Immunotherapy for breast cancer: what does the future hold?

Interview with Prof. Gabriel N. Hortobagyi

US and EU join efforts to accelerate progress in immunotherapies.

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Immunotherapy for breast cancer: where do we stand?

The modulation of immune checkpoints has led to major advances in melanoma and lung cancers. The first step of these advances was to develop anti-PD-1 and anti-PD-L1. The next steps included developing combination strategies and identifying highly sensitive populations. Indeed, combining anti-PD-1 with other immune checkpoint blockers was found to improve outcome, and biomarker studies are generating a profile of “immune sensitive” disease. Interestingly, most of these studies report long duration of response.

Breast cancer as a whole has not traditionally been seen as an immune sensitive disease. Nevertheless, we have learnt from the past 20 years of translational research that breast cancer includes large numbers of different molecular entities, and some of them are clearly “immune-related” subtypes. First, a subgroup of patients with triple negative breast cancer (TNBC) presents important lymphocytic infiltration and this is associated with good outcome for those who receive chemotherapy. Second, HER2-overexpressing breast cancers present a similar pattern, and whether this could define a specific sensitivity to trastuzumab is still matter of debate. Finally, some patients with hormone receptor positive (HR+) disease present lymphocytic infiltration, but greater effort is needed to better understand its clinical implications.

Interestingly, a subgroup (10%) of patients with HR+ metastatic breast cancer presents a high mutational load, a characteristic that has been associated with sensitivity to anti-PD-1 and anti-CTLA4 (Lefebvre, MAP conference, 2015). The development of anti-PD-1/PD-L1 for patients with breast cancer started later than in other cancers. Data suggest that around 15-20% of patients with metastatic TNBC show an objective response when treated with anti-PD-L1 (Nanda et al. Pembrolizumab in Patients With Advanced Triple-Negative Breast Cancer: Phase Ib KEYNOTE-012 Study. J Clin Oncol. 2016 Jul 20;34(21):2460-7. doi: 10.1200/JCO.2015.64.8931, NCT01848834). These numbers go to 12% when patients have HR+ metastatic breast cancer. From this starting point, several questions have arisen about how to optimise immunotherapeutics in breast cancer.

In TNBC, combining chemotherapy with immunotherapy generated encouraging results, but there is a need to better define which chemotherapies are immunogenic and synergise with anti-PD-1. The development of immunotherapies and combinations of immunotherapies with targeted ones could lead to increased response rates. For example, the combination of PARP inhibitors and anti-PD-1 looks extremely promising, but finding the right combinations remains a challenge for the future.

For TNBC, the impact of anti-PD-1 in the early breast cancer setting will have to be carefully investigated. Indeed, the “immune sensitive” phenotype is associated with very good outcome after chemotherapy, and it probably makes more sense to develop combination therapies in patients with marginally immune sensitive disease than to use anti-PD-1 alone in TNBC that is positive for tumour-infiltrating lymphocytes (TILs).

With regard to HER2 breast cancers, Professor Sherene Loi and colleagues have described a strong synergism between trastuzumab and anti-PD-1. The phase II trial PANACEA (NCT02129556) is now ongoing, under the BIG umbrella (BIG 4-13), to explore this combination. In TNBC and Her2 positive early breast cancer, one of the major challenges will be to show the clinical utility of immunotherapy.

Finally, in HR+ metastatic breast cancer, three questions are being addressed. First, is it possible to better identify the 10% of patients who are sensitive to immunotherapy? Second, is it possible to attract lymphocytes on the tumour bed to render these cancers sensitive to anti-PD-1? And, third, are targeted therapies like PI3K, CDK4, mTOR inhibitors synergising or antagonising with anti-PD-1?

In order to address these questions, BIG has created a task force fully dedicated to immunology. This task force has developed a roadmap. Two clinical trials have or are being started: one in Her2+++ metastatic breast cancer (PANACEA) and one in HR+ breast cancer (ULTIMATE). Discussions are ongoing to develop a trial in TNBC. Finally, another goal of the group will be to validate the clinical utility of immune markers, including TILs assessment.

In Jenny Bryan’s article, leading researchers exchange their views about the potential role of immunotherapies in breast cancer and our current understanding of the immune response to this disease. In addition, an interview of Professor Gabriel N. Hortobagyi gives insight into the trans-Atlantic efforts aiming to move the field of immunotherapies forward faster.

I hope you will enjoy the reading.

