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RESISTANCE BIOLOGY MAPPING

The treatment resistance profile comprises five biological processes related to tumor progression and/or treatment resistance, namely: (i) cell proliferation; (ii) immune modulation (iii) inflammation; (iv) angiogenesis; (v) metabolism. Each process is tagged as being 'active' or 'inactive' according to a proteomic enrichment analysis performed by a proprietary algorithm.

The algorithm was developed by OncoHost as follows. Protein sets (corresponding to each of the above-listed biological processes) were manually curated based on extensive searches in literature and protein databases. Among the 7,000 proteins measured in the SomaScan assay, 432, 508, 528, 868 and 200 proteins were associated with immune modulation, inflammation, angiogenesis, cell proliferation and metabolism, respectively. These five curated sets show less than 20% intersection, with the highest intersection observed between the proliferation and angiogenesis sets (18.5%). The algorithm examines whether a protein set is significantly enriched by comparing the patient-specific expression level of the protein set with the expression level in other patients, as well as with other protein sets of the same patient. If a protein set is significantly enriched, the corresponding biological process is tagged as active. Otherwise, the biological process is tagged as inactive.

The patient's treatment resistance profile can potentially be helpful for choosing appropriate combination treatment strategies designed to overcome resistance to standard of care ICI-based therapies, as described below.

CELL PROLIFERATION

Normal cell proliferation is induced by external stimuli that signal the cell to proliferate. One of the main features of tumor cells is their ability to sustain proliferation even in the absence of the external stimuli.

Current treatments that target cell proliferation primarily include chemotherapy, radiotherapy and targeted therapy. Patients displaying a high proliferation signal may potentially benefit from ICI therapy in combination with one of these treatments. Several combination chemotherapies (investigated in KEYNOTE-021, KEYNOTE-189, KEYNOTE-407 and IMpower130 clinical trials) have been approved for NSCLC patients.

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INFLAMMATION

Tumor cells exploit inflammatory mechanisms that enable tumor migration, survival and immune evasion, ultimately supporting tumor progression.
Patients displaying a high inflammatory signal may potentially benefit from ICI therapy in combination with anti-inflammatory treatments currently being investigated in clinical trials.

IMMUNE MODULATION

Tumor cells develop multiple strategies for escaping immune surveillance and destruction. One of the main strategies involves immune checkpoints and immune suppressive mediators that repress immune cell activation.
Patients displaying a high immune modulation signal may potentially benefit from therapies comprising approved combinations of ICIs such as nivolumab and ipilimumab (Checkmate227 and CheckMate-9LA clinical trials) or other combinations currently being investigated in phase 2/3 clinical trials.

ANGIOGENESIS

Angiogenesis is a process by which new blood vessels are formed from existing vasculature. Tumors stimulate angiogenesis by producing angiogenic stimuli. This results in the formation of new blood vessels that supply the tumor with oxygen and nutrients, thereby sustaining tumor survival, growth and spread.
Patients displaying a high angiogenic signal may potentially benefit from approved or investigational combination therapies comprising ICI therapy and an anti-angiogenic drug. The ABCP (Atezolizumab + Bevacizumab + Carboplatin + Paclitaxel) regimen (studied in IMpower150 clinical trial) is an approved combination therapy for NSCLC patients.

METABOLISM

Cancer cells often activate metabolic pathways to generate energy and building blocks required for cell proliferation and tumor progression. Such metabolic changes may also affect the immune system.
Patients displaying a high metabolic signal may potentially benefit from investigational combination therapies comprising ICI therapy and a metabolic intervention, currently investigated in clinical trials.

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