

Expansion Cohorts in First-in-Human Solid Tumor Oncology Trials

Marc R. Theoret, Lee H. Pai-Scherf, Meredith K. Chuk, Tatiana M. Prowell, Sanjeeve Balasubramaniam, Tamy Kim, Geoffrey Kim, Paul G. Kluetz, Patricia Keegan, and Richard Pazdur

Abstract

In 1962, the passage of the Kefauver–Harris Amendment to the 1938 Food, Drug, and Cosmetic Act required that sponsors seeking approval of new drugs demonstrate the drug's efficacy, in addition to its safety, through a formal process that includes "adequate and well-controlled" clinical trials as the basis to support claims of effectiveness. As a result of this amendment, FDA formalized in regulation the definitions of various phases of clinical investigations (i.e., phase I, phase II, and phase III). The clinical drug development paradigm for anticancer drugs intended to support marketing approval has historically followed this "phased" approach with sequential, stand-alone trials, with an increasing number of patients exposed to an investigational drug with each trial in order to fulfill the objectives of that particular stage in development. Increasingly,

it is the Office of Hematology and Oncology Products' experience that commercial sponsors of solid tumor oncology drug development programs are amending ongoing phase I trials to add expansion cohorts designed to evaluate study objectives typical of later-phase trials. For investigational anticancer drugs that demonstrate preliminary clinical evidence of substantial antitumor activity early in clinical testing, use of expansion cohorts as a component of the solid tumor oncology drug development pathway, with appropriate measures to mitigate the risks of this approach, may fit in well with the goals and concepts described by FDA's expedited programs for serious conditions. *Clin Cancer Res*; 21(20); 4545–51. ©2015 AACR.

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Introduction

First-in-human (FIH) solid tumor oncology trials are using expansion cohorts with increasing frequency to serve specific aspects of the drug development program (1). This phenomenon may be driven by greater scientific understanding of molecular derangements in cancer and contemporary investigational drugs that effectively disrupt important molecular derangements in cancer cells or that restore host immune defenses impaired by progressive cancer, potentially translating to clinically important antitumor activity early in clinical trials, often across multiple tumor types (2–4). Recently, sample sizes of expansion cohorts in FIH trials have surpassed 100 patients, with total sample sizes of individual "phase I" trials exceeding 1,000 patients in a limited number of cases. Use of trial nomenclature that categorizes a 1,000 patient protocol as a phase I trial fails to capture the complexity of the evolving objectives of these large expansion cohort trials. This is not a simple matter of semantics, as the infrastructure, data requirements, and monitoring for a traditional 20 to 80 patient phase I trial will be quite different from those for a larger trial intended for FDA submission to support safety and efficacy in a marketing application. Indeed, a single FIH trial

with multiple expansion cohorts evaluating an investigational drug with a large magnitude of a treatment effect (e.g., durable objective response rates) could, in selected cases, serve as the entire clinical drug development program capable of supporting initial marketing approval in patients with cancer and high unmet medical need. The addition of new expansion cohorts by amending ongoing FIH solid tumor oncology clinical trials in order to address new drug development objectives, typically evaluated in stand-alone trials, offers a potential pathway to expedite drug development. At the same time, this strategy poses challenges and potential risks that must be addressed by all stakeholders—commercial sponsors, patients, clinical researchers, institutional review boards, and regulators.

In this article, we provide a perspective on the evolving use of expansion cohorts in FIH trials in oncology drug development programs and discuss some of the factors to consider when using large expansion cohorts as a component of early oncology drug development. Although the focus of this perspective is on FIH trials, considerations would be similar for early clinical development programs where there is prior human experience, such as initial trials evaluating an investigational anticancer drug for use in combination with another investigational drug or FDA-approved anticancer drug.

Office of Hematology and Oncology Products (OHOP), Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland.

