White Paper

IMMUNO-ONCOLOGY CLINICAL DEVELOPMENT

Moving novel therapies forward

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The field of immuno-oncology is undergoing a period of intense innovation. In 2017, the FDA approved 46 novel drugs – more than double the 2016 figure. Among these were two chimeric antigen receptor (CAR)-T cell therapies, and several drugs that inhibit immune checkpoints. These represent new, powerful treatment options for cancer patients worldwide. However, this burst of innovation is resulting in an overcrowded market – especially as combination therapies increasingly become the standard of care – which complicates the landscape for sponsors of new therapies. This white paper examines the discipline of immuno-oncology now and into the future – and ultimately focuses on how IQVIA is empowering the oncology community to advance the science and outcomes of cancer care through its deep bench of domain expertise, innovative solutions and application of human data science.

INTRODUCTION: IMMUNO-ONCOLOGY LANDSCAPE AND CHALLENGES

Cancer is a chronic immunologic disease. Tumors express tumor antigens; these are recognized by the immune system, which eliminates many early tumors. However, tumors have multiple mechanisms to evade the immune system, including expression of molecules that inhibit immune response.

Cancer has been progressively redefined over the past 20 years, with increased biomarker-based segmentation and greater complexity (Figures 1 and 2). Therapy options for multiple tumor types have increased, adding to treatment complexity, both in terms of diverse mechanisms of actions as well as the number of drugs for each mechanism of action (MoA) class. The pace of development has been exceptionally fast in the last decade due to a combination of factors, including an increasing focus on targeted drug development based on biomarker segmentation and favorable regulatory policies such as the introduction of “breakthrough therapy” designations. Currently, multiple agents with similar MoA are available, presenting a complex situation for clinicians with limited clinical data directly comparing newer treatments with established ones.

Executive Summary

Cancer has been progressively redefined over the past 20 years, with increased biomarker-based segmentation and greater complexity.
Figure 1: Cancer has been progressively redefined over the past 20 years

<table>
<thead>
<tr>
<th></th>
<th>1996</th>
<th>2006</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
<td><img src="image1" alt="Pie Chart" /></td>
<td><img src="image2" alt="Pie Chart" /></td>
<td><img src="image3" alt="Pie Chart" /></td>
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<tr>
<td></td>
<td>Non Segmented Lung Cancer</td>
<td>EGFR</td>
<td>ALK</td>
</tr>
<tr>
<td><strong>Breast cancer</strong></td>
<td><img src="image4" alt="Pie Chart" /></td>
<td><img src="image5" alt="Pie Chart" /></td>
<td><img src="image6" alt="Pie Chart" /></td>
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<tr>
<td></td>
<td>HR +ve</td>
<td>HR -ve</td>
<td>HR +ve, Premenopausal</td>
</tr>
<tr>
<td><strong>Colorectal cancer</strong></td>
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<td><img src="image8" alt="Pie Chart" /></td>
<td><img src="image9" alt="Pie Chart" /></td>
</tr>
<tr>
<td></td>
<td>Non Segmented CRC</td>
<td>KRAS-WT</td>
<td>KRAS-MUT</td>
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<tr>
<td><strong>Melanoma</strong></td>
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<td><img src="image11" alt="Pie Chart" /></td>
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<tr>
<td></td>
<td>Non Segmented Melanoma</td>
<td>Melanoma BRAF-Mu</td>
<td>Melanoma BRAF-WT</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
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<td><img src="image14" alt="Pie Chart" /></td>
<td><img src="image15" alt="Pie Chart" /></td>
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<tr>
<td></td>
<td>Unsegmented Prostate cancer</td>
<td>BRCA*</td>
<td></td>
</tr>
</tbody>
</table>

Source: FDA.gov and Drugs@FDA, Mar 2017; IQVIA, ARK R&D Intelligence, Feb 2017; IQVIA.
Immuno-oncology has created an expansion of immune-related molecular, cellular and genetic targets and immune related responses to therapies; these targets and responses are now the objects of new diagnostic assays and new therapeutic agents that modulate the patient’s immune response to tumors. Such assays and therapies can be combined with the older, more restrictive concept of precision medicine, targeting the genes and protein expression of one type of cancer cell only. Therefore, this creates many new levels of patient subpopulations, each with a different possible response to a defined therapeutic combination.

