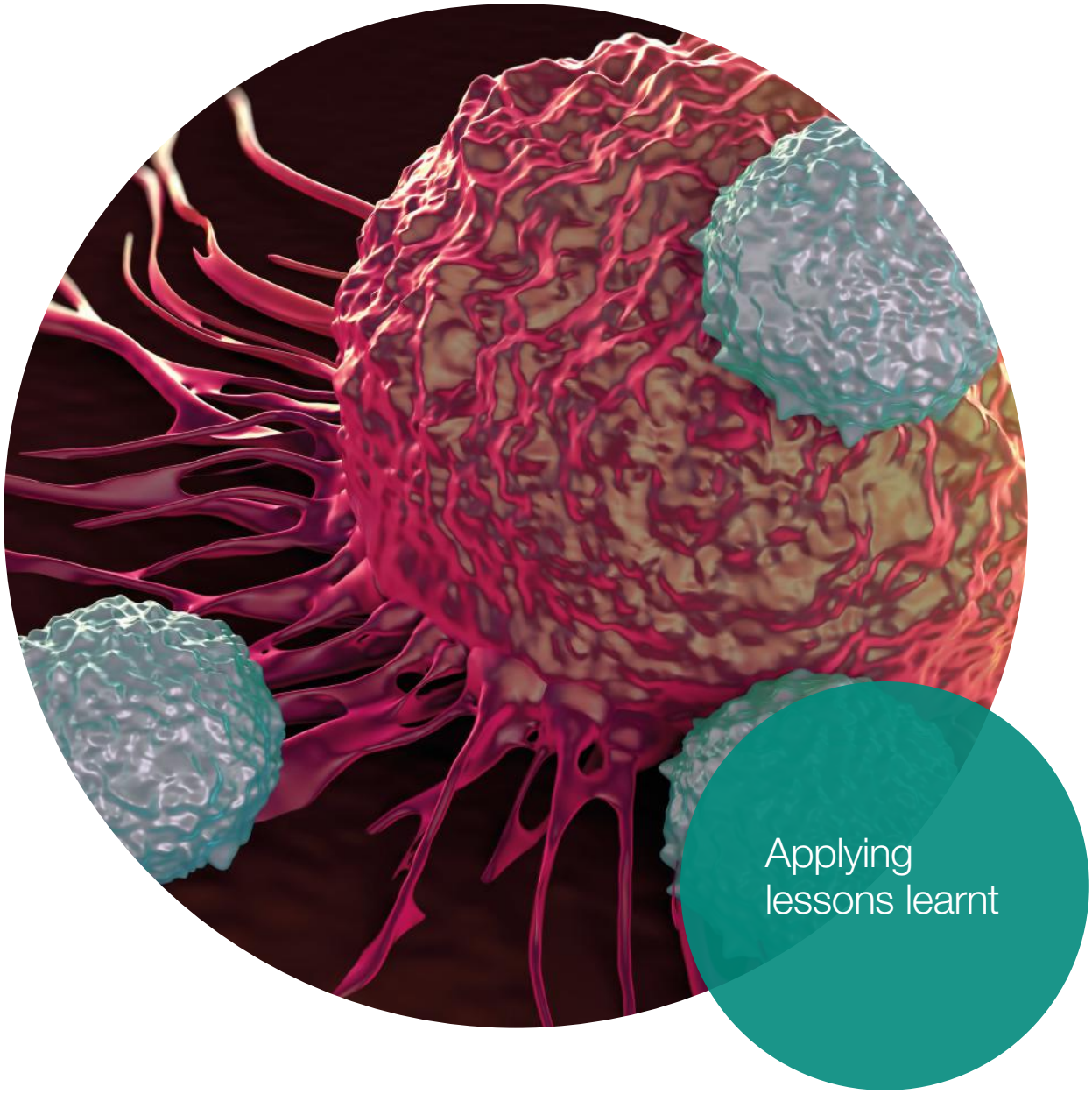
Setting the Scene in Immuno-oncology



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General Aspects of Immuno-oncology

Immuno-oncology (I-O) plays an increasingly important part in cancer treatment, utilising the body's own immune system to fight the disease. Although not a new concept, I-O has progressed considerably in the last 10-15 years with approvals for numerous I-O therapies including vaccines, cytokines, tumour-directed monoclonal antibodies, and immune checkpoint inhibitors.

