Molecular dynamics and mechanisms of acquired resistance in NSCLC patients with *EGFR* PACC mutations treated with firmonertinib

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CONCLUSIONS

- This is the first study evaluating detailed molecular dynamics and mechanism of resistance to TKI in patients with *EGFR* PACC mutations
- Firmonertinib demonstrates robust activity in *EGFR* PACC-mutant NSCLC as supported by rapid clearance of PACC ctDNA
- Resistance mechanisms in patients with *EGFR* PACC mutations may differ from those with the classical *EGFR*-mutant NSCLC
  - No on-target mechanisms of resistance, including *EGFR* C797S mutation, were detected suggesting that bypass mechanisms such as other RTK, MAPK and PIK3CA/mTOR alterations are the predominant mechanism of acquired resistance in these patients' tumors
- ctDNA monitoring may serve as an early biomarker of treatment benefit in patients with *EGFR* PACC mutations
- The efficacy of firmonertinib in 1L *EGFR* PACC-mutant NSCLC is currently being evaluated in the global Phase 3 study ALPACCA (NCT07185997)

BACKGROUND

- P-loop and αC-helix compressing (PACC) mutations comprise a structurally distinct subgroup of *EGFR* mutations in NSCLC (**Figure 1**)[1-3]
- There are limited treatment options for patients with *EGFR* PACC-mutant NSCLC[4-10]
- Firmonertinib is a once-daily oral, brain-penetrant, mutant-selective EGFR TKI, with a unique trifluoroethoxy side chain for broad activity[11,12]
- In the global phase 1b FURTHER (NCT05364073) study, a cohort of patients with *EGFR* PACC-mutant NSCLC were randomized to receive firmonertinib 160 mg (n=31) or 240 mg (n=29) QD[13]
  - In patients receiving 1L firmonertinib 160 mg (n=25) or 240 mg (n=22) QD, confirmed ORRs were 43% and 68%, respectively; median duration of response was not reached and 14.6 months, and median progression-free survival was 11.1 and 16.0 months
  - Here, we assessed molecular dynamics and mechanisms of acquired resistance in 1L patients

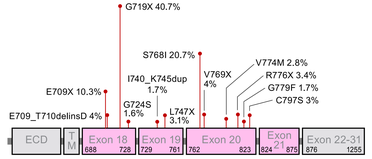


Figure 1. Frequency of the most common (>1%) *EGFR* PACC mutations among all PACC mutations in NSCLC[12]

METHODS

- Analysis of ctDNA from 1L patients with *EGFR* PACC mutations in FURTHER was conducted at baseline, during (at C3D1, after 6 weeks of treatment), and at the end of treatment using PredicineCARE NGS assay
  - Eligible patients could have a single or compound PACC mutation, based on local test results in tumor or blood
- Molecular response was assessed in patients with matched baseline and on-treatment (C3D1) liquid biopsy samples
  - Complete molecular response was defined as a clearance of PACC ctDNA
  - Deep responses were defined as ≥75% (but <100%) reduction in PACC ctDNA
- PFS was determined using Kaplan-Meier analysis measured from ctDNA landmark at C3D1 by ctDNA status
- Co-mutations at baseline and acquired mechanisms of resistance were evaluated in ctDNA
  - Mechanisms of resistance were evaluated in patients with progressive disease or those with clinical progression

RESULTS

Patients

- Of 44 patients treated with 1L firmonertinib who had detectable ctDNA in plasma (the biomarker evaluable population), *EGFR* PACC mutation in ctDNA was detectable in 28 and undetectable in 16 at baseline; demographic characteristics of the biomarker evaluable population were comparable with the overall PACC patient population in the FURTHER study (**Table 1**)

Table 1. Patient characteristics

Characteristic, % or median (range)	Biomarker evaluable population		All patients with PACC mutations	
	160 mg QD n=24	240 mg QD n=20	160 mg QD n=31	240 mg QD n=29
Age, years	67.5 (50-86)	68 (50–83)	65 (48-86)	68 (50–83)
Female	58	65	68	66
ECOG 0 | 1	33 | 67	30 | 70	29 | 71	28 | 72
Brain metastases (history or presence)	29	30	32	34
Current or former smoker	25	15	35	21
Asian | White | other race	79 | 21 | 0	75 | 15 | 10	71 | 23 | 6	72 | 21 | 7