Corresponding Author: Marc R. Theoret, U.S. Food and Drug Administration Building 22, Room 2165, 10903 New Hampshire Avenue, Silver Spring, MD 20993. Phone: 301-796-4099; Fax: 301-796-9845; E-mail: Marc.Theoret@fda.hhs.gov

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Increasing Use of Expansion Cohorts in FIH Trials

The clinical drug development paradigm for anticancer drugs intended to support marketing approval has traditionally relied upon sequential trials (e.g., phase I, phase II, and phase III), with an increasing number of patients exposed to an investigational drug with each trial in order to fulfill the objectives of that

particular stage in development (Fig. 1A). Although a review of the typical goals and objectives sought at each stage of drug development to generate the evidence required to support initial marketing approval is beyond the scope of this publication, at a high level, there are often multiple objectives within each phase. FIH trials, denoted as phase I trials, are typically designed with the goals of assessing initial safety and dose tolerance of a specific dose and schedule of administration as well as delineating pharmacokinetics (PK) and pharmacodynamics (PD) parameters of that dosage regimen (5, 6). With the identification of dose-limiting toxicities, initial PK and PD, and a preliminary safe and tolerable dosage in the phase I trial, drug development programs proceed with exploratory therapeutic trials (phase II) to estimate the antitumor activity of an investigational drug in one or more tumor types while further characterizing the safety profile, and, in some cases, refining the dose or schedule of administration. Therapeutic confirmatory trials (phase III) are generally randomized, active- or placebo-controlled trials designed to demonstrate substantial evidence of the safety and effectiveness of the anticancer drug to support marketing approval. Goals of postmarketing trials, as required or agreed upon between the FDA and the pharmaceutical company, are tailored to the specific questions identified in the individual drug development programs and are discussed elsewhere (7).

FIH trials may include expansion cohorts with objectives separate from the initial dose-escalation portion, for example, assessment of additional PK and PD endpoints, alternative dosage regimens, toxicity characterization, product formulation development, evaluation for predictive biomarkers, and increasingly, preliminary assessment of antitumor activity. In an evaluation of published phase I dose-finding/safety and tolerability trials over a 5-year period, Manji and colleagues reported that use of expansion cohorts increased from 12% of published phase I trials in 2006 to 38% of such trials in 2011 (1). In one-third of these cases, the authors identified evaluation of efficacy as a reported objective of the expansion cohorts. Similarly, in a single institution experience over 25 years, Dahlberg and colleagues reported that the average planned sample size of a phase I trial grew from 34 patients (1988–1992) to 73 patients (2008–2012); importantly, this study further evaluated phase I trials from a single year (2011) and reported that 60% of the trials failed to provide statistical justification for the cohort sample size despite assessment of response being listed as a stated objective in 92% of the trials (8). Increasingly, it is the Office of Hematology and Oncology Products' experience that FIH trials in solid tumor oncology drug development programs are adding large expansion cohorts to estimate the efficacy of an anticancer drug, either in specific primary tumor types or in biomarker-selected populations irrespective of primary tumor origin. In fact, a review of all commercial investigational new drug applications (IND) submitted electronically to the solid tumor divisions in the Office of Hematology and Oncology Products during a 5-year period (June 2010 to May 2015) indicated that approximately 3% of FIH trials of anticancer drugs evaluated as single agents included at least one expansion cohort with a planned sample size of over 100 patients and 1% of FIH trials included a planned total sample size of over 1,000 patients. Further analyses of these trials are under way. Of particular interest is the potential for expansion cohorts in FIH trials to serve as the complete development program to demonstrate sufficient efficacy and safety in a regulatory submission to support an initial marketing approval.

FDA Expedited Programs in Oncology

There are four FDA programs to expedite the development and review of drugs and biologics intended to treat patients with serious conditions (9). Three of these programs are designations granted by FDA in response to a request by the commercial sponsor of the drug (fast track, breakthrough therapy, and priority review designation), although FDA determines whether a marketing application qualifies for priority review designation (versus standard review) even if priority review is not expressly requested. The fourth program, accelerated approval, represents a marketing approval pathway intended to provide earlier access of drugs to patients with serious conditions based on demonstration of treatment effects on a surrogate or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The criteria for each expedited program differ but, in general terms, the therapy under consideration must be intended to treat a serious condition and all expedited programs take into consideration the existing or available therapies to treat this condition (i.e., the therapeutic landscape) for the disease context in order to determine whether there is an unmet medical need, or if the new therapy appears to provide an improvement or advantage over the existing therapies. Fast track designation, the earliest designation for which a drug development program can qualify, requires that the drug demonstrate the potential to address an unmet medical need based on nonclinical or clinical data. Breakthrough therapy designation, the newest addition to FDA expedited programs, is intended for products with preliminary clinical evidence indicating that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies and is ideally granted no later than end of phase II to ensure maximal benefit of the designation. Both fast track designation and breakthrough therapy designation open up the possibility for more frequent interaction with the FDA during the development program; however, breakthrough therapy designation, which is based on the strength of the preliminary clinical evidence, prompts an organizational commitment and defined policies and procedures for intensive guidance by the FDA on development of the breakthrough therapy-designated product, including design of the clinical trial intended to support regulatory approval (10).

