Questions

We have several questions about a basket clinical trial design. First, how do we power this biomarker-driven trial given that both the cancers and molecular alterations are rare? Second, how do we combine baskets to ensure adequate power? Third, how do we design the two stages to decide when to conduct the interim analysis given that the baskets have different recruitment rates?

Background

Many new cancer therapies target molecular alterations in cancer cells by inhibiting a signaling pathway that both drives tumor progression and is activated either by a genetic mutation or receptor amplification. If the mechanism of action is established and the role of the target in the disease pathophysiology is known, then the therapy is expected to be effective in patients whose cancer harbors the target. We illustrate this with the Hedgehog (Hh) signaling pathway. It is linked to the etiology of both basal cell carcinoma and to certain subtypes of medulloblastoma. Furthermore, Hh is involved in other types of human cancer. It promotes tumor growth and confers survival capabilities to cancer cells. Therapies based on Hh pathway inhibitors for cancers that possess a ligand-independent Hh mutation have shown promise in clinical trials.

Targeted cancer therapies affect the design requirements for Phase II clinical trials because the study population is restricted to patients whose cancer harbors the target. Patient selection is based on biomarkers that are used to profile the molecular alterations present in the cancer. If the molecular alteration occurs in multiple cancers, then it is desirable to evaluate the effect of the therapy in groups of patients whose cancers are positive for the biomarker. This leads directly to a basket design for the clinical trial. Each basket consists of patients with a specific cancer. All of the baskets share a common molecular alteration. The targeted therapy is tested in all of the baskets both to determine efficacy and to identify which cancers are sensitive to it. We are considering a basket trial that uses a two-stage design. In the first stage, an initial cohort of patients are recruited into each basket. The cancer therapy is administered to the patients and the efficacy is evaluated in each basket. At the interim analysis, the homogeneity of the efficacy measure is evaluated. If the cancer therapy exhibits homogeneous efficacy in most or all baskets, then the baskets are aggregated in the second stage. Otherwise, the baskets are not aggregated in the second stage. Subsequently, futility testing is applied to decide whether enrollment should terminate or continue. If enrollment continues to completion, then efficacy is evaluated.

Suggested readings