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Classifying a woman’s breast cancer according to its immunological profile could soon be as important for determining optimal treatment as testing for hormone sensitivity and targetable genetic mutations. Although clinical trials of novel immunotherapies, such as checkpoint inhibitors, in breast cancer have lagged behind other forms of the disease, researchers have no doubt that the immune system plays an active role in the biology of breast cancer, mediates the efficacy of some anticancer drugs and can be reinforced to destroy tumour cells.

Professor Laurence Zitvogel, from the Gustave Roussy Comprehensive Cancer Institute, Villejuif, France, believes that immunoscopying should be rapidly introduced as part of breast cancer diagnosis, as already happens with colorectal cancer.

“We need to type breast tumours not only on histology and molecular subtype, but also on immunological type. Only when we have the whole picture can we design the treatment best suited for each patient,” she says.

Associate Professor Sherene Loi, clinician-scientist at the Peter MacCallum Cancer Centre, Melbourne, Australia, explains that, although breast cancer is not as immunogenic as melanoma and renal cell carcinoma, which have been the subject of immune based trials going back to vaccines and interferon, immunotherapy still holds great potential.
“It was logical for pharmaceutical companies to go after melanoma and renal cell carcinoma in first proof of concept studies with checkpoint inhibitors, especially as there are already a lot of successful treatments for breast cancer. But now that they have achieved their first regulatory approvals, companies can feel reassured about looking at less immunogenic tumours, such as breast cancer,” she says.

Anticancer immunotherapy has traditionally been classified as “passive” or “active”, depending on whether or not it activates the immune system to attack tumour cells.12 Passive immunotherapy, such as tumour-targeting monoclonal antibodies and adoptive T cell transfer, does not stimulate the immune system but works directly against tumours, while active forms of immunotherapy, such as checkpoint inhibitors and anticancer vaccines, interact with the immune system to stimulate tumour attack.

“The whole idea behind immunotherapy in the broadest sense is that the immune system does detect and fight cancer cells, but we need to find ways to enhance its effectiveness, particularly after it has deteriorated following chemotherapy and radiotherapy,” says Professor Yosef Yarden, from the Weizmann Institute of Science, Rehovot, Israel. “Until now, passive methods, such as monoclonal antibodies, have proved most successful but the newer active treatments such as checkpoint inhibitors are promising.”

Passive immunotherapy in the form of trastuzumab for HER2 positive (HER2+) disease has been part of breast cancer therapy for nearly 20 years but triple negative breast cancer (TNBC) is the main target for active immunotherapy with checkpoint inhibitors.

Dr Marleen Kok, medical oncologist at the Netherlands Cancer Institute (NKI), Amsterdam, The Netherlands, explains that the clinical need is highest in women with TNBC as tumours tend to be more aggressive and there are currently no targeted treatments. However, as there is a subset of women with oestrogen receptor positive (ER+) tumours who have a high mutational load similar to that in melanoma and triple negative disease, these patients may also benefit from checkpoint inhibitors.

“Our goal must be to target the right combination of immune treatments at the right subgroups of patients,” she says.

Professor Yarden agrees. “We need to break down triple negative and other forms of breast cancer into subdivisions according to different markers, and then personalise immunotherapy – antibodies and checkpoint inhibitors, singly or in combination – for each patient.”

Although breast cancer has not been first in the queue for checkpoint inhibitors, researchers have been aware for some time that both radiotherapy and some forms of chemotherapy, notably anthracyclines, cyclophosphamide and nab-paclitaxel, have immunogenic effects in breast cancer. They can stimulate infiltration of T lymphocytes into tumours – a key component of the immune response against cancer.

For this reason, chemotherapy and other T cell activators are being combined with checkpoint inhibitors in breast cancer studies to enhance their efficacy.

“The aim of most current forms of immunotherapy is to strengthen the ongoing T cell immune response against a tumour when it is recognised as foreign. In effect, we are not treating the cancer – we are treating the immune system,” says Dr Ton Schumacher, Principal Investigator at the NKI, Amsterdam, The Netherlands.

He explains that, for an effective immune response against cancer, there needs to be a tumour that is sufficiently foreign, a patient with an immune status strong enough to mount an immune response, and immune cells that can access the tumour site. Even then, tumour cells may influence the local immune response by a number of different processes such as expression of ligands for T cell checkpoints and production of inhibitory metabolic factors.3

“Only when all conditions are right can an effective immune response develop and, for each individual patient, we need to work out which aspect of the cancer-immune interaction has something wrong and tailor therapy to it,” says Dr Schumacher.

