Executive Summary
National Cancer Institute Breast Cancer Steering Committee
Identification and Treatment of Patients at Risk for Late Recurrence of ER+ Breast Cancer
Clinical Trial Planning Meeting: May 15-16, 2019
Meeting Co-chairs: Drs. Kathy Miller and Eric Winer

Meeting Description

The National Cancer Institute (NCI) Breast Cancer Steering Committee (BCSC) held a Clinical Trial Planning Meeting (CTPM) regarding the Identification and Treatment of Patients at Risk for Late Recurrence of Estrogen Receptor-positive (ER+) Breast Cancer. The meeting occurred May 15-16, 2019 at the NCI Shady Grove in Rockville, MD. The objectives of the meeting were to evaluate existing data on late recurrence in ER+ breast cancer, to discuss and prioritize assays and biomarkers to predict which patients are at risk of late recurrence, to discuss interventions to reduce risk of recurrence, and to develop a framework for clinical trials to test interventions for high risk patients. The meeting attendees included Breast Cancer Steering Committee members, medical oncologists, pathologists, experts in survivorship and quality of life, radiologists, biostatisticians, patient advocates, and NCI staff.

Background

ER+ breast cancer patients, especially those with nodal involvement, face a significant risk of late recurrence and associated poor clinical outcome, with more than half of recurrences occurring beyond five years after diagnosis (1). Although treatment with chemotherapy and adjuvant endocrine therapy may have some benefit, they provide minimal reduction in absolute risk (2) and cause substantial side effects which impact patient quality of life (2,3). Therefore, developing better methods to identify and treat this high-risk patient population, remains a priority.

Epidemiologic cohort studies such as the Nurses' Health Studies (4) have provided recurrence, treatment and survival data pooled in databases such as the Cancer Epidemiology Descriptive Cohort Database (CEDCD) (5) to inform current and future studies. Areas for improvement include better defining recurrence, integrating medical record information and incorporating treatment data. Interventional trials will also be enhanced by efforts to incorporate biomarkers and advanced analytic techniques, broaden cohort diversity and collect information on tumor subtype and recurrence site.

Several factors (6-10) have been identified that can help determine those who would benefit most from additional therapy and provide future insight for treating highly prevalent *early stage* ER+ breast cancer (11-14). For example, the clinical marker CTS5 incorporates tumor characteristics from the ATAC trial and BIG 1-98 study cohort, into a calculated risk score to predict distant recurrence for years 5 through 10 after endocrine therapy (9). In addition, studies evaluating the presence of circulating tumor cells (CTCs) (14) and circulating tumor DNA (ctDNA) (16-17) found an increased risk of relapse in patients expressing these markers. Both CTCs and CtDNA may have utility in distinguishing those at higher risk for late recurrence and can be applied to enhance screening, diagnosis and treatment.

Consensus & Recommendations

- It is feasible and timely to perform a randomized trial(s) to test interventions for patients at high risk of late recurrence of ER+ breast cancer.
- It is important to consider patient reported outcomes as they provide significant insight on toxicity of cancer therapy, impact of intervention on symptoms and patient quality-of life.
- Long-term follow-up beyond 10 years and collection of correlative samples should be included.
- Liquid biopsy is promising but additional data is needed to determine the validity and clinical utility of this potential biomarker. Collection of samples for liquid biopsy should be included in future trials.
- Potential therapeutic agents include cyclin dependent kinase (CDK)4/6 inhibitors, selective estrogen receptor downregulators (SERDs), and a phosphatidylinositol 3-kinases (PI3K) inhibitor.

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 writing team consisting of junior and senior investigators from each of the National Clinical Trials Network (NCTN) Groups will be formed to develop the trial. A biomarker subcommittee will work with the main writing team to ensure translational science is embedded in the protocol. A separate committee will work on smaller pilot trials exploring novel interventions and monitoring strategies

References

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12. Cardoso F, van't Veer LJ, Bogaerts J, et al. 70-Gene Signature as an aid to treatment decisions in early-stage breast cancer. N Engl J Med. 2016;375(8): 717-29.
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14. Henry NL, Hayes DF, Ramsey SD, et al. Promoting quality and evidence-based care in early-stage breast cancer follow-up. J Natl Cancer Inst. 2014;106(4): dju034.
15. Sparano J, O'Neill A, Alpaugh K, et al. Association of Circulating Tumor Cells with Late Recurrence of Estrogen Receptor-Positive Breast Cancer: A Secondary Analysis of a Randomized Clinical Trial.
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17. Chen Y, Hancock B, Solzak J, et al. Next-generation sequencing of circulating tumor DNA to predict recurrence in triple-negative breast cancer patients with residual disease after neoadjuvant chemotherapy NPJ Breast Cancer 2017; 3:24.

