Is immunotherapy the holy grail in the fight against cancer?

The number of new cancer patient cases will almost double in the next 20 years. Even though this increase in incidence is not a new fact, the mortality rate significantly decreases over time. Decreased mortality can be attributed to extensive research resulting in improved treatments and new strategies, as well as earlier diagnosis due to better screening programs. Although conventional therapies for cancer treatment, such as chemotherapy and radiotherapy often result in significant reduction of the tumour or complete remission, the prognosis for advanced tumours remains poor.

THE IMMUNO-ONCOLOGY ERA

One of the most exciting developments lies at the interface of oncology and immunology and prompted the emergence of cancer immuno-therapy by going back to the basics of cancerogenesis, i.e. a malfunctioning immune system. It aims to **shift the balance of a pro-tumoural environment towards an unfavorable setting** for cancer cells by (re)boosting the immune system[1,2]. Although, IL-2 (Proleukin) was the first approved cancer immunotherapy in 1992, the immuno-oncology field really started booming upon the approval of the first therapeutic cancer vaccine Sipuleucel-T (Provenge) in 2010 and the first immune checkpoint inhibitor Ipilimumab (Yervoy) in 2011.

Immune checkpoint inhibitors (CPI) are considered to be the most potent class of immuno-therapy so far and have resulted in FDA approvals in a variety of cancer types. In metastatic melanoma, for example, CPIs have pushed the overall survival significantly higher compared to chemotherapy, i.e. up to a 2-year survival rate of 58% versus 27%[3]. The striking results of CPI in advanced disease enabled testing in early-stage patients and has led to the approvals of pembrolizumab (Keytruda) in 2016[4] and 2017[5] as the first cancer immuno-therapy for first-line treatment of different malignancies as well as for the first tissue/site agnostic indication[6], i.e. microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumours.

Following the CPI success, the next lead novel immunotherapy will be the **IDO-inhibitors**, currently tested in multiple clinical trials[7]. IDO-inhibitors target indoleamine- 2.3 dioxygenase, an enzyme that deprives tryptophan from T-cells which is essential for cell survival and expansion. Altogether, approval of IDO-inhibitors in the future alongside the first-line approvals of CPI will undoubtedly lead to improved standard care regimens of cancer patients.

Despite the booming of the immuno-oncology field due to promising durable responses and prolonged survival obtained in multiple malignancies, there are **still a lot patients that do not benefit** from these approaches. Single-agent response to CPI treatment, for instance, is approximately 20% in unselected patients[8]. It is now more and more unraveled that this can likely be attributed to the combination of multiple immune-suppressive mechanisms together with the inter-tumoural and intra-tumoural heterogeneity of malignancies[9,10]. In this regard, the idea of 'one size fits all' is a false premise which urges to implement a combined approach that is tailored to the patients' profile[11].

PERSONALISED COMBINED APPROACH

Personalised immunotherapy

It is of utmost importance to consider **intertumoural heterogeneity** which results in different 'immune types' of maligancies with each a different immune activity status, i.e. immune inflamed, immune excluded and immune deserted. Since the activity level of the immune system against the tumour indeed has a direct impact on the clinical response of the therapies[12,13], it is not surprising that a personalised treatment approach should become the new standard in cancer treatment[14].

To allow this, the **immune type** should be defined for every patient, Many different immune biomarkers are suggested as valuable prognostic factors to help guide the treatment choice and patient selection (Figure 1). There are, however, still a lot of unknowns in this field of research. Indeed, factors that have been correlated with poor or good individual prognoses are not always accurate and may sometimes even result in inverse effects[15].

Firstly, **immune inflamed** tumours have a high mutational load or a high somatic mutation rate, grow fast and aggressive, nevertheless, these tumours are the easiest to treat of the three immune types and have good clinical outcome[16,17]. Although this seems counterintuitive at first sight, it can be explained by the fact that, due to many mutations, the immune system is constantly triggered against neoantigens that are arising. Therefore these tumours are highly infiltrated with T-cells which can subsequently be revived through CPI therapy. The high success rates obtained with CPIs are thus mainly in malignancies of this immune type[18].

