

## SUCCESS STORIES

The following success stories demonstrate how the methodology and technology of IDDI were key in the conduct of the clinical trials.

### **META-ANALYSES OF CLINICAL TRIALS TO SUPPORT NEW DRUG APPROVAL**

IDDI has been involved in numerous meta-analyses to directly or indirectly support new drug applications. The purpose of these meta-analyses was to combine evidence from several trials in order to confirm efficacy and/or safety of a new drug; to explore different endpoints; to validate earlier endpoints as surrogates for later endpoints; and to look at meaningful subsets reliably (Buyse M. Contributions of meta-analyses based on individual patient data to therapeutic progress in colorectal cancer. *Int J Clin Oncol* 14: 95-101, 2009; Buyse M. Use of meta-analysis for the validation of surrogate endpoints and biomarkers in cancer trials. *Cancer J* 15: 421-5, 2009). Recently published meta-analyses performed with IDDI's input have ranged over a range of therapeutic areas including solid tumors (The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. *J Am Med Assoc* 303:1729-1737, 2010) as well as hematologic malignancies (Buyse M, Squifflet P, Lange BJ, Alonzo T, Larson RA, Kolitz JE, George SL, Bloomfield CD, Castaigne S, Chevret S, Blaise D, Lucchesi KJ, Burzykowski T. Individual patient data meta-analysis of randomized trials evaluating interleukin-2 monotherapy as remission maintenance therapy in acute myeloid leukemia. *Blood* 2011 (in press)).

### **A BAYESIAN DESIGN FOR A SEAMLESS TRANSITION BETWEEN PHASE II AND III**

Data collected by a sponsor suggested a possibility of a differential treatment in subpopulations defined by levels of a biomarker. A Bayesian design has been developed, which allows the sponsor to conduct a randomized Phase II trial to corroborate the finding and to seamlessly continue to Phase III in the subpopulation, which benefits from the treatment. The design was consulted and accepted by a regulatory agency.

### **USING MINIMIZATION FOR A COMPLEX TRIAL DESIGN**

A multi-center phase II trial was conducted in just over 100 patients to compare metabolic changes in the prostate after administration of two treatments for locally advanced prostate cancer. The changes of interest were assessed by a biopsy taken at different randomized times and by magnetic resonance spectroscopy/magnetic resonance imaging (MRS/MRI) in about one third of randomly selected patients. In order to protect against chance imbalances, patients were additionally stratified by their level of prostate-specific antigen (PSA) at baseline. The [methodology](#) adopted to implement this complex trial design was minimization for the various randomized factors.

### **ANALYSING A BIOMARKER AS A PROOF OF CONCEPT**

Two doses of a therapeutic vaccine were tested simultaneously in a randomized phase II trial. While the trial's primary endpoint was not sensitive enough to show efficacy of either dose or any difference between the two, using the advanced statistical [methodology](#) of mixed modelling on repeated measures, it was found that the high dose had a highly significant effect on a relevant biomarker, while the low dose had no such effect. This proof of concept allowed the sponsor to raise additional funding to support further trials.

### **JUMPING AHEAD TO PHASE III**

A new ophthalmic drug was going to enter a phase II dose-ranging trial in order to determine the dose to use in phase III trials. IDDI proposed to jump ahead and test a dose-effect hypothesis in two pivotal phase III trials, using appropriate statistical [methodology](#) to adjust for multiple testing (simulations showed a step-up procedure to be slightly preferable to a closed-test procedure). Although the two trials were far larger than if a single dose had been used, this bold approach resulted in a gain of at least one year of clinical development. The drug has received approval by the FDA (US Food and Drug Administration).

### **A FLEXIBLE PHASE I TRIAL WITH RANDOMIZATION TO PLACEBO**

The maximum tolerated dose of a new drug, supposed to alleviate some adverse effects of anti-cancer chemotherapy, was to be established in a phase I trial. To assess the safety of the drug, information on the background toxicity rate in the enrolled sample had to be collected. By using state-of-the-art methodology, a flexible design was proposed for the trial. It combined the use of the continual reassessment method on a continuous dose scale with a concurrent randomization to placebo. The properties of the design were investigated by conducting a simulation study, which allowed to fine-tune the final form of the trial design. The trial has been initiated using the proposed design.

