Immuno-oncology Clinical Trial Design: Limitations, Challenges, and Opportunities

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Abstract

Recent advances in immuno-oncology and regulatory approvals have been rapid and paradigm shifting in many difficult-to-treat malignancies. Despite immune checkpoint inhibitor therapy becoming the standard of care across multiple tumor types, there are many unanswered questions that need to be addressed before this therapeutic modality can be fully harnessed. Areas of limitations include treatment of patients not sufficiently represented in clinical trials, uncertainty of the optimal treatment dosing and duration, and lack of understanding regarding long-term immune related toxicities and atypical tumor responses. Patients such as those with autoimmune disease, chronic viral infections, limited performance status, and brain metastases were often excluded from initial trials due to concerns of safety. However, limited data suggest that some of these patients can benefit from therapy with manageable toxicities; thus, future studies should incorporate these patients to clearly define safety and efficacy. There are still controversies regarding the optimal dosing strategy that can vary from weight-based to flat dosing, with undefined treatment duration. Further elucidation of the optimal dosing approach and evaluation of predictive biomarkers should be incorporated in the design of future trials. Finally, there are long-term immune-mediated toxicities, atypical tumor responses such as pseudoprogression and endpoints unique to immuno-oncology that are not adequately captured by traditional trial designs; thus, novel study designs are needed. In this article, we discuss in detail the above challenges and propose needed areas of research for exploration and incorporation in the next generation of immuno-oncology clinical trials. *Clin Cancer Res; 23(17); 4992–5002. ©2017 AACR.*

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Introduction

Immune checkpoint inhibitors (ICI) have taken the oncology world by storm and the rapidity of clinical trial enrollment and Food and Drug Administration (FDA)-accelerated approvals have left many unanswered questions to meet the next wave of immuno-oncology trials. In the fall of 2016, there were already more than 800 clinical trials with over 155,000 anticipated enrolling patients on various combinations of immuno-oncology agents (1). This demonstrates the abundance and complexity of clinical trial data that will become available in the future; however, they still may not answer all of the important, yet unclear clinically relevant questions. As increasing resources are dedicated to immuno-oncology research, it will be crucial to identify the limitations that exist in the current literature and prioritize addressing these limitations in designing future trials.

The objective of this article is to discuss the current controversies and limitations in the completed and ongoing clinical trials of ICI therapy (Fig. 1). The discussion will focus on patient populations that have been understudied in the completed studies, as well as limitations in our understanding of the optimal therapeutic administration of various ICI agents. The goal will be to identify factors that could be considered for successful future development and clinical implementation of this novel therapeutic modality.

Patients and disease characteristics in clinical trials

The restrictive eligibility criteria common in early trials of ICI therapy, have resulted in insufficient data to guide treatment decisions in many important patient populations insufficiently represented in clinical trials such as patients with asymptomatic autoimmune disease, well-controlled viral infections, untreated brain metastases, limited performance status, or those who need concomitant radiation. Limited data from retrospective studies and early trials show that ICI therapy may be safe and potentially beneficial in these patients and future trials should consider inclusion of these patients.

Autoimmune disease. Most early trials of ICI therapy including anti–PD-1 (program cell death protein-1) /PD-L1 (program cell death-ligand-1) as well as anti-CTLA4 (cytotoxic T-cell lymphocyte-associated-protein-4) antibodies excluded patients with autoimmune disease given concerns for disease flare. As result, there are insufficient safety data in this patient population, which makes up a significant portion of patients with advanced malignancy. A population study of lung cancer patients from 1991 to

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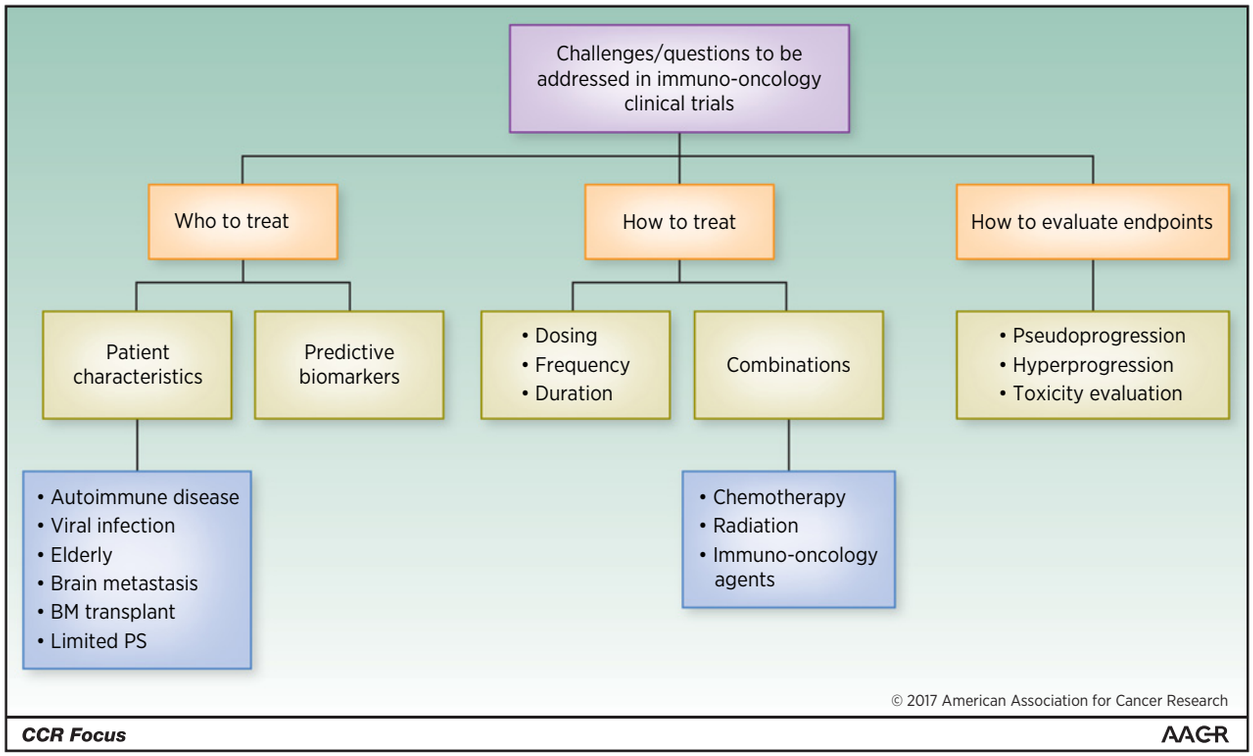

Figure 1.
Challenges and limitations in completed and currently ongoing immuno-oncology clinical trials. Abbreviations: BM, bone marrow transplant; PS, performance status.

