Advanced Clinical

WHITE PAPER

Trends in Immuno-Oncology: Meeting Clinical Trial and Market Access Challenges

Introduction

The decade since the US Food and Drug Administration's 2010 approval for Dendreon's pioneering, immuno-oncology treatment, Provenge, kick-started the beginning of a fascinating period for oncology.

Just as the host immune system is one of the most powerful weapons against a variety of other diseases, so too can it be trained against cancer.

Learning how to use this natural front against different cancers and direct it to specific tumours realises much of the promise of personalised precision medicine.

The sorts of advances heralded by Dendreon's therapeutic cancer vaccine have, for the most part, radically changed the way that cancer patients are treated today, with immuno-oncology heralded as one of the most important advances in tackling cancer.

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.

But it's a field that doesn't stand still and, after 10 years of change, still 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.

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. However, in addition to improving the way immuno-oncology drugs are studied, the industry also faces significant access hurdles for these treatments, preparations for which must run alongside clinical trial efforts.

With the majority of solid tumours predicted to be treated by immuno-oncology medicines by 2050, now is an ideal time to take stock of the key trends in the area and prepare for its exciting future.

Immuno-Oncology Trends

Unmet need is the pre-eminent driving force behind all oncology advances, and that is certainly true for immuno-oncology, where new medicines are helping patients with hard-to-treat cancers to live longer.

These drugs have already made some giant strides forward in a number of 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.

"Immunotherapy of cancer has changed the way cancer patients are treated today for the most part," says Andres McAllister, chief medical officer at BioInvent, a Swedish life sciences company that specialises in immuno-oncology.

"There are still a few areas where that hasn't happened yet, but it will eventually. In just a few years the treatment paradigm against lung cancer, for example, has completely changed."

The advances have been so striking because immuno-oncology is not, theoretically at least, new. The concept was first proposed by Australian Nobel Laureate Sir Frank Macfarlane Burnet more than 60 years ago, but it wasn't successfully applied until the 1990s in work by Professors Tasuku Honjo and James Allison (see box on page 5). Even then, it took a long time for the Nobel Prize-winners' discoveries that reactivating the immune system by blocking two major negative regulators, CTLA4 and PD-1, can cure a significant portion of cancer patients, to move from the bench to the bedside.

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>
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Andres explains: "Although it's a particularly exciting time to be working in oncology now, I've been following and acting on the immunotherapy of cancer for years, and for years and years it was depressing. There were signs it would work, but most of the clinical trials were negative or near negative. That completely turned around in 2010 with the first approval of Provenge."

This and subsequent phase 3 clinical trials successes and approval for other drugs have transformed perceptions of immuno-oncology, as its credibility was first established and then further strengthened. One of the areas in which it has produced breakthrough responses is melanoma, a disease that in its metastatic form used to be seen as incurable and deadly.

Immunotherapy allows for metastatic melanoma to be seen as a controllable, or possibly curable, disease. These durable responses are observed after a few injections or administration of immunotherapy because they work differently to fine-tune the host immune system against a tumour.

A further benefit that has been observed is that, although chemotherapy only works when it's being given to patients, in immuno-oncology that's not the case. In immuno-oncology a durable response is shown for months or even years after the therapy stops.

As knowledge of the uses for immuno-oncology treatments grows, so too does understanding about the drugs' adverse event profile and how to manage it. Like any new treatment approach, there is still much to learn about exactly how it works and what side effects it may cause.[1]

Dr Karina Khidishyan from the NN Petrov National Medical Research Center of Oncology in St Petersburg, Russia, says there is a high level of interest among doctors and patients about both how immuno-oncology treatments work and how to manage their side effect profile. “Many of our physicians are interested in applying and studying immunotherapy. Adverse events are widely discussed in medical oncologist circles too, and it’s also a very interesting topic for patients because of the way it can give them a huge chance to improve their quality of life and to prolong their life as well.”

As awareness and knowledge of immuno-oncology grows, there is a move towards their use against earlier stage disease and as a first-line treatment. Alongside this, it is expected that immuno-oncology drugs will be trained on harder-to-treat diseases, such as pancreatic cancer or castrate-resistant prostate cancer.

