Focus

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"The prospect of seven lean years in the fight against cancer"

"Despite research into anti-cancer drugs continues to be very active, and drugs becoming more a reality, there will be very few breakthroughs in 2019"

In recent years, a lot of progress has been made in the fight against cancer as new techniques have finally found their way to commercialisation. Both therapies described below (i.e. immunotherapy and Car-T) continue to be successful, but it will be another few years before the next big breakthrough. The markets should not expect an outstanding 2019 in terms of announcements, but there are still reasons for optimism.

1. **Immunotherapy**

   The success of immunotherapy and the speed by which these drugs came to the market was unprecedented. Immunotherapy was the first significant breakthrough in solid tumours, as it involved the immune system being re-trained to attack cancer cells. Areas that have shown positive results include skin, lung and bladder cancer, with survival rates increasing to 50%, 20% and 20% respectively.

   - Immunotherapy was viewed promisingly at a time when there were no alternatives to cure the patient. It entailed the classic procedures of surgical removal, radiation, chemotherapy and the use of antibodies. These often had a short- to medium-term effect and at best delayed the progression of the disease. The first results of immunotherapy showed that the disease could be delayed and that survival rates be increased significantly. The probability of being cured enabled the recruitment of appropriate patients in the trial phases to run very smoothly.
   - Both American and European health institutions quickly understood the positive impact of this technology. Consequently, with the prospect of saving many lives, these drugs were channelled through the development and approval stages more rapidly than other drugs. The new cancer drugs were approved on the basis of more limited patient data. Once commercialised, there was no lack of success in selling these drugs.

   The main focus of treatment by immunotherapy is on blocking the PD-1 (or PD-L1) and CTLA-4 pathways. The PD-1 receptor helps to camouflage cancer, while the CTLA-4 receptor suppresses the immune system response to prevent overreaction. By blocking both pathways in the immune system process, the treatment enables cancer cells to become visible again and also helps to maintain the immune system's response to cancer until the cancer cells have disappeared. This method has proved to be very effective particularly against skin cancer. For lung cancer, the therapy was successful in blocking PD-1, but less effective in inhibiting CTLA-4. However, the combination of PD-1 inhibitors with chemotherapy proved to be effective against lung cancer. But that was not all. Other mechanisms in the immune system were also tested at an accelerated rate. Scientists were therefore convinced that by switching on or off other mechanisms in the immune response cascade, the chances of survival would be further increased.

Why expectations are low

- **The bar was set low from the start**
  As mentioned earlier, the bar was not set very high when immunotherapy did not exist. Anything that could even extend a patient's lifespan slightly was better than what was then available. In addition, there were no other alternatives available for patients who had often already been treated. This is different for the next generation of cancer drugs. Immunotherapy ensures that patients who are most receptive to this will also be cured. Patients who exhibit a more limited response to immunotherapy will therefore be more likely to be recruited for new clinical trials. If you know that your patient already has a limited response to immunotherapy, it will be all the more difficult to produce good results using a combination therapy. So, the probability that a combination of a PD-1 inhibitor with something else could generate better results is therefore much smaller.
- **Much disappointment**
  Secondly, the new combinations of immunotherapy-based drugs have all turned out to be disappointing. Combinations other than those mentioned above have either proved to be insufficiently effective or too toxic, and therefore unusable. Indeed, decisions had been taken based on limited datasets to launch extensive studies with these combinations in the race to be the first to introduce a new therapy on the market. If there had been more time, these studies would never have reached the next stage. As a result, the initial results were disappointing. We therefore presume that there are currently still many lengthy, large-scale studies ongoing with a high risk of failure. Moreover, these studies are taking much longer than those carried out in the early years of immunotherapy. Hence, there is a risk of a successful research vacuum in the coming years.
- **Recruitment of patients**
  The success of the PD-1 inhibitor has prompted several large and medium-sized companies to develop their own similar inhibitors. The health care watchdog, which had approved the first generation of drugs on the basis of limited data, wants to see convincing datasets for the next generation before a new cancer drug can be approved. This means that many more patients have to be recruited for clinical trials and patient follow-up has to last longer before the data is deemed sufficient for approval. There are thus several pharmaceutical players which want to test mono- and combination drugs in ever larger and longer-running studies and which are all seeking the ideal patient who will respond best to their drugs. This is making patient recruitment much more difficult than in the early days, which necessarily leads to delays in the research programmes.

2. Car-T

The second important development relates to the treatment of blood cancer and concerns the emergence of CAR-T technology. This involves taking the T cells (active in the immune system) from the body and then reinserting them after altering the cells to activate the immune system. When looking at the results of CAR-T research, we see that the sale of these very expensive drugs has been met with very limited success. This is partly because CAR-T technology uses the patient's own immune system. In other words, the drug can be applied solely to one patient, making it very costly. CAR-T drugs produced from the same donor are being tested only to a limited extent on patients, as the technology is still in its infancy and success and failure alternate at a steady pace. A 'universal' CAR-T drug from a single donor is not yet expected in the coming years. That means no major breakthroughs just yet.

Conclusion: fewer novelties, but there is room for optimism even in 2019

Although the next steps in immunotherapy and CAR-T will be temporarily restricted, we see that progress is still being made. The traditional fight against cancer with antibodies, for example, is still making progress. In addition, more and more research, for instance, is being carried out on the basis of specific abnormalities in tumours. The abnormalities make it easier to develop targeted drugs that can stop the growth of tumours. Hence, patients with a specific abnormality on their tumour can be treated successfully. However, such mutations occur in a limited number of patients (1-2% of all cancer patients).

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