2011 using the Medicare database reported a 12% prevalence of autoimmune disease among patients with metastatic lung cancer—most commonly rheumatoid arthritis, followed by psoriasis and polymyalgia rheumatic (2).

A retrospective study in advanced melanoma (3) reported data in 30 patients with baseline autoimmune disease who received ipilimumab. More than two-thirds of these patients had a history of receiving systemic therapy for their autoimmune disease and more than a third were on an immunosuppressive therapy (e.g., low-dose prednisone, hydroxyquinolone) at the time of ipilimumab initiation. Approximately 50% of patients developed exacerbation of their baseline autoimmune conditions and/or severe ($\geq$ grade 3) immune-related adverse events (irAE), which were mostly reversible with steroid therapy. These toxicities were observed regardless of whether patients were on baseline immunosuppressive therapy at the time of treatment initiation. Approximately 50% of patients did not develop irAEs from therapy and the reported 20% tumor response rate (RR) suggested that clinical benefit was achievable in this patient population. Efficacy and responses were seen in both the patients who developed irAEs requiring steroid therapy and in patients without development of irAEs.

A retrospective review of 119 patients with advanced melanoma with underlying autoimmune disease treated with an anti–PD-1 antibody (90% received pembrolizumab) showed that approximately one-third of patients developed flare of their underlying autoimmune disease and/or other irAEs. Patients who had active autoimmune disease requiring immunosuppressive therapy at the time of anti-PD1 therapy initiation were more likely develop an autoimmune flare. The tumor RR in this series was 33%, which is comparable with the RR reported in clinical trials of anti–PD-1 monotherapy and responses were seen regardless of the onset of autoimmune flare (4).

The above studies indicate that despite the risk of flare of underlying autoimmune disease and development of other immune-mediated toxicities in patients with underlying autoimmune disease, these toxicities were mostly reversible with steroid therapy and a significant portion of patients did not develop irAEs, suggesting ICI may be safely administered in this patient population. ICI should not be strictly contraindicated in this population, but consideration of therapy with caution should be individualized based on the risk–benefit, taking into account the history, extent and type of autoimmune disease, and anticipated complications. Future trials need to consider inclusion of patients with autoimmune disease in order that the safety of ICI agents can be clearly defined prospectively. Trials could be designed with these patients in discrete cohorts so that safety and efficacy could be evaluated independently of the overall trial population.

Viral infections (viral hepatitis, HIV). Patients with viral hepatitis and human immunodeficiency virus (HIV) were excluded from the early clinical trials of ICI therapy given theoretical safety concerns. However, recent studies have shown that inhibitory immune checkpoint pathways may be involved in suppressing viral-specific immune T-cell responses (5), suggesting that targeting such inhibitory pathways could restore viral specific adaptive immune responses.

In a study of nivolumab in advanced hepatocellular carcinoma patients with treated or ongoing hepatitis B virus (HBV) or hepatitis C virus (HCV) infections were eligible if they were Child Pugh score <7 without a history of significant ascites or hepatic encephalopathy (6). The most common AEs were liver enzyme increase and rash, with an overall tolerable safety profile without a viral flare. Interestingly, an antiviral response was reported in a HCV-infected patient. A phase II study of nivolumab in metastatic squamous cell carcinoma of the anal canal allowed enrollment of HIV infected patients on highly active antiretroviral therapy (HAART) with a CD4 count of >300/μL and an undetectable viral load, and HBV or HCV infected patients with liver function tests within 2.5 times of the upper limit of normal (7). The 39 enrolled patients included two patients with HIV and no unexpected AEs were observed in these patients. Several case series report acceptable tolerability with ipilimumab in HIV and viral hepatitis patients (8–10) and ongoing studies with ipilimumab and nivolumab (NCT02408861), and with pembrolizumab alone (NCT02595866) in patients with HIV with advanced malignancy will provide additional safety data.

Limited performance status. Most clinical trials of ICI therapy have limited enrollment to only patients with excellent performance status, usually defined by grades 0 to 1 by the Eastern Cooperative Oncology Group (ECOG) performance status (PS) scoring system. However, the PD-1/PD-L1 ICIs are generally well tolerated by most patients. In fact, a first-line pembrolizumab trial in advanced non–small cell lung cancer (NSCLC) demonstrated that quality of life with pembrolizumab was superior compared with standard platinum doublet-based chemotherapy (11). Safety data are lacking with PD-1 ICIs in patients with limited performance status (e.g., ECOG PS 2 or 3). Nevertheless, with the known toxicity profile of these agents, fatigue may presumably worsen; otherwise tolerability may be similar to patients with good baseline performance status. The CA209-153 trial which assessed nivolumab in advanced NSCLC across community sites included patients with ECOG PS 0 to 2, and found that the rates of treatment-related AEs were similar across patients with differing PS (12), suggesting that patients with limited PS could potentially safely receive ICI therapy. Regardless, prospective studies in patients with ECOG PS 2 to 3 patients are needed as cytotoxic chemotherapy is often not tolerable in this patient population, and ICI therapy is often employed instead in the clinic without clear robust safety data for guidance.