In this environment of increasing precision and individuality, finding the right sites with patients available for a defined clinical trial is harder than ever – and may require a complex definition of tumor gene signature and a defined immune signature. For example, PD-1 expressers, or not? Or checkpoint inhibitor-naive or refractory/resistant? We must now rely on human data science analytics to find patients and sites with the correct combination of diagnostic criteria and previous therapies.

In oncology – especially with immunotherapeutic combinations using checkpoint inhibitors as a “backbone regimen” across many tumor types – data analytics becomes an indispensable tool to efficiently plan and conduct complex modern clinical studies.

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**Figure 2: Increasing treatment complexity over the past 20 years**

Number of treatment options over time for selected tumors (1996–2016)

<table>
<thead>
<tr>
<th>Year</th>
<th>Breast Cancer</th>
<th>Prostate Cancer</th>
<th>Lung Cancer</th>
<th>Melanoma</th>
<th>CLL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>2 6</td>
<td>3</td>
<td>4</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>2006</td>
<td>1 4 7</td>
<td>6 1</td>
<td>7 2</td>
<td>1 2</td>
<td>2 2</td>
</tr>
<tr>
<td>2016</td>
<td>4 4 9 1 1</td>
<td>9 2 1 1</td>
<td>8 1 3 4 3</td>
<td>1 7 4 3</td>
<td>3 4 3</td>
</tr>
</tbody>
</table>

Legend:
- **HER2**
- **Hormonals**
- **Others**
- **Immunotherapy**
- **BRAF**
- **Chemotherapy**
- **EGFR**
- **Anti-CD**
- **Other small molecules**
- **CDK**
- **ALK**

Source: Drugs@FDA, Feb 2017; IQVIA, ARK R&D Intelligence, Feb 2017; IQVIA Institute, Mar 2018.
There is a dynamic relationship between any cancer and the patient’s immune system (Figure 3). Elimination refers to the stage in which cancer cells are identified and effectively eliminated by the immune system. At this stage, the balance favors immune protection. The equilibrium phase is entered when the immune system is not able to completely eliminate all cancer cells but can control or prevent further outgrowth. In this stage, the conceptual seesaw is balanced. This stage is thought to be the longest of the three stages and may persist for many years. The escape phase is characterized by the inability of the immune system to eliminate or control the outgrowth of cancer cells. This stage may occur as a result of immune system exhaustion or when cancer cells acquire phenotypic alterations, thereby allowing them to evade or avoid the immune system. In this stage, the seesaw favors immune evasion, leading to progressive disease.

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repeats itself. The cyclical nature of this process means that even a small amount of initial cancer cell death can lead to a large, sustained, self-repeating immune response, which is a powerful mechanism for targeting and potentially eliminating the tumor. This entire process is termed “cancer immunity,” and represents an exciting and expanding area of clinical research.

**ANTICANCER IMMUNOTHERAPY: MANY TARGETS, MANY CLASSES**

The list of cancer immunotherapy agents is constantly growing. Key classes include:

- **Immunomodulatory monoclonal antibodies** (mAbs) contain checkpoint inhibitors, which seek to release the brakes that normally keep the immune system in check. Several new compounds block the functions of checkpoint molecules such as CTLA-4 and the PD-1/PD-L1 interaction.

- **Immunostimulatory agents** seek to directly stimulate and activate the immune system, including cytokines such as IL-2 and IL-17, as well as agents that target cell surface receptors such as CD137 and CD40.

- **Adoptive cell transfer methods** use entire cells to deliver engineered T cells (such as CAR-T cells), which are manufactured outside of the body from a few starter T cells collected from the patient, then reinfused into the patient to attack the tumor (Figure 4). This variant of cell-based immunotherapy generally involves the collection of circulating or tumor-infiltrating lymphocytes. These may be autologous (from the patient) or allogeneic (from a donor). These lymphocytes are then selected, modified and/or activated outside of the body before being administered to patients, typically after preconditioning with lymphodepletion and in combination with immunostimulatory agents.

