Financial Concerns Prompt Sponsoring Pharmaceutical Company to Halt International Phase I Studies

We would like to bring to your attention an issue that we believe will be of interest to investigators conducting industry-supported studies of new anticancer agents.

Four academic centers in the United States, Canada, the United Kingdom, and The Netherlands were recently performing a series of linked phase I studies of a cell differentiation compound. These studies were stopped without warning by the sponsoring multinational pharmaceutical company. The decision to prematurely close the project was made by the company's portfolio management board and was presumably based on financial concerns. At the time of closure, all studies were proceeding as planned, and there were no issues of safety.

The direct results of this decision were as follows: 1) patients who had already entered the study were denied the opportunity of contributing to a research project that would have a definite conclusion; and 2) investigators and research staff in both academia and industry were left stranded with incomplete studies despite both channelling substantial resources into this project and investing a substantial amount of work into it.

We would like to suggest that, in the future, investigators negotiating contracts with pharmaceutical companies should consider contracts that implement provisions for premature unilateral closures with caution. If a contract states that a project can be closed for other than medical reasons, it should be explicit that premature termination will only be permitted with full agreement of both parties.

We would like to encourage pharmaceutical companies with concerns about their financial capability not to conduct early drug studies on their own, but to work more closely with cooperative study groups.

We hope that other investigators will contribute to this debate and that contractual arrangements between investigators and pharmaceutical companies can be improved.

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Re: Detection of c-Ki-ras Mutation by PCR/RFLP Analysis and Diagnosis of Pancreatic Adenocarcinomas

We read with interest the recent report by Urban et al. (1) in the Journal. Since Almoguera et al. (2) described c-Ki-ras mutations in 21 (96%) of 22 cases of exocrine pancreatic cancer, several studies (3-11) have reported the mutation frequency to range from 70% to 100%, and some authors (14,7,8,10) have proposed that this mutation could be a diagnostic marker for exocrine pancreatic cancer. The average number of patients included in previous studies was 26. As Fearon (12) pointed out in the accompanying editorial, the difficulties in the diagnosis of exocrine pancreatic cancer warrant the investigation of novel markers. However, before accepting that c-Ki-ras mutation detection is clinically useful, several points must be borne in mind:

1) The study of Urban et al. was not adequately designed to evaluate the clinical usefulness of a diagnostic test. Most notably, the prevalence of a definitive diagnosis of exocrine pancreatic cancer was very high (12 [75%] of 16 patients in whom evaluation was possible), and the range of pancreatic cancer-related pathologic conditions was too narrow and did not represent patients who would be subject to the test in practice. Unfortunately, these limitations have not been uncommon [Table 1; (13)].

A broader diagnostic basis in the group of patients being studied is necessary. Restrictive inclusion criteria can seriously overestimate the value of a test (14). In this respect, the 92% sensitivity and the 100% specificity figures mentioned in the discussion certainly overestimate what would happen in the actual practice. The report also lacks a thorough description of the filter through which study patients passed (or did not pass) (14) during the 22 months of the study. The report failed to consider the number of patients in whom an exocrine pancreatic cancer diagnosis was considered, the reasons that eliminated such patients from inclusion in the study, and the usefulness of the test in such a broader group of patients.

2) As in other studies on c-Ki-ras mutation in exocrine pancreatic cancer, the case definition of pancreatic cancer was ambiguous; it was “based upon consensus cytologic or histologic diagnosis using standard criteria and/or surgery or autopsy findings.” Both false-positive and false-negative diagnoses should be avoided, as the studies by Lyon et al. (15), Garabrant et al. (16) and by ourselves (17) clearly indicate.

3) No thorough studies have been conducted to evaluate the reproducibility of the test result (precision) and its interpretation (observer variation). Polymerase chain reaction amplification is not always possible success ranging from 66% to 80% in...