Example of Intersection of FDA Expedited Programs and Use of Expansion Cohorts: Case of Pembrolizumab

The initial drug development program of pembrolizumab (MK-3475; Merck Sharp & Dohme Corporation), a monoclonal antibody that binds the programmed death-1 (PD-1) receptor, is a well-known example of a breakthrough therapy-designated immunotherapeutic product evaluated in an FIH trial that utilized multiple expansion cohorts to fulfill various drug development objectives. Ultimately, this FIH trial provided evidence of safety and efficacy sufficient to support accelerated approval of pembrolizumab for a treatment-refractory melanoma population, that is, patients with unresectable or metastatic melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (11, 12).

The FIH trial for the pembrolizumab development program submitted in the initial IND in December 2010 planned to administer pembrolizumab to approximately 18 patients with melanoma or any type of refractory carcinoma in an initial

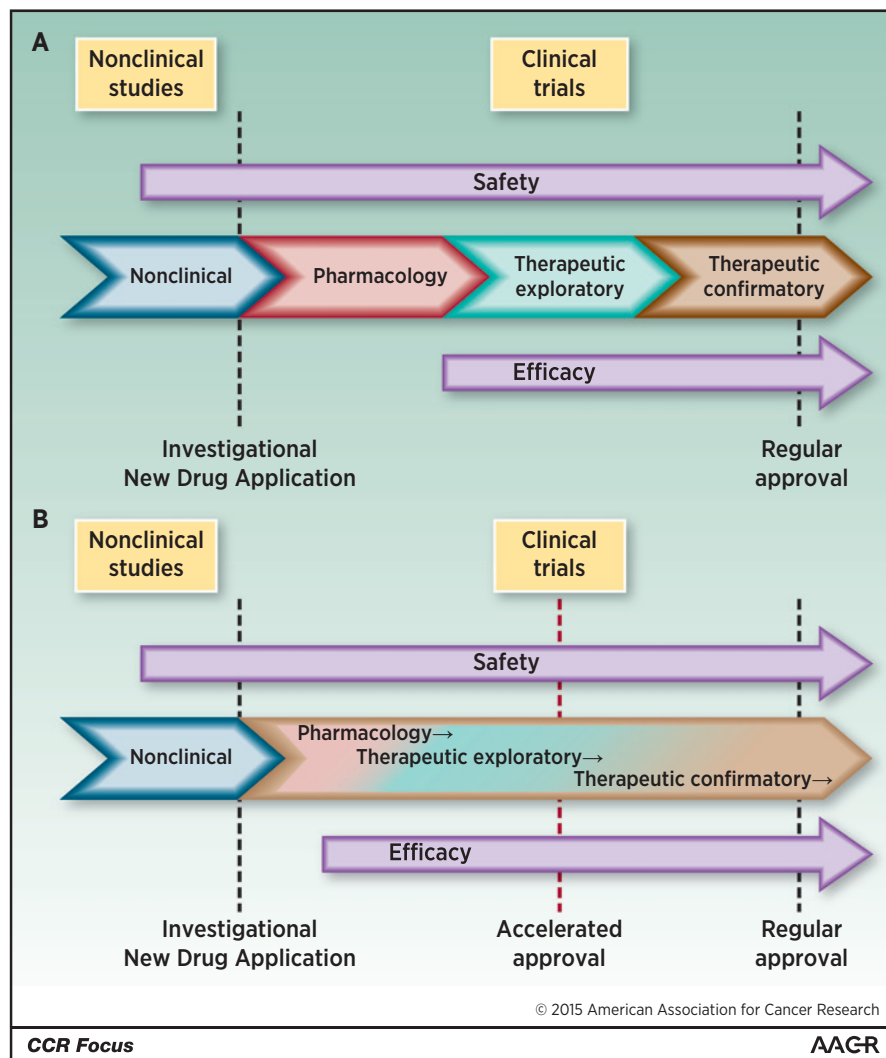


Figure 1.

