

e. To determine the maximal tolerable dose

A run-in period can take the form of a Phase I clinical trial, with a first group of study subjects, where a subsequent Phase II trial uses a totally different group of study subjects. The goal of this sort of study design is to determine the safety profile of the study drug. In a study of lung cancer, Heymach et al. (16) used a run-in period on a small group of subjects in order to determine the safety profile of two different doses of study drug, that is, 200 mg vandetanib in combination with paclitaxel and carboplatin (PC), or 300 mg vandetanib in combination with paclitaxel and carboplatin (PC). Only 25 subjects in all were used for this run-in period. The results from the run-in study demonstrated that the higher dose was well tolerated. According to the authors, “[t]he primary objective of the run-in phase was to establish the appropriate dose of vandetanib to be administered with PC.” PC means the combination of paclitaxel and carboplatin. These 25 subjects were not included in the subsequent, larger clinical trial of 181 subjects (17). Following the run-in study, 181 different subjects were enrolled in a randomized placebo-controlled clinical trial, where the higher dose of vandetanib was used. The results from the 25-subject run-in period were separately published (18).

f. To achieve and ensure steady state in vivo concentrations of study drug

A run-in period can establish that steady state concentrations of the study drug are achieved, as well as to ensure that steady state concentrations of metabolites of the study drug are achieved. In addition, the run-in period can be used as an opportunity for assessing pharmacokinetic (PK) properties of the study drug.

In a study of head and neck cancer, using the combination of erlotinib and cisplatin (19) a run-in period was used where erlotinib only was administered to all study subjects. Erlotinib was administered on a continuous daily schedule. For cycle 1 only, erlotinib was taken alone for the first 7 days as a run-in period, to enable a steady state concentration to be reached at the time of cisplatin dosing. After the run-in period, dosing of erlotinib was continued on a daily schedule, with cisplatin given intravenously on

¹⁶ Heymach JV, Paz-Ares L, Braud FD, et al. Randomized phase II study of vandetanib alone or with paclitaxel and carboplatin as first-line treatment for advanced non-small-cell lung cancer. *J Clin Oncol*. 2008;26:5407–5415.

¹⁷ Johnson BE, Sallaway DL. E-mail of August 16, 2010.

¹⁸ Heymach JV, West H, Kerr R, et al. ZD6474 in combination with carboplatin and paclitaxel as first-line treatment in patients with NSCLC: results of the run-in phase of a two-part randomized phase II study (Abstract). *Lung Cancer*. 2005;49(Suppl. 2):S247.

¹⁹ Siu LL, Soulieres D, Chen EX, et al. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital Phase II Consortium and National Cancer Institute of Canada Clinical Trials Group Study. *J Clin Oncol*. 2007;25:2178–2183.