



## Canadian initiatives for locally advanced breast cancer research and treatment: inaugural meeting of the Canadian Consortium for LABC

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### ABSTRACT

The inaugural Canadian Consortium for LABC (locally advanced breast cancer) conference was held at Langdon Hall, Cambridge, Ontario, April 11–12, 2010. The meeting focused on current and future directions in LABC treatment and research, the specific benefits of LABC as a model for clinical and translational research, strategies for increased national and international collaboration, and ongoing clinical trials. Exciting Canadian initiatives in LABC research are underway, focusing on identifying molecular signatures that will allow for the development of new tailored therapies. The challenge of identifying patient subgroups for accrual is being addressed through strategies to foster and improve national collaboration. This meeting report includes highlights from each presentation at the conference.

### KEY WORDS

Breast neoplasms, cancer treatment, clinical research, translational research, neoadjuvant therapy, biomarkers

### 1. INTRODUCTION

Driven by the advent of molecular profiling and the development of novel targeted therapies, the landscape of breast cancer research and treatment is changing rapidly. This situation is particularly true in the setting of locally advanced breast cancer (LABC), which provides a unique platform for testing the efficacy of new therapies and a forum for correlative tissue studies, allowing for an increased understanding of the effects of these therapies *in vivo*. The hope is that this preoperative model will allow for more rapid development of new treatments and individualized treatment strategies. This new direction has resulted in unique opportunities for clinical and scientific collaboration. The Canadian Consortium for LABC (COLAB) is a multi-disciplinary

team of oncology professionals dedicated to the advancement of LABC research and treatment. The consortium offers diverse expertise in basic and translational research, medical oncology, radiation oncology, pathology, surgery, nursing, and pharmacy, among other specialties. Its vision is to drive progress through increased collaboration across disciplines and throughout Canada. Specific goals include promoting abundant high-quality local basic, translational, and clinical research, and facilitating working relationships, ultimately establishing the infrastructure necessary to launch Canadian-initiated international research trials.

The inaugural 2-day COLAB meeting, held April 11–12, 2010, was chaired by Dr. Muriel Brackstone from London Health Sciences Centre, London, Ontario. Conference highlights included presentations from keynote speaker Dr. Dennis Slamon and a host of Canadian experts addressing the history of, and current and future directions in, LABC treatment and research; the specific benefits of LABC as a model for current clinical research; strategies for increased national collaboration; and ongoing clinical trials. The interactive sessions of the COLAB meeting fostered unique opportunities for academic debate and nurtured collaboration, resulting in a productive step toward increasing collaborative research in Canada.

### 2. MEETING SESSIONS

#### 2.1 Keynote Lecture – Molecular Diversity of Human Breast Cancers: Biologic and Therapeutic Implications

**Presenter:** Dennis J. Slamon, Geffen School of Medicine, University of California at Los Angeles, Los Angeles, California

Locally advanced breast cancer is a heterogeneous disease, with a high degree of molecular variability, vast differences in histopathology, and varying patterns of disease progression and outcome. Traditional

approaches to treatment have been based on a “one size fits all” assumption, without an in-depth understanding of the biology and diversity of the disease. Recently, a more tailored approach to therapy has revolutionized thinking about breast cancer research and treatment. The goal of this new approach, often called the “bench to bedside” approach, is to develop more effective and less toxic therapies through the clinical translation of biologically relevant molecular information. The development of trastuzumab (Herceptin: Genentech, San Francisco, CA, U.S.A.), a monoclonal antibody directed at the human epidermal growth factor receptor 2 (HER2) oncoprotein, marks a major success of this approach to therapy.

The clinical translational approach begins with target identification through molecular analysis of tumour specimens and comparison with histopathologic features and disease outcomes. The next step is molecular target validation, which involves preclinical confirmation *in vivo* using cell lines and animal models and development of agents that modulate expression or function of the target molecule. In clinical trials, validated methods of target modulation are applied to human disease—the context in which the molecular target was originally identified. Subsequent trials then develop and refine the use of targeted agents by varying the dosing, schedules, and combinations with other treatment agents.

Further clinical translational research promises to improve existing therapies as more pathway alterations are recognized in primary tumours and new targets are identified and validated. Large adjuvant studies such as BETH (NCT00625898 at [clinicaltrials.gov/ct2/search](http://clinicaltrials.gov/ct2/search)) and ALTO (NCT00490139 and NCT00553358 at [clinicaltrials.gov/ct2/search](http://clinicaltrials.gov/ct2/search)) focus on the clinical validation of molecular concepts and offer particular promise for advancing early breast cancer treatment. The key challenges of translational research are the definition and identification of patient subpopulations that are eligible for molecularly-directed therapy and the optimal use of such agents in combination with standard therapies.

