VISITING PROFESSORS: Improving the Efficacy of Endocrine Treatment of Metastatic Breast Cancer

An Interactive Grand Rounds Series

CME Information

TARGET AUDIENCE

This activity is intended for medical oncologists and other healthcare providers involved in the treatment of ER-positive metastatic breast cancer (mBC).

OVERVIEW OF ACTIVITY

Among the widely acknowledged BC phenotypes, ER-positive disease, which represents approximately 63% of all cases, is perhaps the most nuanced with regard to therapeutic decision-making in the advanced disease setting. Specifically, unlike other phenotypes for which systemic therapy almost always includes chemotherapy, for patients with hormonally driven tumors, the availability of effective endocrine therapy may initially abrogate and significantly delay the need for cytotoxic intervention. Although this and various other factors have historically defined the management of ER-positive mBC, several groundbreaking advances have added greater complexity to this prevalent clinical situation. Specifically, improved understanding of the mechanisms by which breast tumors develop resistance to endocrine therapy has led to the appreciation that several other biologic pathways may be implicated in this process and has in turn fostered a spate of clinical research designed to evaluate novel therapies with inhibitory activity against these potential targets. Significantly, the results of these efforts have now been actualized in the clinic as over the past several years the FDA has granted approval to several unique treatments that, when combined with hormonal therapy, have been shown to enhance efficacy over endocrine intervention alone. Importantly, although the availability of these therapies undoubtedly provides immense benefit to patients, the many related issues (eg, sequencing, side effects) have increased the demands placed on clinicians and created additional areas of uncertainty.

To bridge this gap between research and patient care, this video presentation by Dr Sara M Tolaney uses a review of recent relevant publications and presentations, ongoing clinical trials and clinical investigator treatment preferences to assist medical oncologists and other healthcare providers involved in the treatment of ER-positive mBC with the formulation of up-to-date clinical management strategies.

LEARNING OBJECTIVES

- Individualize the selection and sequence of systemic therapy for patients with newly diagnosed mBC, considering clinical presentation (eg, age, menopausal status, comorbidities, symptomatology) and prior treatment course (eg, de novo metastatic disease, type and duration of adjuvant therapy).
- Describe known and proposed mechanisms of resistance to hormonal therapy, and identify available therapies and investigational efforts attempting to leverage this knowledge.
- Recognize the FDA approvals of palbociclib, ribociclib and abemaciclib for ER-positive mBC, and discern how these agents can be optimally employed in nonresearch patient care.
- Educate patients regarding the unique side effects associated with approved CDK4/6 inhibitors, and develop preventive and emergent strategies to reduce or ameliorate these toxicities.
- Identify clinical situations in which endocrine therapy alone or in combination with HER2-directed therapy should be considered in the management of ER-positive, HER2-positive mBC.

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Please note, this program has been specifically designed for the following ABIM specialty: **medical oncology**.

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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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PROJECT CHAIR — **Dr Love** is president and CEO of Research To Practice. Research To Practice receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Adaptive Biotechnologies, Agendia Inc, Agios Pharmaceuticals Inc, Amgen Inc, Ariad Pharmaceuticals Inc, Array BioPharma Inc, Astellas Pharma Global Development Inc, AstraZeneca Pharmaceuticals LP, Bayer HealthCare Pharmaceuticals, Biodesix Inc, bioTheranostics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Pharmaceuticals Inc, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech, Genomic Health Inc, Gilead Sciences Inc, Guardant Health, Halozyme Inc, ImmunoGen Inc, Incyte Corporation, Infinity Pharmaceuticals Inc, Ipsen Biopharmaceuticals Inc, Janssen Biotech Inc, administered by Janssen Scientific Affairs LLC, Jazz Pharmaceuticals Inc, Kite Pharma Inc, Lexicon Pharmaceuticals Inc, Lilly, Medivation Inc, a Pfizer Company, Merck, Merrimack Pharmaceuticals Inc, Myriad Genetic Laboratories Inc, Natera Inc, Novartis, Pfizer Inc, Pharmacyclics LLC, an AbbVie Company, Prometheus Laboratories Inc, Puma Biotechnology Inc, Regeneron Pharmaceuticals Inc, Sandoz Inc, a Novartis Division, Sanofi Genzyme, Seattle Genetics, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro Inc, Teva Oncology and Tokai Pharmaceuticals Inc.

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 11 or later, Firefox 56 or later, Chrome 61 or later, Safari 11 or later, Opera 48 or later
Adobe Flash Player 27 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

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Select Publications

Augereau P et al. **Hormonoresistance in advanced breast cancer: A new revolution in endocrine therapy.** *Ther Adv Med Oncol* 2017;9(5):335-46.

Augusto L et al. **Prognostic and predictive value of circulating ESR1 mutations in metastatic breast cancer patients (mBC) progressing under aromatase inhibitor (AI) treatment.** *Proc ASCO* 2016;**Abstract 511**.

Bachelot T et al. **Abemaciclib for the treatment of brain metastases secondary to hormone receptor positive breast cancer.** San Antonio Breast Cancer Symposium 2017;**Abstract P1-17-03**.

Baselga J et al. **Phase III study of taselisib (GDC-0032) + fulvestrant (FULV) *v* FULV in patients (pts) with estrogen receptor (ER)-positive, *PIK3CA*-mutant (MUT), locally advanced or metastatic breast cancer (MBC): Primary analysis from SANDPIPER.** *Proc ASCO* 2018;**Abstract LBA1006**.

