CCR FOCUS

Challenges and Opportunities in Adapting Clinical Trial Design for Immunotherapies

Lillian L. Siu[1], S. Percy Ivy[2], Erica L. Dixon[3], Amy E. Gravell[3], Steven A. Reeves[2], and Gary L. Rosner[4]

Abstract

Immunotherapy adds an exciting new dimension to the treatment of cancer, joining other approaches as a key pillar in the oncotherapeutics armamentarium. Immuno-oncology agents harbor unique mechanisms of antitumor activity by leveraging the host immune system, which may result in response patterns, resistance kinetics, and toxicity profiles that differ from other systemic therapies. These features have led to many discussions on ways to optimally integrate immunotherapy into cancer clinical trials. This overview provides an introduction to the four *CCR Focus* articles that ensue, with special thoughts paid to clinical trial endpoints, biomarker development and validation, combination strategies, and limitations that arise with increasing use of these agents. In addition, this overview examines design concepts that may be applied to invigorate clinical trials and to maximize their impact in the immuno-oncology era. *Clin Cancer Res; 23(17); 4950–8.* *©2017 AACR.*

See all articles in this *CCR Focus* section, "Clinical Trial Design Considerations in the Immuno-oncology Era."

Introduction

In recent decades, practice-altering shifts have transformed the systemic therapy of cancer, including molecular targeting against various oncogenic pathways and genomic sequencing, to identify driver aberrations in pursuit of precision medicine. The focus of drug development had primarily been on perturbation of signals that disrupt the growth and spread of cancer cells; however, with the advent of immunotherapy, the focus turned toward harnessing the host immune system to exert anticancer activity. Immunotherapies have unique properties that distinguish them from other systemic therapies, such as their patterns of response, relapse, and resistance. Dose–response and dose–toxicity relationships are not typically direct or dose-proportional, as in the case of most cytotoxic chemotherapy and many molecularly targeted agents. Furthermore, immunotherapies have the potential to induce not only sustained, long-term benefits, but also lingering adverse effects. With these features in consideration, three articles in this *CCR Focus* examine conventional elements of clinical trials—endpoints, biomarkers, and combination strategies—in the context of immunotherapy to highlight where standard principles prevail and where innovations are needed (1–3). The limitations and challenges encountered thus far in the design, implementation, and integration of immunotherapy clinical trials are discussed in the final article of this series (4).

Overview of current status

The armamentarium that broadly fulfills the definition of immunotherapeutic agents is extensive, including, but not limited to, cancer vaccines, oncolytic viruses, cytokines, adoptive cell transfer, costimulatory molecules, and immune checkpoint inhibitors. The immune checkpoint inhibitors, such as those targeting the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), or its ligand (PD-L1), are furthest along in their clinical development path. As such, a retrospective evaluation of the developmental strategies of some immune checkpoint inhibitors might provide insight on gaps that exist in the era of immunotherapeutics.

The first-in-human phase I studies of many anti–CTLA-4 and anti–PD-1/PD-L1 antibodies, such as ipilimumab (5), pembrolizumab (6), nivolumab (7), durvalumab (8, 9), and atezolizumab (10), all used the 3+3 dose-escalation design in patients with advanced solid tumors. The initial studies of PD-1/PD-L1 inhibitors planned expansion cohorts of limited size, but early signs of promising clinical antitumor activity led to substantial increase in the ultimate sample size. All trials rapidly moved to multi-cohort dose expansions in search of early signals of efficacy across different tumor types. In addition to preliminary activity evaluation during the "tail" of phase I trials, many of these agents are also investigated in stand-alone "basket" protocols with multiple cohorts that enroll a variety of histologies and/or enriched patient subsets (e.g., high microsatellite instability status tumors) at the recommended phase II dose (e.g., KEYNOTE-028; ref. 11). Methodological issues related to these designs are discussed further in the "Seamless Phase I-II Trial Designs" section below.

Table 1 contains selected clinical trials published in 2016 of two anti–PD-1 antibodies, pembrolizumab and nivolumab; although not comprehensive, it provides a contemporary

[1]Princess Margaret Cancer Centre, University of Toronto, Toronto, Ontario, Canada. [2]Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, Maryland. [3]The Emmes Corporation, Rockville, Maryland. [4]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland.

