Biomarkers In Early Clinical Trials: the Committed and the Skeptics

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Disclosure of Potential Conflicts of Interest

P. Workman has licensed intellectual property to Vernalis and Novartis. S. Kaye is a member of the AstraZeneca Advisory Board.

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To the Editors: The article by Goulart et al. (1) and the provocative accompanying editorial by Ratain and Glassman (2) raise important issues. We would like to respectfully take issue with some of the conclusions.

First, the quantitative effect of publication bias in phase I trials with negative pharmacodynamic studies is difficult to determine. Moreover, the lack of analytic validation of the assays used is often limiting. Validated biomarkers are key to affecting decision-making but cannot replace toxicity and pharmacokinetic studies. Nonetheless, target blockade in tumors using validated assays provides robust foundations for future drug development (3).

Ratain and Glassman also raise concerns about biomarker costs. An additional $6,675 per phase I patient seems to be a good value compared with the quoted billion dollars per drug overall. Indeed, the potential cost of suboptimal dosing schedules being taken forward merits such an investment and may reduce expensive late attrition (4), which may reflect the underutilization of pharmacodynamic biomarkers in early clinical trials. In our experience, biomarkers have an important role in phase I trials and we would highlight two examples of work done at our institution: (*a*) the successful use of biomarkers for patient selection in a study with the poly-ADP ribose polymerase inhibitor KU-0059436 leading to responses in individuals with BRCA mutations (5), and (*b*) the application of biomarkers of target inhibition helping to lead dose escalation of the heat shock protein inhibitor 90 (HSP90) 17-allylamino-17-demethoxygeldanamycin (6).

Finally, Ratain and Glassman argue that performing tumor biopsies poses an increased risk that may be unethical. There is little evidence that such biopsies pose an increased risk (7). We endorse the use of tumor biopsies at dose levels that satisfy predetermined pharmacokinetic variables and where target inhibition in surrogate tissue is demonstrable. Indeed, conversely failing to obtain such key tumor biopsy information from patients while putting them through a phase I trial could be deemed unethical.

Overall, the fact that only 503 of 2,458 (20%) analyzed American Society of Clinical Oncology abstracts used at least one biomarker represents an improvement over previous audits. Reduced enthusiasm to use biomarkers at this point could lead to an increase in the taking forward of a number of ineffective drugs or effective drugs using suboptimal schedules, increasing failure rates and costs. In an era in which health economics will dictate the availability of new and expensive agents, robust biomarkers for dose, schedule, and patient selection must remain an important priority.

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