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INTRODUCTION

- Recent phase III trials, including FLAURA2 and MARIPOSA, have demonstrated that upfront combination strategies can provide superior clinical outcomes compared with EGFR-TKI monotherapy in patients with advanced EGFR-mutant NSCLC.
- Notably, these benefits appear particularly relevant in patients with high-risk clinical or molecular features, such as baseline brain metastases, liver metastases, TP53 co-mutations, or other factors associated with early disease progression and poor outcomes with EGFR-TKI monotherapy.
- However, clinically actionable biomarkers to predict response heterogeneity and early progression remain limited.
- We evaluated a patient-derived cell (PDC)-based drug sensitivity platform as a functional biomarker to predict clinical outcomes and identify patients at high risk of early progression.

METHODS

PDC establishment

- Patient-derived cancer cells (PDCs) were established from tumor specimens obtained from patients with advanced EGFR-mutant NSCLC who had not previously received EGFR-TKI therapy.
- Following successful establishment and expansion, PDCs were subjected to high-throughput drug sensitivity testing using a panel of 60 anticancer agents, including clinically relevant EGFR-TKIs.
- Cell viability was assessed across a range of drug concentrations to generate dose–response curves for each PDC–drug combination. Drug sensitivity was quantitatively evaluated using the area under the dose–response curve (AUC), which integrates treatment responses across multiple drug concentrations and provides a continuous measure of overall drug sensitivity.

Statistical analysis

- Clinical outcomes following EGFR-TKI treatment, including best tumor response and progression-free survival (PFS), were evaluated in relation to the ex vivo sensitivity of PDCs to osimertinib, as quantified by the AUC.
- Early failure (EF) was defined as disease progression occurring within 6 months after initiation of EGFR-TKI therapy.
- Associations between osimertinib AUC and clinical outcomes were evaluated using analysis of variance (ANOVA) for comparisons across response groups and time-to-event analyses for PFS.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Osimertinib AUC significantly differed according to tumor response and showed a trend toward association with PFS.
- Patients with EF demonstrated markedly shorter median PFS compared to non-EF patients. EF was significantly associated with higher rates of brain metastasis and TP53 mutation.
- Osimertinib AUC was significantly higher in EF than in non-EF patients.
- Using a cutoff of -1.0, osimertinib AUC independently predicted EF after adjustment for brain metastasis and TP53 mutation.
- Multikinase inhibitors, such as sitravatinib targeting TAM receptors (TYRO3, AXL, MERTK) and VEGFR, showed a trend toward increased sensitivity in the EF group, suggesting potential alternative therapeutic vulnerabilities.

Future Direction for Research

- This approach may enable prospective identification of patients unlikely to benefit from EGFR-TKI monotherapy and support personalized upfront treatment strategies.

REFERENCES & ACKNOWLEDGEMENTS

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During the preparation of this work, the authors used ChatGPT in order to check grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Competing Interests