Evolving drug development paradigm with investigational drugs that have substantial antitumor activity. **A**, example of a traditional drug development paradigm for investigational drugs. A clinical development program traditionally uses sequential, stand-alone studies to address objectives in a “phased” approach. Nonclinical toxicology studies of an investigational drug are submitted in the original Investigational New Drug Application (IND) to select a reasonably safe starting dose and to characterize potential target organs of toxicity to guide safety monitoring plans in human trials. Once the IND is active, human pharmacology (phase I) trials are conducted to evaluate the initial safety and tolerability of a specific dosage regimen, pharmacokinetics (PK), pharmacodynamics (PD), and potentially signals of antitumor activity, which inform the design of exploratory therapeutic trials (phase II trials). The design of phase II trials are often intended to estimate the antitumor activity of an investigational drug in one or more tumor types, further characterize the safety profile, and potentially refine the dose or dosing schedule. Informed by potential treatment effects observed in phase II, therapeutic confirmatory trials (phase III) are generally randomized, active- or placebo-controlled trials designed to demonstrate substantial evidence of the safety and effectiveness of the anticancer drug and inform the benefit–risk analysis to support marketing approval, in this example a regular approval based on treatment effects considered to be clinical benefit. Note that arrows denoting each phase indicate that additional studies meeting the objectives typical of earlier phase trials, such as additional nonclinical studies or human pharmacology trials, may be conducted later in drug development, for example, while phase III trials are ongoing, in order to support a marketing application. Although safety is assessed throughout the drug development program, efficacy is typically a primary objective of later phase trials. **B**, example of an evolving drug development paradigm utilizing an expedited clinical drug development pathway suitable for an investigational drug that demonstrates preliminary evidence of a large magnitude of antitumor activity in solid tumors in early clinical development, for example, a breakthrough therapy designated drug. In the setting of substantial antitumor activity, use of additional expansion cohorts in an ongoing trial, rather than standalone trials, that are well-designed to evaluate objectives of exploratory therapeutic trials (phase II) and, in highly selected cases, therapeutic confirmatory (phase III) trials may be conducted, with appropriate safety measures to the actual stage of development to mitigate the risks of this complex trial design. Concurrent expansion cohorts may be used to fulfill additional drug development objectives, such as those related to manufacturing processes, additional pharmacology objectives, and biomarker development. In this paradigm, safety is continually assessed as in the traditional drug development paradigm, but observation of substantial antitumor activity early in clinical development fosters an earlier evaluation of efficacy, including an evaluation of unestablished surrogate endpoints or intermediate endpoints that would support an accelerated approval while confirmatory trials are ongoing to verify or further describe the clinical benefit of the anticancer drug, that is, trials intended to support a regular approval.

