



Addressing Recent Failures in Immuno-Oncology Trials to Guide Novel Immunotherapeutic Treatment Strategies

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Abstract

The incorporation of checkpoint inhibitors into the treatment armamentarium of oncologic therapeutics has revolutionized the course of disease in many cancers. This has spurred the evaluation of other novel immunotherapy agents in clinical trials with varying levels of success. This review explores possible explanations for differences in efficacy in clinical outcomes among currently US FDA-approved immunotherapy agents, lessons learned from clinical trial failures of investigational immunotherapies, and methods to improve success in the future. An inherent challenge of early phase immunotherapy trials is identifying the maximum tolerated dose and improving understanding of the pharmacokinetics/pharmacodynamics of immunotherapies as they exert their effects indirectly via T cells rather than directly via dose-dependent cytotoxic activity. The wide heterogeneity of the immune system among patients and within an individual patient over time largely affects the results of optimal dose- and toxicity-finding studies as well as the effectiveness of immunotherapy. Therefore, optimization of phase I/II study design is crucial for clinical trial success. These differences may also help elucidate the lack of immunotherapy benefit in certain disease subtypes despite the presence of specific biomarkers. Broader investigation of the tumor microenvironment and its dynamic nature can help in the identification of alternative pathways for targeted therapies, mechanisms of immunotherapy resistance, and more correlative biomarkers. Finally, manipulation of the tumor microenvironment via a single agonist or antagonist may be inadequate, so combination therapies and sequencing of agents must be further assessed while balancing cumulative toxicity risk.

Key Points

Checkpoint inhibitors have transformed the landscape of oncologic care and prompted investigation of novel immunotherapeutic agents, many of which have been unsuccessful in clinical trial investigation.

Improved understanding of the dynamic and complex tumor microenvironment is crucial to identify mechanisms of resistance, novel targets and correlative biomarkers, and optimal treatment combinations and sequencing.

1 Introduction

The landscape of oncologic therapeutics has been revolutionized by checkpoint inhibitors (CPIs). Historically, cytotoxic chemotherapies have been the backbone of treatment for most solid malignancies. Efforts to improve treatment modalities have focused on improving tolerability, increasing disease response, and maintaining prolonged response to therapy. Identification of specific tumor driver mutations and select cancer biomarkers have led to the emergence of new targeted therapies and heralded an era of personalized medicine to achieve these aims. Additionally, over the past decade, advancements in the field of immunotherapy have spurred interest in further understanding and harnessing the power of the innate and adaptive immune systems.

Of particular pharmaceutical and clinical interest is the tumor immune microenvironment (TME), which consists of interactions between T cells, antigen-presenting cells, tumor cells, and cytokines in a milieu of supporting matrixes. The normal immune system pathways maintain immune homeostasis and prevent autoimmunity while responding

