

# BIG RESEARCH IN FOCUS



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# Editorial

Although we've been talking about personalised breast cancer treatment for several years, we're just now on the verge of taking a giant leap from dream to reality. Increasingly sophisticated technologies are helping us to further dissect breast cancer into the individual molecular aberrations driving the disease. In parallel, pharmaceutical industries are developing rich pipelines of potentially powerful drugs. But how can we match the two? How can we make it possible to identify which treatment really will work best for any individual patient at a particular time?



What we urgently need to tackle is outmoded thinking about clinical trial designs. While in the past biomarkers served more as an "add on" to our clinical trials, they increasingly need to be the focus around which our trials are built.

But getting things right is highly complex, and all aspects of this new generation of biomarker-driven trials are now at the center of much debate. How do we determine which molecular aberrations to focus on? How do we determine the right statistical design? How can assays be standardised? What kinds of partnerships are needed to drive this innovation? Who will pay?

Resolving such questions and driving highly innovative research forward is a high priority for the Breast International Group (BIG) and its academic partners in North America. We recently asked Professors Fabrice André (Institut Gustave Roussy, France), Jan Bogaerts (European Organisation for Research and Treatment of Cancer, Belgium), Lisa McShane (US National Cancer Institute), Charles Perou (Comprehensive Cancer Center, USA) and Nick Turner (Royal Marsden Hospital and Institute of Cancer Research, UK) to tell us more about the challenges and rewards of incorporating biomarkers into breast cancer research.

Also, in the present context, an international workshop on "Innovations in breast cancer drug development and next generation oncology trials" took place last October in Bethesda, MD, USA. Co-sponsored by the US Food and Drug Administration (FDA), the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO) and the Breast Cancer Research Foundation (BCRF), the workshop brought together all stakeholders in breast cancer research. We are happy to share with you some of the outcomes of the discussions held there.

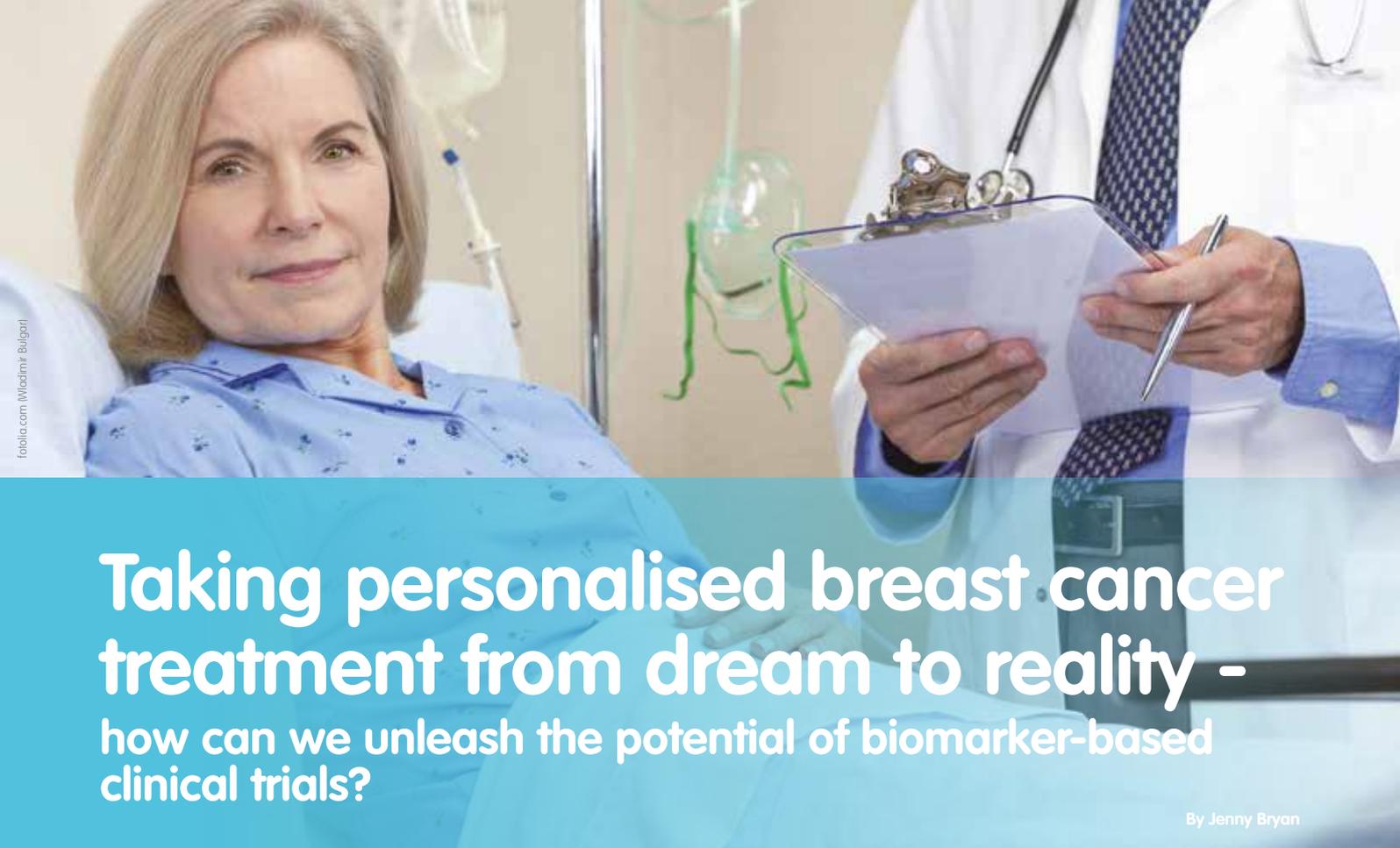
On behalf of the entire editorial board and the Breast International Group (BIG) Headquarters, I hope you will find an intriguing read in this second edition of *BIG Research in Focus*.

