WHITE PAPER

WHAT CAN WE LEARN FROM IMMUNO-ONCOLOGY CLINICAL TRIALS?

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The number of immune checkpoint inhibitors (ICIs) in the marketplace is set to increase markedly in coming years. While cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) has been targeted for immunotherapies for some time, two relatively new targets have developers upping their enthusiasm for the class: programmed cell death 1 (PD-1) and programmed cell death 1 ligand 1 (PD-L1).

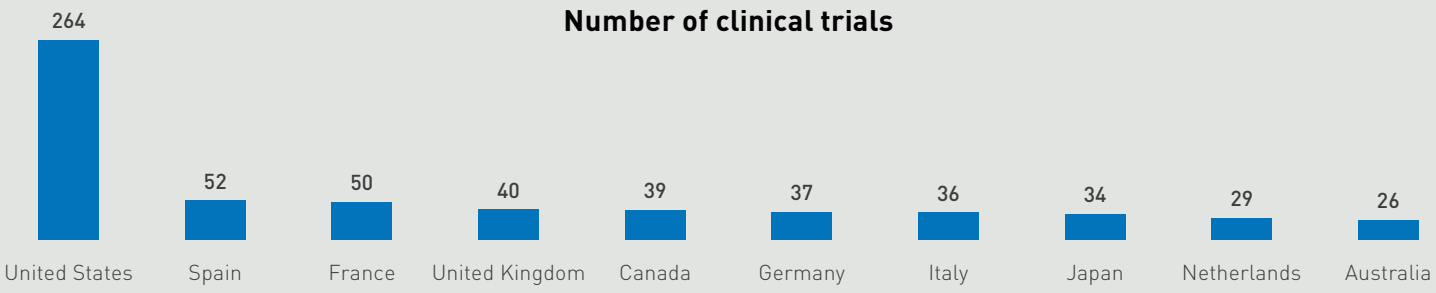
Thus, the goal for drug manufacturers and their partner contract research organizations (CROs) is to ensure timely, safe and successful drug development in this space. Dr. Yeo discussed the burgeoning programmed cell death protein 1 (PD-1) and PD ligand 1 (PD-L1) inhibitor class, revealing the breadth of the clinical development landscape for these agents, and identifying operational considerations for executing a successful clinical trial program.

CLINICAL TRIAL LANDSCAPE FOR PD-1/PD-L1 CHECKPOINT INHIBITORS

According to Citeline, thousands of immune-oncology trials are in progress around the world. The clinical trial sites for PD-1 and PD-L1 inhibitors are also observed to span the globe from North America to Europe, Japan and Australia (Figure 1).

In this drug class, the most common agents under investigation are pembrolizumab (110 trials), nivolumab (98), durvalumab (40) and atezolizumab (32). Non-small cell lung cancer (NSCLC; 98 trials) is the most common cancer type, followed by melanoma (83) and unspecified solid tumor (63). However, PD-1/PD-L1 inhibitors are also being trialed in renal, head and neck, colorectal, breast and pancreatic cancer, among others. In terms of stage of clinical development, the majority are in phase II development followed by phase 1 development. As durvalumab, atezolizumab and avelumab have all reached Phase III, they are likely to be the next market entrants. "These numbers clearly illustrate the highly exciting, but also highly competitive, nature of this market," said Dr. Yeo.

Figure 1. Global distribution of clinical trials of PD-1/PD-L1 inhibitors.



Source: Citeline® Trialtrove 2016.

Meanwhile, trials of PD-1 and PD-L1 inhibitors, as well as other types of ICIs, pose some important challenges for drug developers, some of which are unique to investigating biologics. The trials are considerably more complex to design and execute, compared with traditional oncology trials. A lack of disease screening and awareness in some developing regions also poses a challenge to identify patients for recruitment. Furthermore, a prolonged duration of treatment is required before response can be adequately assessed, and the launched products are expensive and often face limited reimbursement. This contributes to the risk carried by the drug developer. Dr. Yeo advised that, given the current landscape, prioritizing the development of novel, potentially breakthrough new agents and conducting differentiating trials, particularly trials of combination therapies, would provide the greatest opportunity for drug developers.

