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Baseline co-mutations and acquired resistance mechanisms in patients with EGFR-mutated advanced NSCLC: FLAURA2 exploratory analysis

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Objective

- To evaluate the impact of baseline co-mutations on PFS and OS, and investigate acquired resistance mechanisms, in patients receiving osi + plat–pem vs osi mono from the FLAURA2 study

Conclusions

- TP53 was the most common co-occurring mutation with EGFR; other co-mutations were rare
- Regardless of baseline TP53 mutation status, PFS and OS HRs numerically favored osi + plat–pem vs osi mono
- Osi + plat–pem may overcome intrinsic resistance driven by baseline EGFR signal bypass pathway alterations
- Detected acquired resistance alterations were similar across arms, with the exceptions of *EGFR C797S* and *RB1*, which were less common with osi + plat–pem vs osi mono
- No novel acquired resistance mechanisms were detected in either treatment arm

Plain language summary

Why did we perform this research?

- Osimertinib is a drug that blocks the activity of the mutated form of a protein called epidermal growth factor receptor (EGFR) on cancer cells, reducing their growth and ability to spread
- Osimertinib is recommended as the first treatment for patients with advanced non-small cell lung cancer (NSCLC) with an EGFR mutation. However, specific genetic mutations in cancer cells (resistance mechanisms) may be present before or occur during treatment, meaning osimertinib might not work as well and the cancer may spread, grow or get worse (also known as disease progression)
- FLAURA2 is a study designed to compare treatment with osimertinib and the addition of chemotherapy (platinum–pemetrexed) with osimertinib on its own, for patients with advanced NSCLC who have an EGFR mutation. This analysis builds on previous research of resistance mechanisms in blood and tumor samples from the start of treatment until disease progression, or until treatment had been stopped for another reason

How did we perform this research?

- Patients had blood samples taken on the first day of treatment, regularly during treatment and after disease progression, or after treatment had been discontinued for another reason
- This analysis explored how the presence of specific mutations in cancer cells before treatment influences the length of time that patients were alive without the cancer getting worse (progression-free survival) and the length of time patients were alive after starting treatment (overall survival)
- Additionally, blood samples were analyzed to see which mutations had occurred within the cancer cells during treatment in each patient; these mutations were also compared between patients who received osimertinib with the addition of platinum–pemetrexed vs those who received osimertinib alone to see how similar the results were

What were the findings of this research?

- The most commonly identified mutations in addition to EGFR were in the TP53 gene; other mutations were rare
- The progression-free and overall survival benefit of osimertinib with the addition of platinum–pemetrexed vs osimertinib alone appeared to be similar irrespective of mutations present in the TP53 gene before exposure to treatment
- Osimertinib with the addition of platinum–pemetrexed may overcome resistance mechanisms driven by mutations that bypass EGFR signaling that are present before exposure to treatment, although further research is needed
- This analysis showed that patients treated with osimertinib with the addition of platinum–pemetrexed or osimertinib alone have similar resistance mechanisms following treatment, with the exceptions of the *EGFR C797S* and *RB1* mutations, which were less common in patients receiving both osimertinib and platinum–pemetrexed. No new resistance mechanisms were found in patients who received osimertinib with the addition of platinum–pemetrexed compared with those who received osimertinib alone

What are the implications of this research?

- This analysis demonstrated that patients appear to benefit from the addition of platinum–pemetrexed to first-line osimertinib regardless of whether they had mutations in the TP53 gene before starting treatment
- Further, this analysis demonstrated that osimertinib with the addition of platinum–pemetrexed may overcome certain resistance mechanisms

Where can I access more information?

- More information on the FLAURA2 study can be found on ClinicalTrials.gov (NCT04035486); https://clinicaltrials.gov/study/NCT04035486; the previously published results of FLAURA2 are available online[1,2]

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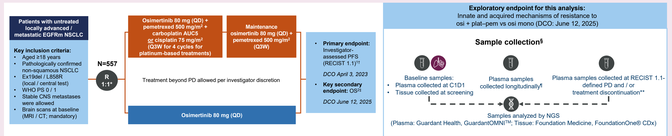
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Introduction

- Osimertinib is a third-generation, irreversible, CNS-active, oral EGFR-TKI that selectively targets EGFR-TKI sensitizing and EGFR T790M resistance mutations[3–11]
- In the Phase III, open-label, randomized FLAURA2 study (NCT04035486), first-line osi + plat–pem significantly improved PFS and OS vs osi mono in patients with EGFR-mutated advanced NSCLC (PFS HR 0.62; 95% CI 0.49, 0.79; p<0.001; planned final OS analysis HR 0.77; 95% CI 0.61, 0.96; p=0.02)[1,2]
- However, co-mutations may influence prognosis and treatment response, and patients can experience treatment resistance leading to PD[12,13]
- Preliminary results from a prespecified, exploratory analysis of acquired resistance mechanisms to osi mono and osi + plat–pem were presented previously[12,13]
- We report final results from an exploratory analysis evaluating the impact of baseline co-mutations on PFS and OS, and updated data on acquired resistance mechanisms

Methods

Study design



This exploratory analysis aimed to answer the following questions:

1. What are the most common mutations co-occurring with EGFR in plasma at baseline?
2. Does baseline TP53 status impact survival outcomes with osi + plat–pem or osi mono?
3. Do specific baseline functional pathway alterations impact survival outcomes with osi + plat–pem or osi mono?
4. Are there any additional acquired resistance mechanisms with osi + plat–pem vs osi mono?

