Biomarker Analysis and Final Efficacy of Lorlatinib in Patients With ALK Positive Advanced Non-Small Cell Lung Cancer

The Pfizer Oncology Medical team is pleased to present findings from a phase 1/2 study that investigated *ALK* fusion variants and co-mutations to predict clinical responses to lorlatinib and identify potential resistance mechanisms through the analysis of collected samples.

Lorlatinib is a novel brain penetrant third generation anaplastic lymphoma kinase (ALK) and and c-ros oncogene 1 tyrosine kinase inhibitor (TKI), approved for patients with metastatic **non-small cell lung cancer** (NSCLC) whose tumors are **ALK-positive.**[1,2]

What is the significance of the study?

- **A study performed analysis of plasma and tissue samples collected from patients with ALK-positive NSCLC during the registrational phase II trial of lorlatinib.**[2]
- In patients treated with lorlatinib after the failure of a second-generation ALK TKI, the detection of ALK mutations were identified as a potential marker of response.[2]

By evaluating ALK fusion subtypes, co-mutations, and other correlates, **this study helped to predict clinical outcomes with lorlatinib and uncover possible resistance mechanisms**, using samples collected during the pivotal phase I/II trial.

Study Design[5]

Samples were collected from a **global phase I/II study**[4]:

- **Plasma sample:** collected at baseline and end of treatment
- **Tumor tissue sample:** collected at baseline

Data cut-off – 27 July 2023 (patients were followed for at least 5 years)

Total patients N =228

- EXP1 (treatment naïve) N= 30
- EXP2-3A (prior crizotinib ± chemotherapy) N= 59
- EXP3B-5 (≥1 prior ALK TKI ± chemotherapy) N= 139

Circulating tumor DNA (ctDNA)

The analysis was conducted with a validated, commercially accessible 73-gene next-generation sequencing (NGS) test (Guardant360, panel version 2.10).

Tumor tissue samples

The analysis was conducted with by NGS (TruSight Tumor 170 panel)

***ALK* fusion subtypes and mutations** and ***TP53* mutation status** were **correlated with clinical outcomes.**

Overall survival (OS) was defined as the time from first dose (cycle 1 day 1) to the date of death due to any cause.

Results[5]

ctDNA samples available at baseline for patients:

EXP1 (N= 28) | EXP2-3A (N= 55) | EXP3B-5 (N= 129

Presence of ctDNA led to shorter OS or lower survival probability at 72 months in the EXP1, EXP2-3A, and EXP3B-5 cohorts.

OS by ctDNA status at baseline

ctDNA status	EXP1 cohort (N=28)		EXP2-3A cohort (N=55)		EXP3B-5 cohort (N=129)	
Survival probability[a] at 72 months (95% CI),[b] %						
ctDNA detected	n=23	63.9 (40.5–80.1)	n=45	53.6 (37.2–67.5)	n=99	15.4 (8.4–24.4)
ctDNA not detected	n=5	100.0 (100.0-100.0)	n=10	67.5 (29.1–88.2)	n=30	30.4 (13.9–48.8)
OS,[a] median (95% CI),[c] months						
ctDNA detected	n=23	NR (51.0–NR)	n=45	NR (37.1–NR)	n=99	17.0 (13.7–23.9)
ctDNA not detected	n=5	NR (NR–NR)	n=10	NR (55.7–NR)	n=30	35.5 (24.7–65.9)

NR, not reached.[a]Estimated from the Kaplan-Meier curve. [b]Calculated using the normal approximation to the log-transformed cumulative hazard rate. [c]Based on the Brookmeyer and Crowley method.

In the EXP2-3A group, patients with short EML4::ALK fusion variant 3 had lower 72-month survival rates than those with longer variants (v1 and v2).

In the EXP1 and EXP3B-5 cohorts, similar OS benefit was observed regardless of the variant type.

OS in *EML4::ALK* fusion variants in ctDNA

	EML4::ALK fusion variant types	EXP1 cohort (N=28)	EXP2-3A cohort (N=55)	EXP3B-5 cohort (N=129)
Survival probability[a] at 72 months (95% CI),[b] %	v1 and v2	**58.3** (18.0–84.4) N=8	**50.0** (18.4–75.3) N=10	**NR** (NR–NR) N=29
	v3	**100.0** (100.0–100.0) N=3	**26.7** (4.1–57.9) N=9	**NR (NR–NR)** N=23
OS,[a] median (95% CI),[c] months	v1 and v2	**NR** (30.7–NR) N=8	**NR** (37.1–NR) N=10	**14.7** (6.5–20.4) N=29
	v3	**NR (NR–NR)** N=3	**28.1** (12.1–NR) N=9	**14.4** (8.0–18.0) N=23

Note: Only patients with *ALK* fusion detected were included. [a]Estimated from the Kaplan-Meier curve. [b]Calculated using the normal approximation to the log-transformed cumulative hazard rate. [c]Based on the Brookmeyer and Crowley method.

