Plasma genotyping to predict treatment benefit in patients with NSCLC
15 April 2016

The benefit of plasma genotyping to predict treatment benefit in patients with non-small-cell lung cancer (NSCLC) is confirmed in three studies presented today at the European Lung Cancer Conference (ELCC) 2016 in Geneva, Switzerland.1 Researchers however warned that plasma tests are unlikely to fully replace tissue biopsies.

Patients with NSCLC are tested for epidermal growth factor receptor (EGFR) mutations which indicate their suitability for targeted EGFR tyrosine kinase inhibitor (TKI) therapy. Tissue biopsies are the gold standard but are not possible in around 20% of NSCLC patients. Plasma is a potential alternative for EGFR mutation analysis through extraction of circulating tumour DNA (ctDNA).

The primary results of the ASSESS trial, presented at ELCC 20152, demonstrated that ctDNA is suitable and feasible for EGFR mutation analysis in real-world practice. The analysis presented today examined whether patient disease or demographic characteristics influenced the detection of EGFR mutations in plasma. There was increased sensitivity of EGFR mutation detection in plasma associated with increasing number and severity of metastases. EGFR mutation detection in plasma was also significantly higher in patients aged less than 65 years old compared with older patients. These findings were independently confirmed by the companion IGNITE study.

"Further studies are required to confirm these findings and identify potential underlying biological mechanisms - the age finding in particular is interesting," said Dr Nicola Normanno, chief of the Cell Biology and Biotherapy Unit, INT-Fondazione Pascale, Naples, Italy, author of one of the studies. "The increased ability to detect EGFR mutations in plasma from patients with a higher number of organs with metastases makes sense biologically, as these patients have higher tumour burden and we could expect more ctDNA to be released in the blood. The same could also be true for patients that have metastases to organs further away from the lungs (M1b)."

He continued: "The link with age is more difficult to understand. Evidence suggests that the biological features of certain tumours change with age. However, the specific biological mechanisms underlying the correlation between the success of plasma analysis and age will need to be investigated further."

Commenting on the implications of the findings for clinical practice, Normanno said: "If plasma testing is more reliable for some patients with certain characteristics, this may have implications in the way that we conduct mutation testing for patients with NSCLC, and ultimately impact upon treatment decisions. Our data suggests that for the majority of patients with metastatic disease a plasma test could be sufficient to determine EGFR mutation status particularly when a robust and reliable methodology is used. Due to the low sensitivity of plasma genotyping (60-70%), a biopsy will still be recommended in plasma negative cases."

Also presented today at the ELCC Conference is an analysis from the phase I AURA trial of osimertinib, a third generation T790M targeting EGFR inhibitor. Eligibility for the drug is currently determined through a positive biopsy test for T790M. The study evaluated the effectiveness of osimertinib, based on tumour results or plasma results, in patients with acquired resistance to first-line EGFR inhibitors who had the T790M mutation L858R or exon 19 deletion.

Positive T790M biopsies correlated with high response rates and long progression free survival (PFS), while those with T790M negative tumours had a low response rate and modest PFS. Patients with T790M positive plasma had high response rates and long PFS. But those with T790M negative plasma had mixed outcomes.
"The first conclusion is that a non-invasive blood test appears to have the ability to find T790M positive patients very effectively," said lead author Dr Geoffrey Oxnard, a thoracic cancer physician at the Dana-Farber Cancer Institute, Boston, US. "But the blood test only has a sensitivity of 70 or 80% so there are false negatives. In other words, if you have a negative result in the blood test it may be that the mutation was present but not detected."

Oxnard continued: "When we studied the tumour results on patients who were T790M negative in the blood we could differentiate those who do better or worse on osimertinib, meaning that a biopsy is an effective fall back to clarify who should and who shouldn't get the drug. We conclude that a two stage approach is needed, starting with the blood test. Patients who test positive for T790M on the blood test can receive osimertinib. Those who test negative should have a biopsy test to clarify their T790M status."

A surprising result was that some patients were T790M negative in the tumour but T790M positive in the blood test. "This suggests that the resistant mutation might be present in just a subset of the cells, or only in some sites of the tumour," said Oxnard. "A biopsy may not capture the cancer's resistance across all sites of disease but a blood test does. Patients with this apparent false negative tissue result did not respond as well to osimertinib as patients with a positive test. It could be that if T790M is only in a subset of resistance cells there may be other resistance mechanisms hidden in the tumour which reduce the effect of the drug."

A second study of osimertinib, limited to patients with an EGFR T790M mutation who had failed a previous EGFR inhibitor, found a high concordance between plasma positive and tissue positive tests. Patients with either positive test responded to the drug to a similar degree.

"The data demonstrates that the responses are equivalent, which hopefully will ultimately lead us to a point where we no longer have to do a biopsy in every patient," said one of the study authors Pasi Jänne, professor of medicine at the Dana-Farber Cancer Institute, Boston, US. "I think we will see more and more plasma testing for genetic alterations in lung cancer, where we are trying to treat a genetically defined patient population."

He added: "Blood can be drawn on every patient whereas biopsies are not feasible in everybody, so that opens up the spectrum of patients who can be tested. With a blood test you can isolate and analyse the DNA much faster than you can do a biopsy so eligibility for treatment could be determined more quickly."

Commenting on the findings of the three studies presented today, Dr Sanjay Popat, consultant thoracic medical oncologist at the Royal Marsden Hospital in London, UK, said: "These studies confirm the potential clinical utility of using ctDNA EGFR genotyping in routine practice and give information on the magnitude of false negatives. We now need validation of ctDNA EGFR genotyping in real world settings to better understand how it can be delivered. Analyses from clinical trial datasets are usually done retrospective to patient accrual in the trial which is very different to a patient waiting for the result in real time."

But he added: "Plasma testing will not routinely replace tissue biopsy for mutation testing which should still be regarded as the gold standard. It would be a complementary test, and may be a replacement in some patients, for example those in whom a tissue biopsy is not possible."

More information: References:

1. 134O_PR: Plasma ctDNA analysis for detection of EGFR T790M mutation in patients (pts) with EGFR mutation-positive advanced non-small cell lung cancer (aNSCLC). S. Jenkins, UK. Friday 15th April 2016 - 10:00-10:15 NSCLC targeted therapy and circulating biomarkers Room C 135O_PR: Plasma genotyping for predicting benefit from osimertinib in patients (pts) with advanced NSCLC. G. Oxnard, US. Friday 15th April 2016 10:15-10:30 NSCLC targeted therapy and circulating biomarkers Room C 58O_PR: Clinical and demographic features that influence EGFR mutation detection in plasma from patients (pts) with aNSCLC: The ASSESS experience. N. Normanno, Italy. Friday 15th April 2016 - 9:45-10:00 NSCLC targeted therapy and circulating biomarkers Room C
2. http://www.esmo.org/Conference...ung-Cancer-Mutations

Provided by European Society for Medical Oncology

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