PEER REVIEWED

The Future Market Dynamics and Opportunities in Immune-oncology

IO is transformative
Long term survival, tumour-agnostic effects and potential for cure in a fraction of patients is the key catalyst for the explosion of research and recent approvals in IO.

What was the catalyst for increased focus on immuno-oncology (IO)?

IO has witnessed a long history of highs and lows. Although conventional cytokines and vaccine immunotherapies were approved for certain cancers, high toxicities, low efficacy and conflicting evidence limited their widespread adoption. Cancer immunotherapy research regained momentum with the finding that blocking inhibitory receptors on T cells can re-invigorate their antitumour function. This led to the discovery of the first checkpoint protein CTLA4, and approval of ipilimumab, a CTLA4-blocking antibody for melanoma, laying the foundation for modern-day IO. Subsequently, discovery of another checkpoint axis, PD-1/PD-L1, along with the finding that anti-PD-1 afforded higher response rates and survival than anti-CTLA4, and further that their combination resulted in even higher benefit, opened the floodgates of IO.

Deep durable responses, including complete responses in a fraction of patients and improved long-term survival rates with these therapies compared with standard treatment options, then led to a series of approvals in multiple tumours, including melanoma, NSCLC, squamous cell carcinoma of head and neck (HNSCC), bladder cancer, renal cancer, triple negative breast cancer (TNBC), hepatocellular carcinoma (HCC), Hodgkin's lymphoma and several others over the last four to five years. FDA approval of anti-PD-1 in microsatellite high (MSI–H) solid tumours also represents the first tissue-agnostic approval of an oncology drug based on a tumour biomarker. Benefits with checkpoint blockers have also been observed in high unmet need segments including patients with poor prognostic characteristics.

Their relative safety, lack of impairment of quality of life, combinability with diverse modalities and potential for cure opened the way for use of these agents in treatment-naïve and early-stage settings. This resulted in their use as backbone therapies across the patient continuum. CAR-Ts and T cell engaging approaches further continued the success story and reinforced IO as a fifth pillar of cancer treatment (after surgery, radiation, chemotherapy and other targeted agents).

Are there any overarching themes emerging from the current MoAs being targeted?

Exploring IO Mechanisms beyond Anti PD-1/L1
Anti-PD-1/L1 redefined treatment in many indications; however, only a limited set of patients respond to these agents. This has led to a revolution in exploring other novel IO approaches that can raise the bar. Several new classes of agents targeting diverse novel immune mechanisms are being assessed, including co-stimulatory or co-inhibitory agents, cytokines, chemokines, oncolytic viruses, neoantigen vaccines, metabolic signalling inhibitors, bifunctional mAbs, fusion proteins, adoptive cell transfer therapies such as CAR-Ts and several others. Immune mechanisms which are examined range from stimulation of innate immunity, adaptive anti-tumour immunity, enhancement of T cell priming and antigen presentation, epigenetic modulation, mechanisms to overcome TME resistance and improve immune cell infiltration.

Clinical experience suggests that single agent efficacy of these therapies will be important not only for their success as monotherapies but also as combinations. Only a few IO agents have been able to pass this benchmark so far.

IO Combinations can Provide Benefit in IO Resistant/Refractory Segments
Several novel IO agents and non-IO drugs are being combined with checkpoint inhibitors primarily to improve rates, depth and durability of responses in low immuno-responsive tumours (e.g. microsatellite stable cancers, PD-L1 low expressors and tumours with low mutational burden). Combinations are also being evaluated with the hope that they will enhance infiltration of immune effector cells into tumour types generally considered to be 'immune excluded' or 'immune deserts' and turn them into 'hot' tumours. Moreover, combinations are also being tried with the goal of restoring responsiveness in tumours that have previously experienced checkpoint inhibitors and have since become refractory or resistant.

Frenzied exploration of mechanisms that can raise the tail of the curve
Mechanisms that can further enhance survival rates seen with anti-PD-1 and anti-CTLA-4 are being intensely investigated in clinic.