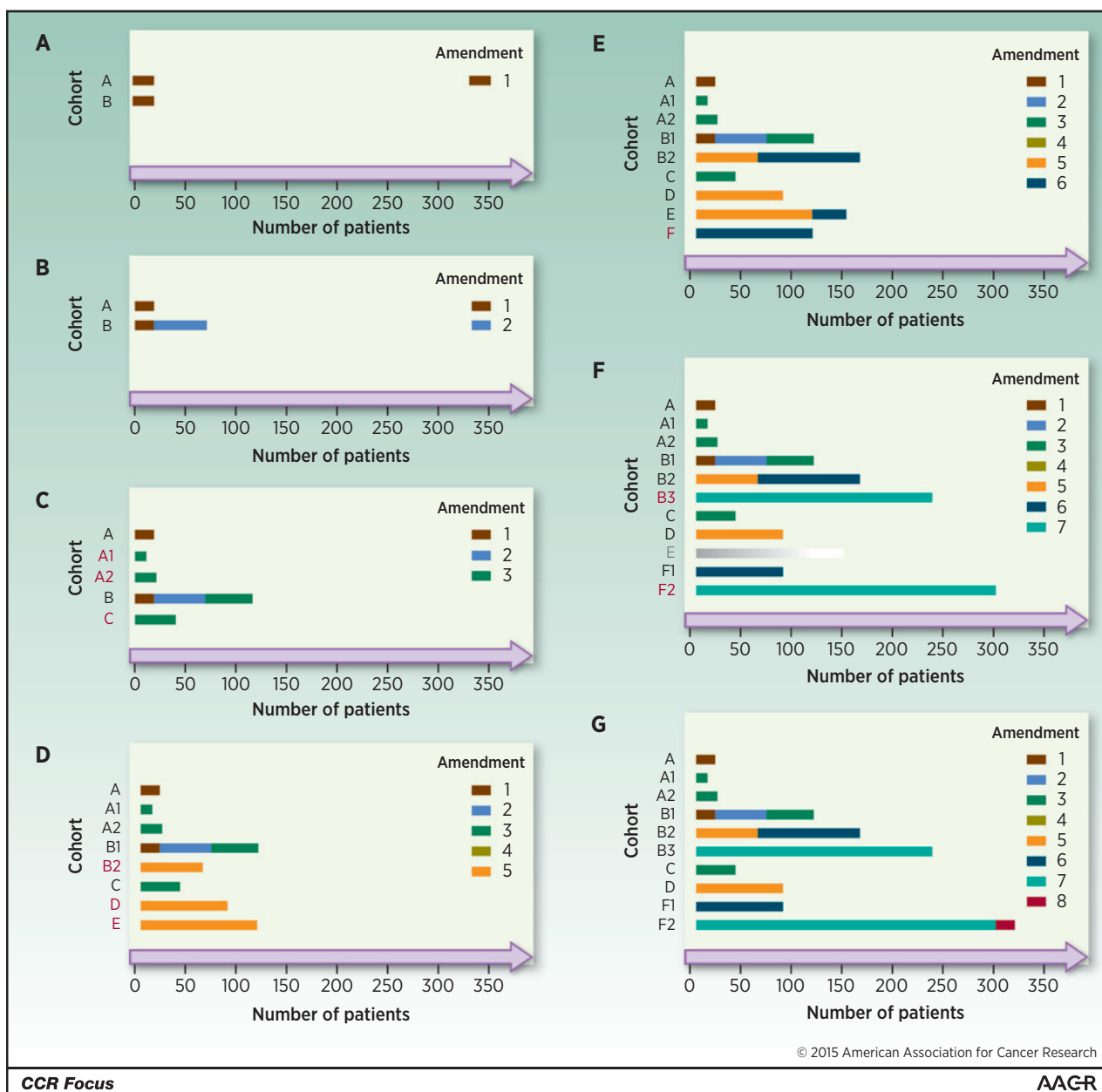


Figure 2. Description of multiple expansion cohorts and selected objectives submitted in amendments to the FIH protocol for pembrolizumab (PN001), the primary trial supporting the original marketing application and accelerated approval of pembrolizumab in treatment-refractory, unresectable or metastatic melanoma (11, 14). **A**, (Amendment 1—total sample size 32): the initial trial described in the IND planned to enroll up to 18 patients with melanoma or any type of refractory carcinoma in an initial modified “3+3” dose-escalation portion (Cohort A) evaluating three dose levels of pembrolizumab followed by cohort B with additional patients enrolled at the preliminary maximum tolerated dose (MTD) in two disease-specific expansion subcohorts (melanoma and renal cell carcinoma) of up to seven patients each to confirm the tolerability of the dose and to provide a preliminary assessment of antitumor activity. **B**, (Amendment 2—total sample size 84): revisions to cohort B to limit enrollment to patients with unresectable melanoma, to expand the selection criteria to allow prior melanoma patients to have received prior ipilimumab, and to increase the sample size from 14 to 66 patients. **C**, (Amendment 3—total sample size 179): addition of two expansion subcohorts, cohort A1 (6 patients) and cohort A2 (12 patients), to more fully characterize the pharmacokinetic (PK) expansion at MTD and to characterize PK and pharmacodynamics (PD) with intrapatient dose escalation at a different dosing schedule; revisions to cohort B to increase sample size to 116 patients in order to evaluate two dose levels and two dosing schedules of pembrolizumab in patients with unresectable melanoma, either ipilimumab naïve or ipilimumab treated; addition of cohort C to evaluate the safety and tolerability and to provide a preliminary assessment of antitumor activity in 35 patients with non-small cell lung cancer (NSCLC) after two prior systemic therapies. **D**, (Amendments 4 and 5—total sample size 439 patients): addition of three expansion cohorts, cohort B2 with 60 ipilimumab-refractory patients with melanoma randomized to receive one of two doses of pembrolizumab; cohort D with 88 ipilimumab-naïve patients with melanoma and no more than two prior systemic treatments randomized to receive pembrolizumab at one of two dose levels to characterize the tolerability and safety and preliminary evaluation of antitumor activity; and cohort E with 112 patients with NSCLC randomized to receive as first- or second-line therapy pembrolizumab at one of two dose levels in combination with a platinum doublet chemotherapy regimen or single-agent chemotherapy to characterize the safety profile in combination with a total of four different chemotherapy regimens (eight subcohorts of approximately 14 patients each), to provide a preliminary assessment of dose and antitumor activity, and to evaluate biomarker predictability of tumor reduction in patients receiving the combination regimen. (Continued on the following page.)

