

Beyond Immune Checkpoint Inhibitors to a New Era of Personalized Medicine: Planning and Conducting Trials of the Latest Immunotherapies

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Immunotherapies are being touted—both in scientific literature and the general media—as the most promising advances in cancer treatment in decades. Indeed, newly approved drugs are improving survival dramatically for patients with many difficult-to-treat cancers such as melanoma, Hodgkin’s lymphoma, and cancer of the bladder, lung, kidney, and head and neck.

Immunotherapies are coming to the fore in cancer treatment as we learn more about tumor genetics, pathophysiology, tumor microenvironment, and as interest grows in attacking tumors on multiple levels. Some—though still few—therapies under development are truly individualized for the patient, potentially ushering in a new, even more tailored approach to personalized medicine.

The field of research has engendered such enthusiasm that there is some concern we may be experiencing a “bubble” in immunotherapy development.¹ Currently, 830 companies are developing 1,578 cancer immunotherapy drugs via 4,062 development projects across 535 different targets. (That is excluding the 624 drugs for which development has ceased and the 19 for which it has been suspended.)² There is fear that many of these products, once in clinical practice, will not live up to the high hopes they’ve raised while in development. Furthermore, the market is unlikely to bear the cost of so many drugs at the price-point of current checkpoint inhibitors. (The Wholesale Acquisition Cost (WAC) of the four checkpoint inhibitors on the market for a 12-week dose runs from \$24k to \$137k, and the estimated cost of CAR-T therapy could be even higher than bone marrow transplants, which can exceed \$500,000.³) Both fears are justified, but have yet to deter enthusiastic researchers.

Clinical trials of cancer immunotherapies are necessarily quite different from those in other therapy areas; they require special planning and are subject to unique medical, regulatory, and operational considerations. Here we discuss the factors that sponsors must take into account as they design and execute clinical trials in this space.

¹ Tolcher, Anthony W MD, “Immunotherapy Clinical Trails: Better Therapies or a Bubble,” ASCO Annual Meeting, 2016.

² BioSeeker Group, August, 2016: <http://www.bioseeker.com/market-research-report/immunotherapy-in-oncology-drug-pipeline-update.html>

³ Ledford, Heidi, “Immune cells boost cancer survival from months to years,” Nature, Dec. 10, 2014.



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Classes of Immunotherapies: Advancing Beyond CPIs

Checkpoint inhibitors (CPIs) are the first of the modern cancer immunotherapy drugs and, with four currently on the US market, are perhaps the best-known class of immunotherapies to date. They work by blocking the pathways on T-cells that inhibit the body's natural immune response and allow cancer cells to elude detection. (Please refer to inVentiv Health's paper, "Critical Success Factors for Clinical Trials of Immune Checkpoint Inhibitors" for more details.)

Several other approaches to using the body's own defense mechanisms to fight cancer are being discovered, however, and they are the focus of this paper:

- **Adoptive Cellular therapy.** These therapies are still experimental and require collecting circulating immune cells from a patient through leukapheresis, amplifying them *ex vivo*, and transferring them back into the body for a bolstered attack on the cancer. (Sometimes, the amplified cells are genetically engineered to recognize specific tumor antigens.) Autologous cell transfers—in which the expanded cells are injected back into the donor patient—are being performed now. There is the potential, however, for treatments to involve allogenic cell transfers whereby the amplified cells from one patient can be used for multiple patients with the same tumor type which is characterized by a specific tumor antigen. Several allogenic cell transfer therapies are currently in development.
- **Bispecific antibodies (BsAb).** This versatile approach uses a single monoclonal antibody which has been engineered to bind two unique targets to increase the efficacy of the therapy, for example by bringing T-cells within striking distance of cancer cells so that the T-cells can attack the cancer effectively. The first generation BsAb was a rat-mouse hybrid antibody that bound a different antigen with each arm. Genetic engineering has since influenced the development of BsAbs, providing more information on the origin of the binding site, its composition, and production. At this writing, there are more than 80 bispecific formats in development.⁴
- **Therapeutic Vaccines.** These are active treatments—not preventative inoculations—that activate the immune system by presenting it with an element of the cancer. The vaccines include peptide/protein, DNA/RNA, viral/bacterial vector and cell-based approaches. While some are patient-specific, most vaccines are broadly prepared based on a tumor-cell antigen that is expected to be common to many patients.

