**18** INVITED

**The Neo BIG programme**

M. Piccart[1], P. Dinh[2], P. Bedard[3], C. Sotiriou[4], J. Baselga[5], D. Fumagalli[2], I. Bradbury[6], R. Gelber[7], S. Loi[4]. *[1]Institut Jules Bordet, Medicine, Bruxelles, Belgium; [2]Institut Jules Bordet, BIG, Bruxelles, Belgium; [3]Princess Margaret Hospital, Division of Medical Oncology and Hematology, Toronto, Canada; [4]Institut Jules Bordet, Translational Research, Bruxelles, Belgium; [5]Vall d'Hebron University Hospital, Chairman, Barcelona, Spain; [6]Frontier Science Ltd UK, Senior statistician, Inverness, United Kingdom; [7]Dana Farber Cancer Institute, Div Biostatistics and Epidemiology, Boston, USA*

Overcoming the "translational research gap" between basic science and clinical medicine is the greatest challenge in oncology today. The clinical trial is the medium through which the value of a new discovery is measured and applied to improve the care of cancer patients. To date, clinical trials have been designed to detect modest average treatment effects in a large heterogeneous group of patients. The formation of large co-operative groups in the 1990s led to the conduct of large, multi-institutional trials designed to provide level-1 evidence of an average treatment effect across a broad range of patients. What has been missing, critically, is a clear understanding of the underlying biology of the disease.

These methodological problems, if not addressed rapidly in an integrated way, will inevitably lead to further waste of precious public health care resources, despite our having entered an era of research burgeoning with potential. We now have many of the technologies and tools needed to identify patients with distinct molecular alterations and a broad array of novel targeted drugs that inhibit specific dysfunctional signaling pathways in cancer cells; however, we risk failing to deliver significant benefit to patients and society if the way in which we use these technologies and tools remains uni-dimensional and fragmented. Since well-designed clinical trials serve as the bridge between scientific discovery and medical application, new and integrated structures must be built to link biomarker identification and validation with earlier phases of new drug development. With harmonized pan-European policies for data protection, existing networks of collaboration, a shared currency, and a proven track record of high participation in international clinical trials already in place, an innovative European translational research network linking cancer research centres, laboratories and other stakeholder groups, would be ideally situated to lead this transition.

NeoBIG has been formed under the umbrella of the Breast International Group (BIG), which is a non-profit organization of academic breast cancer research groups from around the world, with its headquarters in Brussels, Belgium. Comprising over 40 collaborative groups, research partnerships and clinical trial units from Europe, Canada, Latin America, and Asia-Pacific, and collaborating closely with the U.S. National Cancer Institute (NCI) and North American Breast Cancer Group (NABCG), BIG already represents an expansive pool of leading European breast cancer experts, both clinicians and translational research scientists, with a proven track-record of working effectively together, often on practice-changing studies (Piccart-Gebhart, Procter et al. NEJM 2005; BIG 1−98 Collaborative Group NEJM 2009).

NeoBIG plans to create an enduring neo-adjuvant breast cancer research platform to rapidly test novel targeted agents with high potential and potential *predictive* biomarkers. NeoBIG plans to define specific patient subpopulations − based upon shared molecular disease characteristics − for a series of individual neo-adjuvant clinical trials testing novel targeted therapies compared with standard treatments. The trials will use short-term surrogate endpoints, such as pathological complete response rate, a decline in the proliferation antigen Ki67 or significant functional imaging changes with the aim to rapidly evaluate drug activity. Trials are also planned to include serial tissue sampling, the application of emerging biotechnologies to limited tumor specimens, the standardization of image acquisition techniques, data harmonization, innovative biostatistics and bioinformatics with the aim to facilitate identification of predictive biomarkers at an early phase of drug development.

NeoBIG will also develop an integrative data-sharing platform with the aim of dissemination of all clinical and biological data within the NeoBIG consortium and eventually the research public. This resource is anticipated to be compatible with other data networks such as CaBIG which is coordinated by the NCI, the SAGE and ISPY programs and hence is expected to be a huge resource for researchers world-wide.

