Seizing the future in oncology:
Improving the clinical development of immunotherapies

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# Table of contents

**Introduction**

Overview of the clinical immunotherapy landscape  
- Understanding who may benefit most from which approaches  
- Tumor-derived immune suppression reversal  
- Novel immunomodulators  
- Combinations  
- Adoptive T cell therapies  
- Cancer vaccines  
- Pharmacodynamic and predictive biomarkers in immunotherapies  
- Checkpoint inhibitor biomarker strategies  
- Biomarkers in immunotherapy development

Clinical development: goals and cautions  
- Goals for successful drug development  
- Cautions  
- Speculative issues  
- Evaluation of tumor shrinkage related endpoints  
- Management of autoimmune adverse events  
- Patient selection assays  
- Operational considerations before development  
- Key considerations about development  
- Current understanding

**Conclusion**

**References**

**About the authors**
Introduction

Immunotherapy – using small molecules and biologics that provide therapeutic benefit by focusing the capabilities of the immune system on the tumor1 – promises to transform cancer care, having already shown striking patient responses. A recent Wall Street Journal article2 highlights “super-survivors” with exceptionally good responses to experimental immunotherapies. These individuals are described as transforming the world of oncology and charting new territory in both individual duration of survival and the potential for significant numbers of patients to benefit. As the article states, these results are reviving hopes that enlisting the power of the immune system may help to turn the tide against lethal and resistant forms of cancer.

Immunotherapy can be delivered in various therapeutic formats, with checkpoint inhibitors – which work by releasing the natural brakes on the immune system, enabling it to attack tumors – currently sparking the most interest. This represents an exciting and rapidly developing field, but understanding which patients will benefit most remains uncertain. It is not yet clear in all tumor types whether these drugs can be used to treat all patients or need to be targeted to selected populations, using precision medicine (with patient subgroups defined by molecular mechanisms), or personalized medicine (where an individual’s genetic profile is used to guide therapy). While these therapies do not produce universal or equal benefits, improvements in patient outcomes have been documented across many different cancer indications.

The human immune system is highly adaptive, and immunotherapies have the potential to greatly increase the patient’s leverage in fighting cancer. However, this potential requires the right setting and local environment cues. The immune system is an ideal anti-cancer agent, with large numbers of diverse types of immune cells (including $10^{18}$ T cells and $10^{22}$ antibodies); a high degree of specificity, with the ability to distinguish minute chemical alterations; and a long memory, with immunity lasting for up to several decades after effective antigen priming. This system has advantages for the patient and the prescribing physician in that the immune system attempts to target the vulnerabilities of the tumor in real time, rather than the prescriber having to use laboratory tests to hunt for vulnerabilities (which change over time) in the first place.

Among the immunomodulators, defined as medications used to help regulate or normalize the immune system, the immune checkpoint inhibitors are currently leading the way in clinical discovery and enthusiasm, given the exciting data yielded to date. Immune checkpoints refer to the inhibitory pathways that are hardwired into the immune system, and are involved in maintaining self-tolerance, as well as in modulating duration and amplitude of physiological immune responses in peripheral tissues to help minimize collateral tissue damage.4 Tumors take advantage of these systems or checkpoints to prevent the immune system from attacking and destroying the tumor.

Researchers are starting to elucidate the biology behind the anti-tumor immune response that is released by these checkpoint inhibitors, and have begun to clarify why certain patients and indications may be more amenable to this class of agents. Clearly, while the initial promise of immunotherapy rests largely in its aptitude for broad application in various patient populations, the algorithm for effective use in the oncology setting is excruciatingly nuanced, and reduces the reality of broader success at this time. The real hope now is to understand why immunotherapy can work, and when it cannot.