⁴ <http://bispecific.com/>

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Despite the breakthroughs that these treatments represent and the massive investment being made in further advances, we have only just scratched the surface of what there is to learn about the immune system. We do not yet understand, for example, why immunotherapies are more successful against some cancers than others, nor why they are amazingly effective in some patients, but completely ineffective in others. (The response rate varies by therapy area, and is anywhere from 5 to 50 percent.)⁵ So, improving response rates and finding applications in additional cancer types are major goals of researchers.

Estimating Trial Feasibility: Combining Art and Science

Determining what it will take to enroll the required number of patients into a trial within a given timeframe is challenging in the best of circumstances. But it is significantly more difficult for trials of new immunotherapies because there is comparatively little established past history on which to base patient enrollment projections. Many drugs in these classes were granted a Breakthrough Therapy Designation quickly and their approval fast-tracked. Some were even given conditional approval on the basis of early stage trials. Therefore, the feasibility processes of estimating the enrollment rate necessarily involves supplementing evidence with the judgment of a multidisciplinary team of experts.

Even selecting which trials might serve as effective benchmarks is a nuanced decision. A host of factors related to trials' protocol and logistics go into selecting good trial analogues. A match should be based on such protocol details as inclusion/exclusion criteria, the investigative compound's line of therapy and projected toxicity compared to the standard of care, the trial design, and the schedule of patient visits and procedures (such as biopsies). Other factors include the proximity of patients to sites, the footprint of the trial, the affordability of the standard of care, and clinicians' excitement over the experimental therapy compared to other available trials.

Once the appropriate benchmark studies have been identified, it is matter of knowing how much to draw on—or deviate from—they in estimating enrollment rates for the trial at hand. Unfortunately, there is no algorithm that can determine this; it is a judgment call that requires extensive medical and operational knowledge of recent approvals and the standard of care. Specialists have to weigh the plusses and minuses of the various factors in creating plausible ranges that can then be fed into a simulation model. Figure 1 below provides a high-level example of this process, showing how trials can be best matched to a given protocol based on inclusion criteria, previous treatments, and other factors. These trials can then form the basis of early scenario development, further refined and verified through investigator contact and interrogation of their claims or EMR sources.

⁵ Panel discussion, "Precision Medicine in Cancer Research," 2016 Concordia Summit: The Future of Immunotherapy reported in the Cancer Therapy Advisor, Sept. 19, 2016.



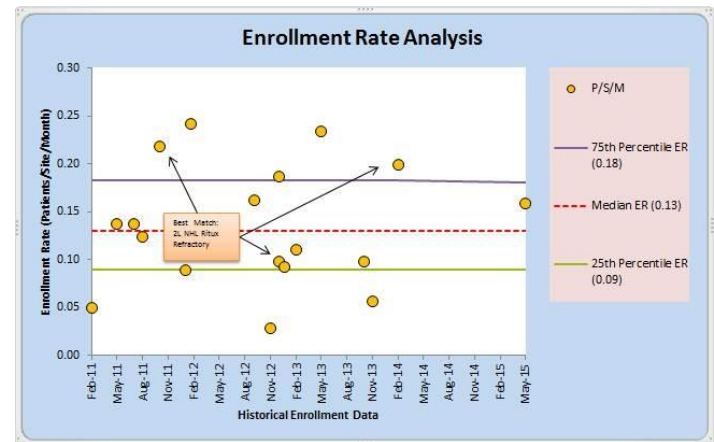
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A trial's feasibility will also be affected by the total number of trials that are enrolling and running for the same indication/tumor type and the type of sites being sought. On the one hand, studies of novel immunotherapies and combination treatments—and especially in earlier phases—may need to be conducted at academic centers for their experienced investigators and sophisticated facilities. Not all community-based hospitals are able to perform biopsies, for example. On the other hand, if patients need to be treatment naïve, it may be best to involve community hospitals (and find ways to train and equip them). Patients who are treated at academic health centers are often those who have been treated elsewhere and whose disease has progressed.

