

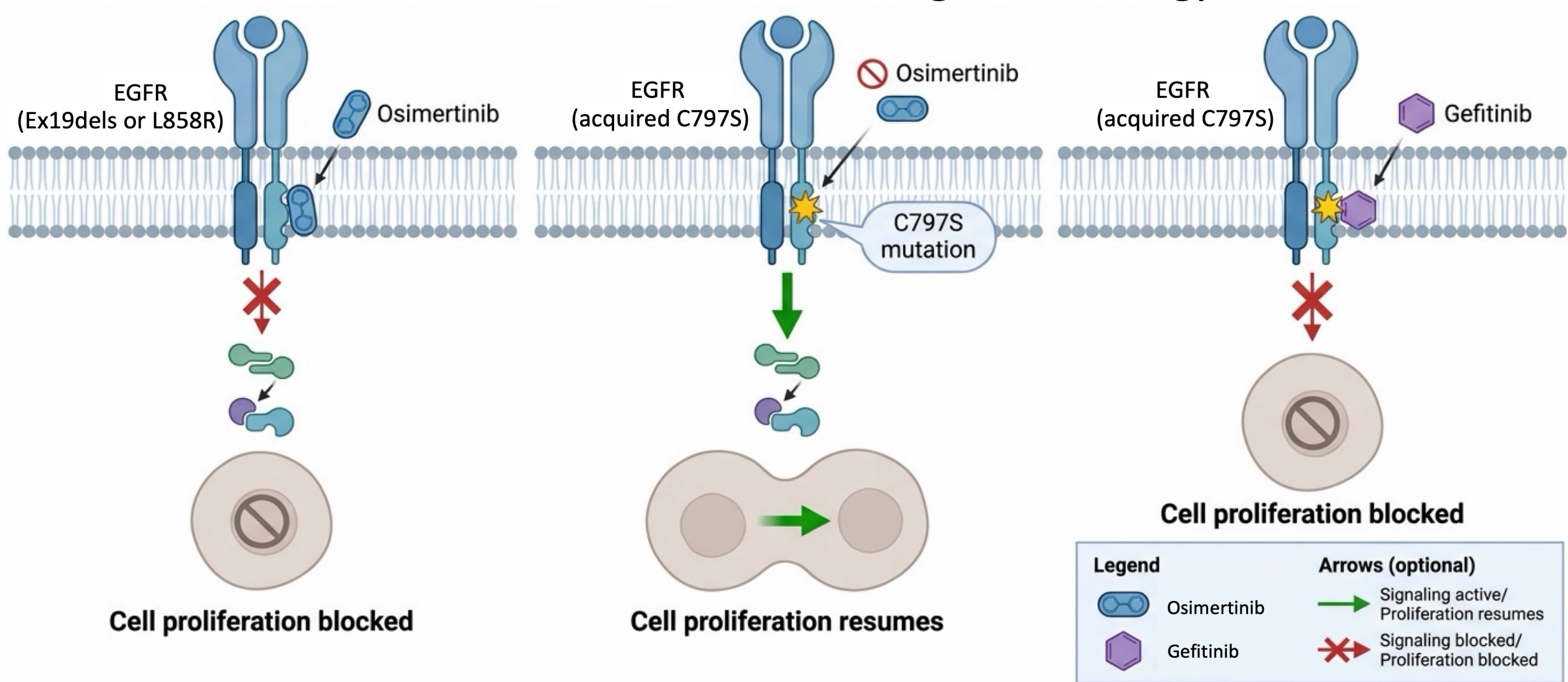
Precision medicine in EGFR-positive NSCLC acquiring p.C797S mutation after first line osimertinib: real-world data from ATLAS database

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BACKGROUND

The emergence of the C797S mutation is the most common on-target resistance mechanism to first-line Osimertinib in EGFR-positive NSCLCs. Although C797S-mutated cancer cells are resistant to Osimertinib, they retain sensitivity to Gefitinib. Real-world evidence for this biomarker-guided strategy remains limited.

