Breast Cancer Steering Committee (BCSC)  
Clinical Trials Planning Meeting (CTPM)  

Next Generation Trials for Estrogen Receptor (ER)-positive Breast Cancer  
May 14-15, 2012  

Meeting Co-chairs: Karen Gelmon, M.D. and Fraser Symmans, M.D.  
BCSC Co-chairs: Nancy Davidson, M.D. and Tom Buchholz, M.D.  

Introduction/Meeting Description  
The National Cancer Institute (NCI) Breast Cancer Steering Committee (BCSC) convened a Clinical Trials Planning Meeting for the Next Generation Trials in Estrogen Receptor (ER)-positive Breast Cancer on May 14-15, 2012 in Bethesda, MD. The goals of the meeting were to address strategies to improve outcomes from clinical trials of any class of treatment in any stage of ER-positive breast cancer with a scientific focus on overcoming mechanisms of resistance to hormonal therapy. This included developing an understanding of key molecular and genetic ‘drivers’ of ER-positive cancers that may be targeted to improve outcomes and recommending directions for future clinical trials in the treatment of ER-positive breast cancer. The meeting attendees included BCSC members, breast cancer clinicians, clinical trials experts, biostatisticians, translational scientists, basic scientists, patient advocates, FDA staff, and NCI staff.  

Background/Importance of Research Topic/Disease/Limitations  
Estrogen receptor (ER)-positive breast cancer leads to for the thousands of lives lost per year in the United States.\(^1\) This breast cancer subtype has a relatively good 5-year prognosis; however, individuals with ER-positive breast cancer continue to relapse over time, making ER-positive breast cancer responsible for the majority of breast cancer deaths.\(^2\) Patients can exhibit *de novo* hormonal resistance or acquired hormonal resistance and there is a need for effective targeted therapies for hormone refractory breast cancer.\(^3\) ER-positive breast cancer is comprised of a very heterogeneous group of tumors.\(^3\) Understanding the very diverse biology of ER-positive breast cancer, mechanisms by which it becomes resistant to hormonal therapy, and identifying promising targeted agents is a high priority. Efforts are ongoing to define molecular markers that could be used to determine which patients with ER-positive disease benefit from chemotherapy and other therapies in addition to hormonal treatment.\(^4\text{-}10\)  

Consensus  
The current North American Cooperative Group system includes several large adjuvant clinical trials, leaving no space for an additional large randomized adjuvant trial of hormonal therapy due to a limited number of patients and resources. Similarly, the current platform in front line hormonal therapy trials for stage IV disease also leaves no space for trial development.
The Cooperative Groups should utilize smaller pre-operative studies and neoadjuvant trials space to address endocrine response. The Cooperative Groups have committed to a large neoadjuvant trial (ALTERNATE).

Considering all of the patients who are just finishing large adjuvant trials, the registry mechanism, as long as it is linked to a parent trial, should be considered for following patients from those trials so that their data can be used to inform the field and future trials.

For premenopausal women with ER-positive breast cancer, results from the SOFT and TEXT trials should be used to determine the next important questions and to design the next trials.

**Recommendations**

- There is a need for common definitions/clinical classification for endocrine resistance, considering early stage and metastatic disease.

- There is a need for standardized guidance on biopsies (compulsory and non-compulsory) and specimen storage.

- The next hormone responsive clinical studies should include the following:
  1. Randomized phase II neoadjuvant studies
  2. Variable designs in metastatic setting
  3. Studies of endocrine therapy backbone plus targeted therapy(ies) or alternating between endocrine therapy plus or minus targeted therapy(ies)
  4. Mandatory biopsies of relapsed disease
  5. Integral biomarkers with clinical assay development plan

**This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.**

**Anticipated Action(s)**

- Publish white papers for scientific and lay communities including key strategic priorities, both near-term and long-term, for future trials.

- Develop and publish common definitions/clinical classification/lexicon for endocrine resistance, standardized guidance on biopsies (compulsory and non-compulsory) and standardized guidance on specimen storage.

- Design concepts for studies as recommended above with input from Cooperative Group representatives, industry, Food and Drug Administration (FDA), Centers for Medicare & Medicaid Services (CMS), and Patient Advocates.
References/Literature

DAY 1: MONDAY, MAY 14, 2012

7:30 AM REGISTRATION Cabinet/Judiciary Suite – Conference Level

8:30 AM – 8:35 AM Welcome and Introduction to the NCI Clinical Trials Planning Meeting
Nancy Davidson and Tom Buchholz, BCSC Co-Chairs

8:35 AM – 8:45 AM Charge for the Clinical Trials Planning Meeting
Karen Gelmon and Fraser Symmans, Meeting Co-Chairs

8:45 AM – 11:50 AM SESSION 1: ENDOCRINE RESISTANCE IN THE CONTEXT OF BIOLOGICAL MODELS
Moderator: Kent Osborne

8:45 – 9:05 Estrogen Receptor and alternative signaling pathways in endocrine resistance
Kent Osborne

9:05 – 9:25 Genomic expression and sequence for endocrine resistant tumors
Matt Ellis

9:25 – 9:35 API activation: the role of AP-1 in endocrine-resistant breast cancer
Rachel Schiff

9:35 – 9:45 ER coregulators
Steffi Oesterreich

9:45 – 9:55 Novel ER-ligands in breast cancer pathogenesis
Donald McDonnell

9:55 – 10:05 Epigenetics of Hormone Resistance
Sara Sukumar

10:05 – 10:25 BREAK

10:25 – 11:40 Moderated panel and audience discussion
Moderator: Kent Osborne
Panel Members: Matt Ellis, Rachel Schiff, Steffi Oesterreich, Donald McDonnell, Sara Sukumar, Patty Spears (Patient Advocate)
11:40 – 11:50 **Session 1 summary**  
*Steffi Oesterreich, Paul Haluska*

