Breast Cancer Steering Committee
Clinical Trials Planning Meeting

Next Generation Trials for HER2-positive Breast Cancer
May 16-17, 2011

Meeting Co-chairs: Lisa Carey, M.D. and Mark Pegram, M.D.
BCSC Co-chairs: Nancy Davidson, M.D. and Charles Geyer, 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 HER-2-positive Breast Cancer on May 16 -17, 2011 in Rockville, MD. The objectives of the meeting were to review the underlying mechanisms of HER2-positive breast cancer, to discuss issues related to the methodology for assessing HER2-positive breast cancer, to address key questions regarding the resistance to HER2 targeting, to discuss HER2-targeted drugs (including new agents), to discuss other therapeutic targets in HER2-positive breast cancer, and to consider issues (i.e., chemotherapy backbone, endocrine options, toxicities) for designing future trials. The goals of the meeting were to recommend directions for future clinical trials in the treatment of HER2-positive breast cancer, to define a research agenda of clinical trials exploring variables such as agents, dose, schedule, biomarkers, endpoints, and to provide a framework for trials of agents to address overcoming primary and secondary resistance to current HER-2 directed therapies. Meeting attendees included BCSC members, breast cancer clinicians, clinical trials experts, biostatisticians, translational scientists, basic scientists, patient advocates, and NCI staff.

Background/Importance of Research Topic/Disease/Limitations

HER2-positive breast cancers, about 15-20%[1] of breast cancers, are generally more aggressive, respond less to hormone therapy, and are more prone to recurrence than breast cancers that do not over-express HER2. Currently, there are two drugs that target HER2 approved by the U.S. Food and Drug Administration (FDA) for the treatment of HER2-positive breast cancer: trastuzumab and lapatinib. However, a significant number of patients with stage II/III disease relapse in spite of trastuzumab or lapatinib-based regimens, which supports the development of alternative HER2-targeted therapies. Moreover, it is increasingly clear that dual HER2-targeting and ongoing HER2-targeting after progression have clinical value highlighting the importance of this pathway across the spectrum of breast cancer settings. A variety of new agents and approaches to target HER2 are under exploration, including monoclonal antibodies, immunoconjugates (T-DM1), HER2 vaccines, small molecule tyrosine kinase inhibitors, hsp90 antagonists. There is a need to determine which agent(s) should be tested in the next generation of phase II and III clinical trials. In order to develop future trials for HER2-positive breast

cancer, it is also essential to develop a more complete understanding of the mechanisms of resistance to HER2-directed therapies.

Multiple trials combining chemotherapy with HER2-targeting suggest high levels of activity across a variety of regimens.[2] What is less clear is whether there is an optimal chemotherapy to combine with HER2-targeted therapy. It is also important to understand the interactions between anti-HER2 agents and chemotherapy, particularly with the combination of oral agents. Although there are fewer data, similar issues surround combination endocrine therapy and HER2-targeting in hormone receptor- and HER2-positive breast cancer. Future trial design will also need to take into account potential toxicities of HER2-directed agents, including cardiotoxicity.

Among the challenges facing the breast cancer community is the wide number of evolving therapies and combinations of therapies of interest, the improved outcome in breast cancer patients across all stages making clinical trials harder to complete, and the importance of embedded tissue-based studies to optimize our understanding of resistance and sensitivity to these drugs.

Consensus

With numerous agents in clinical development, emerging data suggesting that combination approaches may be superior to single agent HER2-targeting, and the importance of tissue-based studies to understand pharmacodynamics and tumor behavior, the neoadjuvant setting has great appeal. This approach can be exploited by allowing several smaller studies to be run simultaneously in order to inform larger definitive adjuvant trials.

There is value in large adjuvant trials with practice-changing endpoints. Given recent data suggesting a high level of activity and less toxicity of the antibody-drug conjugate T-DM1 as well as the broad use of chemotherapy / HER2-targeted regimens even in low stage HER2-positive breast cancer, there was general agreement that pursuing T-DM1 in the adjuvant setting would be worthwhile.

