Clinical trial design issues: Session 2

H.X. Chen a, A. Tinetti b, H. Zwierzina c, a Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI) 6130 Executive Boulevard, Suite 7131, Bethesda, MD 20852, USA. b Quintiles Medical & Scientific Services, Global Therapeutic Head Oncology, Haematology and Transplantation, Park Club des Tanneries-Lingolsheim, 4, Route de la Rivière – B.P. 306, 67832 Tanneries Cedex, France. c Medizinische Universitätsklinik, Anichstrasse 35, A-6020 Innsbruck, Austria

E-mail address: Heinz.Zwierzina@i-med.ac.at (H.X. Chen)

ABSTRACT: This session focused on three topics related to clinical development of novel anticancer therapies: (1) moving clinical testing of new agents in early-stage, (2) strategies for clinical evaluation of combinations between novel/molecularly targeted agents, and (3) clinical development paradigm for vaccine related biological therapeutics.

Monotherapy with molecularly targeted agents has up to now only offered little clinical benefit in most solid tumours where the molecular pathology has not been linked to a single genetic defect or target. While the importance of combining targeted agents is well recognized, clinical development of novel combination studies can be challenging, and requires careful considerations of the regulatory, intellectual property as well as scientific issues.

Traditional design of clinical trials must be adapted to test the clinical utility of new targeted agents in different settings and to allow for translational research.

Cancer vaccines present unique developmental challenges. Some potential solutions exist, but they are not widely known nor is there any consensus about their use. A Cancer Vaccine Consortium (CVC) was established with the goal to use collective knowledge in the field to synthesize a flexible and applicable paradigm, reach a consensus on practical recommendations to improve cancer vaccine development, and offer an accepted, practical approach to cancer vaccine development.

CONFLICT OF INTEREST STATEMENT: The three authors of this paper can confirm that there is no conflict of interest involved in this paper, nor in their participation in this entire event.

Keywords: Trial design; Optimal biological dose (OBD); Interleukin-6; Combination therapies; Cancer vaccines


MOVING CLINICAL DRUG DEVELOPMENT TO EARLY-STAGE DISEASE

B. Berns. Clinical R&D-Haematology & Oncology, Centocor, 50-100 Holmers Farm Way, High Wycombe, Buckinghamshire HP12 4DP, UK

E-mail address: bberns1@cntus.jnj.com

As anti-cancer drug discovery has shifted to a rational, molecularly targeted approach, traditional clinical trial design must be adapted to test the clinical utility of these new agents. Traditional cytotoxic drugs, which evolved from the concept that cancer could be cured by eradicating all cancer cells in the body, have diverse mechanisms of action, but mostly target DNA. Their pharmacological effects are non-selective and irreversible, affecting all cells undergoing replication, normal and neoplastic. Dosing is usually in cyclical pulses administered at the maximum tolerated dose (MTD), which results in substantial toxicity in many patients. Phase I studies aim to establish the MTD, and phase II studies assess response based on tumour shrinkage, usually measured by imaging techniques.

In contrast, target-based therapies are selected on the basis of their mechanism of action and usually target a specific protein that is involved in malignant transformation. The interaction with their target (receptor or ligand) can be described by classical drug-receptor theory. Pharmacological effects are generally reversible. Dosing can be continuous at a tolerable dose. Phase I studies use biological and pharmacokinetic endpoints to estimate the optimal dose for inhibition of the target. Response assessments in phase II is based on prevention of further tumour growth, rather than tumour shrinkage. For many molecurally targeted agents, phase I is relatively uninformative, the heterogeneous patient population often has late-stage disease with limited organ reserves and co-morbidities. Toxicities are uncommon, and the maximum therapeutic effect is usually achieved well below MTD. The goal is to estimate the optimal biological dose (OBD), gauge the interaction between the anticancer agent and its target, and to rule out serious dose-related toxicities. For phase II development, the goal is to assess the probability that the product will have a positive benefit-risk ratio in phase III. This assessment is made by focusing on important pathways and ‘following the biology’. Assessments often include multiple tumour types and involve monitoring of biomarkers and surrogates of patient benefit. Also in phase II, the frequency of safety events is estimated.

Phase III development of targeted agents is similar to that for cytotoxic agents; that is, it involves measuring clinical benefit against a known standard of care (active comparator) in random-