Older patients. Patients with advanced age are often underrepresented in clinical trials. In the landmark phase III trial CheckMate-067, advanced melanoma patients receiving nivolumab, ipilimumab, or nivolumab plus ipilimumab had a mean age of 59, with patients ≥75 years of age representing 12.5% of the overall trial participation (12). Given the observed decline in the immune response and increased autoantibody production with age (13), tumor efficacy and toxicity to immune checkpoint inhibitors may change with advancing age. A phase III randomized trial of nivolumab versus everolimus in patients with advanced renal cell carcinoma demonstrated improvements in survival favoring nivolumab in the overall study population; however, the subset of patients >75 years of age did not demonstrate a survival benefit, although these numbers were small (14). In contrast, a meta-analysis of approximately 5,300 patients across nine randomized trials of ICI therapy reported progression-free survival (PFS) and overall survival (OS) benefits in both younger (<65–70) and older (>70) patients (15). As life expectancy is expected to increase for the general population, it will be crucial to increase efforts to include patients with advanced age in future trials to specifically study their immunologic response and toxicity to ICIs.

Brain metastases. The experience with targeted therapeutics in NSCLC has shown that disease control in the central nervous system (CNS) is crucial to achieving optimal disease control and improving OS. Although ICI therapy may result in systemic disease control, its efficacy in the CNS lacks full prospective definition as patients with brain metastases were excluded from many early phase studies due to safety concerns. A retrospective pooled analysis of four trials (CheckMate-063, -017, -057, and -012) evaluated the efficacy and safety of nivolumab in advanced NSCLC patients with CNS metastatic disease (16). In patients with pretreated CNS metastatic disease, improved OS was observed with nivolumab compared with docetaxel, similar to the overall population. The frequency and time to new CNS lesions, as well as overall safety profile, were similar in those who received nivolumab versus docetaxel, with fewer treatment-related neurologic AEs in the nivolumab arm. Activity was demonstrated with nivolumab therapy in NSCLC patients with untreated asymptomatic CNS disease in the CheckMate-012 trial (arm M): 2 out of 12 patients achieved intracranial responses, including a patient with leptomeningeal disease. In an early analysis of an ongoing phase II study, 22% of melanoma and 33% of NSCLC patients with untreated or progressive CNS metastatic disease treated with pembrolizumab demonstrated intracranial responses (17). Responses were durable and concordant between CNS and systemic responses. Therefore, ICI therapy is likely safe and effective in patients with pretreated or asymptomatic CNS disease. However, rare CNS AEs due to ICIs have been reported. Severe cerebral edema was observed in a patient with pediatric glioblastoma treated with nivolumab, although it is unclear whether this was solely due to treatment (18). The above data indicate promising efficacy of ICI therapy in CNS metastatic disease and additional prospective data are needed. Future trials should include patients with untreated asymptomatic CNS disease to better evaluate the intracranial efficacy.

Hematopoietic stem cell transplant. The benefit of allogeneic hematopoietic stem cell transplantation in hematologic malignancies is dependent on the ability of donor immune cells to engage malignant cells via a graft-versus-tumor effect; however, treatment failure can ensue when immune evasion and exhaustion of donor immune cells occur. Although ICI therapy has emerged as an attractive strategy for potentially restoring donor immune cell activity, there are concerns regarding eliciting a graft-versus-host effect. A study enrolled patients ($n = 28$) with hematologic malignancies who failed allogeneic transplant to receive ipilimumab 3 or 10 mg/kg every 3 weeks for a total of four doses; those who achieved benefit could receive additional doses (19). There were no responses among patients who received the 3 mg/kg dose, whereas among the 20 patients who received the 10 mg/kg dose, 33% of patients demonstrated objective responses. However, 6 (21%) of the 28 enrolled patients developed irAEs, including one death, and 4 (14%) patients developed graft-versus-host disease which precluded additional therapy.

Activity of nivolumab after autologous stem cell transplant has also been observed in Hodgkin lymphoma (HL) patients (20). A phase I study of 23 refractory HL patients, including 78% who had relapsed after an autologous transplant, were treated with nivolumab 3 mg/kg until complete response, disease progression, or unacceptable toxicity. This study showed that nivolumab was highly active in this patient population (87% objective response) and grade 3 to 4 irAEs were uncommon. The above studies show that ICI therapy is likely safe in patients who have history of an autologous transplant; however, safety of ICIs needs to be further elucidated in patients with a history of allogeneic transplant.

Concomitant therapy–Radiation. Radiation therapy (XRT) with concurrent ICI therapy has been of considerable interest given the immune-modulatory effects of radiation in the tumor microenvironment and early reports of an abscopal effect (21–23); nevertheless, the toxicity of such combination has not been well defined. A phase I/II study assessing ipilimumab with or without XRT (a single 8 Gy dose to focal bony lesions, <3 lesions 24–48 hours prior to ipilimumab dose) in hormone-resistant prostate cancer did not demonstrate any increased toxicity with combination therapy (24). Similarly, retrospective data from 53 advanced melanoma patients receiving extracranial and/or intracranial XRT concurrently with an anti-PD1 antibody also demonstrated no excess toxicities with extracranial XRT; however, neurologic AEs such as severe radiation necrosis, acute neurocognitive decline and cerebral edema were seen with intracranial XRT (25). Studies vary as to whether concurrent intracranial XRT and ICI are associated with excess neurologic AEs (26) or not (27) and remains an active area of investigation (28).

