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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

and mTOR), (3) block parallel pathways and cellular processes (e.g., VEGF and epidermal growth factor receptor [EGFR]) or (4) overcome the resistance mechanisms to the first agent.

When it comes to selecting the agents for the targets of interest, the most important factor would be the credentials of the agents, which should be based on either clinical evidence of antitumour activity or demonstrated of effects on the intended targets in patients. It is also preferable to select agents with minimal pharmacokinetic interactions and few, if any, overlapping toxicities. Consistent evidence of synergism or additivity in preclinical studies is also important in considering a combination regimen for clinical testing, especially if one or both of the agents or targets have not yet been clinically validated.

CURRENT EXPERIENCE WITH CLINICAL EVALUATION OF TARGETED AGENT COMBINATIONS: Several clinical trials for combination between targeted agents ongoing (Table 1). Among them is a multi-arm randomized phase II trial of several target agent combinations (bevacizumab + sorafenib, bevacizumab + CCI-779, and CCI-779 + sorafenib) in patients with renal cell carcinoma, with the purpose to select the promising combinations for further evaluations. In the attempts to explore biomarkers predictive of clinical outcome, the study will also incorporate central banking of the tissue and blood samples as well as performance of contract-enhanced dynamic MRIs.

While clinical experience with target agent combination is still limited, some preliminary safety and efficacy data are available and could provide insight to further development of this strategy. A phase I study of combination between the VEGF neutralizing antibody bevacizumab (Avastin®) and the VEGF-receptor inhibitor sorafenib (Nexavar®) was performed. As expected, toxicities related to inhibition of the VEGF target were exacerbated. At the first dose level (bevacizumab 5 mg/kg every two weeks and sorafenib 200 mg BID), which represented half of the single agent Phase II doses, the combination regimen was barely tolerable and required introduction of drug holidays.[2,3] Toxicities such as proteinuria, hypertension, and hand-foot syndrome occurred at earlier onset and with higher severity than expected with the single agents. Similarly, for combination between sorafenib and temsirolimus (an mTOR inhibitor) or erlotinib and temsirolimus, dose reductions were required when the agents were used in combination. On the other hand, combinations of agents with non-overlapping toxicities (e.g. bevacizumab plus erlotinib or cetuximab) were well tolerated at full phase II doses of the single agents.[4]

There are as yet limited data to confirm the benefits that may be derived from combination of targeted agents. Initial efficacy assessments of anti-tumor activity have yielded mixed results. For example, the first report of a phase 2 clinical trial assessing the combination of gefitinib with trastuzumab in patients with metastatic breast cancer did not identify a favorable interaction between the agents.[5] Similarly, while initial results from an uncontrolled clinical trial suggested promising response data for the combination of bevacizumab with erlotinib in renal cell cancer,[6] the subsequent randomized Phase 2 trial failed to demonstrate improvement in objective response rate or progression free survival compared to bevacizumab alone.[7] On the other hand, preliminary results for the combination of bevacizumab and the EGFR targeting antibody cetuximab in colorectal cancer (CRC) were promising, with the response rate and the progression free survival endpoints both exceeding the historical data for cetuximab alone.[4] A confirmatory phase III trial for the addition of cetuximab to bevacizumab and chemotherapy is now ongoing. In addition, the phase I trials with bevacizumab and sorafenib indicated promising activity in renal cell cancer and ovarian cancers,[2,3] although phase II evaluations in these indications are still pending.

SCIENTIFIC HURDLES FOR COMBINATION THERAPIES: Several barriers to effective clinical testing of target agent combinations can be identified, and they are fundamentally related to our limited understanding of the agents mechanisms of actions, the patient selection criteria and the optimal doses and schedules of the drug administrations. Furthermore, the clinical success or failure of combinations that have been evaluated to date has not been clearly predicted by published preclinical data. For example, the clinical results with gefitinib plus trastuzumab in breast cancer or bevacizumab plus erlotinib in RCC were negative despite published preclinical evidence for synergistic or additive activities of the combinations. It was also recognized that in preclinical stud-