NeoBIG, in collaboration with Merck, aims to launch in the last quarter of this year its first trial: the Luminal-B trial. This trial will enroll only those patients identified as Luminal-B or the highly proliferative ER + subtype that are known to have a poor prognosis on hormonal therapy. Patients will be randomized to receive either letrozole alone or letrozole with an IGF1R antibody. The endpoint will be Day 15 Ki67. The trial has 3 interim analyses with futility stopping rules should the combination show signals of being ineffective. This trial is an excellent example of (1) combining preclinical and *in silico* data to develop a clinical trial design and identify potentially the subgroup of patients that may best respond (2) a means of rapidly bringing a potentially exciting combination into the clinical arena and (3) to combine prospective and extensive translational research into an early phase clinical trial.

Other upcoming NeoBIG trials in HER2-overexpressing breast cancer and triple negative disease will also be discussed. Identical time-points for tissue collection, imaging and standard case record forms will be used in order to potentially integrate data *across* all NeoBIG trials.

**19** INVITED

**The UK Network of Experimental Cancer Medicine Centres**

P.W.M. Johnson[1]. *[1]Cancer Research UK, ECMC secretariat, London, United Kingdom*

The Experimental Cancer Medicines Centre (ECMC) Initiative brings together laboratory and clinical studies to expedite the development of new anti-cancer therapies and biomarkers. The aim is to facilitate the evolution of personalised medicine and to speed up the development of novel therapeutics. This is a joint initiative between Cancer Research UK and the Departments of Health in England, Scotland, Wales and Northern Ireland, investing £35 million over five years (2007–2012). Centres were selected following an open competition and external review. Funding supports the infrastructure for experimental cancer medicine in 19 centres of excellence across the UK. The majority of spending is on staff, with over 150 full-time equivalents across the network, of which 37% are laboratory technicians, 23% research nurses and 7% quality assurance staff. Other posts include data managers, tissue banking, pharmacy, radiology and statistics support. The ECMC Network has a diverse study portfolio, covering a range of novel drug and biological therapies, and most cancer types. Four Centres receive additional support for work in Paediatric Oncology. The initiative has made an important contribution to the infrastructure for biomarker discovery and development, including support for tissue collection, bio-banking and genomic analysis. The total number of early phase studies that have been hosted by the Network has grown to over 800, with approximately 200 new studies each year. Most ECMCs have more than doubled the number of early phase studies they have hosted between the first and third year of operation.

Most Centres have invested in infrastructure funding to strengthen their capability and capacity for collaborations with industry, and the number of industry funded trials has increased since the initiative started. Of the early phase clinical trials that have been conducted across the Network, 60% are industry sponsored/funded and an estimated £17 million additional investment has been leveraged from commercial partners using ECMC support. The Network will continue strengthening links with industry to attract more novel anti-cancer agents to the UK in the future. For example, the Network has now formed an alliance with AstraZeneca to conduct novel phase I combination studies.

Network activities are organised to support joint working between Centres and the majority of early phase trials conducted by ECMCs are multicentre studies. This has facilitated progress in the development of cancer therapeutics in the UK to maximise the impact on patient care.

## Wednesday, 17 November 2010 10:15−12:00

**WORKSHOP 4**

# Rational use of targeted therapies

**20** INVITED

**Re-inventing the methodology of early drug development**

J. Doroshow. *USA*

Abstract not received

**21** INVITED

**Rational combination therapies**

J. Baselga. *USA*

Abstract not received

**22** INVITED

**Success and pitfalls of targeted therapy combinations**

R. Schilsky[1]. *[1]University of Chicago, Section of Hematology-Oncology MC 2115, Chicago, USA*

The biological redundancy and plasticity of cancer cells will likely require application of combinations of targeted therapies to optimize therapeutic

