Clinical Trials in Immuno-Oncology & Breast Cancer

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Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial

Voorwerk L et al. – Netherlands Cancer Institute, Ghent University Hospital, NanoString Technologies, GZA-ZNA Ziekenhuizen, Peter Mac Callum Cancer Center.

This phase II trial evaluated the efficacy of the PD-1 blockade nivolumab after induction with low-dose chemotherapy in patients with triple-negative breast cancer (TNBC). The immunomodulatory effects in the tumor microenvironment (TME) and PAM50 subtypes of tumor biopsies were assessed using the nCounter® PanCancer IO 360™ Gene Expression Panel and a PAM50 spike-in panel, respectively. After doxorubicin and cisplatin induction, immune-related genes in PD-1/PD-L1 and T cell cytotoxicity pathways were upregulated. Similarly, doxorubicin induction enriched inflammatory JAK-STAT and TNF-α signaling. Predictive parameters in responders include: 1) high levels of stromal tumor-infiltrating lymphocytes (sTILs), 2) high expression of CD8 and PD-L1 on immune cells, and 3) high gene signature scores for Th1 cells, B cells, and neutrophils. On nivolumab treatments, there were trends of higher T cell receptor (TCR) clonality as well as increased T cell infiltration, CD8 counts, and TCR repertoire diversity in responders. Overall, priming with doxorubicin or cisplatin induces a favorable TME and is associated with better response to nivolumab in TNBC patients.

Successful anti-PD-1 cancer immunotherapy requires T cell-dendritic cell crosstalk involving the cytokines IFN-γ and IL-12

Garris CS et al. – Massachusetts General Hospital, Harvard Medical School, Universitätsspital Basel, Basel, University Hospital Basel, NanoString Technologies Inc., Oncosec Inc., UC San Francisco Medical Center.

In this study, the immunological modulation and pharmacodynamics of PD-1 immune checkpoint blockers were investigated in skin tumor biopsies from melanoma patients and mouse models using real-time imaging, single-cell RNAseq analysis, and the nCounter® PanCancer IO 360™ Gene Expression Panel. These analyses showed induction of antitumor cytokines, IFN-γ and IL-12, by treatment. Dendritic cells (DCs) were activated by IFN-γ that was released from neighboring anti-PD-1-activated T cells. In turn, IL-12 was produced by a subset of tumor-infiltrating DCs, leading to antitumor T cell immunity. Moreover, the NF-κB transcription factor pathway, which is required for response to anti-PD-1, was enriched within IL-12-producing DCs. These findings suggest that activation of antitumor T cells by anti-PD-1 therapy involves the crosstalk between T cells and DCs, mediated by the cytokines IFN-γ and IL-12. In addition, activating the non-canonical NF-κB pathway amplifies IL-12-producing DCs and sensitizes tumors to anti-PD-1 treatment.

Immune landscapes predict chemotherapy resistance and immunotherapy response in acute myeloid leukemia

Vadakekolathu J et al. – Nottingham Trent University, Princess Margaret Cancer Centre, NanoString Technologies Inc., MacroGenics Inc., Erasmus University Medical Centre, Washington University in St. Louis, and others.

This study explored immunological heterogeneity in relapsed/refractory acute myeloid leukemia (AML) as well as its influence on response to the bispecific CD123 x CD3 DART molecule flotetuzumab. Immune-infiltrated and immune-depleted disease subtypes were defined using bone marrow aspirates from three cohorts, and differential expression of immune-related genes were measured by the nCounter® PanCancer Immune Profiling Panel and the PanCancer IO 360™ Gene Expression Panel. GeoMx® Digital Spatial Profiling (DSP) was utilized for high-dimensional analysis of the immunological architecture in formalin-fixed paraffin-embedded (FFPE) bone marrow biopsies. The results indicated that IFN-γ-related gene expression profiles were predictive for chemotherapy resistance as well as response of primary refractory/relapsed AML to flotetuzumab immunotherapy. In all, the immunological stratification improves survival prediction and also provides a framework for delivering T-cell targeting immunotherapy to patients with IFN-γ-dominant AML, who may be resistant to conventional cytotoxic chemotherapy.

Predictive biomarkers for adjuvant capecitabine benefit in early-stage triple-negative breast cancer in the FinXX clinical trial

Asleh K et al. – University of British Columbia, NanoString Technologies Inc., University of Helsinki, Uppsala University Hospital, Helsinki University Hospital, Mayo Clinic Comprehensive Cancer Center, Mayo Clinic.