More broadly, across all cancers, there is expected to be increasing research of, and need for, more indications for monotherapy and combination treatment as Professor Honjo’s prediction (see box) for widespread use of immuno-oncology in the coming decades draws ever nearer.

Widespread Use Predicted for Cancer’s ‘Penicillin’

The 2018 Nobel Prize in Physiology or Medicine was awarded to Professors James Allison and Tasuku Honjo for their independent discoveries of cancer therapy by the inhibition of negative immune regulation, work that established an entirely new principle for treatment.

Speaking at the December 2018 Nobel Banquet, Prof. Honjo explained[2] that their work on the reactivation of the immune system had just been the beginning of immuno-oncology.

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Tasuko Honjo after receiving his Nobel Prize, December 2018

“[Genentech’s head of cancer] Dan Chen described[3] our discovery as the cancer equivalent of penicillin, which gave rise to a whole generation of antibiotics that changed medicine, and consigned most previously fatal infections to history,” he said.

“We encourage many more scientists to join us in our efforts to keep improving cancer immunotherapy. We sincerely hope this treatment will reach far and wide so that everybody on our planet can benefit from this evolutionary gift for healthy life.”

Looking to future applications for these present and forthcoming generations of cancer therapies, Prof. Honjo predicted[4] that by 2050 most cancers will be treated with immunotherapy.

TREATMENT ADVANCES

The 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. Treatments based on these two targets have changed the way cancer is treated.

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. Between them they are licensed for melanoma, lung cancer, stomach cancer, liver cancer and head and neck cancer.

Hot on their heels came Roche's Tecentriq (atezolizumab), the third PD-1/PD-L1 drug to come to market but the first to be approved5 for triple negative breast cancer, which it won a licence for in 2019. Other approved treatments in what is becoming a crowded market include Pfizer/Merck's Bavencio (avelumab) for skin and bladder cancer, AstraZeneca's Imfinzi (durvalumab) for lung and bladder cancer, and Sanofi's Libtayo (cemiplimab) for skin 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 of treatments are the CAR-T (chimeric antigen receptor T-cell) therapies. These require a complicated route of administration that involves a patient's own T cells being harvested and modified to fight his or her cancer and 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, with its 2017 licence coming on the back of astounding trial results.[6] It was followed by Gilead's Yescarta (axicabtagene ciloleucel) in lymphoma.

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. Biomarkers can show if specific tumours are hybrids or over-expressed specific biomarkers, even regardless of the histology of tumour types.

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

There are also cancer treatments where it doesn't matter what the origin of the tumour is or what its histology is. Keytruda was the first of these 'tumour-agnostic' treatments to be approved by the FDA, gaining a license in 2017[7] for any solid tumour with a specific genetic feature, as shown by the presence of a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). Pointing to a wider trend in oncology, Keytruda was followed by the US approval of two non-immuno-oncology tumour-agnostic drugs with Bayer's Vitrakvi (larotrectinib) in 2018 and Roche's Rozlytrek (entrectinib) in 2019.

The approval of tumour-agnostic treatments and rise in biomarker-led treatment within immuno-oncology point to a need for modern cancer treatments to try and understand specific patients and how they will respond.

As this understanding grows there is an expectation that earlier use of immuno-oncology treatments will be seen, most likely first within metastatic disease as options broaden out from aggressive chemotherapy.

Andres notes: "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, now stage three is 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.

Cancer Control in Europe

The need for immuno-oncology treatments in Europe is clear: the region is in the grip of a cancer epidemic. The region contains 9% of the world's population, but accounts for 25% of the global cancer burden.[8] Each year more than 1.9 million people in Europe die from cancer and the World Health Organization estimates that more than 40% of those could be prevented.[9]

Immuno-oncology is an important element of tackling these statistics and improving the condition of the patients they represent. While uptake of new cancer medicines across Europe varies, some of the largest country differences are observed in immuno-oncology drugs.[10] Uptake in poorer countries is around 10–20% of that observed in larger, wealthier countries, reflecting a general pattern of stronger uptake of new cancer medicines in wealthier countries compared to poorer countries.[11]

This situation is improving, especially with some countries that had a much lower uptake of new drugs than western Europe.