It should be noted that while checkpoint inhibitors dominate the current headlines in the clinical care communities, other promising approaches include novel molecular constructs such as chimeric antigen receptors (CARs), therapeutic combinations with old and new drugs, dosing regimen modifications, and vaccines. Older agents including IL-2 and the interferons remain in use, but may lose some visibility to these newer regimens. For researchers and oncologists alike, the most difficult algorithm to solve may not be how the cancer fights back, but rather how best to leverage the various components of the immune system armamentarium in this fight.
Overview of the clinical immunotherapy landscape

While there is currently no conclusive evidence that immunotherapy will be a “magic bullet” as some may hope, there is reason for some confidence that this approach will be a dynamic and responsive treatment platform to fight cancer going forward. This therapeutic approach is undergoing a renaissance, since some of the more promising initial immunotherapy studies (for example, Rosenberg) involving IL-2 in the treatment of metastatic melanoma. The key to clinical efficacy will be to activate the immune system in a way that imparts high specificity to a target on the tumor or within its microenvironment (Figure 1).

Figure 1: Various types of cancer immunotherapy

Immunotherapy is undergoing a renaissance, since some of the more promising initial studies involving IL-2 in the treatment of metastatic melanoma.

Immunotherapy currently involves a wide range of cellular, humoral and other targets, as noted in Figure 1. As mentioned, the key question is how the various treatment options can be leveraged in the clinic to achieve real and durable benefits for patients. For example, basic research and clinical results suggest that certain combinations may induce new targets for the anti-tumor immune response. Options include potentially beneficial combinations of novel therapies and routine approaches such as radio- and chemotherapies. However, throughout the research and clinical care communities, as well as in biopharma companies, there are competing interests and viewpoints as to the best way to proceed.

Understandably, the most competitive arguments – and outcomes – will be those that are evidence-based and have the opportunity to be broadly applied. Some have argued that the notion of broad applicability is not viable, either in the context of precision or personalized medicine. Yet, if the requirement for specificity is inherent to the global response in the host (i.e., the immune system), then its applicability can be leveraged even when faced with overwhelming tumor diversity.

Products currently in development are listed in Figure 2 and include a large continuum of mechanisms and modalities. The immune system is built to recognize and distinguish self-antigens from non-self or foreign ones. As a result, the immune system is able to recognize self from altered-self, which is the case for cancer. While many cancers have circumvented endogenous anti-tumor immune responses, immunotherapy in its various forms has the potential to augment responses in order to mitigate tumor progression. Immunotherapy can operate along both lines of innate and adaptive responses.

Source: Citi Research (Andrew S. Baum, Immunotherapy – The Beginning of the End for Cancer)
Notably, dendritic cells are antigen presenting cells that function at the intersection of innate and adaptive immunity. These are able to cross-present antigen to, and activate, T cells, making their development in the immunotherapy regimen especially important. As such, dendritic cells are a target of various immunotherapeutic approaches either through the use of adjuvant cytokines, which activate dendritic cells, or more directly through the use of dendritic cell vaccines. While the approaches currently in development described in Figure 2 are encouraging, a more complete understanding of the cellular and molecular components of the tumor-immune system interaction will be necessary for the development of rational and efficacious immunotherapies in the future.

Figure 2: Potential cancer immunotherapeutics under investigation (2015)

The current competitive landscape is highly complex, as shown in Figure 3, based on ongoing trials identified on clinicaltrials.gov. At present, competition is particularly strong in the areas of solid tumors, melanoma and non-small cell lung cancer. It remains to be seen whether classical tumor-type classifications will ultimately give way to molecular pathway-based classifications.

Figure 3: The competitive landscape, 2014

Summary: Pipeline radar chart
While the competitive landscape is crowded and promising, the most important aspect to consider is which of these agents in development will help to address the most fundamental limitations in oncology clinical care. Among the notable current challenges in the oncology clinic, the following considerations will largely determine the future success of these competitors:

• Understanding complex immune mechanisms of action and correctly applying therapy
• Determining and utilizing clinically relevant biomarkers to characterize immune response and identify the baseline patient anti-tumor status
• Defining optimal dose and schedule/sequence especially in combination settings
• Patient selection in the absence of clear selection criteria or targeted oncogenic drivers
• Trial design in the context of optimal dose, schedule/sequence and delayed response
• Leveraging increased efficacy versus increased toxicity
• Defining meaningful and standardized clinical endpoints for these classes of agents

Of greatest importance is the fact that the immune system does not operate separately from other biological systems in the patient, including the inflammatory system. Thus, rationally selected targets and targeted patient groups must be defined upfront. To avoid wasted time and money, an informed approach is needed for the immunotherapy platform from the outset of development. The rapidly emerging research results describing immunotherapy targets, drug combinations and responsive patient characteristics should lead to better informed studies and more successful trial outcomes.