Recommendations

- Develop neoadjuvant studies: 3 or 4 concurrent HER2 trials randomizing to same control and prospectively planning data collection and sharing.
- Develop plan on how to change community practice to more frequently incorporate the neoadjuvant paradigm.
- There is a need for thoughtful, standardized tissue-based designs with consideration of how to prioritize and emphasize biopsies and tissue collection. The issue with this is that power in adjuvant studies is defined by events (not sample size) and biomarker prevalence.

- The next large adjuvant trials for HER2-positive breast cancer patients should employ the biological agent T-DM1.

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)

- Design concepts for neoadjuvant studies as recommended above.
- Pursue T-DM1 as the next agent for large adjuvant trials.
- Publish white paper including key strategic priorities, both near-term and long-term, for future trials.

References/Literature

1. http://www.cancer.gov/newscenter/qa/2008/alttoqa

2. Hudis, C.A. *Trastuzumab - Mechanism of Action and Use in Clinical Practice*. N Engl J Med 2007; 357:39-51.

AGENDA
Breast Cancer Steering Committee Clinical Trials Planning Meeting
Next Generation Trials for HER2-positive Breast Cancer
Monday and Tuesday, May 16-17, 2011
*****The Legacy Hotel*****
1775 Rockville Pike, Rockville, MD

Meeting Goal: The goal of this Clinical Trial Planning Meeting is to address key questions regarding the resistance to HER2 targeting, to discuss HER2-targeted drugs (including new agents), to discuss other drugable targets in HER2-positive breast cancer, and to recommend directions for future clinical trials in the treatment of HER2-positive breast cancer.

DAY 1: MONDAY, MAY 16, 2011

11:30 AM – 12:00 PM **REGISTRATION**

12 PM **WORKING LUNCH**

12:00 – 12:05 PM **Welcome and Introduction to the NCI Clinical Trials Planning Meeting - Confidentiality**
Nancy Davidson and Charles Geyer, BCSC Co-Chairs

12:05 – 12:15 PM **Charge for the Clinical Trials Planning Meeting**
Lisa Carey and Mark Pegram, BCSC HER2 CTPM Planning Committee Co-Chairs

12:15 – 1:50 PM **SESSION 1: BASIC AND CORRELATIVE SCIENCE AND KEY PATHWAYS FOR HER2-POSITIVE BREAST CANCER**
Moderator: Laura Van't Veer

(12:15 - 12:40) **Refresher: Basic biology, relevant pathways, and drug classes**
Mark Pegram and Neil Spector

(12:40 - 12:55) **Questions and Discussion**

(12:55 – 1:25) **HER2+ behavior in the trastuzumab adjuvant era**
Edith Perez and Charles Geyer

(1:25 – 1:35) **Site-specific tropism – CNS**
Nancy Lin

(1:35 – 1:50) **Questions and Discussion**

1: 50 – 3:15 PM **SESSION 2: STANDARDIZE AND GENERALIZE METHODOLOGY**
Moderator: Craig Allred

(1:50 - 2:10) **Concordance/discordance issues in HER2 testing: The ASCO/CAP effort and its impact**
Antonio Wolff

(2:10 - 2:30) **Available Measures of HER2 Testing: Clinical trials and clinical practice**
Michael Press

(2:30 – 2:50) **Predictive biomarkers for trastuzumab: A comprehensive survey in NSABP-B31**
Soon Paik

(2:50 – 3:15) **Questions and Discussion**

3:15 - 3:30 PM **BREAK**

3:30 – 4:50 PM **SESSION 3: CLINICAL TRIALS EXPERIENCE IN HER2-POSITIVE BREAST CANCER – LESSONS LEARNED AND CURRENT PORTFOLIO**
Moderator: Kimberly Blackwell

(3:30 – 3:45) **Prior and current phase 3 studies: International**
Gunter von Minckwitz

(3:45 – 3:55) **Prior and current phase 3 studies: North American**
Jo Anne Zujewski

(3:55 – 4:10) **Statistical designs and endpoints of phase 3 trials**
Kenneth Hess

(4:10 – 4:25) **Optimizing tissue collection for correlative science**
Brian Leyland-Jones

(4:25 – 4:50) **Questions and Discussion**

4:50 – 6:30 PM **SESSION 4: ISSUES FOR FUTURE TRIALS**
Moderators: Ruth O'Regan and Liz Frank