modified "3+3" dose-escalation portion and enroll an additional 14 patients with melanoma and renal cell cancer in two disease-specific expansion subcohorts. Over the course of 2.5 years and eight amendments, the protocol expanded to a planned accrual of approximately 1,100 patients with use of nine distinct expansion cohorts (Fig. 2). The initial cohorts served to evaluate PK, PD, safety, and tolerability, and signals of antitumor activity typical of FIH trials. Subsequent amendments incorporated objectives typically reserved for phase II trials, for example, estimations of antitumor activity and randomized comparisons of various doses and schedules—carried out in patients with melanoma and non-small cell lung cancer. Ultimately, the efficacy data from cohort B2 of this FIH trial, a multicenter, open-label, randomized (1:1), dose-comparative cohort of 173 patients with treatment-refractory, unresectable, or metastatic melanoma, demonstrated a large magnitude of antitumor activity as evidenced by objective response rates and prolonged duration of responses. The data from cohort B2, which had been prospectively designed in a protocol amendment to enroll patients with well-defined baseline disease characteristics indicative of a population with a high unmet medical need, were submitted with supporting information from expansion cohorts with long durations of follow-up in patients with unresectable or metastatic melanoma (cohorts B1 and D). Taken together, data from these three melanoma cohorts provided substantial evidence of a treatment effect that is considered reasonably likely to predict clinical benefit in the context of a favorable benefit-risk profile, that is, meeting the criteria for accelerated approval. Pembrolizumab was granted marketing approval under the accelerated approval pathway in September 2014. Additional clinical trials designed to verify and describe the clinical benefit of pembrolizumab, as required by the FDA for an accelerated approval to receive regular approval where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit or of the observed clinical benefit to ultimate outcome, were ongoing at the time of the accelerated approval. There are known challenges in accrual to such trials when a product becomes commercially available; therefore, ongoing and substantially accrued confirmatory trials are considered a strength of an accelerated approval application.

Perspective on Use of Expansion Cohorts in Drug Development

Use of expansion cohorts as a component of the drug development pathway for drugs that demonstrate preliminary clinical evidence of substantial antitumor activity in FIH trials may fit in well with the goals and concepts described by FDA's expedited

programs, such as for drugs meeting the criteria for designation as breakthrough therapy. Based on early signals of clinical antitumor activity, the design and objectives of expansion cohorts are becoming increasingly complex, with the potential to replace distinct phase I and II trials and, at the same time, to serve regulatory purposes, such as providing the preliminary clinical evidence to support requests for breakthrough therapy designation or, in exceptional circumstances, to support accelerated approval (Fig. 1B). Acknowledging these potential efficiencies, the design and conduct of large early-phase trials with multiple expansion cohorts is complicated, and these complexities must be taken into account with strategies to mitigate the potential risks to patients with this approach. Safety of patients is of paramount importance in any clinical trial, and the added potential for risks to patients enrolled in large expansion cohorts within FIH trials must be carefully considered.