**Understanding who may benefit most from which approaches**

Targeting the right therapy to the right patient is likely to become a central goal of immunotherapy. While classic cytotoxic chemotherapy does have tumor type specificity, refinements of this targeting have been elusive. More refined targeting has come from identification of oncogenic drivers that can be targeted by small molecules or antibodies, with examples including Herceptin, Rituxan, and BRAF and ALK inhibitors. Here, the target is identified by the researcher, but, as noted earlier, there are limitations in knowledge of tumor biology and biomarker technology that limit efficacious application for many potential targeted therapies. However, the recent success of some small molecules targeting oncogenic drivers has been dramatic.

It should be noted that immunotherapy follows a new paradigm in tumor targeting. Instead of specifically inhibiting the impact of an oncogenic driver, the immune response mounts a powerful, multi-facetted anti-tumor attack, which is characterized by specificity. This is clearly the case for immunomodulatory approaches and is also true for tumor vaccines. The immune system is believed to have potential to be more successful in identifying tumor vulnerabilities than prior approaches and to have the potential for wide application. However, this new paradigm presents new complexity and uncertainty in identifying and utilizing a precision medicine approach.

**Tumor-derived immune suppression reversal**

A single tumor can employ a cadre of mechanisms to overcome immune responses and orchestrate systemic disease, despite the expanse and specificity brought forth by both innate and adaptive immune mechanisms. Tumor-derived immune suppression involves various pathways, such as:

- **Immune evasion mechanisms** that may involve downregulatory cytokines (TGF-β, IL-4, IL-6, IL-10), immunosuppressive cells (regulatory T cells [T-regs], macrophages), or altered immune activation (loss of major histocompatibility complex [MHC] receptors, indoleamine 2,3- dioxygenase [IDO] production)
- **Immune dysregulation mechanisms** that include: inactivation of or failure to activate tumor-specific T cells; insufficient antigen processing and/or presentation; ineffective clonal priming or homing; disruption of effector cell maturation or expansion; or T-cell anergy, a proposed mechanism of immunologic self-tolerance in which T cells become functionally inactivated after previous stimulation
• Immune editing by developing tumors to shape, altering their appearance to the immune system
• “Non-inflamed” tumors, which are defined as cancer without immune infiltrates or other characteristics of an innate anti-tumor response.

Novel immunomodulators

Immunotherapeutic approaches to cancer involve extensive and sophisticated ligand-receptor interactions at the cellular level, a veritable “checkpoint chess match,” as illustrated in Figure 4. This figure shows co-stimulatory and co-inhibitory interactions between a T cell and a dendritic cell, a tumor cell, and a macrophage, respectively, in the tumor microenvironment. A reasonable question for the researcher to determine may be which of these interactions is most crucial to either host or tumor advantage. A seemingly less reasonable answer may be that all of these interactions are important, and furthermore, there is a dynamic gradient across which this importance fluctuates.

So, while the concept of checkpoint inhibition is encouraging and provocative in terms of therapeutic promise, the understanding of this process is far from complete. It is likely that an integrated and complex set of interactions are involved (Figure 5). However, this complexity also leads to many new drug targets and combinations. The early results from the various checkpoint inhibitors currently in trials and the few combinations of checkpoint inhibitors suggest very promising synergies for future therapeutic strategies.

