

CRITICAL SUCCESS FACTORS FOR CLINICAL TRIALS OF IMMUNE CHECKPOINT INHIBITORS

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Oncologists and their patients have had reason recently to be encouraged by the launch of immune checkpoint inhibitors (ICIs) for the treatment of several difficult-to-treat diseases, including metastatic melanoma and non-small cell lung cancer. These novel agents activate the human immune response against antigens expressed on tumor cells, and the science has generated excitement among physicians, patients, the media and researchers.

Biopharmaceutical companies now are working on a robust pipeline of ICIs, testing a great many experimental immunomodulatory approaches against both clinically validated and novel targets. Agents are being studied as monotherapy, as well as in novel combinations. Clinical trial sponsors are seeking to optimize ICIs based on a rapidly growing body of knowledge about tumor biology and the human immune response.

But bringing the initial group of immune checkpoint inhibitors to market required overcoming a number of developmental challenges. The challenges impacted trial design, efficacy endpoint assessment and safety evaluation. To enhance the possibility of success in the development of immune-oncology drugs, biopharmaceutical sponsors need to understand the special challenges and partner with organizations that have specific expertise with the clinical development of these agents.

This paper summarizes key aspects of evaluating safety and efficacy in studies of immune checkpoint inhibitors and describes operational strategies that support successful trial execution and regulatory approval.

