

## Should We Design Clinical Trials Differently in the Era of Cancer Immunotherapy?

### Abstract

The oncology clinical trials are evolving in the era of cancer immunotherapy. In Phase I trials, some severe immune-related adverse events occur beyond the first cycle. This is important to determine the recommended Phase II dose if the treatment duration is long. If there is no dose–response/toxicity relationship, it will not be necessary to push to the maximum tolerated dose. In Phase II trials, companion predictive biomarkers are valuable in cancers with intermediate response rates. Randomized (comparison, selection, or discontinuation) Phase II trials are needed in cancer immunotherapy combination. In Phase III trials, milestone analysis and restricted mean survival time could serve as the alternatives to hazard ratio to fit the survival kinetics of cancer immunotherapy.

**Keywords:** *Clinical trials, drug development, immuno-oncology*

### Introduction

The designs of Phase I–III clinical trials were established in the era of cancer chemotherapy. To fit the unique feature (dose–response/toxicity relationship) of chemotherapy, the primary endpoints of Phase I trial were to find dose-limiting toxicity (DLT), maximum tolerated dose (MTD), and hence recommended Phase II dose. The primary endpoints of Phase II and III trials were objective response rate (RR) and overall survival (OS), respectively. It implied that a high objective RR can translate to improve OS. Since the beginning of targeted therapy era in 2000, the relevance of traditional primary endpoints had been debated. For example, MTD without chronic toxicity taken into consideration may not define the recommended Phase II dose. Patients with stable disease sometimes derived benefit from targeted therapy. Therefore, objective RRs might not be a surrogate of survival. From the beginning of immunotherapy era in 2010, this issue has become even more complicated as immunotherapy is distinct from chemotherapy and targeted therapy. In this article, I discuss the important aspects of designs of Phase I, II, and III trials under the context of cancer immunotherapy.

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### Phase I Trials

The objective of a Phase I trial is to determine the appropriate dosage of an agent or combination to be taken into further study and to provide initial pharmacologic and pharmacokinetic studies. It is generally assumed, at this stage of testing, that increased dose is associated with an increased chance of clinical efficacy. Therefore, the Phase I trial is designed as a dose-escalation study to determine the MTD, that is, the maximum dose associated with an acceptable level of DLT (usually defined to be Grade 4 or above hematologic toxicity and Grade 3 or above nonhematologic toxicity). The recommended Phase II dose will take MTD, together with pharmacodynamics, pharmacokinetics, and preliminary antitumor activity into consideration.

### Dose-limiting toxicity

In cancer immunotherapy, especially anti-CTLA4 (cytotoxic T lymphocyte antigen 4) antibodies and anti-PD-1 (programmed cell death 1) / PD-L1 (programmed cell death 1 ligand 1) antibodies, the major toxicity is immune-related adverse events (irAEs). The major categories of the irAEs are cutaneous (pruritus, rash, vitiligo [in malignant melanoma]), gastrointestinal (diarrhea and

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colitis), hepatic (transaminitis), endocrine (hypophysitis [in anti-CTLA4 antibodies] and thyroiditis), and pulmonary (pneumonitis [in anti-PD-1/PD-L1 antibodies]).<sup>[1,2]</sup> There are variations in time to onset of irAEs. For example, rash could occur as early as the first cycle and hypophysitis tends to appear beyond Cycle 1 in patients with ipilimumab (anti-CTLA4 antibody).<sup>[1]</sup> The one cycle (3–4 weeks) of the traditional DLT-observing period is not adequate to capture all toxicities severe enough to limit the dose.<sup>[3]</sup> One practical way is to enroll more patients at each dose level and to take DLTs beyond Cycle 1 and intolerable Grade 2 AEs into consideration, similar to the proposal in the era of targeted therapies.<sup>[4]</sup>