Building a better immune response

Raised levels of tumour infiltrating lymphocytes (TILs) correlate well with good outcomes in both TNBC and HER2+ breast cancer.15 But, in an
estimated two thirds of patients, the T cell response is inadequate, and researchers are investigating how to change this.

Professor Zitvogel suggests that immunoscopying should include a breast tumour’s major histocompatibility class (MHC) positivity/negativity, interferon signalling pathways and TIL status, and whether the immune infiltrate is stimulatory, regulatory or exhausted.

“One option to improve T cell response is to modulate the epigenetic modifiers in breast tumour epithelial cells so that they promote secretion of chemokines which recruit T cells towards tumour beds,” she says.

Professor Zitvogel explains that other approaches being investigated include local injections of toll-like receptor agonists, such as polyICLC, interferon type 1 or autophagy-inducing caloric restriction mimetics (CRMs) to recruit T cells into tumours. In a Phase I/II trial, it is planned to inject various combinations of these agents into breast tumours a few weeks prior to surgery so the impact on T cell recruitment can be assessed in biopsy samples.

Local injections of checkpoint inhibitors, such as anticytotoxic T-lymphocyte antigen 4 (CTLA4) or anti-OX40 antibodies, also have potential. By depleting regulatory T cells that suppress effector T cells such as cytotoxic and helper T cells, they may also encourage TILs into tumour beds, adds Professor Zitvogel.

As macrophage infiltration into tumour beds is undesirable, a further technique for optimising the immune response is to inject macrophage depleting agents, such as colony stimulating factor 1 (CSF1) receptor inhibitors, and indirectly aid T cell proliferation.

Getting plenty of TILs into tumour tissue is important but it does not guarantee their effectiveness, points out Professor Zitvogel. She describes one approach to exploit HER2 receptors on tumours in women with HER2+ breast cancer to make TILs work more efficiently. Bispecific antibodies have been developed that crosslink the T cell receptor or CD3 co-receptor with tumour HER2 antigens, making TILs more effective in destroying cancer cells. Also in development is a bispecific antibody which works in a similar way with CD3 and carcinoembryonic antigen (CEA).

“This is a very promising approach and could be a quick way of triggering local immunity for tumours that are already infiltrated but where the TILs are not working efficiently because their affinity for antigens is too low. As trials are already underway, it is something we could see in clinic before very long,” says Professor Zitvogel.

Even when TIL numbers and efficiency are addressed successfully, a further challenge facing researchers is how to resuscitate TILs that become exhausted following a prolonged, often chemotherapy-induced, immune response. This has already been seen in patients with melanoma, and Professor Zitvogel predicts that it will also need to be addressed in breast cancer, by investigating novel immune checkpoints or inhibitory pathways.

“Although we are making progress in understanding a lot of the mechanisms for optimising and maintaining the immune response against breast cancer, we still have a long way to go. My preference would be to intervene earlier in the disease – in locally advanced disease prior to surgery – when we can have the greatest impact on the immune response,” she says.

The checkpoint inhibitor revolution

Checkpoint inhibitors, which are currently taking the world of oncology by storm, “release the brakes” on T lymphocytes by binding to key regulatory proteins of the immune system – CTLA4, programmed death 1 (PD-1), or programmed death ligand 1 (PD-L1). While CTLA4 influences T cell activation, the PD-1–PD-L1 pathway addresses T cell exhaustion and tolerance.6

The CTLA4 inhibitor, ipilimumab, and the PD-1 inhibitors, nivolumab and pembrolizumab, have all shown efficacy in advanced melanoma, and are now licensed for use in that indication in many countries. Nivolumab is also approved for the treatment of non-small cell lung cancer (NSCLC) and renal cell carcinoma, and pembrolizumab has shown additional activity in a number of tumour types.

Although we are making progress in understanding a lot of the mechanisms for optimising and maintaining the immune response against breast cancer, we still have a long way to go. My preference would be to intervene earlier in the disease – in locally advanced disease prior to surgery – when we can have the greatest impact on the immune response.

Prof. Laurence Zitvogel
Early monotherapy studies of checkpoint inhibitors in breast cancer suggest a role for PD-1/PD-L1 inhibitors rather than CTLA4 inhibitors, but results have generally been less impressive than in some other forms of cancer.

