1887P Prediction of response to vemurafenib in BRAF V600E mutant cancers based on a network approach

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Background: Selective small-molecule BRAF inhibitors are approved, alone or in combination with trametinib, for the treatment of patients with BRAF V600 metastatic melanoma and non-small cell lung cancer (NSCLC). So far, several studies showed that different histotypes of BRAF V600 mutant tumors do not respond uniformly to BRAF inhibitor vemurafenib: high response rates in hair cell leukemia and melanoma, intermediate responses in thyroid and NSCLC, low responses in colorectal cancer. Using a bioinformatics tool, we sought to elucidate, through a network unbiased approach, why different tumors harboring BRAF V600E mutation show heterogeneity in response to vemurafenib.

Methods: We exploited SWItchMiner (SWIM) software to analyze gene expression profiles available on The Cancer Genome Atlas. SWIM is able to identify a small pool of regulatory genes (switch genes), which are likely to be critically associated with drastic changes in cell phenotypes. We selected among those genes, the ones who encode for kinases. Then, we employed Geneious R11 desktop platform to identify those kinases with the maximum identity score to kinases reported as known targets of vemurafenib.

Results: Lung adenocarcinoma is the tumor with the highest number of switch genes (298) compared to its normal tissue, followed by thyroid (227) and colorectal (183) cancers. Switch genes codifying for kinases were 14, 7 and 3 respectively. We looked for three homology sequences identified across vemurafenib targets and we found that thyroid cancer and lung adenocarcinoma have a similar number of putative targetable

switch genes kinase (5-6); on the contrary, colorectal cancer has just one, with minor homology sequence.

Conclusions: Our network analysis may provide additional approaches to explore the molecular mechanisms underlying the different response to vemurafenib in BRAF V600E mutant tumors, elucidating how precision medicine cannot leave out of consideration the tumor histology. It is likely that, while different cancers share the major driver event, the response to therapy may vary based on the number of kinases with homology sequences to the druggable kinase targets. In vitro data are needed to validate this prediction.

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