From the Editor

Phase I Testing: 60 Years in the Making

This *CCR Focus* had its genesis in a workshop cosponsored by the FDA and the American Association for Cancer Research that was held in May 2015. The participants were inspired by the discussion of new ideas for early-phase drug testing, and hopeful that appropriate dosing for new molecular entities could be better identified. This *CCR Focus*, with Guest Editors Pasi Jänne and Amy McKee, looks at new approaches for optimizing the dosing of anticancer agents. The need to address the issue of appropriate dosing is underscored by the high rates of discontinuation in several recent registration studies that supported FDA approvals. This meant that for several of the 30 kinase inhibitors approved by the FDA, much work remained to determine the optimal dosing. Thus, the FDA posed the question of how to gain accurate, safe, and effective dosing information as early as possible. The challenge, of course, is how to accomplish this with our current phase I approach, which, although it has served physicians and patients well, is in need of some revamping. The size and complexity of our 60-year-old clinical trial system has made it somewhat less flexible than many would like, which explains why a description of phase I and II trials written by Farber and colleagues (1) 60 years ago still applies:

> *Two somewhat different forms of clinical investigation in cancer chemotherapy may be defined. The first concerns the primary explorative phase of research with a new chemical compound which has been studied previously with great care for toxicity, microbiological, and anticancer properties in laboratory systems and, ideally, for leads concerning mechanism of action, distribution, fate, metabolism, and excretion. In carefully selected patients who have failed to respond to all other forms of therapy, such new material may be administered with caution for the determination of the effective dose level and for observation of possible carcinolytic and carcinostatic properties. The new agents should be tried in such studies against as many different kinds of cancer in man, and in as many different situations within any one form of cancer as possible before a conclusion is reached concerning its probable value.*
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> *A second type of clinical investigation is of value when leads concerning carcinolytic activity of a compound are uncovered by the first kind of study. Now, the special virtues of uniform conditions, carefully defined criteria for selection of patients, and administration of a compound under identical conditions, and from the same batch, are required. In this plan a number of institutions may band together and pool their resources for the detailed study and evaluation of a carcinolytic agent under as ideal conditions as possible.*[1]

The goals and methods for phase I testing were well codified by the mid-1970s (2, 3). It is notable that many of today's challenges were identifiable even 40 years ago when the FDA sponsored a workshop in 1975 to address clinical trial design (4, 5). Making clinical advances while protecting and helping patients was always going to be complicated. But innovations are possible and that is what this *CCR Focus* is about: improving methods of dose finding, while preserving that most important goal—patient safety.

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See all articles in this *CCR Focus* section, "New Approaches for Optimizing Dosing of Anticancer Agents."

References

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[1]Excerpt reprinted from ref. 1: *Advances in Cancer Research*, Vol. 4, Farber S, Pinkel D, Sears EM, Toch R. Advances in chemotherapy of cancer in man, 1–71, ©1956, with permission from Elsevier.

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