However, Associate Professor Loi points out that the PD-1/PD-L1 status of women in early studies of checkpoint inhibitors in breast cancer was not well defined, and often available only from archival biopsies rather than samples taken immediately before the start of treatment. So it is unclear whether treatment was tested in women with PD-1/PD-L1 positive tumours who were most likely to benefit.

The good news is that, when responses to checkpoint inhibitor treatment are achieved, they are likely to be durable: “We are seeing women with incurable triple negative breast cancer still in remission after two years of treatment, and that isn’t something we were used to seeing in this group of patients,” says Associate Professor Loi. “We don’t see it in everyone but, when they do respond, it’s a fabulous thing because it’s fairly non-toxic treatment.”

She explains that patients in trials who achieve objective tumour shrinkage at first re-staging, at nine to twelve weeks, are those most likely to do well.

There is considerable interest in the Phase II Keynote 086 study which is testing pembrolizumab in women with metastatic TNBC. Cohorts include pre-treated women with any PD-L1 status and previously untreated patients with PD-L1 positive tumours. It is hoped that initial results will be reported next year. If good responses are seen in women with PD-L1 positive tumours, a substudy will be performed of pembrolizumab in women with strongly positive PD-L1 tumours.

Other checkpoint inhibitors, such as OX-40, ICOS and CD 137 agonists and IDO inhibitors, are being investigated in some types of cancer. But until potential checkpoint targets are better defined in breast tumours, it remains too early to know whether other agents may play a role in therapy.

Combination strategies: the new promise

Having demonstrated a role for checkpoint inhibitors as single agents in cancer therapy, many researchers believe that the greatest potential lies in combining them with conventional chemotherapy, novel targeted therapies, radiotherapy, other checkpoint inhibitors or alternative types of immunotherapy.

IMpassion 130 is a Phase III study evaluating the addition of the PD-L1 inhibitor, atezolizumab, to nab-paclitaxel as first line treatment for newly diagnosed advanced TNBC and is powered for an overall survival (OS) benefit. Keynote 355 is another Phase III study, and will study pembrolizumab in combination with chemotherapy versus chemotherapy alone in women with previously untreated locally recurrent inoperable or metastatic TNBC, with OS among the endpoints.

In women with advanced HER2+ breast cancer, the International Breast Cancer Study Group’s PANACEA study (BIG 4-13) is investigating the combination of pembrolizumab and trastuzumab and it is hoped that this, like Keynote 086, will report next year.

Dr Kok explains that the chemotherapy/immunotherapy combination may be particularly appropriate for patients with very aggressive tumours which are likely to progress while waiting for the usually slower-onset checkpoint inhibitors to start working.

“The question is whether chemotherapy and immunotherapy are working in synergy from the start, or if chemotherapy buys time at the beginning by reducing tumour load, while we wait for the immunotherapy to kick in,” says Dr Kok.

She and her colleagues are currently recruiting patients with TNBC to the Phase II TONIC study of nivolumab in combination with low doses of different types of chemotherapy or low dose radiotherapy. Dr Kok explains that preclinical
Monoclonal or polyclonal?

A combination strategy is already proving successful in passive immunotherapy for women with HER2+ breast cancer using targeted antibody treatment with trastuzumab combined with pertuzumab and chemotherapy. As Professor Yarden explains, the original Nobel Prize winning development of monoclonal antibodies (MCA) was a groundbreaking technological advance and led to the development of valuable MCA therapies, natural human immunity is based on a polyclonal rather than a monoclonal approach.

“The immune system uses polyclonal antibodies and directs antibodies at every single possible antigenic determinant – sometimes dozens at a time. We always see the immune system decorating antigens from all possible angles with different antibodies, and we now need to move away from monoclonal treatment and build more sophisticated combinations to mimic what happens naturally,” he says.

Professor Yarden differentiates between hom-combinations that use two or more MCA’s to the same antigen (e.g., trastuzumab and pertuzumab against HER2), and hetero-combinations in which MCA combinations act against different antigens (e.g., ipilimumab against CTLA4 and nivolumab against PD-L1).

“I would say that using as few as two monoclonals amounts to polyclonal antibody treatment, but it could be many more than that. We are already seeing four or six antibodies being used in combination in animal models,” he says. “In experimental systems, we may see monoclonal antibodies with little or no activity, but, when we mix some of them together, we often see synergies.”

However, as Professor Yarden points out, there may be significant regulatory challenges in getting such combinations approved.