As such, existing literature suggests that concurrent ICI therapy with most sites of extracranial XRT may be safe, whereas the safety of concurrent intracranial XRT is unclear. Additionally, the safety with extracranial XRT likely varies by organ site and the type of ICI; thus, concurrent therapy needs to be considered with caution. For instance, severe pneumonitis has been reported with concurrent ICI (anti–PD-1/PD-L1/CTLA4) and thoracic radiation (29). Clearly, prospective trials are needed in order to clearly define the safety and synergistic efficacy of XRT and ICI combination therapy. There are many questions to be answered including the optimal dose, fractionation and organ site of XRT, as well as the sequencing, dosing, and schedule of ICI agents. Once these factors and safety parameters are defined, subsequent trials should be designed in such way that clear efficacy data can be obtained (e.g., a randomized phase II study or a single-arm study in ICI-refractory patients).

Therapeutic administration in clinical trials

Pharmacokinetics (PK) and Pharmacodynamics (PD). Due to rapidity of development, competition, and race for FDA approval (Fig. 2), the optimal dosing and schedule of ICIs are still not fully defined and continue to be under study. PD-1 ICI trials assessed administration ranging from a single dose (30), 3× weekly (31), once every 2, 3, or 4 weeks, to every 3 months. Although the PK profile for the PD-1 ICIs has been defined for various doses and schedules (Table 1), these agents do not fit the clear dose–response or dose–toxicity relationships seen with cytotoxic agents and PD data do not completely define the optimal administration schedule with the highest efficacy.

In general, PD-1 ICI exposure increases linearly and proportionally over various concentrations with small volumes of distribution at steady state and limited extra-vascular distribution. For example, nivolumab administered at 0.1 to 10 mg/kg q2 weeks demonstrated 64% to 70% PD-1 receptor occupancy on $CD3^+$ T cells (32). Although pembrolizumab PD-1 target engagement was fully saturated at doses $\geq$1 mg/kg q3 weeks, translational models bridging mouse to human studies predicted robust maximal responses at doses of $\geq$2 mg/kg q3 weeks (33), and clinical randomized dose-level comparisons of pembrolizumab demonstrated equivalence between the 2 mg/kg and 10 mg/kg q3 week dosing (34). Inter-individual PKs can vary by the degree of target-mediated elimination, receptor-mediated endocytosis, concentration dependent half-life, and the amount of circulating soluble targeted surface molecules (i.e., PDL-1; ref. 35). In contrast, clearance of most PD-1 ICIs is not affected by age, sex, race, performance status, or moderate renal/hepatic dysfunction (32, 36–38). One can surmise that therapeutic levels would not increase and toxicity would not be greatly enhanced by these factors. Clearance did increase with increasing body weight, supporting body-weight based dosing in many early ICI trials.

Dosing strategies. FDA-approved ICI agents at varying dosing schedules across several tumor types (Table 2) resulting in confusion in clinical application and design of combination trials. Pembrolizumab received accelerated approval in melanoma at 2 mg/kg q3 weeks (39), while varying doses of 10 mg/kg q2 or q3 weeks, or 2 mg/kg q3 weeks were used in an early NSCLC trial (40). Subsequently, FDA approval was granted at 2 mg/kg q3weeks in NSCLC based on the risk–benefit data for 2 mg/kg and the assumption that the effective dose–response relationship and toxicity profile would be similar across tumor types (41). Later, a 200 mg flat dose was used in the landmark first-line KEYNOTE-024 trial with subsequent FDA approval of the flat dose (42). In squamous cell carcinoma of the head and neck (SCCHN), an initial dose of 10 mg/kg q2 weeks was explored with subsequent expansion at the 200 mg q3 week flat dose, which demonstrated efficacy and tolerability with resultant FDA approval of the flat dose (43, 44).

In regards to nivolumab, the initial FDA-approved dose of 3 mg/kg q2 weeks in NSCLC was subsequently changed to a flat dosing of 240 mg q2 weeks based on population PK and dose–exposure response analyses demonstrating comparability of safety and efficacy in most disease indications (32). A model-based PK analysis of 3,203 patients of multiple tumor types enrolled in clinical trials of nivolumab showed that an alternative flat dosing of 480 mg every 4 weeks resulted in similar exposure, efficacy and safety as the 3 mg/kg q2 week dosing (45) and this dose has been incorporated into various clinical trials of nivolumab (NCT02713867 and NCT 02714218). Investigation of nivolumab dosing for combination therapy continues to be heterogeneous ranging from 1 mg/kg to 10 mg/kg q2 weeks as well as alternative flat dosing strategies at q3 and 4 weeks. Conversely, atezolizumab was developed as a fixed dose every 3 weeks. For the indication of urothelial carcinoma and second-line NSCLC, 1200 mg q3 weeks demonstrated efficacy and survival benefits resulting in FDA approval (46, 47).

The dose and frequency of ipilimumab have been defined in melanoma (Table 2); however, these are still being explored as single agent and in combination with other ICI agents for other