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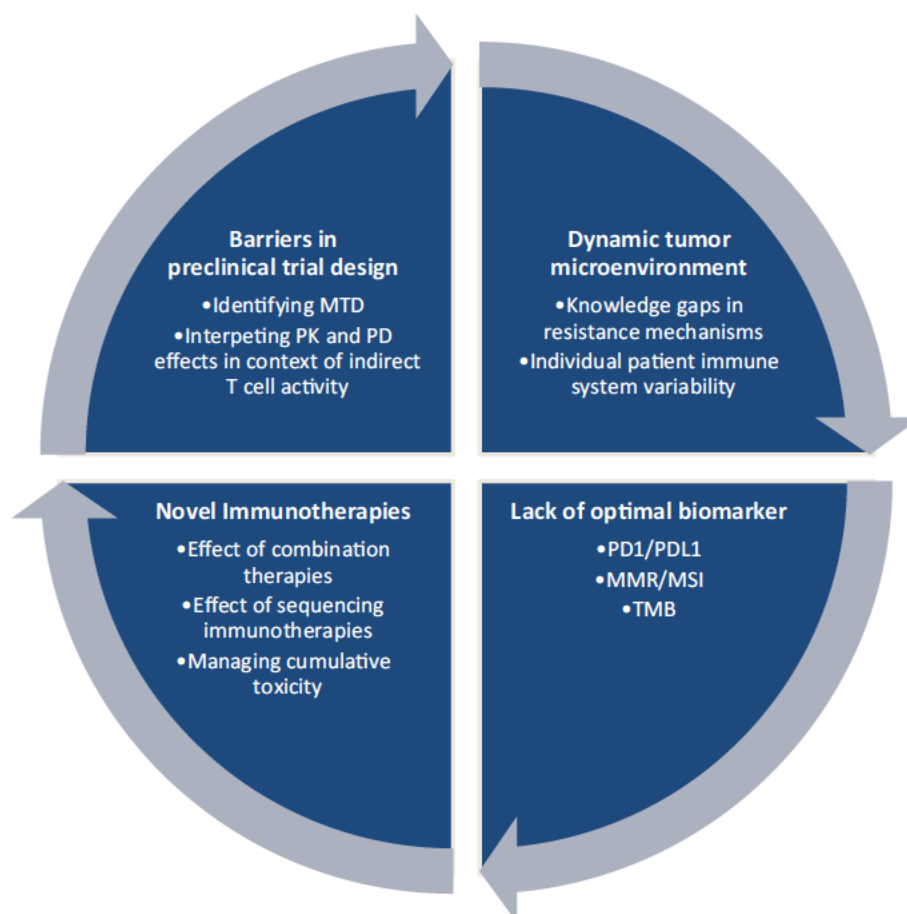
to infections and malignancies. Accordingly, the immune system may have the capacity to distinguish cancer cells from normal tissue. An anticancer response can be elicited by therapeutically manipulating T-cell activity via various costimulatory receptor agonists and inhibitor signal antagonists [1]. Effectively, immunotherapy promotes antitumor effects of T cells by mobilizing a patient's own immune system to target malignant cells. Modulation of memory T-cell responses can enable long-term anamnestic protection against tumor cells [2], which can lead to prolonged responses.

In 2011, ipilimumab became the first CPI to affect survival and was approved by the US FDA for unresectable metastatic melanoma. By 2014, pembrolizumab and nivolumab were approved for advanced melanoma [3–5]. CPIs, which at the time of writing include the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab, programmed death-1 (PD1) inhibitors (nivolumab, pembrolizumab, and cemiplimab), and programmed death ligand-1 (PD-L1) inhibitors (durvalumab, atezolizumab, and avelumab), have been a major breakthrough in oncology, especially in various cancer sites in which prognosis was particularly grim. For example, pembrolizumab more than doubled overall survival (OS) in advanced non-small-cell lung cancer

(NSCLC) with high PD-L1 scores, and nivolumab more than tripled median OS in advanced melanoma regardless of PD-L1 score when compared with traditional chemotherapy [6, 7]. This class of therapy continues to show efficacy in an actively expanding list of malignancies. The extraordinary responses to these first-generation immunotherapies have been the impetus for identifying novel therapies to target other sites within the immune microenvironment, such as indoleamine 2,3-dioxygenase (IDO), inducible co-stimulator (ICOS), OX40, TIM3, GITR, STING, LAG-3, CSF-1, and oncolytic viruses. Unfortunately, successes have also been countered by a multitude of unsuccessful trials.

Unsuccessful trials carry both clinical and financial toxicity. The number of clinical trials conducted in the USA nearly doubled between 2006 and 2014, and—from 2015 to 2017—combination therapy trials including CPIs more than tripled [8, 9]. Secondary to the highly competitive environment and potential financial gains, pharmaceutical companies are eager to recognize early signals of efficacy in phase I trials with hopes of translating them into an FDA approval with a phase III trial [10]. This practice, in particular, has been largely ineffective. Here, we explore lessons learned from prior successes and failures in immunotherapy drug development (Fig. 1).

