

Executive Summary
National Cancer Institute Breast Cancer Steering Committee
Omitting Surgery in Patients with Complete Clinical/Radiologic Response to Neoadjuvant
Chemotherapy: A Paradigm Shift
Clinical Trial Planning Meeting
October 16-17, 2017
Meeting Co-chairs: Thomas Julian, M.D. and Alastair Thompson, M.D.

Meeting Description

The National Cancer Institute (NCI) Breast Cancer Steering Committee (BCSC) convened a Clinical Trial Planning Meeting (CTPM) for Omitting Surgery in Patients with Complete Clinical/Radiologic Response to Neoadjuvant Chemotherapy on October 16-17, 2017 in Rockville, MD. The goal of the meeting was to develop design recommendations for a feasible clinical trial to determine if surgery can be omitted for a subset of breast cancer patients who have a complete clinical/radiologic response to neoadjuvant chemotherapy. The meeting attendees included BCSC members, members of the BCSC Breast Oncology Local Disease (BOLD) Task Force, breast cancer clinicians (medical oncologists, surgical oncologists, and radiation oncologist), radiologists, biostatisticians, patient advocates, and NCI staff.

Background

Certain subtypes of breast cancer patients (triple negative and HER2 positive) have high rates of pathologic complete response (pCR) to neoadjuvant systemic therapy¹. Patients treated with neoadjuvant chemotherapy who achieve a pCR have very low rate of local recurrence and excellent overall survival, leading to interest in the concept of eliminating surgery in these patients. Prior studies^{2, 3, 4} have suggested that it may be feasible to omit surgery, but were not performed using current systemic therapy regimens or imaging techniques. In order for surgery to be safely omitted, there is a need to be able to identify patients that have a high likelihood of achieving a pCR, and therefore a low risk of recurrence. Prior studies have shown clinical exam to have poor predictive value for prediction of pCR. In TBCRC 017, the overall negative predictive value (NPV) of a negative breast MRI was 47%;⁵ NPV improves to 80-87% when multiple imaging modalities are utilized, but this is still not likely sufficient to allow for omission of surgical excision.

Two more recent studies have assessed whether biopsy of the tumor bed can improve prediction of pCR in patients who have received neoadjuvant systemic therapy^{6,7} and results suggest that a biopsy may improve predictive accuracy, but identification of the tumor bed is necessary for sufficient negative predict value.

Two current studies, NRG BR005⁸ and TBCRC 040⁹, will further inform the design of a definitive clinical trial of surgery omission in women treated with neoadjuvant systemic therapy. NRG BR005 is assessing whether the combination of a negative tumor bed biopsy and negative trimodality imaging (mammogram, ultrasound and MRI) is sufficiently accurate to predict whether a patient will have a CR. TBCRC 040 is assessing the role of ctDNA in predicting pCR. The current studies and prior data set the stage for a trial that will definitively determine whether it is safe to omit surgery in patients who are

predicted to have a high probability of pCR. This study could allow for a paradigm shift in the treatment of patients with a good response to neoadjuvant treatment.

Consensus & Recommendations

A clinical trial should be designed to definitively determine whether it is safe to omit surgery in patients who are predicted to have a high probability of pCR. The consensus was for the study to be either a randomized non-inferiority design or a hybrid design in which the lowest risk patients (small, NO tumors with clinical CR) do not receive surgery and are followed for outcomes and higher risk patients are randomized to receive surgery or not receive surgery. The trial should include TNBC and HER2+ patients. Results from NRG BRO05 will inform certain aspects of the next trial, including:

- Are false negative rates different in different biologic subtypes of breast cancer?
- Is trimodality imaging necessary for accurate prediction of pCR?
- How do imaging results from the breast reflect what is happening in the axilla?
- What issues affect physician and patient acceptability?

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

Anticipated Actions

A Working Group consisting of representatives from each of the NCTN Groups, biostatisticians, patient advocates, and subject matter experts will be formed to write a manuscript and design the clinical trial.

References

1. Pennisi, A. *et al.*, Relevance of Pathological Complete Response after Neoadjuvant Therapy for Breast Cancer. *Breast Cancer (Auckl)* **10**: 103–106, 2016.
2. Ring, A. *et al.*, Is Surgery Necessary after Complete Clinical Remission Following Neoadjuvant Chemotherapy for Early Breast Cancer? *J Clin Oncol* **21**: 4540-4545, 2003.
3. Mauriac, L. *et al.*, Neoadjuvant Chemotherapy for Operable Breast Carcinoma Larger than 3 cm: A Unicentre Randomized Trial with a 124-month Median Follow-up. *Annals of Oncol* **10**: 47-52, 1999.
4. Danforth, D.N. *et al.*, Selection of Local Therapy after Neoadjuvant Chemotherapy in Patients with Stage IIIA,B Breast Cancer. *Annals of Surg Oncol* **5(2)**: 150-158, 1998.
5. De Los Santos, J.F. *et al.*, Magnetic Resonance Imaging as a Predictor of Pathologic Response in Patients Treated with Neoadjuvant Systemic Treatment for Operable Breast Cancer (TBCRC 017). *Cancer* **119(10)**: 1776–1783, 2013.
6. Clouth, B. *et al.*, The Surgical Management of Patients who Achieve a Complete Pathological Response after Primary Chemotherapy for Locally Advanced Breast Cancer. *Eur J Surg Oncol* **33**: 961-966, 2007.
7. Heil, J. *et al.*, Diagnosis of Pathologic Complete Response to Neoadjuvant Chemotherapy in Breast Cancer by Minimal Invasive Biopsy Technique. *Br J Cancer* **113(11)**: 1565-70, 2015.
8. <https://clinicaltrials.gov/ct2/show/NCT03188393?term=NCT03188393>
9. <https://clinicaltrials.gov/ct2/show/NCT02743910?term=TBCRC+040>