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**Figure 4: Chimeric antigen receptor T cells (CAR-T cells)**

• **Anti-cancer vaccines** include prophylactic vaccines such as the anti-HPV vaccine used to prevent cervical cancer, and also novel therapeutic vaccines, which seek to elicit an immune response against already established tumors.

• **Oncolytic viruses**: These are non-pathogenic viral strains that specifically infect cancer cells, triggering their demise. Genetic engineering has been used to give oncolytic viruses various advantageous traits, including sequences coding for:
  » Enzymes that convert an innocuous pro-drug into a cytotoxic agent
  » Proteins with potential to trigger lethal signalling cascades in cancer cells only
  » RNAs targeting factors that are required for the survival of transformed cells, but not for normal cells.

• **Inhibitors of immunosuppressive metabolism**, including inhibitors of the immunosuppressive enzyme, indoleamine 2,3-dioxygenase 1 (IDO1). High expression of this enzyme is associated with poor patient prognosis for a broad range of malignancies.\(^4\)

• **Pattern recognition receptor (PRR) agonists** are evolutionarily conserved proteins involved in the recognition of danger signals (including Toll-like receptors [TLRs] and Nod-like receptors [NLRs], which resemble peptides or nucleic acids of infectious agents). The antineoplastic effects of PRR agonists stem from their ability to stimulate the host immune system.

• **Immunogenic cell death (ICD) inducers** include some conventional chemotherapies, often used at metronomic doses, and some forms of radiotherapy.

**IMMUNE-MEDIATED TOXICITIES: A TEAM EFFORT**
A significant issue in running immuno-oncology clinical trials is the need to be prepared for immune-mediated toxicities. Toxicity is mostly low grade and can be managed with supportive treatment. Pulmonary, hepatic, renal, gastrointestinal, endocrine, neurological and dermatological adverse events may occur, requiring vigilance and early intervention. A concerted effort is needed to educate the entire multidisciplinary clinical trials team and develop accessible algorithms to minimize the risk of toxicity. Successful management of checkpoint protein antibody toxicities requires vigilance and early diagnosis, excellent patient-provider communication, and rapid and aggressive use of corticosteroids and other immune suppressants for immune-related adverse events.

**SUMMARY OF CANCER IMMUNITY**
Cancer immunity is a cycle that can be either self-propagating or self-dampening. The goal of immunotherapy agents is to switch the cycle from dampening (which allows growth of the tumor) to self-propagating (which allows the immune system to target and destroy the cancer).

Many different therapeutic interventions can use the immune system, and agents as diverse as small molecules, antibodies, cell-based therapies, and viruses can all be used to generate cancer immunity. Major classes of immunotherapies that are currently in development include checkpoint inhibitors (anti CTLA4, anti PD-L1), T cell stimulatory agents (agonists of CD137, CD40, CD134 [OX-40]), adoptive T cell transfer methods (CAR-T cells, tumor infiltrating lymphocytes [TILs]), cancer vaccines (including dendritic cell vaccines), oncolytic viruses and non-specific immune stimulation (interferon-α, interleukins, GM-CSF).
FINDING PATIENTS FOR TRIALS USING MACHINE LEARNING AND PREDICTIVE ANALYTICS

Clinical trials are more complex today than they were 10 years ago. A study by the Tufts Center for Drug Development found that today’s Phase III protocols involve 70% more procedures (187 per protocol than those from a decade ago (Figure 5). With more procedures and data to collect, risks to quality and costs both increase. Also, with more targeted therapies in development, patient populations are becoming more tightly defined – as illustrated by an increase of 61% in eligibility criteria. The result is a perfect storm of fewer targets that are harder to find.

The industry needs a new approach that is evidence based, predictable, proactive and integrated. And it needs a research partner that is more able to share the risks (Figure 6).

Among projects recently completed at IQVIA are case studies in two critical areas of drug development.