## 2.2 Plenary Lecture – NSABP: Historical Perspective and Future Directions for LABC

**Presenter:** André Robidoux, University of Montreal, Montreal, Quebec

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has been integral in defining the treatment landscape of LABC. That group’s trials, among others, have established the equivalence of neoadjuvant and adjuvant therapy, defined chemotherapy standards (for example, B-18, B-27)<sup>1</sup>, and identified the biomarkers predicting outcomes of targeted therapy (for example, FB-AX-003)<sup>2</sup>. The NSABP has made important advances in incorporating targeted therapy such as bevacizumab (for example, FB-4

and FB-5)<sup>3,4</sup>, and ongoing trials continue to explore emerging strategies such as integration of the oral irreversible pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor pazopanib and use of the dual HER2 receptor and epidermal growth factor receptor tyrosine kinase inhibitors neratinib (HKI-272) and lapatinib [for example, FB-6, FB-7, and B-41 respectively (NCT00849472, NCT01008150, and NCT00486668 at [clinicaltrials.gov/ct2/search](http://clinicaltrials.gov/ct2/search))]. The poly-adenosine diphosphate ribose polymerase inhibitor BSI-201 will also be tested in LABC treatment regimens (B-48)<sup>5</sup>.

This body of research reminds us that LABC is a heterogeneous disease comprising a mixture of slow- and rapidly-growing tumours. Past approaches to preoperative therapy were unselective and based on clinical signs and symptoms. It is now clear that preoperative therapy presents unique opportunities to quickly evaluate new treatments. The ability to monitor response to therapy based on measurable changes in tumour size and on biomarkers of response evident in molecular analyses of tumour samples and the ability to use pathologic complete response (pCR) as a predictor of survival outcomes make this setting well-suited for a rapid assessment of emerging targeted agents. Strategies for future LABC research should include organization of clinics to maximize trial accrual, initiation of trials that enrol patients with high-risk disease (selected by biologic markers) and with postsurgical residual disease, and investigation of specific targets to improve pCR rates.

## 2.3 Plenary Lecture – Reduction in Tumour RNA Integrity Is Associated with Clinical Response to Neoadjuvant Epirubicin/Docetaxel Chemotherapy in Breast Cancer Patients

**Presenter:** Amadeo M. Parissenti, Sudbury Regional Hospital, Sudbury, Ontario

Treatment of certain subtypes of LABC, such as inflammatory disease, can be problematic. Low rates of clinical complete response and pCR in these patients suggest that most patients will experience disease progression. The ability to monitor response to chemotherapy would be highly beneficial, because lack of response could be detected early and alternative treatments such as surgery, radiation therapy, or others may then be used.

Currently, quantification of RNA integrity as a biomarker of response to chemotherapy is under development. Reduced RNA integrity is associated with cell death, and in the context of chemotherapy, cell death indicates a positive response to treatment. In the NCI Clinical Trials Group (CTG) MA.22 trial of docetaxel plus dose-dense epirubicin in LABC patients<sup>6</sup>, the correlation between mid-treatment maximum tumour RNA integrity number (RIN) and drug dose level suggests that RIN is a clear biomarker

of treatment response<sup>7</sup>. Also, although traditional pathology analyses of tumour cellularity at mid-treatment are unable to predict a post-treatment pCR and although other methods for predicting chemotherapy response (for example, fluorodeoxyglucose positron-emission tomography scans) are limited, current data suggest that mid-treatment maximum tumour RIN is predictive of post-treatment pCR<sup>7</sup>. Furthermore, serial oligonucleotide microarrays of samples from patients with threshold RIN values would allow for an analysis of gene cluster expression to identify gene signatures predictive of response to treatment. Further studies are ongoing.

#### 2.4 Plenary Lecture – Neoadjuvant Systemic Therapy: A Surgeon's Revolution

**Presenter:** Jean-Francois Boileau, Sunnybrook Odette Cancer Centre, Toronto, Ontario

The nature of neoadjuvant therapy affords unique opportunities for innovative approaches to breast cancer research and treatment. The systemic administration of neoadjuvant therapy allows for improved breast conservation and *in vivo* tumour response as a biological model for clinical trials and drug development.

