Abstract #352 57P: Acquired Concurrent EGFR T790M and Driver Gene resistance from EGFR-TKIs hampered osimertinib efficacy in Advanced Lung Adenocarcinoma

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Background

- The resistance mechanisms to EGFR-TKIs are inevitable and heterogeneous.
- Secondary T790M mutation was the most frequent acquired resistance mechanism to early-generation EGFR-TKIs and osimertinib was the standard second-line therapy.
- Driver gene alterations like ALK, ROS1, and RET were increasingly observed in resistance mechanisms.
- Additionally, driver gene resistance overlaps with EGFR T790M accounted for 4%-8% in patients resistant to prior early-generation EGFR-TKIs. However, no good consensus was formulated in such circumstances.

Methods

- We searched the lung cancer database of the Second Xiangya Hospital and screened for EGFR-mutant NSCLC patients who developed secondary T790M positive after early-generation EGFR-TKI.
- Further, Patients who had acquired T790M cooperating with driver gene resistance, such as alterations of ALK, ROS1, MET, HER2, RET, KRAS were included.
- Meanwhile, extensive literature reviews in PubMed were conducted to identify characteristics of concurrent EGFR T790M and diver gene resistance. The efficacy and prognosis were evaluated based on the RECIST v1.1.

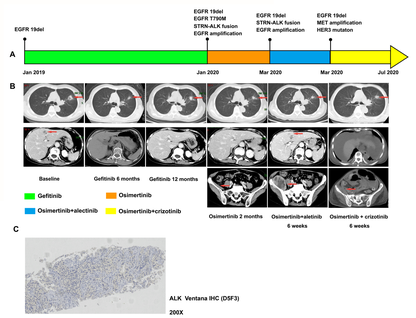

Figure 1. A: Timer shaft of gene testing and treatments measurement of Patient 1; B: Computed tomographic images of primary lung lesion, liver, and iliopsoas mass metastases; C: ALK Ventana immunohistochemistry (D5F3) presented with negative.

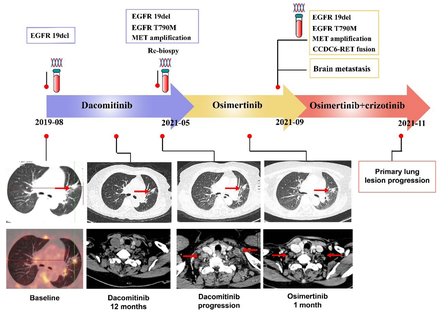

Figure 2. Timer shaft of gene testing and treatments measurement of Patient 2, and the computed tomographic images of primary lung lesion, lymph nodes metastases.

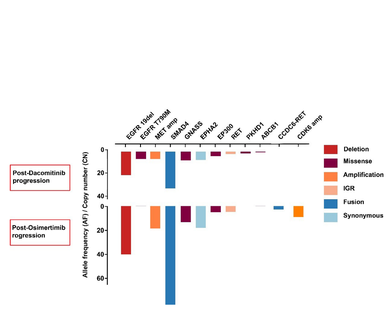

Figure 3. The comparison of resistance mechanisms of genetic alterations between Dacomitinib-progression and Osimertini-progression in patient 2.

Table 1. Clinicopathological characteristics of concurrent EGFR-T790M and driver gene resistance NSCLC patients

Case No.	Age	Sex	Smoking history	Pathology	staging	Baseline driver gene	First-line therapy	Resistance mechanisms	Second-line therapy	Best response [a]	PFS (mo)
1	60	M	Never	ADC	IV	EGFR L858R, HER2 amp	Gefitinib	EGFR T790M, HER2 S310Y mutation, HER2 amp	Osimertinib and trastuzumab	SD	4
2	57	M	Yes	ADC	IV	EGFR L858R	Icotinib	EGFR T790M, HER2 V777L mutation, HER2 amp	Osimertinib	PD	1
3	62	M	N/A	ADC	IV	EGFR L858R	Gefitinib, afatinib	EGFR T790M, HER2 amp	Osimertinib	SD	3
4	69	M	Yes	ADC	IV	EGFR L858R	Gefitinib	EGFR T790M, KRAS G12V	Chemotherapy	PD	2[b]
5	72	M	N/A	ADC	IV	EGFR 19del	Gefitinib	EGFR T790M, KRAS G12V	Osimertinib	PD	3
6	76	F	Yes	ADC	IV	EGFR 19del	Gefitinib	EGFR T790M, STRN-ALK, EGFR amp	Osimertinib and alectinib	SD	4
7	72	F	Never	ADC	IV	EGFR 19del	Dacomitinib	EGFR T790M, MET amp	Osimertinib	SD	3

a: The best response and PFS of second-line therapy. b: The patients had an OS of 2 month

Abbreviations: M, male; F, female; ADC, adenocarcinoma; N/A, not available; PR partial response; SD stable disease; PD, progression disease; PFS, progression-free survival; mo, months.

Results

- 216 EGFR-mutant NSCLC patients who received early-generation EGFR-TKI were identified in the database and 105 patients had detailed gene testing after disease progression.
- 57.1% (65/105) patients developed into secondary EGFR T790M mutation and 61.5% (40/65) patients were identified by the next-generation sequencing.
- Two (2.0%) patients cooperated with MET amplification and ALK Fusion. One patient had acquired EGFR T790M, STRN-ALK fusion, and EGFR amplification after gefitinib progression and was shortly resistant to osimertinib with MET amplification.
- The other patient developed to acquired EGFR T790M and MET amplification post-dacomitinib and acquired CCDC6-RET fusion after 4-month osimertinib treatment.
- Five published cases of co-existence of EGFR T790M and HER2 amplification or KRAS G12X were identified (Table 1).
- The presented 7 cases showed median progression-free survival (PFS) of 3 months and did not benefit from osimertinib monotherapy.

Conclusions

- Patients with concurrent alterations of EGFR T790M and driver gene resistance had poor outcomes from osimertinib.
- Additionally, subsequent new bypass activations were possible resistance mechanisms to second-line osimertinib.
- The T790M accompanying diver gene resistance will be a new subtype after EGFR-TKIs progression and needs effective treatment options.

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Disclosure statement: *The authors declare no conflicts of interest.*