.0	27.6 / 72.4	32.0 / 68.0	27.3 / 72.7
Brain Metastases[1], %	32.3	34.5	28.0	31.8
Non-smoker / Former or current smoker, %	64.5 / 35.5	79.3 / 20.7	76.0 / 24.0	86.4 / 13.6
Race: Asian / White / Other, %	71.0 / 22.6 / 6.4	72.4 / 20.7 / 6.9	80.0 / 20.0 / 0	77.3 / 13.6 / 9.1
Prior metastatic therapies				
Chemotherapy (%)	12.9	17.2	0	0
Immunotherapy (%)	0	10.3	0	0
Other (%)	6.5	6.9	0	0

[1]History or presence of brain metastases.

Data as of July 5, 2024

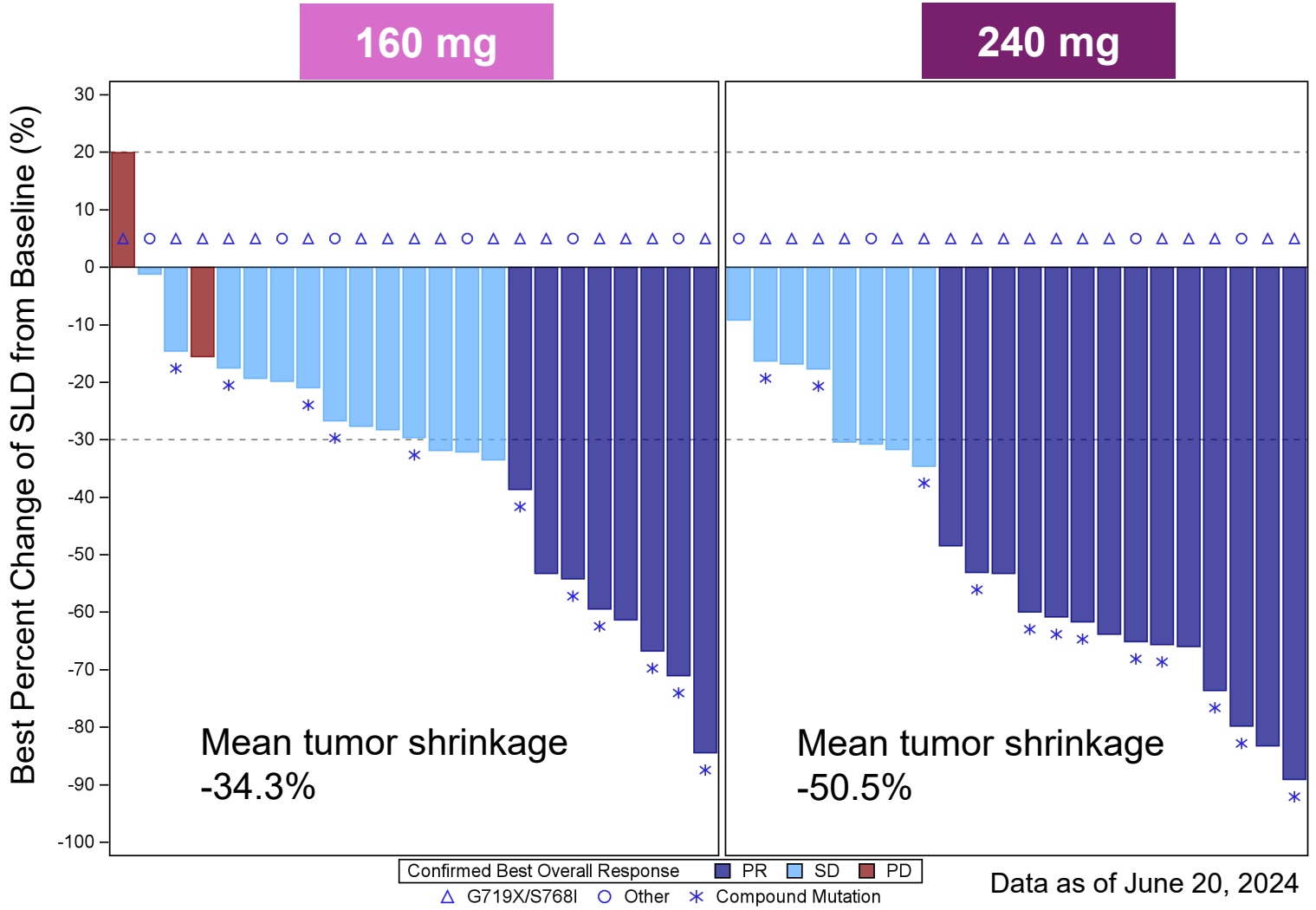
Primary Endpoint ORR (BICR) in 1L PACC NSCLC

