Ultrasonensitive detection of EGFR T790M mutation by droplet digital PCR (ddPCR) in TKI naïve NSCLC harboring EGFR mutation: results of the nationwide program Biomarkers France of the Cooperative Thoracic Intergroup (IFCT)

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Background

The presence of EGFR T790M mutation accounts for > 50% of the acquired resistance to EGFR-TKIs. Earlier studies performed in small cohorts suggest that T790M was also detected in TKI naïve NSCLC, with discordant results.

Methods

We re-analyzed 366 EGFR mutated patients of the IFCT Biomarkers France program (1/2) with available tumor DNA that were finally treated by EGFR-TKIs. ddPCR was performed with QX200 system (BIORAD, Hercules, USA). We used restriction enzyme (Hae III) to improve ddPCR profiles for FFPE DNA analysis. All samples were tested in duplicate (in two independent wells). A cohort of FFPE colon cancer DNA (n=30) was used as negative controls. Theoretical limit of detection was 0.005% and analytical sensitivity was 0.03%. Discordant replicates and false positive results were excluded.

Conclusions

Ultrasonensitive detection of EGFR T790M mutation is related in 9% of EGFR mutated TKI naïve NSCLC patients and has a negative prognostic value for T790M mutation FA over 10%, but no impact on EGFR-TKI response. New strategies of therapies assessed therapies could be tested in such populations.

Background

The frequency of pre-treatment T790M mutation: 23/26% (9).

Methods

Results

Conclusions

Acknowledgements: all patients, clinicians and biologists of the Biomarkers France project.

Disclosure: none

Funding: IFCT, AstraZeneca. Funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Table 1: Patients’ characteristics (n=233)

<table>
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<th>T790M status</th>
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<td>T790M negative</td>
<td>37 (21.3%)</td>
<td>108 (62.1%)</td>
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FA

| 0 | 37 (21.3%) | 108 (62.1%) | 29 (16.7%) | 0.007 |
| 0.01-0.1% | 0 | 3 (60.0%) | 1 (20.0%) | |
| 0.1-1% | 0 | 3 (70.0%) | 1 (20.0%) | |
| 1-10% | 0 | 3 (42.9%) | 1 (20.0%) | |
| ≥ 10% | 0 | 1 (25.0%) | 1 (20.0%) | |

Table 2: Correlation between T790M mutation fractional abundance (FA) and time of progression (n=194)

- Slow progression: PFS ≤ 3 months; classical progression: PFS 3-6 months; rapid progression: PFS > 6 months

Figure 1: median overall survival (OS) and progression-free survival (PFS) according to T790M mutation status.

Figure 2: 2D representation of a T790M mutation positive case.

Figure 3: repartition of T790M mutation FA.

In multivariate analysis, OS was associated with the presence of a pre-treatment T790M mutation with FA between 1-10% (HR 3.5; CI 0.96-6.5, p = 0.04) or FA ≥ 10% (HR 16; 5.95 CI 4.7, p < 0.0001); PFS was associated with the presence of a pre-treatment T790M mutation only with FA ≥ 10% (HR 21; 5.95 CI 5.5, p = 0.001).

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