improvement in overall survival in a small subset of patients. Clearly, the incidence of MPE and lack of effective treatments has created an urgent unmet need to develop an effective treatment.

Our studies of the pleural secretome in non-small cell lung cancer and mesothelioma, as well as extensive secretomic data in MPE from other cancers, indicate that the IL-6/IL-6Rα axis is prominent in pleural effusions and drives the epithelial to mesenchymal transition (EMT). We have identified additional cytokines that are absent in normal pleural fluid but prominent in malignant effusions. We have also found that MPE T cells, removed from their environment, are capable of expansion in culture, polyfunctional cytokine response, and are cytolytic to autologous tumor. Because the pleural space is lined with mesothelial cells joined by tight junctions, we hypothesize that it acts as a cytokine-rich bioreactor which promotes EMT in cancer cells metastatic to the pleura, and redirects the abundant immune infiltrate to promote, rather than inhibit, tumor growth. We hypothesize that as a master cytokine, IL-6 and its soluble receptor drive this process. Therefore, local blockade of sIL-6Rα will alter the pleural cytokine milieu, inhibiting aggressive tumor behavior and promoting anti-tumor immune response. Once unleashed in the pleural space, tumor-specific T cells could be expected to migrate to the periphery through the draining lymphatics and respond to extra-pleural metastases. Further, based on our current data, we are confident that the 100 million MPE T cells that are routinely recovered during routine therapeutic MPE drainage can be expanded in culture for an adoptive cellular therapy product that is faster, better and cheaper than conventional solid-tumor derived culture-expanded tumor infiltrating lymphocytes (TIL).

What remains to be determined is whether blockade of dominant cytokines in MPE together with anti-PD-1/PD-L1 therapy can condition the pleural environment sufficiently to support and expand the existing anti-tumor responses.

Combining the knowledge derived from these studies we propose to devise a personalized combined treatment strategy that conditions the pleural environment without incurring systemic toxicities and facilitates local and systemic anti-tumor immune response.

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Sp10

CAR T-CELL

Francesco Saglio

Chimeric Antigen Receptor (CAR)-T cell therapy is emerging as one of the most powerful and promising therapeutictool for the treatment of malignat diseases. CAR-T cells are T-lymphocytes modified *in vitro* to harbor an artificial molecular construct (CAR) made by an extracellular domain consisting of a single-chain variable fragment (scFv) recognizing a specific tumor antigen joined to a transmembrane domain which is linked to the signaling unit CD3ζ and co-stimulatory units CD28 or 4-1BB of the T-cell receptor, making them capable to recognize and to kill tumor's cell in a HLA-independent manner. CAR T-cell therapy consists in the selection of patient's normal T-cells via leukapheresis, activation, transduction to express CARs using lentiviral or retroviral vectors, expansion of transduced cells and infusion of the final product back to the patient. After the CAR T-cells are infused back into the patient, the engineered cells proliferate, recognize and kill tumor cells bearing the specific antigen the CAR is directed against.

In recent years US Food and Drug Administration (FDA) and European Medicine Agency (EMA) approved CD19 CAR T-cells in patients affected by relapsed and refractory ALL under the age of 25 years, adult patients affected by Non-Hodgkin Lymphomas and more recently adult patients affected by Multiple Myeloma and this technology is moving from an experimental approach available for very selected patients treated in a small number of Centers to a standard-of-care therapy available almost worldwide.

The diffusion of commercially available CAR-T cells has increased the number of patients treated by this cell therapy products and has also permitted to confirm their safety and efficacy profile in the "real life".

The diffusion of this technology requires a re-definition of the role of all the other therapy options currently available including other forms of immuno-therapy as monoclonal antibodies, bi-specific monoclonal antibodies and, upon all, allogeneic hematopoietic stem cell transplantation (alloHSCT).

Until now data are limited, and the above-mentioned question is far from being answered but there are some observations derived from pivotal clinical trials that probably will help us in building future trials aimed to define this topic.

Another open question is represented by the persistence of these cells in the patients that is related to the definition of the need for patients responding to CAR-T cells to proceed to other therapies, especially to alloHSCT, to consolidate disease remission. Moreover CAR-T cells are characterized by some peculiar side effects as the Cytokines Release Syndrome or CNS toxicity that if are not properly detected and treated may lead to very severe consequences with a significant mortality rate.

Finally, some technological, practical and economical considerations need to be defined in order to extend the use of this technology worldwide, in respect to the other currently available therapies.

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Sp11

TARGETED THERAPY IN AML TREATMENT

Giovanni Martinelli

Prof. Martinelli will speak about new drugs in the treatment of acute leukemias, starting from mechanisms of actions of the compounds and explaining strategies for clinical research.

Venetoclax is a bcl-2 inhibitor that is entering in the therapy of AML. The use of venetoclax will be explored with particular attention to combination with purine and pyrimidine analogs and metabolism.