“Ipilimumab and nivolumab had both been approved as individual agents, so getting approval for the combination was not a problem. That could be very different in the future for combinations of antibodies that are not licensed individually because they showed minimal activity as monotherapy, but have considerable potential in combination.”
However, improvements are needed in both vaccine design and in the techniques used to identify the neoantigens that are most likely to be needed for a vaccine.

At present, genomic information is compared for healthy and tumour tissue to predict which mutations may be presented to the immune system, but these predictions are not yet sufficiently accurate and vaccines that are generated may contain epitopes that are not relevant.

"When patients are given current generation neoantigen-based vaccines, they do mount an immune response, but it is not profound," says Dr Schumacher. "We need to improve our ability to identify the most relevant neoantigens and then build a vaccine around them for patient specific treatment. If we can solve those two issues, it is quite likely that there will be synergy between vaccines and checkpoint inhibitors – first mounting a strong immune response and then enabling those T cells to work at maximum capacity at the tumour site."

Dr Schumacher and his colleagues have developed a platform to help streamline the process of using genomic information to identify suitable neoantigens for vaccines and then test them for their ability to generate an immune response. Human leucocyte antigen (HLA) reagents are loaded with a patient’s mutant peptides and exposed to T cells from their peripheral blood or tissue sample to see if they react against them.

"Initially we used the platform to understand whether recognition of neoantigens is common in human disease but we are now starting to use it to help guide clinical studies. For example, we are currently following the immune response against neoantigens in peripheral blood of patients with Stage III melanoma during anti-CTLA4 and anti-PD-1 treatment to help us determine the best time to give checkpoint blocking therapy," says Dr Schumacher.

Neoantigen vaccines have advantages over vaccines using antigens, such as prostatic acid phosphatase in the prostate cancer vaccine sipuleucel T, because they are only found in tumour cells and are therefore perceived as totally foreign by the immune system. But, as Dr Schumacher points out, they have the disadvantage that they are unique to each patient because every tumour has different mutations.

"They will need to be patient-specific vaccines but, to those who see this as impossibly difficult and expensive, I would say that the same is true of surgery. Each operation is patient-specific, but we still do it because it works!" he says.
Rethinking traditional trial design for immunotherapy

Immunotherapy is turning key elements of traditional chemotherapy trial design on their head. Patients typically take longer to show signs of response, progression free survival (PFS) may be less indicative of likely benefit, and overall survival (OS) is regaining its status as pre-eminent outcome measure.

Clinicians are getting used to the fact that they are unlikely to see tumour shrinkage in response to breast cancer immunotherapy after a single cycle of treatment; indeed the tumour volume may increase initially due to infiltration by T cells and other immune cells. A response may only become visible after two or more cycles of treatment.

"With conventional chemotherapy, a patient with a chemosensitive tumour may walk into your office and tell you they can't feel their lump any more, but that's very unlikely to happen with immunotherapy. I would say that, with nivolumab, it takes several weeks to get an impression of the response," says Dr Kok.

Lessons have been learned from early studies of ipilimumab in which low response rates of 5% to 15% in melanoma could have resulted in the drug being discarded. Instead, measures of clinical efficacy were redefined to include delayed response, prolonged stable disease and response in the presence of new lesions to give an overall detectable effect of 30%. In a subsequent Phase III study, PFS was approximately three months, while OS was just over 10 months.

Dr Kok explains that objective response has been low in clinical trials of immunotherapy in breast cancer, and it is too early to say whether this correlates with survival. However, it has been suggested that a combined endpoint of overall response and duration of response may be a better endpoint than overall response alone.

"You may see a patient whose response is not enough to call it a partial response but if the duration is very long, it's very likely that treatment will benefit the overall clinical picture. It's too early to change the regulatory process, but we need to discuss what direction we should go with our endpoints, and I think we will see changes for immunotherapy trials over the next five to ten years," says Dr Kok.

Which biomarker?

Being able to predict which patients with breast cancer are most likely to respond to immunotherapy is an important priority both for clinicians and for payers who are being called upon to fund what are inevitably expensive treatments.

PD-1/PD-L1 expression on tumours and the presence of infiltrating immune cells appeared to be logical choices of biomarkers for predicting response to inhibitors of these checkpoints. But, although there is evidence from some cancer studies that patients with PD-1/PD-L1 positive tumours respond better to inhibitors such as nivolumab and pembrolizumab than those whose tumours are negative for these biomarkers, the link is not universal.