Fig. 1 Challenges to immunotherapeutic drug and clinical trial development. *MMR* mismatch repair, *MSI* microsatellite instability, *MTD* maximum tolerated dose, *PD* pharmacodynamics, *PD1/PDL1* programmed death 1/programmed death ligand 1, *PK* pharmacokinetics, *TMB* tumor mutation burden



2 Lessons Learned from Prior Immunotherapy Trials

2.1 Importance of Tumor Type

CPIs have shown durable responses, improved OS, and unique, generally favorable toxicity profiles when compared with traditional cytotoxic chemotherapy. These responses can vary drastically across tumor types. In the initial phase I/II study of nivolumab, the expansion cohort groups included patients with NSCLC, melanoma, renal cell carcinoma (RCC), castration-resistant prostate cancer (CRPC), and colorectal cancer (CRC) in second- or later-line settings. Overall response rates were 17% for patients with NSCLC, 31% with melanoma, and 29% with RCC, but no responses were seen in the CRC or CRPC groups [11]. The remarkable survival data noted in this study led to phase III trials in NSCLC, melanoma, and RCC that confirmed the efficacy of CPIs in these disease subtypes [12–14]. On the other hand, there has been no meaningful clinical activity for single-agent checkpoint inhibition in the vast majority of patients with metastatic CRC or CRPC, except for the approximately 3–4% of patients who harbor deficiency in mismatch repair genes or who have high microsatellite instability (MSI-H) [15, 16], despite early evidence for broader efficacy in pre-clinical studies [17, 18]. The drastic differences in response between cancer disease sites illustrate the effect of patient selection and tumor type on outcomes in early clinical trials. Unfortunately, this has also created an impediment to exploring newer approaches in patients with “immunologically cold” tumors.

2.2 Importance of Biomarker Selection

Outside of individual cancer disease sites, various biomarkers have been studied to better identify which patients may respond. Identification of a single surrogate marker for immunotherapy response across all malignancies and different classes of immunotherapy has been a challenge, in part because of the dynamic nature of the TME and the complexity of inhibitory and stimulatory signaling that occurs in the immune system [19]. While response rate across most disease sites has had some correlation with degree of PD-L1 tumor expression, predictive therapeutic relevance is lacking in patients who test negative and in current standardization for PD-L1 testing or cutoff values. Two separate assays may provide discordant results from the same sample, and results in a single patient may vary according to biopsy of primary or metastatic site [19, 20]. Discordance also occurs within the same biopsy site, and expression is influenced by prior therapy.

In similarly designed separate phase III evaluations of pembrolizumab and nivolumab in first-line metastatic or recurrent NSCLC compared with standard chemotherapy, the outcomes were unique according to differences in PD-L1 tumor marker cutoffs. Of note, two separate PD-L1 assays were used in these studies. In the nivolumab trial (Check-Mate-026) in which a PD-L1 cutoff of > 5% was used, there was no statistically significant improvement in progression-free survival (PFS) or OS when compared with standard chemotherapy [21]. However, in the pembrolizumab trial, which used a PD-L1 cutoff of > 50%, the median PFS and OS were improved [22].

Malignancies with high neoantigen burden have demonstrated response to immunotherapy potentially via induction of the adaptive immune system in response to neoantigen production. These malignancies include lung cancer and melanoma caused by damage from tobacco and ultraviolet light exposure, respectively, and also in cancers caused by DNA repair pathway mutations, such as colon cancer with mismatch repair deficiency (MMR-D) or MSI-H [19]. Tumor mutation burden (TMB) is one marker that has been studied as a correlative to neoantigen burden and immunotherapy response. While a TMB of ten or more mutations per megabase has improved response and PFS in patients with NSCLC with ipilimumab and nivolumab, OS benefit was not seen [23, 24]. Additionally, no difference in outcomes was seen with pembrolizumab in NSCLC with a TMB cutoff of 175 mutations per exome [25, 26]. Therefore, the role of TMB as a biomarker is undetermined at this time. On the other hand, MSI or MMR-D, which have been historically studied in colon cancer [27], have also recently shown correlation with immunotherapy response in other cancer types, though only 2% of screened patients harbored MMR-D [28]. Accordingly, a “one size fits all” approach cannot necessarily be applied to all tumor marker testing in future immunotherapy trials.