The increasingly high level of informed patients will be one crucial element that will drive future improvements. It's also something that Dr Karina Khidishyan from the NN Petrov National Medical Research Center of Oncology has observed across the Russian Federation, noting that patients there "are highly informed and interested in immuno-oncology."

"Our patients are well informed about the new trends in treating cancer and, over the last few years, immuno-oncology. The first question when the patient comes to me is, 'Is it possible for me to have immunotherapy?' They are very open to this treatment."

In Russia, as elsewhere, the diagnostic shift from a biopsy-based histology approach to more complete secure diagnostic molecular genetic testing allows targeted use of immuno-oncology drugs as both treatment and diagnosis advances. An additional element of cancer prevention in the country is its top-down strategy for fighting cancer (see box on page 9).

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Spotlight on Russia and its National Strategy for Fighting Cancer

Russia's National Cancer Control Plan (NCCP) was launched in 2019 with an ambitious target of an 8.5% cut in cancer mortality by 2024[12] and an estimated budget of $16.2 billion.[13]

To help it achieve this, the strategy includes a range of guidelines on prevention, screening, early diagnosis, treatment, rehabilitation and palliative care in patients.

"I think that it's a good invention and will provide a good trend to make immunotherapy available to each patient in a few years too," says Dr Karina Khidishyan.

"Before, physicians in Russia would often not know anything about immunotherapy and immuno-oncology, except in terms of interleukins or interferon, which was not so good and effective for the patient. Now, the situation has changed and physicians have more information and opportunities to use immunotherapy."

In common with many other countries, immuno-oncology treatment was often previously limited to Russia's larger cities like Saint Petersburg. However, Russia's size exacerbated the effect of this limited availability and the consequent travel burden for patients needing treatment.

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.

Combinations of immuno-oncology treatment are still a relatively unexplored . with one of the main challenges they present is in terms of their toxicity. So how do these two different types of immunotherapy interact with each other?

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. More sophisticated trial designs are needed, especially for early phase and dose escalation trials, and they'll need to be based on adaptive trial principles.

As part of this, pharmaceutical companies will need to think carefully about how to set optimal timings for initial responses, dose escalation and trial duration. They'll need to figure out 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.

At BioInvent they have spent the last five years exploring mechanisms of resistance to immunotherapy. 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.'[14] "An improved understanding of the mechanism's underlying resistance, and in particular those common to antibody drugs as a class – including direct-targeting and immune checkpoint antibodies, is needed for rational development of drugs that could help boost efficacy, and prevent or overcome antibody drug resistance," it said. [15]

As immuno-oncology understanding increases and resistance, toxicity and combination testing move centre-stage, thoughts are turning to how best to test cancer vaccines and build on Dendreon's pioneering work with Provenge.

Improving Cost and Access for New Treatments

Although more remains to be done to explore the possibilities offered by immuno-oncology, the current wave of treatments offer some major advances in cancer treatment, but in doing so they come with hefty price tags.

The likes of Keytruda and Opdivo typically cost hundreds of thousands of dollars a year for treatment,16 while CAR-T treatments can be even more expensive. When launched for its first leukaemia indication, Kymriah cost $475,000,17 though the need for the drug and others like it to harvest a patient's T-cells, genetically modify them to attack cancer and then inject them back into the body will likely always be an expensive endeavour.

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Nevertheless, costs in immuno-oncology present a number of patient access issues, as payers weigh their considerable benefits against their significant costs.

Andres says: "Prices of drugs are clearly a source of strain to healthcare payers and often out of reach for a very large number of patients. You can imagine that if that were to work on solid tumours then the strain on the payers would be even higher. It's definitely a matter of concern in this early stage. Until it's possible to make these treatments more 'off the shelf' this is going to be a challenge for the industry."

Ensuring cancer patients across the globe are treated equitably is an equal challenge for healthcare systems.

Immuno-oncology is changing the way cancer can be treated, but for it to completely change the way that cancer is actually treated around the world requires attention to be paid to how the drugs are priced.

One way of addressing this is by improving manufacturing processes so that costs can be lowered. However, given how complex and expensive current processes are, these changes will not happen overnight.