	BICR[1]		INV[1]	
	160 mg QD N=23	240 mg QD N= 22	160 mg QD N=25	240 mg QD N=22
Best ORR, % (95% CI)[2]	**47.8** (26.8-69.4)	**81.8** (59.7-94.8)	**52.0** (31.3 - 72.2)	**81.8** (59.7 - 94.8)
Confirmed ORR, % (95% CI)	**34.8** (16.4 - 57.3)	**63.6** (40.7 - 82.8)	**52.0** (31.3 - 72.2)	**68.2** (45.1 - 86.1)
Best Overall Response, n (%)				
Partial response (PR)	8 (34.8)	14 (63.6)	13 (52.0)	15 (68.2)
Stable disease (SD)	13 (56.5)	8 (36.4)	10 (40.0)	7 (31.8)
Progressive disease (PD)	2 (8.7)	0	1 (4.0)	0
Not Evaluable	0	0	1 (4.0)	0
DCR (CR+PR+SD), % (95% CI)	**91.3** (72.0 - 98.9)	**100** (84.6 - 100)	**92.0** (74.0 - 99.0)	**100** (84.6 - 100)

[1]Received ≥ 1dose; have at least 1 measurable lesion at baseline as assessed by BICR or INV using RECIST v1.1
[2]includes confirmed and unconfirmed responses

