The Changing Nature of Phase I Trials

Lillian L. Siu
Princess Margaret Cancer Center, University of Toronto, Toronto, Ontario, Canada

Phase I clinical trials in oncology are critical for characterization of the tolerability and adverse event profiles of new anticancer agents such that a dose and schedule can be recommended for subsequent later phase evaluation. In the traditional drug development framework, phase I oncology trials focus on determining drug safety, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity. By comparison, phase II trials are designed to determine efficacy in specific tumor types, as measured by ORR, time to progression (TTP), and PFS. Phase III trials determine whether investigational regimens provide a meaningful benefit in overall survival (OS) in a randomized setting against existing standard therapy.

In the current era of genomics and immunotherapy, however, the traditional drug development paradigm has decreasing relevance for oncology research. Instead, the early stages of drug development focus on a proof of mechanism, including safety and tolerability associated with on-target and off target effects; preliminary tumor activity; and evidence of target engagement with valid pharmacodynamics biomarkers. Later-stage trials delve more deeply into the proof of concept with the exploration of predictive biomarkers; the demonstration of antitumor activity with surrogate endpoints (e.g., ORR, TTP, or PFS); and validation using a clinical endpoint (e.g., OS).

In light of the changing drug development process, the nature of phase I trials has changed substantially in recent years, with key changes in multiple areas of trial design, implementation, and interpretation (Table 2). Two of these trends—increased sample size and increased use of expansion cohorts—are explored in detail below.

**Increased Sample Size**

A recent analysis of phase I trials conducted at the Dana-Farber/Harvard Cancer Center during the 25-year period from 1988 to 2012 showed the average sample size has increased from 33.8 patients to 73.1 patients. Phase I trials with a target enrollment of 200-300 patients are now being seen. As phase I trials grow in complexity, the consequences can be substantial. The cost-per-case and regulatory burden are also increasing. With growing competition among phase I trials, the average recruitment per center has decreased. Therefore, clinical trial centers must conduct multiple studies to remain economically viable. With limited experience, centers must remain in frequent contact with study sponsors to share toxicity data by grade and frequency.

**Increased Use of Expansion Cohorts**

Samples sizes in phase I trials are often increased due to the inclusion of expansion cohorts. Bugano and colleagues recently evaluated the impact of phase I expansion cohorts on the probability of success in reaching phase II development and subsequent FDA approval. Among 133 phase I trials using expansion cohorts to evaluate 112 drugs, 64 drugs (57%) reached phase II trials and 21 drugs (19%) were subsequently FDA approved. By comparison, among 400 trials that did not include expansion cohorts to evaluate 269 drugs, 102 drugs (38%) reached phase II development, and 13 drugs (3%) were FDA approved. Overall, the probability of drug approval within 5 years increased more than 4-fold in the setting of phase I expansion cohorts (HR, 4.4; P < 0.0001). Furthermore, in a multivariate analysis, having a larger expansion cohort (>20 patients) predicted a significant 6-fold increase in the probability of drug approval (HR, 6.6; P < 0.0001), whereas a smaller expansion cohort (≤20 patients) did not significantly influence the likelihood of drug approval (OR, 2.1; P = 0.14).

Another recent review examined the use of expansion cohorts in 611 phase I cancer trials conducted between 2006 and 2011. During this period, the prevalence of expansion cohorts increased more than 3-fold from 12% in 2006 to 39% in 2011. Phase I studies that incorporated expansion cohorts were more likely to evaluate non-cytotoxic agents such as targeted therapies (OR, 2.0) and were more likely to be multicenter (OR, 1.8) and sponsored by industry (OR, 1.6). The mostly commonly cited objec-
tives of expansion cohorts were to examine safety (80%), efficacy (45%), pharmacokinetics (28%), and patient enrichment (14%). Among expansion cohorts evaluating safety, 54% identified new treatment-emergent toxicities, and 14% modified the maximum-tolerated dose.

**Summary**

Changes in phase I trials have evolved as the knowledge of molecular biology accumulates and as molecularly targeted and immuno-oncology agents have become important parts of the oncology therapeutic armamentarium. Furthermore, because patient and infrastructure resources are limited, the need to accelerate the drug development process to bring active compounds to the clinic has also fueled these changes. Regardless of the changing landscape in phase I clinical trials, the guiding principle of ensuring patient safety must be maintained. Regular communications among trial sponsors and participants are crucial to ensure an ongoing exchange of new information as it arises during study conduct.

**Financial Disclosures**

Dr. Siu discloses the following financial relationships: **Consultant/advisory role**: Boehringer-Ingelheim (uncompensated), Regeneron (uncompensated), Merck (uncompensated), and Novartis (compensated – Institution. **Research Funding**: Novartis, Bristol-Myers Squibb, Pfizer, Boehringer-Ingelheim, Regeneron, GlaxoSmithKline, Roche, Karyopharm, AstraZeneca, Merck, and Celgene. **Ownership interests**: Agios (spouse) and Entremed (spouse).

**Acknowledgements**

This summary was created from the proceedings of the 2015 Chabner Colloquium: Collaboration in Clinical Trials, which was held on Monday, October 26, 2015, in Boston, MA. The Society for Translational Oncology received educational grants in support of this activity from AbbVie Inc., Chugai Academy for Advanced Oncology (CHAAO), Epizyme, Inc., Incyte Corporation, Lilly USA, LLC, Merrimack Pharmaceuticals, Inc., Novartis Pharmaceuticals Corporation, Otsuka America Pharmaceutical, Inc., and Pfizer Inc.

**References**