**Martine Piccart-Gebhart**  
Breast International Group (BIG) Chair

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# Taking personalised breast cancer treatment from dream to reality - how can we unleash the potential of biomarker-based clinical trials?

By Jenny Bryan

**Personalised breast cancer treatment is starting to move from dream to reality – thanks to the growing battery of biomarkers being identified and tested for their potential to target therapy at patients most likely to benefit. Essential for the success of this new approach are innovative clinical trials. These include BIG’s AURORA initiative, which comprises extensive molecular characterisation of patients with metastatic breast cancer and the subsequent possibility to enter clinical trials assessing molecularly-targeted agents. In other studies, the identification of predictive biomarkers associated with either sensitivity or resistance to such targeted agents is being actively pursued. European and US researchers involved in some of these state-of-the-art trials talked to Jenny Bryan about the challenges and rewards of incorporating biomarkers into breast cancer research.**

Distinguishing between women with hormone sensitive, human epidermal growth factor receptor 2 positive (HER2+) and triple negative tumours is now just the first step in recruiting patients to breast cancer clinical trials. Stratifying according to some of the increasing number of genetic aberrations identified in these three core tumour groups is transforming the design, objectives and endpoints of a new generation of studies, and the complexity of recruitment is becoming apparent.

“The days of large breast cancer trials with all-comers are over because we are increasingly focused on more and more homogeneous, biologically defined groups. Many trials are still founded on the three main clinical groups – hormone receptor positive, HER2+ and triple

negative – but biomarkers are then used to stratify within those groups so that pretty much every trial going forward has some genomic component,” says Charles Perou, Professor of Genetics and Pathology and Laboratory Medicine, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, North Carolina, USA.

He explains that, in the current generation of trials, biomarkers may not be the primary endpoint, but instead are integrated as a secondary endpoint or included as exploratory endpoints. But, in each case, the aim is to establish more homogeneous groups for predicting response to both old and new therapies for breast cancer.



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“**Each cancer is driven by a small number of mutations and we need first to identify these drivers and target them. When we’ve achieved this in a large number of cases we’ll be ready to address intratumour heterogeneity and how it impacts the development of resistance.**”

Professor André

“Thanks to the quantum leap forward in our ability to sequence genomes or exomes, we’ve found a lot of mutations and potential biomarkers. At the same time, pharmaceutical companies have given us a rich pipeline of potential therapeutic agents, so the challenge is now to match them together and find the right combination for each patient,” says Professor Perou.

Although biomarker-driven therapy is clearly needed in triple negative breast cancer, where treatment options are currently limited, investigators in personalised breast cancer trials, such as Dr Nick Turner, Academic Consultant Medical Oncologist at the Royal Marsden Hospital and Institute of Cancer Research, London, UK, believe there are opportunities across all three traditional categories of breast cancer:

“Biomarker research has potential right across the board. Triple negative disease has the worst prognosis, but although estrogen receptor positive (ER+) cancer is relatively treatable, it’s so common that more women die from it than triple negative disease. So it’s important to continue research into the genetics of all types of breast cancer. The big challenge for biomarker research is to identify what’s causing each individual cancer to grow and how to bring that knowledge through to clinical trials to develop treatments that target those individual mutations.”

Professor Fabrice André, Research Director, Head of INSERM Unit U981, Gustave Roussy Cancer Center, Villejuif, France, agrees that it is the driver mutations and/or copy number aberrations of cancer progression that are the priority:

“Each cancer is driven by a small number of mutations and we need first to identify these drivers and target them. When we’ve achieved this in a large number of cases we’ll be ready to address intratumour heterogeneity and how it impacts the development of resistance. But it’s the driver mutations we need to address first.”

Including biomarkers in major breast cancer trials is not cheap. As Professor Perou points

out, it adds significantly to the cost and work of a study. However, he urges governments and industry to fund the use of biomarkers as an integral component of breast cancer trials, not as a separate, optional extra:

“We’re selling ourselves and our research short if breast cancer trials are not funded to their full potential. Biomarkers may not be a primary therapeutic endpoint now, but in the long term they’ll be just as important. A lot of breast cancer studies will never get redone and each is a rare opportunity to learn something about genomic biomarkers. We should be taking full advantage of that.”

#### Stratifying according to biomarkers

Using genetic profiling, breast cancer can be divided into four main molecular sub-types – luminal A and luminal B, HER2 enriched/erb-B2 overexpression and basal-like<sup>1,2</sup>. These broadly equate with ER+ (luminal A and B), HER2+ (HER2 enriched/erb-B2 overexpression) and triple negative (mainly basal-like), with some overlap. For example, luminal B tumours can be HER2+ or HER2-

Professor Perou explains that key genetic mutations in breast cancer are found across all sub-groups of the disease, but at widely differing frequencies.

The phosphoinositide 3-kinase (PI3K) pathway has been the focus of substantial biomarker research, and mutations in *PIK3CA*, the second most common genetic mutation in breast cancer, are the most frequent in ER+ disease, especially in luminal A disease where they are found in around 45% of tumours<sup>1</sup>.

*PIK3CA* inhibitors are already being tested in early phase clinical trials, and Professor Perou predicts that the next generation of studies will dig deep into the molecular differences between luminal A and luminal B disease to target novel drugs at the most appropriate patient population.

“We know that there are genetic variations and differences in signalling pathways between luminal A and luminal B disease, and future



studies are likely to compare the effects of new kinase inhibitors between these sub-types,” he says.

