Predictive value of ctDNA in patients with EGFR positive NSCLC receiving 3rd generation TKI

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BACKGROUND

The third generation TKI (osimertinib) according to AURA III trial results achieved longer PFS compared to standard platinum based chemotherapy in patient's resistant to 1st and 2nd generation TKIs due to T790M mutation (10.1 vs 4.4 months)[1]. The evolution of resistance profile during this therapy can be analyzed based on ctDNA[2-3].

RESULTS

From August 2016 to December 2018 22 patients with T790M positive progression were identified. 18/22 (81.9%) were women, 4/22 (18.1%) - men. The mean age was 61.2 years (50-75). Only 1/22 had a smoking history > 30 pack/years.

Figure 1. Sample flow

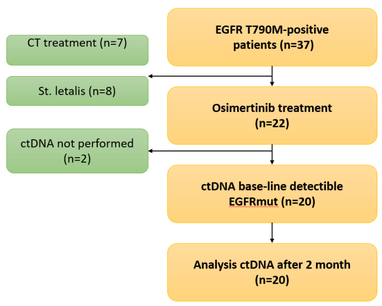


Table 1. Demographic and Clinical Characteristics of the Patients at base-line

Characteristic	Osimertinib (n=22)
Age – yr.	
Median	61.2
Range	50 – 75
Sex – no.(%)	
Male	4 (18.1)
Female	18 (81.9)
Smoking status – no.(%)	
Never	21 (95.5)
Former	1 (4.5)
EGFR mutation type – no.(%)	
ex19del	16 (72.7)
L858R	5 (22.8)
G719S + S768I	1 (4.5)
PFS on 1st line TKI, month	
Median	21.7
Range (95% CI)	10.8 – 53.3
Type of progression – no.(%)	
New metastases	13 (59.1)
Growth of previously identified metastases	9 (40.9)

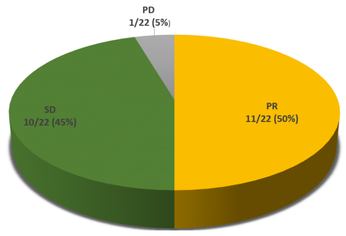
Primary activating mutations in EGFR gene were ex19del, L858R and G719S + S768I in 16, 5 and 1 patients respectively. Median PFS on the first line TKI was 21.7 months (CI 95%, 10.8 – 53.3). In 59.1% (13/22) progressive disease was characterized by the appearance of new metastases and in 40.9% (9/22) by the growth of previously identified metastases.

METHODS

In this study we included patients with metastatic EGFR mutated NSCLC, with a confirmed disease progression during treatment with 1st and 2nd generation TKIs and T790M who received osimertinib 80 mg daily. Before the treatment and then every 2 months, whole blood was taken, for qualitative assessment of ctDNA dynamics by RT-PCR. The aim of the study was to assess the relationship between the disappearance of T790M+ ctDNA and the time to progression on osimertinib.

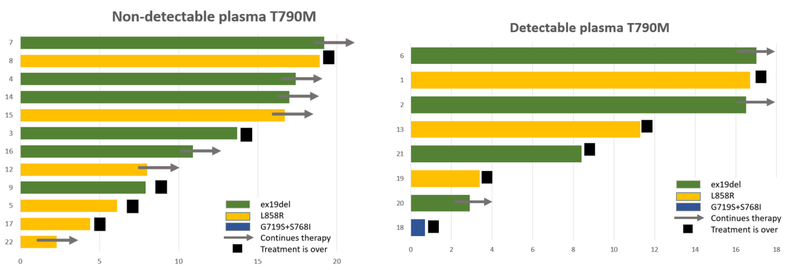
RESULTS

Figure 2. Response rate on osimertinib



22 patients were evaluable for response. PR and SD were achieved in 11/22 (50%) and 10/22 (45.5%) respectively.

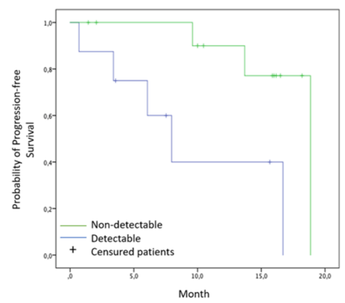
Figure 3. Duration of therapy in patients with detectable and non-detectable plasma T790M after 2 month of osimertinib



RESULTS

Median PFS was in a whole group 16.7 months (CI 95%, 11.4 - 22.0). T790M in ctDNA was negative after 2 months of osimertinib treatment in 12/22 patients. Median PFS was 18.9 months (CI 95%, 14.8–19.7) in patients with undetectable T790M in ctDNA after 2 month of therapy compared to 8.0 months (CI 95%, 4.2 – 11.8) in patients remaining ctDNA T790M positive. No clinical factors were associated with the disappearance of ctDNA by statistical analysis.

Figure 4. PFS in patients with detectable and non-detectable plasma T790M after 2 month of TKI 3rd generation



	DETECTABLE (n=8)	NON-DETECTABLE (n=12)
mPFS, month (95% CI)	8.0 (4.2, 11.8)	18.9 (14.8, 19.7)
p-value	p=0,015	

CONCLUSIONS

The disappearance of T790M+ ctDNA after 2 months of 2nd line osimertinib therapy might predict greater PFS.

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