People tend to think that immune checkpoint modulators, because of monoclonal antibody in nature, are relatively safe. There were no DLTs in the Phase I trials of agonistic antibodies against OX40 (CD134, MORX0916<sup>[5]</sup> and PF04518600<sup>[6]</sup>); 4-1BB (CD137, BMS663513 [urelumab]<sup>[7]</sup> and PF05082566 [utomilumab]<sup>[8]</sup>); and GITR (CD357, BMS986156<sup>[9]</sup> and TRX518<sup>[10]</sup>). We should not forget the tragic lesson we learned from the Phase I trial of TGN1412, an anti-CD28 agonistic antibody.<sup>[11,12]</sup>

### Maximum tolerated dose and recommended Phase II dose

The assumption behind the MTD is that the dose–response (toxicity) relationship exists. The higher dose of ipilimumab, anti-CTLA4 antibody, confers the higher OS and irAE rate in patients with malignant melanoma.<sup>[13]</sup> However, the dose–response relationship does not exist in anti-PD-1/PD-L1 antibodies.<sup>[14–16]</sup> To push the dose of cancer immunotherapy to the highest tolerable (or administered) needs to reconsider.

### Pharmacokinetics and pharmacodynamics

The main aspects of pharmacodynamics are the tissue, the assay, and the level of target modulation. All of these are closely related to the appropriate sample size for the pharmacodynamic endpoint. In cancer immunotherapy, tumor biopsies repeated before treatment and on treatment are a better tissue source to study pharmacodynamics. We need more preclinical effort to develop the best assay and the right level of target modulation given that the dose–response (toxicity) relationship might not exist in certain cancer immunotherapy. If we do not have other means to determine the recommended Phase II dose, pharmacodynamics will be the primary endpoint rather than just a proof-of-principle study.

### Preliminary antitumor activity – Cohort expansion

Because antitumor activities were observed in malignant melanoma and non-small cell lung cancer (and led to the Food and Drug Administration approval of these two indications) in the Phase I trial of pembrolizumab (KEYNOTE-001), people were optimistic

that we will see promising preliminary antitumor activities in each and every Phase I trial in the era of cancer immunotherapy.<sup>[17]</sup> The sample sizes of the cohort expansion still need to be justified with respect to their primary aim (dose seeking based on dose-limiting toxicities, ineffectiveness, or target modulation) and include interim analyses to allow for early stopping.

### Phase II Trials

The objective of Phase II trials is to determine if the drug has antitumor activity against the tumor type in question. For this objective, RR is an appropriate endpoint for evaluating the question posed by the trial. However, it is important to recognize that tumor response is not a direct measure of patient benefit.

#### Objective response rate

The highest RRs (50%–90% except for microsatellite instability–high colorectal cancer) of single-agent anti-PD-1/PD-L1 antibody are in Hodgkin's lymphoma, Merkel cell carcinoma of the skin, squamous cell carcinoma of the skin, and microsatellite instability–high colorectal cancer (40%). A second group of cancers with intermediate RRs (15%–25% except for cutaneous melanoma) are in cutaneous melanoma (40%), nonsmall cell lung cancer, head-and-neck cancer, gastric cancer, urothelial carcinoma, renal cell carcinoma, and hepatocellular carcinoma. In microsatellite-stable colorectal cancer, pancreatic cancer, prostate cancer, and triple-negative breast cancer, the RRs of single-agent anti-PD-1/PD-L1 antibody are lowest (<10%).<sup>[18,19]</sup> One practical way is to develop biomarkers (e.g., tumor PD-L1, tumor mutational burden, mismatch repair, and T-cell-inflamed gene signature) predictive of higher RR in the intermediate group. This topic is beyond the scope of this review.<sup>[20,21]</sup>

### Phase III Trials

#### Progression-free survival

Progression-free survival (PFS) curves, although commonly used for conventional treatment modalities, are not an ideal endpoint for cancer immunotherapy clinical trials. First, on initiation of anti-PD-1/PD-L1 therapy and the subsequent promotion of T-cell recruitment/expansion, preexisting tumor lesions may initially increase and new radiological lesions may transiently appear before obtaining a stable disease or partial/complete response. These pseudo-progressions are classified as progressive diseases per the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.<sup>[22]</sup> Therefore, it seems necessary to use dedicated radiological criteria, such as immune RECIST (iRECIST), to assess these atypical tumor responses, and to capture the spectrum of clinical benefits of cancer immunotherapies.<sup>[23]</sup> Second, PFS curves do not correlate with the OS benefits of cancer immunotherapies that are explained by long-term responses and by