Corresponding Author: Lillian L. Siu, University Health Network, 610 University Ave Suite 5-718, Toronto, Ontario M5G 1Z5, Canada. Phone: 416-946-2911; Fax: 416-946-4467; E-mail: lillian.siu@uhn.ca

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Table 1. Selected immune checkpoint inhibitor studies published in 2016

Agent	Phase	Number of people enrolled	Tumor type	Design	Biomarkers (selection)	Endpoints	Reference
Late phase (randomized)							
Pembrolizumab Keynote-024	III	305	NSCLC	Randomized 1:1 Pembrolizumab vs. investigator's choice chemotherapy	PD-L1 $\geq$ 50% TPS	PFS Target HR 0.55	Reck et al. (41)
Pembrolizumab Keynote-021	II	123	NSCLC	Randomized 1:1 Pembrolizumab plus chemotherapy vs. chemotherapy	Stratified by PD-L1 (<1% vs. $\geq$1%)	ORR by RECIST 1.1 (30% difference in ORR) Target HR 0.5 (PFS is secondary endpoint)	Langer et al. (42)
Pembrolizumab Keynote-010	II/III	1,034	NSCLC	Randomized 1:1:1 Pembrolizumab (2 doses): chemotherapy	PD-L1 $\geq$ 1% TPS Stratified by PD-L1 (TPS <50% vs. $\geq$50%)	OS and PFS Target HR 0.6	Herbst et al. (43)
Nivolumab Checkmate-141	III	361	SCCHN	Randomized 2:1 Nivolumab vs. investigator's choice systemic therapy	Not selected by PD-L1	OS Target HR 0.667	Ferris et al. (44)
Nivolumab Checkmate-064	II	140	MM	Randomized 1:1 Nivolumab followed by ipilimumab or vice versa	Not selected by PD-L1	Treatment related grade 3–5 adverse events till week 25 (end of induction)	Weber et al. (45)
Early phase							
Pembrolizumab Keynote-012	Ib	32	TNBC	Part of a multicohort study	PD-L1 in stroma or $\geq$1% of tumor cells	ORR by RECIST 1.1 P0 = 0.2, P1 = 0.45	Nanda et al. (46)
Pembrolizumab	II	36	MM or NSCLC with brain metastases	Single-arm phase II, 2 parallel cohorts	Not selected by PD-L1	Brain metastasis response by modified RECIST	Goldberg et al. (47)
Pembrolizumab Keynote-012	Ib	60	SCCHN	Part of a multicohort study	PD-L1 in stroma or $\geq$1% of tumor cells	ORR by RECIST 1.1 P0 = 0.1, p1 = 0.35	Seiwert et al. (48)
Pembrolizumab	II	26	MCC	Single-arm phase II study	Not selected by PD-L1 or by MCPyV status	ORR by RECIST 1.1 P0 = 0.05, P1 = 0.25	Nghiem et al. (49)
Pembrolizumab Keynote-013	II	31	HL	Single-arm phase II study	Not selected by PD-L1	CRR by IHP criteria P0 = 0.1, P1 = 0.3	Armand et al. (50)
Pembrolizumab Keynote-012	Ib	39	Gastric	Part of a multicohort study	PD-L1 in stroma or $\geq$1% of tumor cells	ORR by RECIST 1.1	Muro et al. (51)
Pembrolizumab Keynote-001	I	655	MM	Expansion cohort of phase I study	Not selected by PD-L1	ORR by RECIST 1.1	Ribas et al. (52)
Nivolumab Checkmate-032	I/II	86	UC	Single-arm phase II study	Not selected by PD-L1	ORR by RECIST 1.1 P0 = 0.1, P1 = 0.25	Sharma et al. (53)
Nivolumab Checkmate-012	Ib	52	NSCLC	Part of a multicohort study	Not selected by PD-L1	Safety and tolerability	Gettinger et al. (54)
Nivolumab Checkmate-205	II	80	HL	Single-arm phase II study part of a multicohort study	Not selected by PD-L1	ORR by IHP criteria	Younes et al. (55)
Nivolumab	Ib	81	HM	Phase I dose escalation study	Not selected by PD-L1	Safety and tolerability	Lesokhin et al. (56)
Nivolumab Checkmate-032	I/II	216	SCLC	Multiple cohorts with nivolumab alone or nivolumab plus ipilimumab	Not selected by PD-L1	ORR by RECIST 1.1	Antonia et al. (57)

