Updated Clinical Results from FURTHER: A Study of Firmonertinib in TKI-Naïve, Advanced NSCLC with *EGFR* PACC Mutations

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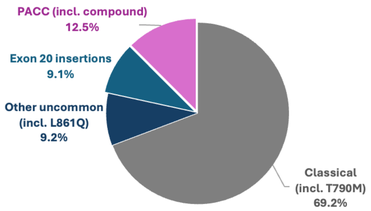
INTRODUCTION

Figure 1. *EGFR* PACC mutations are the most frequent uncommon *EGFR* mutation in NSCLC and have an unmet medical need



- Approximately 70 different missense mutations (including compound) in Exons 18-20[1]
- G719X and S768I are the most frequent PACC mutations at 40.7% and 20.7%, respectively[2]
- Exist as single OR compound mutations with additional PACC or other *EGFR* mutations[1,2]
- Affects tyrosine kinase inhibitor (TKI) binding by narrowing the drug-binding pocket (similar to exon 20 insertions)[1]
- Early CNS spread common[3]
- Large medical need for new treatment options for NSCLC patients harboring *EGFR* PACC mutations

Table 1. Prospective Clinical Trial Benchmarks for *EGFR* uncommon mutations for EGFR-TKI

Agent	Study	# of Patients	Mutations[a]	mPFS (months)
Osimertinib	UNICORN[4]	40	Includes single L861Q mutation (17.5% ; 7/40)	9.4[b]
Afatinib	ACHILLES[5]	73 (afatinib arm)	Includes single L861Q mutation (19.2% ; 14/73)	10.6

[a] UNICORN and ACHILLES studies enrolled non-Exon 20 insertion uncommon *EGFR* mutation patients including L861Q (classical-like) single mutations which are non-PACC mutations.
[b] In UNICORN study L861Q single mutation patients had longer median progression-free survival (mPFS 22.7 months) than the overall population.

Firmonertinib: An oral, highly CNS-penetrant EGFR inhibitor, selected for broad activity and selectivity across EGFR mutations including PACC

Preclinical

- Patient drug levels exceed IC50 values across representative PACC mutations in *in vitro* cell models[6]
- Increased contact points within drug-binding pocket of *EGFR* PACC mutants mediated by unique side-chain[2]
- Inhibited tumor growth in patient-derived xenograft models harboring *EGFR* PACC mutations[2]

Clinical

- Studied across a range of doses up to 240 mg QD
- Approved in China for classical and T790M *EGFR* mutations (80 mg QD)
- Proof of concept (FAVOUR[7]) and ongoing Phase 3 study (FURVENT[8]) in *EGFR* Exon20 insertions (160 mg QD and 240 mg QD)

METHODS

Figure 2. 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

1:1 *Randomized*

- **Firmonertinib 160 mg QD**
- **Firmonertinib 240 mg QD**

- Tumor assessments every 6 weeks
- Treatment until progression, intolerable toxicity, or death

Primary endpoint: ORR by blinded independent central review (BICR)
Key secondary endpoints: DOR, CNS ORR, PFS, overall survival (OS)

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

Other Stages and Cohorts
Stage 1: Dose escalation/backfill/PK in *EGFRm, HER2* Ex20ins NSCLC, or EGFR activating mutations*
Stage 2, Cohort 1: *EGFR* Exon 20ins w/prior treatment (240mg QD)
Stage 2, Cohort 2: *HER2* Exon 20ins w/prior treatment (240mg QD)
Stage 2, Cohort 3: *EGFRm* w/prior treatment (non-Ex20ins/non-PACC) (240mg QD)

*PACC mutations, exon 19 and exon 21 mutations, such as exon 19 deletion, L858R, and L861Q, with or without *EGFR* T790M mutation.

Data presented from final data cut date Jun 3, 2025

RESULTS

Table 2. 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[a], %	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 / 6.5	72.4 / 20.7 / 6.8	80.0 / 20.0 / 0	77.3 / 13.6 / 9.1
Prior Treatment Type, %				
Chemotherapy	16.1	17.2	4.0	0
Immunotherapy	3.2	13.8	0	4.5[b]

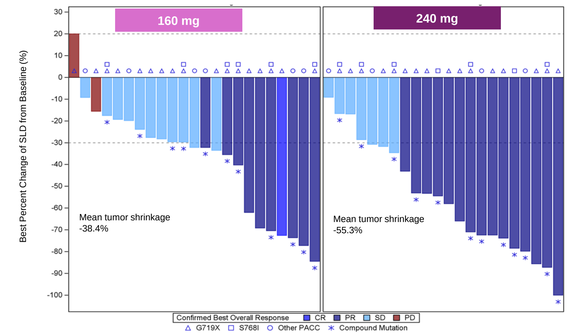
[a]History or presence of brain metastases.
[b]One patient had prior Recombinant Mutant Human Tumor Necrosis Factor (adjuvant therapy).