**Table 1: Comparison of clinical trial design among chemotherapy, targeted therapy, and immunotherapy, as well as immunotherapy combination**

	Chemotherapy	Targeted therapy	Immunotherapy	Immunotherapy combination*
Phase I trials				
DLTs	Mainly hematologic in Cycle 1	Mainly nonhematologic in Cycle 1 and beyond	Mainly immune related in Cycle 1 and beyond	Combination of each component
RP2D	Usually MTD	Probably optimal biologic dose	Sometimes maximum administered dose	Probably RP2D+RP2D
Pharmacodynamics	Surrogate tissue	Surrogate tissue and tumor tissue	Tumor tissue	Tumor tissue
Phase II trials				
Primary endpoint	RR	RR or survival	Survival or RR	Survival or RR
Design	Single arm	Single arm or randomized	Single arm or randomized	Single arm or randomized
Phase III trials				
OS assumption	Proportional hazard model	Proportional hazard model	Landmark analysis or restricted mean survival time	Proportional hazard model, landmark analysis, or restricted mean survival time

\*Immunotherapy combination means: immunotherapy + chemotherapy (e.g., pembrolizumab + platinum doublet in nonsmall cell lung cancer), immunotherapy + targeted therapy (e.g., avelumab + axitinib in renal cell carcinoma), or immunotherapy + immunotherapy (e.g., nivolumab + ipilimumab). DLTs: Dose-limiting toxicities, MTD: Maximum tolerated dose, OS: Overall survival, RP2D: Recommended Phase II dose, RR: Response rate

possible sensitization of the tumor to the next line of chemotherapy.

### Overall survival

For the design of randomized Phase III trials using OS as the primary endpoint, the paradigm has shifted from the conventional approach based on a proportional hazards model to those that account for the unique survival kinetics observed in immuno-oncology trials. The results of the Phase III trial of ipilimumab in metastatic melanoma demonstrated a 4-month delay (overlapping of the survival curves) and long-term OS of approximately 20%.<sup>[24]</sup> In Phase III trials comparing chemotherapies with anti-PD-1/PD-L1 antibodies, a “crossing of survival curves” can be observed at about 3 months after starting treatment whereby the survival rate is lower in the immunotherapy arm in the early stages of the study.<sup>[25-29]</sup> One of the explanations of a “crossing of the survival curves” is hyperprogression which means that a subset of patients might present with accelerated progressive disease on treatment with anti-PD-1/PD-L1 antibodies.<sup>[30]</sup> At least two randomized Phase III trial designs were proposed based on milestone analysis (e.g., 2-year milestone survival)<sup>[31]</sup> and restricted mean survival time (e.g., the area under the Kaplan–Meier curves within the window of 36–72 months)<sup>[32]</sup> to simplify the process of sample size determination while keeping OS as the primary endpoint. The new designs are unaffected by the uncertainty of the survival kinetics demonstrated by cancer immunotherapies.

This is even more complicated when we design the Phase III trials of immunotherapy combination, including immunotherapy plus immunotherapy (e.g., nivolumab + ipilimumab in malignant

melanoma), immunotherapy plus chemotherapy (e.g., pembrolizumab + platinum-based doublets in nonsmall cell lung cancer), and immunotherapy plus targeted therapy (e.g., avelumab + axitinib in renal cell carcinoma) versus standard therapy. First, single-agent control arm should be available to show synergism, for example, avelumab + axitinib versus avelumab versus sunitinib in renal cell carcinoma. Second, the “long-term” survival benefit needs to be demonstrated. Third, predictive biomarkers of immunotherapy combination might not be the same as those of immunotherapy single agent.

### Summary

In the era of cancer immunotherapy, the designs of clinical trials should be adjusted to find the best dose and schedule of the new drugs and to demonstrate the efficacy in the most precise and efficient way [Table 1].

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