Phase I trials: not all are made equal

Phase I trials form the foundations of evidence-based oncology. Here, we explore the ethical controversies surrounding how participation in such trials should be presented to patients.

The December issue of *Nature Reviews Clinical Oncology* sees the publication of two articles advocating different positions on the role of phase I trials and, specifically, whether these should be presented to patients as a therapeutic option. In a Perspectives, Jacob Adashek and co-authors note that phase I trials have improved: many are now biomarker stratified; innovative study designs, such as expansion cohorts, are enabling more patients to participate, with lower levels of risk; and some of these trials are even leading to regulatory approval. In a Comment, Jonathan Kimmelman suggests otherwise, arguing that response rates typically remain low; that patients enrolled in these trials are more likely to have life-threatening toxicities; and that enrolment in phase I trials with an expectation of therapeutic effects amounts to little more than gambling. Both articles are in agreement, however, on the notion that phase I trials remain a foundation of evidence-based medicine, and are also a highly heterogeneous set of research activities.

In phase I trials, new interventions are often tested in patients for the first time, and practically all our readers will know that promising findings from animal models have a long history of failing to translate into clinically meaningful effects. Do we think, for example, that investigators conducting the successful phase I trials that led to the FDA approvals of pembrolizumab[1], or larotrectinib[2], knew beforehand that these agents would have such high levels of efficacy?

Nonetheless, results from these trials provided meaningful improvements, and the former trial included an expansion cohort that was contingent on efficacy and safety signals emerging from the original cohort — for these few patients, perhaps enrolment in the expansion cohort of this phase I trial could justifiably be offered as a therapeutic option. However, this example clearly does not reflect the norm, and even if it did, a high response rate among a small cohort is not robust evidence, and might reflect a false-positive result. Furthermore, promising response rates do not always lead to improvements in overall survival and fail to account for delayed-onset toxicities, among many other variables.

Thus, apart from a few notable exceptions, the majority of phase I trials do not provide therapeutic benefit for most of the patients who enrol in them, irrespective of therapeutic intent on the part of the investigators. This unfortunate fact highlights an important ethical dilemma: how best to counsel patients regarding the likelihood of therapeutic benefit, relative to adverse outcomes, such as toxicities or even death. Can phase I trials be routinely offered to patients as therapeutic options? The answer lies in the title of this Editorial: phase I trials are not all made equal, and should not be viewed as such.

Not all patients are equal either: in fact, no two are the same, and attitudes towards, and motivations for participation in phase I trials vary considerably and need to be taken into account. For some patients, enrolment in a phase I trial will genuinely be the best available therapeutic option, having exhausted all available standards-of-care; other phase I trials might enable patients with tumours harbouring a specific targetable alteration that has not previously been targeted in the context of their specific tumour type to gain access to an effective treatment. Either way, adopting a blanket position on the validity of phase I trials as therapeutic options seems like a bad idea.

A further relevant consideration is the capacity of patients with advanced-stage cancers to fully comprehend the purpose of a phase I trial, and how this relates to their likelihood of benefit and risks of adverse events. Evidence also exists that more complex trial designs, involving combinations containing a single novel therapy, might be more challenging for patients to truly understand than trials involving single agents[3].

Clinical staff, including oncologists, will continue to have an important role in counselling patients who might be willing to participate in phase I trials. The issues of therapeutic intent, the increased complexity of modern phase I trials, and the fact that seriously ill patients are often desperate, but might lack the knowledge required to understand a complex risk:benefit ratio, and might even have some degree of cognitive impairment, point towards a common need: better tools and protocols that facilitate optimal patient education, while respecting the basic human need to remain optimistic, even when faced with a desperate situation.

1. Hamid, O. Safety and tumor responses with lambrolizumab (anti–PD-1) in melanoma. *N. Engl. J. Med.* **369**, 134–144 (2013).
2. Drilon, A. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N. Engl. J. Med.* **378**, 731–739 (2018).
3. Reeder–Hayes, K. Informed consent and decision making among participants in novel-design phase I oncology trials. *J. Oncol. Pract.* **13**, e863–e873 (2017).