Second Opinion

Investigator Perspectives on Current Cases, Clinical Issues and Ongoing Research in the Management of Breast Cancer

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists, hematology-oncology fellows and other allied healthcare professionals involved in the treatment of breast cancer (BC).

OVERVIEW OF ACTIVITY

BC remains the most frequently diagnosed cancer in women, and in 2016 in the United States alone the disease will culminate in an estimated 246,660 new cases and 40,450 deaths. The current clinical management of BC is multidisciplinary and includes surgical resection of local disease with or without radiation therapy and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy or combinations of these approaches. The indication and/or utility of these local and systemic treatment options is largely based on a number of prognostic and predictive risk factors present within the patient or her tumor at the time of diagnosis. In fact, as the field of oncology is challenged to improve the precision with which it therapeutically targets malignant cells, biomarker-driven treatment algorithms have become the "norm" for many tumor types, particularly BC. Although the diagnosis and treatment of BC remain, in many ways, more advanced than in other solid cancers, challenging issues in the basic management of this disease continue to require refinement.

Several consensus- and evidence-based treatment guidelines are available and aim to assist clinicians with making BC management decisions in the face of this dynamic clinical and research environment, but despite the existence of these tools many areas of controversy persist within academic and community settings. By using the perspectives of leading BC clinical investigators regarding a number of questions and cases provided by a panel of community-based oncologists as well as a review of key data sets that support this case-based discussion, this activity will assist medical oncologists, hematology-oncology fellows and other healthcare professionals in the development of evidence-based strategies for the treatment of BC.

LEARNING OBJECTIVES

- Appraise recent data on therapeutic advances and changing practice standards in early and advanced BC, and integrate this information, as appropriate, into current clinical care.
- Consider the use of available biomarkers and genomic assays to assess risk and individualize therapy for patients in the neoadjuvant, adjuvant and extended-adjuvant settings.
- Individualize the selection of evidence-based neoadjuvant and adjuvant chemobiologic regimens for patients with HER2-overexpressing early BC.
- Implement a long-term clinical plan for the management of metastatic HER2-positive BC, incorporating existing, recently approved and investigational targeted treatments.
- Develop an evidence-based algorithm for the treatment of hormone-sensitive advanced BC, including the use of endocrine, biologic and chemotherapeutic agents.
- Recognize the recent FDA approval of palbociclib for ER-positive metastatic BC, and discern how this agent can be optimally integrated into clinical practice.
- Develop an understanding of the mechanisms of action, available data and potential clinical roles of late-stage investigational compounds in preparation for their potential introduction into BC clinical practice.
- Appraise the rationale for and clinical data with investigational anti-PD-1 and anti-PD-L1 antibodies for patients with metastatic BC.
- Counsel appropriately selected patients with BC about participation in ongoing clinical trials investigating novel therapeutic agents and strategies.

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FACULTY — The following faculty (and their spouses/partners) reported relevant conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Expiration date: September 2017

Select Publications

George W Sledge Jr, MD

A randomized phase II study of trastuzumab emtansine (T-DM1) vs paclitaxel in combination with trastuzumab for stage I HER2-positive breast cancer (ATEMPT trial). NCT01853748

APHINITY: A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer. NCT01358877

Denduluri N et al. **Selection of optimal adjuvant chemotherapy regimens for human epidermal growth factor receptor 2 (HER2)-negative and adjuvant targeted therapy for HER2-positive breast cancers: An American Society of Clinical Oncology guideline adaptation of the Cancer Care Ontario clinical practice guideline.** *J Clin Oncol* 2016;34(20):2416-27.

Gianni L et al. **Five-year analysis of the phase II NeoSphere trial evaluating four cycles of neoadjuvant docetaxel (D) and/or trastuzumab (T) and/or pertuzumab (P).** *Proc ASCO* 2014;**Abstract 505**.

Gianni L et al. **Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): A randomised multicentre, open-label, phase 2 trial.** *Lancet Oncol* 2012;13(1):25-32.

