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Clinical trial design issues: Session 2

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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

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MOVING CLINICAL DRUG DEVELOPMENT TO EARLY-STAGE DISEASE

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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.[1] 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 molecularly 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-

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ized controlled studies and ensuring that an adequate safety profile is achieved.

THINKING ABOUT EARLY-STAGE DISEASE: Two tumour types where drug development is moving to investigate early-stage disease were presented: (1) Non-small cell lung cancer, one of the leading causes of cancer-related mortality. Even after adequate surgical resection, the majority of patients develop recurrence of disease, an estimated two-thirds at distant sites. The presence of micrometastatic disease at the time of resection is the likely reason for the recurrence and provides a rationale for the use of adjuvant chemotherapy for patients with early-stage disease following surgical resection.[2] Currently, neoadjuvant chemotherapy[3] or chemoradiation[4,5] are also being investigated.

(2) Prostate cancer is typically a disease of men over age 50, but the incidence is projected to increase by 3.4% annually. Family history is a significant risk factor, but benign prostate hypertrophy is not. The key to thinking about early treatment is that prostate cancer progresses through well-described stages. Prostatectomy remains the cornerstone of treatment. Prostate-specific antigen (PSA) is a tumour marker, but the correlation between PSA response and final clinical benefit is not 100%. When PSA increases after surgery, androgen ablation is the usual treatment. When the PSA concentration rises again and the tumour becomes resistant to androgen ablation, chemotherapy is the usual treatment. Only at late stages does the cancer growth become androgen-independent. The mechanisms behind the so-called 'androgen independence' are being investigated to identify targets for preserving responsiveness to anti-androgen therapy and inhibiting invasion and metastatic spread. An agent that could prevent or delay the 'escape' of the tumour from androgen dependence could be used in combination with anti-androgen therapy. Interleukin-6 (IL-6) is a secreted, multifunctional cytokine that is produced by tumour cells and tumour-associated stroma in response to inflammation, stress and injury, and is upregulated in many types of cancer.[6] In a prospective study of 80 patients with prostate cancer serum levels of IL-6 (and TNF) correlated directly with the extent of malignant disease.[7] Levels of IL-6 are increased in therapy-resistant prostate cancer. It is a positive growth factor in late-stage prostate cancer and its autocrine loop appears to be a factor causing the tumour to become androgen independent. It may also play a role related to the inflammation and growth of early-stage disease.

Several exploratory studies across the disease-spectrum of prostate cancer have been started with CNTO 328, a mouse–human chimeric anti-IL-6 antibody. These studies offer opportunities for translational research, and should thus increase our understanding of the IL-6 biology in prostate cancer.

INFLAMMATION AND CANCER: Cancer initiation, promotion, and progression are normally repressed by redundant intra- and extracellular control mechanisms. One hypothesis is that dysregulated inflammatory processes are evident in cancer from an early stage and that cytokine mediators promote tumour growth and cancer-related morbidity. Investigators have shown that anti-inflammatory drugs can inhibit tumour formation and that chronic inflammation is associated with increased incidence of malignancy.[8]

Tumour necrosis factor-α (TNFα) has a long history. Since the early 20th century, there has been considerable interest in the effects of bacterial infection or bacterial 'products' on malignant tumours in man. The discovery of TNFα in 1975 by E.A. Carswell[9] ended a search for an important component of novel therapy developed by Willam B. Coley, a New York surgeon and pioneer in immunotherapy for cancer who 75 years earlier demonstrated that a crude bacterial filtrate from cultures of *Streptococcus pyogenes* and *Serratia marcescens* induced high fever and tumour necrosis in patients with sarcomas, carcinomas, and lymphomas.[10] Coley achieved a cure rate of better than 10%.[11] The composition of 'Coley's toxins' remained an enigma until 1975, when E.A. Carswell demonstrated that endotoxin stimulated the production of a host-specific factor from macrophages that could cause haemorrhagic necrosis of tumours. The same protein, secreted by macrophages, initially found to suppress the expression of enzymes of lipid metabolism in adipocytes *in vitro*, induced a cachectic state *in vivo* caused by systemic suppression of the enzyme lipoprotein lipase.[12] Subsequently, cachectin was found to be identical to TNFα.[13]

The action of macrophages on tumour cells provokes the release of TNFα, leading to induction of *myc, ras*, and β-catenin proto-oncogenes; induction of angiogenesis; and induction of metalloproteinases involved in tissue remodeling and metastasis. Down-regulation of cadherins leads to increased cell motility.