Table 3. PACC Cohort: Efficacy Outcomes by BICR for 1L Patients

	160 mg QD n=23	240 mg QD n=22
Best ORR, % (95% CI)[a]	**52.2%** (30.6–73.2)	**81.8%** (59.7–94.8)
Confirmed ORR, % (95% CI)	**43.5%** (23.2–65.5)	**68.2%** (45.1–86.1)
Best overall response, n (%)		
Complete response (CR)	1 (4.3%)	0 (0%)
Partial response (PR)	9 (39.1%)	15 (68.2%)
Stable disease (SD)	11 (47.8%)	7 (31.8%)
Progressive disease (PD)	2 (8.7%)	0 (0%)
Median Duration of Response, months	NA	14.6
DCR (CR+PR+SD), % (95% CI)	**91.3%** (72.0% – 98.9%)	**100%** (84.6% – 100%)

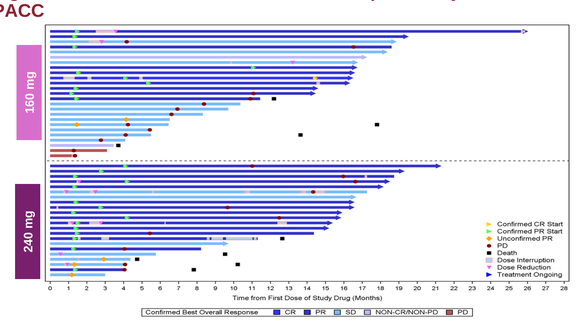
[a]Includes confirmed and unconfirmed responses.

Figure 3. Best Tumor Reduction by BICR in 1L PACC



- Confirmed PRs in wide range of *EGFR* PACC mutations
  - Responses by mutation frequency:
    - Frequent (mutations including G719X, S768I): cORR — 160 mg: 41.2% (7/17); 240 mg: 72.2% (13/18)
    - Less frequent (PACC mutations other than G719X, S768I; categorized as "Other PACC" in Fig 3; e.g., E709X, V774M)
      cORR — 160 mg: 50% (3/6); 240 mg: 50% (2/4)
  - Responses by mutations type:
    - Single *EGFR* PACC mutations: cORR — 160 mg: 25% (3/12); 240 mg: 60% (6/10)
    - Compound *EGFR* PACC mutations: cORR — 160 mg: 63.6% (7/11); 240 mg: 75% (9/12)

Figure 4. Treatment Duration & Time of Responses by BICR in 1L PACC



- Responses at first tumor assessment in majority of patients
- Median DoR: 14.6 months (240 mg QD) and not reached (160 mg QD)
- Dose holds and dose reductions if needed tend to occur early

Figure 5. Kaplan-Meier Curve for Progression-Free Survival by BICR in 1L PACC

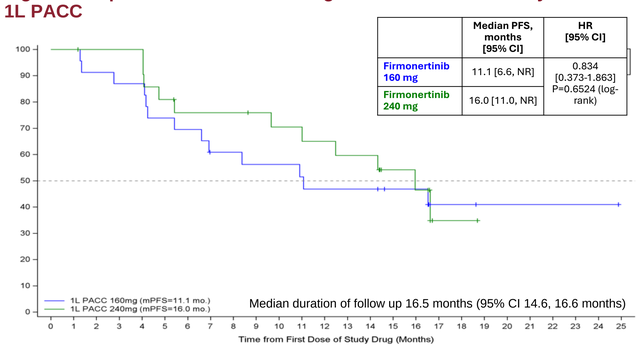


Table 4. CNS Confirmed ORR by BICR in Response Evaluable CNS Population in PACC

	160 mg N=9[a]	240 mg N=8[a]	1L Only N=14[b]
Confirmed ORR, % (95% CI)	**55.6%** (21.2–86.3)	**37.5%** (8.5–75.5)	**42.9%** (17.7–71.1)
Best Overall Response, n (%)			
Complete response (CR)	4 (44.4)	3 (37.5)	5 (35.7)
Partial response (PR)	1 (11.1)	0	1 (7.1)
Stable disease (SD)	1 (11.1)	1 (12.5)	2 (14.3)
Non-CR/Non-PD[c]	2 (22.2)	3 (37.5)	4 (28.6)
Progressive disease (PD)	1 (11.1)	1 (12.5)	2 (14.3)
DCR (CR+PR+SD), % (95% CI)	**88.9%** (51.8–99.7)	**87.5%** (47.3–99.7)	**85.7%** (57.2–98.2)