2.3 Importance of Drug and Combination Selection

The specific clinical efficacy differences within classes of CPIs have not been compared in head-to-head studies. On a molecular level, nivolumab and pembrolizumab are both immunoglobulin G4 (IgG4) anti-PD1 monoclonal antibodies that block the interaction of PD-1 to the ligands PD-L1 and PD-L2 and very weakly induce complement activation. Nivolumab is fully human, whereas pembrolizumab is humanized. These therapies share similar pharmacokinetic and pharmacodynamic properties [29]. However, a number of clinical studies of pembrolizumab and nivolumab have been completed in what appear to be similar populations with similar study designs. It is intriguing to note the relative success of pembrolizumab compared with nivolumab in these indications [21, 22]. While such observations cannot

be considered proof of a difference, they are at least hypothesis generating.

The relevance of antidrug antibodies (ADAs) is uncertain. Monoclonal antibodies, in particular, can illicit an immune response against the drug itself. Antibodies can be neutralizing, potentially negating the effect of the drug. Studies have investigated the immunogenicity of CPIs. A potentially significant ADA has been detected against ipilimumab, with a small study associating its development with shortened survival [30]. The development of ADAs to nivolumab and pembrolizumab has been reported at 12.7% and 3.6%, respectively [31, 32], although the clinical significance of this is unknown. In the absence of a head-to-head comparison, pharmaceutical companies should carefully consider variables that may have clinical impact, such as ADA development or the specificity and sensitivity of a biomarker to select a given population.

Since the initial efficacy data for single-agent CPI therapy, further progress has been made in analyzing the efficacy and tolerability of combination therapies. In metastatic melanoma, the addition of nivolumab to ipilimumab more than doubled median OS [14]. Additionally, in disease sites such as metastatic prostate cancer where single-agent checkpoint inhibition has been unsuccessful, dual checkpoint inhibition has shown efficacy in early clinical trials [33]. The combination of immunotherapy and cytotoxic chemotherapy has also been studied with the hypothesis that chemotherapy-mediated cell death and presentation of released antigens may enhance immunogenic responses by T cells and thereby improve the rate and duration of response [34]. The efficacy of this strategy is supported by results from the KEYNOTE-189 trial, which evaluated the addition of first-line pembrolizumab to standard chemotherapy (carboplatin and pemetrexed) and revealed improved OS with combination therapy across all PD-L1 scores, including those with scores < 1%, even though a pemetrexed-based regimen includes supraphysiologic doses of glucocorticoid premedication, which is classically associated with immunosuppression [35]. In addition, the sequencing of immunotherapy may also play an important role. For example, a novel investigational CSF-1R antibody had greater efficacy when administered after or concurrently with a CTLA-4 inhibitor, whereas anti-OX40 antibody was more efficacious when administered before but not after a PD-1 inhibitor [36, 37]. Additionally, the sequencing of administration with chemotherapy and/or targeted therapy must be considered. The SECOMBIT (Sequential Combo Immuno and Target Therapy) trial is one such study that aims to help answer some of these pressing questions.

The benefits of combination therapy must be carefully weighed against added toxicity. In patients with metastatic melanoma treated with combination nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses and then

single-agent nivolumab onwards had a significantly higher rate of grade 3 or 4 adverse events (59%) than patients receiving either nivolumab or ipilimumab as a single agent (22% and 28%, respectively) [14]. Despite improved survival in this population with combination therapy, physicians treating metastatic melanoma do not routinely prescribe the combination regimen to all because of the toxicity risk [14]. To capitalize on the improved survival but minimize the toxicity, the inverse dosing regimen has been studied. Patients who received nivolumab 3 mg/kg with ipilimumab 1 mg/kg were compared with patients who received nivolumab 1 mg/kg and ipilimumab 3 mg/kg, with both regimens followed by the same single-agent nivolumab dose. The patients in the former group had a decrease in grade 3–5 adverse events without a decrease in efficacy [38].