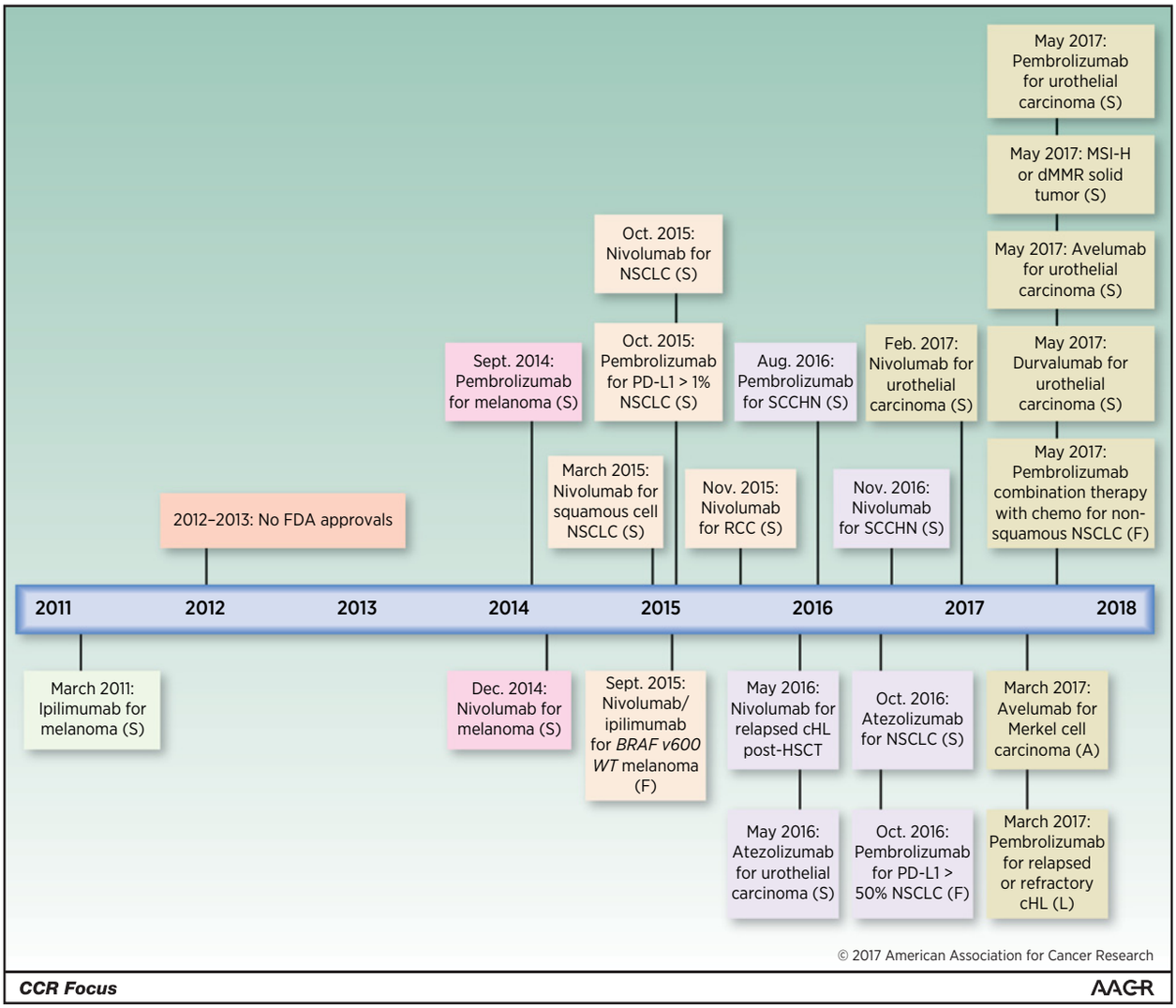

Figure 2.
FDA approval timeline of immune checkpoint inhibitors in advanced/metastatic malignancies (https://www.fda.gov/drugs, retrieved May 31, 2017). Abbreviations: A, any line; cHL, classical Hodgkin lymphoma; dMMR, mismatch repair deficient; F, first line; HSCT, hematopoietic stem cell transplant; L, fourth or beyond line; MSI-H, microsatellite instability-high; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma; S, second or beyond line; SCCHN, squamous cell carcinoma of the head and neck; WT, wild-type.

malignancies. Ipilimumab in combination with nivolumb at doses used for advanced melanoma demonstrated initial excess toxicity in the Checkmate 012 first-line NSCLC population, necessitating changes to 1 mg/kg every 6 to 12 weeks in combination with nivolumab at 3 mg/kg which improved tolerability while maintaining efficacy (48). In small–cell lung cancer, alternative dosing and schedules also demonstrated activity and tolerability (Table 2; ref. 49).

The varied dosing of ICI agents creates difficulty in clinical use and future development. Currently existing PK and clinical trial data better support weight-based dosing than flat dosing; however, the optimal dose has not been fully determined for many of the ICI antibodies. As there is no clear dose–response or dose–toxicity relationship with ICI antibodies, there likely will not be substantial changes in efficacy or toxicity with small changes in dosing. Therefore, flat dosing may be more attractive than weight-based dosing, as it appears to result in similar anti-tumor activity in the majority of population weights and body surface areas while providing ease of administration and less drug wastage. However, further cost-effectiveness data are needed to define the more efficient dosing strategy that optimizes efficacy as well as cost-effectiveness.

Differences between the ICI antibodies and the presence of anti-drug antibodies. In addition to PK and PD of the ICI antibodies, IgG class of the drug may affect bioactivity. IgG1 and IgG3 may elicit more natural killer cell antibody-dependent cell-mediated cytotoxicity while IgG4 may demonstrate more complement pathway activation (Table 1; ref. 50). Furthermore, whether the degree of humanization–either fully human or humanized–

Table 1. Pharmacokinetics of select CTLA4 and PD-1 checkpoint inhibitors in development

Target antigen	Agent name	IgG class	Degree of humanization	Elimination half-life days (percent coefficient of variation)	Clearance mL/h or L/day (percent coefficient of variation)	Volume of distribution at steady state L (percent coefficient of variation)
CTLA4	Ipilimumab	IgG1	Fully Human	15.4 (34%)	16.8 mL/h (38%)	7.2 L
CTLA4	Tremelimumab	IgG2	Fully human	14.7 days (30.1%)	15.3 mL/h (38.5%)	7.21 L (10.5%)
PD-1	Nivolumab	IgG4	Fully human	26.7 (101%)	9.5 mL/h (49.7%)	8.0 L (30.4%)
PD-1	Pembrolizumab	IgG4	Humanized (from mouse)	23 days (30%)	First dose 267 mL/day; at steady state 212 mL/day	6.1 L (21%)
PD-L1	Atezolizumab	IgG1	Humanized	27 days	200 mL/day	6.9 L
PD-L1	Durvalumab	IgG1	Fully human	17 (23.2%) days	8.24 mL/h (37.3%)	5.6 L (17%)
PD-L1	Avelumab	IgG1	Fully human	6.1 days	0.59 L/day (41.7%)	4.72 L

affects efficacy and/or toxicity is unclear. Anti-drug antibodies (ADA) have been detected but the actual presence of neutralizing ADAs is low and do not significantly impact the clearance, safety, PK, PD, or efficacy of pembrolizumab, pidilizumab, atezolizumab, or nivolumab (37, 38, 51, 52). It is unknown whether the differences among the various anti–PD-1/PD-L1 IgG subclasses, humanization, and binding affinity affect clinical outcomes and whether such clinical impact will differ between the various tumor types. Head-to-head comparative studies should be considered to clarify these issues.

