Contents

From the editor

Phase II Trial Design: Still Seeking Nirvana

This issue of *CCR Focus* with Guest Editors Alex Adjei, Michaele Christian, and Percy Ivy considers the methods by which anticancer drug development proceeds in the Phase II setting and advocates for systematic new approaches at multiple levels. From the vantage point of the overview, the guest editors argue forcefully that we need to improve our phase II clinical trial design so that the outcome of these trials is more predictive of success in Phase III. A number of Phase III trials incorporating novel agents have unfortunately shown no benefit with inclusion of the novel agent. As this goes to press, a Phase III trial incorporating cetuximab with capecitabine, oxaliplatin, and bevacizumab in metastatic colorectal cancer has been reported and, like too many phase III trials before it, the experimental arm is not better than the standard therapy (NEJM 360:563–572, 2009). In this case the experimental arm is, in fact, worse. The cancer community can ill afford to accept such outcomes given the time, energy, and money that is represented in a 755-patient Phase III multicenter trial.

Experts in drug development, the authors in this issue of *CCR Focus* tackle the question of how the predictive power of our Phase II trials might be improved. Two underlying suppositions could be debated. One is that the era of cytotoxic therapies has been superseded by the era of targeted therapies. The second is that targeted therapies are distinct from conventional, cytotoxic therapies because their activity is much more difficult to assess and may not show response. At the risk of appearing reactionary, it could be argued that the best targeted therapies have led to measurable response (Clin Cancer Res 13:7247–7288, 2007). The new endpoints being explored serve as surrogates for response. It could also be noted that measuring clinical trial outcome is no more difficult in this era than it has been in the past. The WHO criteria were introduced in 1979 in order to standardize response assessment; and the RECIST criteria were introduced in 1998 to address problems with the WHO criteria and to again standardize methods. A 2009 version, RECIST 1.1, that seeks to further simplify and optimize methodology, has just been reported (Eur J Cancer 45:225–310, 2009). Thus, targeted therapies have not brought us a new problem in measuring anticancer efficacy. Rather, they have illuminated the point that our measures of success are still insufficient.

This parsing aside, the expert authors in this issue of *CCR Focus* examine multiple strategies that could make Phase II trials better. Dhani et al. review and propose alternate endpoints including response assessment as a continuous variable; Shankar et al. urge the inclusion of new imaging tools such as FDG-PET; McShane et al. discuss the appropriate use of biomarkers in Phase II trials; and Rubenstein et al. explain the utility of different trial designs. Together, the articles in this issue of *CCR Focus* offer important insights into the task before us. As with every issue, it is our hope to inform and interest both the expert in the field and the concerned but non-expert observer. In this case, it is our hope that we can provoke real change in how we design and interpret Phase II trials.

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Clin Cancer Res 2009;15:1865.