Combinations

Elaboration of basic innate and adaptive tumor immunity research has improved the potential for developing efficacious treatments. Clinical evaluation of multiple regimens used in concert has gained increased acceptance and traction over the past decade. This has included the combinatorial use of cancer vaccines, monoclonal antibodies, recombinant cytokines, and adoptive cellular infusions, all with or without some level of conventional chemotherapy and/or radiotherapy in an adjuvant setting. Yet, while these combinations increase tumor immunity in many patients, the majority still succumb to progressive disease. As such, some investigations have highlighted efficient dendritic cell activation and inhibition of negative immune regulation as central pathways for intervention. Early-stage clinical testing raises the possibility that combinatorial approaches that augment tumor antigen presentation and antagonize negative immune regulation may accomplish significant tumor destruction without the induction of serious autoimmune disease.
Adoptive T cell therapies
Adoptive T cell therapy begins with ex vivo stimulation of lymphocytes in a non-tolerizing environment, which is then followed by re-infusion of activated T cells into patients for the purposes of measurable, clinically relevant anti-tumor outcomes. There are varying sources and types of T cells used for adoptive therapy, which include tumor infiltrating lymphocytes (TILs), T cells engineered to express a cancer-specific TCR, and most notably T cells engineered to express a chimeric antigen receptor (CAR), which combines the extracellular portion of an antibody with the T cell receptor signaling machinery. Of these approaches, CAR T cells, with uniform specificity, appear to be especially promising, demonstrating at times considerable clinical efficacy and durable responses, but are technically limited to some degree by transduction efficiency and potential toxicity. At this time, further research and successful applications are needed to warrant long-term continued development.

Cancer vaccines
Cancer vaccines have also shown promise based on advances in adjuvants, combinations, biomarkers and new targets. These vaccines, which contain tumor cells or antigens, stimulate the patient’s immune system to produce orchestrated cellular and/or humeral responses that destroy tumors and, in theory, prevent relapses of the cancer. However, unlike vaccines for other disease that prevent the occurrence of the disease in the first place, there is not a vaccine in development that can prevent the onset of cancer. Cancer vaccines are used primarily as a treatment after diagnosis, and this may account for their limited clinical utility to date. Nevertheless, a variety of vaccination platforms have been put into clinical development, including antigen vaccines, tumor cell vaccines, anti-idiotype antibody-based vaccines, dendritic cell vaccines, DNA vaccines and viral-vector based vaccines.

Pharmacodynamic and predictive biomarkers in immunotherapies
The immune system and tumor biology present many biomarker options. For the immune system, immune and inflammatory status and response to therapy can be measured. For the tumor, metrics include the tumor profile and response to therapy, including resistance mechanisms. Other metrics include: lymphocyte profiling (using flow cytometry), serum factors (using immunosassays), infiltrating cells (immunohistochemistry), gene expression (array-based GEP or RNA-sequencing), human leukocyte antigen (HLA) classification (multiplex polymerase chain reaction [PCR]), and T cell repertoire (NGS).

Checkpoint inhibitor biomarker strategies
These typically focus on target expression such as PD-L1 immunohistochemistry or biomarkers reflecting anti-tumor immune response such as tumor infiltrating lymphocytes, serum factors or immune cell profiles and spectrum of genetic abnormalities in the target tumor.

Recent literature suggests that the number of somatic mutations or mutation load may also predict response. This idea emerged when a correlation between mutation load and patient response was first noted.8 Reports in the New England Journal of Medicine and Nature9,10,11 have described how patients with many tumor mutations provide neo-antigens to the immune system that can be processed into antigen peptides, resulting in a T cell response. These responses may be followed by various NGS or mass spectrometry-based methods to characterize specific immunogenic peptides, T cell repertoires and transcriptome response signatures. Not only can an immune response to the neo-antigens be identified, but common antigenic peptides have been identified that are shared with antigens found in infectious disease. The size of the T cell repertoire or the clonal diversity also reflects the immune response and correlates with patient response to the therapy. Response signatures using the transcriptome or gene expression profile have also been identified, promising to improve understanding of responders and non-responders, and to predict response.
Examples of pharmacodynamic and predictive biomarkers for proof of concept and approval are:

- **Pharmacodynamic biomarker endpoints** for demonstration of target engagement and biological activity, including: target engagement and dose, receptor occupancy, biological activity, lymphocyte profile and serum factor panel, TILs, standardization and reproducibility; feasibility of pre- and post-sample collection; quantification of TILs; immunohistochemistry or multiplex immunofluorescence (IF); and digital pathology scoring.