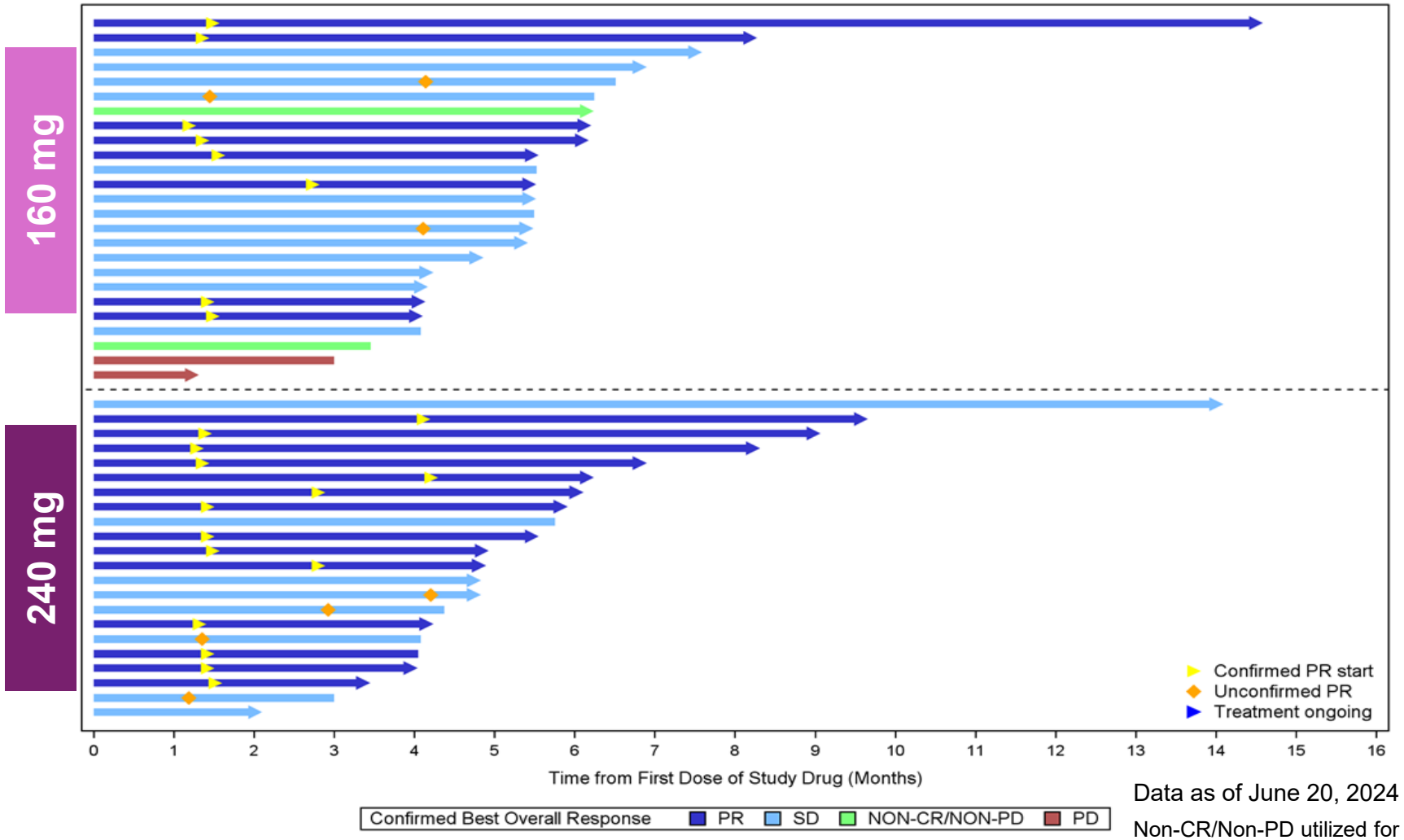
Data as of July 5, 2024 for INV
Data as of June 20, 2024 for BICR

Best Tumor Reduction 1L PACC NSCLC (BICR)



- Confirmed PRs observed in a wide range of EGFR PACC mutations including:
  - Responses in more frequent EGFR PACC mutations (G719X or S768I) as well as less frequent mutations (E709X and V774M)
  - Responses in single and compound EGFR PACC mutations.

Treatment Duration and Time of Responses by BICR in 1L Patients



- Responses seen at first tumor assessment in the majority of patients
- Median follow-up for DoR 4.2 months
- Median DoR has not been reached
  - 90.9% (n=20 of 22) of responders are still on treatment
- PFS and OS data immature

Data as of June 20, 2024

Non-CR/Non-PD utilized for non-measurable by BICR patients

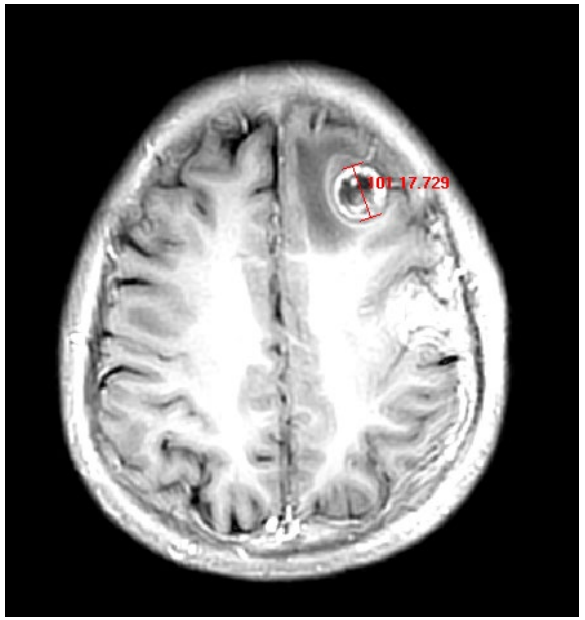
Confirmed CNS ORR in Response Evaluable CNS Population