Toxicity determination and trial design. The typical early phase I 3+3 dose-escalation design using the first two cycles as a dose-limiting toxicity (DLT) assessment period has been unable to capture the true toxicity profile of ICI agents and is insufficient in guiding the optimal dosing and schedule. Severe irAEs with the PD-1 inhibitors are rare and infrequent (<5%; refs. 53, 54) and are often seen late, from months to even years. Therefore, the clinical dose/recommended phase II dose (RP2D) has been determined to be the maximal administered dose based on PK/PD profiling, or a maximal feasible dose rather than a maximal tolerated dose.

Future trial designs should incorporate longer DLT periods and should take into account late toxicities to determine the clinical/RP2D. A DLT period of at least 6 to 8 weeks could be considered before escalating to higher doses and both the early and late toxicity data should be considered to make recommendations regarding the RP2D. The effect of steroids and immunosuppressive therapy to treat irAEs on continued efficacy should be captured in clinical trials, as well as the incidence of irAE recurrence with continued therapy. Additionally, as the immunologic effects of these agents persist, there are many anecdotal reports of patients experiencing improved responses or enhanced immune-related toxicities with subsequent therapies (55) months to years post therapy. This requires trials designs to incorporate longer follow-ups in order to better characterize the late toxicities and effects on subsequent therapies. For example, at least a 90-day follow-up could be considered for evaluation of immune-related toxicities and long-term follow-up of up to 1-year could be incorporated into studies so that long-term toxicities, including effects on subsequent therapies, could be evaluated.

Clinical response and benefit. In most clinical trials, initial response assessments generally occur at 8 to 12 weeks; however, immunologic responses can be delayed and pseudoprogression has been described (56). The onset of response and the incidence of pseudoprogression may vary across tumor types and should be noted in addition to standardized immune-response criteria. Although pseudoprogression has been notable in malignancies where immune modulation has a substantial role (i.e., melanoma), in malignancies such as NSCLC and SCCHN where response rates are lower, pseudoprogression is rare and often difficult to distinguish from true progression. Moreover, the benefit of treatment after a true progression is unclear. A recent FDA analysis of a completed trial of nivolumab in advanced NSCLC reported that among patients who received treatment after progression per Response Evaluation Criteria in Solid Tumors (RECIST), 5% were found to have subsequent tumor response and this comprised 2% of the overall trial population (57). This suggests that continuing therapy beyond progression is unlikely to be beneficial in the majority of patients; however, clinicians often do so as there are no clear clinical characteristics or highly predictive biomarkers across the various malignancies that can identify patients who are more likely to have delayed response. Predictive biomarkers of response to ICIs need to be further studied and incorporated into trials and are discussed in the series (see accompanying article by Mehnert and colleagues, ref. 58). Also, some have observed that a subset of patients develop "hyperprogression" defined by rapid progression of disease after initiation of ICI therapy (59). The mechanism and risk factors for identification of such phenomenon have not been clearly defined. Ongoing and future trials should take into consideration the atypical outcomes such as pseudo- or hyper-progression as efficacy endpoints, in addition to the traditional RECIST response assessments, so that these can be better defined and understood.

Duration of therapy, maintenance, and retreatment. Although the use of anti-CTLA4 antibodies (i.e., ipilimumab) is usually limited to four doses, the optimal treatment duration of PD-1/PD-L1 ICI therapy is undefined. The initial phase I trials (60, 61) established a 2-year limit to therapy; however, subsequent studies allowed ongoing therapy as long as there is clinical benefit (62). Clinical trial protocols vary from 6 months to 1.5 to 2 years, to indefinite therapy. Unlike vaccines, ICIs are passively administered antibodies with uncertainty and variability in their ability to engage the adaptive immune system. It is unknown whether ongoing therapy is truly superior to limited treatment of a defined duration or to the use of a maintenance regimen with less frequent administration. Moreover, there may be long-term toxicities that emerge after years of treatment that may not occur with limited therapy. An ongoing study of nivolumab in advanced NSCLC (63) randomizing patients at 1 year to treatment continuation versus discontinuing therapy with the option of re-treatment at progression may help address this question but clearly, additional studies are

Table 2. Select CTLA4 and PD-1/PD-L1 checkpoint inhibitors in development and FDA-approved indications and dosing