(4:50 – 5:05) **HER2-resistance**
Ian Krop

(5:05 – 5:35) **Novel HER2-targeted agents in development – phase 1 and 2 studies**
Francisco Esteva

(5:35 – 5:50) **Choice of chemotherapy backbone**
Stacy Moulder

(5:50 – 6:05) **Endocrine options and implications of ER cross talk**
Kent Osborne

(6:05 – 6:20) **Planning for and managing toxicities**
Hope Rugo

(6:20 – 6:30) **Questions and Discussion**

6:30 – 6:45 PM **BREAK**

6:45 PM **WORKING DINNER – PREPARATION FOR DAY 2**
Moderators: Lisa Carey and Mark Pegram

(6:45 – 7:05) **Impact of Cooperative Group Reorganizations and Considerations for Future Trial Planning**
Jeff Abrams

(7:05 – 7:25) **Patient-Reported Outcomes**
Claire Snyder

(7:25 – 7:55) **Biomarker Challenges for Future Trial Planning**
Lisa McShane

SESSION 4 (continued): Panel discussion

Continued discussion: Logistical issues, biomarker challenges, barriers to success, and accrual issues

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DAY 2: TUESDAY, MAY 17, 2011

7:15 – 8:00 AM **Coffee**

8:00 – 8:05 AM **Welcome and Charge**
Nancy Davidson and Charles Geyer, BCSC Co-Chairs

8:05 – 8:10 AM **Summary of Day 1**
Lisa Carey and Mark Pegram, BCSC HER2 CTPM Planning Committee Co-Chairs

8:10 – 8:40 AM **Integration of current trials with unmet needs**

- **Settings**
    - **Neoadjuvant vs. adjuvant vs. metastatic**
- **Approach**
    - **Chemo-based vs. endocrine-based vs. all biologics**

Eric Winer

8:40 – 9:00 AM **Questions and Discussion**

9:00 AM – 2:30 PM **SESSION 5: DEVELOPMENT OF FUTURE TRIALS**
Moderators: Nancy Davidson and Charles Geyer

(10:00 – 10:15 AM) **MORNING BREAK**
(12:15 PM) **WORKING LUNCH**

2:30 – 3:00 PM **Meeting Summary and Future Directions**
Nancy Davidson, Charles Geyer, Lisa Carey, and Mark Pegram

Participants
Breast Cancer Steering Committee Clinical Trials Planning Meeting
Next Generation Trials for HER2-positive Breast Cancer
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First Name	Last Name	Title	Affiliation
Jeff	Abrams	Associate Director	National Cancer Institute
Craig	Allred	Professor	Washington University School of Medicine
Sunil	Badve	Professor	Indiana University
William	Barlow	Senior Biostatistician	Southwestern Oncology Group Statistical Center
Kimberly	Blackwell	Associate Professor of Medicine	Duke University Medical Center
Virginia	Borges	Associate Professor	University of Colorado Cancer Center
Lynn	Butler	Contractor	The EMMES Corporation
Aman	Buzdar	Ad Interim Vice President	The University of Texas M. D. Anderson Cancer Center
Lisa	Carey	Professor of Medicine	University of North Carolina at Chapel Hill
Stephen	Chia	Medical Oncologist	British Columbia Cancer Agency
Patricia	Cortazar	Clinical Team Leader	U.S. Food and Drug Administration
Joseph	Costantino	Director	University of Pittsburgh Graduate School of Public Health
Nancy	Davidson	Director	University of Pittsburgh Cancer Institute
Zoneddy	Dayao	Assistant Professor	University of New Mexico
Susan	Dent	Medical Oncologist	University of Ottawa
Francisco	Esteva	Professor	The University of Texas M. D. Anderson Cancer Center
Liz	Frank	Patient Advocate	Dana-Farber Cancer Institute/Harvard Cancer Center
V. K.	Gadi	Assistant Professor	University of Washington
Charles	Geyer	Director Medical Affairs	National Surgical Adjuvant Breast and Bowel Project Foundation
Elizabeth	Hammond	Professor of Pathology	Intermountain Healthcare
Lyndsay	Harris	Associate Professor	Yale University
Daniel	Hayes	Professor, Clinical Director	University of Michigan Comprehensive Cancer Center
Jennifer	Hayes	Program Director, Breast Cancer Steering Committee	National Cancer Institute
Kenneth	Hess	Professor	The University of Texas M. D. Anderson Cancer Center
Gabriel	Hortobagyi	Chairman	The University of Texas M. D. Anderson Cancer Center