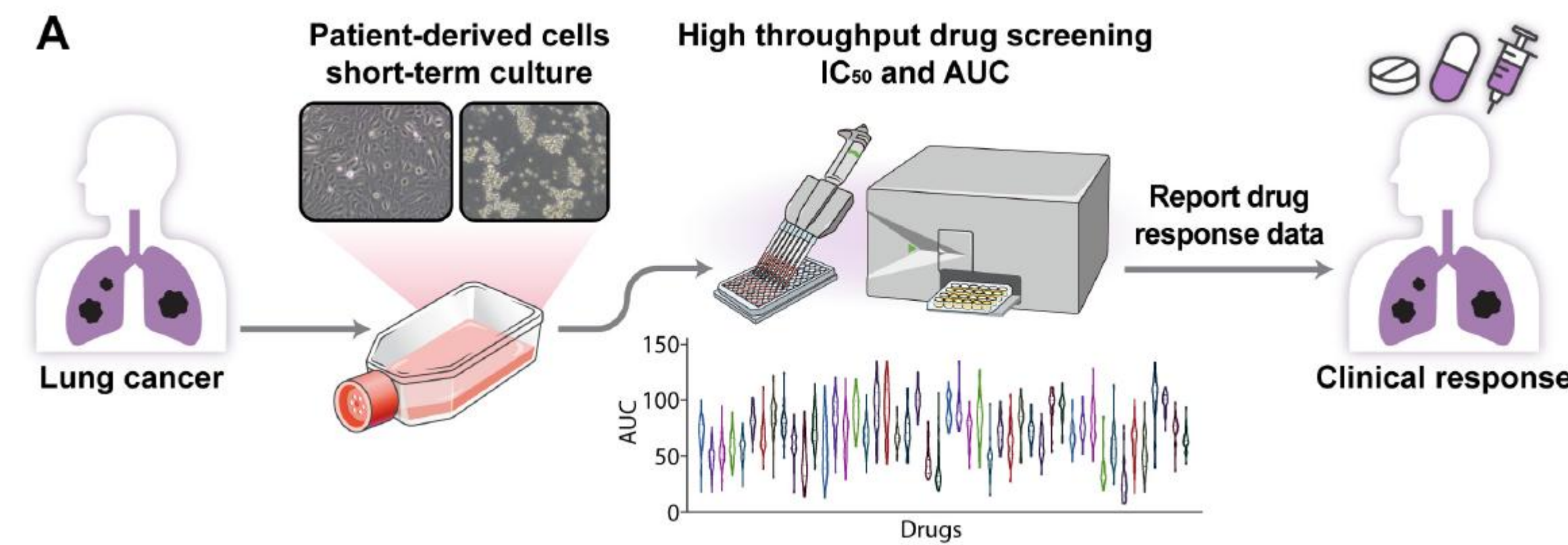
Youngjoo Lee declare no Competing Non-Financial Interests but the following Competing Financial Interests; Consulting fee: AstraZeneca, Roche, Merck, Yuhan, Bayer, and Amgen.

Reference

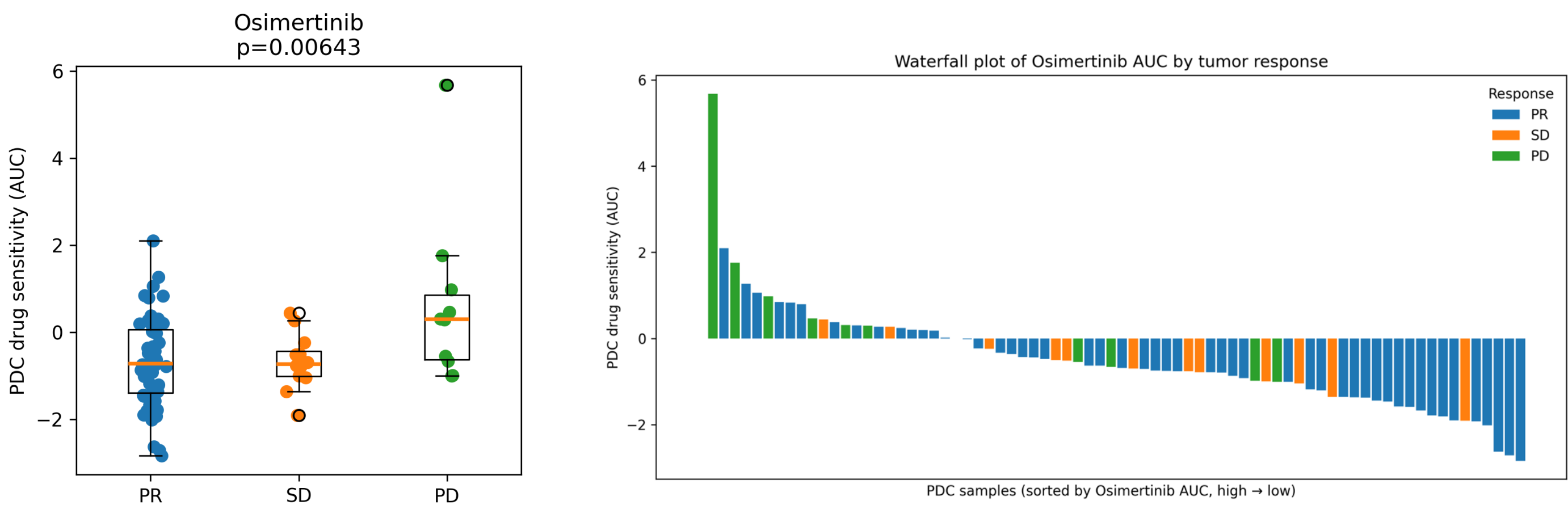
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RESULTS

