Public Summary

Investigational Drug Steering Committee

Friday, July 24th 2009

Clinical Trial Design TF (CTD-TF) Recommendations for Phase 2 Clinical Trial Design

Phase II trials evaluate the activity, and toxicity, of a new agent either as monotherapy or in combination. Trial designs with a single arm, based on response, are acknowledged as having limitations, especially when agents are used in combination or to study molecularly targeted agents - which may have significant clinical activity but low complete or partial response rates.

The CTD-TF has attempted to provide guidance by developing these general recommendations. These recommendations primarily focus on trial designs to demonstrate activity but may include secondary objectives exploring toxicity, scheduling or biomarkers.

The recommendations are intended to be general guidelines that may be used to inform the development of a robust phase II study design, rather than rigid rules dictating the design of all trials irrespective of the agent under study. The trial design should always be tailored to the specific agent or combination under study, and the most appropriate endpoint.

Recommendations

The first and critical decision point for the design of a phase II trial is based on the choice of the most appropriate primary endpoint, which should be tailored to the disease and drug(s) under investigation.
• Response-based endpoints such are that defined by RECIST, are standard, especially in early phase II trials. Other qualified biomarkers, such as molecular imaging or tumor markers, may be appropriate in select circumstances. Response based endpoints are appropriate primary endpoints if unambiguous and clinically relevant direct anti-tumor activity (such as tumor shrinkage) is hypothesized.
• If a response-based endpoint is not appropriate, especially in later phase II trials, progression-free survival is recommended as the primary endpoint. Other biomarker endpoints (such as tumor burden, tumor markers, novel imaging, tumor response, molecular biomarkers) and Patient Reported Outcomes (PROS) are always encouraged as secondary endpoints, especially in the context of studies that aim to qualify such endpoints. It is acknowledged that once qualified, these biomarker endpoints will become appropriate primary endpoints.

1) Study Design

a) <u>If 'Tumor Response' is the primary endpoint</u>
   1) Monotherapy trials
   Single arm designs are acceptable. However, randomization should be encouraged to optimize dose and schedule or to benchmark activity against known active therapies.
   2) Combination trials
   With some exceptions (e.g. availability of a well validated robust control database), randomization is usually required for trials testing combinations of agents to establish efficacy. An example is standard therapy ± novel agent or combinations of novel agents.

b) <u>If Progression Free Survival or another qualified biomarker is the primary endpoint (monotherapy or combinations)</u>
   (1) With some exceptions (e.g. availability of a robust control database), randomization is required
   (2) For randomized trials, blinded designs are encouraged where feasible. While placebo controlled trials are challenging, they are encouraged whenever possible. Alternatives include dose ranging, randomization vs. active controls or other novel agents, and randomized discontinuation and other crossover designs.
   (3) It may be informative to prospectively incorporate crossover to the standard therapy + novel agent for those patients initially assigned to the standard therapy alone, although careful consideration should be given to the timing of crossover (for e.g., only after the primary endpoint has been observed). Such cross-over designs increase the access of patients to investigational agents, and also provide additional information about the activity of the study arms.

2) Patient Selection/Enrichment Strategies (all trial designs)

a) A goal of Phase (I and) II development should be to define biomarkers predictive of efficacy and/ or toxicity. Where feasible and appropriate, molecular biomarkers should be explored in order to identify subsets of patients of interest for future study.
b) However, enrollment should in general not be limited by biomarker status unless there are strong confirmatory and supportive *clinical* data justifying the enrichment strategy. Adaptive statistical designs may be used to allow modification of enrollment if data suggest a biomarker is predictive.
c) In an un-selected trial, the patient population of primary interest (i.e. defined by a biomarker) should be predefined and the study powered accordingly to detect an effect in that subset.
d) Multi-disease phase II designs should be considered, especially if the objective is to test a biomarker-focused hypothesis.

3) Statistical Designs

Prospective designs that adapt to what is learned during the trial can improve the efficiency of drug development and provide greater precision. Available adaptations include stopping early, continuing longer than anticipated, dropping arms (or doses), adding arms, focusing on patient subsets, assignment of better performing treatment arms with greater probability, and seamlessly moving from Phase I to II or Phase II to III during a single trial.