Abbreviations: CRR, complete response rate; HL, Hodgkin lymphoma; HM, hematological malignancies; ICI, immune checkpoint inhibitor; IHP, International Harmonization Project; MCC, merkel cell carcinoma; MCPyV, merkel-cell polyomavirus; MM, malignant melanoma; NSCLC, non–small cell lung cancer; SCCHN, squamous cell carcinoma of the head and neck; SCLC, small-cell lung cancer; TNBC, triple-negative breast cancer; TPS, tumor proportion score; UC, urothelial cancer.

benchmark of clinical trial design methodologies and selection biomarkers that have been applied. Following the identification of clear signals of antitumor activity, there are two common developmental strategies undertaken in the evaluation of immune checkpoint inhibitors. One approach relies on single-arm or small noncomparative phase II trials (12); others transition seamlessly from phase I trial to multi-cohort expansion phase or basket trial in specific histologies. These studies seek accelerated approval by meeting the FDA criteria for unmet medical need based on a surrogate endpoint, such as objective response rate (ORR). To achieve accelerated regulatory approval, the therapeutic index of the investigational agent must weigh favorably against the standard therapy (if it exists) for the patient population under consideration. The other approach is to directly compare against standard-of-care therapy through randomized phase II and randomized-controlled phase III trials seeking clinically meaningful benefit in a definitive endpoint such as progression-free survival (PFS) or overall survival (OS), respectively. These randomized comparisons often occur after or near completion of dose expansion in phase I trials to avoid delay; many of these trials aim for large reductions in risk (i.e., HRs, 0.5–0.6). In this *CCR Focus*, Anagnostou and colleagues (1) examine the challenges of utilizing the traditional endpoints of ORR, PFS, and OS in immuno-oncology clinical trials. Further, as discussed by Mehnert and colleagues (3), selection biomarkers are not yet universally validated to accurately predict response or resistance to immune checkpoint inhibitors. PD-L1 expression on tumor or immune cells by immunohistochemistry has been the most frequently considered, although this biomarker is confounded by the multiple antibodies and disparate scoring criteria that accompany the various PD-1/PD-L1 inhibitors (13).

Identification of gaps in immunotherapy clinical trials

The articles in this *CCR Focus* provide a critical appraisal of the gaps that exist in the current clinical trial landscape for immunotherapies and suggest ways that the drug development paths for this class of agents can be improved and modernized.

Anagnostou and colleagues (1) reviewed nuances associated with applying traditional efficacy and toxicity endpoints to immuno-oncology agents, given potential differences in response and resistance kinetics from other systemic therapies. The emergence of various response criteria to meet the specific effects of these agents [e.g., irRC (14), irRECIST (15), and iRECIST (16)] has added further complexity to the field. Standardization of universally accepted tumor immune response criteria is of top priority. Likewise, the description and attribution of immune-mediated adverse events arising from autoimmunity developing in host tissue need to be appropriately documented, including the need for intervention (e.g., corticosteroids), as well as the timing of onset and resolution. As for efficacy evaluation, Kaplan–Meier plots for PFS and OS in many immuno-oncology trials have a distinctive configuration, characterized by a delay in clinical effect and a nonzero tail representing long-term survivors (17). Landmark survival estimates and nonproportional hazard models have been proposed as more appropriate for reporting clinical outcomes from immunotherapy. Health-related quality of life and patient-reported outcome evaluations are underrepresented in immuno-oncology research, and increased attention should be paid to these patient-based endpoints.

Mehnert and colleagues (3) proposed key recommendations related to immuno-oncology biomarker research, highlighting the complex and dynamic characteristics of many biomarker candidates being interrogated for their ability to predict for response, resistance, or toxicity to immunotherapy. The need for high-quality preanalytics such as biospecimen acquisition, standardized assays, and clinical annotation is emphasized, which resonates with the mandate of the U.S. National Cancer Institute's new program under the Cancer Moonshot directive called the Partnership for Accelerating Cancer Therapies (PACT; ref. 18). Strategic incorporation of biomarker endpoints into early- and late-stage immuno-oncology clinical trials must consider their scientific value to the development of these agents and, importantly, the perspectives of patients under study.