Table 1 – Combination of targeted/novel agents in clinical trials

	Targets	Clinical trial	Tumour types
Block parallel pathways	VEGR + EGFR	Bevacizumab + cetuximab	Colon, Pancreatic
		Bevacizumab + erlotinib	Breast, SCCHN, RCC, etc.
	VEGF + PDGF/c-kit	Bevacizumab + imatinib	Melanoma, GIST
	HER-2 + HER-1	Trastuzumab + gefitinib	Breast
Maximize inhibition of one target	VEGF + VEGFR/raf	Bevacizumab + sorafenib	RCC
	EGFR + EGFR TKI	C225 + erlotinib	Colon
Vertical inhibition of pathway	VEGF + mTOR	Bevacizumab + temsirolimus	RCC
	HER-2 + mTOR	Trastuzumab + everolimus	Breast
	EGFR + mTOR	EGFR TKI + temsirolimus	NSCLC, Glioma
	HER-2 + CDK	Trastuzumab + flavopiridol	Breast
Modulating multiple biological processes	HDAC + VEGF	SAHA + bevacizuamb	RCC
	Vaccine + modulator	Vaccine + anti-CTLA4 antibody	Melanoma, Prostate
	VEGF, PDGF, VEGFR, c-kit	Bevacizumab + sunitinib	RCC

SCCHN, squamous cell carcinoma of the head and neck; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

ies a same combination could demonstrate synergism or antagonism across different model systems.

The variable results of the same combination across different tumour models is reflective of the heterogeneity of cancers, pointing to the importance of patient selection. However, most targeted agents were developed in unselected patients and the activities were defined by the population average, often without knowledge of the predictive markers. For combination regimens with more than one targeted agent, the lack of patient selection would not only compromise the efficiency of the clinical studies but also make the outcome data misleading. For example, improved efficacy of a combination may not be detectable in the overall patient population if synergism is dependent on a specific molecular context that is only present in a small subset of patients. Conversely, an improvement in the overall response rate or progression free survival may not necessarily mean benefit of the combination in individual patient, as the results may simply reflect the summation of the outcomes of individual components in different subsets of patients.

Also at issue is the limited guidance for optimal doses for the combination regimens. Specifically, if dose reduction of individual agents is required for combination therapies due to safety issues, would the combination still perform better than single agents at full dose? In addition, it is possible to differentially reduce the doses of the two agents and multiple MTDs may be defined for the same combination. It is however difficult to determine which dose ratio would be optimal.

In addition the sequence of agent administrations is often critical to the outcome of the combination, given the unique mechanisms of actions of targeted agents. Indeed synergism of many combination regimens has been found to be sequence-dependent. However, not uncommonly, different tumour models may produce conflicting results regarding the optimal sequence for the same combination. Without knowledge of the molecular contexts and clinical relevance of the preclinical models, it is difficult to apply these observations to clinical studies.

IMPROVING PRECLINICAL STUDIES: Clearly, more and better preclinical and nonclinical studies are needed for overcoming these barriers. Such non-clinical studies have the potential to enhance our knowledge of the individual agents and their combination, the mechanisms of actions, and markers for responsiveness or resistance, all of which critical to optimizing the strategy for clinical development of combination regimens. Nevertheless, the limitations of preclinical studies must also be appreciated in order to appropriately use the model systems.

Some ideas to improve preclinical studies were offered. A systematic effort is needed to molecularly characterize the human tumours and preclinical models. Experiments for specific combinations should be carried out in multiple tumour models and include clinically relevant doses and exposures. The single-agent control should be based on the full dose for comparison with the combination regimen. More importantly, results should be interpreted in the molecular context of the models to maximize translatability to the clinical settings.

One also cannot overemphasise the importance of correlative studies for the search of predictive and pharmacodynamic markers. These correlative studies are not only important in clinical trials but should start from non clinical studies, including those on cell lines and animal models.

CONFLICT OF INTEREST STATEMENT: Dr. Helen Chen is an employee of Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI) and it can be confirmed that there is no conflict of interest involved in this paper, nor in her participation in this entire event.

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A CLINICAL DEVELOPMENT PARADIGM FOR CANCER VACCINES AND RELATED BIOLOGICS

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INTRODUCTION: Cancer vaccines present unique developmental challenges. Some potential solutions exist, but they are not widely known nor is there any consensus about their use. The Cancer Vaccine Clinical Trial Working Group (CVCTWG), a joint initiative of the Cancer Vaccine Consortium (CVC) and the international society for biological therapy of cancer (iSBTc), has proposed a new clinical development paradigm for cancer vaccines and immunotherapies through workshops conducted between October 2004 and November 2005.

The goal of CTCVWG was to use collective knowledge in the field to synthesize a flexible and applicable paradigm, reach a