Outcomes

- Among 28 patients with *EGFR* PACC mutation detected in ctDNA at baseline, *TP53* mutation occurred in 50%, *PIK3CA* mutation in 7%, and *EGFR* amplification in 10% (**Figure 2**)
- Among 25 patients with a matching C3D1 sample, 20 (80%) had a complete molecular response (**Figure 3**)
  - These patients had a higher confirmed ORR compared to those without complete molecular response (70% vs 20%; **Figure 4**) and longer mPFS (16.5 months [9.7–NA] vs 4.4 m [2.8–NA]; **Figure 5**)
- In 16 patients with undetectable PACC mutation at baseline, mPFS was not reached (95% CI, 11.0–NA months; **Figure 5**) and confirmed ORR was 38% (**Figure 4**)
- ctDNA from 13 patients was evaluated at progression (**Figure 6**)
  - No acquired *EGFR* C797S mutation or other *EGFR* alterations were detected (**Figure 7**)
  - Instead, bypass (EGFR-independent) mechanisms, including mutations in other RTKs, MAPK, and/or PI3K/mTOR pathways were detected as likely mechanisms of acquired resistance in *EGFR* PACC-mutated NSCLC treated with 1L firmonertinib

Figure 2. Baseline mutation profile of ctDNA in 1L PACC patients

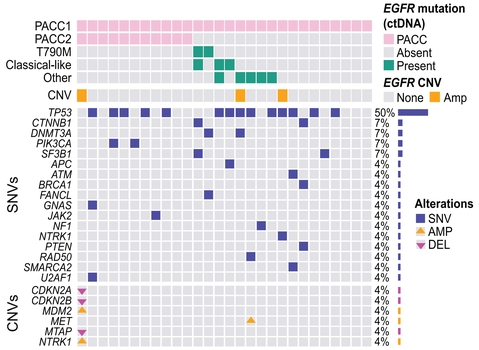


Figure 3. Molecular response for patients with matched baseline and C3D1 plasma samples

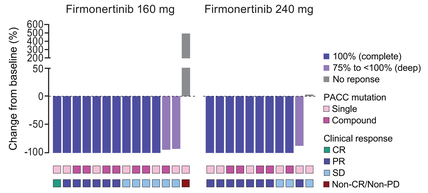


Figure 4. ORR by PACC ctDNA status

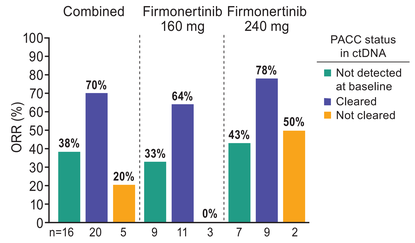


Figure 5. PFS by PACC ctDNA status

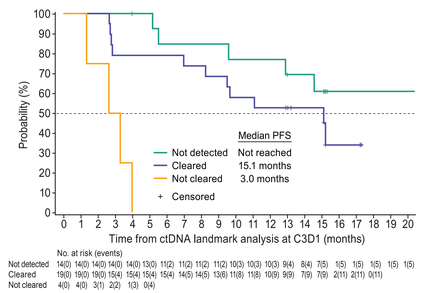


Figure 6. Investigator-assessed change in tumor size from baseline for patients assessed for acquired resistance (n=13)

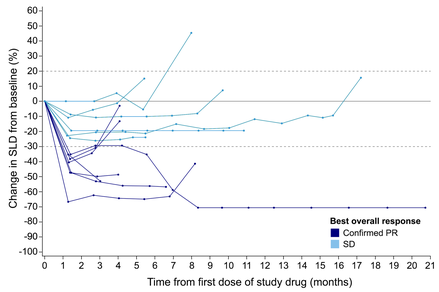
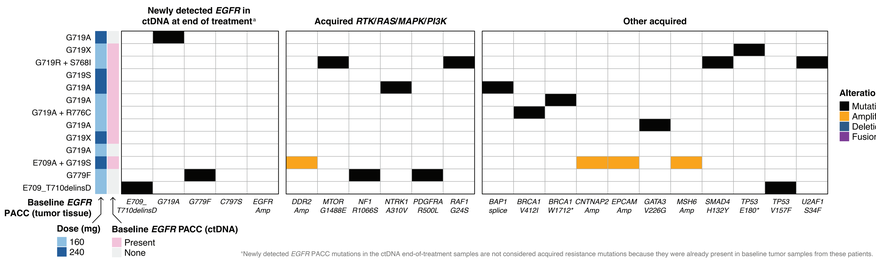


Figure 7. Acquired alterations in ctDNA at progression in patients with *EGFR* PACC mutations treated with firmonertinib



*Newly detected *EGFR* PACC mutations in the ctDNA end-of-treatment samples are not considered acquired resistance mutations because they were already present in baseline tumor samples from these patients.

Abbreviations

1L, first-line; Amp, amplification; C3D1, cycle 3 day 1; CNV, copy number variant; ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; MAPK, mitogen-activated protein kinase; mTOR; mammalian target of rapamycin; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; ORR, overall response rate; PACC, P-loop and αC-helix compressing; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PR, partial response; QD, once daily; RTK, receptor tyrosine kinase; SLD, sum of longest diameters; SD, stable disease; SNP, single nucleotide polymorphism; TKI, tyrosine kinase inhibitor; X, any amino acid.

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