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Figure 5: Clinical trial dynamics and complexity

<table>
<thead>
<tr>
<th># Procedures</th>
<th># I/E Criteria</th>
<th># Countries</th>
<th># Sites</th>
<th># Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>31</td>
<td>4.7</td>
<td>124</td>
<td>729</td>
</tr>
<tr>
<td>110</td>
<td>50</td>
<td>9.5</td>
<td>196</td>
<td>597</td>
</tr>
<tr>
<td>+70%</td>
<td>+61%</td>
<td>+102%</td>
<td>+58%</td>
<td>-18%</td>
</tr>
</tbody>
</table>
CASE STUDY 1: RETHINKING TRIAL DESIGN TO AVOID PROTOCOL AMENDMENTS

IQVIA was approached to help a top-five, global pharmaceutical company where more than 50% of protocols required amendments prior to enrolling the first patient. We recently applied our design analytics to a large Phase I oncology study for this client. Many of our quality improvement findings were confirmatory, supporting the client’s design decisions. However, we discovered five inconsistencies that might increase risk, at least two of which were significant enough to drive an amendment:

• The protocol misidentified a key eligibility criterion as exclusionary, when it should have been inclusionary. This would have omitted a patient population with one of the greatest chances of benefitting from the therapy, conceivably a first approval indication.

• The protocol specified that only patients with adequate cardiac function evidenced by echocardiogram would be eligible for the trial, but the protocol schedule did not indicate that an echocardiogram should be performed at the patient-screening visit. Left unresolved, this protocol error alone could have resulted in enrollment of 5-10% of ineligible patients.

As a result of this data-informed protocol review, the client was able to avoid a costly protocol amendment and mitigate the risk of extending the study by up to three months, saving as much as $600,000 (Figure 7).

Figure 7: Case Study 1: Rethinking trial design to avoid protocol amendments

<table>
<thead>
<tr>
<th>IQVIA data informed protocol assessment</th>
<th>IQVIA findings</th>
<th>Results: Protocol revised to avoid two major risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Audit for design consistency, extraneous and costly non-core procedures</td>
<td>Detected 5 inconsistencies with increased risk</td>
<td>1. Significant omission, preventing study failure</td>
</tr>
<tr>
<td>Compare to competing trial designs</td>
<td></td>
<td>2. Potential to enroll 5-10% ineligible patients</td>
</tr>
<tr>
<td>Test for patient and/or site burden</td>
<td></td>
<td>Mitigated study delays +3 months</td>
</tr>
</tbody>
</table>

Confirmatory | Increased Risk |
---|---|
Consistency | Competitive | Burden |
3 | 4 | 1

Confirmatory | Increased Risk |
---|---|

CASE STUDY 2: A TRULY TARGETED APPROACH TO SITE ID USING CLAIMS DATA

Innovative approaches have also been used in non-small cell lung cancer (NSCLC) trials that focused on recruiting naïve patients for treatment with checkpoint inhibitors. The challenge was that the market place is crowded, with 27 FDA-approved indications for six checkpoint inhibitors. Some 1,209 checkpoint inhibitor trials are ongoing, involving 141,000 patients; of these trials, 945 exclude patients who have previously been treated with checkpoint inhibitors. By leveraging claims data, it was possible to map the density of NSCLC patients, identifying oncologists with a high number of available NSCLC patients that are naïve to checkpoint inhibitors (Figure 8).

Figure 8: Case Study 2: A truly targeted approach to site ID

**The challenge**

- 27 FDA approved indications with 6 checkpoint inhibitors
- 1,209 checkpoint inhibitor trials ongoing for more than 141,000 patients
- 945 protocols have the exclusion criterion of “Prior Checkpoint Inhibitor”

**Strategic considerations for site selection**

- High concentration of checkpoint naïve patients
- Trial experience
- Leverage of community practices as referral sites
- Trial competition – within indication, checkpoint inhibitors

**Count of metastatic NSCLC patients by site**, oncologists with ≥50 checkpoint naïve mNSCLC patients

**Overlay current clinical trial activity for I/Os in mNSCLC**
POSITIONING A NEW THERAPY FOR SUCCESS IN A CROWDED MARKET

The pipeline of oncology drugs in clinical development has expanded by 45% over the past 10 years. Oncology R&D activity remains concentrated on targeted therapies, which made up 90% of the late phase pipeline in 2016. These targeted therapies include small molecule protein kinase inhibitors, biologic monoclonal antibodies and a range of new mechanisms that can identify or block the cell processes that cause cancer cells to multiply. Particular focus is being placed on targeted therapies that use genetic marker tests to indicate a greater likelihood of tumor response, or amplify the patient’s own immune response to target the cancer. The late phase oncology pipeline includes 278 biologic therapies, including 15 gene therapies, 133 new monoclonal antibodies (mAbs) and 14 biosimilars of existing mAbs. The late phase pipeline also includes 82 potential vaccines for a wide variety of tumor types. Immunotherapies are one of the fastest growing areas within oncology R&D, and will undoubtedly make up a larger portion of the pipeline in 2021.