In HER2+ disease, there is also heterogeneity of genetic aberrations, with distinctions between HER2+/luminal disease, which is mainly ER+, and HER2+/HER2-enriched disease, which is mainly ER-. The PI3K pathway is thought to play a role in HER2+ disease, with the potential to mediate resistance to HER2+ targeted treatment. In addition, about 75% of HER2-enriched sub-type tumours carry mutations in *TP53*, so trials of targeted therapy could also be an option in this group<sup>1</sup>.

In triple negative disease, *PIK3CA* mutations are relatively rare – at around 10%<sup>1</sup>. Instead, *TP53* is the most common gene mutation, and is present in 80% of basal-like tumours<sup>1</sup>. Also common in triple negative disease is *Myc* amplification and, to a lesser degree, mutation or loss of *RB1*<sup>2,3</sup>.

Professor Perou explains that, for many years, oncologists may have been inadvertently targeting *TP53* and *RB* with chemotherapy regimens typically used in triple negative disease:

“We and others have published evidence of correlations between loss of those two important tumour suppressors and sensitivity to chemotherapy. So, if we could target *TP53* more effectively and also get at *Myc*, then patients with basal-like breast cancers would be a major population for these biomarker-driven clinical trials,” he says.

Although targeting *TP53*, *Myc* and *RB* may be beneficial for patients with basal-like tumours, it may be less helpful in the 10% of triple negative patients with tumours that share some genetic characteristics with ER+ luminal breast cancers, or for those with other non-basal tumour types<sup>3</sup>.

“A number of studies are underway and if we consistently see differences in response to treatment between basal versus non-basal in triple negative disease, then knowing you’re basal will become

an important therapeutic biomarker in deciding treatment options,” says Professor Perou.

Another avenue in triple negative disease is the potential for T-cell mediated immunotherapy in patients with *CTLA4* and *PDL1* expression and, most recently, immunomodulatory support for antitumour B-cell responses in basal-like breast cancer<sup>4</sup>. Promising results with a checkpoint inhibitor of programmed cell death 1 (PD-1) protein in *PDL1+*, triple negative disease have recently been reported. Tumours can use the PD-1 receptor-ligand pathway to evade immune surveillance, and PD-1 blockers have previously shown efficacy in melanoma<sup>5</sup>.

### Biomarker-based clinical trials in breast cancer

Biomarker-based trials can be divided into two broad groups, explains Professor Fabrice André, a member of BIG’s Executive Board. In one group, trials investigate whether genomic testing can improve outcomes in the overall population, so the design incorporates use of genomics versus no use of genomics. In the second group – molecular screening studies – a large number of genes are investigated in order to identify cohorts of patients each defined by a specific genetic mutation, such as *PIK3CA*. These mutations can then be used as targets for drug therapy.

Among the first breast cancer trials to incorporate biomarker testing were the I-SPY (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And moLecular Analysis) trials. I-SPY 1 in women with locally advanced breast cancer showed that biomarkers could be identified that correlated with pathologic complete response (pCR) and recurrence-free survival (RFS)<sup>6</sup>.

I-SPY2 is investigating whether adding experimental agents to standard neoadjuvant medications increases the probability of pCR over standard neoadjuvant chemotherapy, for each biomarker signature established at trial entry<sup>7</sup>. Up to 12 different experimental agents will be tested in I-SPY2, and these will move into phase III trials or get dropped according to their efficacy in patients with target biomarkers<sup>8</sup>.

The primary objective of the multicentre SAFIRO1 trial was to get 30% of patients with metastatic breast cancer into clinical trials of targeted therapy on the basis of their biomarker profile<sup>9</sup>. A targetable genomic alteration was identified in 46% of patients, most frequently in *PIK3CA* (25% of identified genomic alterations), *CCND1* (19%),



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and *FGFR1* (13%). Thirty-nine per cent of patients with genomic test results had rare genomic alterations (occurring in less than 5% of the general population), including *AKT1* mutations, and *EGFR*, *MDM2*, *FGFR2*, *AKT2*, *IGF1R*, and *MET* high-level amplifications. It was possible to personalise therapy to genomic mutations in 13% of the total number of women in the study. Of those who were assessable and received targeted therapy, 9% had an objective response, and 21% had stable disease for more than 16 weeks.

“The key messages from SAFIR01 were that it’s feasible to carry out a multicentre trial using genomics in daily practice but that even in big centres, it’s difficult to get patients into phase I trials according to genomics. When this was achieved, the efficacy that was seen was average,” says Professor André.

He explains that, as a result of lessons learned in SAFIR01, extra technologies are being used in SAFIR02 to help identify women with targetable aberrations. In addition, a number of partnerships have been developed with pharmaceutical companies to ensure better access to novel agents.

“The first step was to show that we could successfully carry out genomic screening in a clinical trial and, having done that, we’re more able to gain access to the targeted therapies we want to use in SAFIR02,” says Professor André.

In SAFIR02, which started in April 2014, women with HER2-negative metastatic breast cancer will be randomised to interventions with eight targeted treatment options to investigate their ability to improve progression-free survival compared with maintenance therapy consisting of standard chemotherapy.

Acknowledging the importance of stratifying patients according to biomarkers, BIG has recently launched genotype-driven clinical trials within different settings of breast cancer. Such efforts are exemplified by the OLYMPIA and BRAVO randomised trials that will assess PARP inhibitors for patients with germline *BRCA1/2* mutations in the adjuvant and metastatic setting respectively. Additionally, the FINESSE study focuses on an agent targeting the fibroblast growth factor (FGF) signalling pathway for patients with metastatic breast cancer with *FGFR1*-amplified, *FGFR1*-non-amplified with 11q-amplification, or *FGFR1*-non-amplified without 11q amplification disease. Similarly, the LORELEI trial is investigating an alpha-selective PI3K blocking agent combined with letrozole in the neoadjuvant setting of hormone receptor-positive breast cancer; this trial is powered to assess the efficacy of this combination in patients whose tumours are both *PIK3CA* mutated and wild type.