This phase III Finland capecitabine trial (FinXX) identified diagnostic and research signatures that cover key pathways in the tumor, tumor microenvironment, and immune response in triple-negative breast cancer (TNBC) patients who received adjuvant capecitabine. FFPE tumor tissues were analyzed on the nCounter® system using the Breast Cancer 360™ Gene Expression Panel and a panel of 30-custom genes related to capecitabine metabolism and activity. In capecitabine-treated patients, longer recurrence-free survival (RFS) was associated with expression of genes related to antitumor immunity (cytotoxic cells), endothelial, mast cells, and checkpoint expression (PD-L2). In addition, 38 genes involved in immune response and capecitabine activation (e.g. CES1, SLC28A1, and TYMP) showed predictive trends for capecitabine benefit. Taken together, expression profiles of genes related to antitumor immunity, immunomodulation, and capecitabine activation could predict TNBC patients who are more likely to benefit from adjuvant capecitabine treatment.

Phase I clinical trial of the combination of eribulin and everolimus in patients with metastatic triple-negative breast cancer

Lee JS et al. – City of Hope National Medical Center and Beckman Research Institute, NanoString Technologies, Inc., OncoGambit.

This phase I trial was designed to evaluate the safety and tolerability of eribulin plus everolimus in patients with metastatic triple-negative breast cancer (TNBC). Among 25 eligible patients, 9 patients (36%) achieved the best response as partial response, 9 (36%) had stable disease, and 7 (28%) had progression. For RNA profiling of FFPE tumor tissues from patients, the nCounter® PanCancer Pathways Panel and Breast Cancer 360™ Gene Expression Panel (BC 360) were used. PanCancer Pathways analysis revealed 5 downregulated genes (CDKN2A, WNT5A, CNTFR, DDIT4, and SPP1) and 9 differentially expressed genes involved in the PI3K pathway in partial responders. In addition, the immune-related genes CD19, IL7R, IL6, and CCR7 were upregulated. Furthermore, lower CDKN2A expression and higher CALML5 expression correlated with better response to therapy. BC 360 analysis revealed diverse tumor and tumor microenvironment pathway features, where HER2-enriched subtype was associated with poor response to therapy. Overall, the combination of eribulin and everolimus is safe and its efficacy is modest, and HER2-enriched subtype is associated with poor prognosis in this metastatic TNBC cohort.

Oral metronomic vinorelbine combined with endocrine therapy in hormone receptor-positive HER2-negative breast cancer: SOLTI-1501 VENTANA window of opportunity trial

Adamo B et al. – Hospital Clínic de Barcelona, IDIBAPS, Vall d'Hebrón University Hospital, SOLTI Breast Cancer Research Group, Hospital Clínico Universitario de Valencia/INCLIVA/CIBERONC, and others.

In this window of opportunity study, the anti-proliferative effect of letrozole (LTZ) plus metronomic vinorelbine (mVNB) was examined to determine whether this combination therapy is superior to monotherapy in patients with hormone receptor-positive (HR+)/HER2-negative breast cancer. A comprehensive panel of breast cancer-related genes as well as the PAM50 11-gene proliferation score were evaluated using the nCounter® Breast Cancer 360™ Gene Expression Panel. Gene expression profiling showed that LTZ + mVNB treatment induced high expression of immune-related genes and signatures, including CD8+ T cell signature and PD-L1 gene, along with downregulated expression of ER-regulated genes (e.g. progesterone receptor) and cell cycle-related and DNA repair genes. Following the treatment with LTZ alone or LTZ + mVNB, a significant increase in stromal tumor-infiltrating lymphocytes (sTILs) was observed. Together, short-term mVNB treatment in combination with LTZ was well tolerated and showed anti-proliferative activity, but not higher than LTZ monotherapy. As LTZ + mVNB treatment increased expression of immune-related gene signatures and sTILs, further investigation of this combination with immunotherapy is warranted.

Significant clinical activity of olaparib in a somatic BRCA1-mutated triple-negative breast cancer with brain metastasis

Pascual T et al. – Hospital Clinic of Barcelona.

Inhibition of poly-ADP-ribose polymerase (PARP) with olaparib or talazoparib has shown to prolong progression-free survival in patients with advanced HER2-negative breast cancer harboring a BRCA germline mutation. This case report further demonstrated a durable response of breast cancer brain metastasis to olaparib in a heavily pretreated patient with triple-negative breast cancer (TNBC) with a BRCA1 somatic mutation. Gene expression profiling of the prepectoral lesion from the patient using the nCounter® Breast Cancer 360™ Gene Expression Panel revealed a PAM50 basal-like subtype with the features of high expression of BRCAness, DNA scar signatures, proliferation-related genes, and immunosuppressive signatures (e.g. TGF-β and Treg signatures, TNBCtype mesenchymal subtype). In addition to minimal expression of androgen-receptor and estrogen-regulated genes, expression of CD8+ T cells and PD-L1 was low. After 2 weeks of olaparib treatment, neurologic symptoms improved. The size of the brain lesions significantly reduced at week 8, followed by no evidence of disease progression after 4 months. In summary, comprehensive molecular profiling can provide insights into the strategies to re-sensitize refractory tumor cells to PARP inhibitors.

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