ICON-6: the danger of changing study design midstream

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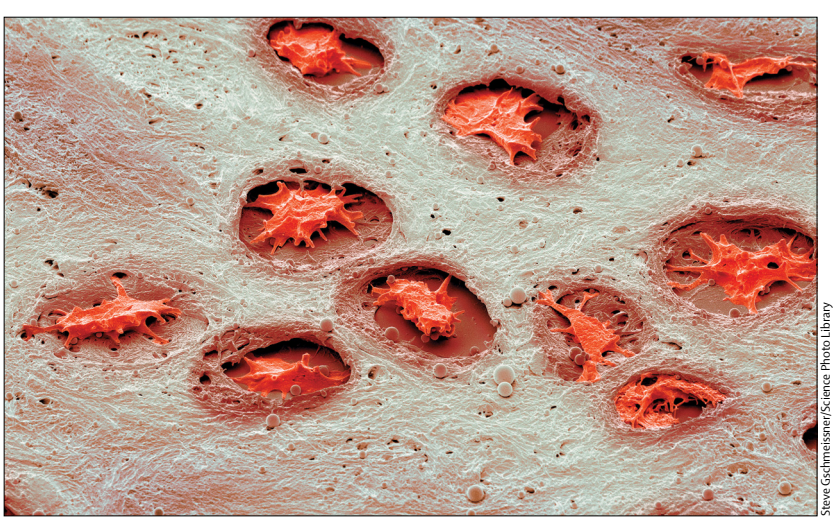
Jonathan Ledermann and colleagues[1,2] report the ICON-6 randomised trial findings for the tyrosine kinase inhibitor cediranib in relapsed platinum-sensitive ovarian cancer. Cediranib offered the prospect of improved efficacy with tolerable side-effects, and ICON-6 was a pragmatic trial to provide real-world evidence of the effectiveness, safety, and acceptability of cediranib plus chemotherapy (either concurrent or concurrent plus maintenance as long as patients were deriving benefit), compared with chemotherapy plus placebo. ICON-6 found "meaningful improvement in progression free survival"[2] (hazard ratio 0·56, 95% CI 0·44–0·72) for concomitant plus maintenance cediranib compared with placebo, as well as significantly more diarrhoea, hypothyroidism, and voice changes. However, after unexpected and major design changes were enforced, we still await data for overall survival; the safety data are less informative than might be necessary, and there are no convincing data yet for patient acceptability and quality of life, which can be particularly relevant to inform trade-offs between improved efficacy and increased side-effects. These design changes should not have been necessary, and clinical trials should be better structured to make sure this does not recur.

The original study design promised more reliable evidence, but instead of randomly assigning roughly 2000 participants, the study underwent a major revision with just 387 participants randomly assigned because the drug company involved (AstraZeneca) decided (on Sept 14, 2011) to cease commercial development of cediranib, owing to negative findings for overall survival in three pivotal phase 3 studies on different cancers.[3–5] With insufficient remaining drug stock and its short shelf life, as well as AstraZeneca being unwilling to manufacture additional supplies, a fundamental redesign (or complete abandonment) became necessary.

The researchers, in partnership with the independent Data Monitoring Committee (iDMC), and the funders should be congratulated on having the vision and creativity to redesign the study, within the constraints of the remaining drug available. They redefined the primary outcome from overall survival to progression-free survival, focused on comparing concomitant plus maintenance cediranib with placebo, and reduced power from 90% to 80%, with overall survival, toxic effects, and quality of life becoming secondary outcomes. This change meant that a revised sample size of 440 patients (for those on cediranib, 20 mg after the initial 30 mg dose was dropped) was used. The study finally randomly assigned 486 patients, of whom 456 receiving the 20 mg dose were analysed.

Designing and executing large multinational trials is challenging, with many stakeholders (patients, clinicians, funders, regulators, ethics committee members, drug companies, health-care providers) to accommodate and many reasons for why a study might not be completed as planned (stopping early for safety, efficacy, or so-called futility reasons). Over the past few decades, statistical methods for sequential[6] and Bayesian designs[7] and more recently a plethora of innovative adaptive designs,[8] coupled with improved remits and increased experience within iDMCs, and funders looking for better and more efficient designs, have allowed clinical trialists to deliver more efficient and responsive clinical trials. So there are many legitimate reasons to redesign or terminate trials on scientific grounds, and well established statistical methods to achieve this in an orderly fashion. However, having to terminate or majorly redesign a trial because a stakeholder decides to cease manufacturing the relevant drug is not, in our view, a legitimate reason—from a scientific perspective insight is lost into that compound and mechanism of action, and we are letting down participants who agree to take part in research by allowing this to happen. When trials are redesigned midstream, there are ethical challenges in consenting future participants, and also potentially re-consenting those recruited under the



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original process of informed consent, to make sure the participants are properly aware of the reasons for the redesign and the scientific value of the new study. Here, the redesign was driven by the cessation of manufacture of the drug, but likewise a public funder might withdraw support for a study midstream due to a change in policy or a re-assessment of the evidence value for the health-care system. Often, it is just as valuable to know with good precision that an intervention doesn't work, particularly if it is expensive or associated with considerable side-effects.

Most importantly, we must do everything we can as clinical trialists to reassure the patients and the public that their participation is always considered with the utmost care and constant vigilance around the emerging risk–benefit ratio, and never taken for granted. To get patients to participate in research is already challenging, and we are too permissive of stakeholders changing their minds midstream. This issue could be avoided by requiring all stakeholders to commit to seeing the study through, backed by the required resources to complete this study (and with adequate insurance cover for the case of commercial failure), with subsequent changes to design only occurring through agreed scientific criteria mediated through appropriate statistical procedures. We owe participants this protection to properly safeguard their contribution, as well as improving the scientific yield of our trials.

Interestingly, after the initial conference presentation[1] of the potentially positive findings in 2013, and more recent promising early phase findings,[9] interest from AstraZeneca appears to have been rekindled, and after company review of the outcomes and survival methods, the possibility now exists of using these data for regulatory submission. However, these data will obviously be less convincing for that purpose than if the trial had continued under its original design—in terms of evidence of effectiveness, safety, and acceptability. It appears to us that now this situation has been fully played out, no one has gained any advantage from the 2011 decision to stop manufacturing cediranib. We should try hard to make sure—particularly for the sake of patients—that this type of avoidable problem isn't allowed to happen again.

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I declare no competing interests.

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Primary progressive multiple sclerosis—why we are failing

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In *The Lancet*, Fred Lublin and colleagues[1] report negative results of a randomised, double-blind trial (INFORMS) assessing the efficacy of fingolimod, an oral sphingosine 1-phosphate receptor (S1PR) modulator, on disability progression in patients with primary progressive multiple sclerosis. This result is particularly disappointing because no US Food and Drug Administration (FDA)-approved disease-modifying therapies exist for primary progressive multiple sclerosis at present. In contrast to drastic advances during the past 20 years in treatment of relapsing multiple sclerosis, the number of unsuccessful studies in primary progressive multiple sclerosis is substantial. This poor record reflects the fact that the cellular and molecular mechanisms underlying clinical progression in multiple sclerosis are poorly understood.