2.4 Importance of Early Phase Studies

Phase I trials have long been seen as an opportunity to understand the maximum tolerated dose (MTD) of a drug and have been used with efficiency to exploit this need. Phase I trials have historically had only about a 10% rate of response [39]. In the era of immunotherapy, respective responses in phase I studies have been much higher and have led to accelerated FDA approval based on phase I/II data in many cancer disease sites [4, 27, 40–45]. For example, the phase I clinical study of pembrolizumab began in 2011; within 3 and 5 years, respectively, this therapy gained FDA approval for unresectable or metastatic melanoma and PD-L1-expressing metastatic NSCLC [46]. The rapid procession from phase I to phase III studies has been enabled with the use of expansion cohorts that circumvent the traditional drug development schema and provide for shortened drug development timelines [47].

In the hopes of providing patients with important new therapies, the FDA adopted accelerated approval pathways, contingent upon confirmatory studies for full approval. While this is a laudable and important effort, phase I/II trial successes have not always been “confirmed” in the subsequent phase III setting, and these instances prompt a close evaluation of modern clinical trial design in the era of immunotherapy. For example, in patients with advanced urothelial carcinoma, atezolizumab showed no improvement in OS over chemotherapy in patients with platinum refractory disease with PD-L1 overexpression, despite phase II evidence revealing an improved overall response rate when compared with historical controls [48, 49]. Similarly in small-cell lung cancer (SCLC), nivolumab gained accelerated FDA approval for advanced disease that had progressed on platinum-based therapy based on phase I/II studies and a randomized expansion cohort that revealed an overall response rate of 10% with nivolumab monotherapy and a 23% response rate in the nivolumab/ipilimumab combination group [44]. However, a

phase III study of single-agent nivolumab failed to improve survival over chemotherapy in the second-line setting [50]. Additionally, combination nivolumab/ipilimumab failed to show efficacy as maintenance therapy after first-line chemotherapy in SCLC [51].

While more rapid FDA approval can allow potentially life-prolonging therapies onto the market sooner, clinical trial failures should prompt a closer review regarding the safety of these approvals. In an effort to speed drug development, lessen the number of patients treated with an inadequate dose, decrease the total number of patients needed in a trial, and to enhance confidence regarding the MTD, a number of designs have been implemented over the “standard” 3 + 3 design. However, phase I trials are often critical in understanding dosing frequency and scheduling and better characterizing pharmacokinetic and pharmacodynamic effects. Notably, there are inherent challenges to early phase study design in the era of immunotherapy that warrant further discussion. Specifically, MTD becomes difficult to define as the effect of immunotherapy is exerted indirectly via T-cell effects rather than dose-dependent cytotoxic activity. Additionally, immune side effects from immunotherapy do not necessarily occur in the first cycle, which affects identification of dose-limiting toxicities [9]. Unique immune system variability among patients poses an additional challenge in identifying the optimal dosage in terms of not only efficacy but also timing, severity, and type of adverse immune events.

Use of RECIST (Response Evaluation Criteria in Solid Tumors) criteria may also underestimate response to immunotherapy in an uncommon but notable phenomenon called “pseudo-progression.” This may be considered when a response to immunotherapy is seen after an apparent initial increase in tumor burden. While < 10% of patients demonstrate this [52], it has been associated with improved survival. On the other hand, “hyper-progression” describes a true unexpected rapid progression on immunotherapy, which is a poor prognostic sign but likely occurs in part via a similar mechanism of T-cell infiltration into the tumor [53]. Using RECIST criteria, pseudo-progression would also be characteristic of progressive disease despite actually being favorable [52]. Therefore, an immune-related response criterion has been developed (iRECIST) to guide response evaluation, which does not automatically define such progression [54].

Phase I trials have historically focused on a heterogeneous “all-comers” population of solid tumor and lymphoma in which there was also the potential to realize a particularly promising disease site to explore further. However, it is becoming increasingly common to restrict phase I to specific disease sites, even in the dose-escalation phase, because of biases from preclinical studies, other clinical studies, competitive information, or sponsor disease preference given

potential market share. When the disease site is restricted, the number of patients treated is small, leading to unrecognized biases and challenges in determining efficacy. Broadly speaking, this practice does not appear to inform positive pivotal phase III outcomes.