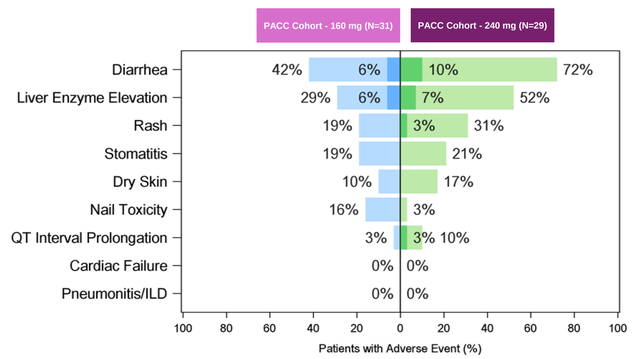
Response Evaluable CNS Population: Received ≥ 1 dose; at least 2 post-baseline CNS tumor assessment by BICR (modified RECIST) or had PD or discontinued from the study.
[a] Combined 1L and 2L+ PACC patients
[b] 1L for both 160 mg and 240 mg combined
[c] Non-CR/Non-PD utilized for only non-measurable CNS patients

Table 5. Safety and Tolerability Profile

	All PACC Patients		All Patients in FURTHER	
Treatment-related adverse events (TRAEs), n (%)	160 mg (N=31)	240 mg (N=29)	160 mg (N=42)	240 mg (N= 116)
TRAEs any grade	28 (90.3)	28 (96.6)	36 (85.7)	101 (87.1)
TRAEs Grade ≥3	8 (25.8)	6 (20.7)	9 (21.4)	25 (21.6)
Treatment-related serious AEs (SAEs)	2 (6.5)	1 (3.4)	3 (7.1)	11 (9.5)
Dose interruption	9 (29.0)	11 (37.9)	13 (31.0)	45 (38.8)
Dose reduction	6 (19.4)	7 (24.1)	7 (16.7)	24 (20.7)
Dose discontinuation	1 (3.2)	0	2 (4.8)	8 (6.9)

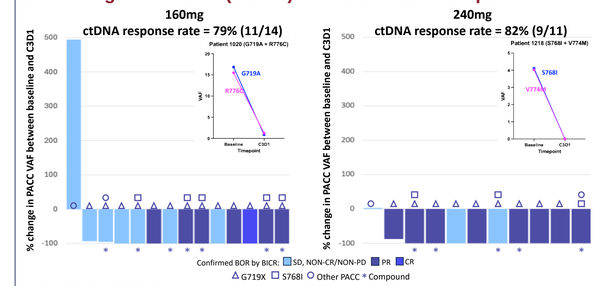
- Includes all patients who have received ≥1 dose
- No Grades 4-5 TRAEs observed

Figure 6. TRAE of Clinical Interest[a]



[a]Based on group search terms

Figure 7. Changes in EGFR Variant Allele Frequency (VAF) in Circulating Tumor DNA (ctDNA) at C3D1 in 1L PACC patients



- 41/47 (87%) 1L PACC patients had baseline and C3D1 paired samples with evaluable ctDNA; and *EGFR* PACC at baseline was detected in 25 patients.
- ctDNA was analyzed with PredicineCARE NGS-based assay.
- Waterfall plots show a change in PACC VAF variants from baseline to C3D1; only patients with *EGFR* PACC detectable at the baseline are shown.
- For patients with compound mutations, a consistent change across all variants was observed; for those patients only 1 of the variants is shown on the waterfall plots.
- Examples of consistent PACC VAF changes in patients with PACC + PACC compound mutations are shown in plots in right top corners.
- ctDNA response was defined as *EGFR* PACC ctDNA clearance (i.e., detectable at the baseline and undetectable at C3D1 and marked as -100% on the waterfall plot).

DISCUSSION AND CONCLUSION

- Firmonertinib continues to show promising antitumor activity in a broad range of *EGFR* PACC mutant NSCLC patients
  - Firmonertinib 240 mg QD showed confirmed ORR 68.2%, mDOR 14.6 months, and mPFS 16.0 months by BICR in 1L PACC patients
  - Encouraging CNS antitumor activity observed including CNS complete responses
  - Active across a broad range of *EGFR* PACC mutations including single and compound
- Rapid molecular ctDNA responses observed in patients treated with firmonertinib 160mg QD and 240mg QD
- Firmonertinib showed an acceptable and manageable safety profile at both dose levels
- These data support further investigation of firmonertinib (240 mg) as a once daily oral therapy in patients with *EGFR* PACC mutant NSCLC in the ALPACCA (FURMO-006) study, a planned global registrational 1L study

Figure 8. ALPACCA (FURMO-006): Randomized, Global, Phase 3 Study in 1L mNSCLC with *EGFR* PACC Mutations

Key Eligibility Criteria:
- PACC mutation*
- No prior therapy for metastatic disease and no prior EGFR-TKI
- Allows untreated brain metastases if clinically stable
- N=480

**Excludes Classical-like (ex. L861Q) unless compound with PACC*

1:1 *Randomized*

- **Firmonertinib 240 mg QD**
- **Investigator's Choice: osimertinib 80 mg or afatinib 40 mg**

Primary endpoint:
ORR (Interim Analysis) & PFS (Final Analysis) by BICR with RECIST v1.1

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