Determining a trial's feasibility also entails knowing how many trials particular sites can handle, and that comes from being in close contact with sites and staying abreast of what is happening in the field. Some sites, for instance, may be able to participate in 20 trials at once. Others may be tapped out much sooner. Maintaining relationships with investigators is critical to understanding how protocols will be received by potential investigative sites. It is also critical to be able to train investigators well on new immunotherapies so that community centers with strong patient access can be included in these trials.

Figure 1: Sample Enrollment Rate Analysis of Best Matched Benchmark Trials



To improve the accuracy of feasibility assessments, sponsors should:

- Develop and maintain relationships with investigators interested in new and innovative treatments. Investigators who welcome contact about potential validation of protocol components are especially valuable.
- Maintain an internal repository of data for comparison to new treatments
- Develop and implement quick immunology site trainings for those community centers with strong patient access
- Open pathways of communication among clinical, medical, operational, and feasibility teams to provide up-to-the-minute strategy around new protocols/treatment



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Medical Challenges: Novel Issues with Novel Treatments

Selecting Relevant Endpoints

Because cancer immunotherapies work differently than chemotherapies and targeted therapies, some conventional endpoints used for regulatory approval and marketing access are not necessarily valid or practical. Researchers should evaluate which endpoints are most useful for both early- and late-phase studies.

Most chemotherapies and targeted therapies affect a measurable response in a relatively short time—generally 8 to 12 weeks. And, typically their regulatory approval is based on demonstration of Progression-Free Survival (PFS) or Overall Survival (OS), with PFS often being an acceptable surrogate endpoint for OS.

Immunotherapies, however, have a much different effect in that:

- Sometimes, they do not initially show tumor shrinkage. They can even result in a transient increase in the appearance of tumor radiographic dimensions. Yet, even when this is the case, they may produce a survival benefit. It is not that surrogate endpoints such as tumor burden are irrelevant with immunotherapies, it is rather that they do not always predict the magnitude of the survival benefit.
- The pattern of Kaplan-Maier curves for PFS and OS with immunotherapies frequently show a distribution of decline to a certain point and then a plateau, creating a long “tail” along the X-axis. In other words, some percentage of patients experience a very long-term benefit that could take years to demonstrate statistical maturity. In this circumstance, the median of the measure for the entire population may not reflect the potential long-term benefit of the drug for a subgroup.

These treatment characteristics have several consequences for sponsors. First, it makes go/no-go decisions during Phase I difficult because it takes so long for OS results to emerge. It also makes it very difficult to determine, based on an interim analysis, if a trial should be closed due to lack of response. As a solution, sponsors might use surrogate endpoints, such as landmark PFS (PFS at certain points in time) and Overall Response Rate (ORR) measured by Immune-Related Response Criteria (irRC), to capture the specific patterns of response. In the future, optimal clinical endpoints might be developed using an adaptive randomization scheme based on biomarker positivity, or assessment of impact on the tumor microenvironment through study of biopsy obtained early in the patient’s course of treatment.



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Second, relying on OS as endpoints for immunotherapies could conceivably require running trials for years—which, of course, could be both cost-prohibitive and impractical. And third, because immunotherapies that become the standard of care are dramatically improving OS, the bar will continue to be raised in terms of what is clinically meaningful to providers, payers, and patients. If, for example, the last treatment to be approved showed a PFS of 24 months, by what margin will a new compound have to surpass that to gain the confidence of providers and to satisfy payers?

Considering these difficulties, landmark PFS rates at one year, two years, and three years should be consistently reported in clinical trials as a standard practice. However, given that Health Technology Assessment (HTA) agencies currently require PFS and OS for final pricing, agencies may need to consider these additional measures of benefit.

The bottom line is that sponsors of immunotherapy drugs should have extensive conversations with regulators to agree on the endpoints that will be acceptable for approval, and any request to use landmark PFS rates will need to be supported with very strong justification.

Patient Selection

In all clinical trials, of course, there is benefit to selecting those patients for whom the treatment will be most successful. And doing so is more than usually critical in trials of immunotherapies because of the extremes in response: although immunotherapy benefits less than half of treated patients, it does produce substantial survival benefits for some. To confound the situation, there have been some immunotherapy trials in which patient selection via a biomarker was key to treatment success, while there have been others in which the biomarker was shown to have no impact on treatment outcome. In the latter cases, it could be that there is another, as yet undiscovered, biomarker that would differentiate patients.