Unprecedented Rise in IO Combination Trials Worldwide
Combinations that can improve the therapeutic index of IOs and extend their applicability to low immune-responsive tumours or IO experienced patients are being vigorously pursued. However, this has resulted in intense competition to enroll trial participants and increased times and costs for drug development in the IO arena.

Although optimal combinations are yet to be identified, a few have been approved, including the combined IO/IO regimen of PD-1 and CTLA-4 blockade mentioned above. While other novel IO/IO combinations are still exploratory, promising early results have been seen in trials of checkpoint inhibitors combined with TLR agonists, stimulatory cytokines and oncolytic viruses. This still needs to be validated in a broader spectrum of indications. On the other hand, combinations of checkpoint inhibitors with conventional chemotherapies and radiation have shown some benefit and also resulted in some approvals, however, benefit with chemotherapy combinations is inconsistent across tumours and is not evident in some tumours

such as gastric cancer. Anti-PD-1/L1 agents with tyrosine kinase inhibitors (TKIs) have demonstrated meaningful efficacy in low immune-responsive tumours. Combination of anti-PD-1 Pembrolizumab with Lenvatinib was recently approved in endometrial cancer (September 2019). The potential of TKI combination strategies should be investigated further.

One major challenge is the virtual explosion IO combination trials worldwide which has put severe constraints on resources. A recent analysis showed that there are 1716 open trials of anti PD-1/L1 antibodies attempting to enroll 380,900 patients.

PD-1 Experienced Population Represents a Significant Unmet Need

PD-1 pathway blockade provides benefit in only a subset of patients. A majority of patients either fail to respond to PD-1 pathway blockade or eventually progress. No effective therapies are available for a large population of patients progressing on anti PD-1/L1 therapy in tumours where anti-PD-1/L1 are the standard of care. Identification of mechanisms of resistance and ways to overcome it, characterisation of patterns of progression and defining "true progressors" has become a key pharma focus. Several IO and non IO strategies are in clinical evaluation to explore therapeutic potential in PD-1 progressors including monotherapy or IO combinations with other checkpoint inhibitors, T cell agonists, stimulatory and inhibitory cytokines, metabolic targets, TLR agonists, vaccines, oncolytic viruses, HDAC inhibitors, tyrosine kinase inhibitors, antibody drug conjugates and cellular therapies, besides conventional modalities. While most of these strategies have provided modest objective response rates below 30%, some approaches appear more promising than others, such as IO combinations with TLR agonist, multi TKI, and ADCs. The success of the ADC approach is reflected in the first FDA approval of Enfortumab Vedotin, a Nectin-4 ADC, in IO progressors for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have received prior treatment with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.

Expanding Applicability of CAR-Ts to Solid Tumours

A new IO modality called CAR-T – for chimeric antigen receptor T cell therapy – has been gaining a lot of buzz since the approval of two agents in this class in 2017 for blood cancers. While their utility in inducing life-saving remissions in refractory and relapsed lymphomas and leukaemias is a true breakthrough, one must acknowledge that they come with severe side-effects and a heavy price tag. A number of trials are now evaluating CAR-Ts against various targets in both haematological and solid tumours. Successful application of CAR-Ts in solid tumours hinges on improving CAR-T persistence, overcoming barriers in the microenvironment and manufacturing challenges. Intense innovation is being pursued in technical designs of CAR-Ts to engineer and develop improved versions that address the unmet needs in solid tumours notably "armoured" CARs, integration of safety switches and additional genes to reduce toxicities, improve tumour infiltration, CAR-T persistence and functionality, combat suppressive tumour microenvironment, and overcome T cell exhaustion.

Development of tumour-agnostic/modular platforms, off-the-shelf allogeneic CAR-Ts, use of iPSCs and better gene editing methodologies are other areas where many companies are concentrating their efforts to develop next-generation CAR-Ts. Innovative technologies brought to the clinic by companies such as Gracell Biotechnologies have considerably shortened the duration of the manufacturing from weeks to a day, thus significantly reducing vein-to vein time and accessibility. These next-generation engineered cellular therapies are expected to address the current challenges to make them widely available.