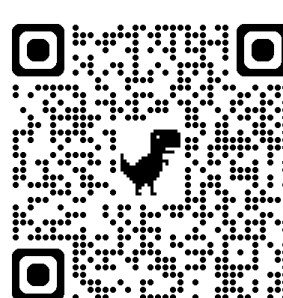
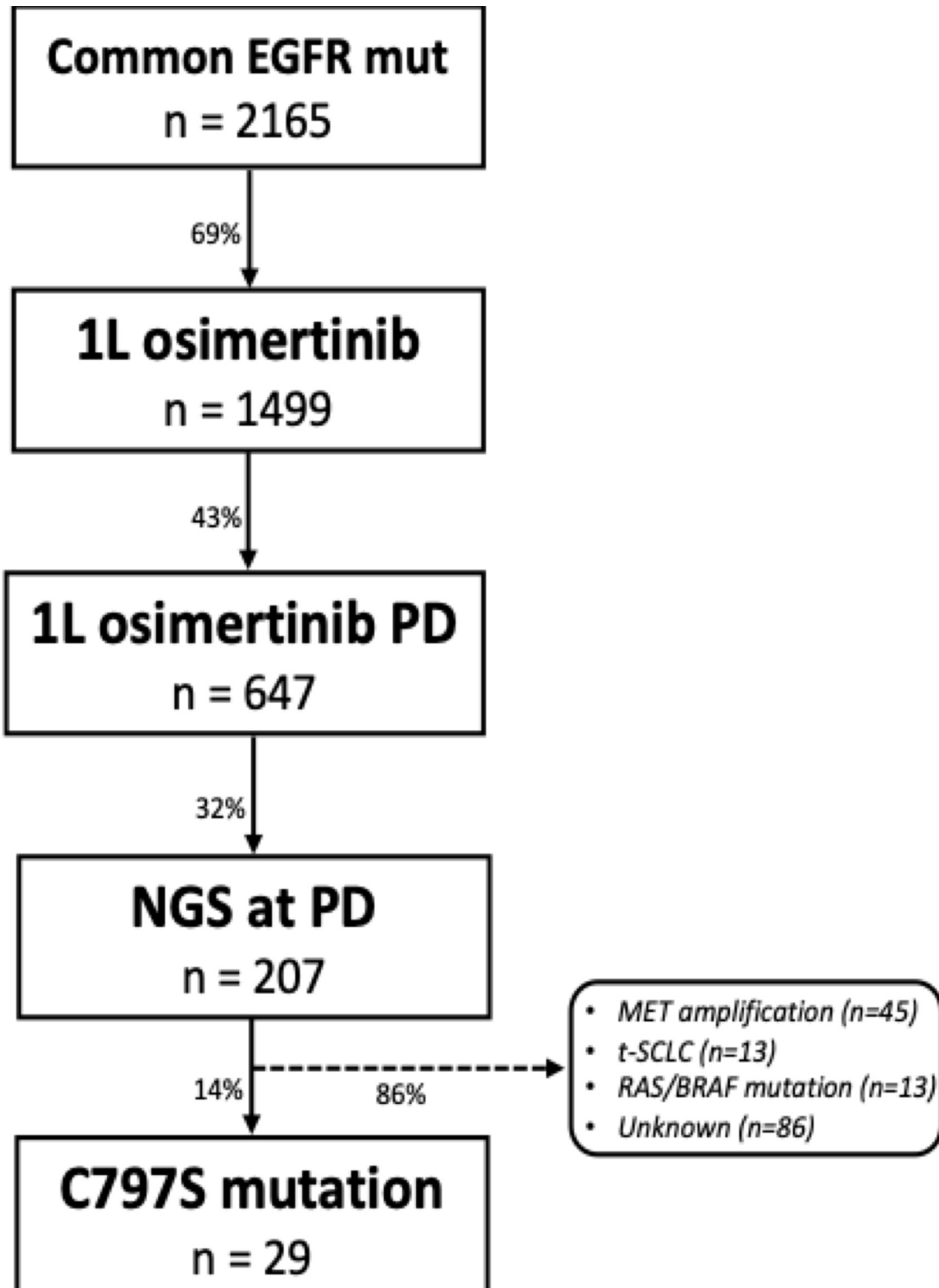


MATERIAL AND METHODS

We analysed clinicopathological characteristics of NSCLCs acquiring the C797S mutation in the ATLAS database and evaluated outcomes of gefitinib following first-line osimertinib failure.



ATLAS



Declaration of interest: Giovanni Farinea (giovanni.farinea@unito.it) declares no conflict of interest for this poster.

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RESULTS

Between December 2021 and January 2026, 208 out of 647 NSCLCs harbouring common EGFR mutations who progressed on first-line Osimertinib were molecularly profiled, identifying 29 cases (13.9%) with acquired C797S mutations.

Overall, 20 C797S-mutated patients (69%) were female, 17 (58%) never smokers and the median age was 61 years (range, 34-81). The most frequent site of progression was the lung (50%), followed by lymph nodes (29%). Exon 19 deletions were more frequent than L858R as the primary EGFR mutation (76% vs 24%), and baseline TP53 co-mutations were detected in 48% of cases.