- **Predictive biomarker endpoints** include PD-L1 expression, which may be of limited value, especially in combination studies; TILs, lymphocyte profile, gene expression, and potentially, inflammatory signature; T cell repertoire NGS profiling, which may have potential for implementation in global studies; somatic mutation profiling and combination studies; and translation of early correlations to robust CTAs and future companion diagnostic tests.

Checkpoint negativity can be an unreliable biomarker, placing into question how useful it will be going forward. There are several reasons for this. First, assays are technically imperfect, and results may differ depending on the antibody/assay (tumor vs. immune cells). Second, there may be variable expression, tumor heterogeneity, and inducible gene sampling error (false negative). Third, archived tissue may provide a less predictive test result than recently biopsied tissue. As a result, checkpoint negativity may be more useful in determining which tumors (rather than which patients) to treat. Expression may be less relevant for combination therapies as the expression of PD-L1 and possibly other immunotherapy targets are often impacted by targeted agents as well as radiation or chemotherapy.

In biomarker strategies for cancer vaccines, critical issues to be addressed include the patient’s immune status and ability to mount an immune response, and whether the immune response predicts patient outcomes. Two major goals in a cancer vaccine strategy are the ability to determine immune response, and to identify biomarkers that are predictive of immune response and patient outcome. Candidate biomarkers include target antigen expression, tumor burden, lymphocyte or serum factor inflammatory profile, TILs, antigen-specific immune response, predictive gene expression signatures and mutation load. However, to date, no successful single biomarker or approach has been confirmed.

The question remains as to whether there will be a need for predictive biomarkers for immunotherapies. Examples of complexities in this area are broad responses in many tumor types, the fact that combination therapies induce targets, responses are observed in biomarker negative patients, and complete responses are observed with checkpoint inhibitors while cancer vaccines lack candidate predictive markers. With pharmacodynamic analysis, biological activity is easily demonstrated, yet complexity is not captured. Safety biomarkers reflecting autoinflammatory response may also be important, and biomarkers may be useful in evaluating resistance where mechanisms are unknown. Early results examining resistance mechanisms to CTLA4 treatment in melanoma indicate that expression of parallel checkpoint proteins may be one mechanism that could be determined in a biomarker testing strategy.
Biomarkers in immunotherapy development

Biomarkers and related technologies offer potential strategies to support drug development and patient care including approaches that include immunotherapies.

A biomarker is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or biological responses to a therapeutic intervention

– National Institutes of Health (NIH)

Biomarker classification and utility: supporting clinical study objectives and endpoints

Biomarkers offer two types of information that can support clinical study objectives and endpoints: pharmacodynamic, revealing target engagement and the magnitude of biological response post therapeutic intervention; and predictive, identifying patients who are susceptible to a particular drug effect, which may involve benefit or harm.

Biomarkers can also provide markers of drug efficacy, toxicity or resistance. In addition, they may be useful in pharmacodynamics-based therapeutic drug monitoring, as surrogate endpoints (validated indicators of future clinical outcome), or as non-surrogate endpoints (unvalidated indicators of future clinical outcomes).

In patient care, biomarkers may be diagnostic, indicating the presence or absence of pathogenic processes, or prognostic, providing information on the likely future clinical course in the absence of a therapeutic intervention. Used in companion diagnostics, biomarkers help predict responses to therapy. They may also be used in multiplex or multi-analyte diagnostic panels, in next-generation sequencing (NGS) genomic panels, or in whole exon sequencing (WES) or whole genome sequencing (WGS).

The complexity of the immune system and tumor biology also results in a wealth of biomarkers and potential targeted indications and patient populations. New diagnostic tools, such as more powerful and better standardized flow cytometry and next-generation sequencing, can better profile immune response and utilize the immune repertoire for patient selection. Application of these tools in clinical development and patient care has yet to be fully exploited. Optimal clinical strategies, including drug dose and schedule to minimize risk of toxicity and the most appropriate clinical endpoints, must address the unique mechanisms of action of these drugs.