Patient population considerations

Accrual to FIH oncology trials is generally limited to patients with cancer who have exhausted available therapies known to be effective for their disease. In the setting of an FIH trial of an anticancer drug that demonstrates early signals of substantial antitumor activity in one or more disease settings, the potential safety risks, both serious risks of a drug that occur at a low frequency and risks associated with cumulative toxicity, are poorly characterized based both on the limited number of patients exposed and a relatively short duration of exposure. Given these safety issues, sponsors should consider limiting accrual to initial expansion cohorts to disease types and settings where the tolerance for risk would be similar in all cohorts. Addition of expansion cohorts designed to enroll patients with less refractory disease should be justified based on the observed antitumor activity and the safety experience in patients who have received the investigational drug. In addition, comprehensive safety information should be made available in the revised protocol to the FDA, Institutional Review Boards (IRB), and other independent data monitoring bodies. As patients enrolling in this expansion cohort may be forgoing effective therapeutic options to participate in the trial, an adequate informed consent document would similarly require updates as to the risks and clinical benefits of the investigational drug, in the context of available therapies for their stage and type of disease. Frequent updates to the summary sections of the protocol, to the investigator brochure, and other communications to investigators are even more important in multicenter, FIH trials where the initial experience with an investigational drug is no longer concentrated within a single investigator group or institution.

(Continued.) **E**, (Amendment 6—total sample size 693 patients): revision to cohort B2 to increase sample size to 160 ipilimumab-refractory patients with melanoma; revisions to cohort E to increase sample size to 146 patients with NSCLC, to evaluate three dose levels of pembrolizumab as part of the combination regimen, and to limit the evaluation of the combination to first-line chemotherapy regimens; addition of cohort F with 120 patients with PD-L1 positive, nonsquamous NSCLC enrolled either to a randomized subcohort to receive one of two pembrolizumab doses (treatment-naïve patients) or to a single-arm subcohort to receive the same pembrolizumab dose (after two or more prior systemic regimens) to evaluate safety and tolerability, to provide a preliminary assessment of antitumor activity, and to evaluate biomarker correlates with antitumor activity. **F**, (Amendment 7—total sample size 1,047 patients): addition of cohort B3 with 230 patients with melanoma (irrespective of prior treatment with ipilimumab) randomized to receive pembrolizumab at one of two dosing schedules to compare the safety profile and tolerability and to evaluate the clinical activity; removal of cohort E from the protocol; and separation of cohort F into cohort F1 (treatment-naïve NSCLC) and cohort F2 (at least one prior line of systemic therapy), with addition of 270 patients with previously treated NSCLC to cohort F2, 250 PD-L1 positive patients randomized to receive pembrolizumab at one of two dosing schedules and 20 PD-L1 negative patients following at least two lines of prior systemic therapy at a single dosing schedule, to compare the safety profile and tolerability, to evaluate the clinical activity, and to assess biomarker expression levels with antitumor activity. **G**, (Amendment 8—total sample size 1067): revision to cohort F2 to increase sample size by 20 patients with previously treated (at least two lines of prior systemic therapy) PD-L1 negative NSCLC. Statistical analysis plan revised to evaluate antitumor activity of pembrolizumab to RECIST v1.1 by blinded independent central review.

Safety monitoring

Sponsors of clinical trials evaluating investigational drugs are required to monitor safety in the trials. In large, multicenter, clinical trials evaluating survival or reduction in risk of another serious health outcome, sponsors typically use additional measures to monitor safety by establishing an independent panel of experts, external to the sponsor and clinical study investigators, to oversee patient safety and ensure adequate protection is in place for participants based on the emerging safety profile of the investigational drug. For investigational drugs where use of large expansion cohorts to expedite drug development may be justified based on the preliminary clinical activity, and the clinical activity is expected across multiple tumor types, establishment of an independent panel to oversee the safety of the trial should be considered and implemented early in the design of such trials. The considerations for use of an independent panel to ensure the safety of research subjects in an FIH trial planning to enroll hundreds of patients are similar to those when establishing a data safety and monitoring committee for a trial intended to provide substantial evidence of effectiveness to support a marketing application (e.g., phase II; ref. 13).