### Innovation in trial design

Using biomarker profiling as well as traditional histological classification to recruit patients to clinical trials is having a major impact on study design. In just a few years biomarkers have moved from a useful “add on” to standard clinical trials comparing two or more treatments, to a key component around which trials are being built.

Terminology is evolving but commonly used descriptors for some of the newest biomarker-driven clinical trial designs include:

- Master protocol: framework for multiple-arm treatment in a “basket” or “umbrella” trial
- “Umbrella” trial: multiple biomarker-based cohorts of patients with a single histology/type of cancer, each matched to a drug, e.g., AL-CHEMIST, I-SPY2, EORTC SPECTA series (SPECTACOLOR, SPECTALUNG, etc)
- “Basket/bucket” trial: biomarker-driven, mixed histology/cancer type, e.g., NCI MATCH, EORTC CREATE
- “Platform” trial: standing trial structure, multiple agents enter and exit, single cancer type, possibly biomarker-driven

Dr Lisa McShane, from the Biometric Research Branch of the US National Cancer Institute (NCI), Rockville, Maryland, explains that the key challenges that need to be addressed when designing a biomarker-based trial are that:

- The number of molecular alterations is potentially large
- The prevalence of a single molecular alteration or profile may be small

“ In just a few years biomarkers have moved from a useful “add on” to standard clinical trials comparing two or more treatments, to a key component around which trials are being built. ”

- The available amount of tumor specimen may be small
- There may be uncertainty about the best biomarker(s) (and assays to evaluate them) to identify the patients who benefit from the new therapy

For example, the ALCHEMIST umbrella trial of adjuvant treatment in early stage non small cell lung cancer will need to screen 6000 to 8000 patients for two genetic mutations, *EGFR* and *ALK*, in order to assign approximately 400 patients each to trials of *EGFR* or *ALK* targeted therapy, given the prevalence of about 10% and 5% respectively of the two biomarkers.

In contrast to umbrella trials, the MATCH basket trial will analyse biopsies, using next generation DNA sequencing, from up to 3000 patients with a range of advanced solid tumours and lymphomas<sup>10</sup>.

“Instead of treating by site of cancer, patients in MATCH will be treated according to molecular characteristic, with each ‘basket’ corresponding to a type of genomic alteration, which could be a mutation in a particular gene, perturbations in an entire genetic pathway, over-expression of a protein, or some other characteristic that may be indicative of response to treatment,” says Dr McShane.

Up to 1000 patients whose tumours have genetic mutations that may respond to selected targeted drugs will be assigned to phase II trials, each with approximately 30 patients. In these trials, multiple drugs will be tested for their effects against target mutations. Patients whose cancers progress during the first assigned treatment may be able to enter a second MATCH trial arm if they have another suitable molecular abnormality.

“One of the beauties of the MATCH trial is that it has an extensive infrastructure set up and overseen by the National Clinical Trials Network, but community oncologists can take advantage of exciting new targeted therapies by enrolling their patients on a nationwide trial. Many oncologists are a bit intimidated by some of the reports generated by these next generation sequencing panels but, in MATCH, they don’t have to worry about the details. They can just plug into the system and get information about which of their patients are eligible for the trials,” says Dr McShane.

In Europe, the EORTC is launching the SPECTA umbrella trials, which aim to ensure efficient clinical trial access for patients with a range of

tumour types, initially melanoma, colorectal, lung and neurological cancers<sup>11</sup>. Other trials, including prostate cancer, are in development. Patients will be screened for genetic mutations for which targeted treatments are being tested, and then recruited to appropriate clinical trials.

Another approach, though not a therapeutic clinical trial, is to follow prospectively a longitudinal cohort of patients undergoing molecular characterisation. For example, in AURORA, about 1000 patients will be enrolled and a panel of 411 genes will be used to identify potentially actionable mutations in tumour samples in archival, primary and metastatic biopsies, as well as in blood<sup>12</sup>. Patients will be treated at the discretion of their physician, either according to standard local practice or within downstream phase II clinical trials of emerging targeted agents in metastatic breast cancer, either as monotherapy or in combination regimens.

#### Pros and cons of adaptive trial designs

Adaptive design features have attracted a lot of attention in biomarker-based clinical trials as they include opportunities to:

- Open and close treatment arms
- Adjust drug doses
- Add, drop or modify molecularly defined patient subgroups
- Re-weight treatment arm allocation probabilities (i.e., outcome adaptive randomisation)
- Incorporate “go/no-go” decisions based on early endpoints in order to move seamlessly from a phase II to a phase III trial.

“It’s ‘living’ research that changes as the study progresses in response to what we find, so some of the initial hypotheses may become obsolete by the time we get to the end. It’s very exciting, but it doesn’t remove the importance of starting out with clear, well defined objectives and a good understanding of the problem we are trying to address,” explains Dr Jan Bogaerts, Methodology Vice Director, at the European Organisation for Research and Treatment of Cancer (EORTC).

Statistically rigorous decision-making is essential in adaptive trial designs.

“Depending on the particular change that is made, you have to be clear about how the data are being analysed and the sensitivity analyses being done, in order to convince people that the answers are correct and the conclusions are fair,” says Dr Bogaerts.



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Dr Bogaerts





Some people believe that this approach is more ethical because you are using all the information you have to increase the likelihood that the next patient is assigned to the better treatment. In contrast, some feel that it's unethical to randomise patients at all if the triallists already have strong beliefs about which treatment is better.

Dr McShane



Dr McShane draws attention to the dilemma of outcome adaptive randomisation whereby results are analysed after every few patients enrolled in a trial and, if preliminary data suggest that one arm may be doing better, subsequent randomisation is weighted more heavily to that arm.