A wide range of companies have active late-phase oncology programs (Figure 9).

Figure 9: Companies with active late phase oncology pipelines

Immuno-oncology agents have significantly altered the treatment landscape for several tumor types. While anti-PD-1 and PD-L1 agents have already been approved in multiple tumor types, agents with newer immuno-oncology MoAs are currently in early development across various tumor types, being evaluated both as monotherapy and in combination with already approved immuno-oncology agents. Most agents are in development for solid tumors but development of potential therapies for hematologic malignancies is increasing.

CONCLUSION

Cancer immunotherapy is a rapidly growing and changing field. Immunotherapy mechanisms range from traditional drug-target interventions (checkpoint inhibitors, T-cell stimulatory mechanisms) to whole-cell derived treatments (TILs, CAR-T cells, cancer vaccines). But cancer and immunity strike a delicate balance: if the immune response is too weak, the result is active cancer; and if the immune response too strong, this can cause autoimmunity. A growing understanding of the cancer-immunity cycle will lead to a growing list of potential targets and sites for therapeutic intervention.

In oncology, especially with immunotherapeutic combinations using checkpoint inhibitors as a “backbone regimen” across many tumor types, machine learning and predictive analytics becomes an indispensable tool to efficiently plan and conduct complex modern clinical studies.

Innovative approaches have potential to change the status quo in three critical areas:

1. Help to re-think design: If a protocol has already been developed, this can be validated with real-world data to ensure a solid, realistic plan. A clinical development strategy can be mapped out from a very early point, including long-term commercial forecasting in design scenarios, to help shorten development timelines and realize the greatest ROI.

2. The process of site identification: This has undergone a major transformation, based on pinpointing the locations of target patient populations, then selecting the right sites to deliver the patients for the protocol with a high level of quality. This reduces the overall time for site identification and activation.

3. Based on site-level intelligence, recruitment planning is becoming more realistic. When clinical research associates have access to site-level anonymized patient data, they are more effective at working with the sites. In addition, alternative channels can be employed where needed to increase the number of patients per site and accelerate overall recruitment.


5. https://www.nature.com/articles/nrd.2017.65

Dr. Forrest Anthony is responsible for early engagement with emerging oncology companies. He serves as Medical Advisor for ongoing clinical trials, trains IQVIA experts on new immuno-oncology product trials and uses strategic planning to foresee technology trends. He brings over 25 years of pharma and biotech senior executive experience, with 15 years in oncology trial management. He has experience as founder, CEO or CMO at several small companies and is a past president of ABC biotech trade association, then founding board member at BIO. Dr. Anthony received his M.D. from Oregon Health Sciences University; M.S. and B.S. from Dartmouth Medical School; B.S. from Dartmouth College and Ph.D. Biomedical engineering from the University of Virginia.

Nobu Kawasaki leads cross-functional and geographic teams in the delivery of complex analytics to support sales, trial design and delivery, and new analytics innovations. Mr. Kawasaki has nine years of experience in pharmaceuticals consulting and analytics and has worked with a broad range of pharmaceutical clients throughout his career. In his role at IQVIA, he works with his analytics team in the delivery of innovative solutions addressing core challenges for clinical trial design and execution, including study design, site identification and patient recruitment. He also works with commercial clients to help shape strategic decisions within pharmaceutical organizations, including new commercial models, sales force effectiveness and brand management. Mr. Kawasaki received his Master of Science in Business in Paris.

Paul Cariola manages key oncology client initiatives and insight platforms. He is also responsible for designing solutions with custom data and research to support specific client needs. Mr. Cariola has more than 18 years of experience in pharmaceutical marketing and marketing research, business development and consulting – including 12 years’ experience with IQVIA and more than 17 years of patient level data analytics. His expertise is in oncology data for use in sales, marketing and commercial strategy. Mr. Cariola has a B.S. in Accounting and Risk Management from Temple University.