Increasing Focus on Differentiated Modalities

While discovery of new MoAs/targets still remains the heart of new drug development, an increasing thrust is being observed towards developing differentiated modalities/engineered bio-therapeutics in the form of bi-specifics/multispecific fusion proteins or mAbs, immunomodulatory ADCs, engineered CAR-Ts and other immune cells, engineered oncolytic viruses either against multiple targets to address drug resistance/relapse or to confer enhanced features which can improve safety, specificity, pharmacokinetic or immune properties. On one hand, these developments have expanded the treatment choices; on the other hand, they have complicated the portfolio and drug development decisions for the innovator companies.

What will the IO market look like in five years? What will be the key developments? How will these developments come about?

Rapid Growth of the Global IO Market
The global IO market will reach $100 billion by 2022. Investment in IO will rely heavily on innovative research, pinning down appropriate patient populations, and on partnerships by biotech and pharma companies

The global cancer immunotherapy market is set to reach about $30 billion in 2019 and will steadily rise to about $100 billion by 2022. This is expected to be driven largely by use of these agents in nine key tumour types (melanoma, NSCLC, urothelial, RCC, HNSCC, TNBC, gastric, esophageal and HCC). The four key players will include BMS, Roche, Merck and Astrazeneca. These players are investing heavily in both basic research and clinical trials which will contribute to market growth. Increasing innovation and approval of novel treatments in the Asia Pacific region will also contribute to market growth. A large share of this growth will be the result of key IO approvals in early disease, such as adjuvant and neoadjuvant settings. It is likely that these advances could result in cannibalisation of market share from the advanced disease settings but will pave the way for differentiated strategies that will work in those settings. Another constraint on market growth will be the high cost of these therapies.

IO Biomarkers: Where do we Stand?

The limited efficacy of IOs demonstrated in unselected populations thus far, coupled with several failures, indicates that appropriate predictive biomarkers that enrich for responders, will be crucial in order to enhance benefit rates and for developing tailored therapies. This recognition has led to the exploration of a range of immune markers predictive of IO monotherapy and combination response in pivotal and early-phase studies. Consequently, there has been

a rapid rise in the market for various IO assay reagents and technologies. According to some recent reports, the global IO assays market was ~ 2.9 billion USD in 2018 and is expected to exceed 6 billion USD by 2025, growing at a CAGR of around 12.9% between 2019 and 2025.

There is also substantial interest in developing predictive biomarkers from liquid biopsies and other non-invasive methods, although identification of appropriate biomarkers is severely limited by (a) complexity of tumour, microenvironment and immune system interactions, (b) variability in assay development and interpretation, and (c) lack of validation in large prospective trials. The high cost of new technology and diagnostics required for many of these unique biomarkers will also be a challenge.

What other key areas are clinical immuno-oncologists currently exploring?

Despite several successes, IOs still remain a difficult area to tackle. Clinical immuno-oncologists are challenged with several key questions on multiple fronts. Besides identifying promising next-gen drug candidates, predictive biomarkers of response, combinations that can improve the efficacy and/or immune sensitivity of the low responsive tumours, other areas of focus in IO are:

Trial Design, Endpoints and Regulatory Considerations

FDA's commitment to bring new lifesaving treatments into the market has contrasted with the recent failure of many such drugs that were conditionally approved on the basis of endpoints other than survival, which has raised several questions regarding appropriate trial designs. One issue being hotly debated is whether such failed IO drugs should be withdrawn or continued to be given to patients, considering their benefit in some patients.

