Background and objective

Osimertinib is the new standard of care in epidermal growth factor receptor (EGFR)-mutated non-pretreated advanced non-small-cell lung cancer (NSCLC). The MELROSE study, a French multicentric, open label, phase II trial (NCT03865511) was designed to identify resistance mechanisms at the time of disease progression in treatment-naive advanced EGFR-mutated NSCLC. All patients received osimertinib (80 mg/dL). Tumor assessment was performed every 3 months, with brain and thoracoabdominal CT-scan (RECIST 1.1). Blood was collected in Streck tubes at admission and after 7 days of treatment. Cell free DNA was extracted from plasma (3 mL) using the Maxwell RSC LV baseline and after 7 days of treatment. EGFR-L858R and/or exon 19 deletion (NSCLC). All patients received osimertinib (80 mg/dL). Tumor assessment was performed every 3 months, with brain and thoracoabdominal CT-scan (RECIST 1.1). Blood was collected in Streck tubes at admission and after 7 days of treatment. Cell free DNA was extracted from plasma (3 mL) using the Maxwell RSC LV kit (Promega). EGFR mutations were quantified by digital PCR using a Naica system (Stilla Technologies), and the IDEGFR SENS! detection kit (IDSolutions).

Methods

The MELROSE trial enrolled 150 patients with treatment-naive advanced EGFR-mutated (L858R or exon 19 deletion) NSCLC. All patients received osimertinib (80 mg/dL). Tumor assessment was performed every 3 months, with brain and thoracoabdominal CT-scan (RECIST 1.1). Blood was collected in Streck tubes at admission and after 7 days of treatment. Cell free DNA was extracted from plasma (3 mL) using the Maxwell RSC LV kit (Promega). EGFR mutations were quantified by digital PCR using a Naica system (Stilla Technologies), and the IDEGFR SENS! detection kit (IDSolutions).

Key findings

- The presence of ctDNA at baseline was associated with the presence of liver metastases (p=0.001).
- High baseline ctDNA concentrations were associated with worse PFS, and were an independent prognostic factor for PFS in multivariate analysis (p=0.014).
- PFs was correlated with the presence of ctDNA after 1 week on osimertinib (p=0.009 ; HR 1.971 ; 95% CI 1.187-3.272).
- Patients presenting a significant increase in ctDNA concentration between baseline and d7 had a greatly reduced PFS (3.3 months) as compared to patients with a significant decrease in ctDNA concentration (19.6 months) (p=0.002 ; HR 8.685 ; 95% CI 1.581-4.761).

Results

Patients

<table>
<thead>
<tr>
<th>Patients enrolled</th>
<th>Patients analyzed</th>
<th>Missing data</th>
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<tr>
<td>n = 150</td>
<td>n = 138</td>
<td>n = 4</td>
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PFS of the entire population

- Median PFS: 10.6 months
- 1-year PFS: 69.8%
- 2-year PFS: 44.9%

ctDNA detection

Baseline vs. Day 7

- Detectable ctDNA
- Undetectable ctDNA

Examples of dPCR analysis. Patient 12-026 at baseline (left panel), patient 07-023 at day 7 (right panel)

Conflicts of interest (MG Denis) : Advisory boards and lectures (AstraZeneca, Takeda, AMGEN, Pfizer), research funding (AstraZeneca, Takeda, BluePrint Medicines)

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