The last decade has seen a sustained period of progress in cancer treatment with the emergence of immuno-oncology as a serious therapeutic option in the years since the US Food and Drug Administration’s 2010 approval for Dendreon’s pioneering Provenge.

Today, many other mechanisms have built on the ground broken by Provenge. Leading the way have been checkpoint inhibitors of PD-1/PD-L1 and CTLA-4, the leading products of which have already been phenomenally successful.

However, immuno-oncology is a field that doesn’t stand still and, after 10 years of change, more advances are anticipated as understanding improves about how the various immuno-oncology treatments available and in development work, both on their own and in combination.

The COVID-19 pandemic has placed immense stress on healthcare provision, but the emergency may also make major advances in cancer treatment even more relevant – if studies can continue to improve.

Solving immuno-oncology trial challenges in the COVID-19 era
Now, widely heralded as the future of oncology, immuno-oncology’s favourable safety profile and beneficial treatment characteristics may also see it take on greater relevance in light of the COVID-19 pandemic.

Improvements are needed to the way immuno-oncology drugs are studied, and a host of different pharmaceutical companies are ramping up their clinical research efforts to test these types of drugs in different settings, combinations and treatment lines.

As pharmaceutical companies train their research efforts on unmet needs in oncology, some standout applications are being seen as new immuno-oncology medicines help patients with hard-to-treat cancers to live longer.

According to Dr Pavel Tyan, therapeutic area lead, oncology at global contract research organisation Advanced Clinical, unmet medical need is the main driver for all oncology drug development, but especially for immuno-oncology. He notes: “Metastatic melanoma used to be seen as an incurable and deadly disease. Now, with immunotherapy, we see it as a controlled disease or even potentially curable.”

Immuno-oncology has also made some large steps forward in a number of other cancers in terms of overall survival and progression-free survival – importantly, without increasing toxicity. Indeed, the perception of certain tumour types is undergoing huge changes, based on these therapies’ performance, including in hard-to-treat diseases, like pancreatic cancer or prostate cancer.
Andres McAllister is chief medical officer at BioInvent, a Swedish life sciences company that specialises in immuno-oncology. He says: “Interestingly, in the area of immunotherapy the first trials had to be done in very advanced disease. Now you see those targets moving into earlier stage disease. For instance, in lung cancer, stage three is now being addressed with immunotherapy. I think that will be the trend, to see earlier stage disease being treated with immunotherapy. You will see neoadjuvant therapy used as part of the treatment paradigm.”

Looking at the current treatment options, particularly for advanced metastatic tumours, he sees the next few years bringing greater understanding of the role of combinations of immunotherapy with other agents such as chemotherapy and radiotherapy. “There is a lot to do here that hasn’t yet been done and it’s likely to come in the next few years,” says Andres.

Treatment advances

The striking advances made to date in immuno-oncology have primarily come from treatments focused on two targets – PD-1/PD-L1 and CTLA-4 – which both negatively regulate the T-cell immune function to increase activation of the body’s own immune system.

PD-1, or programmed cell death protein 1, and its associated programmed death-ligand 1 (PD-L1) have so far proved most profitable for the pharmaceutical industry. Merck & Co’s Keytruda (pembrolizumab) and Bristol Myers Squibb’s (BMS) Opdivo (nivolumab) were the first two PD-1 inhibitors to come to market and have each built blockbuster brands that brought annual sales in 2019 of $11.1 billion and $7.2 billion respectively from melanoma, lung cancer, stomach cancer, liver cancer, and head and neck cancer. Meanwhile, a smaller number of drugs have been developed to target CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), most notably BMS’ Yervoy (ipilimumab).