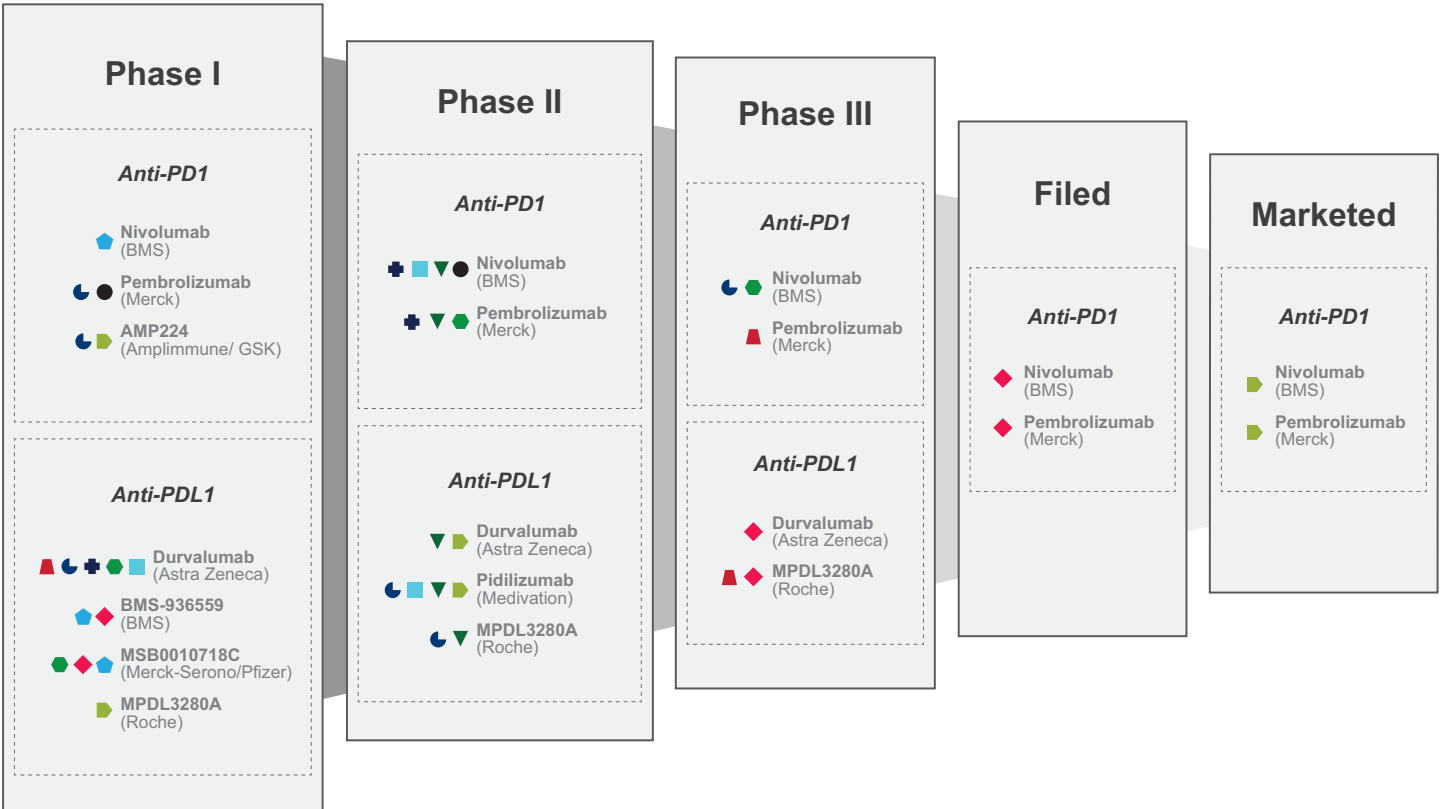
THE PROMISE OF IMMUNE CHECKPOINT INHIBITORS

At this writing, three immune checkpoint inhibitors (ICIs) are marketed in the United States. The first, Yervoy® (ipilimumab), a CTLA-4 receptor inhibitor¹ from Bristol-Myers Squibb (BMS), gained U.S. Food & Drug Administration (FDA) approval in 2011. It has also received approval and marketing authorization in the EU and other regions.

In 2014, and nearly two months ahead of schedule, Merck received approval for Keytruda® (pembrolizumab), an anti-PD-1 indicated for advanced melanoma following treatment with Yervoy. In late 2014, Bristol-Myers Squibb also received FDA approval for Opdivo® (nivolumab), an anti-PD-1², for metastatic Non-Small Cell Lung Cancer (NSCLC) with progression on or after chemotherapy treatment, as well as for metastatic melanoma pretreated with Yervoy. Both Opdivo and Keytruda received a “breakthrough therapy designation” from the FDA.

As shown in Figure 1, the pipeline for anti-PD-1s and anti-PD-L1s is quite active, with research targeting a variety of tumor types.

Anti-PD-1/ PDL-1 Therapy Development Pipeline



Legend

Stomach cancer	Colorectal cancer	Renal cancer	Hodgkin's lymphoma	Melanoma
Pancreatic cancer	Ovarian cancer	Bladder cancer	Breast cancer	Non-small cell lung cancer

Meanwhile, in Phase 2 clinical trials, the approved immune checkpoint inhibitors are demonstrating anti-tumor activity in a variety of tumor types, raising the hope that they could be therapeutically useful in a broad range of tumors. Indeed, the Society for Immunotherapy of Cancer (SITC) has suggested, “These clinical advances and newly approved therapeutics are moving cancer immunotherapy from a niche approach in limited indication, primarily for melanoma and renal cancer, to a broadly applicable and effective treatment for many common and deadly cancers.”³

Market forecasts reflect the excitement that this new drug class is generating. The three approved ICIs are projected to “dominate the immunotherapy market and capture a staggering 85 percent market share in 2022”⁴ and the overall market for checkpoint inhibitors is “expected to peak at nearly \$35 billion a year.”⁵ Indeed, a new performance index is being developed for market analysts on cancer immunotherapies.⁶

FEATURES OF THE ANTI-CANCER IMMUNE RESPONSE AND IMPLICATIONS FOR EVALUATING EFFICACY

General Observations

It’s been observed that tumors respond differently to immunotherapy than they do to molecularly targeted agents or cytotoxic chemotherapy. These responses have been characterized in several ways:⁷

