Cancer immunotherapy: Harnessing the body’s immune system to fight cancer

For the past five decades, Roche has been dedicated to the development of innovative medicines to transform the lives of people with cancer. Cancer immunotherapy, one of the latest areas of innovation in oncology, brings the opportunity to harness the body’s own immune system to identify and kill cancer cells. Roche’s cancer immunotherapy programme focuses on identifying key pathways in the immune response and as our knowledge of the biology of cancer and the immune system increases, we aim to further advance cancer care in the years ahead.

Advancing the science of cancer immunotherapy research

The breakthroughs in cancer research that have translated to the clinic have established the standard of care in multiple tumour types. Now, Roche is expanding the impact of our current medicines with a robust cancer immunotherapy development programme, examining unique targets and combinations with high synergistic potential. Through our disciplined study of the biology and immunology of cancer, Roche has invested large research efforts to build on our understanding of the interplay between immune system, tumour microenvironment and tumour.

This research enables us to better characterise the pattern of immune activation and identify novel therapeutic targets. In 2013, Daniel S. Chen and Ira Mellman at Genentech (a member of the Roche Group) elegantly described the cancer–immunity cycle1,2, a framework to illustrate how the human immune system interacts with a tumour to elicit an anti-cancer immune response (Figure 1).

For an anti-cancer immune response to lead to effective killing of cancer cells, the cancer–immunity cycle must be initiated and allowed to proceed. When 1 or more steps of the cancer–immunity cycle is disrupted, tumour immune escape occurs3.

Each step of the cancer–immunity cycle is associated with a specific, essential T-cell activity, and disruption in 1 or more of these steps as a result of tumour immune escape3 leads to 3 primary histological immune phenotypes – immune desert, immune excluded and inflamed, with each immune phenotype describing the level of T cell presence and activity within the tumour microenvironment.4 Tumours with an immune desert phenotype are characterised by an absence of T cells from the tumour and the tumour microenvironment. In the immune-excluded phenotype, T cells have accumulated, but are not efficiently infiltrating the tumour microenvironment. The inflamed phenotype describes tumours into which T cells have infiltrated, but are not functioning properly4.

These immune phenotypes form the basis of rational combinations designed to address relevant mechanisms of immune escape. For the immune-desert phenotype, agents are being tested that affect antigen generation, release or delivery. For the immune-excluded phenotype, therapies that recruit T cells into the tumour, anti-stromal agents that address stromal barrier exclusion and T cell bispecific antibodies that redirect and engage T cells are in development. Therapeutic approaches required for the inflamed tumour phenotype aim to reinvigorate exhausted T cells to kill the tumour3,4.

Figure 1. The Cancer–Immunity Cycle.

In the first step, antigens are released when cancer cells die. The second step is the capture of these antigens by antigen-presenting cells (APCs), such as dendritic cells, and transportation to the lymph nodes for presentation to T cells. In step 3, T cells encountering APCs are primed and activated to attack tumour cells. Next in step 4, the activated T cells enter the bloodstream and traffic to the site of the tumour. In step 5, the activated T cells infiltrate the tumour microenvironment via the blood vessels. Step 6 is the recognition of cancer cells by activated T cells through binding of the T-cell receptor to its cognate major histocompatibility complex class I presented antigen. Finally, in step 7, activated effector T cells directly kill tumour cells by cell-mediated cytotoxicity, which then releases additional tumour-associated antigens, reinitiating the cancer-immunity cycle.2
Diverse and comprehensive cancer immunotherapy pipeline

Our cancer immunotherapy clinical development programme is rationally designed to address the immune system and tumour biology. We investigate novel molecules and combinations that build on anti-programmed death-ligand 1 (PD-L1) to reactivate the anti-cancer immune response. Atezolizumab (an anti-PD-L1 checkpoint inhibitor) is an engineered monoclonal antibody that inhibits the binding of PD-L1 to its receptors programmed death-1 (PD-1) and B7.1, thus restoring tumour-specific immunity. Atezolizumab monotherapy has been approved by the United States Food and Drug Administration and European Medicines Agency for locally advanced or metastatic urothelial carcinoma in patients who have received prior platinum-containing chemotherapy or who are considered cisplatin ineligible, and for locally advanced or metastatic non-small-cell lung cancer after prior chemotherapy.

Using atezolizumab as a foundational combination partner, we seek to address immune escape mechanisms at multiple points in the cancer-immunity cycle. For example, combining atezolizumab with chemotherapeutic agents or therapies that target the MEK pathway promotes both tumour antigen release and anti-cancer T-cell activity. Other regimens that combine atezolizumab with drugs that target vascular endothelial growth factor (VEGF) may enhance T-cell generation, trafficking, and recognition of cancer cells, as well as T-cell-mediated tumour cell killing. These and other combination therapies that aim to address multiple escape mechanisms are being actively explored in Roche’s comprehensive clinical trial programme.

To deliver transformative medicines in an accelerated manner, Roche leverages a continuous learning process that begins with rationally designed clinical studies that are based on tumour biology and patient immune profiling. The patient-level biomarker data collected from these studies drive bench research studies that seek to identify biomarkers associated with both immune response and immune escape. Results from the bench then inform the design of innovative clinical trials such as MORPHEUS (NCT03280563, NCT03193190, NCT03281369), our multi-indication, multi-basket cancer immunotherapy combination trial platform has been developed to identify the best combinations using tumour phenotypes and flexible treatment crossover. Cutting-edge approaches to drug development such as these can accelerate the delivery of novel therapeutics to patients.

Future directions in cancer immunotherapy

Although checkpoint inhibitors have become a successful treatment strategy for a wide range of cancers, many patients do not achieve long-lasting responses. Our clinical studies have begun to uncover various elements that reveal the immunologic status of individual patients with cancer. This individual immunologic status can be thought of as a cancer-immune set point, a threshold that must be surpassed to generate an effective anti-cancer response and perpetuate the cancer-immunity cycle. Multivariate factors that contribute to the set point combine to reveal the tumour immune profile of an individual patient and include tumour immunogenicity and the responsiveness of an individual’s immune system. There is a balance between these factors that contribute to the set point, and thus the anti-cancer immune response. Overcoming this set point is necessary to generate effective cancer immunity in an individual. As we identify tumour immune profiles, we will have the ability to select the most appropriate combination of immune-targeted therapies. With these novel cancer immunity insights, we aim to shift cancer from a life-threatening disease to a chronic, manageable one by using the patient’s own immune system to fight his or her disease, and this, ultimately, has the potential to drive a paradigm shift in cancer care.

References

8. TECENTRIQ (atezolizumab) [summary of product characteristics], Welwyn Garden City, United Kingdom: Roche Registration Limited; 2017.

Authors

Florin Sirinţă, Luisa Veronesi, and Charlotte Colthorpe

1. F. Hoffmann-La Roche Ltd, Basel, Switzerland.
NP/ONCO/1711/0114