18 INVITED

The Neo BIG programme

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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.

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The UK Network of Experimental Cancer Medicine Centres

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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.

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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

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