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Phase I Clinical Trials in the Era of Immunotherapy

James Kuo, C.

Scientia Clinical Research & Prince of Wales Clinical School, University of New South Wales, Sydney, Australia

***Correspondence to:** Dr. James Kuo, C., Scientia Clinical Research & Prince of Wales Clinical School, University of New South Wales, Sydney, Australia.

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Immunotherapy has changed the landscape of cancer care and has become the most promising area of cancer research over the recent years. Various stakeholders anticipate a rapid-fire development of immune-oncology (IO) agents and an accelerated regulatory approval timeline has been modernized with, most notably, the breakthrough therapy designation by the US Food and Drug Administration (FDA) in July 2012. Once biomarkers for novel IO agents are identified, the success in obtaining FDA approval for drugs with breakthrough therapy designation, such as ceritinib and durvalumab, after a single-arm phase I/II trial will be multiplied.

However, it should be noted that the success rate of gaining FDA approval of all oncology agents entering Phase I clinical trials has not increased over the past three decades between 1993 and 2015, and has remained the lowest among all therapeutic classes.[1-3] Nevertheless, an encouraging surge in the probability of success for approval, likely attributable to the success with IO agents, was observed between 2014 and 2015, during which time nivolumab alone was approved five times by FDA for different indications [3].

In recognition of the uniqueness and the rapid expansion of IO clinical trials, the American Society of Clinical Oncology (ASCO) and Society for Immunotherapy of Cancer (SITC) jointly published recommendations to improve the reporting of these trials [4]. The need for a new set of recommendations specifically for IO trials also indicates the challenges in conducting Phase I clinical trials in the era of immunotherapy.

Assessing Pseudo-Progression and Immune-Related Response

Firstly, efficacy is increasingly a secondary endpoint in phase I trials. The distinct immune-related patterns of response has led to the development of various response assessment frameworks, although none is yet validated and RECIST remains the gold standard still adopted by all IO trials in assessing response endpoints [5].

The usefulness of the first restaging scan in detecting disease progression may have been overshadowed by the maintenance of a stable clinical status. To allow for continuing treatment in light of perceived clinical benefit beyond the traditional RECIST-defined disease progression, "disease control" and clinical benefit" need to be uniformly defined and pre-specified. Of note is the lack of guideline in managing pseudo-progression. The endeavour to avoid premature cessation of potentially effective trial treatment should not delay what would constitute standard of care. For example, palliative radiation therapy should proceed for a newly detected yet presently asymptomatic bony lesion, which, if progressed, could lead to dire consequences such as spontaneous fracture or spinal cord compression.

In the absence of predictors for eventual immune response, and the possibility of hyperprogression being a true entity with possibly a higher incidence than pseudoprogression [6], decision for continued treatment beyond progression should be made with caution as well as informed consent from the patients.

Durable response could be anticipated in IO responders, and a strategy for assessing such, even beyond trial discontinuation and other post-trial treatments, needs to be considered.

Managing Immune-Related Adverse Events

As IO dose-toxicity relationship is being established, development, severity and duration of immune-related adverse events (irAE) remain unpredictable. Presently, late-onset irAE occurring beyond the dose limiting toxicity (DLT) evaluation period is not taken into consideration in the decision for dose escalation in phase I trial. Dose finding may continue into later phase trials, and even postmarketing, for small-molecule targeted therapy [7], and the same could be considered for IO agents, particularly in relation to the dosing schedule and duration.

Although the importance of early diagnosis and management of irAE is recognized, management of irAE, including self-vigilance, may not have been standardized. Patient-reported outcomes (PRO) may merit incorporation into the routine care of trial patients, given it has been recently demonstrated to be associated with increased survival [8].

Ascertaining RP2D

Evidence to support a clear dose-response relationship in IO is lacking, although with ipilimumab there are phase III data to support improved survival benefit with a larger dosage [9]. The traditional goal of phase I trials, that of ascertaining the maximal tolerable dose (MTD) and the recommended phase II dose (RP2D), may need to be revised uniformly to be the determination of the optimal biological dosing (OBD) instead, providing the most practical dose and schedule. As MTD is not always reached, parameters other than

toxicity, such as pharmacokinetic and pharmacodynamic data, have been incorporated in ascertaining RP2D; an association between defining RP2D using endpoints additional to toxicity and the eventual FDA approval has been previously suggested [10].

Combination Strategies

Phase I IO trials are getting more complex as combination immunotherapy, either with novel bi-specific agents or one immune checkpoint inhibitor as backbone in combination with another IO or other anti-cancer therapy, represents a prime research focus for cancer that has either primary or acquired resistance to single-agent immunotherapy. In the setting where combination immunotherapy is being evaluated as early as in the phase Ib expansion cohorts, competitiveness for patient recruitment for single-agent dose escalation has heightened. Adaptive trial designs, exemplified by Keynote-001 trial with pembrolizumab [11], evaluate multiple dosing regimens and indications, and may either randomise patients into different arms or choose to enrich patient subsets based on biomarkers. With the rapidly shifting standards of care and regulatory approval of novel agents, a trend towards an adaptive trial design to incorporate multiple protocol amendments and large expansion cohorts is foreseeable, and this will further increase the complexity of phase I trials.

Precision Oncology

More phase I trials are no longer recruiting "all-comers" as enrichment with tumour types recognized to be sensitive to immunotherapy is favoured. Biomarker will drive future development of IO agents, following the footsteps of pembrolizumab in obtaining FDA approval for non-tumor-specific indications [12], and basket trial design restricting inclusion to patients having specific biomarkers will be more commonplace. With the growing relevance of efficacy assessment in phase I trials, a shift in the traditional sequential paradigm for oncology drug development across different phases is being realized; leaping into phase III after having phase I data may become a possibility. Furthermore, research biopsies are increasingly becoming mandatory in the dose escalation cohorts for in-depth examination of putative biomarkers, expediting the prospective validation previously performed only in phase III studies.

In conclusion, it is an exciting era to conduct phase I clinical trials. The challenges will herald innovative designs to move the revolutionary wave of IO forward.

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