success. Targeting a single pathway may prove ineffective or only transiently effective if parallel signaling pathways remain active or are upregulated, downstream pathway activation occurs or feedback loops overcome target inhibition. Both scientific and regulatory challenges exist in the efficient development of targeted therapy combinations. The foremost requirement is a strong scientific rationale to develop the combination coupled with non-clinical experimental data that supports that rationale and a thorough understanding of the consequences of pathway inhibition by the agents being combined. Evidence of synergy of the combination in *in vitro* cell lines and enhancement of the activity of the combination compared to the activity of either agent alone in *in vivo* nonclinical models should be sought. It is also desirable to identify biological indicators for likely responders in a patient population. The clinical development of targeted therapy combinations first requires characterization of the toxicity profile of each drug when given as a single agent as well as knowledge of potential pharmacokinetic interactions. Perhaps the most challenging clinical scenario is the development of a combination when one or both drugs in the combination has little or no anti-tumor activity as a single agent but the combination is expected to produce significant anti-tumor effects, the so-called synthetic lethality model. Co-enhancement refers to scenarios in which each agent is modestly active as a single agent in model systems, but the combination is highly active in the exact same model systems. Factorial clinical trial designs may be necessary to optimally evaluate drug combinations in these scenarios.

Few clinical examples of success in development of targeted therapy combinations exist at present although some pitfalls have been identified, most notably the lack of improved efficacy and increased toxicity observed when combining anti-EGFR antibodies with bevacizumab and chemotherapy in treatment of advanced colorectal cancer. Modest successes have been reported for the combination of EGFR-directed therapies in breast cancer (e.g., trastuzumab plus lapatinib superior to lapatinib in previously treated Her2 positive patients) as well as for adding arsenic trioxide to ATRA-based therapy in APL and combinatorial approaches are currently being evaluated in many other disease settings with agents hypothesized to produce more than additive anti-tumor activity. Well designed clinical trials will be necessary to clearly demonstrate the clinical benefit of such approaches and incorporation of biomarker studies will be essential in an attempt to explain both therapeutic successes and, more importantly, therapeutic failures.

**23** INVITED

**Targeted agents combined with radiation**

E. Deutsch[1]. [1]*Institut Gustave Roussy, Department Of Radiation Therapy, Villejuif, France*

Combination of chemotherapy and radiotherapy is a mainstay in the management of patients with locally advanced tumors. Our increased knowledge of cancer at the molecular level has transformed our understanding of tumor radiation response. Preclinical models have shown that several biologic agents designed to target specifically these molecular processes can increase tumor response to ionising radiation. Many of these agents are in the process of clinical evaluation with radiotherapy. In contrast to the preclinical findings, clinical results from clinical trials combining radiotherapy to targeted therapies such as anti EGFR or anti VEGF has been sometimes associated to an increase in toxicities underscoring the need for appropriate models of tumor versus normal tissue response assessment in vivo. The challenging concept of tumor addiction and the increasing pharmacological tools available to reverse these signals may represent a novel step in the concept of tumor radiosensitization. We have developed a strategy for the treatment of HPV related tumors: the use of antiviral agents to modulate the radiosensitivity. However, in lung tumors, some data suggest that inhibition of cancer 'addiction' pathways may not necessarily translate in better response to IR into the clinic.

These data justify the importance of evaluating new agents in combination with irradiation with an appropriate methodology at the preclinical stage in order to avoid unnecessary exposure of patients to potentially ineffective or detrimental combinations.

This preclinical evaluation needs to be able to answer the following questions:

- What is the toxicity profile, is there a differential effect?
- How to compare the antitumor efficacy observed with other anticancer agents?
- What is the optimal tumor profile?
- What is the sequence adapted to the optimal antitumor effect?

An important aspect is also to take into account the mechanisms of action of ionizing radiation such as DNA damage and cell cycle check-point induction during repeated DNA daily fractions. These aspects can be used to increase tumor response to irradiation. In particular, induction of mitotic catastrophe, one key mechanism of tumor cell death after irradiation can be increased by the use of agents that override the radiation induced G2/M arrest such as CHK1/2 and aurora inhibitors. Of interest, this latter approach exploits differences in radiation response of p53 deficient versus p53 wild type cells which could eventually provide exploitable differential effect in the clinic.