"Some people believe that this approach is more ethical because you are using all the information you have to increase the likelihood that the next patient is assigned to the better treatment. In contrast, some feel that it's unethical to randomise patients at all if the triallists already have strong beliefs about which treatment is better," explains Dr McShane. "The problem is that beliefs do not always prove true, and it's important to base these decisions on careful statistical evaluation of the evidence."

Dr McShane adds that another drawback is that when randomisation is imbalanced, statistical power is lost, so a larger trial is needed.

"Although the use of outcome-adaptive randomisation may mean that more patients are enrolled on the treatment arm that is ultimately shown superior, more patients may also be enrolled on the inferior arm," she says. "It's important that the statistical properties of these designs are well understood and clearly communicated."

#### The challenge of assay standardisation

Using large scale, next generation sequencing panels in studies such as MATCH and AURORA means that a few core needle biopsies can supply enough tissue for a vast array of molecular abnormalities to be checked simultaneously –

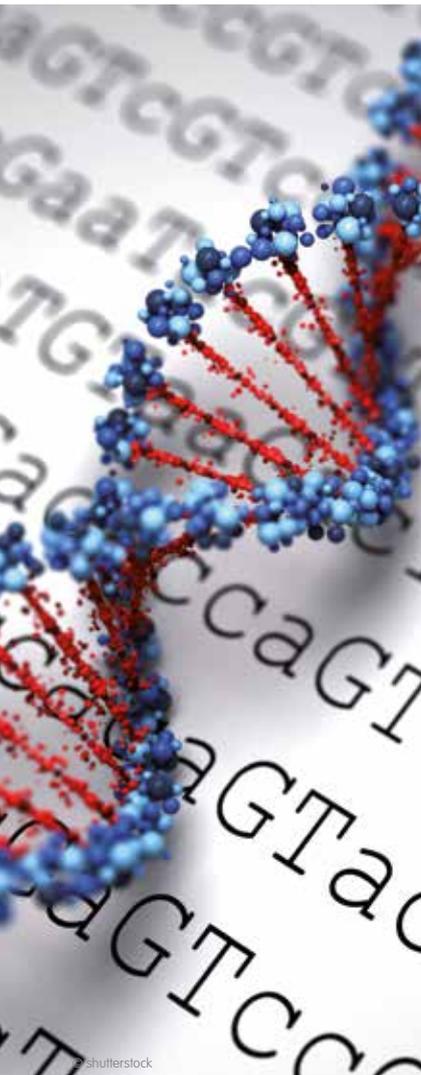
something which would have been impossible with previous generation tests, which required individual tissue samples for each genetic test.

But, as Dr McShane points out, a challenge in using such high-throughput genetic screening is ensuring that biopsy results from tumour samples are accurate, sensitive, specific and reproducible within and between multiple laboratories involved in a trial.

"In cancer trials in advanced disease you need to get biopsy results quickly because patients are very sick and can't wait long to be assigned to a treatment arm. In MATCH we will use four laboratories to ensure rapid, coordinated turnaround of biopsy results, and we also have to take account of the changing regulatory landscape to ensure that we satisfy FDA requirements for assay performance. So it's taking time to ensure standardisation of analytical methodology," she says.

Commercial assay panels are continuing to evolve and, although it is hoped that standardised methodology will emerge to allow greater national and international conformity, regular changes in the bioinformatics software needed to translate raw data into lists of molecular variants are another challenge.

"There are good reasons to keep tweaking the software to improve the overall performance of the assay but people running big biomarker-based trials want to be able to 'lock down' the bioinformatics software as well as all the technical aspects of the assay platform. It's unlikely that we'll ever reach a point of no more tweaks ever, but we need to get things as tight as possible before a trial gets underway," says Dr McShane. "We also need rigorous approaches for versioning assays during the course of a trial, should evolving understanding of biology suggest that it's needed."



Assay changes after a trial has been completed can raise additional questions. For example, changes to *BRAF* assays after treatment trials targeting *BRAF* mutations in malignant melanoma mean that additional mutations can now be identified but, as these were not included in original studies, it remains unclear whether treatment should be extended to patients who have them.

“By necessity we have to lock down the assay when we do a trial, but that doesn’t mean the world will stop and there won’t be new variations on that assay. How we absorb that new information and work out if we can give a targeted treatment to additional patients identified by a broader assay is something we’re grappling with,” she says.

One way forward is to ensure good specimen storage so that biopsies can be re-tested with new, broader assays and results matched with patient efficacy and safety data to check for differential response.

#### A role for liquid biopsy

Despite advances in next generation sequencing techniques, it can still be a challenge to obtain biopsy material for analysis, especially from poorly accessible tissue sites in very sick patients, and for rarer molecular abnormalities, with a prevalence of perhaps 2% to 3%.

Dr Nick Turner explains that circulating tumour DNA (ctDNA) analysis has great potential for getting around these problems of insufficient material for tissue biopsy:

“A lot of people are interested in looking at how we can use a simple blood test to get the data we currently get from tumour biopsies. Circulating tumour DNA holds a lot of promise in the near term for how we screen enough women with breast cancer to find these rare but potentially very key genetic events so that we can develop targeted therapies.”

In a study reported at the American Society of Clinical Oncology’s (ASCO) Annual Meeting in 2014, Dr Turner showed that ctDNA could also be used to identify patients at high risk of relapse. In a cohort of women with early breast

cancer who had completed apparently curative surgery and chemotherapy, he and his team showed that those who still had ctDNA in their plasma were at high risk of early relapse.

“We are now discussing how to develop the criteria for a positive ctDNA test so we can start to build that into intervention trials focused on those who are at very high risk of relapse,” says Dr Turner.