Clearly, we do not yet know how to target immunotherapies optimally, and uncovering the right biomarkers appears to be a vital step toward that end. Unfortunately, the challenges in identifying the best biomarkers are going to become exponentially more complex with the use of combination therapies. What, for instance, would be the right biomarker when one treatment is stimulating the immune system and another is inhibiting it?

Studying archived tumor tissue for the immune markers that were in patients' original biopsies may help explain why some patients respond and others do not. But, looking at what was happening two or three years earlier will not necessarily explain what is happening with a patient's tumor in the present... nor how the patient's immune system is currently behaving. One solution, from a



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clinical design point of view, would be to take a biopsy immediately before treatment starts and then again after the patient has received two or three doses of the medication. That, of course, would present other challenges as it is not always safe or practical to re-biopsy a tumor.

Another challenge to patient selection is that some intense therapies, such as CAR-T cell infusion for example, require relatively healthy patients who can stand to wait several weeks for their treatment to be manufactured. If the protocol does not accommodate for this, the trial may experience a high screen-failure rate; sponsors may incur the cost of enrolling patients into trials who never get to participate because their cancer progresses in the interim between enrollment and first dose.

When developing protocols for immunotherapy trials, sponsors should take a zero-based review of the eligibility criteria. Criteria developed for chemotherapy trials should not be automatically carried forward into immunotherapy trials. It may be, for example, that the usual baseline hematologic criteria used in studies of myelosuppressive chemotherapy drugs may not be appropriate for immunotherapies.

Surveillance of Immuno-modulated Adverse Reactions

A significant proportion of patients receiving immunotherapy experience inflammatory reactions in various organs caused by non-specific immune activation. And, as more patients have been exposed to immunotherapy, it has become clear that some treatments can cause unusual toxicities. For example, cytokine release syndrome is a serious, and potentially life-threatening reaction seen with some treatment modalities.

By now, the majority of clinical investigators at academic centers are familiar with these Immuno-modulated Adverse Reactions (imARs) and know how best to communicate with patients, monitor them, and treat their symptoms. Staff at some sites, however, may need additional training specific to newly emerging drugs. Nonetheless, sponsors must be prepared with emerging strategies to manage toxicity and to monitor sites including through site visits after the first dosing to evaluate compliance with available treatment-management guidance. Moreover, with the potential for prolonged biological activity with engineered T-cells, long-term surveillance for potential imARs after adoptive T-cell therapy becomes especially critical.

It remains to be seen if treatments that combine two immunotherapy drugs will exacerbate imARs, although it is likely that the impact may depend on whether their mechanisms of action are the same or different. Ideally, combination therapy will allow for a lower dose of one of the drugs,



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thereby reducing the incidence of imARs, while also improving the pharmacodynamics and overall effectiveness of manipulating the immune system.

Given the potential for prolonged biologic activity with some therapies (e.g., CAR T cells) the FDA is requiring patients be monitored for up to 15 years to detect possible emergence of late second malignancy or other effects.

Regulatory Considerations: Complex and Ever Evolving

The new immunotherapies pose challenges for sponsors in ensuring regulatory approvability and compliance, given that there is a separate and very different regulatory framework for each novel mechanism of action. In both the US and EU, distinct regulations apply to cell-based medicinal products, gene therapy, antibodies, and therapeutic vaccines. Regulators in both regions exchange information on a regular basis, and their thinking is generally aligned with regard to requirements for immunotherapy trials. There are, however, some notable differences.

Given the complexity of the applicable regulations—and that they are continuously evolving—sponsors should take care to stay abreast of agency requirements very early in the development process, ideally at the proof-of-concept phase.

Sponsors will need to hold discussions with regulators as early as possible, especially for combination studies, which can be complex. These meetings are an opportunity to ask questions and to negotiate study design, provided that the sponsor presents a study design rationale that is both logical and grounded in science. The benefit of these discussions for the sponsor is the assurance that the regulatory agency agrees with the design of the study before tremendous effort is expended in selecting and activating sites. The sponsor also benefits from insight into how and why the regulatory agency prefers one approach over another.