Because neoadjuvant therapy precedes surgery, the advancement of LABC research rests in large part with surgeons. Surgeons play a pivotal role in clinical trial accrual and neoadjuvant treatment selection. They are experts in the management of patients selected for neoadjuvant systemic therapy: They order the molecular analyses (for example, estrogen and progesterone receptors, HER2) on the diagnostic core biopsies to guide subsequent treatment, and they often have to arrange for the clipping of lesions and marking of the tumour site to plan for breast-conserving surgery after neoadjuvant therapy. Additionally, surgeons act as research scientists because they can procure core biopsy and surgical samples and are skilled at measuring response to treatment by clinical examination.

The National Comprehensive Cancer Network guidelines indicate that the best management of any cancer patient occurs in a clinical trial. Establishing neoadjuvant chemotherapy as a standard of care for certain subtypes and stages of breast cancer—and favouring delivery of treatment as part of a clinical trial—was the impetus for a new model of patient care formulated at the Sunnybrook Odette Cancer Centre in Toronto, Ontario. In this model, surgeons and medical oncologists run concurrent clinics, allowing them to quickly identify patients who are eligible for neoadjuvant trials and to discuss enrolment with those patients. The clinical trial-based model improves efficiency by facilitating patient accrual and provides the highest quality patient-centred care.

#### 2.5 Plenary Lecture – Neoadjuvant Therapy for Triple-Negative LABC

**Presenter:** Rebecca Dent, Sunnybrook Odette Cancer Centre, Toronto, Ontario

Triple-negative disease is a subset of breast cancer with a unique biologic signature and pattern of disease progression<sup>8</sup>. It represents approximately 15% of all breast cancers and consists of patients with tumours that are estrogen and progesterone receptor-negative and also HER2-negative by immunohistochemistry (1+) or fluorescence *in situ* hybridization, or both. Basal-like breast cancer is another subgroup with a particularly poor prognosis; it also overlaps the triple-negative subgroup. Identification of basal-like disease is often difficult, because a definitive diagnosis requires microarray analysis of an expanded panel of marker genes. Thus, immunohistochemical assays indicating triple-negative status are often used as surrogate markers for basal-like breast cancer, and yet not all triple-negative disease is basal-like.

Retrospective reviews and subgroup analysis of prospective neoadjuvant chemotherapy trials have both provided important insights into the biology and chemosensitivity of triple-negative breast cancer (TNBC) compared with other subtypes. Those studies have consistently reported increased objective response rates and pCRs in TNBC compared with non-TNBC<sup>8–11</sup>.

Although patients with TNBC have an overall increased risk of relapse and death, patients who do achieve a pCR with neoadjuvant treatment have a favourable prognosis that is not statistically different from that in patients with non-TNBC<sup>8,10,12</sup>. Evidence suggests that anthracycline-taxane combinations and dose-dense or metronomic schedules may be particularly effective in this patient group. One of the largest studies to evaluate response to neoadjuvant therapy in TNBC compared with non-TNBC included 1118 patients treated between 1985 and 2004 at the MD Anderson Cancer Center<sup>8</sup>. Patients with TNBC who achieved a pCR had 3-year overall survival rates similar to those in the non-TNBC group (94% and 98% respectively,  $p = 0.24$ ), but patients with TNBC who had residual disease after neoadjuvant therapy had a worse 3-year overall survival (68% vs. 88%,  $p = 0.0001$ ). Although there is no direct evidence to recommend the routine use of neoadjuvant therapy over adjuvant therapy, the neoadjuvant approach provides an opportunity to determine *in vivo* tumour response to chemotherapy and remains an attractive option for the treatment of TNBC.

#### 2.6 Plenary Lecture – Phase 0 and Window-of-Opportunity Studies in Primary Operable Breast Cancer: Are We Ready?

**Presenter:** Stephen Chia, BC Cancer Agency, Vancouver, British Columbia

In an era of targeted treatment strategies, the need to understand the biology of tumour response to targeted drug exposure is increased. Phase 0 and window-of-opportunity (wo) studies likely have little or no immediate benefit for the patient, and yet their results may accelerate the pace of molecular target identification and bench-to-bedside clinical translation.

A phase 0 clinical trial is a first-in-human proof-of-concept study that evaluates target modulation and the biologically effective dose of a new therapeutic agent, including both pharmacodynamic and pharmacokinetic analyses. The phase 0 trial is not designed to provide therapeutic benefit to patients. Unlike traditional dose-escalation phase I trials, only non-toxic drug doses are administered for a short period of time to a limited number of patients with incurable disease.

By contrast, preoperative wo studies involve patients with primary operable breast cancer and target a particular period during the wait for surgery to expose systemic treatment-naïve tumours to targeted agents. The wo studies involve a curable patient population, and therefore more safety and toxicity data on the new therapeutic agents are needed before such studies can be initiated. The ability to assess changes in molecular pathways and signalling before and after exposure to new targeted agents can provide critical insights into the level of specificity of those agents and can aid in the design of future clinical trials.