### **SWITCHING FROM PAPER CRFs TO EDC**

Switching from paper CRFs to EDC not only significantly reduced the time taken issue and respond to queries, it also allowed us to lock our database 2 weeks after the last patient visit. This would not have been possible with paper CRFs. IDDI made process of switching from paper to electronic CRFs mid-study easy for us and easy for our sites.

### **VALIDATING ADVERSE EVENTS ON A LARGE SCALE**

Two pivotal trials were conducted (one in the US, one in Europe) to seek approval of a new treatment for a chronic condition in elderly patients. The safety of the new drug was of particular concern. Adverse events and medications were coded by IDDI using proprietary coding system ID-code, based on the standard MedDRA and WHO-drug dictionaries. More importantly, the large volume of over 36,000 coded terms could easily be validated by the Sponsor using real-time, [web systems](#). This cut the time required by several months, and the budget by almost half a million dollars.

### **VALIDATION OF A GENETIC SIGNATURE FOR WOMEN WITH NODE-NEGATIVE BREAST CANCER**

A 70-gene signature was shown in a single institution to have prognostic value in patients with node-negative breast cancer. The purpose of this study was to validate this signature in independent patient samples. Hazard ratios were estimated by IDDI's [methodology](#) group of experts, to compare rates in high versus low risk groups for the time related endpoints. The models were or not stratified by a clinic-pathological risk group to verify if the gene signature added independent prognostic information to clinic-pathological risk factor.

### **APPLYING LIKELIHOOD METHOD FOR DATA SAFETY MONITORING**

Formal safety monitoring, often performed by independent committees of physicians, biostatisticians and ethicists, has become common in modern clinical trials. Safety

monitoring often includes reading of many pages of tabulated adverse events classified by body system, type and severity. Monitors look for within treatment incidence and between treatment differences in incidence that may be of concern. Frequentist statistical [methodology](#) is not appropriate for this type of surveillance due to multiplicity issues and the inappropriateness of the background repeated sampling assumption. A safety monitoring committee in an international ophthalmology clinical trial used the principle of support and support intervals based on the log likelihood function for incidence parameter conditional on the data at hand. Rates were calculated as poisson random variables and support methods were used for both incidence and treatment differences.

#### **META-ANALYSIS TO ASSESS EFFICACY IN COLORECTAL CANCER**

Tumor responses and survival were analyzed combining the data from the different trials using patient individual data. The statistical [methodology](#) was based on the classical notion of stratification, consisting of estimating a treatment effect within each trial, and then overall. A statistic for heterogeneity between the trials was calculated. A test of overall treatment effect was calculated. The following quantities were used in the calculation:  $O$ , which is the number of untoward events observed in the treatment group,  $E$ , which is the number of events that would be expected in the treatment group if there were no differences between treatment and control, and  $V$ , the variance of the number of events. Those data were shown graphically in a forest plot.

#### **USING REMOTE DATA ENTRY FOR COMPLEX PATIENT ELIGIBILITY ASSESSMENT**

A randomised phase II trial was conducted to compare three chemotherapy regimens as First Line Therapy in Women with HER2 Negative Locally Recurrent or Metastasis Breast Cancer. Patient registration forms were designed by IDDI on its EDC platform and used by the sponsor to capture and check patient eligibility data. A dedicated interface between the EDC and the randomization (ID-net) was implemented: patient registration performed by the investigator in ID-net populated the patient registration forms in the EDC. The randomization step was enabled in ID-net when patient eligibility data was fully captured in the EDC platform. This integrated [web-based solution](#) met the sponsor's expectation in the patient screening process.

#### **DISCOVERING NEW PROGNOSTIC BIOMARKERS FOR BREAST CANCER**

A range of biological markers were analyzed by polymerase chain reaction and immunohistochemistry in tissue microarrays from patients treated in several past and ongoing clinical trials for breast cancer. The obtained marker measurements were combined with the clinical data and analyzed using survival analysis methodology, including some advanced modelling techniques, to investigate whether any of the markers had prognostic value. The investigation was successful for at least one of the potential markers analyzed. The project is ongoing to validate further biologically interesting candidate biomarkers.