Immunotherapies that are the first treatment in their class may be able to take advantage of accelerated approval pathways via the priority medicine designation: PRIME, in the EU; breakthrough designation/accelerated approval (with a surrogate endpoint) in the US; and fast-track review (Sakigake) in Japan. (Please refer to the inVentiv Health paper, “Pursuing Accelerated Approval in Oncology Indications,” for more details.) However, companies with follow-on products may have to run Phase III trials demonstrating Overall Survival (OS) in head-to-head comparisons with the standard of care. The need to show OS presents major challenges to sponsors, as discussed below.



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As explained above, in many immunotherapies, the discovery of a biomarker—and therefore the use of a companion diagnostic—is key to success because it identifies those patients who will be responsive to treatment. Thus, sponsors pursuing personalized applications or biomarkers will need to be familiar with the specific regulations pertaining to companion diagnostics.

EU

In the EU, products created using cell-based cancer immunotherapy and genetically modified cell-based immunotherapy are regulated as Advanced Therapy Medicinal Products (ATMPs). ATMPs that target an unmet medical need and that involve non-routine manufacturing (because they are developed for an individual patient) may qualify for a “Hospital Exemption” from the usual approval pathway. When this is the case, biomarkers can be accepted as a surrogate endpoint, and market access may be granted after a Phase I study that has been designed to show both safety and efficacy. The sponsor will have to commit to following up with patients and to measuring hard clinical endpoints on efficacy. Hospital Exemptions are regulated at a national level.

Trials that involve a genetically modified organism (GMO) must also be approved by the biosafety board in the countries where the clinical trial is to be conducted—a process that includes an environmental risk assessment. Participating sites must hold permits to handle GMOs and for site pharmacists to dispense the GMO trial supply to the patient.

The ability to target medicines to individual genes (the traditional definition of personalized medicine) is recognized as a need, and EMA established a working party (PgWP) to address the pharmacogenomics when optimizing the use of medicines. The agency is currently in the process of gathering scientific viewpoints on the use of genomic biomarkers.

Currently, there is no common definition of “companion diagnostic” in EU directives as each member state has a different opinion on the concept. New regulations, however, are expected to be published in 2017 that will bring changes and added clarity to the definition of companion diagnostics.

US

US Regulations for Precision Medicine—treatments targeted to specific patients based on a companion test identifying the need for such a treatment—are still evolving to meet the developmental requirements of the rapidly evolving and complex technologies. The Food and Drug Administration (FDA) is aware of the complexity involved in ensuring the safety and efficacy of



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immunotherapies. Therefore, in addition to publishing guidance documents to aid developers, the agency encourages sponsors planning to initiate studies with adoptive immunotherapeutic products for cancer to discuss the details of the proposed studies with the appropriate review division(s) as soon in development as possible.

The FDA recognizes that co-development of in vitro device (IVD) companion diagnostics and therapeutic products is critical to the advancement of precision medicine and to preventing delays in the introduction of new therapies. In July 2016 the agency released a new and more detailed draft guidance that streamlines the process by which companies can co-develop a therapeutic alongside an in vitro companion diagnostic device. The draft, "Principles for Co-development of an In Vitro Companion Diagnostic Device with a Therapeutic Product," is intended to be a practical guide to assist drug and IVD sponsors in developing these two products simultaneously.⁶

Also in July 2016 and in support of the President's Precision Medicine Initiative, the FDA issued two draft guidance documents that, when finalized, will provide a flexible and streamlined approach to the oversight of tests that detect medically important differences in a person's genomic makeup⁷. Powerful new technology—such as next generation sequencing (NGS), which can scan a person's DNA to detect genomic variations—may determine whether a person has or is at risk of disease or may help to inform treatment decisions for immunotherapies in the future. While current regulatory approaches are appropriate for conventional diagnostics that measure a limited number of substances associated with a disease or condition, such as blood glucose or cholesterol levels, the new sequencing technologies can examine millions of DNA variants at a time, and thus require a flexible approach to oversight that is adapted to the novel nature of these tests.