As the field moves beyond initial successes, it will be important to explore these biomarker opportunities as well as address the critical questions in clinical trial design to best advance immuno-oncology clinical research.
Clinical development: goals and cautions

Goals for successful drug development
The process for developing immunotherapy drugs follows the same steps as other biopharma products, including establishing safety, efficacy, dose and schedule, target indication and patient population, and providing support for clinical and reimbursement aspects of the target product profile. Progress to date in each of these areas for tumor vaccines, immunomodulators, cell-based therapies and combinations is illustrated in Figure 6.

Figure 6: Goals for successful drug development: Progress to date

<table>
<thead>
<tr>
<th>Goal</th>
<th>Tumor vaccine</th>
<th>Immuno-modulator</th>
<th>Cell based</th>
<th>Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose and schedule (fed/fasting)</td>
<td>Relationship to efficacy difficult</td>
<td>MTD and PK/blood concentrations</td>
<td>Empiric</td>
<td>Ill defined</td>
</tr>
<tr>
<td>Target indication/patient selection</td>
<td>Defined by vaccine antigens</td>
<td>Appears broad but empiric</td>
<td>Defined by MOA</td>
<td>Empiric</td>
</tr>
<tr>
<td>Registration efficacy data</td>
<td>Has been problematic</td>
<td>Exciting</td>
<td>Unknown</td>
<td>Exciting</td>
</tr>
<tr>
<td>Adequate toxicity profile</td>
<td>Usually benign</td>
<td>Ranges from tolerable to challenging</td>
<td>Ranges from tolerable to challenging</td>
<td>Likely challenging</td>
</tr>
<tr>
<td>Support for the clinical and reimbursement aspects of the TPP</td>
<td>Requires attention</td>
<td>Requires attention</td>
<td>Requires attention</td>
<td>Requires attention</td>
</tr>
<tr>
<td>Supporting: Pop-PK, Special populations, Companion diagnostic support</td>
<td>Requires attention</td>
<td>Requires attention</td>
<td>Requires attention</td>
<td>Requires attention</td>
</tr>
</tbody>
</table>

Cautions
Potential pitfalls in the development of new products in this area include failure to anticipate unique properties of the response to the immunomodulator. For example, the mechanism-of-action (MOA) model may be unrepresentative, leading to targeting of unresponsive subpopulations; patient selection assays may be weak; classic endpoints can be problematic; combinations of immunomodulators may lead to unexpected autoimmune syndromes, and may interfere with desired immunomodulatory effects in ways not seen in animal models. There may also be issues relating to accrual of patients in the target subpopulation (due to requirements for a novel screening process, or to the small size of the subpopulation). Monitoring of pharmacodynamic (PD) responses can also pose challenges related to sample handling, lack of availability of clear surrogates of desired bioactivity, or the fact that relevant samples may only be obtainable from repeated tumor biopsies.

Speculative issues
Other issues that may pose challenges are the potential for HLA-related ineffective immunodominance or novel adverse events (AEs), and the fact that repeated use of cytotoxic therapies may eliminate the relevant immunologic response. Unanticipated immune escape mechanisms may also occur, and promising immunomodulators may fail because of the need for multivariate patient selection assay systems.

Evaluation of tumor shrinkage related endpoints
Endpoints related to tumor size can be complicated by the potential for delayed tumor shrinkage following therapy, or for flare before shrinkage. Here, training of investigators and response evaluators is essential.

Management of autoimmune adverse events
To date, vaccines have not been limited by AEs, but cellular therapy side effects have not been well characterized. For immunomodulators, there may be serious AEs. For example, high dose IL-2 may be associated with significant capillary leak with potential intensive care requirement; CTLA-4 inhibitors have potential for multiple autoimmune AEs; PD-1 inhibitors are better tolerated but may be linked to pneumonitis,
immune mediated colitis, hepatitis, hypophysitis, nephritis (and renal failure), hypo/hyperthyroidism and other adverse reactions. Combinations of CTLA-4 and PD-1 look clinically promising but toxicity management is a challenge. There is a need to anticipate the need to develop official guidance for patient management in these areas.

