

ER-Positive, HER2-Negative Metastatic Breast Cancer

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I. Background

- Breast cancers that are hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER2) negative represent the most common subtype of breast cancer (BC) (Blows et al, 2010).
- Endocrine therapy is currently the cornerstone of treatment for advanced HR-positive breast cancer (Partridge et al, 2014; Gradishar et al, 2016); however, not all patients respond to first-line endocrine therapy, and those that do respond eventually experience disease relapse.
- Recurrence can occur multiple years after diagnosis (Colleoni et al, 2016; Cossetti et al, 2015); the most common sites of recurrence are bone, liver, lung, distant lymph nodes, brain, and pleura (Hess & Esteva, 2013; Kennecke et al, 2010).
- Key prognostic factors include degree of HR expression, extent (if any) of prior therapy, visceral vs. bone-only metastatic disease, and disease-free interval since original diagnosis (Taneja et al, 2010; van de Vijver, 2014).
- The 5-year and 10-year survival rates for mBC are 26% and 5% to 10%, respectively (Clements et al, 2012; American Cancer Society, 2016).
- Current clinical research is focused on novel agents that target critical pathways involved in the development of resistance to endocrine therapy.

II. Hormone Therapy

NCCN guidelines for endocrine therapy for Stage IV or recurrent mBC are as follows (Gradishar et al, 2016):

- In premenopausal women without previous exposure to an antiestrogen, initial treatment is with selective ER modulator alone or ovarian suppression/ablation plus endocrine therapy as for postmenopausal women.
- In premenopausal women who received a prior endocrine therapy within 12 months, the preferred second-line therapy is ovarian ablation or suppression followed by endocrine therapy as for postmenopausal women.
- In postmenopausal women, endocrine therapies include nonsteroidal aromatase inhibitors (anastrozole and letrozole), steroidal aromatase inhibitors (exemestane), serum ER modulators (tamoxifen or toremifene), ER down-regulators (fulvestrant), progestin (megestrol acetate), androgens

(fluoxymesterone), and high-dose estrogen (ethinyl estradiol).

- New combination therapies with novel agents that have recently become available include exemestane with everolimus, palbociclib in combination with fulvestrant, and palbociclib with letrozole.

A. Selective estrogen receptor modulators (SERM)

- SERMs (*tamoxifen*, *raloxifene*, and *toremifene*), which prevent estrogen binding to its receptors, have been used for more than 30 years to treat hormone receptor-positive BC.
- The most common adverse events associated with SERMs are fatigue, hot flashes, night sweats, vaginal discharge, and mood swings.

B. Selective estrogen receptor degraders (SERD)

- *Fulvestrant* is the only FDA-approved approved SERD (Osborne et al, 2002).
 - Fulvestrant antagonizes and degrades ER- α and is active in patients who have progressed on anti-hormonal agents.
 - However, fulvestrant must be administered by intramuscular injections that limit the total amount of drug that can be administered and thus leads to incomplete receptor blockade.
- *ARN-810* is a next-generation, orally bioavailable, ER antagonist that induces proteasomal ER degradation in BC cell lines at picomolar concentrations and tumor regression in tamoxifen-sensitive and resistant BC xenograft models (Lai et al, 2015).
 - In a phase 1 trial of 32 previously treated patients with ER+ HER2- breast cancer, administration of ARN-810 led to a clinical benefit rate (complete response, partial response, or stable disease \geq 6 months) of 41% (Bardia et al, 2014).
 - The most common adverse events were grades 1-2 nausea, diarrhea, fatigue, and abdominal pain; there was one dose-limiting toxicity (grade 3 diarrhea).
 - In phase II, ARN-810 will be studied in patients previously treated with aromatase inhibitors and fulvestrant, including those with *ESR1* mutations.
- *AZD 9496* is a nonsteroidal small-molecule inhibitor of ER α and is a potent and selective antagonist and down-regulator of ER α in vitro and in vivo in ER-positive models of breast cancer (Weir et al, 2016).
 - AZD9496 is currently being evaluated in a phase I dose-escalation trial in patients with ER+ HER2- BC with or without *ESR1* mutations.

