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430P Resistance mechanisms causing first-line epidermal growth factor receptor-tyrosine kinase inhibitor treatment failure

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Background: Patients with epidermal growth factor receptor (EGFR) mutant advanced non-small cell lung cancer receiving first-line EGFR-tyrosine kinase inhibitor (TKI) inevitably developed disease progression after 9-13 months.

Methods: Before 1st January 2017, patients were investigated for resistance mechanisms upon failure of first-line EGFR-TKI by means of tissue re-biopsy or liquid biopsy to detect secondary T790M mutation in plasma cell free tumor-DNA (cfDNA) if tissue re-biopsy could not be performed. After that, liquid biopsy followed by tumor re-biopsy if cfDNA was negative for T790M mutation or if the patients had rapidly enlarging tumors.

Results: Of 45 patients who were tested, 31(68.9%) underwent tissue re-biopsy and 14 (31.1%) underwent liquid biopsy as the first investigation to determine the presence of T790M mutation. For the latter group, 4 (8.9%) subsequently also had tumor re-biopsy. T790M mutation was detected in 30 (66.7%) of the 45 patients. C-Met amplification was tested in 7 T790M mutation-negative patients for possible recruitment into a clinical trial with 4 showing c-Met amplification. Small cell lung cancer transformation and ALK rearrangement were detected in 2 (5.7%) and in 1 (2.9%) of the re-biopsy tissue specimens, respectively. The resistance mechanisms in 8 patients (17.8%) was unknown. In short, two-third (66.7%) of our patients had T790M mutation upon first-line EGFR-TKI failure; while another one-third (33.3%) failed first-line EGFR-TKI due to other resistance mechanisms. The demographic, clinical and treatment characteristics were equally distributed among these 2 groups of patients. (Table)

Conclusions: T790M mutation is the commonest acquired resistance mechanism causing first-line EGFR-TKI treatment failure. There was no difference in the clinical and treatment characteristics between patients with and without acquired T790M mutation as causes of resistance to first-line EGFR-TKI treatment.

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Table: 430P Demographic, clinical and treatment characteristics of 45 patients with first-line EGFR-TKI treatment failure

Characteristic	Total number of patients (n = 45)	Patients with T790M mutation (n = 30)	Resistance mechanism other than T790M (n = 15)	P value of univariate analysis*
Gender, No. (%) Male Female	18 (40.0) 27 (60.0)	13 (43.3) 17 (56.7)	5 (33.3) 10 (66.7)	0.780
Smoking history, No. (%) Never smoker Previous or current smoker	39 (80.0) 9 (20.0)	22 (73.3) 8 (26.7)	14 (93.3) 1 (6.7)	0.963
EGFR mutation subtype, No. (%) Exon 19 deletion Exon 21 L858R mutation Others Unsure	26 (57.8) 16 (35.6) 2 (4.4) 1 (2.2)	17 (56.7) 12 (40.0) 1 (3.3) 0	9 (60.0) 4 (26.7) 1 (6.7) 1 (6.7)	0.999
Treatment received, No. (%) EGFR-TKI EGFR-TKI followed by chemotherapy	34 (75.5) 11 (24.5)	22 (73.3) 8 (26.7)	12 (80.0) 5 (20.0)	0.484
Best tumour response, No. (%) Partial response Stable disease Progression of disease	38 (84.4) 6 (13.3) 1 (2.2)	27 (90.0) 2 (6.7) 1 (3.3)	11 (73.3) 4 (26.7) -	0.419
Progression-free-survival on first-line EGFR-TKI, months Median	13.0	13.0	11.7	0.538