Clifford	Hudis	Chief	Memorial Sloan-Kettering Cancer Center
Sally	Hunsberger	Mathematical Statistician	National Cancer Institute
Deborah	Jaffe	Program Director	National Cancer Institute
Gene	Kraus	Program Director	National Cancer Institute
Ian	Krop	Assistant Professor of Medicine	Dana-Farber Cancer Institute
Constance	Lehman	Professor and Vice Chair of Radiology	University of Washington Seattle Cancer Care Alliance
Ann	Leitch	Professor of Surgery	University of Texas Southwestern Medical Center
Brian	Leyland-Jones	Professor	Emory University
Nancy	Lin	Assistant Professor of Medicine	Dana-Farber Cancer Institute
Tracy	Lively	Associate Chief	National Cancer Institute
Cynthia	Ma	Assistant Professor of Medicine	Washington University School of Medicine
Eleftherios	Mamounas	Medical Director	Aultman Hospital
Jacob	Mathew	Junior Investigator	Mayo Clinic
Worta	McCaskill-Stevens	Acting Chief	National Cancer Institute
Lisa	McShane	Mathematical Statistician	National Cancer Institute
P. K.	Morrow	Assistant Professor	The University of Texas M. D. Anderson Cancer Center
Stacy	Moulder	Assistant Professor	The University of Texas M. D. Anderson Cancer Center
Rita	Nahta	Assistant Professor	Emory University
Ruth	O'Regan	Associate Professor	Emory University
Kent	Osborne	Professor	Baylor College of Medicine
Soon	Paik	Director	National Surgical Adjuvant Breast and Bowel Project
Mark	Pegram	Chief	University of Miami
Edith	Perez	Deputy Director	Mayo Clinic
Raymond	Petryshyn	Program Director	National Cancer Institute
Michael	Press	Professor	University of Southern California
Priya	Rastogi	Associate Director of Medical Affairs	National Surgical Adjuvant Breast and Bowel Project
Steven	Reeves	Program Director	National Cancer Institute
Ken	Rowland	Director of Research	Carle Foundation

Melanie	Royce	Professor of Medicine	University of New Mexico Cancer Center
Hope	Rugo	Professor of Medicine	University of California, San Francisco
Gisele	Sarosy	Interim Medical Director	National Cancer Institute
Victoria	Seewaldt	Professor	Duke University
Claire	Snyder	Associate Professor of Medicine	Johns Hopkins School of Medicine
Joseph	Sparano	Professor of Medicine and Professor of Obstetrics, Gynecology, and Women's Health	Albert Einstein College of Medicine
Patty	Spears	Advocate	Breast Cancer Steering Committee
Neil	Spector	Co-Director	Duke Cancer Institute
Patricia	Steeg	Chief	National Cancer Institute
Sandra	Swain	Medical Director	Washington Hospital Center
Antoinette	Tan	Associate Professor	The Cancer Institute of New Jersey
Abdul	Tawab Amiri	Program Director	National Cancer Institute
E. Aubrey	Thompson	Professor of Biochemistry and Molecular Biology	Mayo Clinic College of Medicine
Laura	Van't Veer	Leader, Breast Oncology Program	University of California, San Francisco
Sunil	Verma	Medical Oncologist	Sunnybrook Odette Cancer Centre
Gunter	von Minckwitz	Managing Director	German Breast Group Forschungs GmbH
Julia	White	Professor of Radiation Oncology	Medical College of Wisconsin
Eric	Winer	Chief	Dana-Farber Cancer Institute
Antonio	Wolff	Associate Professor of Oncology	Johns Hopkins Kimmel Cancer Center
William	Wood	Professor	Winship Cancer Institute of Emory University
Jo Anne	Zujewski	Senior Investigator	National Cancer Institute