He points out that, for such an approach to be possible, it is necessary to get a highly personalised profile of genetic mutations for each patient’s primary tumour in order to get the specificity and selectivity that are needed when looking for really rare genetic events in the blood that can indicate a risk of relapse.

“Within genes such as *PIK3CA* or *TP53*, some of these mutations will be relatively common, but in others we see mutations that are really unique to that individual cancer,” says Dr Turner.

To find out more about liquid biopsy techniques, see *BIG Research in Focus Issue 1*, accessible on [www.BIGagainstbreastcancer.org](http://www.BIGagainstbreastcancer.org).

#### The importance of partnership

For the success of downstream phase II clinical trials in initiatives such as AURORA, MATCH and SPECTA, much will depend on effective partnerships between research organisations and pharmaceutical companies with innovative pipeline drugs that target genetic mutations, such as *PIK3CA*, *EGFR* and *ALK*.

Dr Jan Bogaerts explains that, traditionally, pharmaceutical companies have carried out simple A versus B comparator studies, partly to satisfy

regulatory requirements to get products on to the market. Now they are being asked to take part in downstream phase II trials that include a number of novel targeted therapies from a variety of different companies. Are companies willing to team up in large, academia-led trials, or do they prefer to go it alone?

Dr Bogaerts suggests that if regulators and payers follow the growing trend of asking which markers can predict response to drug therapy, then



“Circulating tumour DNA holds a lot of promise in the near term for how we screen enough women with breast cancer to find these rare but potentially very key genetic events so that we can develop targeted therapies.”

Dr Turner

## Meet the experts



► **Fabrice André, MD, PhD**  
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► **Jan Bogaerts, PhD**  
Methodology Vice Director, at the European Organisation for Research and Treatment of Cancer (EORTC)



► **Lisa McShane, PhD**  
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► **Nick Turner, MD, PhD**  
Academic Consultant Medical Oncologist at the Royal Marsden Hospital and Institute of Cancer Research, London, UK

pharmaceutical companies will want to work in partnership on the new, large studies of biomarker-targeted treatments.

"Today's environment of financial restriction is very much attuned to marker and sub-group questions, so it's becoming common to ask in which patients a drug works better and to which patients it should not be given," he says.

He also points out that having a good marker early on will facilitate the development of a new drug because the treatment effect will be much stronger in the correct population. Studies can thus be smaller and results more convincing. However, if the underlying mechanism of a compound is unclear when it goes into early stage clinical trials, using it in a population whose tumours turn out

to be genotypically unsuitable may do lasting damage to the drug's long term potential.

“If regulators and payers follow the growing trend of asking which markers can predict response to drug therapy, then pharmaceutical companies will want to work in partnership on the new, large studies of biomarker-targeted treatments.”

Dr Bogaerts

"If trastuzumab had been put into a study of all types of breast cancer, it would not have become a successful drug; but it was fortunate to have its marker identified at an early stage, so it's become a success story that many companies would like to copy," says Dr Bogaerts.

"My advice would be to start a phase II programme in several tumour types, in several basket trials, to gain as much marker information as possible in a limited amount of time before going forward with phase III studies. If this can happen, I believe that pharmaceutical companies will be able to achieve strong confirmatory effects in smaller phase III trials." ➤

### References

1. References
1. Ellis MJ, Perou CM. The genomic landscape of breast cancer as a therapeutic roadmap. *Cancer Discov.* 2013 Jan;3(1):27-34.
2. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B, Senn HJ; Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Ann Oncol.* 2013 Sep;24(9):2206-23
3. Turner NC, Reis-Filho JS. Tackling the diversity of triple-negative breast cancer. *Clin Cancer Res.* 2013 Dec 1;19(23):6380-8
4. Iglesias MD, Vincent BG, Parker JS et al. Prognostic B-cell signatures using mRNA-seq in patients with subtype-specific breast and ovarian cancer. *Clin Cancer Res.* 2014 Jul 15;20(14):3818-29.
5. Nanda R, Chow LQ, Dees EC, et al. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. Presented at the 2014 San Antonio Breast Cancer Symposium, December 9-13, 2014. San Antonio, Texas. Abstract S1-09
6. Esserman LJ, Berry DA, DeMichele A et al. Pathologic complete response predicts recurrence-free survival more effectively by cancer subset: results from the I-SPY 1 TRIAL--CALGB 150007/150012, ACRIN 6657. *J Clin Oncol.* 2012 Sep 10;30(26):3242-9
7. Sleijfer S, Bogaerts J, Siu LL. Designing transformative clinical trials in the cancer genome era. *J Clin Oncol.* 2013 May 20;31(15):1834-41.
8. I-SPY2 Innovations. Accessible at: <http://www.ispy2trial.org/about/i-spy-2-trial>
9. André F, Bachelot T, Commo F et al. Comparative genomic hybridisation array and DNA sequencing to direct treatment of metastatic breast cancer: a multicentre, prospective trial (SAFIR01/UNICANCER). *Lancet Oncol.* 2014 Mar;15(3):267-74.
10. Abrams J, Conley B, Mooney M et al. National Cancer Institute's Precision Medicine Initiatives for the new National Clinical Trials Network. *Am Soc Clin Oncol Educ Book.* 2014:71-6.
11. Lacombe D, Tejpar S, Salgado R et al. European perspective for effective cancer drug development. *Nat Rev Clin Oncol.* 2014 Aug;11(8):492-8.
12. Zardavas D, Maetens M, Irrthum A et al. The AURORA initiative for metastatic breast cancer. *Br J Cancer.* 2014 Nov 11;111(10):1881-7.