	160 mg N=9*	240 mg N=7*	1L Only (N=13)
Confirmed ORR, % (95% CI)	**55.6 (21.2 - 86.3)**	**42.9 (9.9 - 81.6)**	**46.2 (19.2 – 74.9)**
Best Overall Response, n (%)			
Complete response (CR)	4 (44.4)	3 (42.9)	5 (38.5)
Partial response (PR)	1 (11.1)	0	1 (7.7)
Stable disease (SD)	1 (11.1)	0	1 (7.7)
Non-CR/Non-PD**	2 (22.2)	3 (42.9)	4 (30.8)
Progressive disease (PD)	1 (11.1)	1 (14.3)	2 (15.4)
DCR (CR+PR+SD) % (95% CI)	**88.9 (51.8 - 99.7)**	**85.7 (42.1 - 99.6)**	**84.6 (54.6 – 98.1)**

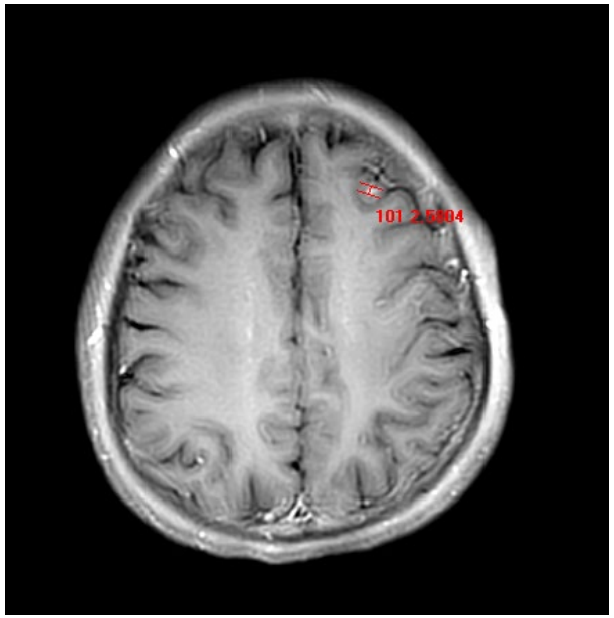
Data as of June 20, 2024

Response Evaluable CNS Population: Received ≥ 1 dose; at least 2 post-baseline CNS tumor assessment by BICR (modified RECIST) or had PD or discontinued from the study.
* Combined 1L and 2L+ PACC patients
** Non-CR/Non-PD utilized for non-measurable CNS patients.

1L patient with no prior CNS radiotherapy
Treated with firmonertinib 160 mg QD



Screening MRI
CNS target lesion 17.7mm



Week 24 MRI
CNS target lesion 3.1mm
(-82.5% change in size)

