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The Blurring of Phase 1, 2, and 3 Trials in Oncology: Expansion Cohorts in Phase 1 Trials

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Introduction

With the advent of more effective drugs to treat some forms of cancer has come a desire for greater efficiency in drug development. Particularly in situations where clear benefit is being observed for conditions that otherwise lack satisfactory treatment options, the traditional stepwise approach to drug development may not always be appropriate. The potential benefits of moving away from this paradigm to a more continuous approach can be seen in the recent development of the PD-1 inhibitor pembrolizumab (Keytruda; Merck) for treatment of metastatic melanoma.[1,2] While the first-in-human trial, KEYNOTE-001, was initiated in 2011 to determine the recommended phase 2 dose in patients with advanced solid tumors, the striking responses observed in initially enrolled patients prompted an increase in the sample size for an initial evaluation of overall response rate and disease control rate in patients with melanoma. Additionally, the potential for activity in non-small cell lung cancer prompted the addition of a cohort to assess overall response rate in this population. As promising results were obtained with each additional cohort, the trial continued to be expanded, and ultimately over 1200 patients were treated in this trial. One cohort within the trial included 173 patients with unresectable or metastatic melanoma who were randomized to two different doses of pembrolizumab, and the efficacy results in this cohort were sufficient to support accelerated approval in September 2014 - just three years after the initiation of the first-in-human trial.[3] Subsequently, data from the lung cohorts led to approval in lung cancer as well as the approval of a companion diagnostic for tumor PD-L1 expression.[4]

The development of pembrolizumab demonstrates how this approach has the potential to make transformative therapies available to patients in need years before they would have been at the standard pace of oncology drug development. However, KEYNOTE-001 represents only one of many of an increasing number of first-in-human cancer clinical trials that have enrolled hundreds of patients through multiple expansion cohorts.[5,6] The FDA Office of Hematology and Oncology Products (OHOP) reported in May 2015 that its portfolio included more than 3 dozen such trials.[7] Although these are nominally phase 1 clinical trials, they deviate from traditional phase 1 trials not only in sample size but in the nature of data collected as well as their ultimate goals: phase 1 trials are historically intended to evaluate the toxicity of a new drug and determine a safe dose range, while these newer phase 1 trials may include expansion cohorts assessing efficacy, often in a variety of tumor types or molecularly-defined subsets, and often with the intent of using the data to support FDA approval of the drug. Unlike the development of pembrolizumab, for many of these trials, sample size justification or description of the objectives of

additional cohorts has not been provided, and in many cases, informed consent has not been revised appropriately as trials have been expanded. This has raised concern about patient safety and communication between investigators, sponsors, institutional review boards (IRBs), and the FDA.

In this document, we aim to provide consensus recommendations and best practices for the use of expansion cohorts in the development of a new drug, biologic, or therapeutic combination with the goal of informing future FDA guidance on this topic. Such guidance should acknowledge the advantages this paradigm can provide – quick and nimble development, while ensuring that appropriate patient protections are in place.

Phase 1 Trials and Beyond

Phase 1 trials are frequently expanded and it may be unclear at what point a trial moves beyond the goals of a typical Phase 1 trial, or even a typical Phase 2 trial, and additional rigor should be implemented. Typical expansion cohorts in a phase 1 study enroll approximately 20 patients at a time for a given tumor type, or across tumor types with similar genetic aberrations, for exploratory evaluation of safety. A study that exceeds the typical cohort size and moves beyond its primary goal of establishing a safe and reliable dose to further explore efficacy, requires additional considerations to be in keeping with good clinical practice that is expected of all larger trials. The following guidelines help define thresholds for phase 1 trials that exceed traditional goals.

- When an individual cohort exceeds the typical size of a traditional phase 1 study cohort, thus requiring a formal statement of hypothesis and statistical analysis plan for assessing the hypothesis that also provides justification for its expansion. Additional oversight may need to be established as part of the trial governance plan, once a trial has reached its initial objectives or enrolled well beyond the typical size, e.g., over 100 patients at the recommended phase 2 dose within a single tumor type, or when multiple cohorts are added across multiple tumor types.
- When randomization is introduced into the study, at which time the study becomes inherently comparative and can provide the basis for formal statistical inference.
- When a sponsor has intent to use the study for registration.

Study Plan Expectations

It is important that data from these trials be collected in a systematic way so that we are learning as much as we can from patient volunteers. Clear and appropriate objectives, endpoints, a valid statistical plan, and trial governance appropriate for the intended scale-up should be described:

- The purpose for the expansion should be defined (e.g., further evaluating PK, toxicity, dosing, activity signal, companion diagnostic development, pharmacodynamic studies, evaluating additional tumor types), and the rationale should be provided along with the preliminary data from the earlier part of the trial which supports that rationale.
- The sample size and study design should be consistent with the objectives and sufficient to evaluate the objectives. Justification should be provided for the proposed sample size.
- A minimal bar for futility or activity should be proposed before expanding.
- Statistical analysis plan should be updated as cohorts are expanded. Early stopping rules should be included and/or analyses should occur at pre-specified time points or after target sample sizes have been reached (in terms of numbers of patients or of events).
- Informed consent documents should be updated as cohorts are expanded.
- Both IRBs and regulatory authorities should be notified of substantial cohort expansions.
- Plans for expanding the study to additional sites and addressing heterogeneity in study sites should be described.

