ADDRESSING IMMUNOTHERAPY DRUG DEVELOPMENT CHALLENGES

An Evidence-Based Approach

Frank Makosiej, PharmD,
Executive Director of Strategy and Planning, Oncology
Covance Clinical Development and Commercialization Services

The field of immunotherapy is rapidly evolving. With substantial progress in response rates in heavily pre-treated patients, success in the first line treatments of patients with metastatic disease, as noted in Merck's recent data on non-small cell lung cancer, along with positive signs of activity across varied cancer types, the field is poised for additional success.

Despite this great promise, many development challenges exist. Due to the unique nature of immunotherapy drug development, drug sponsors need to consider how to implement a flexible, evidence-based approach to development and must proactively identify failure points through the interrogation of relevant data to improve overall performance.

Current Progress and Future Trends

Significant progress has been made in immunotherapy development, ranging from exploration of novel drug classes and immune checkpoint targets to vaccines. In addition, many late phase trials are underway for currently marketed drugs to expand indications to additional cancer types.

Biomarkers are another exciting area of focus for immunotherapy development, but effectively predicting expression may be very complex. For example, in one published experiment[1], when predicting efficacy of anti-PD-L1 drug, researchers assumed expression of a biomarker on tumor cells but, in fact, the expression of PD-L1 on immune cells infiltrating the tumor correlated to the response rather than expression of the tumor.

Another area of exploration is the combination of two drugs to target immune checkpoints in different ways. This approach has shown remarkable results[2], but may also introduces the potential for additional toxicity.

Understanding Differences in Development

Given that immunotherapy drugs can display atypical toxicity patterns, deliberate attention to methods for early recognition and intervention may be prudent, especially when combining drugs or exploring new targets. The following points should be considered when developing immunotherapies.

- Efficacy evaluation: With different patterns ranging from rapid response to pseudo-progression, evaluating efficacy remains a critical issue for the development of immunotherapies.
- Proof of concept data: Rapid data, blood tests and other circulating factors all provide important data points, but tissue-based biomarker assessment is paramount to provide early key proof of concept data.
- Treatment paradigms: While being treated for past progression, patients can experience progression or pseudo-progression. If re-treated, patients may experience significant responses. Therefore, treatment should be managed very carefully.
- Historical indications: Melanoma, non-small-cell lung cancer and renal cell carcinoma have been historical areas of attention but as the industry expands its reach, (indications now also include bladder cancer and Hodgkin's lymphoma) attention needs to be placed on increased mobilization and the implications of working with patients who have not yet used these drugs.
- Fierce competition: With the recent success of immunotherapies, the industry is exploring additional indications, lines of treatment and regions, creating a hypercompetitive space for trials. Given the increasing number of immunotherapy oncology trials, finding the right patients for each trial has become challenging, especially with trials that focus on the same mechanism of action.

Strategies to Mitigate Recurring Immunotherapy Challenges

Due to the unique development issues associated with immunotherapy drugs, embracing a pragmatic, execution plan that proactively addresses these recurring challenges, may improve study success. Several of these issues are outlined below.

- Obtaining tissue: Sample collection can be particularly challenging, especially in early phase studies designed to drive key proof of concept data. With careful planning and intervention, sponsors can perform an assessment of site-specific diagnostic practices to determine success rates in obtaining tissue samples, experience with open or core biopsies and the impact of these methodologies on diagnoses.
- Site performance: When sites are selected, determining the site's ability to set up feasibility assays and provide feedback may not be enough. High-performing study sites should have the infrastructure to support translational research, along with enthusiastic investigators who can identify surgeons and interventional radiologists as collaborators during the trial to obtain fresh biopsies.
- Protocol deviations: Noncompliance can represent another pitfall if sites are not familiar with immunotherapy drug development. Drafting a document with definitions and delineations of potential trigger points prior to a trial's start can ensure that the selected investigators understand the process, meet turnaround times for obtaining tissue and informed consent forms, and follow the protocol without deviation.