Sample size justification

One criticism of the use of expansion cohorts concerns the frequent absence of a statistical justification in the protocol for the sample size of the cohort (8). FIH trials that use expansion cohorts should include in the protocol the scientific rationale for each existing and new expansion cohort and adequate information to justify that the planned sample size is required to achieve the specific development objectives of that cohort. For example, a protocol with an expansion cohort added to estimate the antitumor activity in a specific disease or biomarker-targeted subset should consider the statistical power and type I error in the evaluation of a treatment effect size of interest, with clear rules for termination of enrollment based on inadequate antitumor activity. In the absence of adequate justification of the sample size of the expansion cohort, additional patients could be exposed to the risks of an investigational drug, including the risk of receiving ineffective therapy, after the objectives of the cohort were met, for example, preliminary estimation of antitumor activity.

Development program

In the traditional drug development paradigm, there are pre-defined opportunities, that is, milestone meetings, for IND sponsors (e.g., pharmaceutical companies) to meet with the FDA to discuss the development program, for example, pre-IND meetings, end-of-phase I or end-of-phase II meetings, and pre-New Drug Application (NDA) or pre-Biologics License Applications (BLA) meetings. Although the goals of each meeting are tailored to address the questions posed by the IND sponsor, the milestone meetings also provide an opportunity for FDA to provide assistance with the evaluation of the development program, the identification of solutions to emerging scientific challenges associated with the investigational drug, and the challenges posed by an evolving treatment landscape. In an evolving drug development paradigm where traditional milestones may no longer be marked by submission of new, stand-alone protocols (i.e., phase I, phase II, and phase III), there is an increased risk of development programs that inadequately characterize the drug from a manufacturing perspective. Furthermore, development plans may be inadequate to support a proposed dose or schedule, fail to

identify an appropriate patient population, or lack sufficient external independent oversight in safety and efficacy monitoring of the trial. IND sponsors are encouraged to obtain feedback from the FDA early in the planning stage of any major cohort expansion to assist with a safe and efficient drug development process. Use of expansion cohorts as an expedited approach to drug development intended for initial approval should prompt similar types of meetings between IND sponsors and the FDA at critical development time points, as have historically occurred in more traditional, "phased" drug development plans.

Conclusions

Use of a single trial with expansion cohorts as a mechanism to expedite a drug development program in patients with solid tumor oncology presents both opportunities and challenges that must be addressed by multiple stakeholders—commercial sponsors, patients, clinical researchers, institutional review boards, and regulators. For investigational anticancer drugs where the preliminary clinical evidence suggests a substantial improvement over available therapies in a patient population with a high unmet medical need—for example, drugs meeting the criteria for designation as breakthrough therapies—the use of expansion cohorts as a component of the drug development pathway could be consistent with the goals and concepts of FDA's expedited programs for serious conditions. When using this drug development strategy, the risks of adding multiple expansion cohorts to an FIH trial should be identified and thoughtfully addressed by IND sponsors *a priori* with appropriate measures taken to mitigate these risks. A critical component of the safe and successful conduct of such trials is early and frequent communication between the sponsor, investigational sites, IRBs, and the FDA, particularly when amending protocols to add expansion cohorts with varying degrees of alternative effective therapy. Finally, it is incumbent upon the sponsor to request meetings with the appropriate solid tumor oncology review division within FDA's Office of Hematology and Oncology Products to aid in the drug development and evaluation process. Although expediting cancer drug development is a commonly shared goal, of equal importance is a continued focus on patient safety in cancer clinical trials; with thoughtful design and conduct of multiple expansion cohorts in FIH trials, both can and should be realized.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: M.R. Theoret, R. Pazdur
Development of methodology: M.R. Theoret, L.H. Pai-Scherf, R. Pazdur
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M.R. Theoret, M.K. Chuk
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.R. Theoret, P.G. Kluetz, P. Keegan, R. Pazdur
Writing, review, and/or revision of the manuscript: M.R. Theoret, L.H. Pai-Scherf, M.K. Chuk, T.M. Prowell, S. Balasubramaniam, T. Kim, G. Kim, P.G. Kluetz, P. Keegan, R. Pazdur
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): M.R. Theoret, R. Pazdur
Study supervision: R. Pazdur

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