Finally, one of the major issues preclinical evaluations is to minimize exposure to excessive risks for patients during phase I. The development of more relevant preclinical models of drugs-radiotherapy toxicities will be illustrated through the evaluation of the impact of new strategies on the response of non-tumor tissues developed at our lab.

## Wednesday, 17 November 2010 10:15–12:10

**WORKSHOP 5**

# Pharmacokinetics/pharmacodynamics in cancer

**24** INVITED

**Factors affecting the pharmacokinetics (PK) and pharmacodynamics (PD) of nanoparticle and nanosomal anticancer agents**

W. Zamboni[1,2,3,4], H. Wu[1], N. La-Beck[1], P. Gehrig[2,5], G. Song[1], M.H.S. Walsh[1], A. Gabizon[6], R. Ramanathan[7], W. Caron[1]. [1]*University of North Carolina, Eshelman School of Parmacy, Chapel Hill, USA;* [2]*University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, USA;* [3]*University of North Carolina Institute for Pharmacogenomics and Invidualized therapy, Chapel Hill, USA;* [4]*Carolina Center for Cancer Nanotechnology Excellence, USA;* [5]*University of North Carolina, School of Medicine, Chapel Hill, USA;* [6]*Shaare Zedek Medical Center, Department of Oncology, Jerusalem, Israel;* [7]*TGen, Phoenix, USA*

Carrier-mediated agents (CMA) are classified as nanoparticles, nanosomes and conjugates. Anticancer CMA offer many unique advantages over their traditional counterparts, including improved solubility, longer duration of exposure, tumor-selective delivery, increased antitumor response and reduced toxicity. The PK of nanoparticle agents, such as nanosomes, is dependent upon the carrier and not the parent-drug until the drug is released from the carrier. The drug that remains encapsulated in the nanocarrier is an inactive-prodrug and thus the drug must be released from the carrier to be active. The PK variability associated with nanoparticles is greater compared with small molecules. The factors affecting the PK and PD variability of these agents remain unclear, but most likely include the monocytes, macrophages and dendritic cells of the RES. Thus, we evaluated the factors affecting the PK and PD of PEGylated liposomal formulations of doxorubicin (Doxil, PLD) and CKD-602 (S-CKD602) in patients (pts). The inter-patient variability in the PK and PD of these agents was associated with age, body composition, monocytes and presence of tumors in the liver. There was an inverse relationship between pts age and % decrease in monocytes at nadir with younger pts having a higher % decrease in monocytes. Pts with a higher % decrease in monocytes at nadir have an increased clearance of encapsulated drug and increased release of drug from the liposome. These results suggest that monocytes engulf PEGylated liposomal agents which causes the release of drug from the liposome and toxicity to the monocytes, and that the effects are more prominent in pts <60 years old. The development of phenotypic probes of RES function may be used to individualize the therapy of nanoparticles as a mechanism to reduce the PK and PD variability.

**25** INVITED

**Role of pharmacokinetics/Pharmcodynamics in dose selection of molecular targeted therapies**

J.H.M. Schellens[1]. [1]*The Netherlands Cancer Institute, Clinical Pharmacology, Amsterdam, The Netherlands*

Pharmacokinetics (PK) and pharmacodynamics (PD) are basic pharmacological principles that serve many purposes during drug development and daily clinical therapeutic practice. Increasingly the power of PK and PD is being recognized in the early phase of drug development, especially at the transition of preclinical to clinical development. In addition, PK–PD modeling is being explored of biomarkers that may enable safer drug development of drugs that do not show classical bone marrow toxicity and/or mucositis as dose-limiting toxicity (DLT). This is especially the case in the development of tyrosine kinase inhibitors that show hypertension and/or proteinuria as DLTs.

In the case of the transition of preclinical to clinical development often a wealth of PK and PD data exist that is more or less being ignored in the