Target antigen	Agent name	Populations studied	Clinical trial dosing	FDA approved indications	FDA-approved dosing[a]
CTLA4	Ipilimumab	Inoperable or metastatic melanoma	3 mg/kg q 3 weeks x 4 cycles, alone and in combination with nivolumab	Inoperable or metastatic melanoma	3 mg/kg q 3 weeks
		Advanced NSCLC (48)	1 mg/kg q 6 to 12 weeks (in combination with nivolumab)	N/A	N/A
		Advanced small cell lung cancer (49)	1, 3 mg/kg in combination with nivolumab	N/A	N/A
CTLA4	Tremelimumab	Multiple tumor types (67)	1, 3, 10 mg/kg; 75 mg flat dose q 4 weeks	N/A	N/A
		Locally advanced or metastatic NSCLC (68)	1 mg/kg q 4 weeks in combination with durvalumab	N/A	N/A
		Recurrent or metastatic SCCHN (69)	1 mg/kg q 4 weeks in combination with durvalumab	N/A	N/A
PD-1	Nivolumab	Inoperable or metastatic melanoma	0.1–10 mg/kg q 2 or 3 weeks	Inoperable or metastatic melanoma	240 mg q 2 weeks flat dose
		Advanced NSCLC	0.1–10 mg/kg q 2 or 3 weeks	Second line NSCLC – (squamous and non-squamous histology)	240 mg q 2 weeks flat dose
		RCC	0.1–10 mg/kg q 2 or 3 weeks	Second-line RCC	240 mg q 2 weeks flat dose
		Relapsed or progressed cHL	0.1–10 mg/kg q 2 or 3 weeks	Relapsed or progressed cHL	3 mg/kg q 2 weeks
		SCCHN	3 mg/kg q 2 weeks	Platinum refractory or pretreated	3 mg/kg q 2 weeks
		Bladder cancer	3 mg/kg q 2 weeks	Platinum pretreated/platinum refractory bladder cancer	240 mg q 2 weeks flat dose
PD-1	Pembrolizumab	Melanoma	1–10 mg/kg q 2 or q 3 weeks	Inoperable or metastatic melanoma	2 mg/kg q 3 weeks
		First- and second-line advanced NSCLC	1–10 mg/kg q 2 or q 3 weeks; 200 mg q3 weeks	First-line (PDL1 positive $\geq$ 50% only)[b] and second-line in (PDL1>1%) advanced NSCLC, First line in combination with pemetrexed/platinum in non-squamous histology	2 mg/kg q 3 weeks; 200 mg q3 weeks (first line)
		SCCHN	1–10 mg/kg q 2 weeks	Platinum-pretreated recurrent incurable, metastatic SCCHN	200 mg IV flat dose
		Bladder cancer	200 mg q 3 weeks	Platinum pretreated/platinum refractory bladder cancer	200 mg q 3 weeks
		Relapsed or refractory cHL	200 mg q 3 weeks	Refractory cHL, or relapse after 3 or more prior lines of therapy	200 mg q 3 weeks (adult); 2 mg/kg q 3 weeks (pediatric)
		Microsatellite instability-high cancer	200 mg q 3 weeks; 10 mg/kg for q 2 weeks	Unresectable or metastatic MSI-H	200 mg q 3 weeks (adult); 2 mg/kg q 3 weeks (pediatric)
PD-L1	Atezolizumab	Bladder cancer	1–20 mg/kg to q 3 weeks 800-1,200 mg IV q 3 weeks flat dose	Advanced platinum pretreated/ platinum ineligible bladder cancer Bladder cancer	1,200 mg IV q 3 weeks
		Advanced NSCLC	1 mg/kg to 20 mg/kg q 3 weeks	Second-line advanced NSCLC	1,200 mg IV q 3 weeks
		Multiple tumor types (70)	800–1,200 mg IV q 3 weeks flat dose in combination dosing	N/A	N/A
PD-L1	Durvalumab	Bladder cancer	3, 10, 15, 20 mg/kg; 1,500 mg flat dose q 4 weeks	Platinum pretreated/platinum refractory bladder cancer	10 mg/kg q 2 weeks
PDL1	Avelumab	Merkel cell carcinoma	10 mg/kg q 2 weeks	Merkel cell	10 mg/kg q 2 weeks

Abbreviations: cHL, classical Hodgkin lymphoma; FDA, U.S. Food and Drug Administration; IgG, immunoglobulin G; NA, not approved; NSCLC, non–small cell lung cancer; SCC, squamous-cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck.

[a]Clinical trials supporting FDA approved dosing are listed on FDA.gov.

[b]PDL1 high expression at a tumor proportion score $\geq$ 50% only.

needed. In the melanoma data, the majority of patients with complete responses who stopped therapy appeared to remain in remission with a median duration of response ranging from 17 to 43 months (64). However, for other malignancies, especially in patients who have stable disease or partial response as best response, discontinuation of therapy poses potential risk due to the inability to consistently re-induce responses at the time of progression. Without guidance from the literature, many clinicians and patients have opted to continue therapy indefinitely in the absence of a complete response, especially in situations where there is a lack of effective therapeutic options at progression, but this comes at a substantial cost. This area has

implications not only in disease outcomes but also in financial costs to the individual and society at large; thus, there is an urgent need to address this issue in clinical trials.

Next generation of immuno-oncology clinical trials: what are the challenges in rationally designing next generation of clinical trials

ICIs have been predominantly approved in advanced disease and there are ongoing studies to explore these agents in earlier settings (Table 3). In addition, there are an expanding number of clinical trials of immuno-oncology combination therapy in which multiple immune pathways are concurrently targeted (see accompanying article by Day and colleagues).

One of the important areas in the next phase of development is to understand the mechanisms of primary and acquired resistance to ICI therapy. Despite the reported efficacy of ICIs in a number of solid tumors, the response rates are often modest and patients who achieve complete response are rare.

Table 3. Select current neoadjuvant/adjuvant trials involving CTLA4 and PD-1 checkpoint inhibitors in the non-metastatic setting