Day and colleagues (2) focused on one of the most challenging areas in immuno-oncology drug development—creating a rational framework to design and assess combination therapy. Priority should be given to combinations that have the strongest scientific evidence for additivity or synergy and a favorable therapeutic index, although interspecies differences limit the utility of most nonclinical models to nominate the most appropriate drug schedules and sequences to enter clinical testing. Many clinical trials evaluating immunotherapy-based doublets or even triplets with an anti–PD-1/PD-L1 backbone are ongoing or being planned; the vast majority of these emerge from empiricism or minimal scientific justifications. Lessons learned from the nivolumab and ipilimumab combination are examined to further inform patient selection, dose and schedule optimization, and toxicity management.

Baik and colleagues (4) offered a thoughtful interpretation of the limitations and challenges in immuno-oncology clinical trials. Insufficient representation of patient subsets including those with autoimmune disease, virally initiated diseases, etc. in immunotherapy trials negatively affects the generalization of results to these individuals. Unless clinical trials are inclusive of these patient populations or are specifically designed to enroll such patients, their access to promising immuno-oncology compounds will be restricted. Furthermore, with the regulatory approval of anti–PD-1/PD-L1 antibodies in multiple indications, compounded by the large number of ongoing clinical trials incorporating these agents alone or in combination, it has become increasingly difficult to identify research participants who are naïve to PD-1/PD-L1 inhibitors. Other unaddressed questions, such as the optimal length of therapy of immune checkpoint inhibitors in patients whose tumors demonstrate response, tracking of effects on subsequent therapies in those who discontinued such drugs, and documentation of late toxicities, are also discussed.

Checklists for early- and late-phase immunotherapy trials

The rapid entry of new immuno-oncology compounds into the clinic has led to an exponential increase in the number of early- and late-phase trials, a phenomenon that is likely unsustainable due to limited patient, infrastructure, and financial resources. Despite the broad activity observed with PD-1/PD-L1 inhibitors in many tumor types (Fig. 1), there are clear instances that such agents exert minimal antitumor activity, as in the case of pembrolizumab in microsatellite stable