**Patient selection assays**
Current assays for patient selection may not always have adequate specificity and sensitivity. Researchers face the question of whether to raise the threshold to assure more specificity, a move that might exclude some potential responders. Another issue is setting a price point for a new product in an environment where the target population may shrink due changes in the approach to patient selection. Current assays may require patient tumor biopsies, driving a need to focus on patient selection assays using blood or urine.

**Operational considerations before development**
Key operational considerations before starting development of a new immunotherapeutic include the need to:

- Fully understand the clinical question to be answered
- Appreciate the value proposition of the drug that is being developed
- Employ dedicated teams with operational expertise and vision
- Focus on achieving simplified interpretations in complex systems
- Apply rigor in graduating the drug to the next phase of development
- Ask the tough questions to address qualifications that must be met.

**Key considerations about development**
Regulatory agencies, including the U.S. Food and Drug Administration and European Medicines Agency, are showing significant interest in the potential of immunotherapy. When antitumor activity is high, regulators typically value objective response rate (ORR) over progression-free survival (PFS) in single-arm trials. Controlled Phase 3 studies will remain extremely important here, because they take into account prognostic factors. Post-marketing safety monitoring is particularly critical, due to the low patient numbers treated in an accelerated drug development model.

**Current understanding**
Currently available information indicates that targeted small molecule therapy can yield high response rates, but is often prone to resistance, while immunotherapy can produce durable antitumor responses in some patients with cancer. Treatment of patients with immune checkpoint inhibitors can differ from use of conventional therapies in the need to identify unconventional responses, and to understand and manage immune-related adverse events. Accumulating evidence indicates that checkpoint inhibitors are active in multiple tumor types, yet clinical management and safety monitoring remain key for therapeutic success. Drug sequencing may be critical to the design and implementation of complex drug combinations, and ongoing studies will help define the optimal use of checkpoint inhibitors in different tumor types as single agents or as part of combination therapy.
Conclusion

The landscape for immunotherapies in oncology is expected to expand greatly in the near future as the initial checkpoint inhibitors come to market, while development continues on a broad set of immunomodulators and cancer vaccines. Follow-up checkpoint inhibitors targeting LAG3, OX40, IDO1 and other novel proteins and novel combinations may provide new options for cancer patients.

This is an area with many potentially competing products, and a need for these to be differentiated from one another. Results to date provide a new understanding of the mechanisms of action of immunotherapies and provide predictive approaches for selecting indications and patients. It remains to be seen how this information may be used to differentiate immunotherapy drugs and aid clinicians in their decision-making.

For clinical trials, the overarching goal remains to achieve quick and efficient immunotherapy studies that yield high-quality data, and accelerate delivery of much-needed, new cancer therapies to patients. The trials must also provide a greater understanding of which patients respond and why. These approaches provide more evidence that cancer is a genetic disease that is translated through proteins, peptides and cellular mechanisms into sickness or cures. Immunotherapies are proving to be a very powerful approach to attack these disease-related alterations, leading to significant patient benefit.
References


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Brad Smith currently is a Vice President of Translational Medicine within the Integrated Clinical Services Group at Quintiles. In this position, Brad supports laboratory, clinical and diagnostic strategies for drug development as well as the development of innovative tools for targeted drugs and companion diagnostics. Previously, Brad led Corporate Development at Cell Signaling Technology, an innovative biotechnology company in the life sciences field. In this position, he focused on new diagnostic and clinical partnerships and markets. His previous positions at Cell Signaling Technology include management of research and clinical technology development departments and laboratories. Previous to Cell Signaling Technology, Brad directed product development and production at Santa Cruz Biotechnology, helping to build that company into one of the largest supplier of research tools for basic research. Brad’s scientific background includes research positions at Stanford University and University of California, San Francisco focused on cellular signaling mechanisms of disease. He holds a Doctoral degree from Stanford University and Master’s and Bachelor’s degrees from University of California, Santa Cruz.

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