Trial watch

TRIAL AND ERROR

Why is it that so many drugs fail at phase III? Could this failure rate be reduced by changing the design of phase II trials? This question has been addressed by Mark Ratain and colleagues in a recent publication in the *Journal of the National Cancer Institute*.

Phase II trials generally assess whether a new drug or treatment regimen has sufficient efficacy to warrant further trials. These trials are normally single-arm trials for which the primary outcome is complete or partial response in patients with solid tumours as assessed by RECIST (response evaluation criteria in solid tumours) guidelines. Although this might effectively select against non-efficacious drugs, it does not indicate whether a treatment should continue into a phase III trial.

So, when designing a phase II trial of the tyrosine kinase inhibitors sorafenib and erlotinib in patients with non-small-cell lung cancer, the primary endpoint chosen was changes in tumour size treated as a continuous variable instead of categorized changes in tumour size. Although randomized phase II trials are often avoided because of the number of patients needed, using changes in tumour size as a continuous variable reduces patient numbers. The size of the trial was determined by examining four previous trials with these agents and making assumptions about the likely effect of the drugs and the variability in the changes in tumour size. The resulting trial design consisted of three treatment groups (150 mg erlotinib daily with placebo; 150 mg erlotinib daily with 200 mg sorafenib twice daily; and 150 mg erlotinib daily with 400 mg sorafenib twice daily) with 50 patients in each group.

The authors conclude that treating tumour size as a continuous variable rather than categorizing the changes, along with the placebo control group, should give more useful information than a standard single-arm phase II trial.

ORIGINAL RESEARCH PAPER Karrison, T. G., Maitland, M. L., Stadler, W. M. & Ratain, M. J. Design of phase II cancer trials using a continuous endpoint of change in tumor size: application to a study of sorafenib and erlotinib in non-small-cell lung cancer. *J. Natl Cancer Inst.* **99**, 1455–1461 (2007)

ALL OR NOTHING?

Callisto Pharmaceuticals, Inc. has completed enrolment ahead of schedule of 40 patients to its phase II clinical trial of atiprimod, a new drug to treat low- to intermediate-grade neuroendocrine carcinoma (carcinoid cancer).

What makes this small molecule interesting is that it has multiple targets and its mechanism of action is unclear. It can inhibit the secretion of vascular endothelial growth factor and interleukin 6, suppress tumour angiogenesis, induce apoptosis and inhibit phosphorylation of Akt and signal transducer and activator of transcription 3 (STAT 3). Because this trial was initiated in November 2006, some patients in the trial have been taking atiprimod, an orally bioavailable small molecule, for 11 months and most will have been given the drug for 6 months by January of next year.

WEB SITES http://www.callistopharma.com/ | http://www.clinicaltrials.gov/