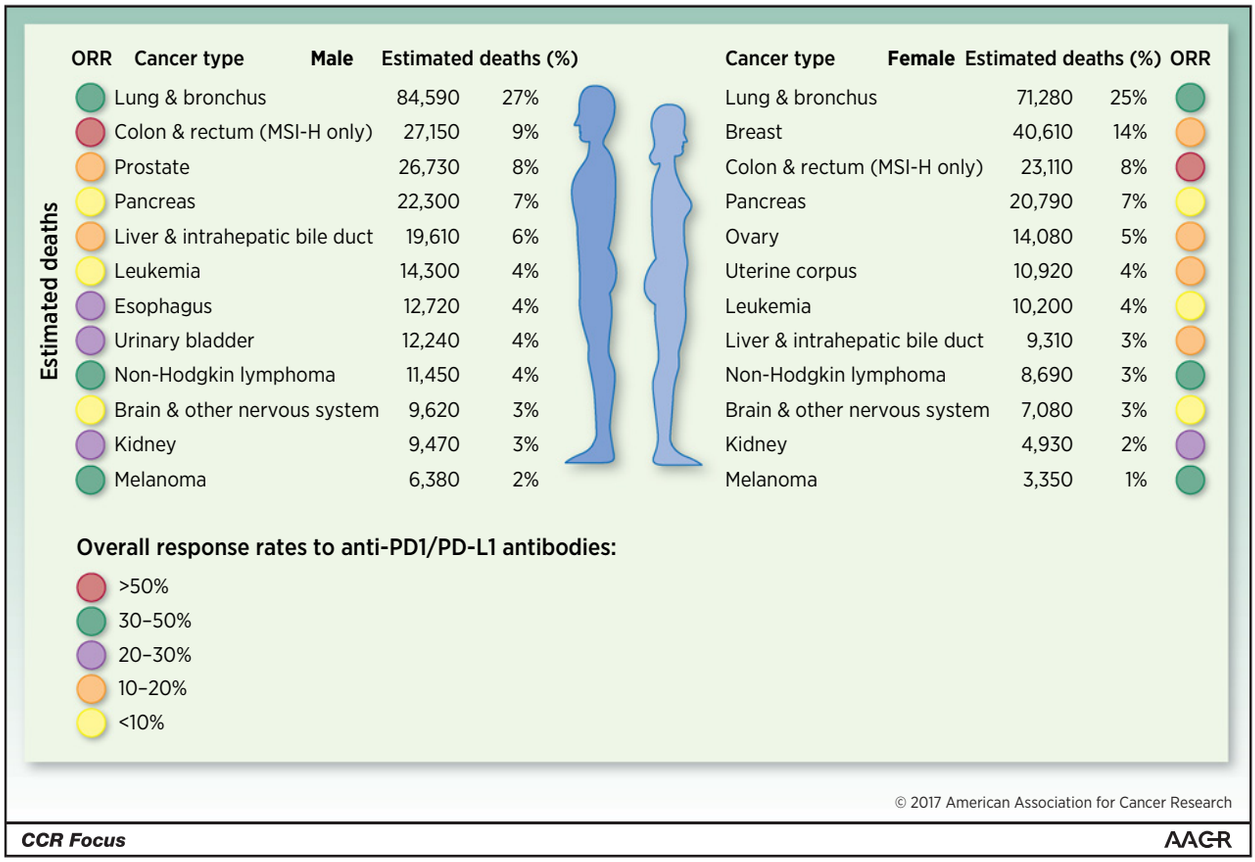

Figure 1.
Objective response rate to anti–PD-1/PD-L1 antibodies in the most lethal cancers. Estimated deaths data from the American Cancer Society (58).

colorectal cancer or castrate-resistant prostate cancer (7). There is an urgent need for efficient and nimble clinical trials to seamlessly advance the most promising drugs or drug combinations while stopping futile efforts in a decisive and reasonable timeframe. Table 2 provides checklists of important items that should be considered during the conduct of early- and late-phase immunotherapy clinical trials. Figure 2 provides an outline of the structure of the clinical developmental pathway for immune-oncology agents.

Areas for innovation and impact in the design of immunotherapy clinical trials

Innovations in clinical trial designs to increase operational efficiency and optimize patient outcomes are needed as immunotherapy becomes integrated as a key therapeutic pillar in oncology; some examples are described below.

Evaluation of tumor growth modulation

Although tumor shrinkage remains one of the most validated biomarkers of antitumor activity, many drugs with primarily growth-inhibitory potential, including some immuno-oncology agents, demonstrate only cytostatic effects when given to patients with heavily pretreated and highly resistant cancers in early-phase clinical trials. This may be particularly relevant in cases of patients previously exposed to PD-1/PD-L1 inhibitors who have primary or acquired resistance to these agents and subsequently enter clinical trials evaluating immuno-oncology combinations (e.g., the combination of a costimulatory molecule and a PD-1/PD-L1 inhibitor). Although objective responses may occur in some cases, the preliminary efficacy of such combinations in the absence of tumor shrinkage may be based on the achievement of clinically meaningful disease stabilization, which remains an elusive endpoint in a heterogeneous early-phase trial patient population with variable tumor biology. Some experts consider prolonged stable disease of at least 6 months or longer as evidence of clinical benefit, whereas others have attempted to use patients as their own controls by comparing tumor growth rate or PFS on current regimen versus the same parameter on immediate prior regimen (19, 20). The application of these measures of cytostasis as surrogates of efficacy requires systematic validation in clinical trials and demonstration of reproducibility. There are also ongoing efforts to develop novel radiomics biomarkers of response or resistance to immune checkpoint inhibitors by using advanced image processing techniques to extract quantitative texture and geometric features from CT or MRI scans and subject them to machine-learning algorithms (21). The

Table 2. Important steps for consideration in the conduct of early- and late-phase immunotherapy trials