AGENDA
NCI Breast Cancer Steering Committee (BCSC) Clinical Trial Planning Meeting (CTPM)
Identification and Treatment of Patients at Risk for Late Recurrence of ER+ Breast Cancer

NCI Shady Grove, 9609 Medical Center Drive, Rockville, Maryland 20850
Meeting Room: Seminar 110, Terrace Level

DAY 1 – WEDNESDAY, MAY 15, 2019

1:00 – 1:10 pm Introductions, objective(s) of meeting, deliverables *Kathy Miller & Eric Winer*

1:10 – 3:10 pm Current landscape
1:10 – 1:25 pm **Extended adjuvant endocrine therapy** *Kathy Miller & Eric Winer*
1:25 – 1:40 pm **Risk of late recurrence, data on clinical and genomic predictors of risk** *Terry Mamounas*
1:40 – 1:55 pm **CTCs** *Joe Sparano*
1:55 – 2:10 pm **ctDNA** *Matthew Ellis*
2:10 – 2:25 pm **Are liquid biopsies ready for prime time?** *Lisa McShane*
2:25 – 3:10 pm **Discussion**

3:10 – 3:40 pm Cohort data overview *Rulla Tamimi*
3:30-3:40 pm **Discussion**

3:40 – 4:10 pm Opportunities for low risk patients *Lynn Henry*
4:00-4:10 pm **Discussion**

4:10 – 5:30 pm Possible Interventions for Patients at Risk of Late Relapse
4:10 – 4:25 pm **CDK4/6 inhibitors** *Erica Mayer*
4:25 – 4:40 pm **Other targeted therapies** *Kevin Kalinsky*
4:40 – 5:00 pm **Biomarkers for agent selection** *Kathy Miller*
5:00 - 5:30 pm **Discussion**

5:30 – 5:45 pm BREAK

5:45 – 7:15 pm Strawman proposals

7:15 – 7:30 pm Summary of Day 1 *Kathy Miller & Eric Winer*

7:30 pm ADJOURN

DAY 2 – THURSDAY, MAY 16, 2019

7:30 – 8:00 am Opportunities to validate biomarkers in ongoing trials *Larissa Korde*
7:40 – 8:00 am **Discussion**

8:00 – 8:45 am **Trial Design Discussion**

8:00 – 8:10 am	**Statistical Design**	*Liz Garrett-Mayer*
8:10 – 8:20 am	**Imaging**	*David Mankoff*
8:20 – 8:30 am	**Health services/cost**	*Ann Partridge*
8:30 – 8:45 am	**Patient Perspective**	*Mary Lou Smith*

9:00 – 11:00 am BREAKOUT GROUPS

1. **Defining an appropriate patient population** **Moderator:** *Lisa Carey*
2. **Possible treatment interventions** **Moderator:** *Angie DeMichele*
3. **Biomarkers for late recurrence** **Moderator:** *Priyanka Sharma*
4. **Health services/patient reported outcomes** **Moderator:** *Ann Partridge*

11:00 am – 12:00 pm BREAK

12:00 – 2:00 pm Consensus for trial design **Moderator:** *Chuck Geyer*

12:00 – 12:40 pm **Breakout group reports:**

12:00 – 12:10 pm	**Defining an appropriate patient population**	*Lisa Carey*
12:10 – 12:20 pm	**Possible treatment interventions**	*Angie DeMichele*
12:20 – 12:30 pm	**Biomarkers for late recurrence**	*Priyanka Sharma*
12:30 – 12:40 pm	**Health services/patient reported outcomes**	*Ann Partridge*
12:40 – 2:00 pm	**Discussion**	

2:00 pm Action Items *Kathy Miller & Eric Winer*

3:00 pm ADJOURN

NATIONAL CANCER INSTITUTE'S BREAST CANCER STEERING COMMITTEE (BCSC) CLINICAL TRIAL PLANNING MEETING: IDENTIFICATION AND TREATMENT OF PATIENTS AT RISK FOR LATE RECURRENCE OF ER+ BREAST CANCER NCI SHADY GROVE, ROCKVILLE, MARYLAND MAY 15-16, 2019

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