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Simplified Interventional Mapping System (SIMS): A novel strategy for the selection of tri-targeted therapy combinations for Non-Small Cell Lung Cancer (NSCLC)

Lazar Vladimiir
WIN Consortium, France

Background: Combining three targeted therapies significantly improved outcomes in AIDS. A similar strategy could theoretically benefit patients with metastatic NSCLC but a scientific method for rational selection of drug combinations is needed.

Methods: We assessed genomics and the transcriptome (including miRNA), utilizing defined subsets of relevant genes/gene products and scored information about the relationships between targeted drugs and genes based in part on the biological hallmarks of cancer. Interventional points (genes/group of genes) that when activated could be blocked by a customized therapy combination were identified. The underlying algorithm integrates and weighs the genomic (DNA sequencing) and transcriptomic data (mRNA and miRNA differential expression between tumor and normal-bronchial mucosa-tissues).

Results: Key genes (N=183) grouped in 24 interventional points forming the Simplified Interventional Mapping System (SIMS) were elucidated. Frequency and trends of co-activation derived from 121 NSCLC patients defined a list of candidate triple therapy combinations. The focus in order to limit toxicity was on the application of two small molecules (TKI) and an immune-modulator (anti-PD1L). Twenty-eight percent of NSCLC patients displayed the simultaneous activation of PD1L, Ras/Raf and mTor/PI3K interventional points. Overall, fifty two percent of NSCLC patients could be targeted by atriple combination that includes an anti-PD1L agent. Most individuals could benefit from two or even more triple combinations to overcome resistance.

Conclusions: The SIMS's strategy enables conversion of thousands of genomic and transcriptomic measurements into a simple and actionable result (1-10 score) that may be usable by physicians to select triple drug therapy. Comparing tumor and normal tissue biopsies has proven feasible in the ongoing WINTHER trial (NCT01856296). This novel strategy may allow deployment of personalized tri-targeted therapies that will be prospectively tested in a clinical trial with the objective to significantly impact survival inadvanced NSCLC and other malignancies.

Biography

Lazar Vladimiir obtained his MD (1989) with high honors at The University of Timisoara (Romania). He became a specialist in medical clinical biology and obtained his PhD in molecular biology (1997) with highest honors and the prize of the university at The University Rene Descartes in Paris. He is specialized in clinical biology, molecular biology, and molecular pathology, and has postgraduate degrees in biotechnology and project management. He is the author of six patents, and has authored/co-authored over 100 publications. He initiated the WIN Consortium and serves as its Chief Operating Officer.

vladimir.lazar@winconsortium.org

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