C797S mutations emerged predominantly among osimertinib responders (82% of cases), exclusively as an acquired resistance mechanism. Median time to C797S-mediated resistance was 25.1 months (95%CI, 20.2–29.9), longer than for MET amplification (10.8 months; p<0.01) and other resistance mechanisms.

After osimertinib progression, 13 pts received Gefitinib with or without Osimertinib. The ORR was 46% (95%CI, 23–70%), the mPFS was 5.1 months (95%CI, 3.0–NA) and the mOS was 9.4 months (95%CI, 5.6-NA).

BASELINE CHARACTERISTICS

Median age (min-max)	61 (34-81)
Sex (%)	
• Male	9 (31)
• Female	20 (69)
ECOG PS (%)	
• 0-1	28 (96)
• > 1	1 (4)
Smoking History (%)	
• Positive	11 (38)
• Negative	17 (58)
• Not reported	1 (4)
Stage at diagnosis (%)	
• I-III	0 (0)
• IV	29 (100)
Metastatic site (%)	
• Pleural	16 (55)
• Brain	6 (20)
• Liver	6 (20)
• Bone	18 (62)
• Lymph Nodes	23 (79)
EGFR mutation (%)	
• Ex19 dels	22 (76)
• L858R	36 (24)
TP53 status (%)	
• Mutated	12 (48)
• Wild type	13 (52)
Osimertinib efficacy	
• ORR (%)	82 (IC95% 62-94)
• mPFS (months)	25.1 (IC95% 21.4-30.3)
• mOS (months)	45.8 (IC95% 36.6-NR)
MP at Osi PD (%)	
• Tissue alone	21 (72)
• Liquid Biopsy	5 (18)
• Both	3 (10)
Sites of progression (%)	
• Pleural	5 (18)
• Brain	5 (18)
• Liver	4 (14)
• Bone	7 (25)
• Lymph Nodes	8 (29)
• Lung	14 (50)