Early-phase trials

1. Provide justification for the human starting dose and anticipate risk of acute toxicity such as cytokine release syndrome based on drug profile and nonclinical evaluations
2. Define patient selection criteria based on:
   a. Histology—inclusion of all comers versus enrichment for specific tumor types?
   b. Biomarker selection—is there a compelling biological rationale to include only biomarker-positive patients and exclude biomarker-negative patients? Is the companion diagnostic test fit for the trial purpose with a reasonable turnaround time for results?
   c. Prior immune checkpoint inhibitor exposure—are there any reasons to recruit immune checkpoint inhibitor–naïve patients in tumor types that already have proven antitumor activity or drug approval? How feasible is it to recruit such patients?
3. Select a suitable dose escalation method—consider nonclinical data or existent clinical data from same drug class; risk of narrow therapeutic window, risk of acute, delayed or late toxicity; availability of patient population; availability of biostatistics support; possibility of no DLT; speed to completion; etc.
4. Determine the need for sentinel patients in each cohort based on anticipated risk of acute toxicity such as cytokine release syndrome
5. Define DLT and timeframe for DLT evaluability; RP2D should take into account late or delayed toxicity
6. Report treatment emergent adverse events and immune-related adverse events, including need for intervention (e.g., corticosteroids), onset, and duration of toxicity
7. Incorporate pharmacokinetic sampling at appropriate time points to evaluate the pharmacologic behavior of the drug and relevant metabolites
8. Include pharmacodynamic biomarkers in surrogate or tumor tissues if they have the potential to provide proof of mechanism
9. Use a consistent response criteria across participating sites (e.g., RECIST 1.1) but can collect additional response data (e.g., irRECIST, iRECIST)
10. Plan judicious use of expansion cohorts with clear objectives, e.g., biomarker enrichment, etc.
11. Consider dose range studies to refine RP2D
12. Identify drugs or drug combinations suitable for accelerated approval path
13. Engage patients and patient advocacy groups to appreciate their perspectives and to manage expectations

Late-phase trials

1. Define the research hypothesis to be addressed and an effect size that is considered clinically meaningful
2. Determine the most relevant endpoint(s)—median PFS or OS, or landmark analysis (e.g., 1-year OS rate)
3. Define the allowance for treatment beyond RECIST 1.1 progression
4. Collect long-term survival and toxicity data given the potential for late effects of immunotherapy
5. Engage patients and patient advocacy groups to appreciate their perspectives and to manage expectations

Abbreviation: RP2D, recommended phase II dose.

ability to distinguish pseudo-progression (i.e., an uncommon phenomenon observed with some immuno-oncology agents associated with the appearance of initial tumor growth and/or development of new lesions, presumably due to immune cell infiltration into tumor, followed by subsequent tumor regression) from true progression early, to avoid exposing the latter group of patients to ineffective treatment, is challenging to understand and predict, and one of the highest research priorities.

Seamless phase I–II trial designs

Many studies seek to evaluate both the appropriate dose and schedule, and to identify histologies that appear to respond to these agents. Protocols begin with dose finding and then enroll patients across multiple histologies (22); sometimes, they include a safety run-in for each cancer subtype due to context-dependent toxicity. The goal of these designs is to increase efficiency by allowing the study to add different cancers via protocol amendments instead of developing new protocols. By combining dose finding with subsequent assessment of activity in disease-specific cohorts, these master protocols progress seamlessly from phase I to phase II. The rapid pace at which immuno-oncology agents are entering the clinical research arena has sometimes meant that disease-specific cohorts receive treatment without the protocol specifying a statistical design. Even though these "expansion" cohorts are part of a phase I study, in fact, the cohort is providing evidence of the agent's activity. These protocols should include appropriate statistical designs to protect patients in expansion cohorts, either through safety stopping boundaries after the initial dose escalation or through futility boundaries to avoid treatment with ineffective therapies. Further research into efficient study designs that balance the desire for rapid drug development against the need for generation of rigorous scientific evidence is a high priority.

Adaptive designs in combination trials

Most clinical studies in cancer are adaptive in some sense, including study designs with group-sequential boundaries guiding decisions relating to interim analysis results, futility analyses, dose-escalation rules, adaptive enrichment, and adaptive randomization. Several high-profile clinical trials in cancer have incorporated adaptive randomization by allowing the probabilities governing treatment assignments to change in favor of better performing treatment regimens (23). Examples of such trials are the BATTLE studies (24, 25) and I-SPY-2 (26, 27), the latter has "graduated" two agents to further study (28, 29). Both studies use relatively quickly available endpoints (i.e., 8-week disease control and pathologic complete response in the neo-adjuvant setting, respectively) to inform activity assessment. Studies evaluating immuno-oncology agents may require longer follow-up of patients, because clinical response is not always seen immediately. Immune-related biomarkers that can show efficacy-related activity earlier than clinical endpoints may emerge as intermediate endpoints, allowing adaptive randomization to be more useful for studies of immuno-oncology agents. Although such adaptations may well accelerate the development of effective treatment regimens, careful thought must go into the study's design to weigh potential benefits against possible problems (30, 31). Studies that adapt ongoing randomization to pair sensitive disease subtypes to their more active treatment