The goal of I-O therapy is to restore the ability of the immune system to eliminate cancer cells by either activating the immune system directly (active immunotherapies) or by inhibiting mechanisms of suppression by tumours (passive immunotherapies). By harnessing the body's own immune system to elicit an immune response that fights cancer, active immunotherapies such as therapeutic cancer vaccines, cytokines, and mediators of T-cell activation can strengthen the anti-tumour response. While passive immunotherapies such as tumour-directed monoclonal antibodies (mAbs) and cell therapies act on the tumour, they do not require the patient's own immune system to initiate a response. ICON continues to be immersed in the development of both passive and active immunotherapy approaches, allowing sponsors to overcome the challenges of I-O.

Developing I-O trials requires thoughtful planning and must take into account unique challenges presented by immunotherapies, including:

- Delayed clinical benefit, including evaluating true progression versus pseudo-progression
- Identifying meaningful endpoints that may extend beyond progression free survival and overall survival
- Managing safety concerns within the trial
- Perspectives of patients, physicians, and payers

Recent developments in I-O offer great opportunities for all stakeholders in the war on cancer, including:

- The approval of a cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)–binding antibodies e.g. ipilimumab.
- The approval of programmed cell death protein 1 (PD-1)–targeted antibodies and the rapid development of other PD-1 and programmed cell death protein 1 ligand (PD-L1)–targeted agents, e.g. nivolumab, pembrolizumab, atezolizumab.
- Interesting results with genetically engineered chimeric antigen receptor T-cells (CAR-T cells) developed by Kite Pharma, Novartis, Juno and Bluebird Bio.

These agents, along with a very long list of vaccines, antibodies, and small molecules that trigger immune cell activation, elimination of regulatory cells, or signals that extinguish the immune response, are likely to dominate therapeutic advances in oncology for the next 10 years.

ICON experience in Immuno-oncology trials for the last 5 years

78 studies

Over 11,000 patients

4,400 sites

Lessons Learned from I-O Trials

In conducting almost 80 I-O trials to date, ICON has been able to accrue expertise to manage specific challenges.

Pseudo-Progression and I-O Therapy

Cancer immunotherapy may result in limited tumour shrinkage and such tumour shrinkage can take a longer time to observe. Immune-related tumour response is often observed with I-O therapies. Pseudo-progression, in which the tumour size increases compared to that seen at baseline assessment, may occur when T cells infiltrate the tumour site and cause tumours to inflame/flare. Physicians must bear in mind this property of the immune-related response in cancer immunotherapy and should not be classified as true progression.

There are considerations for evaluating a true progression vs. pseudo-progression:

True progression may be indicated if the patient is experiencing deterioration in performance status and a worsening of systemic symptoms and/or symptoms of tumour enlargement. True progression is also accompanied by an increase in baseline tumour burden and an appearance and growth of new lesions, which biopsies may confirm the evidence of tumour growth.

However, **pseudo-progression** may be present if the patient's performance status and systemic symptoms remain stable or improve, and if any increase in baseline tumour burden or new lesions is followed by a noticeable response. There may be evidence of T-cell infiltration in tumour biopsies if pseudo-progression is present.

ICON has used additional training and special refreshers to address these issues with the sites and therefore keep early unnecessary patient withdrawals to an absolute minimum. Implementation of immune-related response criteria is essential for the assessments of the true efficacy of a cancer immunotherapy. Working with experienced sites becomes all the more critical taking these factors into consideration.

Detection of Immune Receptor "Signal", or Tumour Marker/Protein Expression

Normally inclusion in an I-O trial is dependent upon the patients having a specific immune receptor "signal", or a specific tumour marker/protein expression. The challenge with this is that the site laboratory facilities are often not set up to consistently assess such parameters in a timeframe commensurate with the need to ensure consistent application of the trial qualification requirements of patients. The solution is to establish strong feasibility criteria with very specific requirements for local laboratories capabilities and considering a central laboratory to confirm the local laboratories results. The central laboratory is the better option for consistency but can be costly and extend the qualification/screening time.