The future of breast cancer research is likely the more frequent use of combinations of targeted agents with conventional therapies. In Canada, expert investigational teams are motivated to carry out such research initiatives. However, the challenges that remain are to establish the necessary funding and infrastructure (for example, those for imaging, biopsies, tissue acquisition, molecular analysis), to attract the interest of the developers of novel targeted agents, and to ensure timely initiation and completion of wo trials.

### 2.7 Plenary Lecture – Creation of Pan-Canadian Standard Operating Procedures for Patients Receiving Preoperative Therapy for Locally Advanced Breast Cancer

**Presenters:** Nathaniel Bouganim and Mark Clemmons, Ottawa Regional Cancer Centre and University of Ottawa, Ottawa, Ontario

Interest in the use of neoadjuvant therapy in the treatment of LABC is increasing, and greater national collaboration will advance knowledge of LABC and improve treatment outcomes. Those goals will be achieved by increasing the number of available clinical trials, increasing patient accrual, and enabling greater access to existing tissue and data banks. Improved access to those resources will promote

identification of new biologic targets, expedite the development of novel therapeutics, and result in ever-improving treatment strategies.

A particularly important aspect of collaborative clinical research efforts is trial design. Trial design can be enhanced by working with established Canadian and international partners from academia and industry (NSABP, Neo-Big, I-SPY2) who bring significant expertise and experience in trial design and implementation. There is also a need for the development of pan-Canadian standard operating procedures to guide existing collaborative efforts and to standardize the way in which new collaborations are planned and accomplished.

Standardized guidelines for the collection of samples during surgery will promote tissue banking of LABC samples and ensure uniformity of tissue and patient data collection between provinces, thereby improving quality control in the collection and handling of data during trials. Ultimately, design and implementation of standard operating procedures to guide Canadian LABC research in the context of neoadjuvant treatment will provide a wealth of linked clinical data and tissue to researchers while respecting ethical requirements.

### 2.8 Plenary Lecture – Building Successful Clinical Trials for LABC

**Presenter:** John Mackey, Cross Cancer Institute, University of Alberta, Edmonton, Alberta

The biologic diversity of breast cancer is staggering<sup>13,14</sup>, and the application of drugs to unselected patient populations without a specific molecular rationale is unlikely to yield useful results. It is therefore critical to target treatment to specific patient populations defined by the biology of the disease.

Cell lines represent a powerful tool through which the molecular subtypes of common cancers can be represented. The process begins with large panels of cultured breast cancer cells that are characterized by whole-genome expression analysis, comparative genomic hybridization, and DNA sequencing for mutations in key proto-oncogenes and tumour suppressor genes. These cells are then used in high-throughput screening to study drug sensitivity, to identify mechanisms of action for novel agents, and to determine the potential for synergistic activity in combination with other agents. The molecular profiles of drug-sensitive lines are then applied to the breast cancer population to select the patients most likely to respond to clinical therapies.

The chances of success in clinical trials can be greatly improved by planning biology-based trials for molecularly and geographically targeted LABC populations. Trials designed to evaluate efficacy in a subset of patients with a specific set of molecular markers cannot readily be accrued solely within

Canada, which means an increased need for partnerships and a global research perspective. To address those challenges, translational research groups such as Translational Research in Oncology are expanding to South America (Uruguay office) and Mexico with financial assistance from private donors. Basing LABC trials in developing countries with a very high prevalence of LABC improves the local breast cancer care, speeds trial accrual, and augments the research needed to improve breast cancer treatment globally.

### 2.9 Panel Discussion – Exploring Barriers to Tissue Banking and Involvement of the Ontario Institute for Cancer Research

**Panel:** Susan Done, Ontario Cancer Institute and Princess Margaret Hospital, Toronto, Ontario; Tony Magliocco, University of Calgary, Calgary, Alberta; and Sugy Kodeeswaran, Ontario Institute for Cancer Research, Toronto, Ontario

Pathology experts from the Ontario Institute of Cancer Research were invited to participate in a group discussion panel to determine the optimal means of organizing a national shared tumour bank. The discussion addressed issues of setting up and maintaining the tumour bank and the merits of a centralized compared with a virtual tumour approach. A consensus was reached that a virtual approach, with a centralized database linking patient information to details of tumour samples held at individual institutions would be the best starting point. This virtual tumour bank would assist researchers in accessing samples from various institutions, while avoiding the costs and logistical challenges of establishing a centralized tumour bank.