Study title	Phase	Type	Trial identification numbers
A Study of Nivolumab, Compared to Placebo, in Patients with Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer	Phase III	Adjuvant	CA209-274 NCI-2016-00764 2014-003626-40 NCT02632409
Study of Adjuvant Nivolumab or Placebo in Subjects with Resected Esophageal or Gastroesophageal Junction Cancer	Phase III	Adjuvant	CA209-577 NCI-2016-00858 2015-005556-10 NCT02743494
Pembrolizumab in Treating Patients with Triple-Negative Breast Cancer	Phase III	Adjuvant	S1418 NCI-2016-01595 S1418/BR006 NCT02954874
A Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients with Stage III Unresectable Non-Small Cell Lung Cancer	Phase III	Adjuvant	D4191C00001 NCT02125461
Phase II Trial of Adjuvant Cisplatin and Radiation with Pembrolizumab in Resected Head and Neck Squamous Cell Carcinoma	Phase II	Adjuvant	UCCI-HN-15-01 NCI-2016-00322 NCT02641093
Pembrolizumab and High-Dose Recombinant Interferon Alfa-2b before and after Surgery in Treating Patients with Locally/Regionally Advanced or Recurrent Melanoma	Phase I	Neoadjuvant / adjuvant	UPCI 14-102 NCI-2015-00111 NCT02339324
Nivolumab before Surgery in Treating Patients with Non-metastatic High-Risk Kidney Cancer	Phase I	Neoadjuvant	J15179 NCI-2016-00269 CRMS-62598 IRB00068726 NCT02575222
Neoadjuvant Pembrolizumab in Combination with Gemcitabine Therapy in Cis- eligible/Ineligible UC Subjects	Phase II Phase I	Neoadjuvant	HCRN GU14-188 NCI-2015-01257 NCT02365766
Vaccine Therapy with or without Nivolumab Before and After Surgery in Treating Patients with Stage I-IIb Pancreatic Cancer that can be Removed by Surgery	Phase II Phase I	Neoadjuvant/adjuvant	J1568 NCI-2016-00268 CRMS-61622 IRB00050517 NCT02451982
Pembrolizumab, Combination Chemotherapy, and Radiation Therapy before Surgery in Treating Adult Patients with Locally Advanced Gastroesophageal Junction or Gastric Cardia Cancer that can be Removed by Surgery	Phase II Phase I	Neoadjuvant	MC1541 NCI-2016-00508 NCT02730546
Nivolumab in Treating Patients with Stage I–IIIA Non-small Cell Lung Cancer that can be Removed by Surgery	Phase II	Neoadjuvant	J1414 NCI-2015-00243 CIR00010768 NA_00092076 NA_00092076/J1414 NCT02259621
Nivolumab with or without Ipilimumab before Surgery in Treating Patients with Stage IIIB–IV Melanoma That Can Be Removed by Surgery	Phase II	Neoadjuvant/adjuvant	2015-0041 NCI-2015-01520 NCT02519322
Nivolumab with or without Ipilimumab in Treating Patients with Locally or Regionally Advanced or Recurrent Melanoma that can be Removed by Surgery	Phase II	Neoadjuvant/adjuvant	UPCI 15-113 NCI-2016-00593 NCT02736123
Pembrolizumab, Decitabine, and Standard Chemotherapy before Surgery in Treating Patients with Locally Advanced HER2-Negative Breast Cancer	Phase II	Neoadjuvant	MCC-15-11083 NCI-2016-01980 NCT02957968
Pembrolizumab before and after Surgery in Treating Patients with Stage IB–IIIA Non-small Cell Lung Cancer	Phase II	Neoadjuvant/adjuvant	Pro00071629 NCI-2017-00093 NCT02818920

In trials of advanced NSCLC patients treated with an anti-PD1 antibody, approximately 20% of patients achieved objective responses lasting 13 to 17 months (40, 62) before developing resistance, whereas >40% progressed (62) with primary resistant disease. Recently, in tumor samples with acquired PD-1 resistance, loss-of-function mutations in *JAK1* (Janus kinase 1) and *JAK2 (*Janus kinase 2) genes were present in melanoma (65), and loss of putative tumor neoantigens were reported in NSCLC (66). The mechanisms of resistance are likely to be heterogeneous across different tumor types and the success of the next wave of immuno-oncology clinical trials, particularly in patients with primary and/or acquired resistance, will depend on the extent of our biological understanding of such mechanisms. Therefore, studies of pre- and posttreatment correlative samples will be paramount in understanding the mechanism of resistance, development of predictive biomarkers, and rational design of the next generation of clinical trials.

Conclusion

Immuno-oncology is undergoing rapid development with initial trials resulting in meaningful improvements in patient outcomes. The next generation of clinical trials has the opportunity to address areas of need such as the inclusion of inadequately represented patient populations, optimization of drug dosing and duration, better characterization of long-term toxicities and design of rational drug combinations in patients with primary and acquired resistance. Until such studies are conducted, use of these agents in the clinic should be carefully selected to ensure safety. For example, treatment in patients with autoimmune disease should be limited to those with limited organ involvement and perhaps to later lines of therapy, and off-label combination therapies should be avoided until robust efficacy and safety data are available.

Successful design and conduct of the needed studies will require participation of the various stakeholders. Academic research groups and cooperative trial networks, in collaboration with industry partners, may be best poised to lead designing studies in understudied populations that may not be studied otherwise. Regulatory bodies could demand follow-up studies to address questions such as drug dosing and duration. To fully develop an effective immuno-oncology therapeutic strategy and overcome the limitations addressed will require collaboration among industry, academia, and regulatory bodies where sharing and pooling of information will be crucial.

Disclosure of Potential Conflicts of Interest

C.S. Baik is a consultant/advisory board member for Novartis. P.M. Forde is a consultant/advisory board member for AstraZeneca, BMS, Boehringer, Celgene, EMD Serono, Merck, and Novartis. J.M. Mehnert reports receiving other commercial research support from AstraZeneca, EMD Serono, Incyte, Macrogenics, and Merck and is a consultant/advisory board member for EMD Serono, Genentech, Merck, and Pfizer. M.O. Butler reports receiving commercial research grants from Merck and is a consultant/advisory board member for Bristol-Myers Squibb, EMD Serono, Immunocore, Immunovaccine, Merck, Novartis, and Turnstone. L.Q.M. Chow is a consultant/advisory board member for Amgen, AstraZeneca/Medimmune, Bristol-Myers Squibb, Genentech, Merck, Novartis, Pfizer, and Seattle Genetics. No potential conflicts of interest were disclosed by the other authors.

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