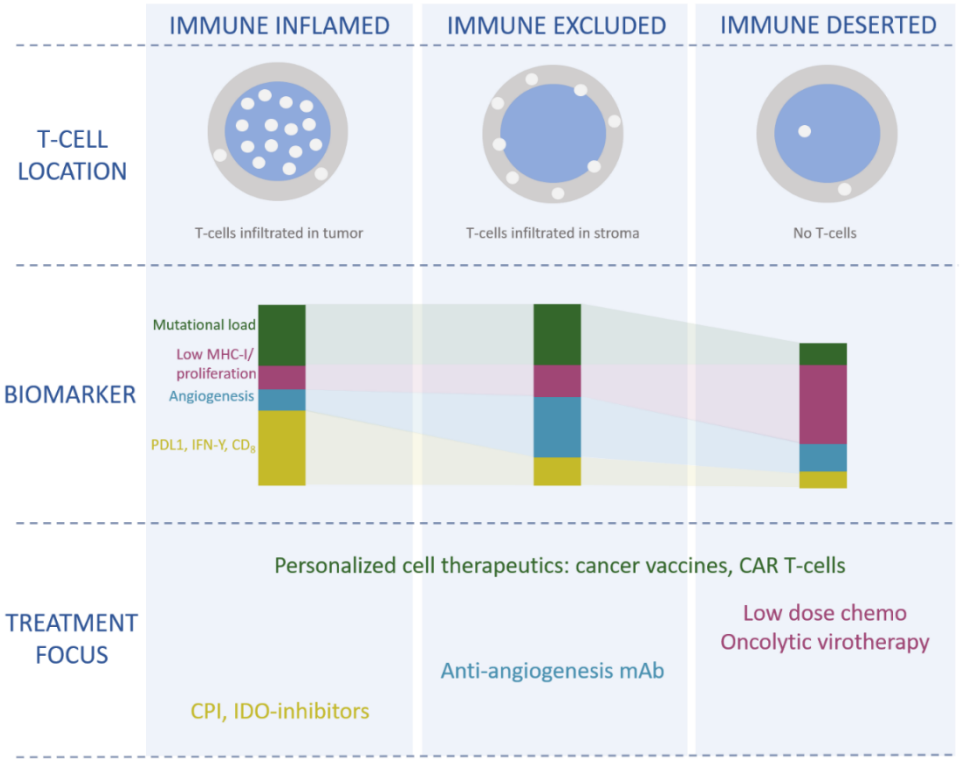

Figure 1. The immune types of malignancies defined by T-cell location, biomarker and treatment focus.

Secondly, **immune excluded** tumours do have an active immune system, however, the T-cells are unable to enter to the tumour due to dense stroma architecture. In this case, monoclonal antibody therapy directed against angiogenesis is needed to allow T-cell infiltration in the tumour.

Thirdly, **immune deserted** malignancies have rather low mutational load and are the most difficult type to treat as the immune system is not active and is not even present near the tumour vicinity. Recently it has been elucidated that it is imperative to revert these 'cold' tumour types into a 'hot' tumour, i.e. immune inflamed, prior to immunotherapeutic treatment. This can be achieved via low dose chemotherapy[19] or oncolytic virotherapy[20], both therapies that cause cancer cell lysis resulting in sudden release of cancer antigens, damage proteins and pro-inflammatory cytokines that attract and trigger the immune system against the cancer.

Personalised cell-based therapeutics

Next, cell-based therapeutics are very interesting to consider as they can be **effective in all immune types** (see Figure 1). CAR T-cells have been shown to be very effective in hematological cancers leading the FDA approval of Kymriah® and Yescarta®. In contrast, solid tumours do not seem to benefit from CAR T-cell therapy but do show response to cancer vaccination. So far however, only one cancer vaccine, i.e. Sipuleucel-T (Provenge), was approved by FDA.