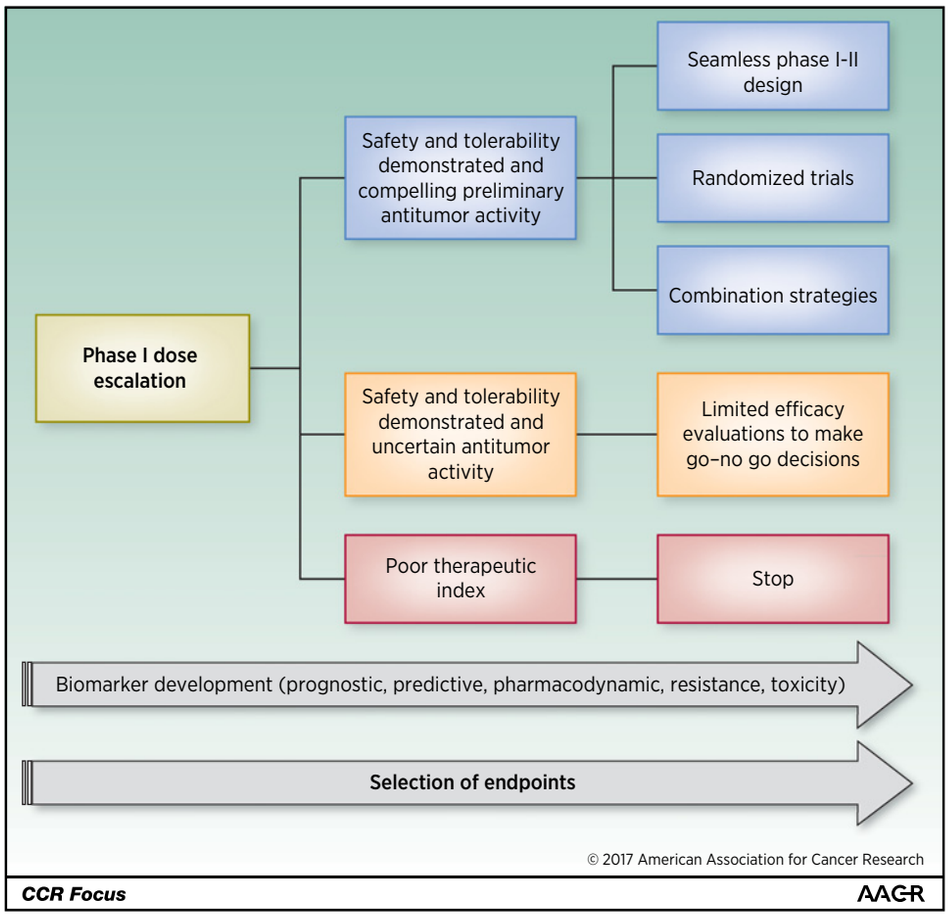

Figure 2.
Clinical developmental pathway for immuno-oncology agents.

regimens will likely find greatest use in the phase II setting, where screening for activity takes precedence over performing a confirmatory trial.

Duration of therapy and dose sequencing trials

As discussed in Baik and colleagues (4), the optimal duration of therapy is unclear for immuno-oncology agents that are typically delivered by repeated dosing, such as costimulatory molecules and immune checkpoint inhibitors. This uncertainty exists not only in the setting of advanced disease for patients whose tumors achieved sustained objective response or prolonged disease stabilization, but also in the curative scenario whereby such agents are given as adjuvant therapy. As such, clinical trials evaluating short courses of maintenance or adjuvant immunotherapy (e.g., 3–6 months) versus longer courses are needed. In addition, clinical trials specifically designed to ascertain the effect of dosing schedule for immune combinations are lacking, and this gap also needs to be corrected. For instance, whether anti–PD-1/PD-L1 antibodies and adoptive cell therapies can be safely combined is unknown; whether they should be administered concurrently or sequentially to achieve the most favorable therapeutic index requires exploration (32). From the clinical trials design perspective, many of these questions pose noninferiority hypotheses and require large sample sizes to address. Despite the potential impact on patient outcome that the answers to these questions may bring, pharmaceutical companies are generally not financially incentivized to conduct such trials. They will likely rely on the concerted efforts of cooperative groups or other research consortia to complete.