*Stratified by race (Asian Chinese / Asian non-Chinese / non-Asian), EGFR mutation test (local / central) and WHO PS (0 / 1). †RECIST 1.1 assessment was performed at 6 and 12 weeks, then Q12W until RECIST 1.1–defined radiological PD. ‡Survival follow-up Q12W until data cut-off for the planned final OS analysis. §Due to local restrictions, no samples from mainland China were analyzed. ¶Every week for Cycle 1, Q3W until Cycle 7 Day 1, Q12W until Cycle 17 Day 1 and then Q12W until RECIST 1.1–defined PD or treatment discontinuation. **Collected until June 16, 2025.

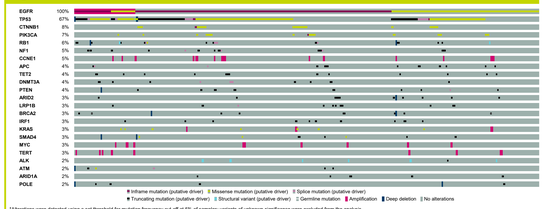
Results and interpretation

1. What are the most common mutations co-occurring with EGFR in plasma at baseline?

Baseline genomic landscape

- TP53 was the most common primary co-mutation across treatment arms (**Figure 1**)
- Other individual baseline co-occurring alterations were rare (each ≤8% across arms)
- Due to low incidence of co-mutations other than TP53, individual gene alterations were grouped by signaling pathways and the frequency of baseline co-occurring alterations in the DDR, Rb / cell cycle and EGFR signal bypass pathways are shown in **Table 1**

Figure 1. Baseline plasma co-mutations (n=353)*



*Alterations were detected using a set threshold for mutation frequency cut-off at 5% of samples; variants of unknown significance were excluded from the analysis.

Table 1. Baseline altered signaling pathways (n=353)

Signaling pathway group	Genes included	Osi + plat–pem, n (%) n=175	Osi mono, n (%) n=178
DDR	*ATM, ATR, BRCA1 / 2*	12 (3)	9 (3)
Rb and cell cycle	*RB1, CDKN2A / B, CCND / E1, ARID1 / 2*	25 (7)	31 (9)
EGFR signal bypass	*NKX2-1, MYC, CTNNB1, APC, PTEN, PIK3CA, ALK, KRAS, NF1, DNMT3A, ERBB2–4, FGFR 1–4, MET, TET2*	75 (21)	64 (18)

2. Does baseline TP53 status impact survival outcomes with osi + plat–pem or osi mono?

Baseline TP53 status and survival outcomes

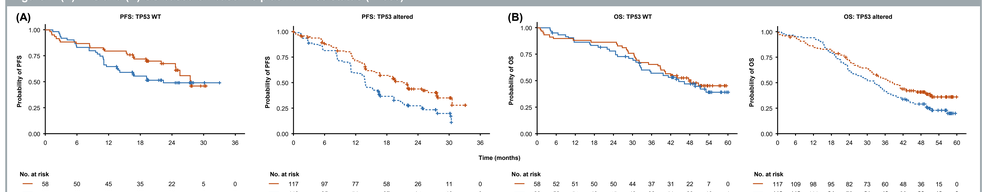
- Baseline TP53 status was prognostic for both PFS and OS: patients with altered TP53 had shorter PFS and OS vs WT TP53 across both treatment arms (**Figure 2**)
- Regardless of baseline TP53 status, PFS HRs and OS HRs numerically favored osi + plat–pem vs osi mono (**Figure 2**)

Supporting analysis

Impact of CHIP on TP53 status

- Analyses of PFS / OS by plasma (n=353) vs tissue (n=150) TP53 status showed similar trends; however, the sample size was larger for plasma-based analyses, resulting in smaller CIs (**Supplementary Figure S1; scan QR code**)
- The majority (84 / 108; 78%) of matched tissue and plasma samples were concordant for TP53 status
- CHIP therefore likely has a nominal impact on plasma TP53 status, supporting the use of plasma samples when assessing the relationship between TP53 status and survival outcomes

Figure 2. (A) PFS and (B) OS based on baseline plasma TP53 status (n=353)*



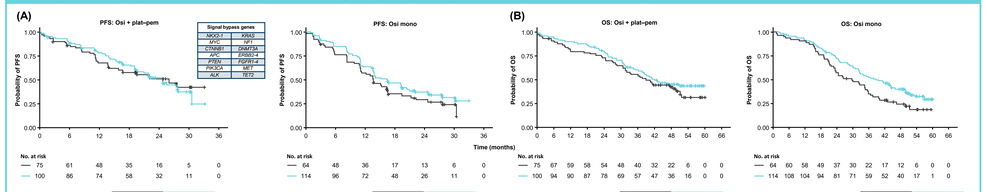
*HRs (95% CI) were calculated using a Cox proportional hazards Log-Log test.

