“Liquid Biopsy” May Help Earlier Detection of Lung Cancer Treatment Resistance

PHILADELPHIA — A blood test to regularly monitor for the presence of rearrangement of the EML4-ALK gene fusion in patients with non-small cell lung cancer (NSCLC) may help clinicians predict the outcome of treatment with crizotinib, according to research presented here at the AACR Annual Meeting 2015, April 18-22.

“By using the platelets isolated from venous blood specimen collections we have an opportunity to follow the therapy in real time by determining alterations occurring in the tumor during treatment, and this makes it possible to tailor the therapy for each patient,” said Jonas A. Nilsson, PhD, a researcher in the Department of Radiation Sciences at Umeå University in Sweden. “As a complement to imaging modalities, we may help doctors to be informed on when the tumor starts to regrow, when to switch therapy, and whether second-generation ALK inhibitors may be effective.”

A subgroup of patients with NSCLC harbors EML4-ALK rearrangements in their tumors, making them responsive to targeted treatment with crizotinib, an ALK inhibitor. Although the drug is effective in these patients, many eventually develop resistance to the treatment.

In this study, Nilsson and colleagues analyzed the efficacy of a blood-based “liquid biopsy” in assessing the presence in blood platelets of EML4-ALK in patients with NSCLC. Unlike assessment with advanced imaging techniques, such as computed tomography, the researchers theorized that the liquid biopsy would allow for real-time monitoring of the disease and earlier identification of patients who have developed resistance to treatment.

The researchers analyzed blood samples from 77 patients with NSCLC with known mutation status, and among them, 38 patients had EML4-ALK rearrangements in the tumor.

The liquid biopsy identified 65 percent of the patients with confirmed EML4-ALK rearrangement. In the 29 patients treated with crizotinib, those whose blood test was EML4-ALK-positive had a progression-free survival of 3.7 months compared with 16 months in those with EML4-ALK-negative blood tests.
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“We showed that if we detected EML4-ALK in the platelet fraction before therapy starts and it does not disappear during treatment, it indicates that the patient is not responding to the therapy, which is associated with a shorter time to recurrence and, therefore, other therapies could be tried,” Nilsson said.

Finally, in a case study of a patient followed for 2.5 years during crizotinib therapy, the researchers detected the presence of EML4-ALK in the liquid biopsy two months before disease progression could be confirmed using imaging modalities.

“This study shows that platelet-powered diagnostics may add another layer of information to clinicians, and this information can be used to help in the clinical decision-making process,” Nilsson said. “Therefore, the platelet platform is an interesting biosource for the next generation of liquid biopsies and in the development of personalized health care.”

This study has been conducted as an international collaboration between Amsterdam, Barcelona, Boston, and Umeå. It was funded by the European Research Council, the Dutch Organization of Scientific Research, the U.S. National Institutes of Health, CFF Norrland (RJAN), the Swedish Research Council (RJAN), the “La Caixa” Foundation, and the Redes Temáticas de Investigación en Cáncer. Nilsson is a co-founder and shareholder of thromboDx B.V.


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Abstract Number: 8728

Title: Monitoring rearrangement of EML4-ALK in blood platelets predicts outcome to crizotinib treatment in non-small-cell lung cancer patients

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Background: Novel targeted therapies have been successfully used against subgroups of non-small-cell lung cancer (NSCLC) patients, however, despite initial good response the cancer will eventually relapse. One of those subgroups harbors a rearranged EML4-ALK fusion gene that makes them responsive to crizotinib treatment, but therapy resistance often soon occurs. Real-time monitoring of rearrangement status over the course of treatment will help identify patients showing therapy resistance, but monitoring through serial tumor biopsies has been an obstacle. Therefore, new blood-based “liquid biopsy” platforms need to be developed to monitoring biomarkers in the circulation. Here we present one platform using the ability of platelets to sequester RNA released by tumor cells and represent an attractive source for non-invasive biomarker assessment.

Methods: EML4-ALK rearrangements were analyzed by reverse transcription-polymerase chain reaction (RT-PCR) in platelets and plasma isolated from blood obtained from 77 NSCLC patients, 38 of whom had EML4-ALK rearranged tumors. In a subset patients (n=29) that were treated with crizotinib, progression-free survival (PFS) and overall survival (OS) were correlated with presence of EML4-ALK rearrangements in platelets.

Results: The study was designed with three parallel objectives: firstly to determine the sensitivity and specificity of detecting EML4-ALK rearrangements in platelets; secondly, to examine the potential impact of EML4-ALK rearrangement in platelets on outcome to crizotinib; thirdly, to test the feasibility of monitoring patients throughout treatment with EML4-ALK rearrangement assessment in platelets.Detection of EML4-ALK rearrangements in platelets demonstrated 65% sensitivity and 100% specificity. The PFS in patients treated with crizotinib was 3.7 months in patients with a positive EML4-ALK platelet status compared to 16 months for a negative EML4-ALK status (hazard ratio, 3.5; P=0.02). Furthermore, longitudinal monitoring of EML4-ALK rearrangements in platelets was feasible, as demonstrated in an index patient where crizotinib resistance was observed two months prior to radiographic disease progression.

Conclusions: Platelets may provide a useful source for non-invasive assessment of EML4-ALK rearrangements and may prove useful for predicting outcome to crizotinib. Serial analyses of EML4-ALK rearrangements in platelets may help improve clinical decisions based on radiographic imaging alone by detecting resistance to therapy sooner.