In 2016, the FDA also launched a pilot project to develop a clinical database to examine safety in trials using CAR T-cells. The agency's goal is to be able to examine safety and Chemistry, Manufacturing, and Control (CMC) data across multiple investigational new drug applications to build a safety profile for these therapies.⁸

Operational Excellence: A Very Hands-On Approach

Trials of immunotherapies are challenging from an operational perspective as well, requiring special processes all along the way, perhaps including manufacturing, transport, and storage

⁶ <http://raps.org/Regulatory-Focus/News/2016/07/14/25332/FDA-Offers-New-Draft-Guidance-on-How-to-Co-Develop-IVDs-Therapeutics/>

⁷ <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm509814.htm>

⁸ <http://www.raps.org/Regulatory-Focus/News/2016/03/16/24549/FDA-Proposes-New-Databases-to-Monitor-CAR-T-Cell-Safety-Across-INDs/#sthash.yPDYlctX.dpuf>



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issues and continuing through to treatment administration and monitoring. This is especially true for the new generation of personalized treatments (autologous cell transfer therapies and select cancer vaccines) that require drawing cells from a patient, shipping the patient's sample to a manufacturing facility, shipping the resulting customized therapy to a hospital, administering the treatment to the patient within a hospital, and monitoring the patient during hospitalization and beyond.

Manufacturing

Uniquely, some immunotherapies, such as cell therapies and customized vaccines, involve a manufacturing step between patient enrollment and first dosing. Sponsors should be aware of the surrounding logistical issues, which include:

- **Limited manufacturing capability.** Getting a facility certified to comply with Good Manufacturing Processes is a significant and complicated undertaking. Once certified, many facilities are only able to produce six to eight doses per month.
- **Elapsed time.** Typically, the individualized manufacturing process takes from 18-40 days, during which time patients awaiting treatment may need to receive alternative treatment, if they show evidence of progression.
- **Stability testing.** With personalized treatments, enough of the drug is manufactured to treat the patient over the course of the trial, which can be as much as two years. Consequently, the product must be proven to be stable for that length of time.
- **Failure rates.** Manufacturing failure rates tend to be high for both patient and process-related reasons. This calls for corrective and preventive actions to be implemented (e.g., increasing the collection volume and applying stringent inclusion criteria) to ensure optimal processing.

Transportation and Storage

There are also complications to contend with in transporting and storing patient samples and cell therapies and vaccines, in particular. These include:

- **Time-sensitivity.** It is not uncommon for blood draws, for instance, to have to be performed during a critical window of time before they reach the manufacturing facility. This has obvious implications for transport arrangements and may limit the geographic distance that patients can be from manufacturing facilities.



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- **Special shipping and storage requirements.** Most samples and immunotherapies have special storage and handling requirements that demand sophisticated temperature monitoring and GMP-certified storage facilities. In some cases, materials cannot be transported in the cargo area of planes, but must be hand carried on airplanes and shepherded from person to person during transport. The consequences of a temperature excursion are not just financial; it could be devastating for a patient who cannot afford to wait another 40 days for a second batch of the therapy to be manufactured.
- **Chain of custody.** Sponsors need to be able to track and trace shipments back through the whole chain of custody. While this is no different than for any other type of study drug, it is far more complex given the logistical supply chain needed for cell therapies and vaccines, often requiring far more manpower to ensure adequate tracking and reporting.

Given these challenges, and despite the enthusiasm engendered by some notable successes with CAR T- cell therapy, many question whether these will ever be logistically and affordably deployed on a global basis or whether they will be reserved only for use at elite institutions in economically advantaged countries.

Coordination and Monitoring

These restrictions demand that someone, such as the project manager within the Contract Research Organization (CRO), carefully coordinate all of the steps involved in treating patients on an individual patient level. Managing trials of immunotherapies—especially personalized treatment—must be a very hands-on affair. Sites also need to be fully informed of, trained on, and equipped for the special handling of samples and therapies. And, sponsors and their CROs must be prepared to have many more touchpoints with sites as trials progress. The longer-than-usual time between the site initiation visit and the first blood draw, and then again before the first dose is administered, suggest the need for refresher calls with sites to ensure that they know how to proceed.