**11:50 AM – 1:00 PM** **BREAK**

**1:00 PM – 3:45 PM** **SESSION 2: TRANSLATIONAL RESEARCH OF ENDOCRINE RESISTANCE IN HUMAN SUBJECTS**  
*Moderator: Charles Geyer*

1:00 – 1:20 **Defining endocrine resistance in the clinical setting**  
*Stephen Johnston*

1:20 – 1:30 **Tissue issues in endocrine resistance**  
*Fraser Symmans*

1:30 – 1:40 **Breast Cancer Pharmacogenomics**  
*Matt Goetz*

1:40 – 2:00 **Dealing with large cohorts to define resistance and translating pathway science to clinical samples**  
*Mitch Dowsett*

2:00 – 2:10 **Expectations for integral versus integrated diagnostics within prospective clinical trial designs**  
*Mickey Williams*

2:10 – 2:20 **Tissue-based research in clinical trials: Patient Advocate perspective**  
*Mary Lou Smith*

2:20 – 3:35 **Moderated panel and audience discussion**  
*Moderator: Charles Geyer*  
*Panel Members: Stephen Johnston, Fraser Symmans, Matt Goetz, Mitch Dowsett, Mickey Williams, Mary Lou Smith (Patient Advocate)*

3:35 – 3:45 **Session 2 summary**  
*Lajos Pusztai, Antonio Wolff*

**3:45 PM – 3:55 PM** **BREAK**

**3:55 PM – 4:10 PM** **Accrual issues and NCI AccrualNet**  
*Linda Parreco*

**4:10 PM – 4:40 PM** **Tackling endocrine resistance – the pharmaceutical industry’s perspective**  
*Stephen Johnston*

**4:40 PM – 6:00 PM** **Discussion and wrap-up of day 1**  
*Karen Gelmon and Fraser Symmans*
DAY 2: TUESDAY, MAY 15, 2012

7:30 AM REGISTRATION Cabinet/Judiciary Suite – Conference Level

8:00 AM – 8:10 AM Welcome and charge for day 2
Karen Gelmon and Fraser Symmans

8:10 AM – 11:00 AM SESSION 3: ENDOCRINE RESISTANCE IN THE CONTEXT OF PROSPECTIVE CLINICAL TRIALS
Moderator: Karen Gelmon

8:10 – 8:25 Defining who are likely cured from current chemotherapy +/- endocrine therapy
Fabrice Andre

8:25 – 8:40 Neoadjuvant clinical trial opportunities for ER-positive breast cancer
Angela Demichele

8:40 – 8:50 The most pressing loco-regional questions for clinical trials of ER-positive breast cancer
Marilyn Leitch

8:50 – 9:00 Addressing compliance in clinical trials of oral therapies
Dawn Hershman

9:00 – 9:10 One clinical trial approach to overcome de novo endocrine resistance
Cynthia Ma

9:10 – 9:20 One clinical trial approach to overcome acquired endocrine resistance
Paul Haluska

9:20 – 9:40 How do we design the best trials to address endocrine resistance?
Eric Winer

9:40 – 9:50 BREAK

9:50 – 10:50 Moderated panel and audience discussion
Moderator: Karen Gelmon
Panel Members: Fabrice Andre, Angela Demichelle, Marilyn Leitch, Dawn Hershman, Cynthia Ma, Paul Haluska, Eric Winer, Liz Frank (Patient Advocate)

10:50 – 11:00 Session 3 summary
Cliff Hudis, Edith Perez

11:00 AM – 12:45 PM SESSION 4: WORKING SESSION

11:00 – 11:30 Break-out group charge and audience discussion
Karen Gelmon and Fraser Symmans
11:30 – 11:45  Move to break-out rooms

11:45 – 12:45  Break-out Group Discussions
   1. Biological strategy and targeted therapy
      Location: Susquehanna/Severn/Potomac Suite – Conference Level
      Chair: Jim Ingle

   2. Translational research
      Location: Old Georgetown Room – Conference Level
      Chair: Dan Hayes

   3. Clinical trial strategies
      Location: Cabinet/Judiciary Suite – Conference Level
      Chair: Gabe Hortobagyi

12:45 PM – 12:50 PM  BREAK

12:50 PM – 2:30 PM  SESSION 5: REPORT-OUT, DISCUSSION AND ACTION PLAN
   Location: Cabinet/Judiciary Suite – Conference Level
   Moderators: Nancy Davidson and Tom Buchholz

   12:50 – 1:00  Report-out from biological strategy and targeted therapy break-out group
      Chair: Jim Ingle

   1:00 – 1:10  Report-out from translational research break-out group
      Chair: Dan Hayes

   1:10 – 1:20  Report-out from clinical trial strategies break-out group
      Chair: Gabe Hortobagyi

   1:20 – 2:00  Moderated panel and audience discussion of priorities and post-meeting action plan
      Moderators: Nancy Davidson and Tom Buchholz
      Panelists: Fraser Symmans, Kent Osborne, Jim Ingle, Steffi Oesterreich, Paul Haluska, Dan Hayes, Lajos Pusztai, Antonio Wolff, Karen Gelmon, Gabe Hortobagyi, Cliff Hudis, Edith Perez, Patty Spears (Patient Advocate)

   2:00 – 2:30  Meeting summary and action plan
      Nancy Davidson and Tom Buchholz
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