EIT PACMAN Study preliminary results: OncoSignal pathway analysis identifies actionable cancer targets

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ABSTRACT

Introduction: Precision medicine refers to tailoring of treatment to each individual patient, although identifying tumor driving signaling pathways (SP) that are functionally active is still a challenge. OncoSignal pathway tests quantitatively measure activity of SP such as *estrogen receptor (ER), androgen receptor (AR), PI3K, MAPK, Hedgehog (HH), TGF-β, Notch* on fresh frozen and formalin-fixed paraffin-embedded (FFPE) tissue samples. OncoSignal pathway analysis aimed at assessing clinically actionable SP and retrospectively predicting targeted drug response on a series of patients' (pts) samples from the MOSCATO trial run at Gustave Roussy.

Methods: OncoSignal pathway analysis (ER, AR, PI3K, MAPK, HH, Notch, TGF-β) was performed blinded by Molecular Pathway Dx (Philips, Eindhoven) on metastatic tumor tissue samples from breast cancer (BC), prostate (PC), and high grade serous ovarian cancers (OC). Using Affymetrix expression array data from public GEO datasets, SP activity was analyzed in healthy prostate, breast, and ovarian tissue to define abnormal SP activity thresholds for tumor tissue pathway analysis. For each *individual* sample, SP alterations were considered tumor driving SP if sample SP activity exceeded the 95th percentile of SP activity within healthy tissue. Results by OncoSignal were also combined with clinical characteristics and molecular alterations identified in the MOSCATO trial.

Results: Identified tumor driving SP were ER, AR, MAPK-AP1, HH, PI3K pathway in BC (n=5), AR in PC (n=30); AP1, Notch, TGFβ in OC (n=17). OncoSignal identified clinically actionable tumor driving pathways in all BC samples (median tumor cellularity [MTC]: 40%, range 15-80%); 30/31 PC samples (MTC: 62%, range 25-90%), 16/17 OC samples (MTC 62%, range 15-80%). Actionable mutations were previously identified in 4/5 BC; 13/31 PC; 6/17 OC. Seven pts with BC and PC were treated with targeted therapy. OncoSignal pathway analysis correctly predicted response/resistance in 4 of these pts (57%).

Conclusion: OncoSignal pathway analysis correctly identified SP activity alterations and predicted targeted drug response in this series of patients. OncoSignal will be further validated prospectively in precision medicine studies at Gustave Roussy in which patients are stratified for targeted treatment by mutation analysis.