3. Do specific baseline functional pathway alterations impact survival outcomes with osi + plat–pem or osi mono?

Baseline functional pathways alterations and survival outcomes

- Within the osi mono arm, PFS and OS were shorter in patients with vs without baseline EGFR signal bypass pathway alterations; this trend was less apparent in the osi + plat–pem arm (**Figure 3 / Supplementary Figure S2; scan QR code**)
- There were no clear associations between survival outcomes and the DDR or Rb / cell cycle pathways (**Supplementary Figure S2; scan QR code**)

Figure 3. (A) PFS and (B) OS based on baseline plasma EGFR signal bypass pathway alterations by treatment arm (n=353)*



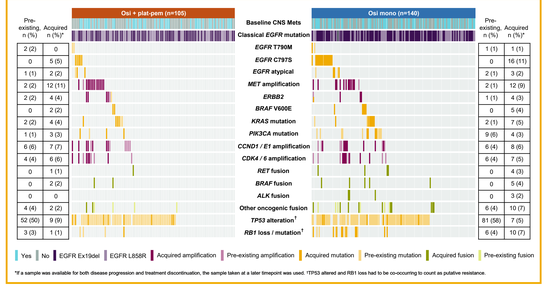
*HRs (95% CI) were calculated using a Cox proportional hazards Log-Log test.

4. Are there any additional acquired resistance mechanisms with osi + plat–pem vs osi mono?

Acquired resistance mechanisms

- In patients with detected baseline EGFR mutation ctDNA and plasma samples at PD / treatment discontinuation (245 / 557 [44%]), acquired alterations were generally similar across osi + plat–pem vs osi mono arms (**Figure 4**)
- In the osi + plat–pem arm, acquired *EGFR C797S* and *RB1* alterations were less common vs the osi mono arm (**Figure 4**)
- Overall, fewer patients had ≥1 potential resistance alteration with osi + plat–pem (56%) compared with osi mono (61%; **Figure 4**)
- The change in tumor mutational burden was similar across treatment arms (**Supplementary Figure S3; scan QR code**)

Figure 4. Acquired resistance mechanisms (n=245)



*If a sample was available for both disease progression and treatment discontinuation, the sample taken at a later timepoint was used. †TP53 altered and RB1 loss had to be co-occurring to count as putative resistance.

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Disclosures

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Abbreviations

AUC, area under the curve; C1D1, cycle 1 day 1; CHIP, Clonal Hematopoiesis of Indeterminate Potential; CI, confidence interval; CNS, central nervous system; CT, computed tomography; ctDNA, circulating tumor DNA; DCO, data cutoff; DDR, DNA damage response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; Ex19del, exon 19 deletion; HR, hazard ratio; Mets, metastasis; mono, monotherapy; MRI, magnetic resonance imaging; NGS, next-generation sequencing; NR, not reached; NSCLC, non-small cell lung cancer; OS, overall survival; osi, osimertinib; PD, progressive disease; PFS, progression-free survival; plat–pem, platinum–pemetrexed; Q12W, once every 12 weeks; Q3W, once every 3 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status; WT, wild type.

References

1. Planchard D, et al. N Engl J Med 2023;389:1935–1948
2. Jänne PA, et al. N Engl J Med 2026;394:27–38
3. Ramalingam SS, et al. N Engl J Med 2020;382:41–50
4. Cross DAE, et al. Cancer Discov 2014;4:1046–1061
5. Reuss JE, et al. J Clin Oncol 2025;43:e31–e44
6. Hendriks LEL, et al. Ann Oncol 2025;36(10):1227–1231
7. Soria JC, et al. N Engl J Med 2018;378:113–125
8. Mok TS, et al. N Engl J Med 2017;376:629–640
9. Wu YL, et al. N Engl J Med 2020;383:1711–1723
10. Wu YL, et al. J Clin Oncol 2018;36:2702–2709
11. Reungwetwattana T, et al. J Clin Oncol 2018;36:3290–3297
12. Yang JC, et al. J Thorac Oncol 2024;19(10):S101–S102
13. Lee CK, et al. Ann Oncol 2023; 34(4):S1669–S1670