THE CLINICAL TRIALS CONCEPT

A clinical trial is a planned experiment designed to answer questions concerning the most appropriate treatment of future patients with a specific medical condition. Clinical trials use results based on a limited sample of patients to make inferences about how treatment should be conducted in the general patient population.

Most clinical trials are designed to assess the toxicity and establish the proper dose schedule of a particular regimen (Phase I studies), to assess whether a regimen has sufficient activity to merit further study (Phase II), or to compare two or more regimens (Phase III). Ancillary studies evaluating the natural history of a particular cancer or the usefulness of certain laboratory techniques in defining high risk patient groups are also done.

Approximately 5,000 patients are currently being registered to SWOG trials each year.

**Phase I Studies**

Designed to determine the feasibility, toxicity, and acceptable dosage schedule of a treatment, Phase I trials generally involve a small number of patients with advanced cancer who have exhausted other conventional treatments. These patients are less likely to benefit from the study than patients eligible for Phase II and III trials.

The purposes of Phase I testing are listed below:

1. Determine a safe maximum dosage for a new drug, normally referred to as the MTD, or maximum tolerated dose.
2. Identify acute effects (toxicities) on normal tissues (or in specified populations).
3. Establish a dosage schedule for implementation in Phase II trials.
4. Possibly specify the first evidence of anti-tumor activity.

**Phase II Studies**

Phase II trials study the potential efficacy of a single or multi-agent treatment plan. In a multi-agent study, one or more drugs are combined when it is hypothesized that anti-tumor activity against a specific disease is greater than that of individual agents. For either treatment plan, these trials usually involve patients for whom standard treatment has failed or there is no effective standard treatment, and there is some possibility of benefit from the new treatment.

The purposes of Phase II testing are listed below:

1. Continue testing drug doses and schedules determined during Phase I studies in selected populations.
2. Evaluate the level of anti-tumor activity against a specific tumor type.
3. Further define normal tissue toxicities.
4. Decide whether to continue testing the agent or regimen in clinical studies.
Phase III Studies

Phase III studies are controlled trials comparing two or more therapeutic regimens having shown sufficient and acceptable toxicity levels in Phase II studies, to determine relative effectiveness. Both adjuvant therapy and advanced disease regimens are studied in these trials. Randomization is required for elimination of bias to balance such variables as age, sex, and race, and to dilute the effect of unknown factors that could influence outcome. A large sample is required in order to distinguish between true differences and differences which arise due to variability.

Patients participating in adjuvant studies are clinically free of disease, having undergone curative treatment. These studies treat the patient in an attempt to prevent recurrence or metastasis. The general purposes of adjuvant trials are listed below:

1. Compare the regimens for differences in disease-free survival and overall survival.
2. Evaluate toxicity levels.

In advanced disease studies, patients have residual, recurrent, and/or metastatic disease present. The general purposes of trials for advanced disease are to compare:

1. Response rates.
2. Time to disease progression.
4. Toxicities.

Additional types of clinical trials include ancillary, natural history, and cancer control studies.

An ancillary study is defined as a study open only to patients who are registered or have been registered on a treatment or cancer control study, and which is not in itself a treatment study. These studies typically address biologic questions, such as the utility human tumor stem cell assays for predicting response.

Natural history studies are designed to determine the normal course of disease for patients with specified characteristics, or to determine whether differences in specified non-treatment factors predict differences in the course of the disease.

Cancer control research is aimed towards identifying interventions that will reduce cancer incidence, morbidity, and mortality in a defined population. Included are studies on prevention, symptom control, quality of life, toxicity management, treatment compliance, and rehabilitation.