For example, in a key Phase III study of nivolumab versus docetaxel in advanced squamous NSCLC, the survival benefit of nivolumab was seen in all patients, irrespective of PD-L1 expression. It was suggested that use of archival tumour tissue may not have reflected PD-L1 status during treatment and that other complex interactions between tumour and immune system may have played a role.

Dr Schumacher points to additional potential predictive biomarkers including mutation burden, extent of CD8 tumour infiltration and genetic signatures that reflect ongoing T cell activity, such as induction of genes that are expressed upon local production of interferon gamma. Data, especially in melanoma, also support the use of biomarkers including absolute lymphocyte count, C reactive protein and lactate dehydrogenase.

"I don't think there will ever be a single biomarker and there's more likely to be a combination of biomarkers that will guide treatment decisions, but it will take a while before we know the optimal combination, which will of course vary between tumour types," says Dr Schumacher.

Associate Professor Loi agrees that clinical endpoints may need to be revised and points out that, in a number of studies in lung cancer and renal cell carcinoma, PFS results have been equivocal, but OS has shown significant benefit. She suggests it may therefore be more useful to look at the slope of PFS – the slowing down of progression rather than the result at any particular time point. But endpoint decisions may be further complicated because researchers may see a reversion to more typical patterns of response when immunotherapy is combined with chemotherapy.

"It does appear that immunotherapy is slowing the course of disease rather than triggering a rapid response, and most studies are currently powering for overall survival as well as progression free survival," says Associate Professor Loi.

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Professor Sherene Loi
**Meet the experts**

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**Extending the benefit of immunotherapy to more patients: a challenge**

As with most novel forms of cancer treatment, early immunotherapy studies in breast cancer have been done mainly in the advanced setting when most patients will have received multiple courses of treatment. Their immune system may already be very suppressed, making it hard to reactivate it.

Having demonstrated proof-of-concept in women with heavily pre-treated TNBC, researchers are turning their attention towards earlier line treatment where they believe immunotherapy may have the greatest chance of success.

“Newly diagnosed women with advanced disease and those who haven’t had a lot of treatment are likely to have more pre-existing immunity that we can enhance, but it’s going to be challenging to find the right patients in the advanced setting,” says Associate Professor Loi.

She adds that bone and liver, to which breast cancer frequently spreads, may be more immunosuppressive microenvironments compared with the lung, so immunotherapy may seem less effective simply due to the sites of metastases.

In early stage disease the focus is likely to remain with TNBC as hormone sensitive disease appears to have less immune infiltrate involvement and there are currently plenty of other effective treatment options.

Associate Professor Loi explains that there is a lot more immune infiltration in triple negative disease and immune activation is correlated with survival, making TNBC a more rational option for proof-of-concept studies in early stage disease.

“I think there will be a subgroup of women with oestrogen receptor breast cancer who may benefit from immunotherapy, but at this stage it’s difficult to know exactly who they are. So it’s better to focus attention on early stage triple negative disease at this time,” she says.

Immunotherapy is already being evaluated as neoadjuvant treatment in TNBC, for example, pembrolizumab is being investigated in combination with chemotherapy as neoadjuvant therapy in TNBC (Keynote 173) and the anti-PD-L1 antibody, durvalumab, is being studied with nab-paclitaxel and dose-dense chemotherapy in women with stage I-III TNBC.

“Many triple negative and HER2-positive breast cancers can be cured with current forms of chemotherapy/trastuzumab therapy but their use is associated with risk of long term cardiac damage and secondary cancers such as leukaemias,” concludes Associate Professor Loi. “Combining chemotherapy with immunotherapy may enable us ultimately to de-escalate chemotherapy and reduce that risk, but it will be a while before we have those answers.”

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**References**

Improving knowledge about immunotherapy and its biological and clinical aspects
Outcome of the BIG-NABCG annual meeting 2016

For more than ten years now BIG and the North American Breast Cancer Group (NABCG) have been meeting annually and in topic-specific working groups. Together they identify difficult aspects of breast cancer research and collaborate to resolve common problems. This collaboration is supported by the generous help of the Breast Cancer Research Foundation. Throughout the year, experts in the working groups join efforts to debate issues and design new research projects suitable for the two networks. This collaborative work concludes with a yearly two-day brainstorming meeting held alternatively in the US and in Europe.