In addition, the PD-1/PD-L1 and CTLA-4 inhibitors, the other prominent immuno-oncology class are the CAR-T (chimeric antigen receptor T-cell) therapies, whose complicated route of administration involves a patient’s own T-cells being harvested, modified to fight his or her cancer and then injected back into the patient’s body. The first CAR-T to be approved in the US was Novartis’ Kymriah (tisagenlecleucel) in acute lymphoblastic leukaemia in 2017, followed by Gilead’s Yescarta (axicabtagene cileucel) in lymphoma.
These advances are being extended by the beginnings of a new wave of tumour-agnostic drugs – led by Roche’s Rozlytrek (entrectinib), Bayer’s Vitrakvi (larotrectinib) and Keytruda.

Hand-in-hand with these treatment advances have come new ways to diagnose and look at cancer with biomarkers, as diagnosis and treatment become ever more interconnected.

Pavel explains: “Previously, we just looked into the cancer histology and whether or not it showed adenocarcinoma, sarcoma or any other type of tumour. Then, based on that, we decided what kind of drugs will be useful. Biomarkers are a different approach. We can see if specific tumours are hybrids or over-express specific biomarkers, even regardless of the histology of tumour types. So, there is a shift in how we see the tumour.

“The histology itself is still an important factor, but it no longer means as much now as it once did. For example, lung cancer was previously considered a single disease, but now it is seen as a family of diseases of which there are numerous different types of biomarker-based treatment strategies and approaches.”

Meanwhile, at BioInvent they have spent the last five years exploring mechanisms of resistance to immunotheraphy. Andres explains: “If you look at, for instance, mechanisms of resistance in T-cell-driven cell theory, such as PD-1, PD-L1 and CTLA-4, all of those things basically step on the brakes of the immune responses against cancer, but that is all part of the adaptive immune response. An area where people haven’t really looked is the innate immune response.”

The company is exploring ways of using Fc gamma receptor proteins to enhance cancer immunotherapy by targeting these proteins which, BioInvent says act as ‘antibody checkpoints’.

Immuno-oncology and COVID-19

Amid these medical advances the current global COVID-19 has had a major impact on cancer and clinical trials, affecting treatment and oncology patients in a number of different ways.

The significant pressure and increased workload due to the massive hospitalisations of COVID patients has led to the re-profiling of many hospitals and departments including oncology clinics for treating patients with the COVID infection. Consequently, many diagnostic and treatment procedures have been cancelled or postponed around the world, including as many as 2.3 million cancer surgeries according to one study.

The real impact could be much wider, according to Pavel. “Not only surgeries, but also the medicinal treatments have been affected as the majority of them require either visits to clinics or overnight stays and there is also an increased risk of severe COVID disease due to the toxic
anticancer therapy. Also, as they are patients from a high-risk group due to multiple organ system dysfunctions, especially those with advanced disease, they must be isolated from others as much as possible. The global oncology community is concerned about the rise of cancer cases and the increase of the portion of advanced disease in the near future.

Clinical trials in oncology, as in other therapy areas, have also been affected, with about 170 studies suspended due to COVID-19, according to a report by Evaluate Vantage.

In many oncology trials the number of participants that have completed, or are in the process of completing, a study has decreased, while the number of protocol deviations being registered has increased. As well as sending clinical trial costs higher, the pandemic can have other impacts on studies.

Pavel explains: “COVID-19-related deaths could potentially affect survival endpoints in some studies. Both survival and PRO-based endpoints are affected due to the enormous stress, anxiety and fear oncology patients are now experiencing.”

Immuno-oncology may also come into its own at this time, given the benefits that it has traditionally shown over chemotherapy – particularly combinations of chemotherapy agents – and other more traditional cancer treatments, in terms of its safety profile.

“The recently published TERA VOLT study has confirmed that the chemotherapy was an additional risk factor for the development of COVID disease compared to immuno-oncology or target therapy,” Pavel says. “Even though cancer immunotherapy is not intended to treat infections, I think it has the same vector and works in the same direction towards boosting the patient’s immune system rather than abating it as chemotherapy does.

