

## Cellular Therapies CS 2018: Emerging role of MMR, MSI, TMB and neoantigen testing in cancer patients receiving immunotherapy- Nefize Sertac Kip- Icahn School of Medicine at Mount Sinai, USA

Nefize Sertac Kip

### Abstract

Immunotherapy is one of the most promising methods to treat, cure, and ultimately prevent cancer, which can take many forms, including antibodies, vaccines and T cells, during when one uses the immune system components to destroy the tumor cells. This presentation will focus on the use of checkpoint inhibitors for molecules such as PD1, and personalization of tumor vaccines, manipulation of the tumor microenvironment to improve the efficacy of such therapies. One powerful approach is the Adoptive Cell Transfer (ACT), as autologous tumor-reactive T cells derived from Tumor-Infiltrating Lymphocytes (TILs) and then genetically engineered to express highly active T Cell Receptors (TCRs) or Chimeric Antigen Receptors (CARs) can have potent antitumor activities. In 2017, CAR-T cell therapy targeting the B cell antigen CD19 has been approved by the FDA for the childhood ALL. Similarly, immune Check Point Blockade (CPB) has also emerged as another effective approach in the setting of cancer. Monoclonal antibodies directed against the programmed cell death protein 1 (PD1) or Cytotoxic T Lymphocyte Antigen 4 (CTLA4) signaling pathways have demonstrated clinical efficacy in a wide spectrum of solid and hematologic malignancies. This, once again, has led to approvals by the FDA for the treatment of not only NSCLCs but also other types of solid tumors. However, it is important to note that, both ACT and CPB have limitations, as not all benefit from these therapies. CAR-T cell therapy is directed against a single antigen target, and therefore, the clinical efficacy has thus far been achieved primarily in those with B cell tumors, as they are mostly uniform and express a Common Dominant Antigen (CD19).

Solid tumors, in contrast, typically lack a common surface antigen, which poses a challenge for this approach to be widely available to all cancer patients. Similarly, despite some promising results that have been noted from CPB, the Objective Response Rate (ORR) of a single-agent CPB has been limited to 30% in most tumors. However, there is a subgroup of cases who may benefit more when compared to others, and these exceptions include those tumors that are Microsatellite-Unstable (MSI-high by a molecular assay or MMR deficient by IHC), high tumor mutation burden as well as high neoantigen content. In this subgroup of cases and those with Merkel Carcinoma and Hodgkin lymphoma, ORRs of CPB can be in the range of 50-80%. Furthermore, the antitumor activity of CPB has been reported to be absent or minimal in microsatellite-stable, tumor mutation burden or neoantigen content low cancers. Therefore, it is critical to predicting those who would benefit from such immunotherapeutic modalities to better stratify them. The molecular testing can also predict if chemotherapy can be not administered, as those with high MSI would not do well with chemotherapy and they would benefit substantially from immunotherapeutic agents. We can now test for MSI, TMB, and neoantigen status of solid and hematologic tumors, while simultaneously providing their molecular signature. This is crucial for personalized therapy, hence, determining prognosis, selecting the most beneficial therapy and minimizing side-effects.

This work is partly presented at Joint Event on Annual Congress on Cellular Therapies, Cancer, Stem Cells and Bio Medical Engineering & 5th International Conference on Pain Medicine and Pain Management, October 17-18, 2018

Nefize Sertac Kip  
Icahn School of Medicine at Mount Sinai, USA, E-mail: sertac.kip@sema4.com