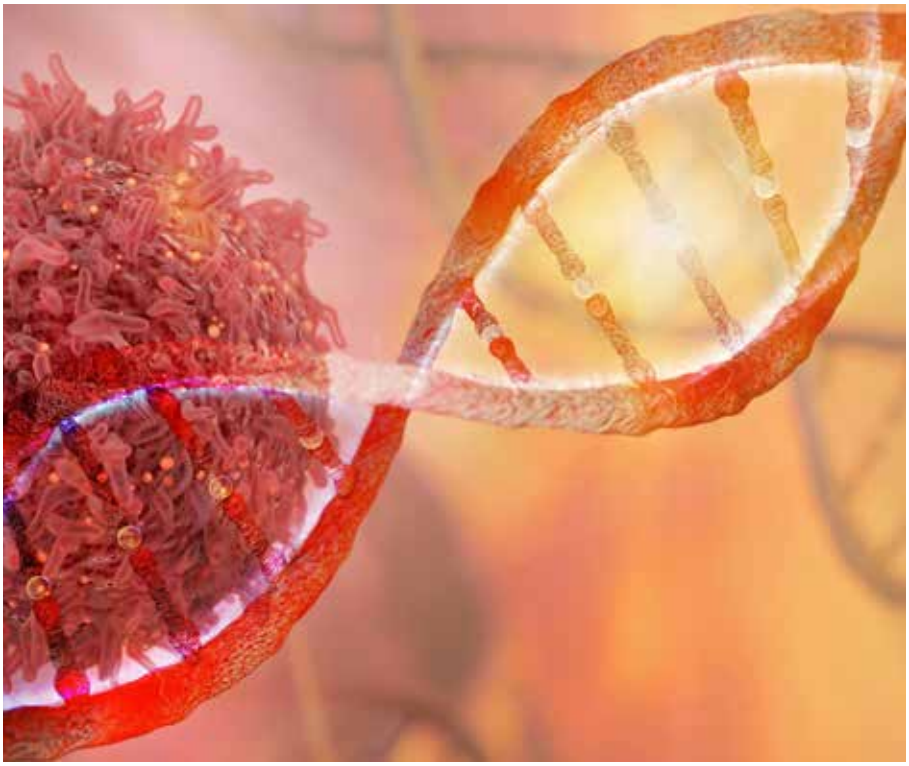
The guidelines for next-gen innovative therapies such as bispecific/multispecific molecules, fusion proteins and cellular therapy products are also rudimentary and will need to be clearly defined.

Potential in Early-stage Disease, Treatment Sequencing, Duration and Impact on Later Line Therapy

Immunotherapies are shifting to early-stage disease settings in many indications. Positioning in early disease, treatment-naïve settings and as maintenance will delay disease progression but will also modulate patient immune profiles, which will impact initiation and choice of next-line therapy. Tumour immune characteristics influence not only response to IOs but also efficacy of conventional therapies and targeted agents given post IO which will complicate treatment sequencing decisions. Other challenging questions are optimal duration of IO treatment, continuation beyond progression and when to discontinue the treatment. Many trials are trying to address these issues.

Value-based Frameworks for Immune-oncology

Given the unique pattern of responses with immunotherapies, current value frameworks are inadequate to measure the magnitude of clinical benefit. It has also become essential to address the cost-effectiveness of these new and expensive therapies.



Jaideep V. Thottassery

Jaideep V. Thottassery, Director, Life Sciences Consulting, Oncology at SmartAnalyst. With a PhD in biochemistry from the University of Missouri-Kansas City, Jaideep performed postdoctoral research at the University of Tennessee Health Sciences Center, and at St. Jude Children's Research Hospital in Memphis. At SmartAnalyst, he provides technical expertise in executing oncology projects, including clinical development strategies, life cycle management, and asset and disease strategies. He has a focus on new cancer immunotherapies and targeted agents.

Nidhi Dhingra

Nidhi Dhingra, Associate Director, Oncology at SmartAnalyst. Nidhi has over 12 years' experience in pharmaceutical research/drug discovery and has worked at Dr Reddy's Labs, Matrix-Mylan Laboratories and Panacea Biotec Ltd. At SmartAnalyst, she has led projects involving clinical trial profiling of key immunotherapy compounds in solid and haematological malignancies, as well as leading efforts on a proprietary IO database, the IO Navigator. Nidhi holds a PhD degree in molecular biology.