With a specific, immunotherapy-focused plan to address possible pitfalls, sponsors will be better prepared to identitfy optimal clinical sites, thereby increasing their trial's success.

Making Insightful Choices

A robust plan can enable efficiencies in a program, but other inherent challenges such as site selection, may impact clinical trial success. High-performing sites influence the execution of trials, but our historical data provide objective evidence that greater than 50 percent of oncology investigators are non-performing (defined as recruiting 0-1 patients in total).

COVANCE®
SOLUTIONS MADE REAL®

To mitigate this risk, it is advisable to utilize a data-driven approach to identify and select optimized oncology sites from the start. The Xcellerate® Informatics Suite may be used to deliver strategic insights and inform decision-making. Xcellerate mines data from the Covance Central Laboratory – currently utilized in more than 40 percent of the world's trials.

Leveraging past performance is an effective means to reduce selection of underperforming sites and may also improve country selection and timelines. For example, in a single client portfolio of oncology studies, we applied site profiling to reduce a 54 percent non-performance rate to just under 14 percent.

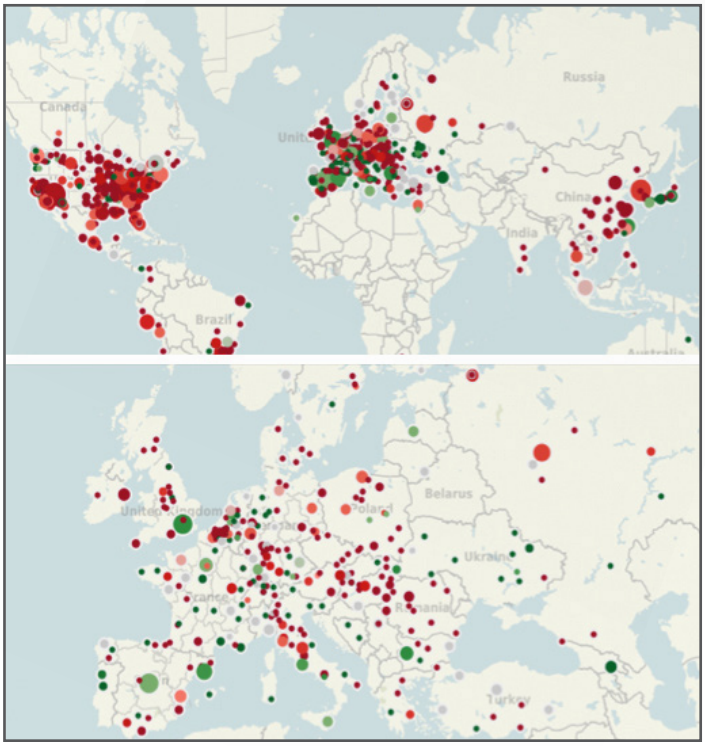
Analyzing clinical trial data may facilitate more accurate forecasting through better management of study risk and optimization of resources. With access to over 11,000 protocols and 175,000 investigators in our proprietary database, Xcellerate is an exceptional tool that delivers powerful real-world insights – the industry's most extensive view on trial performance. The database also spans a broad set of indications. In oncology alone, Xcellerate may be utilized to effectively analyze recruitment for specific study types in the Phase II/III space and via simple dashboards, providing a visual summary of enrollment data for various regions and countries.

Recruitment rate, however, isn't the only factor to consider. Some countries may boast faster recruitment but take much longer to initiate a trial. Understanding these insights may help during the decision-making process.

Revealing Opportunities with Informatics

Applying past performance data and metrics allow sponsors to gain perspective and insights. Below, Figure 1 is a visual representation of a trial experience with PD-L1, PD-1 and CTLA-4, some of the most common targets in recent immunotherapy studies. This evaluation was performed to examine a sponsor's portfolio of immunotherapy studies so we could provide feedback as to where and how they've been performing. The larger circles represent sites recruiting a greater number of patients than the smaller circles; darker green represents the most utilized sites while dark red represents the least utilized sites. These circles feed into an average utilization index, which assigns each country a color.