Hurwitz SA et al. **Pathologic complete response (pCR) rates after neoadjuvant trastuzumab emtansine (T-DM1 [K]) + pertuzumab (P) vs docetaxel + carboplatin + trastuzumab + P (TCHP) treatment in patients with HER2-positive (HER2+) early breast cancer (EBC) (KRISTINE).** *Proc ASCO* 2016;**Abstract 500**.

I-SPY 2 trial (investigation of serial studies to predict your therapeutic response with imaging and molecular analysis 2). NCT01042379

KATHERINE: A randomized, multicenter, open-label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumor present pathologically in the breast or axillary lymph nodes following preoperative therapy. NCT01772472

Schneeweiss A et al. **Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: A randomized phase II cardiac safety study (TRYPHAENA).** *Ann Oncol* 2013;24(9):2278-84.

Slamon DJ et al. **Ten year follow-up of BCIRG-006 comparing doxorubicin plus cyclophosphamide followed by docetaxel (AC → T) with doxorubicin plus cyclophosphamide followed by docetaxel and trastuzumab (AC → TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2+ early breast cancer.** San Antonio Breast Cancer Symposium 2015;**Abstract S5-04**.

Tolaney SM et al. **Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer.** *N Engl J Med* 2015;372(2):134-41.

Hope S Rugo, MD

A phase 3 randomized, placebo-controlled trial of carboplatin and paclitaxel with or without the PARP inhibitor veliparib (ABT-888) in HER2 negative metastatic or locally advanced unresectable BRCA-associated breast cancer. NCT02163694

A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician's choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer patients. NCT01905592

A randomized, placebo-controlled, double-blind, phase 3 study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in subjects with early stage triple negative breast cancer (TNBC). NCT02032277

ABRAZO: A phase 2, 2-stage, 2-cohort study of talazoparib (BMN 673) administered to germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer. NCT02034916

Adams S et al. **Phase Ib trial of atezolizumab in combination with *nab*-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC).** *Proc ASCO*;**Abstract 1009**.

Brightness: A randomized, placebo-controlled, double-blind, phase 3 study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in subjects with early stage triple negative breast cancer (TNBC). NCT02032277

Cortes J et al. **Overall survival (OS) from the phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) signaling inhibitor, in AR+ advanced triple-negative breast cancer.** *Proc ECC* 2015;**Abstract 1802**.

Select Publications

Doane AS et al. **An estrogen receptor-negative breast cancer subset characterized by a hormonally regulated transcriptional program and response to androgen.** *Oncogene* 2006;25(28):3994-4008.

EMBRACA: A phase 3, open-label, randomized, parallel, 2-arm, multi-center study of talazoparib (BMN 673) versus physician's choice in germline BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received prior chemotherapy regimens for metastatic disease. NCT01945775

Gianni L et al. **ETNA (Evaluating Treatment with Neoadjuvant Abraxane) randomized phase III study comparing neoadjuvant *nab*-paclitaxel (*nab*-P) versus paclitaxel (P) both followed by anthracycline regimens in women with HER2-negative high-risk breast cancer: A MICHELANGO study.** *Proc ASCO* 2016;**Abstract 502**.

Gucalp A et al. **Phase II trial of bicalutamide in patients with androgen receptor-positive, estrogen receptor-negative metastatic breast cancer.** *Clin Cancer Res* 2013;19(19):5505-12.

Lehmann BD et al. **Identification of human triple-negative breast cancer subtypes and preclinical models for selection of targeted therapies.** *J Clin Invest* 2011;121(7):2750-67.

Loi S et al. **Tumor infiltrating lymphocytes are prognostic in triple negative breast cancer and predictive for trastuzumab benefit in early breast cancer: Results from the FinHER trial.** *Ann Oncol* 2014;25(8):1544-50.

Mittendorf EA et al. **PD-L1 expression in triple-negative breast cancer.** *Cancer Immunol Res* 2014;2(4):361-70.

Nanda R et al. **Pembrolizumab in patients with advanced triple-negative breast cancer: Phase Ib KEYNOTE-012 study.** *J Clin Oncol* 2016;34(21):2460-7.