Baselga J et al. **Buparlisib plus fulvestrant versus placebo plus fulvestrant in postmenopausal, hormone receptor-positive, HER2-negative, advanced breast cancer (BELLE-2): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet Oncol* 2017;18(7):904-16.

Brufsky AM, Dickler MN. **Estrogen receptor-positive breast cancer: Exploiting signaling pathways implicated in endocrine resistance.** *Oncologist* 2018;23(5):528-39.

Brufsky AM. **Long-term management of patients with hormone receptor-positive metastatic breast cancer: Concepts for sequential and combination endocrine-based therapies.** *Cancer Treat Rev* 2017;59:22-32.

Chandarlapaty S et al. **cfDNA analysis from BOLERO-2 plasma samples identifies a high rate of ESR1 mutations: Exploratory analysis for prognostic and predictive correlation of mutations reveals different efficacy outcomes of endocrine therapy–based regimens.** San Antonio Breast Cancer Symposium 2015;**Abstract S2-07**.

Cortés J et al. **The next era of treatment for hormone receptor-positive, HER2-negative advanced breast cancer: Triplet combination-based endocrine therapies.** *Cancer Treat Rev* 2017;61:53-60.

Cristofanilli M et al. **Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): Final analysis of the multicentre, double-blind, phase 3 randomised controlled trial.** *Lancet Oncol* 2016;17(4):425-39.

Dickler MN et al. **MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory $HR^+/HER2^-$ metastatic breast cancer.** *Clin Cancer Res* 2017;23(17):5218-24.

Di Leo A et al. **Buparlisib plus fulvestrant in postmenopausal women with hormone-receptor-positive, HER2-negative, advanced breast cancer progressing on or after mTOR inhibition (BELLE-3): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet Oncol* 2018;19(1):87-100.

Fanning SW et al. **Estrogen receptor alpha somatic mutations Y537S and D538G confer breast cancer endocrine resistance by stabilizing the activating function-2 binding conformation.** *Elife* 2016;5:e12792.

Finn RS et al. **Palbociclib and letrozole in advanced breast cancer.** *N Engl J Med* 2016;375(20):1925-36.

Goetz M et al. **MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer.** *J Clin Oncol* 2017;35(32):3638-46.

Hortobagyi GN et al. **Ribociclib as first-line therapy for HR-positive, advanced breast cancer.** *N Engl J Med* 2016;375(18):1738-48.

Kornblum NS et al. **Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor–positive, human epidermal growth factor receptor 2–negative metastatic breast cancer resistant to aromatase inhibitor therapy: Results of PrE0102.** *J Clin Oncol* 2018;36(16):1556-63.

Krop IE et al. **Pictilisib for oestrogen receptor-positive, aromatase inhibitor-resistant, advanced or metastatic breast cancer (FERGI): A randomised, double-blind, placebo-controlled, phase 2 trial.** *Lancet Oncol* 2016;17(6):811-21.

Martin M et al. **Final results of NeoMONARCH: A phase 2 neoadjuvant study of abemaciclib in postmenopausal women with hormone receptor positive (HR+), HER2 negative breast cancer (BC).** San Antonio Breast Cancer Symposium 2017;**Abstract PD5-01**.

Metzger-Filho O et al. **PATINA: A randomized open label phase III trial to evaluate the efficacy and safety of palbociclib + anti HER2 therapy + endocrine therapy vs anti HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive, HER2 positive metastatic breast cancer.** San Antonio Breast Cancer Symposium 2017;**Abstract OT3-05-07**.

Razavi P et al. **Use of next generation sequencing and quantitative mass spectrometry to determine HER2 status.** *Proc ASCO* 2016;**Abstract e23237**.

Rugo HS et al. **Safety and antitumor activity of pembrolizumab in patients with estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer.** *Clin Cancer Res* 2018;24(12):2804-11.

Select Publications

Rugo HS et al. **Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): A single-arm, phase 2 trial.** *Lancet Oncol* 2017;18(5):654-62.

Slamon DJ et al. **Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3.** *J Clin Oncol* 2018;36(24):2465-72.

Slamon DJ et al. **Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2–) advanced breast cancer (ABC): Results from MONALEESA-3.** *Proc ASCO* 2018;**Abstract 1000**.

Sledge GW Jr et al. **MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy.** *J Clin Oncol* 2017;35(25):2875-84.

Spoerke JM et al. **Heterogeneity and clinical significance of ESR1 mutations in ER-positive metastatic breast cancer patients receiving fulvestrant.** *Nat Comm* 2016;7:11579.

Tolaney SM et al. **Updated efficacy, safety, & PD-L1 status of patients with HR+, HER2- metastatic breast cancer administered abemaciclib plus pembrolizumab.** *Proc ASCO* 2018;**Abstract 1059**.

Toy W et al. **Differential activity and SERD sensitivity of clinical ESR1 mutations.** *Proc AACR* 2016;**Abstract 863**.

Toy W et al. **ESR1 ligand-binding domain mutations in hormone-resistant breast cancer.** *Nat Genet* 2013;45(12):1439-45.

Tripathy D et al. **Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): A randomised phase 3 trial.** *Lancet Oncol* 2018;19(7):904-15.

Turner NC et al. **Efficacy of palbociclib plus fulvestrant (P+F) in patients (pts) with metastatic breast cancer (MBC) and *ESR1* mutations (mus) in circulating tumor DNA (ctDNA).** *Proc ASCO* 2016;**Abstract 512**.

Yardley DA et al. **Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis.** *Adv Ther* 2013;30(10):870-84.