

Phase I Clinical Trials: Hypothesis Testing

Faculty Presenter

Keith Flaherty, MD, Massachusetts General Hospital Cancer Center, Boston, MA, USA

*Authored by **Xin Gao, MD**, Beth Israel Deaconess Medical Center, Boston, MA, USA*

There are several considerations which are specific for drug development in oncology. Most importantly, oncology drugs are developed for life-threatening diseases, and there may be a natural tension between providing patients early access to the drugs and having adequate data on the safety and efficacy of such drugs. As a result, oncology drug approvals are often based on small populations of patients with relatively short exposures to the drugs and limited longer-term safety data. Furthermore, severe toxicities may be deemed more acceptable in oncology drugs in order to achieve modest gains in efficacy. Large registration trials may not readily predict real-world experiences as clinical trials often exclude patients based on marginal performance status, end-organ dysfunction, diminished marrow reserve, or brain metastases.

The Food and Drug Administration (FDA) has developed several mechanisms to expedite drug development and review which are particularly relevant in oncology. These include (i) fast track designation, (ii) priority review, (iii) accelerated approval, and (iv) breakthrough therapy designation. First, fast track designation may be granted to a drug early in its clinical development and entitles the company to a rolling New Drug Application (NDA) or Biologic License Application (BLA) submission. Second, priority review is a designation granted to companies after the NDA or BLA submission for products thought to represent a significant improvement compared to marketed products or if no satisfactory alternative therapy exists. Priority review typically expedites the goal date for regulatory action to 6 months from the standard 10-month review process. Third, accelerated approval is an FDA approval based upon a surrogate endpoint that is reasonably likely to predict clinical benefit and requires validation of an established clinical benefit via a subsequent confirmatory trial. Accelerated approval is particularly relevant for oncology drugs as the mechanism is meant to expedite the availability of drugs for serious or life-threatening diseases for which few or no good alternative therapies exist. Finally, the breakthrough therapy designation may be granted for drugs intended to treat a serious or life-threatening disease and has preliminary clinical evidence indicating potential substantial improvement over existing therapies on at least one clinically significant endpoint. The breakthrough therapy designation is of greatest value early in drug development as it allows the company to receive early input from subject matter experts from all disciplines in review divisions and “real-time” response to development strategy.

Despite the complexities of the drug development and regulatory process, FDA regulators view clinical benefit in terms of whether the net benefit-risk ratio of a drug is favorable. In other words, would cancer patients be better off having widespread access to this drug or not? This question may be more salient in oncology, where the stakes are higher due to the acuity and life-threatening nature of the disease. Whether we are involved in direct patient care, clinical investigation, drug development, or regulatory affairs, it is imperative that oncologists bear in mind that the good of the patient should be first and foremost and let this be the guiding compass in everything that we do.