Immune-related RECIST criteria (irRECIST)

Applying the standard chemotherapy based response assumptions to immunotherapy trials could result in inaccurate interpretation of response, premature therapy termination, and unnecessary removal of participants from a trial. Because of these difficult response assessments in I-O trials special immune related RECIST criteria were developed, the so called irRECIST. ICON's imaging group has used these criteria extensively over the last years.

In order to accurately assess response assessments in I-O trials, immune related RECIST (irRECIST) criteria have been developed.

ICON's imaging group has applied these criteria in:

More than **14 studies**

5000 patients

1500 sites

Operational experience identifies the following factors as key to success:

- Ensure that a clear "read design" has been established at the start of a study to avoid any misunderstanding and confusion.
- Ensure adequate training for the Independent Reviewers on the irRECIST rule set.
- Due to the competitive nature of the projects timelines are often very aggressive. Close cooperation is needed with the clinical research assistants to ensure timely submission of scans and query resolution. Implementing a strong escalation process up front can help mitigate these challenges.

Safety Aspects of I-O Trials

As with any cancer study, physicians management of toxicity is critical. Although hair loss, nausea, and vomiting, all vexing issues associated with chemotherapy, are not issues with I-O drugs, the drugs are far from being free of toxicities. Notably, with CAR-T therapies, significant sequellae remains an omnipresent and sometimes lethal risk, because of Cytokine Release Syndrome and neurotoxicity, both of which are largely related to therapeutic efficacy.

Dependent on the type of immunotherapy used, a new characteristic safety profile could emerge which need specific considerations on how to manage patients. Most notable is that these immune activators can generate unwanted immune or inflammatory responses. To date, the principal toxicities have been diarrhea (sometimes severe and long lasting), rash, and fatigue. Less common side effects have included dysfunction of the kidneys and liver; more worrisome, a variety of endocrine effects causing abnormalities in the thyroid, pancreas, and pituitary gland that sometimes require long-term hormone replacement.

The latter is a new set of toxicities for oncologists who will need to quickly learn to keep these toxicities “top of mind” and become accustomed at evaluating and managing them. Many of the tissue toxicities, such as colitis, require steroids and occasionally other expensive agents. Endocrine abnormalities must first be recognised and then managed with hormone replacement therapy, which will require oncologists to either form closer relationships with endocrinologists or take the time to increase their endocrinology knowledge.

An obvious means of assessing toxicity results is by monitoring the expression of Tumour-Associated Antigens (TAAs) in normal tissue. Antibodies raised against these TAAs can react against normal cells either by inducing complement-mediated lysis or facilitating antibody-dependent cell-mediated toxicity (ADCC) by leukocytes. It is becoming increasingly clear that cancer immunotherapy is a balancing act between antitumour immunity and immune toxicity. The association between immune toxicity and increased antitumour effects after immunotherapy highlights the need for strategies that can mitigate the risk of these toxicities during immunotherapy while preserving activity against malignancy.

ICON has managed specific challenges in safety management in I-O studies through a variety of specific measures which can be easily adapted to the specific needs of any I-O programme:

- Having well trained physicians available to address safety questions in real time
- Site visits by medical monitors to reiterate training / safety signal identification/ treatment algorithms
- Understanding the safety signals and clearly educating investigators on these signals and early identification. E.g. investigators have been instructed in case of a vaccination and several inoculations planned, the site of application should be changed between the inoculations to minimise the number and severity of reactions
- Developing patient information packets so patients know what to report (and how quickly). E.g. in a vaccination programme subjects used a diary to record local injection site reactions at certain time points after the injection when they have been already discharged and are at home
- Having enough information on treatment paradigms for safety events or ensuring that each case is documented in terms of treatment in order to develop algorithms / recommendations for treatment
- Subjects should be observed immediately after immunotherapy application for signs of an acute allergic reaction. If symptoms such as difficulty in breathing, angioedema, diffuse and significant urticaria, and/or hypotension are observed, immediate emergency medical attention has to be provided. Therefore the selection of clinics/hospitals having experience in I-O programmes and having an emergency unit are preferred
- Providing regular forums where case studies can be reviewed or shared with Investigators

Current I-O Market

The Patient and Physician Perspectives

I-O has had a singular impact on patients and providers. Patients have a growing recognition of the potential of I-O agents. With the current approvals, patients with a variety of metastatic malignancies are, or soon will be, hearing of potentially positive results in their particular disease. Up until recently, access for patients to these new agents has largely been through clinical trials, although there is some anecdotal evidence of patients receiving these agents off label. As these drugs are expensive, even with marketing authorisation, reimbursement through payers is not guaranteed.