C. mTOR inhibitors

- The mTOR inhibitor *everolimus* was approved in 2012 for the treatment of postmenopausal women with advanced ER+ HER2- breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole (Baselga et al, 2012).
 - The median PFS was 7.8 months for patients receiving everolimus and 3.2 months for patients receiving placebo.
 - The most common all-grade adverse reactions ($\geq 30\%$ of patients) were stomatitis, infections, rash, fatigue, diarrhea, and decreased appetite; the most common grade 3-4 adverse reactions ($\geq 2\%$) were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis, and diarrhea.

III. Novel Agents

A. Cyclin-dependent kinase (CDK) inhibitors

- The CDK 4/6 inhibitor *palbociclib* was approved in 2015 (first-line, in combination with letrozole) and in 2016 (in women with disease progression following endocrine therapy, in combination with fulvestrant) for the treatment of ER+ HER2- mBC.
 - At the 8 month interim analysis, the confirmed ORR was 17.4%, the clinical benefit rate (CR + PR + SD ≥ 6 mos) was 42.4%, and the median PFS was 5.7 months.
 - The 5 most common treatment-related AEs were diarrhea, fatigue, nausea, decreased appetite, and abdominal pain; discontinuations due to AEs were infrequent (6.8%).
- *Abemaciclib* is an oral, selective inhibitor of CDK4 and CDK6 that is being investigated in the MONARCH1 phase II trial of 132 women with ER+ HER2- mBC whose disease progressed on or after endocrine therapy and chemotherapy (Dickler et al, 2016).
 - The trial was stopped early in May 2016 due to a significant improvement in PFS compared with letrozole alone (Novartis, 2016).
 - In a previous phase Ib trial, the most common all-grade AEs related to ribociclib were neutropenia (85%), nausea (39%), leukopenia (39%), fatigue (23%), anemia (23%), lymphopenia (23%), and increased creatinine (15%) (Munster et al, 2014).

B. Anti-angiogenic agents

- The data on anti-angiogenic agents, including bevacizumab, sunitinib, ramucirumab, pazopanib, sorafenib, and others, in patients with ER+ HER2- mBC have been mixed, with most trials demonstrating modest clinical benefit and significant toxicity (Rugo, 2012).
- Further translational research and identification of predictive biomarkers may lead to the development of more effective novel anti-angiogenic agents in breast cancer (Bozza et al, 2015).

C. Phosphoinositide 3-kinase (PI3K) inhibitors

- *Buparlisib* is a pan-PI3K inhibitor that was evaluated in combination with fulvestrant in the phase III BELLE-2 trial of 1147 postmenopausal women with refractory ER+ HER2- advanced BC (Baselga et al, 2015).
 - Buparlisib increased median PFS (5.0 to 6.9 months vs placebo), increased ORR (8% vs 12%), and increased clinical benefit rate (42% to 44%).
 - Median PFS, ORR, and CBR were significantly improved in patients with *PIK3CA*-mutant tumors but not in patients without.
 - The most common Grade 3-4 adverse events ($\geq 5\%$ of pts) in the buparlisib arm were increased alanine aminotransferase (26 vs 1%), increased aspartate aminotransferase (18 vs 3%), hyperglycemia (15 vs 0.2%), and rash (8 vs 0%).

D. Histone deacetylase (HDAC) inhibitors

- *Entinostat*, an oral isoform selective HDAC inhibitor that targets resistance to hormonal therapies in ER+ BC, was evaluated in combination with exemestane in the randomized ENCORE 301 phase II trial of 130 postmenopausal women (Yardley et al, 2013).
 - Treatment with entinostat improved median PFS to 4.3 months versus 2.3 months with exemestane/placebo and improved overall survival to 28.1 months versus 19.8 months,
 - Fatigue and neutropenia were the most frequent Grade 3-4 toxicities; treatment discontinuation because of adverse events was higher in the entinostat group (11% vs 2%).

E. Checkpoint inhibitors

- *Nivolumab*, an anti-PD-1 antibody, is being evaluated in combination with nab-paclitaxel (ClinicalTrials.gov ID NCT02309177) and in combination with the anti-CTLA4 antibody ipilimumab and the HDAC inhibitor entinostat (NCT02453620) in women with HER2- BC.

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