OlympiA: A randomised, double-blind, parallel group, placebo-controlled multi-centre phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with gBRCA1/2 mutations and high risk HER2 negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy. NCT02032823

OlympiAD: A phase III, open label, randomised, controlled, multi-centre study to assess the efficacy and safety of olaparib monotherapy versus physicians choice chemotherapy in the treatment of metastatic breast cancer patients with germline BRCA1/2 mutations. NCT02000622

PARP inhibition after preoperative chemotherapy in patients with triple negative breast cancer or ER/PR+, HER2 negative with known BRCA1/2 mutations: Hoosier Oncology Group BRE09-146. NCT01074970

Traina TA et al. **Results from a phase 2 study of enzalutamide (ENZA), an androgen receptor (AR) inhibitor, in advanced AR+ triple-negative breast cancer (TNBC).** *Proc ASCO* 2015;**Abstract 1003**.

Untch M et al. ***Nab*-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (Gepar-Septo-GBG 69): A randomised, phase 3 trial.** *Lancet Oncol* 2016;17(3):345-56.

Wang Y et al. **Clonal evolution in breast cancer revealed by single nucleus genome sequencing.** *Nature* 2014;512(7513):155-60.

Joyce O'Shaughnessy, MD

Piccart M. **Lessons learned from an expedition exploring the world of HER2 positive breast cancer.** San Antonio Breast Cancer Symposium 2015;**Abstract BL2**.

Sara M Tolaney, MD, MPH

Barroso-Sousa R et al. **Clinical development of the CDK4/6 inhibitors ribociclib and abemaciclib in breast cancer.** *Breast Care (Basel)* 2016;11(3):167-73.

DeMichele A et al. **Characterization of isolated, uncomplicated neutropenia–related to the CDK4/6 inhibitor palbociclib.** *Proc ASCO* 2014;**Abstract 2547**.

Dickler MN et al. **MONARCH1: Results from a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as monotherapy, in patients with HR+/HER2- breast cancer, after chemotherapy for advanced disease.** *Proc ASCO* 2016;**Abstract 510**.

Finn RS et al. **The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): A randomised phase 2 study.** *Lancet Oncol* 2015;16(1):25-35.

Finn RS et al. **Clinical patterns of palbociclib associated neutropenia in the PALOMA-1/TRIO-18 trial.** *Proc ESMO* 2014;**Abstract 368P**.

Select Publications

Finn RS et al. **PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro.** *Breast Cancer Res* 2009;11(5):R77.

Infante JR et al. **A phase I study of the single-agent CDK4/6 inhibitor LEE011 in pts with advanced solid tumors and lymphomas.** *Proc ASCO* 2014;**Abstract 2528**.

Patnaik A et al. **Efficacy and safety of abemaciclib, an inhibitor of CDK4 and CDK6, for patients with breast cancer, non-small cell lung cancer, and other solid tumors.** *Cancer Discov* 2016;6(7):740-53.

Sahebjam S et al. **Assessment of concentrations of abemaciclib and its major active metabolites in plasma, CSF, and brain tumor tissue in patients with brain metastases secondary to hormone receptor positive (HR+) breast cancer.** *Proc ASCO* 2016;**Abstract 526**.

Turner NC et al. **PALOMA3: A double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and post-menopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy.** *Proc ASCO* 2015;**Abstract LBA502**.

Turner NC et al; PALOMA3 Study Group. **Palbociclib in hormone-receptor-positive advanced breast cancer.** *N Engl J Med* 2015;373(3):209-19.

Angelo Di Leo, MD, PhD

Badwe R et al. **Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer: An open-label randomised controlled trial.** *Lancet Oncol* 2015;16(13):1380-8.

Baselga J et al; CLEOPATRA Study Group. **Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer.** *N Engl J Med* 2012;366(2):109-19.

Turner NH, Di Leo A. **HER2 discordance between primary and metastatic breast cancer: Assessing the clinical impact.** *Cancer Treat Rev* 2013;39(8):947-57.

Verma S et al; EMILIA Study Group. **Trastuzumab emtansine for HER2-positive advanced breast cancer.** *N Engl J Med* 2012;367(19):1783-91.