PDCs establishment



PDCs sensitivity to osimertinib

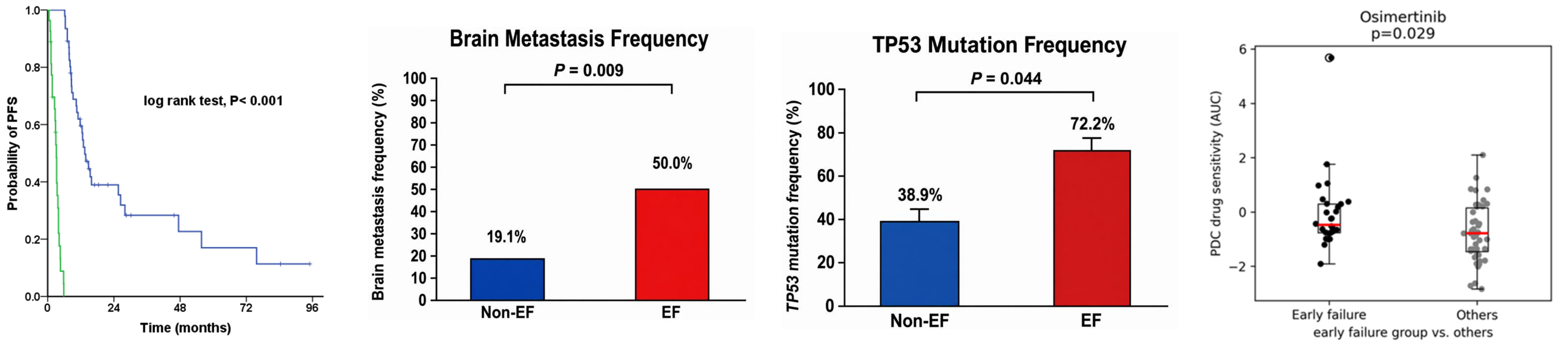


- Osimertinib AUC significantly differed according to tumor response (p=0.006) and showed a trend toward association with PFS (HR 1.27, 95% CI 1.00–1.61; p=0.055).