Chaired by Professor Gabriel Hortobagyi1 and Professor Fabrice André2, the 2016 edition of the BIG-NABCG annual meeting took place in Chicago on 1-2 June and focused its discussions on the role of immunotherapy in breast cancer research and treatment.

Insights into this intensive meeting and the trans-Atlantic collaboration are described here by Dr Gabriel Hortobagyi.

Why a specific focus on breast cancer (BC) immunotherapy for this year’s BIG-NABCG meeting?

There is much excitement in the oncology world about immunological interventions, especially in view of the marked clinical benefit seen with immunotherapy in malignant melanoma, renal cell carcinoma, non-small-cell lung cancer and other solid tumours. Similarly exciting data are emerging from hematological malignancies. At the same time, there is a strong impression in the breast cancer community that we have reached a plateau with cytotoxic chemotherapy and, to a large extent, endocrine therapy. There is also a realisation that, despite major efforts, it has been a challenge to identify and validate molecular targets in some breast cancer subtypes, such as triple negative breast cancer, and that other therapeutic approaches needed to be explored.
Which themes were discussed and what are the main highlights of the meeting?

First of all, there was much interest in understanding the basic immunology of breast cancer, which is felt to differ from the malignancies traditionally considered for immune interventions. Thus, understanding the mechanisms of development of neo-antigens, surveying what is known about neo-antigens in breast cancer and its various subtypes was felt to be fundamental. In addition, the BIG-NABCG group wanted to explore further the prognostic implications of tumour-infiltrating lymphocytes. It also wanted to understand the possible associations of TILs with genetic anomalies, as well as the complexity of genomic anomalies as predictors of neo-antigen formation and, therefore, the probability of successful targeting with immunotherapy.

What are the main needs in the field of breast cancer immunotherapy that could potentially be unlocked by the BIG-NABCG collaboration?

There is much to be done and much to be learned about breast cancer immunology before successful therapeutic development can be undertaken. It is clear that breast cancer has not been considered as “immunogenic” as other human tumours (e.g., melanoma, renal cell carcinomas, etc.). We also know very little about methods that might enhance the immunogenicity of breast cancer and its subtypes. For instance, there is much interest in studying the effects of conventional therapies (chemotherapy, radiotherapy, etc.) on the development of neo-antigens or the formation and migration of TIL deposits in primary and metastatic breast cancer. There are so many aspects of this puzzle that, in order to accelerate progress, we need multiple teams and multiple laboratories to focus on these questions.

There are multiple avenues of immunological intervention that could be explored: checkpoint inhibitors, vaccines, CAR-T cells, and combinations of each of these with each other or with conventional therapies. All these avenues might need to be explored and a division of labour would move the field forward faster than independent and uncoordinated efforts.

What can we achieve with a trans-Atlantic collaboration: what are the future areas of potential therapeutic gain? What would be the best strategy for joint biomarker research?

There is much expertise in breast cancer research on both sides of the Atlantic, where there is also much expertise in cancer immunology (although not necessarily focused on breast cancer). Ideally, teams that focus on fundamental immunological research and teams that have expertise in breast cancer and developmental therapeutics should be brought to collaborate. Since there are so many questions to be answered and so many therapeutic options, it would be helpful to coordinate efforts so that most questions can be answered in an organised manner. In addition, because of technological heterogeneity, it might be helpful to approach similar (or even identical) problems with different technological strategies. This would enhance the probability that the answers found are indeed accurate and reproducible.

The US Cancer Moonshot initiative was launched recently, with a dedicated working group on breast cancer immunotherapy. What are the goals of this working group? Will NABCG be involved in this effort?

The US Cancer Moonshot is indeed an exciting opportunity to create even greater awareness about cancer research and its challenges. It is also the perfect moment to induce greater involvement from the wider population and political decision makers in fundraising, fund allocation and overall support of cancer research. Having said that, this effort will represent a token contribution to the overall cancer research effort. The portion of the Moonshot focused on breast cancer immunotherapy will help to expand ongoing efforts with checkpoint inhibitors in triple negative breast cancer. As discussed previously, this is a small and limited aspect of a much bigger field and the NABCG needs to make sure it does not limit its concerted efforts. It is crucial to learn broadly about breast cancer immunology, assess and develop multiple approaches to therapeutic immunology, and prioritise efforts on the basis of the best evidence developed by multiple teams and laboratories. In this, we hope to partner with BIG, so that jointly we can accelerate progress, distribute effort and expedite the integration of immunology and immunotherapy into the diagnosis and management of breast cancer.