The reason for many clinical trial failures is related to the immunesuppressive microenvironment as well as the design of the vaccines which is often not personalised (not autologous) and not sufficiently efficient to evoke a therapeutic effect. The failures of the gp100 vaccine[21], the GVAX vaccine[22] and the MAGE-3 vaccine[23] have unfortunately revealed these challenges. This has pushed the field towards optimisation of vaccine design and **targeting patient-specific cancer epitopes** rather than tumour-associated antigens. The latter results in boosting the immune system specifically against the tumour epitopes of the patient itself thereby avoiding lack of efficacy seen for therapeutics that target an overexpressed antigen[24]. In this respect, recent trials have shown that personalised and optimised cancer vaccines can result in clinical benefit and thus are very promising[25,26,27].

Combined immunotherapy

Due to inter- and intra-tumoural heterogeneity and the multiple immune escape mechanisms, it is highly unlikely for a monotherapy to be adequate. Therefore, a well-chosen combined approach is necessary to weaken the malignancy on different levels. It goes without words that inclusion of the immune type of the malignancy is part of the criteria (vide supra). As an example, Epacadostat combined with Pembrolizumab has recently resulted in a 34% response rate opposed 16% to 18% for CPI monotherapy in head and neck squamous cell carcinoma patients with primarily more then 2 prior lines of therapy[28,29].

Also, the **timing of the different treatments** can be critical as well for the efficacy. For instance, it was demonstrated that an anti-OX40 antibody, followed later by a PD1-inhibitor provided a beneficial effect, whereas the opposite was true for the reverse order[30]. This implies that we need to think about the order of combination immunotherapies in clinical trials.

WHAT IS NEXT?

Extensive research has been done and many clinical trials are ongoing in this field. One could even wonder if it is strategically still wise to invest in new immuno-oncology research. The answer is clearly affirmative, since the global cancer immunotherapy market is expected to reach USD 101.6 billion by 2023 from USD 36.8 billion in 2016 (14.8% CAGR).

Overall, the holy grail in the fight against cancer is yet to be found. We believe personalised cell therapeutics combined with other anti-tumour immune-therapies – such as CPIs or IDO-inhibitors – and/or conventional or targeted therapies, based on patient- and tumour specific markers, holds major promise. However, there are still hurdles and challenges to overcome. Indeed, the complex interaction of various types of immune cells with cancer cells, alongside patient variability, hinders the establishment of an all-embracing screening platform that allows to predict the clinical outcome.

Overall, we can not ignore the potency of cancer immunotherapy and the effect it has on the way we tackle cancer now. It led to more targeted treatment of cancer patients alongside less (severe) side effects. Nevertheless, as stated earlier, **the idea of 'one size fits all' is a false premise** and a well-chosen combined approach of immunotherapy with conventional and/or targeted therapies that is personalised and thus tailored to the patients' profile is of essence.

About myNEO

myNEO (Ghent, Belgium) developed a platform enabling genomic-informed drug discovery in the key therapeutic areas of oncology and immunology. The data-driven ImmunoEngine identifies the most efficacious targets (epitopes) for each cancer patient, uniquely presented on the tumour cells and capable of redirecting a patient's immune system, leading to elimination of the cancer cells. The discovery platform enables targets to be identified even in hard-to-treat tumours with a cold/lowly mutated profile. Similarly, the company has applied its technology to identify immunogenic sequences in infectious diseases, capable of protecting populations with strong broad immune responses. myNEO is one of the companies that emerged from the Novalis biotech incubator fund at the end of 2018, founded by two leading entrepreneurs already known for several successes in the biotech industry: Wim Van Criekinge, professor of computational biology at Ghent University, and childhood friend Jan Van den Berghe.

Contact us

Interested in more information about myNEO? Contact us!

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