Evidence supporting the use of anti-TNF regimens is mounting in renal and ovarian cancers and haematological malignancies such as myelodysplastic syndrome. Because of the pro-inflammatory effects of TNFa in para-neoplastic syndromes, anti-TNF therapies warrant investigation in supportive care indications such as cachexia, fatigue, asthenia and depression, as well as therapy of solid tumours.

This approach has required novel studies designs and 'out of the box' thinking. Thus far, in several studies that included over 300 cancer patients in total, mainly in late stage disease, there has been no evidence that blocking TNF accelerated malignant growth or progression. The side effect profile is satisfactory compared to that of cytotoxic drugs. The investigators have seen clinical benefit in terms of fatigue scores, subjective patient reports, and some evidence of antitumour activity. Possibilities to move into early stage disease and combination regimens are being investigated.

CONCLUSION: The recommendation is to (1) perform more studies to explore the safety and efficacy of cytotoxic drugs and drug combinations in early stages of cancer; (2) develop molecularly targeted agents for use in early-stage disease, with an emphasis on proof-of-concept for novel hypotheses and endpoints; (3) define biomarkers before moving to phase III; and (4) collaborate more closely with pre-clinical researchers.

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OPTIMISING STRATEGIES FOR CLINICAL DEVELOPMENT OF COMBINATIONS OF TARGETED AGENTS

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WHY COMBINE TARGETED AGENTS?: While a number of targeted agents have demonstrated clinical proof of principle as cancer therapeutics, the clinical benefits conferred by these targeted agents are still limited, except in few circumstances where the tumour pathogenesis is dominated by a single molecular abnormality. Reasons for resistance to or escape from targeted agents can be multiple, including absence or biological irrelevance of the intended targets, redundant tumour growth and survival pathways, or heterogeneity of tumour subclones. Optimization of the therapeutic strategies should therefore include identification of predictive markers for individualized selection of therapies, and combination of targeted agents to simultaneously block the multiple molecular pathways. Discussions in this session were focused on strategies to overcome a host of intellectual property, regulatory, and scientific challenges in the development of regimens containing multiple targeted agents.[1]

INTELLECTUAL PROPERTY CHALLENGES: Combining targeted agents when they are still investigational presents special challenges concerning intellectual property (IP), since individual agents of interest are commonly under development by different industry sponsors. Broad experience exists at the Cancer Treatment Evaluation Program (CTEP) at the National Cancer Institute (NCI) in the United States in sponsoring combination studies. With access to more than a hundred investigational agents through collaborative agreements with industry partners, CTEP is uniquely positioned to provide a common platform to facilitate studies combining two or more investigational agents. To encourage sponsors to provide proprietary agents for combination studies, CTEP has developed common intellectual property language, which stipulates the option for each collaborator to receive non-exclusive, royalty-free licenses to the combination IP for all purposes including that of commercial use. (The template language is available on the CTEP Website at http://CTEP.cancer.gov/industry/ipo.html).

This template language has been well accepted by collaborators and investigators. Under such agreements CTEP has sponsored >100 clinical trials and executed >60 preclinical materials transfer agreements (MTAs) for studying combinations between investigational agents.

REGULATORY ISSUES: Based on experience as sponsor of clinical studies, preclinical toxicology for a combination regimen is usually not required if adequate safety information in patients are available for the individual agents. For approval of two experimental agents in combination, it would probably be necessary to demonstrate the contribution of each component of a fixed combination regimen. Such evidence could generally be obtained in clinical studies or form compelling preclinical data on the value of combination and absence of activity with single agent.

GENERAL CONSIDERATIONS FOR CLINICAL EVALUATION OF TARGET AGENT COMBINATIONS: Given the number of targeted agents and almost limitless possibilities of combinations, a strategy of prioritization would clearly be necessary.

Priority can be established based on the rationale of the targets, the credentials of the agent, and the strength of the preclinical data for the combination. The primary target should be relevant to the tumour being treated. The second target of the combination regimen may be selected to (1) maximize inhibition of the same signal (e.g., targeting both vascular endothelial growth factor [VEGF] and its receptor), (2) maximize inhibition of a pathway through inhibition of vertical targets (e.g., HER-2