- **Stable disease:** a long-term stabilization in total tumor volume and an improvement in the clinical symptoms associated with the cancer
- **Mixed response:** an initial, significant size reduction of some lesions, with enlargement observed in others
- **Delayed response:** a reduction in tumor volume observed months after the initiation of therapy; importantly, delayed responses can occur in patients who experience an initial increase in tumor volume or appearance of new lesions

It is the second and third scenarios in which the tumor is only temporarily enlarged that deserve particular attention. Two distinct mechanisms can lead to an initial increase in

Why Immune Checkpoint Inhibitors Represent a Breakthrough

Immunotherapy has been in use for decades via treatments that activate the immune system to attack and destroy cancer cells. One limitation of this approach has been that certain cell interactions involving immune “checkpoints” automatically dampen the activated immune system to avoid autoimmunity. So, “when you stimulate [the immune system], you also put on the brakes.”* Meanwhile, cancer cells are fiendishly good at mutating, adapting and avoiding detection by the body’s natural radar, and the effectiveness of immunotherapy often wanes over time.

In some tumor types, these hurdles appear to be overcome by the newest class of drugs targeting the immune system: immune checkpoint-blocking antibodies, or immune checkpoint inhibitors (ICIs). ICIs block the pathways on T-cells that inhibit immune response. In other words, they release the brake pedal and allow the immune system to remain activated, often producing a strong and sustained anti-tumor response. (T-cells are regulator cells that orchestrate the immune response against infections or cancer cells.)

*Ribas, Antoni quoted by Malini Guha in “The New Era of Checkpoint Inhibitors,” *The Pharmaceutical Journal*, Nov. 18, 2014.

the size of a tumor lesion, followed by an ultimate decrease as measured in the imaging follow-up investigations. First, it may take time for the immune system to become aware of the tumor antigen, creating a delayed response. With immune checkpoint inhibitors (ICIs) such a delay can be quite extended. Whereas initial signs of anti-cancer activity including partial responses may be seen in the first three months after start of treatment the development of the best overall response in responders typically develops over a prolonged period of time. In a meta-analysis of three studies on Yervoy for metastatic melanoma, “it took an average of 30 months to reach an official complete response.”⁸ Second, the tumor enlargement may actually be pseudo progression, the mere appearance of progression. This commonly occurs because upon activation of the host’s immune system, inflammatory T-cells infiltrate the tumor, often leading to an enlargement of existing lesions that mimic progression.

Immune-Related Response Criteria

Thus, if the industry standard Response Evaluation Criteria in Solid Tumors (RECIST) were applied to immunotherapy trials, patients who might actually be starting to benefit from treatment could be withdrawn from therapy prematurely. Faced with this, a coalition of oncologists in 2009 developed a special set of immune-related response criteria (irRC). Many studies, however, still apply dual assessments using both RECIST and irRC.

Whereas initial clinical studies on immune checkpoint inhibitors were based on the background of bidimensional tumor assessments (WHO tumor assessment criteria) recent progress in the development of the irRC criteria indicated that irRC criteria can be applied to unidimensional measurements (based on the international RECIST standard).

Table 1 and Table 2 describe and summarize the comparability of RECIST based irRC with WHO-based irRC, presenting the advantages of RECIST-based irRC, as published by Nishino et al.

Central imaging is not only a crucial element of pivotal studies, but can also be used to evaluate and compare responses under both the standard tumor assessment guidelines such as RECIST and the revised irRC criteria. While central imaging results may be adjudicated as a requirement

Table 1: Summary of Measurement and Response Assessment Approaches for Bidimensional and Unidimensional Assessment Based on irRC.

	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	≥5 × 5 mm ² by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm ²)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir	PD: ≥20% increase from the nadir
	PR: ≥50% decrease from baseline	PR: ≥30% decrease from baseline
	CR: Disappearance of all lesions	CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	

Table 2: Best Immune Related Response According to Bidimensional Versus Unidimensional Assessment.