Clinical trials that target large differences in effect size

Many contemporary randomized clinical trials evaluating immune checkpoint inhibitors have set a reasonably high efficacy bar seeking large reductions in risk (i.e., HRs, 0.5–0.6) for PFS or OS, which translate to doubling or near doubling of these time-based parameters (Table 1). Small incremental gains are not affordable in the context of scarce resources. Unless there are system-wide solutions to the prohibitively high prices of cancer drugs including immunotherapy (33), their access to many patients will remain limited. As such, it is critical to design clinical trials that demonstrate substantial benefits via clinically meaningful efficacy endpoints, which may vary by patient population and disease status, while also considering the treatment's toxicity profile and patients' health-related quality of life. For instance, in 2016, the FDA provided accelerated approval for nivolumab in combination with ipilimumab for the treatment of patients with unresectable or metastatic malignant melanoma based on PFS [CHECKMATE-067 (34): 11.5 months with the combination, vs. 2.9 months with ipilimumab alone, and 6.9 months with nivolumab alone]. Approval was given despite a higher rate of grade 3

or 4 treatment-related adverse events observed with the doublet than either agent given alone. As the OS data from this study become available (35), continued approval for this indication may depend on confirmation of a sustained benefit that is reflected by relevant reductions in death rates (36). The enrichment for biomarker-positive subgroups is a logical approach to achieve large effect size in clinical trials (3), but this strategy is currently challenged by the lack of validated predictive biomarkers in immunotherapy.

Clinical trials at minimal residual disease stage to increase cure rates

Although there continues to be tremendous hope that immunotherapy offers cures to some patients with advanced disease, the present reality is that only a small proportion qualify as long-term survivors. Clinical trials targeting patients with minimal residual disease after definitive therapy but are at high risk for relapse have the greatest potential to improve cancer cure rates. EORTC 18071 evaluated adjuvant ipilimumab in patients with stage III resected melanoma and demonstrated a 5-year rate of recurrence-free survival of 40.8% in the ipilimumab group versus 30.3% in the placebo group [HR, 0.76; 95% confidence interval, 0.64–0.89; ref. 37]. Similar studies with other immuno-oncology agents are ongoing [e.g., KEYNOTE-054 (38), CHECKMATE-238 (39)]. Likewise, the Canadian Cancer Trials Group BR.31 trial evaluates the role of adjuvant durvalumab in patients with completed resected stage IB, II, and IIIA non–small cell lung cancer (NCT02273375). These patient populations also offer the opportunity to examine the role of circulating tumor and immune biomarkers (i.e., circulating tumor DNA, exosomes, cytokines) that may further refine patient selection and enable monitoring of therapeutic resistance.

Conclusion

Several national and international initiatives seek to leverage approaches in immune-oncology, including the NCI Cancer Moonshot, which received a boost when the U.S. Congress passed the 21st Century Cures Act, creating the Blue-Ribbon Panel working group to define strategic initiatives in clinical cancer research (40). This initiative bolsters cancer discovery to accelerate treatment and cures over the next 7 years and provides $1.8 billion in funding. Working through the Foundation of the National Institutes of Health, the PACT is actively exploring public–private partnerships with government, academe, and the pharmaceutical industry to broaden the expansion of immunotherapy and combination therapy research in biomarkers and treatment. The NCI has embarked on major initiatives in precision medicine using genomics, proteomics, and transcriptomics that can be directly applied to immune-oncology as predictive biomarkers are identified for response, resistance, pseudo-progression, and progression. Evidence-driven biomarker development will enable the precise selection of patients whose tumors are most likely to respond to immunotherapy and combination clinical trials, and to segment successful treatment of cancer patients. Efficient and effective novel clinical trial designs that are purposely suited for immunotherapy should also accelerate drug development in general.

Disclosure of Potential Conflicts of Interest

L.L. Siu is a consultant/advisory board member for AstraZeneca/Medimmune, Boehringer Ingelheim, Celgene, Merck, and Pfizer and reports receiving clinical trial research support from Abraxis, AstraZeneca/Medimmune, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Genentech/Roche, GlaxoSmithKline, Merck, Novartis, and Pfizer. G.L. Rosner is a consultant/advisory board member for Novartis. No potential conflicts of interest were disclosed by the other authors.

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