The Payer Perspective

The implications for insurance companies, employers, and now patients are likewise daunting. It is important to note that the PD-1 inhibitors have an undefined duration of treatment, with some patients on therapy for over a year. A 1-year course of a PD-1 inhibitor is approximately $180,000. If early results on the aforementioned cancers pan out, it is possible that 250,000 to 500,000 patients per year might be eligible to receive a course of an I-O agent or agents in the United States alone.

Of note, combinations started to demonstrate an improved outcome. Studies in melanoma and early results in other tumours suggest that a CTLA-4–binding antibody is likely to work better in combination with a PD-1 inhibitor than either drug alone. Although a person's size would determine the total costs associated with treatment with I-O agents, pricing of currently approved drugs, of those expected to be approved soon, and associated healthcare costs will all be very significant. If current drug prices are any indication, it is not hard to imagine that a significant proportion of cancer patients will be prescribed a regimen with a price tag in excess of $200,000 if they remain on therapy for a year.

$30B+

Predicted market size for immune-oncology agents by 2020

It is important to appreciate that the I-O market is very young, and it is possible that the approval of multiple PD-1 and PD-L1 inhibitors might allow for intra-class price competition, as witnessed with the emerging market of hepatitis C drugs. While first-in-class agents generated a hefty price tag, the entrance of alternative curative therapies led to marked price concessions by manufacturers. The same may happen with immune-oncology agents, largely driven by a consolidating payer landscape.

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Conclusion: Future in I-O

With the implementation of immunotherapy regimes in the apothecary of cancer therapies a couple of further challenges in Drug Development strategies are foreseen in the future:

– Treatment algorithms are changing quite rapidly and therefore trial design planning and the selection of comparator/ SOC is becoming more and more challenging
– Complexity of especially early phase studies is increasing
– New safety signals are seen and this will continue with the introduction of new combination therapies

In taking a closer look at over 2,500 commercially relevant and active I-O clinical trials there are two classes experiencing interesting trends, each with their unique challenges. Therapeutic cancer vaccine trials have seen a shift in sponsors while steadily decreasing in number. Checkpoint inhibitors, meanwhile, have been rapidly gaining momentum and Adoptive Cellular Transfer techniques are in the ascendancy.

Checkpoint Inhibitors

On the opposite end of the spectrum, checkpoint inhibitor trials are exhibiting a rapid-fire growth pattern and tremendous success. Since 2010, they have experienced a twenty-fold increase in the number of commercially relevant trials as compared to those started in 2005.

Advanced metastatic cancers, those where other treatments have failed, remain the top patient segments in checkpoint inhibitor trials. Challenges in this space lie in identifying predictive and prognostic biomarkers. Correlating response rate to the PD-L1 biomarker, which is currently seen in 39 percent of checkpoint inhibitor trials measuring biomarkers, is not always possible.

CAR-T Cells

Investments into updated adoptive cellular transfer (ACT) initiatives, such as CAR-T cells, continue to develop and expand quickly in both the pharma and biotech sectors. Of note, while the CD8+ CAR-T therapeutic platform has historically been anchored in monotherapy for CD19-expressiong lymphomas and leukemias (demonstrating great improvement in PFS, OS and ORR in the relapsed setting), recent scientific conferences have showcased a variety of new research focusing on novel cell surface targets (a few tumour-specific, i.e. mutant/truncated receptors, transmembrane signaling variants, but most tumour-associated, i.e. ‘stemness’ markers, clusters of differentiation, growth factor receptors), as well as additional ACT immune effectors (NK cells, CD 4+ T cells, and T cells).

As such, CAR-T cells may either stand alone as a single modality or they may be combined with some in the above list of novel agents. A current review of ClinicalTrials.gov reveals more than 150 trials underway in this space, including a significant proportion in combination with other novel immune-modulatory agents. However, as CAR-T monotherapy still elicits notable and sometimes lethal toxicity profiles and off-target effects, combinatorial approaches will require enhanced clinical vigilance and oversight; especially if the combining agent(s) remains largely investigational in its own right.

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