	Best response by bidimensional assessment			
Best response by unidimensional assessment	irCR	irPR	irSD	irPD
irCR	1	0	0	0
irPR	0	7	0	0
irSD	0	0	41	3
irPD	0	0	1	4

Source: Mizuki Nishino, Anita Giobbie-Hurder, Maria Gargano, et al., “Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements,” Clin Cancer Res 2013;19:3936-3943. Published OnlineFirst June 6, 2013.

for regulatory submission, adjudicated decisions come too late to affect a patient's care during the trial. Investigators, themselves, must, therefore, be thoroughly familiar with the response criteria for ICIs.

Leading oncologists certainly understand how to evaluate patients being treated with immunotherapy. However, their investigative sites are often saturated with oncology trials. Sponsors may, therefore, need to work with other Principle Investigators (PIs) who may not be as familiar with the way that tumors respond to immunotherapy. It is essential that all site personnel—from the PI to study coordinators—be trained thoroughly on the irRC and be given clear guidance on how to encode responses.

In conjunction with this, the electronic Case Report Form (eCRF) needs to be modified to capture irRC, sometimes along with RECIST. And, as ICI trials progress, Medical Monitors should maintain frequent contact with principle investigators to address questions and ensure that they are applying the criteria uniformly.

When a patient is removed from immunotherapy treatment due to lack of response, the standard practice is to conduct a confirmatory scan at a designated interval—at least four weeks after treatment withdrawal. However, in the absence of clinical deterioration, it is not unusual for eight or more weeks to pass between the initial scan showing disease progression (as per RECIST) and the confirmatory scan. This is critically important in ICI trials in order to rule out pseudo progression and determine true progression. The sponsor's clinical research organization should be tracking the completion of the confirmatory scan and its results, or capturing the reasons that it has not been performed. In fact, the extent to which investigators perform confirmatory scans might be considered a surrogate metric on the degree to which investigators apply the irRC.

Endpoints in Immuno-Oncology: Importance of Capturing Survival-Related Endpoints

The use of irRC has increased the awareness and recognition of short-term (i.e., within three-six months) and, in particular, long-term anti-tumor effects of ICIs. Importantly, several randomized clinical studies to date indicate that ICIs and other immune-oncology approaches contribute to prolonged survival

in patients even when the objective anti-tumor response is no greater than that of the standard of care. This effect was considered as an indicator that the anti-cancer immune functions—once activated—continue to be active even if patients are switched to alternative therapies in the course of their treatment path. Overall survival was a successful primary endpoint in the approval of Yervoy.

IMMUNE-MEDIATED ADVERSE REACTIONS

A consequence of the downmodulation of immune regulatory pathways to obtain a robust immune response to cancer cells is that a significant proportion of patients experience non-specific immune activation, creating inflammatory reactions in various organs. The pattern and intensity of these reactions are dependent on the specific type of ICI.

Adverse events and inflammatory reactions are termed “immune-mediated Adverse Reactions” (imARs) (also sometimes referred to as immune-related Adverse Events, irAEs). “Although imARs are different in character from adverse events caused by traditional chemotherapy or targeted therapy, the rate of grade 3 or 4 toxicity with immune checkpoint blockade (approximately 10% to 20%) is no greater than that seen with many standard chemotherapy or targeted therapy regimens.”⁹

Adverse events caused by inflammation from ICI treatments can occur in any organ system, but thus far are most common in skin, the gastrointestinal tract, the liver and the endocrine system. Figure 2 lists the incidence of imARs found by organ system across all three types of selected ICIs. Clearly, each ICI has a different imAR profile. Because it has been extensively studied for several years and on the market the longest, CTLA-4 (Yervoy) has produced the largest irAR database.