CNS tumor shrinkage with firmonertinib

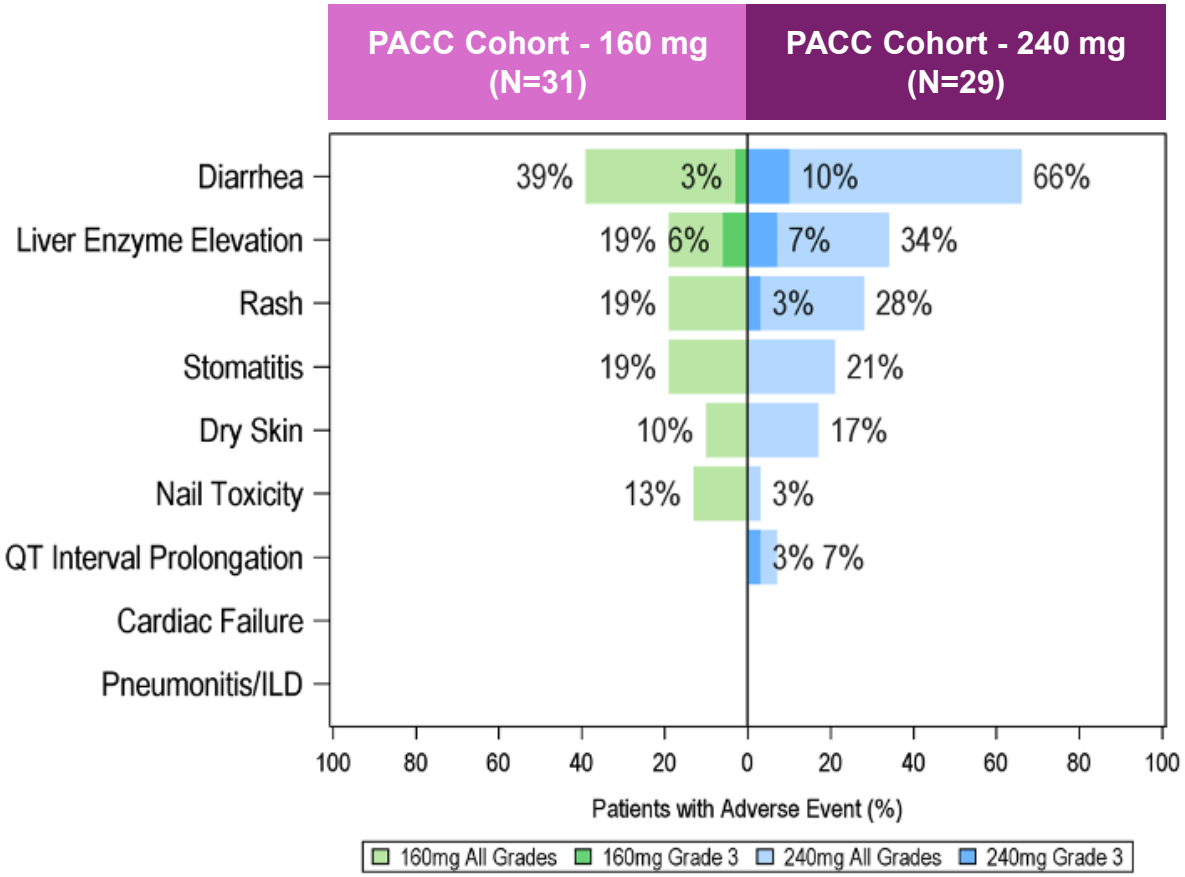
FURTHER: PACC Cohort Safety and Tolerability Profile

Overview of TRAEs (n, %)	PACC Cohort		All patients in FURTHER	
	160 mg (N=31)	240 mg (N=29)	160 mg (N=42)	240 mg (N= 116)
TRAEs any grade	26 (83.9)	25 (86.2)	34 (81.0)	95 (81.9)
TRAEs Grade ≥3	4 (12.9)	6 (20.7)	5 (11.9)	24 (20.7)
Treatment-related SAEs	1 (3.2)	1 (3.4)	2 (4.8)	11 (9.5)
Dose interruption	6 (19.4)	10 (34.5)	10 (23.8)	43 (37.1)
Dose reduction	4 (12.9)	7 (24.1)	5 (11.9)	24 (20.7)
Dose discontinuation	0	0	1 (2.4)	6 (5.2)

Data as of July 5, 2024

- Includes all patients who have received ≥1 dose
- No Grades 4-5 TRAEs observed

TRAE of Clinical Interest[1]



- Includes all patients who have received ≥1 dose
- No Grades 4-5 TRAEs observed

[1]Based on group search terms

Conclusions

- Firmonertinib showed promising antitumor activity in a broad range of EGFR PACC mutant NSCLC.
  - Firmonertinib 240 mg QD showed confirmed ORR 63.6%, best ORR 81.8%, and DCR 100% by BICR.
  - Firmonertinib had encouraging CNS antitumor activity in EGFR PACC mutant NSCLC.
- Firmonertinib showed an acceptable and manageable safety profile in FURTHER.
- This data supports further investigation of firmonertinib as a once daily oral therapy in EGFR PACC mutant NSCLC patients.

Acknowledgments

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- We thank our global site investigators and their teams for conducting the FURTHER study.
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