2.5 Importance of Identifying Resistance Mechanisms and Immunotherapeutic Targets Outside of Cytotoxic T-Cell Activity

An important development in our understanding of the TME is that mechanisms outside of cytotoxic T cells can be affected by CPIs for antitumor immune activation and also serve as a mechanism of resistance to these agents. For example, ipilimumab was designed to block signals of suppression to cytotoxic T cells to facilitate antitumor activity, but a second key mechanism is with CTLA-4-targeted inhibition of T-regulatory cells (Tregs) [55]. Tregs normally maintain immune homeostasis and self-tolerance and counterbalance cytotoxic T-cell function [56]. However, tumor immune evasion may be overcome with Treg inhibition. Tregs inside the TME may also use alternative pathways to maintain immunosuppression, and these are under active preclinical and clinical investigation [55].

Interestingly, drugs within the same class of immunotherapy can have differences in secondary mechanisms of adaptive immune activation, which can be critical to clinical outcomes. The two most widely studied CTLA-4 inhibitors, ipilimumab and tremelimumab, were both evaluated in separate trials in metastatic melanoma. Ipilimumab statistically improved OS, but tremelimumab failed to show improvement over standard chemotherapy [3, 57]. The divergence in efficacy has been attributed in part to the fact that the ipilimumab IgG1 isotype may enable antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity, whereas the tremelimumab IgG2 isotype does not [58].

Efforts to boost the T-cell-mediated immune response of CPIs have also been made. Talimogene laherparepvec (T-VEC) is an HSV-1-derived oncolytic immunotherapy designed to work similarly to traditional vaccines but with the goal of antitumor immunity via increased antigen presentation and T-cell priming [59]. In advanced melanoma, T-VEC showed promising single-agent activity, which improved when combined with CPI therapy [60, 61].

Mechanisms of resistance also exist in the innate immune system, including the vasculature and myeloid-derived immune suppressor cells. Tumor vasculature is marked by suboptimal vessel networks, which can facilitate immune evasion and also decrease the delivery of therapy and cytotoxic T cells to the tumor [62]. Vascular endothelial growth factor (VEGF) signaling promotes vessel formation in the normal physiologic state but can be overexpressed in solid

tumors, causing dysfunctional vasculature and may promote Treg, myeloid-derived suppressor cells, and tumor-associated macrophage immunosuppressive activity [62–64]. Targeting of VEGF with bevacizumab has been efficacious in a variety of chemotherapy combinations and more recently in combination with checkpoint inhibition [65–69].

3 Current and Future Directions

The immune system is complex and has numerous inhibitory and stimulatory factors aimed at mounting an appropriate response (largely to foreign antigens) while minimizing damage to the host. In short, this complex interplay is not readily circumvented through the manipulation of a single agonist or antagonist and will require a much more nuanced approach through further technologic innovation. Other mechanisms of adaptive immune resistance are actively being studied to find novel ways of overcoming T-cell exhaustion and gaining neoantigen exposure to T cells [70]. Additionally, by addressing immunosuppressive pathways in the innate immune system, such as myeloid cells and tumor vasculature, we may expand disease sites in which immunotherapy may be efficacious [55].

The success of these endeavors relies on optimizing preclinical and early clinical studies to identify key on-target and off-target effects, dosing, and pharmacologic properties. Companion biomarker identification can significantly contribute to the selection of tumor types in which these agents are successful. Combination immunotherapeutic regimens require careful safety analysis as clinically significant improvements in efficacy may not always outweigh the harm associated with cumulative toxicity.

The necessity of these measures is illustrated by the recent data on the IDO inhibitor, epacadostat. The IDO pathway takes part in CTLA-4- and cluster of differentiation (CD)-40-mediated immune regulation and has been hypothesized as a potential mechanism of resistance to CPIs. Expression of IDO as a tumor marker on various tumor types has been reported, making this a particularly attractive target for therapy [71, 72]. Epacadostat was tested with three CPIs—ipilimumab, pembrolizumab, and nivolumab—with promising results [73–75]. In phase I analysis with ipilimumab, preliminary efficacy results suggested a robust response rate of 26%, which compares quite favorably with historic controls of ipilimumab alone, which are closer to 10–15%. It is notable that the previously well-tolerated single-agent epacadostat dose of 300 mg twice daily led to unexpected hepatic transaminase elevation when combined with ipilimumab, leading to necessary but significant dose reductions of epacadostat [73]. In a companion phase I trial of epacadostat with pembrolizumab, Mitchell et al. [74] reported an apparent 55% response rate in melanoma, and

responses were also realized in NSCLC, RCC, urothelial, head and neck, and endometrial cancer. However, and just as surprising, an MTD of the IDO inhibitor was not found, and 300 mg twice daily with the PD-1 inhibitor did not lead to a significant increase in adverse events [74].