Figure 2: ICI Type Determines Clinical Aspects of Selected imARs

Organ	AE	αCTLA 4%	αPD- 1%	αPD- L1%	Organ	AE	αCTLA 4%	αPD- 1%	αPD- L1%
SKIN	rash	29	12	9	LIVER	ALT +	3	4	1
	pruritus	31	10	6	JOINTS	arthralgia	NR	4	7
	vitiligo	3	3	2	LUNG	cough	16	3	1
GASTRO- INTESTINAL	diarrhea	35	11	9		pneumonitis	NR	3	–
	nausea	33	8	6	ENDOCRINE	hyperthyroid	0	1	0
GENERAL	fatigue	36	24	16		hypothyroid	6	2	3
	pyrexia	12	5	3		hypo- pituitarism	3	0	0
CENTRAL NERVOUS SYSTEM	headache	14	3	4	INFUSION	reaction		3	10

Hodi F. S., M.D., et al, “Improved Survival with Ipilimumab in Patients with Metastatic Melanoma,” NEJM, August 19, 2010.

Topalian, Suzanne L., M.D. et al, “Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer,” NEJM, June 28, 2012.

Robert C., et al, “Anti-Programmed-Death-Receptor-1 Treatment with Pembrolizumab in Ipilimumab-Refractory Advanced Melanoma: a Randomised Dose-Comparison Cohort of a Phase 1 Trial,” Lancet, September 20, 2014.

Investigators should be alerted to the fact that imARs may be inadvertently overlooked if it is assumed that a patient’s general symptoms, such as fatigue or asthenia, are a reflection of the underlying disease rather than an endocrine disorder due to an imAR.

Interest is growing within the research and medical communities in combining ICIs with one another, with other immunotherapies, or with other oncology agents (such as the standard of care for a particular tumor type). Such combinations will likely be the focus of many trials in the foreseeable future, and it remains to be seen how combining different treatments will affect the incidence and severity of imARs. Trials testing the efficacy and imAR profile of two ICIs used in unison are in their early stages, but suggest that the toxicity profile is manageable.

OPERATIONAL RECOMMENDATIONS FOR CONDUCTING CLINICAL STUDIES WITH ICIs

Because trials of ICIs employ a special set of response criteria and pose additional risk to patients, managing such trials is a complex undertaking. The challenges are heightened by the fact that the class of drugs is new, and their treatment algorithms, safety profiles and disease responses are not yet well known or understood within the oncology community. Additionally, the complexity of ICI trials is bound to increase with the exploration of combination therapies and the need to test different therapy sequencing.

Overall, a central aspect of success is early detection and careful management imARs, with the multiple objectives of minimizing interruption or discontinuation of patients’ participation in the trial, improving patients’ quality of life

and optimizing the investigative product's efficacy parameters. To achieve these goals, ICI trials require robust education, enhanced communication and vigilant monitoring. Strategies for the early detection and treatment of imARs should include the following key elements:

Study and Protocol Planning:

- **Selection of the patient population.** Pre-clinical and early clinical information should be integrated into decisions about the appropriate patient population.
- **Dosing considerations.** Dosing should reflect patients' immune status at study start, as patients with advanced cancer tend to have a more suppressed immune status, and this could require higher dosing or more frequent dosing intervals.
- **Pharmacokinetic (PK)/Pharmacodynamic (PD) aspects.** Apart from PK assessments, ICI studies often must integrate specialized immuno-monitoring and provisions for tumor biopsies. The goal is to measure the effect of the ICI on the anti-cancer immune response and to potentially provide insight into the subpopulation of patients with the best response.
- **Consideration of survival endpoints for Phase III studies.** Survival endpoints—and overall survival in particular—have been successful in the past in supporting pivotal ICI studies.
- **Implementation of efficacy and safety aspects of ICIs in the protocol.** Protocols require specialized sections on how to manage imAR and irRC.
- **Special factors involved in combination therapy.** For those studies involving combinations of ICIs with other therapies, special attention should be given to potential drug interactions.

Start-Up:

- **Site selection criteria.** Site identification and selection are critical success factors, just as they are in all clinical studies. With ICI studies, the ideal is to find sites with prior experience in such trials, or at least with other areas of immunotherapy. Investigators who lack this specialized experience will need additional training.