Presence of *TP53* mutation led to shorter OS or lower survival probability at 72 months in the EXP1, EXP2-3A, and EXP3B-5 cohorts

OS by *TP53* mutation status in ctDNA

	TP53 mutation status	EXP1 cohort (N=28)	EXP2-3A cohort (N=55)	EXP3B-5 cohort (N=129)
Survival probability[a] at 72 months (95% CI),[b] %	*TP53* positive	**50.0** (18.4–75.3) N=10	**43.5** (20.3–64.8) N=19	**NR** (NR–NR) N=44
	TP53 negative	**79.4** (48.8–92.9) N=15	**64.3** (42.6–79.6) N=28	**28.7** (17.2–41.2) N=59
OS,[a] median (95% CI),[c] months	TP53 positive	**NR** (22.8–NR) N=10	**45.2** (12.1–NR) N=19	**15.1** (8.6–19.2) N=44
	TP53 negative	**NR** (NR–NR) N=15	**NR** (52.5–NR) N=28	**22.7 (14.8–41.4)** N=59

Note: Only patients with cell-free DNA detected were included. aEstimated from the Kaplan-Meier curve. bCalculated using the normal approximation to the log-transformed cumulative hazard rate. cBased on the Brookmeyer and Crowley method.

Results from tumor tissue confirmed the results from ctDNA

Median OS

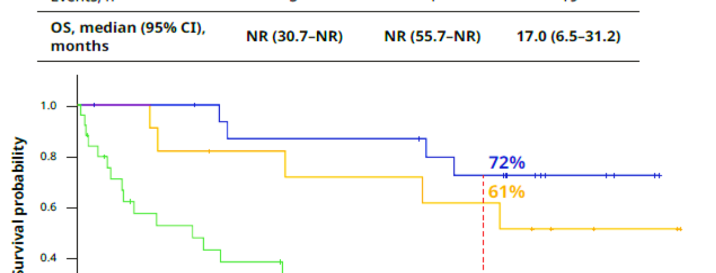
EXP2-3A cohort, patients with
- EML4::ALK v3 — 16 months
- EML4::ALK v1 and v2 — NR

EXP3B-5 cohort, patients with
- EML4::ALK v3 — 27 months
- EML4::ALK v1 and v2 — 17 months

OS in patients with EML4::ALK fusion variants in tumor tissue

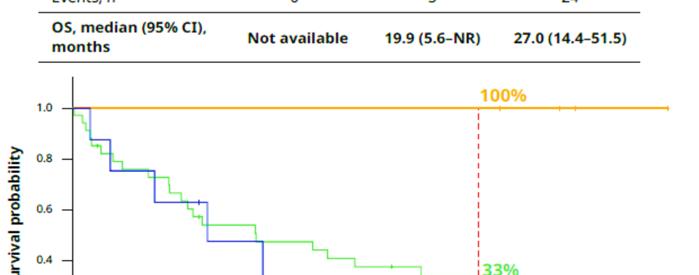
v1 and v2

	EXP1 cohort (n=11)	EXP2-3A cohort (n=17)	EXP3B-5 cohort (n=25)
Events, n	5	4	19
OS, median (95% CI), months	NR (30.7–NR)	NR (55.7–NR)	17.0 (6.5–31.2)



v3

	EXP1 cohort (n=4)	EXP2-~3A cohort (n=8)	EXP3B-5 cohort (n=33)
Events, n	0	5	24
OS, median (95% CI), months	Not available	19.9 (5.6–NR)	27.0 (14.4–51.5)