Disappointingly, the subsequent phase III trial in patients with metastatic melanoma was negative and led to the closure of other phase III attempts in other disease sites [76]. In this situation, the phase I results regarding efficacy were clearly influenced by factors not readily recognized in the patient population. In hindsight, perhaps the better-than-expected tolerability profile, in stark contrast to the ipilimumab combination, could have offered some insight. It is usually more plausible to predict that an adverse event profile may run in parallel to enhanced efficacy. While not definitive, the lack of new or worsening adverse events may provide sponsors and investigators a rationale to more carefully consider efficacy and safety in the phase II setting before embarking on a phase III strategy.

Nonetheless, other promising targets in the TME continue to be actively investigated with the aim of improving response to novel immunotherapy and overcoming resistance mechanisms to CPI therapy, particularly by targeting co-expression of inhibitory receptors. One such target is ICOS, which was upregulated on peripheral T cells after ipilimumab therapy, which makes this a rational target for combination immunotherapy. JTX-2011 is an IgG1 antibody that targets the ICOS pathway to activate T-effector cells but also to reduce intratumoral Tregs, according to preclinical data. In the ICONIC phase I/II trials, JTX-2011 was studied alone and in combination with nivolumab in patients with heavily pretreated disease. In the phase I arm, all solid tumors were studied regardless of ICOS expression; the phase II arm included only patients with high ICOS expression. The disease control rate was approximately 20% with monotherapy and 30% when combined with nivolumab, and the emergence of an ICOS high CD4 T-cell population while on therapy was associated with increased antitumor activity. However, this trial had a high rate of early discontinuation (60%) for unclear reasons despite eliciting fewer grade 3–4 toxicities than other immunotherapy combinations [77]. These discontinuation rates must be more closely explored as potential barriers to success in later phase studies.

4 Conclusions

The human immune response is highly regulated and involves complex interactions of agonists and antagonists. While we have witnessed great success and broad applicability of immunotherapeutics, there have likewise been a number of disappointing results secondary to a failure to translate encouraging preclinical and early clinical data into

phase III trials. Unfortunately, numerous factors significantly impede our full understanding of the immune system and its interaction with tumors. These include but are by no means limited to theoretical ADA effects, suboptimal biologic doses, resistance mechanisms, and the dynamic nature of the TME. The success of late phase clinical trials relies on optimizing preclinical and early clinical studies to identify key on-target and off-target effects, dosing, and pharmacologic properties. Associated biomarker identification can significantly contribute to the selection of tumor types in which these agents are successful. Combination immunotherapeutic regimens require careful safety analysis as clinically significant improvements in efficacy may not always outweigh the harm associated with cumulative toxicity. Ultimately, the future of the immunotherapeutic armamentarium will depend on a more measured approach in early clinical trials while we continue to unravel the mysteries of the TME in preclinical studies.

Compliance with Ethical Standards

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Conflict of interest Shazia K. Nakhoda has no conflicts of interest that might be relevant to the contents of this manuscript. Anthony J. Olszanski sits on advisory boards, with commensurate honorarium, for Array, BMS, Merck, Novartis, and Pfizer. Additionally, the institution receives funding from trials for which he is participating, including from Adaptimmune, Astellas, BMS, Boston Biomedical, Checkmate Pharmaceutical, EMD Serono, GlycoNex, Immoncore, Incyte, Intensity Therapeutics, Kadmon, Kartos, Kura, Nektar, NGM Biopharmaceutical, Oncoceutics, OncoSec, Seattle Genetics, Sound Biologics, Spring Bank, Takeda, and Targovax.

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