AGENDA
NCI Breast Cancer Steering Committee (BCSC) Clinical Trial Planning Meeting (CTPM)
Omitting Surgery in Patients with Complete Clinical/Radiologic Response to Neoadjuvant
Chemotherapy: A Paradigm Shift
October 16-17, 2017

NCI Shady Grove Building
9609 Medical Center Drive
Rockville, Maryland 20850
Meeting Room: Seminar 406, Terrace Level

MONDAY, OCTOBER 16

1:00 pm **Welcome and meeting objectives** *Tom Julian and Alastair Thompson*

Review of prior and current studies

1:15 pm **Background** *Alastair Thompson*

1:35 pm **NRG BR005** *Tom Julian*

1:55 pm **TBCRC 040** *Ben Park*

2:15 pm **Discussion**

Current Landscape and Setting the Stage

2:30 pm **Study population, eligibility considerations** *Eric Winer*

2:50 pm **Discussion**

3:00 pm **Imaging** *Jennifer De Los Santos*

3:20 pm **Discussion**

3:30 pm **Pathology/cytology assessment** *Savitri Krishnamurthy*

3:50 pm **Discussion**

4:00 pm **BREAK**

4:15 pm **Surgical Management** *Mark Basik*

4:35 pm **Discussion**

4:45 pm **Radiation Treatment Without Surgery** *Julia White*

5:05 pm **Discussion**

Trial Design

- 5:20 pm** **Trial Design**
Moderators: Lisa McShane, Shelley Hwang, Bill Barlow, Chuck Geyer, Jamie Wagner
- 6:50 pm** **Summary of day 1 and preparation for day 2** *Tom Julian, Alastair Thompson*
- 7:00 pm** **Adjourn**

TUESDAY, OCTOBER 17

- 7:00 am** **Welcome, overview of day 2 and charge** *Tom Julian, Alastair Thompson*
- 7:10 am** **Imaging: Working Session**
Moderators: Connie Lehman, Heidi Umphrey
- 8:40 am** **Surgical Management: Working Session**
Moderators: Marilyn Leitch, Terry Mamounas, Julia Tchou
- 10:10 am** **BREAK**
- 10:20 am** **Radiation Treatment Without Surgery: Working Session**
Moderators: Reshma Jagsi, Tim Whelan, Rich Zellars
- 11:50 am** **LUNCH (on your own)**
- 12:30 pm** **BREAKOUT SESSIONS**

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| Study population/eligibility: Room: Seminar 406, Terrace Level <i>Moderators: Lisa Carey, Gabe Hortobagyi</i> | Biomarkers Room: Seminar 110, Terrace Level <i>Moderators: Peggy Porter, Fraser Symmans, Antonio Wolff</i> | QOL/PROs Room: 2E908 (2nd floor) <i>Moderators: Liz Frank, Lynn Henry, Susie McCloskey</i> |
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- 1:40 pm** **BREAK/Return to Meeting Room: Seminar 406, Terrace Level**

Breakout Session Report Outs and Discussion

- 1:55 pm** **Study population/eligibility:** *Lisa Carey, Gabe Hortobagyi*
- 2:15 pm** **QOL/PROs** *Liz Frank, Lynn Henry, Susie McCloskey*
- 2:35 pm** **Biomarkers** *Peggy Porter, Fraser Symmans, Antonio Wolff*

Practical issues

- 2:55 pm** **Patient & physician acceptability** *Jane Perlmutter, Reshma Jagsi*
- 3:15 pm** **Timeline, Funding, “Ownership”** *Larissa Korde*
- 3:45 pm** **Summary and consensus on trial design elements, action items** *Tom Julian, Alastair Thompson*
- 4:00 pm** **ADJOURN**

**NCI BREAST CANCER STEERING COMMITTEE (BCSC) CLINICAL TRIAL
PLANNING MEETING (CTPM)**

NCI SHADY GROVE
CONFERENCE ROOM TE406
ROCKVILLE, MARYLAND

OCTOBER 16-17, 2017

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