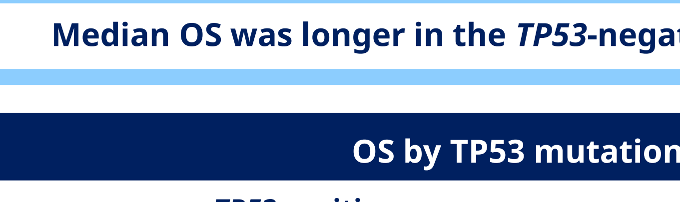


Median OS was longer in the *TP53*-negative than -positive groups in all cohorts

OS by TP53 mutation status in tumor tissue

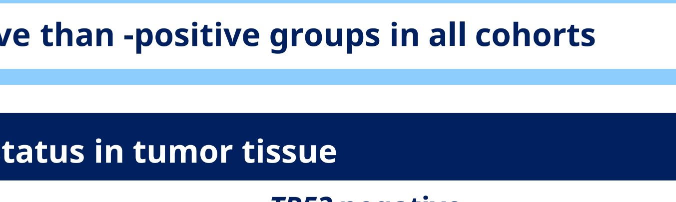
***TP53* positive**

	EXP1 cohort (n=6)	EXP2-3A cohort (n=15)	EXP3B-5 cohort (n=27)
Events, n	3	9	23
OS, median (95% CI), months	NR (16.3–NR)	24.4 (20.9–NR)	15.0 (6.4–19.2)



***TP53* negative**

	EXP1 cohort (n=16)	EXP2-3A cohort (n=24)	EXP3B-5 cohort (n=61)
Events, n	5	5	43
OS, median (95% CI), months	NR (62.5–NR)	NR (NR–NR)	27.1 (17.8–38.5)

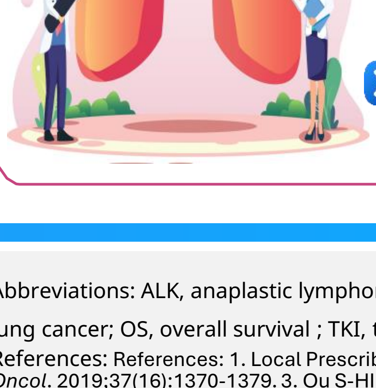


In patients with matched paired ctDNA samples, *ALK* single or compound mutations were absent in the EXP1 cohort but present in the EXP2-3A and EXP3B-5 cohorts.

Summary of resistance mechanisms

	EXP1 cohort (n=8)	EXP2-3A cohort (n=17)	EXP3B-5 cohort (n=64)
Resistance mechanisms at end of treatment, n (%)			
New single *ALK* mutation	0	1 (5.9)	1 (1.6)
ALK compound mutation	0	1 (5.9)	4 (6.3)
Bypass mechanism, n (%)			
MAPK pathway aberration	0	0	1 (1.6)
PI3K/MTOR/PTEN pathway aberration	0	0	2 (3.1)
RTK pathway aberration	0	0	5 (7.8)
Cell cycle pathway aberration	0	0	2 (3.1)
Other gene aberration, n (%)	2 (25.0)	6 (35.3)	15 (23.4)
Unknown, n (%)	6 (75.0)	10 (58.8)	40 (62.5)

Conclusion[5]



- In the final analysis of this phase I/II study with up to five years of follow-up, lorlatinib demonstrated **robust and prolonged OS in both treatment-naïve and previously treated patients** with ALK-positive advanced NSCLC, **regardless of ctDNA biomarker status**.
- Results from tumor **tissue analysis supported results observed with ctDNA.**
- **No *ALK* mutations were found in treatment-naive patients**, but new **single and compound mutations appeared** in a few patients **previously treated** with an ALK TKI.
- **Bypass mechanisms were identified in patients who previously received ≥1 ALK TKI**, with or without prior chemotherapy.

Abbreviations: ALK, anaplastic lymphoma kinase; ctDNA; circulating tumor DNA; EXP, expansion; NGS; next-generation sequencing; NSCLC, non-small cell lung cancer; OS, overall survival ; TKI, tyrosine kinase inhibitor; TP53, tumor protein p53

References: References: 1. Local Prescribing Document for Lorlatinib version 8 Pfizer India _LPDLOR072024. 2. Shaw AT, et al. *J Clin Oncol*. 2019;37(16):1370-1379. 3. Ou S-HI, et al. *J Thorac Oncol*. 2025;20(4):513-520. 4.Solomon BJ, et al. *Lancet Oncol*. 2018;19(12):1654-1667. 5. Bauer TM, et al. Biomarker Analysis and Final Efficacy of Lorlatinib in Patients With ALK-Positive Advanced Non-Small Cell Lung Cancer. Presented at IASLC 2025 World Conference on Lung Cancer, September 6-9, 2025, Barcelona, Spain. Poster P3.12.21.

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