# Generating the next generation of oncology trials

## OUTCOMES OF THE BREAST CANCER WORKSHOP, 21 OCTOBER 2014

By Drs Dimitrios Zardavas<sup>1</sup> and Patricia Cortazar<sup>2</sup>

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In October 2014, a workshop titled “Innovations in Breast Cancer Drug Development – Next Generation Oncology Trials”, co-sponsored by the US Food and Drug Administration (FDA), the American Association for Cancer Research (AACR), the American Society of Clinical Oncology (ASCO) and the Breast Cancer Research Foundation (BCRF), took place in Bethesda, Maryland, USA. Co-chaired by Drs Jose Baselga and Patricia Cortazar, the workshop brought together an internationally renowned group of breast cancer experts, the FDA, industry representatives, and patient advocates to discuss several aspects of developing an international, genomically-driven protocol for metastatic breast cancer. Speakers and panellists extensively discussed the planning needed to launch a genomically-driven trial to test multiple agents (single or in combination) in a population of patients with metastatic breast cancer. The main messages from this initiative are as follows:

1. In the era of personalised cancer medicine, with numerous molecularly targeted agents under clinical development, the empirical paradigm of designing clinical trials with patients selected according to the clinico-pathological characteristics of their disease should be revisited. In particular, genomically-driven trials should be pursued, in which the clinical development of targeted agents should focus on molecular niches of the disease bearing molecular alterations potentially sensitive to those agents.
2. A few genomically-driven clinical trials conducted in different cancer types have led to the marketing authorisation of targeted anti-cancer agents. Such trials provide the proof-of-concept for further promotion and adoption of this approach in the metastatic breast cancer setting.
3. This new paradigm has challenges. Developing targeted agents for populations with low prevalence requires the screening of large numbers of patients. Taking into account the extensive inter-tumour heterogeneity governing breast cancer, new approaches will be needed to develop such genomically-driven trials in an efficient way. Master protocols can be viewed as such an approach, where multiple independent molecularly-defined strata are opened and targeted agents are triaged to patients with specific genotypes of the disease.
4. Combinational approaches of targeted agents should be favoured over monotherapies, to combat the compensatory pathways of breast cancer cells. The latter, manifested as the molecular rewiring of the oncogenic intracellular network in response to the selective pressures imposed by anticancer agents, fuels resistance to treatment. Biologically rational combinational approaches that take into account the adaptive responses of cancer cells hold promise to yield improved anticancer activity.
5. Combinational approaches using targeted agents can be classified into the following categories: i) vertical inhibition, aiming to block two different molecular components of the same intracellular signalling pathway; ii) horizontal inhibition, through which molecular components operating in different intracellular signalling pathways are blocked; and iii) inhibition of the same target with different agents, a strategy exemplified by the dual HER2 blockade.

“Taking into account the extensive inter-tumour heterogeneity governing breast cancer, new approaches will be needed to develop such genomically-driven trials in an efficient way. Master protocols can be viewed as such an approach.”



9. Adopting genomically-driven trials to facilitate the clinical development of molecularly targeted agents demands innovative statistical designs and/or tools to support the former. With regard to new trial designs, master protocols, basket trials or trials following an adaptive design have been proposed.

10. Concerning innovative statistical tools to be implemented in genomically-driven clinical trials, the following ones were proposed: i) imbalanced randomisations; ii) use of external or historical control data (e.g., in single-arm studies); iii) sharing of control groups across protocols; and iv) model-based analysis methods for the pooled analysis of multiple tumour types, markers, body sites, etc.

11. Taking into account the increasing amount of data generated by both clinical trials and clinical practice in the era of genomic-driven oncology, the need to optimise data collection and sharing was identified. Considerable progress can be achieved by further expanding the use of electronic health records. ASCO's Cancer-LinQ initiative assembling a vast, valuable pool of data from cancer patients has the potential to take a major step in this direction.

The above points represent the pillars of modern clinical trials assessing investigational agents in the field of breast cancer. Numerous challenges lie ahead of us, in particular in terms of securing funding for the extensive molecular profiling efforts needed. Globally agreed definitions are also needed, so that results from across different genomically-driven clinical trials can be compared. A reinforcement of the already existing international collaborative efforts between networks involved in breast cancer research is essential to our being able to tackle these challenges. This need for increased collaboration becomes even more imperative when we consider the increasing molecular fragmentation of breast cancer and its impact on the number of patients needed to be screened before enrolment in a clinical trial. The 'Innovations in Breast Cancer Drug Development – Next Generation Oncology Trials' Breast Cancer Workshop served as a promoter of such initiatives. 

**“**  
**This need for increased collaboration becomes even more imperative when we consider the increasing molecular fragmentation of breast cancer and its impact on the number of patients needed to be screened before enrolment in a clinical trial**  
**”**

6. In terms of the clinical development of combinations of targeted anticancer agents, the FDA has issued detailed guidelines about both the criteria to be fulfilled and the most efficient study designs to be implemented. (Available on <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf>).

7. The different nodes to be targeted have been classified as follows: i) primary dependencies, such as the estrogen receptor (ER) and the human epidermal growth factor receptor 2 (HER2); ii) secondary additional alterations, such as *PIK3CA* mutations or *FGFR1* amplifications; iii) mechanisms of intrinsic resistance; and iv) mechanisms of acquired resistance.

8. Another dynamically evolving area with tremendous potential for personalised cancer medicine is the development and implementation of 'liquid biopsies', corresponding to the isolation and characterisation of cell-free circulating tumour DNA and circulating tumour cells. To this end, standardisation of the respective technologies used is needed. Additionally, clinical validity must be demonstrated prior to implementation in clinical practice, ideally within the context of randomised clinical trials.