Patient characteristics

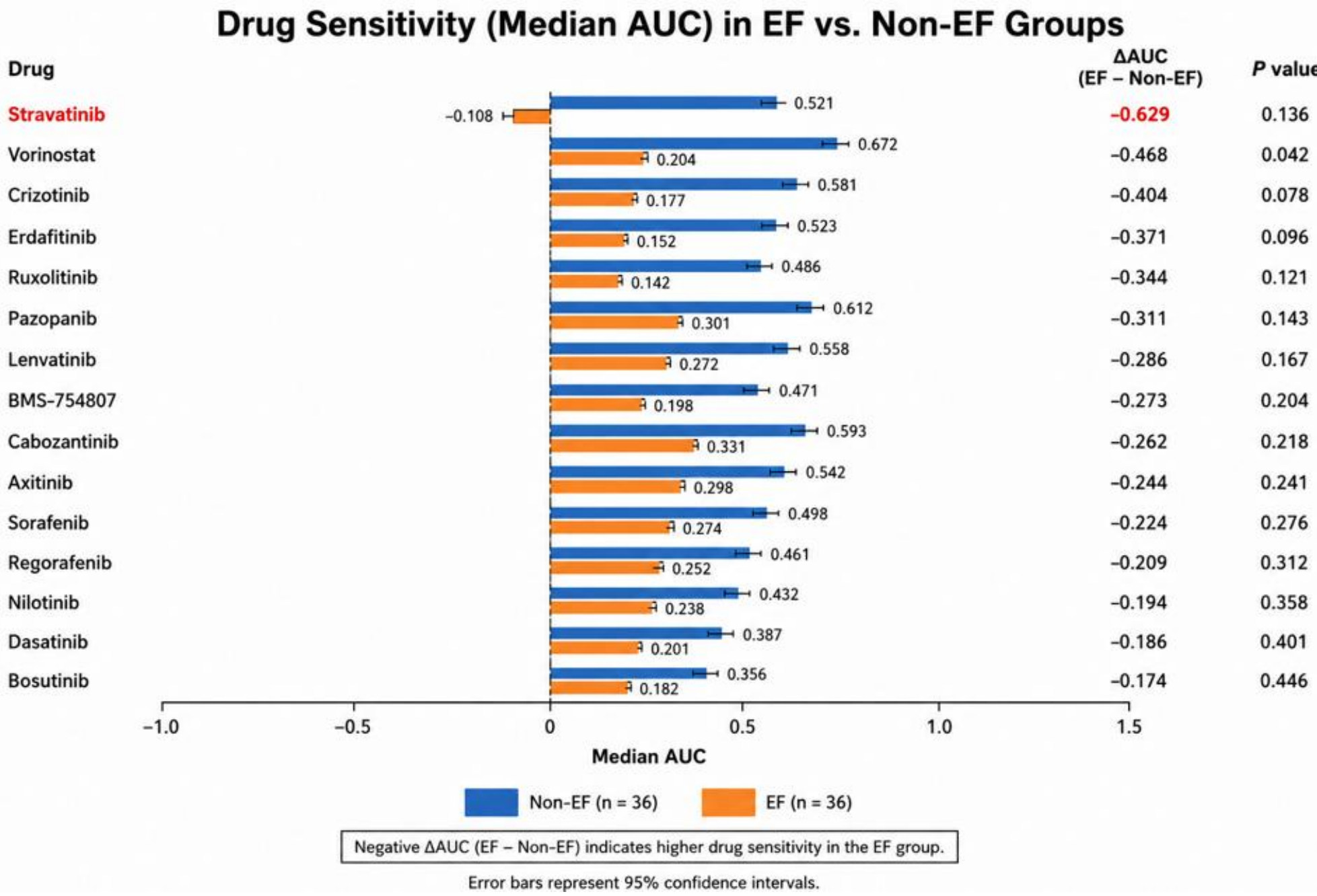
Patient characteristics and treatment outcomes	
Variable	Value
Total patients	74 (100%)
Age	
≥65	37 (50.0%)
<65	37 (50.0%)
Sex	
Male	28 (37.8%)
Female	46 (62.2%)
Smoking	
Never	46 (62.2%)
Ever	28 (37.8%)
ECOG	
0–1	52 (70.3%)
≥2	22 (29.7%)
Histology	
Adenocarcinoma	69 (93.2%)
Non-adenocarcinoma	5 (6.8%)
Brain metastasis	
Yes	23 (31.1%)
No	51 (68.9%)
EGFR-TKI	
1st/2nd generation	30 (40.5%)
3rd generation	44 (59.5%)
Best response	
PR	52 (70.3%)
SD	12 (16.2%)
PD	10 (13.5%)
median followup time	40.6 (95% CI, 11.6-69.5)
median PFS	8.6 (95% CI, 7.0-10.2)
median OS	26.9 (95% CI, 20.6-33.2)

Clinical outcomes and PDC sensitivity of Early failure group



- Patients with EF (n=28) demonstrated markedly shorter median PFS compared to non-EF patients (n=46) (3.16 vs. 13.45 months, p<0.001). EF was significantly associated with higher rates of brain metastasis (60.9% vs. 26.9%, p=0.005) and TP53 mutation (65.0% vs. 31.3%, p=0.044). Osimertinib AUC was significantly higher in EF than in non-EF patients (median -0.6 [-0.9 to 0.1] vs. -1.2 [-1.8 to -0.6], p=0.029).
- Using a cutoff of -1.0, osimertinib AUC independently predicted EF after adjustment for brain metastasis and TP53 mutation (OR 0.081, 95% CI 0.009–0.717, p=0.024).

Candidate drugs for PDCs of Early failure group



- Multikinase inhibitors, such as sitravatinib targeting TAM receptors (TYRO3, AXL, MERTK) and VEGFR, showed a trend toward increased sensitivity in the EF group, suggesting potential alternative therapeutic vulnerabilities.