Epilunar: epigenomic profiling of liquid biopsy and immunotherapy resistance in non-small cell lung cancer

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Abstract

Background: Immune checkpoint inhibitors (ICIs), such as anti-PD1, have revolutionized metastatic non-small cell lung cancer (mNSCLC) treatment. However, only a small proportion of patients benefit from this therapy, and effective biomarkers to predict primary and secondary resistance are lacking. A key limitation is the difficulty in obtaining sufficient lung tumor samples for clinical testing. Liquid biopsy (LB) provides a non-invasive alternative by analyzing cell-free DNA (cfDNA), circulating tumor cells (CTCs), and circulating long non-coding RNAs (lncRNAs). In addition to blood, malignant pleural effusions (MPEs) represent a promising non-invasive source. LB enables the detection of tumor-derived epigenetic alterations, such as DNA methylation and lncRNA changes. We hypothesize that epigenomic profiling of cfDNA, CTCs, and lncRNAs (in blood and MPEs) will allow the identification of novel non-invasive biomarkers and mechanisms of resistance to ICIs in mNSCLC, providing critical insights into the mechanisms driving resistance and help refine patient selection for immunotherapy.

Objective: The EPILUNAR project aims to discover novel non-invasive epigenetic biomarkers and resistance mechanisms associated with ICIs in mNSCLC to personalize immunotherapy management and improve treatment outcomes.

Methods: Adult mNSCLC patients (n=250) before initiating first-line anti-PD1-based therapy will be recruited and monitored by four Spanish groups from CIBERONC. Therapy response will be assessed during the follow-up. We will integrate epigenomics, artificial intelligence (AI), and LB to identify key biomarkers and mechanisms driving resistance. By combining genome-wide methylation profiling of cfDNA with AI, we will develop non-invasive cfDNA methylation signatures to predict ICI resistance. Additionally, whole-genome DNA methylation profiling of single CTCs will be performed to uncover novel resistance mechanisms. The molecular phenotype of circulating immune cells will also be characterized. Moreover, MPE-derived organoids will be generated as tumor models to validate the identified resistance mechanisms. The role of stable intronic sequence RNAs (sisRNAs), a specific lncRNA subtype, in ICI resistance will also be explored.

Conclusion: This EU project is expected to identify non-invasive epigenetic biomarkers for predicting immunotherapy resistance, uncover novel mechanisms impairing treatment efficacy, and pave the way for innovative strategies to overcome this resistance in mNSCLC, ultimately contributing to more effective and personalized therapeutic approaches.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.