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A trial involving 500 patients from about 100 hospitals worldwide

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The POSITIVE study will evaluate the pregnancy outcomes and safety of interrupting endocrine therapy for young women with ER+ breast cancer who wish to become pregnant.
Our vision: Together we will find a cure for breast cancer through global research and collaboration

The Breast International Group (BIG) is a not-for-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 56 groups and data centres based in Europe, Canada, Latin America, the Middle East, 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 interacting force in the breast cancer research arena.

www.BIGagainstbreastcancer.org

The 56 breast cancer research groups of the BIG network

ABCSG
Austrian Breast & Colorectal Cancer Study Group

AGO-B
Arbeitsgemeinschaft Gynäkologische Onkologie Breast Study Group

ANZ BCTG
Australia & New Zealand Breast Cancer Trials Group

ARGASY-DINECO
Association de Recherche dans les Cancers dont Gynécologiques – Groupe d’Investigateurs Nationaux pour l’Étude des Cancers Ovariens et du sein

BGICS
Breast-Gynaecological International Cancer Society

BIEI
Breast Intergroup of Eastern India

BOOG
Borstkanker Onderzoek Groep

BREAST
Breast European Adjuvant Study Team

CCTG
Canadian Cancer Trials Group

CEECO
Central and East European Oncology Group

CT-IRE
Cancer Trials Ireland

CTRG
Cancer Therapeutics Research Group

DBC
Danish Breast Cancer Cooperative Group

EORTC BCG
European Organisation for Research and Treatment of Cancer, Breast Cancer Group

FBCG
Finnish Breast Cancer Group / Suomen Rintasyöpäpäryhmä

FBI
Francilien Breast Intergroup

GAICO
Grupo Argentino de Investigacion Clinica en Oncologia

GEICAM
Grupo Español de Investigacion en Cancer de Mama

GBG
German Breast Group

GECO PERU
Grupo de Estudios Clinicos Oncologicos Peruano

GECAM
Grupo Español de Investigacion en Cancer de Mama

GCCHI
Chilean Cooperative Group for Oncologic Research

GOCR
Grupo Oncologico Cooperativo Uruguayo

GOIRC
Italian Oncology Group for Clinical Research

GONO
Gruppo Oncologico Nord-Ovest

HBSS
Hellenic Breast Surgical Society

HeCOG
Hellenic Cooperative Oncology Group

HKBOG
Hong Kong Breast Oncology Group

HORG
Hellenic Oncology Research Group

IBCG
Icelandic Breast Cancer Group

IBCSG
International Breast Cancer Study Group

IBG
Israeli Breast Group

IBIS
International Breast Cancer Intervention Studies

ICCG
International Collaborative Cancer Group

ICON ARO
Indian Co-Operative Oncology Network

ICRC
Iranian Cancer Research Center

ICR-CTSU
Institute of Cancer Research – Clinical Trials & Statistics Unit

IIOG
Indian Oncology Study Group

ITMO
Italian Trials in Medical Oncology

JCBCG
Japan Breast Cancer Research Group

LACOG
Latin American Cooperative Oncology Group

MICHIELANGELO
Fondazione Michelangelo

NBCG
Norwegian Breast Cancer Group

NCRI-BCSG
National Cancer Research Institute - Breast Cancer Clinical Studies Group

SABO
Swedish Association of Breast Oncologists

SAKK
Swiss Group for Clinical Cancer Research

SBCG
Sheba Breast Collaborative Group

SweBCG
Swedish Breast Cancer Group

SKMCH & RC
Shaukat Khanum Memorial Cancer Hospital & Research Centre

SLO
Société Luxembourgeoise d’Oncologie

SOLO
Study Group

TCG
Taiwan Cooperative Oncology Group

TROG
Trans Tasman Radiation Oncology Group

UCBG
Unicancer Breast Group

WSG
Westdeutsche Studiengruppe
15th St.Gallen International Breast Cancer Conference 2017
Primary Therapy of Early Breast Cancer – Evidence, Controversies, Consensus
15–18 March 2017, ACV (Austria Center Vienna), Vienna/Austria

Abstract Submission Deadline 15 December 2016

Information
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The goal of the IMPAKT Breast Cancer Conference is to build bridges between researchers and clinicians by turning the latest scientific discoveries and new technologies into real improvements for breast cancer patients.

**Chairs**
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Sibylle Loibl, Neu-Isenburg, Germany