OSIMERTINIB ACQUIRED RESISTANCE MECHANISMS

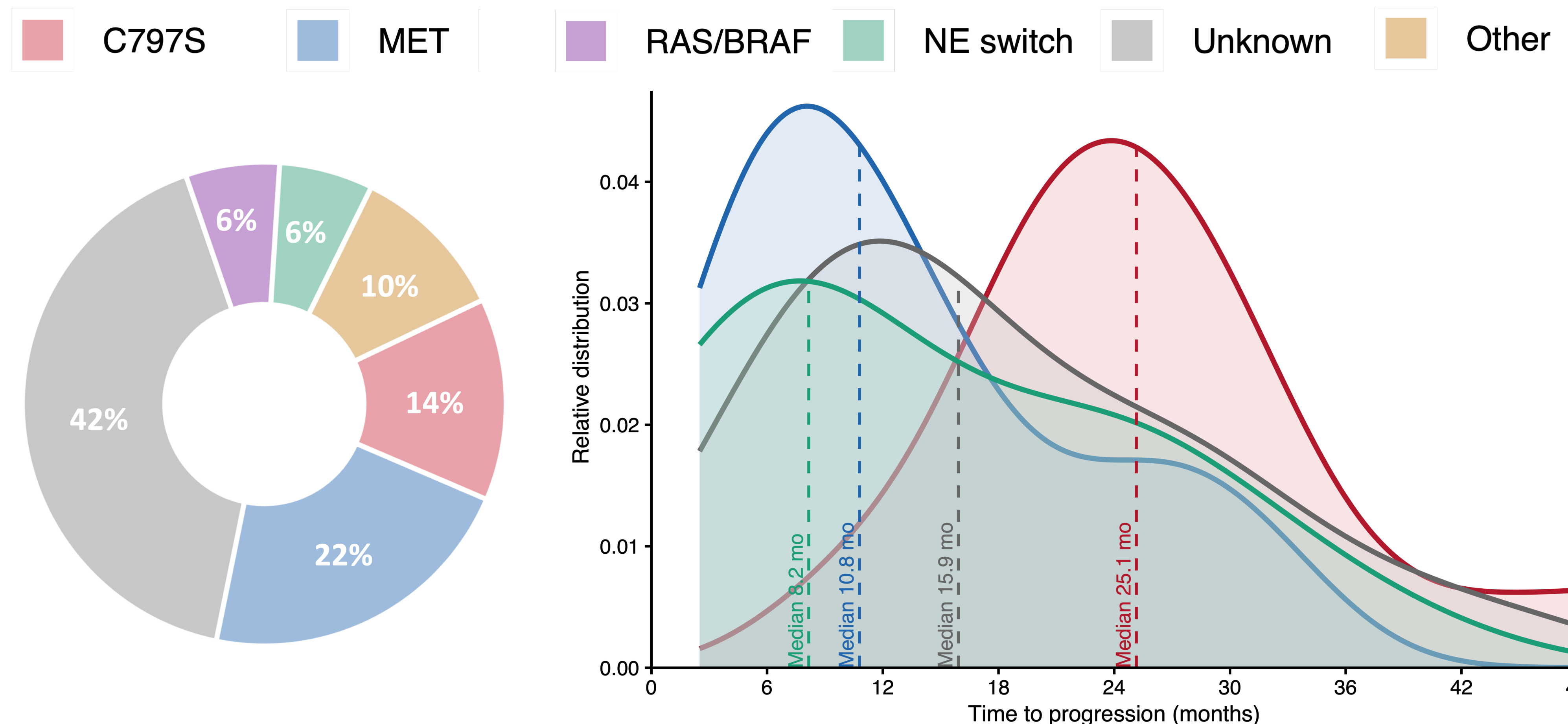


Figure 1. Incidence of acquired resistance mechanisms following first-line osimertinib.

Figure 2. Temporal distribution and time to emergence of acquired resistance mechanisms following first-line osimertinib.

GEFITINIB EFFICACY IN C797S-MUTATED NSCLCs

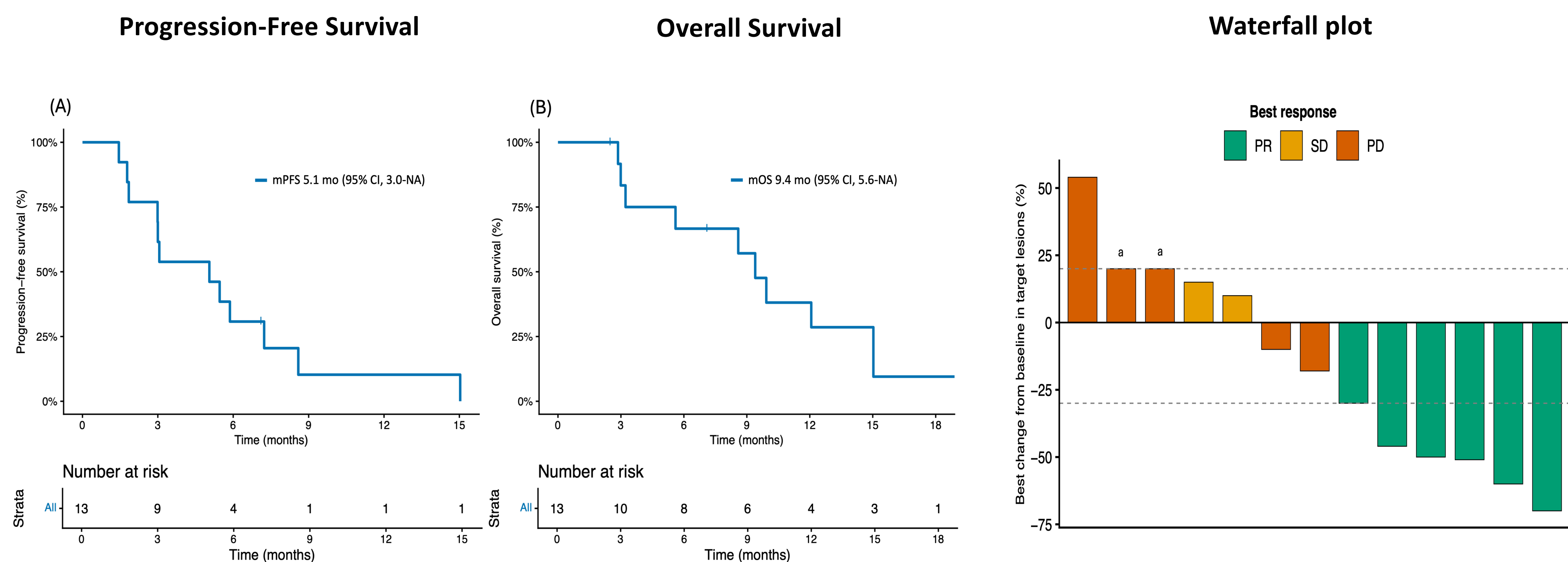


Figure 3. Kaplan-Meier curves showing median PFS and median OS of C797S-mutant patients treated with gefitinib ± osimertinib.

Figure 4. Waterfall plot of best percentage change from baseline in target lesions during gefitinib treatment.

CONCLUSIONS

EGFR C797S is a frequent, late-onset, and potentially targetable mechanism of resistance to first-line osimertinib. Gefitinib demonstrated modest clinical activity as a molecularly matched treatment for C797S-mutant NSCLCs and could be potentially considered a valid option, particularly for patients unsuitable for chemotherapy.

