

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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## The Seamless Approach to Drug Development in Oncology



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### **H&O** What are some drawbacks to the 3-phase approach to drug development?

**RP** A major drawback to the conventional 3-phase program is that a stop occurs at each of the phases, which can delay development of the drug. The 3-phase approach often requires that new study sites be identified and undergo orientation. Each phase usually requires extensive contract negotiations with an institutional review board. These built-in stops between phases 1, 2, and 3 can lead to a very long, drawn-out process. The main goals of a seamless drug-development paradigm are to improve efficiency of financial resources and patient resources, as well as shorten the time needed for evaluation. Reducing the time to approval is especially important for drugs that treat unmet medical needs.

### **H&O** What is the seamless approach?

**RP** The seamless design begins with a phase 1 trial. If activity is seen, then expansion cohorts are added. The expansion cohorts incorporate new protocols to focus on specific areas, including different treatment endpoints, such as overall survival or disease control rate; various aspects of treatment, such as different doses; specific diseases; and different patient populations. For example, if a trial is evaluating a drug associated with a biomarker, then an expansion cohort might enroll patients with that particular biomarker. A pediatric population could be included in an expansion cohort to more rapidly develop drugs for children. The US Food and Drug Administration (FDA) would like to see earlier initiation of pediatric studies once an active dose is defined in adults.

To date, the seamless approach has been used mostly in melanoma and lung cancer, but it could be used in a

variety of diseases. The main criterion is for a drug to show impressive activity in a single-arm, nonrandomized trial.

### **H&O** How have advances in the understanding of cancer biology modified the approach to drug development?

**RP** This new approach to drug development has arisen from an enhanced understanding of the drugs. There have been several important advances in the last decade. We are moving away from the conventional cytotoxic chemotherapy drugs developed in the past 50 years to drugs with a rationale for use based on an identified pathway or the tumor immunology. Increased understanding of the diseases and immunology is leading to a better sense of how the drugs interact with the disease. This is a major issue. We are currently seeing oncology drugs that have better activity and provide more benefit to patients. The seamless design makes sense for drugs that have the potential to be true advances in the management of a particular disease. As I mentioned in a recent blog, moving away from the conventional 3-phase development paradigm to a more seamless approach could expedite the regulatory pathway and provide earlier access to highly effective drugs.

### **H&O** How common is this approach?

**RP** Overall, there are more than 40 active commercial investigational new drug applications for large, first-in-human oncology trials that are using the seamless strategy. In contrast to traditional phase 1 trials, these newer trials might be designed with expansion cohorts that assess efficacy in a variety of tumor types or molecularly defined

subsets. The investigators may intend to use the data to support FDA approval of the drug.

Patients are expressing great interest in enrollment in these trials. Usually, the demand for these clinical trials exceeds their capacity for enrollment because it is anticipated that the drugs will have a major impact.

### H&O Are there examples in oncology of a drug developed in this way?

**RP** In oncology, a good example of the seamless approach involves the monoclonal antibody pembrolizumab (Keytruda, Merck). Early data from the first-in-human KEYNOTE-001 trial (Study of Pembrolizumab [MK-3475] in Participants With Progressive Locally Advanced or Metastatic Carcinoma, Melanoma, or Non-Small Cell Lung Carcinoma) showed impressive response rates and durations of response, particularly in patients with metastatic melanoma and non-small cell lung cancer (NSCLC). These findings led investigators to rapidly increase the sample size. Expansion cohorts were added to evaluate efficacy in patients with metastatic melanoma or NSCLC, and to assess dosing regimens and predictive biomarkers. More than 1200 patients were ultimately enrolled in the trial. Three years after initiation of this trial, data from a cohort of 173 patients with melanoma were used to support accelerated approval of pembrolizumab in this setting. Subsequent data from this trial also led to accelerated approval of pembrolizumab in NSCLC, as well as to the approval of a companion diagnostic test for expression of programmed death-ligand 1.

### H&O What are the challenges in implementing seamless expansion cohort trials?

**RP** The built-in stops in the conventional 3-phase design allowed time for adequate communication, and to develop and vet a statistical plan. Missing from the seamless design are built-in stops after the completion of each phase. There must be a high degree of interaction among the sponsors, the clinical investigators, the FDA, and the institutional review board. A formal pattern of communication should be instituted by the commercial sponsor. There must also be well-designed statistical plans for each of the cohorts to calibrate enrollment of appropriate numbers of patients to address the questions raised by the study. These are not insurmountable problems, and they must be addressed to ensure patient protection.

### H&O What is the role of an independent data and safety monitoring committee?

**RP** The focus of an independent data and safety monitoring committee has been on safety signals. Standard ran-

domized clinical trials typically enroll hundreds or even thousands of patients. A study is stopped early if predetermined safety parameters are crossed, even by drugs that are very effective. The seamless clinical trials are also enrolling large numbers of patients. There should be some external oversight of these trials to ensure assessment of safety and efficacy at preplanned points throughout a drug's development. In a trial employing multiple expansion cohorts, an independent data and safety monitoring committee could review safety and efficacy data at predefined intervals, advise investigators regarding the addition or termination of cohorts, provide external transparency, and ensure the trial's statistical validity.

### H&O How might the approach to drug development continue to evolve?

**RP** The FDA is encouraging pharmaceutical companies to look at other areas of clinical trial design under the Cancer Moonshot initiative. It may be possible to modify the eligibility criteria to expand the number of patients who qualify for a study, thereby expanding opportunities for participation. Trials could share a common control arm, even if they are evaluating multiple drugs for the same indication. A common control arm could decrease the number of patients needed for enrollment, optimizing trial resources and potentially reducing the time needed to start the study. Trials that use easily measured endpoints and optimize the collection of data for safety or secondary efficacy endpoints could reduce the amount of required data compared with conventional randomized trials.

#### Disclosure

*Dr Pazdur has no conflicts of interest to report.*

#### Suggested Readings

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