The Future of Immunotherapy: A Mainstay in Cancer Treatment

Is immunotherapy destined to become the cure for cancers which patients and the healthcare community has been seeking?

It seems unlikely that cancer immunotherapies will eliminate the need for surgical excellence, availability of radiation technology and expertise, or chemotherapy for all cancers. The immune



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system isn't equally robust in all patients, tumors in the same patient are heterogeneous in their makeup and we have not yet cracked the code as to why immunotherapy works in some patients and some cancers, but not others. While companion diagnostics/biomarkers are important in targeting patients in some cancers, it is not clear that they will be important across the board.

On the other hand, we are really in the early days of learning how to marshal the body's immune system and certainly have not discovered its full potential. Right now, there is no type of cancer that is "off the table" as far as exploring immunotherapy.

It seems probable that immunotherapy will become one of the main pillars of cancer treatment—along with chemotherapy, radiation, and surgery—and that determining when and where immunotherapy fits into a treatment regimen will be a complex process. It may well be that patients will have to cycle through various types of therapies, only one of which will be immunotherapy.

It is also probable that cancer immunotherapies with different modes of action used in combination will become a new paradigm. There is great appeal in being able to simultaneously "step on the gas" to stimulate the immune system and "take the foot off of the brake," blocking the mechanisms that inhibit the immune system. Currently, there are many studies underway that combine marketed products with experimental products or that combine two marketed products. We expect that interest in such combinations will continue.

Implications for Sponsors: A Brave New World

The market will clearly demand that new cancer immunotherapies provide higher margins of efficacy. To demonstrate better outcomes and ensure commercial success for their immunotherapies, sponsors should:

- Evaluate the potential for a biomarker or companion diagnostic to refine the patient population. This adds upfront cost to the sponsor, increases complexity during launch planning and preparations, and requires additional coordination to ensure a simultaneous launch of the immunotherapy and companion diagnostic. Yet, in most cases, biomarkers and diagnostics will improve the success rate of trials, help sponsors from overinvesting in treatments that don't show promise, and limit patients' exposure to those treatments that will be effective for them.
- Discuss the best study endpoints with not only regulators, but also with payers. Increasingly, payers are seeking additional data on outcomes and impact to patients beyond safety and efficacy of the therapy. Given the US healthcare system, the diversity of payers may result



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in differing data requests and sponsors must make decisions based on their patient population and associated payer mix.

- Prepare to contend with different pricing models. The high cost of immunotherapy is going to be at odds with reimbursement systems' limited funds. As pricing pressures and payment models evolve, manufacturers may need to consider novel pricing and reimbursement schemes. As an example, CMS and commercial payers are currently piloting multiple models in oncology that may influence the future reimbursement of immunotherapies (e.g., Oncology Care Model, episodic payments, value-based pricing, etc.).
- Demonstrate value for the money. This will require strong health economics and outcomes research based on the cost of treatment alternatives (e.g., immunotherapy versus chemotherapy or a stem cell transplant). Ultimately, it will be critical to determine if the up-front cost results in long-term savings, through avoidance of the utilization of healthcare resources to address progressing cancer, as well as economic benefit of restored ability to work and participate in society.
- Develop strong competencies in business development and alliance management. As the practice of combining immunotherapies continues, sponsors should consider if their commercial organization will be able to execute on clinical development strategies that involve combination of their therapies with the therapies of other sponsors. To optimize value, strong deal-making capabilities are needed. Additionally, co-development and launch with another sponsor adds significant complexities which require alliance management and project management to ensure both sponsors are meeting required deliverables for launching on time.
- Partner with a CRO that has the experience to ensure patient safety through maintained clinical expertise that is applied to intense monitoring, accurate collection of efficacy data, and management of the demanding operational aspects of immunotherapy trials.

Conclusion

The scientific advances that are producing the newest immunotherapies are exciting for all stakeholders in the fight against cancer. It seems only a matter of time before researchers unlock the keys as to why these therapies are only effective in some tumor types and for some patients. Science will find the answers. In the meantime, sponsor companies must contend with myriad fresh challenges in the way that they design and conduct clinical trials and launch these unique therapies. The new immunotherapies are unlike any treatments to date and working with them will test sponsor's creativity and organizational capabilities.



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