# “Sapins de Noël des Créateurs belges”: Or the story about how Christmas trees can support breast cancer research!

In late 2014 the “Sapins de Noël des Créateurs” returned to Brussels for the second Belgian edition of a very special charitable event. The concept originated in Paris 18 years ago, when designers from the worlds of fashion, design and architecture first came together to present their interpretations of the Christmas tree, and to auction their work for a good cause.



Gala dinner held at SMETS Premium Store. Christmas tree designed by Raf Simons.

**The Sapins de Noël des Créateurs belges celebrates not only the spirit of Christmas, but also the spirit of creativity and innovation, as showcased by the designers and their artwork. Creativity and innovation similarly drives BIG scientists to pursue new discoveries for the benefit of men and women with breast cancer all over the world.**

In 2013 the first Belgian edition raised over € 60 000 to benefit the AURORA programme (better known as the “Metastatic Breast Cancer GPS” by the general public), focussed on helping patients with an advanced stage of the disease.

This amount covers the molecular screening analysis (on both the primary and metastatic tumour samples) for approximately 30 patients participating in the programme.

In 2014 more than 30 designers participated in the event, including special guest designer Stella McCartney. This year’s auction of the designer Christmas trees raised more than €118 000 in support of other BIG projects.

Following the opening on 24 November, attended by over 400 people, the trees were on display to the public at SMETS Premium Store in Brussels



Serge Schmitz of BIG participates as a judge in the Liberty Global bake-off.

for one week. On the evening of 1 December, SMETS hosted the gala dinner and auction of the trees, which was attended by some 250 guests. BIG would like to thank all those present that night for their generous support.

Together, the designers of the Sapins de Noël des Créateurs belges and BIG against breast cancer bring to the Belgian public some truly unique, Christmas-inspired creations at a special time of year, in support of a cause that touches the lives of families everywhere.

**Liberty Global and UPC support BIG against breast cancer during Breast Cancer Awareness Month**

The international media companies Liberty Global and UPC raised funds and awareness during the month of October 2014 through creative activities such as an employee bake-off competition (with guest judge Serge Schmitz from BIG), a fundraising raffle and an employee donation challenge that was matched by the company.

As part of the campaign, BIG visited the Netherlands and Luxembourg offices to deliver "Look and Feel" workshops encouraging breast health. BIG staff demonstrated the breast self-examination method advised by breast specialists and encouraged employees to become comfortable with checking themselves. The take home message from these workshops was "Know your breasts!"



Altogether, Liberty Global and UPC raised more than € 26 000 for BIG against breast cancer. The funds will support the POSITIVE trial (also known as "Baby Time" by the general public), which will permit young women who are being treated for hormone-sensitive breast cancer, and who wish to start a family, to pause their endocrine treatment in order to become pregnant.

The study will enable us to evaluate the safety of treatment interruption and to better understand the correlation between pregnancy and the risk of breast cancer recurrence. It will also provide critical information about the success and risks of pregnancy itself after breast cancer, which is important to so many young women.

**BIG would like to thank the employees for their enthusiastic participation in the campaign throughout Breast Cancer Awareness month. 📌**

"BIG against breast cancer" is the name used for the public face of Breast International Group (BIG), for outreach and fundraising activities.

**“ This year’s auction of the designer Christmas trees raised more than €118 000 in support of other BIG projects. ”**



**We will find a cure for breast cancer through global research and collaboration**

**The Breast International Group (BIG)** is a non-profit organisation for academic breast cancer research groups from around the world.

Founded by leading European breast cancer experts in 1999, BIG now constitutes a network of 55 groups based in Europe, Canada, Latin America, Asia and Australasia. These entities are tied to several thousand specialised hospitals and research centres worldwide. About 30 clinical trials and several research programmes are run or are under development under the BIG umbrella at any one time. BIG also works closely with the US National Cancer Institute and the North American Breast Cancer Group, so that together they act as a strong integrating force in the breast cancer research arena.

[www.BIGagainstbreastcancer.org](http://www.BIGagainstbreastcancer.org)

### **BIG means:**

#### **Truly international reach**

BIG is a truly international body focused exclusively on conducting and coordinating breast cancer research, primarily through clinical trials and innovative research programmes. To test new treatments with enough patients to be confident about the results, most research cannot be limited to one institution, or even to one country.

#### **Real research**

BIG designs and conducts its own research through its member groups and their extended network of hospitals and investigators – BIG does not simply redistribute funding to other third parties. BIG trials that are conducted in collaboration with the pharmaceutical industry are done so in a manner designed to maintain independence and eliminate bias, keeping patients' interests at the heart.

#### **Research principles**

BIG facilitates academic research but also works closely with the pharmaceutical industry in a way that is "win-win" for all. BIG trials respect specific principles of research conduct to ensure that data collected are handled and analysed independently, generating highly credible results. Moreover, patients are followed long after treatment ends, with the aim to detect long-term side effects. BIG studies are also governed by committees and policies designed to reduce bias and protect the patient. Finally, the processes surrounding access by scientists to precious tumour and other tissues donated by patients for future research are subject to strict rules to ensure that only the best research ideas are supported.

#### **Faster results**

BIG has the ability to achieve faster results and greater patient benefits by enrolling larger numbers of patients into clinical trials more quickly, and doing so in many countries around the world.



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KNOWLEDGE THROUGH  
TRANSLATIONAL RESEARCH  
IN BREAST CANCER**

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Martine Piccart, BE and José Baselga, USA

7<sup>th</sup> IMPAKT edition  
**7-9 May 2015**, Brussels, Belgium

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**MAIN THEMES**

The molecular origin of **breast cancer** and **clinical** significance of genomic patterns. Mutations and **therapy resistance**. **Microenvironment** and **metastatic cascade** in breast cancer. Translational studies in early stage breast cancer. The role of chemotherapy in the context of **precision medicine**. **Triple negative** breast cancer: **Tackling diversity**.

Organisers



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