OPERATIONAL CHALLENGES AND STRATEGIES FOR EFFECTIVE TRIAL MANAGEMENT

Operational challenges

Tumor assessment is a fundamental aspect of oncology trials and, apart from deciding whether a central reader or local assessors will perform the assessment, immuno-oncology agents pose the specific challenge of setting and interpreting immune-related response criteria (irRC). Clinical investigators involved in oncology research are usually well acquainted with the RECIST criteria for solid tumors, but experience with the irRC is less widespread. Immunotherapeutic trials also involve continuing treatment past progressive disease, which may raise patient anxieties and hinder subject recruitment and must also be adequately addressed in the trial protocol to satisfy regulatory agencies. The sheer number of trials being conducted within this area poses the most fundamental of recruitment challenges; thus, other, more modifiable, barriers to subject recruitment must be eliminated through careful planning and design.

The high number of trials underway also serves to underline the time-sensitive nature of the development process for these agents. Lengthy start-up times and slow patient enrolment (only 2-3% of cancer patients who are eligible for clinical trials participate) can potentially impact the timely study completion. The experience and market intelligence available within the CRO will serve to minimize delays by recruiting suitable study sites (at country and site levels) that have the capabilities, resources and patient pool to allow timely progress.

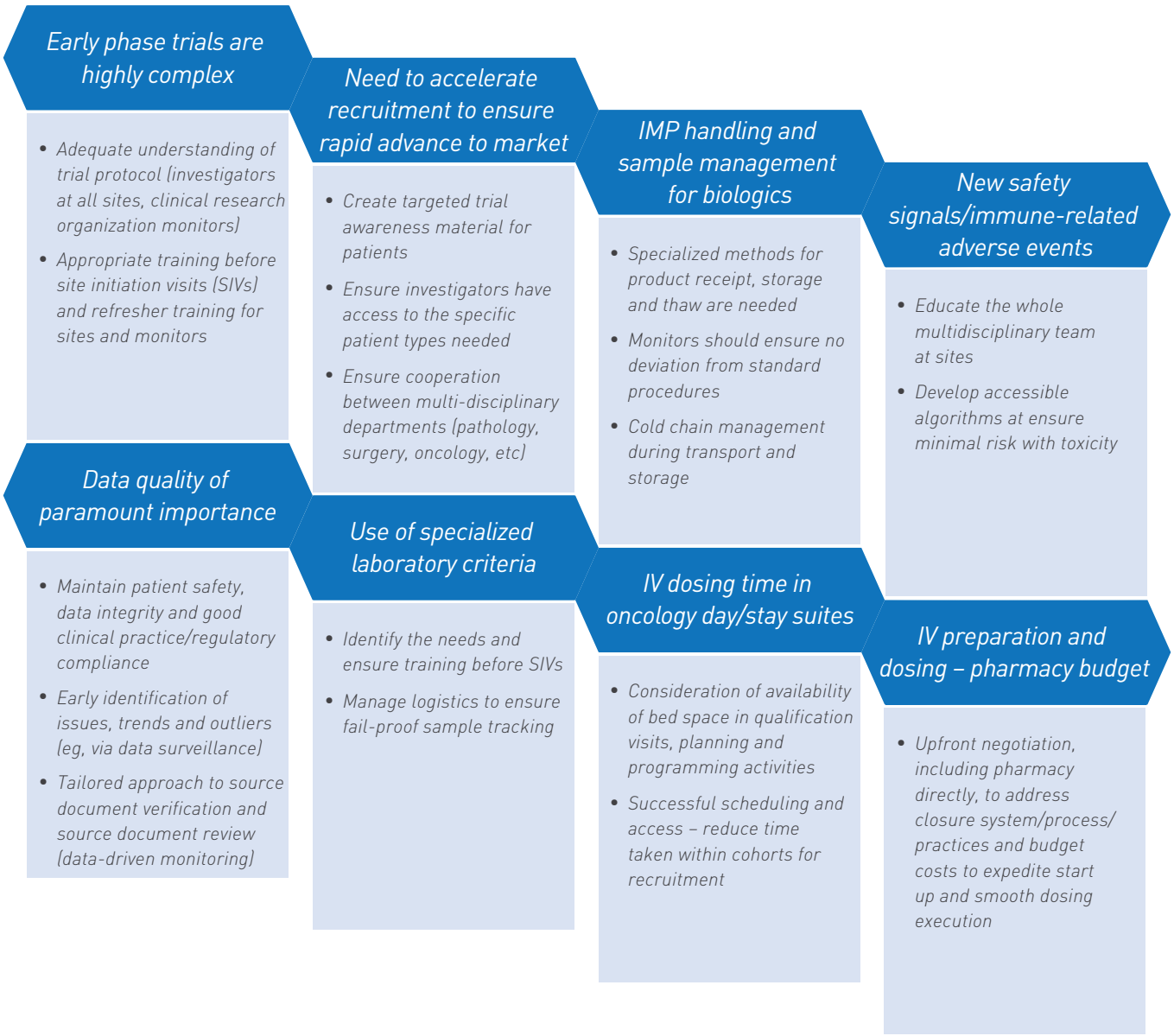
Potential study sites must be carefully assessed and chosen on their ability to service the demanding nature of immune-oncology clinical trials. Ideal settings will have an adequate patient pool to meet the strict eligibility criteria; established multidisciplinary team cooperation (eg, oncology, radiology, pathology); and the special equipment and skills needed for investigational product handling and biosample collection, processing and shipping.