- **Comprehensive education and communication.** Strategies for the early recognition and treatment of imARs should include the following program components:

- **eCRF design.** The electronic Case Report Form must be modified so that it can capture the necessary details on both the irRC and the imAR. Sites must be given clear guidance on how to encode imARs, to make note of the concomitant medications given to treat them, and to report on the reversibility of the imAR. Again, much comes down to how well sites are trained in the reporting requirements and procedures. A literature review covering 50 trials revealed that in 13 studies (26%), no details were reported on the outcome of AEs, while 22% omitted information on how the AEs were managed.¹⁰
- **Development of patient training and education materials.** Patients must, of course, receive an explanation of the possible imARs they may experience. Just as important, they must also be taught how to recognize emerging symptoms of imARs. Their education must stress how important it is to contact the site at the first sign of a problem so that the imAR can be caught early and treated immediately. Addressing low-grade imARs promptly will prevent their exacerbation into high-grade events that could impact the patient's safety. Patients experiencing high-grade events may be permanently discontinued from further treatment. Special patient brochures should be available to convey this information.

Study Conduct:

- **Surveillance of the safety signals using a specific set of data reviews.** Active surveillance should be maintained using a combination of staff and technology so that responsibility for monitoring for imARs is widespread, cutting across data management and clinical operations. The data obtained during the course of the study is crucial to forming the basis of a communication plan for health providers and patients to educate them on early recognition and appropriate treatment of imARs. The trial data must be able to stand up to all scrutiny for reliability and validity.

Thorough and systematic medical reviews can ensure the consistency of reported data and patient profiles. The trial's Medical Director should review the imAR tables at specified intervals, analyzing the rate of occurrence, grade and resolution time for imARs, center by center.

Clinical Research Associates (CRAs) should be trained to spot potential imARs—particularly those of special concern, such as diarrhea. At the same time, audit checks imposed on the data management tool can spot potential issues (through lab values, for example) and trigger alerts for follow-up actions in patient care. All the while, the trial's operations and medical teams need to be in close contact, with frequent communications concerning trends that each group is seeing.

Throughout ICI trials, proper monitoring is necessarily a very hands-on exercise with frequent site contact, especially as the safety profile can be rather fluid. Therefore, immunotherapy trials are not, at this point, good candidates for a Risk-Based Monitoring (RBM) strategy that relies heavily on centralized monitoring.

- **Supervision of how irRC are applied.** For example, regular data checks can be used to determine the percentage of times confirmatory scans are completed and to assess the reasons that investigators cite for not conducting them. The completion of the irRC section of electronic case report form is another way to track the completeness and quality of irRC recording.

- **Supporting investigators' imAR treatment decisions.** The many general guidelines for addressing imARs focus on patient education, early recognition of symptoms, and prompt treatment. Such general guidelines should be supported with recommendations on the specific requirements and treatment options for each organ system (e.g., the gastrointestinal system), according to the severity of the event. (See Figure 3.)

Tapering patients off of corticosteroid or immunosuppressive therapy to treat imAEs is at least as important as initiating treatment quickly with the correct dose, since early discontinuation of treatment to suppress imAEs can lead to rebound imARs.

Figure 3: Guidelines for Managing Patients with imAR: to Be Adapted Based on Clinical Considerations*

CTCAE grade	Management*	ICPI treatment
Grade 1 (mild)	- Increase frequency of supervision e.g. to daily - Supportive care	Continue
Grade 2 (moderate)	- Supervision - Supportive care - Topical steroids as indicated (skin/colitis) - For symptoms ≥ 7 days start prednisolone eq 1 mg/kg BW - Symptoms increase - Oral or iv prednisolone 1 mg/kg	Interrupt and restart when \leq grade 1
Grade 3-4 (severe or life-threatening)*	- Start prednisolone eq 2 mg/kg BM	Discontinue

*isolated skin grade 3 and endocrinopathies are exempt from discontinuation as frequently resolve (skin) or can be substituted (endocrinopathy)
Modified according to Weber, Jeffrey S. MD, PhD, et al., "Toxicities of Immunotherapy for the Practitioner," *J Clin Oncol*, April 2015.