Figure 1: Evaluating a Sponsor's Study Performance in their Immunotherapy Portfolio



For example, the Ukraine is shown as green as it has an average utilization index of 76 percent, a figure based on 35 ongoing trials in 17 sites, as well as a measurement on how well the sponsor is using those sites. In summary, the sponsor is using 76 percent of the sites in that country, indicating a high saturation.

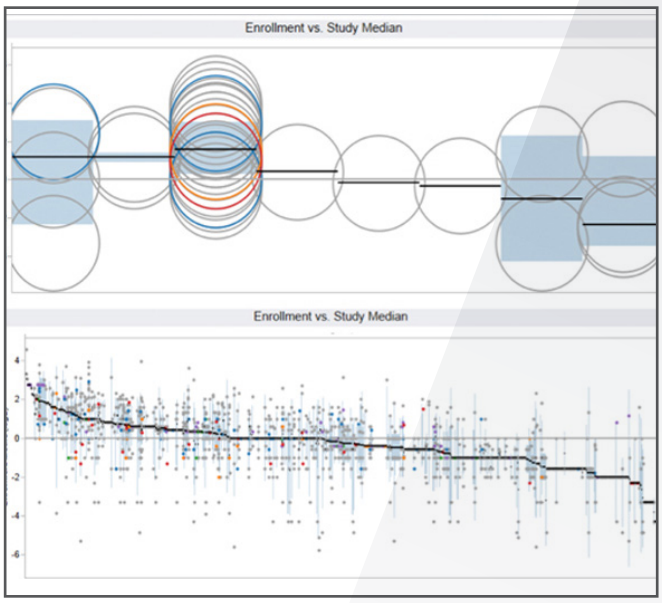
On the other end of the index with the Czech Republic, which is shown in the lowest panel as dark red, there are 25 known immuno-oncology trials with 13 sites. This particular sponsor has no sites engaged in that country and the map quickly identifies an area of opportunity for the sponsor.

COVANCE®
SOLUTIONS MADE REAL®

Figure 2 further quantifies an actual performance and their site. Each ring represents an investigator's experience in an investigator's individual trial as compared to their peers (top panel); multiple rings indicate experience in multiple studies. The study mean is the midpoint on the Y-axis, which allows a visual separation of the investigator's average enrollment performance, denoted by the solid black line.

The Xcellerate Informatics Suite also allows clinical teams to look at data from an entire country (bottom panel), where each individual investigator represents a vertical column with the dots representing the circles from the panel above to display individual enrollment performance – key information to help a sponsor uncover new options for site selection.

Figure 2: Comparing Peer-to-Peer Investigator Performance



Applying these analytical tools and proprietary data to our client's rescue study, we were able to recommend the closure of 31 sites and the 51 additional sites. This recommendation doubled their recruitment rate and delivered according to the new projection, demonstrating the strength and impact of this evidence-based approach.

Aligning for Success

Whether reviewing trends across the globe or analyzing the granular details of an individual investigator's performance, powerful data can improve trial success.

Even with the help of advanced informatics, oncology trials are undeniably complex, underscoring the need for a strategy that plans for the differences in immunotherapy development and proactively monitors execution. When these considerations are integrated into a comprehensive plan, sponsors can successfully mitigate risks and maximize success for their trials.

References

1. Powles, T et al. (2014). MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature,* 515, 558-62. doi:10.1038/nature13904

2. Sznol, M et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL) (abstract LBA9003). 2014 American Society of Clinical Oncology (ASCO) meeting.

Learn more about our drug development solutions at **www.covance.com**

The Americas + 1.888.COVANCE (+1.888.268.2623) + 1.609.452.4440
Europe / Africa + 00.800.2682.2682 +44.1423.500888
Asia Pacific + 800.6568.3000 +65.6.5686588

COVANCE®
SOLUTIONS MADE REAL®