Subject safety is the overriding priority in clinical trials, perhaps even more so in trials of biologics as they have the potential to cause severe immune reactions and toxicities. Although toxicity is less common with PD-1 and PD-L1 inhibitors than with the anti-CTLA-4 ICIs, PD-1/PD-L1 inhibitors can cause life-threatening reactions.[1,2] Robust protocols for safety monitoring and reporting and risk mitigation must be in place early and rigorously applied.

PAREXEL recommendations for effective trial management

Dr. Yeo also noted that there are several key success factors to overcoming the operational challenges (Table).

Table. Critical success factors for effective management of clinical trials of PD-1/PD-L1 inhibitors



IMPORTANCE OF BIOMARKERS AND COMPANION DIAGNOSTICS

Biomarkers are widely used in oncology studies of biologic agents for predictive and prognostic purposes. For new targeted anticancer drugs, biomarker assays are typically incorporated into companion diagnostics that are developed

and tested in parallel to the drug. The reliability of PD-L1 assays as a meaningful biomarker for PD-1/PD-L1 inhibitor trials remains controversial, and further studies are needed before their value can be fully defined. Biomarkers and companion diagnostics represent a highly complex issue within the development process for biologic agents, but creating a validated companion diagnostic is now viewed as mandatory for regulatory approval.

SUMMARY

ICIs have been game changers in the immuno-oncology field and the leaders to market, nivolumab and pembrolizumab, will soon be joined by the many ICIs now in various stages of development. This rapidly expanding pool of competitors means that achieving a fast track to market will be central to maximize the potential returns on the enormous R&D investment that biologics like ICIs require. Drug developers and CROs must work together toward successful immune-oncology trials. Learning from experiences and sharing knowledge will ensure that best practice is applied to study design and conduct.

The abiding interest in ICIs is driven by robust evidence of their effectiveness, often in cancer cases that previously had few effective therapy options, and the potential for long-lasting protection from disease progression. This is a therapy area that has only just 'scratched the surface', and is likely to remain an exciting, inspiring and fruitful landscape for many years.

References

1. Weber JS, et al. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol* 2012;30:2691-2697.

2. Weber JS, et al. Toxicities of immunotherapy for the practitioner. *J Clin Oncol* 2015;33:2092-2099

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