Conversely, prolonging treatment of the imAR may lead to unnecessary immune-suppression and infections.

Given the number of organ systems that can potentially be involved, instructions for investigators can quickly become complex and voluminous.

Sponsors can select from two basic educational strategies for ensuring that investigators have the information they need to treat patients properly. The first is to orient site staff with complete details on the treatment protocol for every potential imAR across organ systems. While this approach has the advantage of covering all the bases, it can be overwhelming for trial staff and may, in the end, be counterproductive.

The second strategy is to provide the staff with an overview of what symptoms to watch for along with an easy-to-reference summary of the protocol and how it is affected by the grade and duration of the imAR. Investigators should then be instructed to call the trial's Medical Director for organ-specific protocols as needed. The vast majority of events are low grade (Grade 1 and Grade 2) and are treated primarily with topical or low-dose, systemic steroids. However, should first line treatment fail, the options are very specific to the imAR, and include escalating treatment to a high-dose, systemic corticosteroid treatment and even more potent immune-suppressive agents. Dose interruption or even permanent discontinuation from further dosing may be warranted, depending on the severity of the event.

Sponsors can monitor how well imARs are managed by tracking the number of resolved imARs and the degree to which investigators follow the requirements for re-interventions after tapering or discontinuing the initial interventions. This information should be compared to benchmarked data for the same drug class or for specific ICIs.

Study close:

- **Data quality reviews to capture and confirm—and if necessary—query imAR and irRC.** Systematic data reviews should be performed to demonstrate data consistency and gather evidence on the correct use of the study's operational and medical guidelines.

- **Experience in developing the reports and publications for ICIs.** After the study is completed, a thorough Risk Mitigation and Evaluation Strategy (REMS) should be developed to ensure that once the drug is marketed, its benefits outweigh its risks. Experience in developing clinical study reports is important. Due to the high scientific interest in ICIs, sponsors should strive for rapid publication and consider having CRO experts contribute.

Working with Clinical Research Organizations

Sponsors are well advised to insist on clinical and operations teams that have prior experience in working with this unique class of drugs. Only those who have previously been involved in such trials will have a proper appreciation for all of the medical and practical considerations required for successful study execution. Specifically, sponsors should look for ICI experience across all necessary functions—including regulatory, medical, operations and pharmacovigilance. Sponsors should involve their clinical research partner early in the trial planning process, given the extra strategic planning needed for smooth trial operation.

Sponsors may also need to open their site selection to new sites, regions and countries to find sites that are not already saturated with oncology trials. The caveat in doing so is that more time and effort will have to be put into training investigators and site staff who are likely less familiar with immunotherapy trials. Given the particular toxicity profile and response pattern of ICIs, only a Clinical Research Organization (CRO) with in-depth experience in immune-oncology will be able to guide sites through these extremely demanding studies.

Due to the excitement that ICIs are generating, CROs and investigative sites need to be prepared to handle a dramatically accelerated enrollment timeline, as enrollment rates can be markedly higher than with other therapies. For example, one ICI trial for a rare form of cancer enrolled almost 0.5 patients per site per month, whereas other therapies in the area enrolled about 0.17 patients per site per month.

FUTURE PERSPECTIVE

The complexity of trials involving ICIs is bound to increase with the exploration of combination therapies and the need to test different therapy sequencing.

The next stage of research will be about testing combinations and engaging multiple physiologic and cytotoxic mechanisms to attack tumors. In working with a research partner that has previous experience in ICI trials, sponsors can improve clinical programs to more accurately measure clinical endpoints, better ensure patient safety and position trials for successful completion and regulatory approval. It is an exciting time in the development of immunotherapies and the world will be watching the development of these drugs that give home to cancer patients worldwide.

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*2009-2013