### 2.10 Ongoing Clinical Trials

Ongoing research highlights were presented by Canadian investigators from London and Toronto, Ontario. More information about each trial can be found by visiting the Web sites linked here:

- Phase I/II trial of neoadjuvant chemoradiation for LABC  
**Presenter:** Jacqueline Spayne  
a list of trials for download can be found at [sunnybrook.ca/content/?page=OCC\\_Breast\\_ClinicalTrials](http://sunnybrook.ca/content/?page=OCC_Breast_ClinicalTrials)  
OR  
search for OCT1159 at [www.canadiancancertrials.ca](http://www.canadiancancertrials.ca)
- Functional Imaging of Neoadjuvant Chemotherapy Response in Women with Locally Advanced Breast Cancer  
**Presenter:** Gregory J. Czarnota  
Search for NCT00437879 and NCT00438074 at [www.clinicaltrials.gov/ct2/search](http://www.clinicaltrials.gov/ct2/search)

- Neoadjuvant Concurrent Chemo/Radiation for Locally Advanced Breast Cancer—Translational Clinical Trial to Predict Treatment Resistance  
**Presenter:** Muriel Brackstone  
Search for OCT1202 at [www.ontario.canadiancancertrials.ca/](http://www.ontario.canadiancancertrials.ca/)
- Does Performing a Confirmatory Biopsy at the Time of Metastatic Recurrence Alter Patient Management: DESTINY trial  
**Presenter:** Mark Clemons  
Search for OCT1194 at [www.ontario.canadiancancertrials.ca/](http://www.ontario.canadiancancertrials.ca/)

### 3. SUMMARY

The ever-changing landscape of breast cancer research and treatment is driving a greater interest in, and focus on, the benefits of treating patients in the neoadjuvant setting. The merits of neoadjuvant therapy include the ability to observe tumour response during treatment, the capacity to collect tumour samples, and the ability to characterize molecular response to treatment. The shift to a biology-driven approach and the accelerating pace of translational research highlights the need for increased collaboration across disciplines and throughout the country.

This year's COLAB meeting discussed the current state of clinical and translational research in Canada and established a functional definition of LABC as stages IIB and III disease. It is clear that exciting Canadian initiatives in LABC research are underway, focusing on identifying molecular signatures to allow development of new tailored therapies, on subtyping the patient populations that are most likely to respond to targeted agents, and on developing methods to measure response to treatment in LABC patients. The creation of patient subgroups presents a challenge for patient accrual, which is being addressed by global expansion of clinical trials. The sharing of clinical samples and data to identify patients eligible for trial enrolment and the establishment of funding partnerships are becoming even more critical. Initiatives to foster and improve collaboration are imperative to ensure ongoing progress in LABC research and treatment. Priorities include forming a strong national research infrastructure that supports multidisciplinary national collaboration, establishing partnerships to design and run clinical trials, and creating a nationally linked Web-based platform to facilitate the sharing of clinical data and research materials.

The COLAB is dedicated to ongoing progress in LABC research. Initiatives to increase collaboration continue, as demonstrated by the publication of this manuscript and the organization of the most recent COLAB meeting, which was held at Langdon Hall, Cambridge, Ontario, May 1–2, 2011, and was chaired by Dr. Jean-Francois Boileau. We thank all who attended the inaugural meeting in 2010 and all who helped to make that meeting a

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#### 5. CONFLICT OF INTEREST DISCLOSURES

MB has received research funding (AstraZeneca, Roche) and honoraria (AstraZeneca); AR has received research funding (AstraZeneca, Novartis, Pfizer, Amgen, GlaxoSmithKline, Roche, Abraxis) and honoraria (AstraZeneca, Novartis, Amgen, Pfizer, GlaxoSmithKline, Roche, Abraxis); SC has received research funding (AstraZeneca, Novartis, Roche); JM has received honoraria (Roche, AstraZeneca, Sanofi–Aventis, GlaxoSmithKline, Amgen); RD has received honoraria and consultancy fees (Roche, AstraZeneca, Amgen, Sanofi–Aventis); JFB has received research funding (Burrroughs Wellcome, Hoffmann–La Roche) and honoraria (AstraZeneca, Genomic Health, GlaxoSmithKline, Novartis, Roche, Sanofi–Aventis); MC has received research funding (AstraZeneca, Novartis, Amgen, Pfizer, Sanofi–Aventis) and honoraria (AstraZeneca, Novartis, Amgen, Pfizer, Sanofi–Aventis, Roche).

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