In addition to working to lower costs, another way to increase access to new immuno-oncology drugs is expanding the geography of clinical research. Most clinical trials in the area are conducted more or less in the same location, ignoring a number of 'untapped' regions.

This coud provide a company access to a larger pool of eligible patients, and the patients will have a chance to receive new effective treatments. Biotechs could also benefit from this as they generally don't have a lot of research centres to start with.

Conclusion

There is a lot of activity in immuno-oncology and much more potential still to be uncovered in the field.

Pharmaceutical companies' future efforts will need to establish how to make effective immuno-oncology drugs even more effective, and there is a clear need for further trials of different combinations of these new cancer drugs with each other as well as with more traditional treatments.

In tandem with this, there is room to do more to tackle a greater number of hard-to-treat cancers with immuno-oncology drugs. Their ground-breaking performances to date must be investigated as far and wide as it is scientifically reasonable to do so.

However, the need for further clinical trials must see them undertaken in as patient-centric a manner as possible. Patient awareness of these new medicines and the efficacy they may have in new indications or cancers places perhaps a greater than usual burden of responsibility on pharmaceutical companies.

Finally, companies must also manage the undoubted budgetary strain that immuno-oncology treatments can place on healthcare systems.

These will be challenges for the pharmaceutical industry, but can be overcome - indeed they must, if the healthcare benefits of immuno-oncology are to be realised.

References

1. What you need to know about immunotherapy side effects
https://www.cancer.net/blog/2018-02/what-you-need-know-about-immunotherapy-side-effects

2. Professor Tasuku Honji's banquet speech, December 2018
https://www.nobelprize.org/prizes/medicine/2018/honjo/speech

3. Closing in on Cancer, by Andy Coghlan in New Scientist, March 2016
https://www.sciencedirect.com/science/article/abs/pii/S0262407916600854?via%3Dihub

4. Nobel winner Tasuku Honjo sees bigger role for immunotherapy in battling cancer
https://www.japantimes.co.jp/news/2018/12/07/national/science-health/nobel-winner-tasuku-honjo-sees-bigger-role-immunotherapy-battling-cancer/#.XqZ1odNKjOT

5. Roche gets first checkpoint inhibitor OK in breast cancer
https://pharmaphorum.com/news/roche-gets-first-checkpoint-inhibitor-ok-in-breast-cancer

6. Pioneering cancer drug, just approved, to cost $475,000— and analysts say it's a bargain
https://www.statnews.com/2017/08/30/novartis-car-t-cancer-approved

7. FDA approves first cancer treatment for any solid tumor with a specific genetic feature
https://www.fda.gov/news-events/press-announcements/fda-approves-first-cancer-treatment-any-solid-tumor-specific-genetic-feature

8. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018
https://www.ejcancer.com/article/S0959-8049(18)30955-9/abstract

9. Cancer: Data and statistics
http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics

10. Comparator Report on Cancer In Europe 2019 –Disease Burden, Costs and Access to Medicines
https://www.efpia.eu/media/413449/comparator-report-on-cancer-in-europe-2019.pdf

11. Comparator Report on Cancer In Europe 2019 –Disease Burden, Costs and Access to Medicines
https://www.efpia.eu/media/413449/comparator-report-on-cancer-in-europe-2019.pdf

12. Creation and development of the National Cancer Control Plan in Russia
https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.10524

13. Russia to shell out billions of dollars to fight cancer
https://tass.com/society/1008459

14. Targeting the Antibody Checkpoints to Enhance Cancer Immunotherapy – Focus on FcγRIIB
https://www.frontiersin.org/articles/10.3389/fimmu.2019.00481/full

15. BioInvent announces publication of review article in Frontiers in Immunology on resistance to antibody drugs
https://bioinvent.com/media/press-releases/releases?id=7ACFEC426737602B

16. Bristol-Myers will sell Opdivo in China at half of US cost, setting precedent for checkpoint wave — report
https://endpts.com/bristol-myers-will-sell-opdivo-in-china-at-half-of-us-cost-setting-precedent-for-checkpoint-wave-report

17. Novartis matches Gilead on price in new CAR-T use
https://pharmaphorum.com/news/novartis-matches-gilead-kymriah

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