- Appropriate plan for patient follow-up should be established, such that additional safety issues and efficacy signals can be tracked once a study is concluded.
- An external oversight committee to review safety in the context of potential benefit may need to be established

Governance and Oversight

The formation of a trial steering committee, including study investigators, should be considered to provide governance and ensure that the study plan expectations described above are met. In addition, it may be appropriate to establish an external oversight committee once the number of patients treated reaches a certain threshold or when it becomes clear the trial might be used to support registration. Many recent and ongoing phase 1 trials with multiple expansions have sample sizes exceeding those of typical randomized Phase 3 trials, which frequently have a Data and Safety Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) in place [8]. Establishment of a similar monitoring committee when an expansion cohort exceeds a certain threshold would ensure the usual level of patient protection for a trial of this size and reduce bias in decision-making. An external committee may monitor safety and ensure adequate communication of potential safety issues among the investigators responsible for each cohort. If a safety signal is seen in one cohort, the committee can help coordinate an appropriate response across all cohorts. This committee can also work with the sponsor and the trial steering committee to objectively review the evolving data and ensure that there is sufficient rationale and apparent benefit relative to risk to continue expanding the trial.

FDA-Sponsor Interactions & Best Practices for Cross-Division INDs

The established series of FDA-sponsor meetings generally occur at specific points between traditional Phase 1, 2, and 3 trials (e.g., End of Phase 2 meetings). Because this approach often condenses these distinct phases into a single trial, there are few pre-defined opportunities for meetings between companies and the FDA. These meetings are important to ensure that the study design is sufficient to support approval of the drug in the intended patient population. In addition, many drugs going through these programs may have activity or be tested in multiple tumor types or these trials may also be testing a biomarker and companion diagnostic. Therefore an alternative approach to FDA-sponsor interactions is needed to ensure that appropriate subject matter experts at FDA are engaged.

- If an early signal of efficacy is seen, sponsors should consider a phone call with the agency in real-time. From the FDA, this should include the team leader, primary clinical reviewer, and primary statistical reviewer, but not necessarily all members of the review team. Likewise, this should include key members of the study team, such as the primary investigator and statistician, but not necessarily all members of the study team. Sponsors should also prepare a brief (1-2 page) memo describing their plan for the trial.
- Trial amendments do not typically receive the same level of scrutiny from the FDA as an IND submission. Amendments for these expansions should be labeled as such (e.g., "expansion with intent to register") in order to receive a more thorough and timely review. They should also summarize the efficacy and safety to date and describe the rationale for the expansion.
- Sponsors should request administrative split of IND for new indications that cross FDA divisions and request meetings with relevant FDA centers/offices (such as CDRH if there is a potential need for a companion diagnostic).

Conclusion

This development paradigm is becoming more common for very active drugs intended for a population with high unmet need – often the same drugs receiving Breakthrough Therapy designation. Due to the high pressure for patient access to these drugs, trials may accrue rapidly, demanding a more continuous approach. Making these transformative therapies available to patients in need as early as possible is an urgent priority shared by all in the field. However, it is important to remember that not every drug with

exciting early results will ultimately prove itself to be a true therapeutic advance. There is an ethical obligation to ensure that the studies to test these drugs are designed and conducted with the same rigor expected of any other trial. The patient volunteers participating in trials as well as those future patients who may receive these drugs deserve no less.

References

[1] Robert C, Ribas A, Wolchok JD, Hodi FS, Hamid O, Kefford R, et al. "Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial." *Lancet*. 2014 Sep 20;384(9948):1109-17.

[2] Patnaik A, Kang SP, Rasco D, Papadopoulos KP, Elassaiss-Schaap J, Beeram M, et al. "Phase I Study of Pembrolizumab (MK-3475; Anti-PD-1 Monoclonal Antibody) in Patients with Advanced Solid Tumors." *Clin Cancer Res*. 2015 Oct 1;21(19):4286-93.

[3] Pembrolizumab Approval Summary, unresectable or metastatic melanoma: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm412861.htm

[4] Pembrolizumab Supplemental Approval Summary, PD-L1-positive metastatic non-small cell lung cancer: http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm465650.htm

[5] Dahlberg SE, Shapiro GI, Clark JW, Johnson BE. "Evaluation of statistical designs in phase I expansion cohorts: the Dana-Farber/Harvard Cancer Center experience." *J Natl Cancer Inst*. 2014 Jun 24;106(7).

[6] Theoret MR, Pai-Scherf LH, Chuk MK, Prowell TM, Balasubramaniam S, Kim T, et al. "Expansion Cohorts in First-in-Human Solid Tumor Oncology Trials." *Clin Cancer Res*. In press.

[7] Prowell T. "Large Phase 1 Studies with Expansion Cohorts: Clinical, Ethical, Regulatory and Patient Perspectives" 2015 Accelerating Anticancer Agent Development and Validation Workshop.

[8] FDA. "Guidance for Clinical Trial Sponsors Establishment and Operation of Clinical Trial Data Monitoring Committees." 2006. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm127073.pdf