“We also see some similarities between the COVID manifestations and cytokine release syndrome, which is one of the expected complications of anticancer immunotherapy. The immune modulator cancer drug tocilizumab is one of the drugs being tested as a treatment for COVID-19.”
Immunotherapy has also been found to have a durable treatment response in patients after just a few courses of therapy, for example in cases where patients can’t continue with their treatment. The drugs reveal the cancer to the body’s immune system, turning it against the cancer and, when treatment stops, the immune system can continue killing the cancer itself. That, Pavel says, is in contrast to cytotoxic chemotherapy, which can only kill tumour cells when treatment is ongoing and can do nothing to prevent the cancer relapsing after the chemotherapy is stopped.

Clinical trial challenges in immuno-oncology

As advanced as the use of immuno-oncology appears to be today, there is still plenty more to learn about these medicines. One of the most pressing issues to assess is how to ensure they are as effective as they can be, which increasingly requires testing combinations of different drugs to look for synergistic effects.

Pavel explains: “Combinations of immuno-oncology treatment are still a relatively unexplored area for us. One of the main challenges they present is in terms of their toxicity, as we don’t know much about it. So how do these two different types of immunotherapy interact with each other? We need to know whether or not there will be overlapping toxicity or additional toxicity, for example.”

For all types of immuno-oncology studies trial design is a challenge. It requires sponsors to move on from traditional clinical trial designs that were invented for chemotherapy and look to the unique characteristics, features and responses of immuno-oncology.

“The old standards may not always be applicable for a new immunotherapy or combinational therapy,” says Pavel. “More and more sophisticated trial designs are needed, especially for early phase and dose escalation trials, and often they’ll need to be based on adaptive trial principles rather than conventional ones.”
As part of this, he says, pharmaceutical companies will need to think carefully about how to set optimal timings for initial responses, dose escalation and trial duration. “Another question is how to choose correct endpoints and assessment criteria for these trials. This makes a huge impact on a study design, development strategy and also on the cost of a drug.”

These are crucial questions to answer correctly within such a competitive and crowded environment and, as further trials are required, their importance will only increase.

As Pavel confirms: “We will see more and more immuno-oncology combination trials because, even if we know that immuno-oncology is quite an effective treatment, especially in certain types of tumours, there is still resistance to immuno-oncology drugs. In research now, we look to see how to overcome this resistance and how to make these effective drugs even more effective.”

Still more to do

This is a fascinating time for immuno-oncology research, as pharmaceutical companies work hard to test their drugs in optimal settings, combinations and treatment lines, with the aim of building on the area’s early advances to make immuno-oncology treatment even more effective.

As part of those efforts the industry has more work to do in tackling hard-to-treat cancers and there are ongoing challenges to be overcome in making clinical trials more patient-centric, both of which have been long-term issues for research.

Progress will come, but the additional trial issues raised by the COVID-19 pandemic are certain to continue providing companies with additional obstacles to navigate, at least for the short to medium term.

Nevertheless, while there is still more work to do, the future for immuno-oncology trials, and the treatments they result in, is bright. As Andres notes: “Immunotherapy of cancer has changed the way cancer patients are treated today for the most part. There are still a few areas where that hasn’t happened yet, but it will.”

Download the Trends in Immuno-Oncology white paper from Advanced Clinical
Pavel Tyan, therapeutic area lead, oncology, Advanced Clinical

Pavel has over 20 years’ experience working in hospital, pharmaceutical and clinical research roles and has degrees in General Medicine, General Surgery and Medical Oncology; he is an active member of American Society of Clinical Oncology (ASCO) and European Society of Medical Oncology (ESMO).

Andres McAllister, chief medical officer, BioInvent

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Graham Belgrave, senior vice president, head of european operations, Advanced Clinical

Graham Belgrave has over 35 years of experience leading pharmaceutical development across clinical operations (phases I-IV), outsourcing and contract management, project, programme and vendor management. During that time, he has held senior management roles overseeing clinical operations, outsourcing and vendor management at global pharma and biotech companies.

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