Emerging Therapies & Clinical Trial Opportunities for ER-Positive, HER2 Negative Metastatic Breast Cancer and HER2-Positive Breast Cancer

HER2-Positive Metastatic Breast Cancer

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I. Background

- The 5-year and 10-year survival rates for metastatic breast cancer (mBC) are 26% and 5% to 10%, respectively (Clements et al, 2012; American Cancer Society, 2016).
- For the 20% to 25% of patients with tumors that overexpress human epidermal growth factor receptor-2 (HER2), the disease course is more aggressive and associated with shorter survival times (Prat and Baselga, 2008).
- The advent of HER2-targeted therapies has dramatically improved patient outcomes in HER2-positive breast cancer (Santa-Maria et al, 2016); nevertheless, mBC eventually progresses.
- New molecular targets that can evade resistance mechanisms to HER2-directed therapies are being investigated in multiple ongoing trials.

II. Approved and Emerging Agents

A. Anti-HER2 Agents

- *Trastuzumab*, the first agent approved for the treatment of HER2+ BC, is a recombinant humanized monoclonal antibody that inhibits ligand-independent HER2 and HER3 signaling and also triggers antibody-dependent cellular cytotoxicity.
  - *Trastuzumab* was approved in 2006 as part of a treatment regimen containing doxorubicin, cyclophosphamide, and paclitaxel for the adjuvant treatment of women with node-positive, HER2-overexpressing BC.
  - The most important adverse event in the metastatic setting was cardiac dysfunction, which occurred in 27% of the group given an anthracycline, cyclophosphamide, and trastuzumab; 8% of the group given an anthracycline and cyclophosphamide alone; 13% of the group given paclitaxel and trastuzumab; and 1% of the group given paclitaxel alone (Slamon et al, 2001).
- *Pertuzumab*, a humanized monoclonal antibody that inhibits ligand-dependent signaling induced by HER2-HER3 dimers, was approved in 2012 in combination with trastuzumab and docetaxel for the treatment of patients with HER2+ mBC who have not received prior anti-HER2 therapy or chemotherapy for metastatic disease.
  - The most common (>30%) AEs in patients who received pertuzumab plus trastuzumab and docetaxel were diarrhea, alopecia, neutropenia, nausea, fatigue, rash, and peripheral neuropathy (Baselga et al, 2012).
- *ONT-380* is a small molecule inhibitor of HER2 that has been evaluated in a small phase 1b study in combination with capecitabine and/or trastuzumab following prior treatment with trastuzumuab and ado-trastuzumab emtansine (T-DM1) (Hamilton et al, 2015).
  - From 8 patients, 4 partial responses, 2 stable disease, and 2 progressive disease were reported.
  - Most toxicities were Grade 1 or 2, the most common being nausea, vomiting, diarrhea, palmar-plantar erythrodysesthesia, and fatigue.
  - A randomized, placebo-controlled, phase 2 trial is evaluating ONT-380 in combination with trastuzumab and capecitabine in heavily pretreated patients with HER2-positive mBC with or without brain metastases (NCT02614794).

B. EGFR Tyrosine Kinase Inhibitors (TKI)

- In 2007, lapatinib, a small-molecule inhibitor of HER1/EGFR and HER2 tyrosine kinases, was approved for use in combination with capecitabine for the treatment of patients with HER2+ advanced/metastatic breast cancer and who have received prior therapy including an anthracycline, a taxane and trastuzumab.
  - In 2010, *lapatinib* was also approved for use in combination with letrozole for the treatment of postmenopausal women with ER+ metastatic breast cancer that overexpresses HER2 and for whom hormonal therapy is indicated.
  - The most common adverse events associated with lapatinib are diarrhea, hand-foot syndrome, nausea, vomiting, fatigue, and rash distinct from hand-foot syndrome (Geyer et al, 2006).
- *Neratinib* is an irreversible tyrosine kinase inhibitor of HER1, HER2, and HER4 that has been investigated in a phase I/II trial in combination with capecitabine in patients with HER2+ mBC (Saura et al, 2014).
  - The most common drug-related AEs were diarrhea (88%) and palmar-plantar erythrodysesthesia syndrome (48%).
  - ORR was 64% in patients with no prior lapatinib exposure and 57% in patients previously treated with lapatinib; median PFS was 40.3 and 35.9 weeks, respectively.

C. mTOR Inhibitors

- mTOR inhibitors such as *everolimus* are hypothesized to reverse trastuzumab resistance via the hyperactivated PIK/AKT/mTOR pathway due to PTEN loss, by sensitizing PTEN-deficient tumors to trastuzumab (Hurvitz et al, 2015).
- The phase III BOLERO-1 trial assessed the efficacy and safety of adding everolimus to trastuzumab and paclitaxel as first-line treatment for 719 patients with HER2+ advanced BC (Hurvitz et al, 2015).
  - In the full population, median PFS was not statistically significant between the groups (14.95 months with everolimus versus 14.49 months with placebo).
  - The most common AEs were stomatitis (67% everolimus vs 32% placebo), diarrhea (57% vs 47%), and alopecia (47% vs 53%).
  - In the HR-negative, HER2+ subgroup, a 7.2-month prolongation in PFS was reported with the addition of everolimus, warranting further investigation.
- In the BOLERO-3 trial, everolimus added to trastuzumab and vinorelbine significantly improved PFS for patients with trastuzumab-resistant previously treated mBC (André et al, 2014).

D. Phosphatidylinositol-3-kinase (PI3K) Inhibitors

- Constitutive activation of the PI3K pathway has been proposed as a mechanism of trastuzumab resistance in HER2+ mBC (Jain et al, 2015).
- The PI3K inhibitor *buparlisib* (BKM120) was investigated in a phase Ib trial of 17 patients with HER2+ advanced/metastatic breast cancer resistant to trastuzumab-based therapy (Saura et al, 2014).
  - Common (>25%) adverse events included rash (39%), hyperglycemia (33%), and diarrhea (28%).
  - At the recommended phase II dose, there were two (17%) partial responses, 7 (58%) patients had stable disease (≥6 weeks), and the disease control rate was 75%.
- *Alpelisib* (BYL719), the first oral PI3K inhibitor that selectively inhibits the PI3K alpha isoform, was evaluated in combination with T-DM1 in 8 patients with trastuzumab-refractory HER2+ mBC (Jain et al, 2015).
  - The most common treatment-related AEs were fatigue (86%), nausea (75%), aspartate aminotransferase increase (50%), and thrombocytopenia (50%); grade 3 AEs were rash (n = 3), hyperglycemia (n=1), hypertension (n=1), and thrombocytopenia (n=1).
  - ORR was 86% (1 confirmed CR, 2 confirmed PRs, and 3 unconfirmed PRs).

E. Antibody-drug conjugates

- *Ado-trastuzumab emtansine (T-DM1)*, an antibody-drug conjugate incorporating the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1, was approved in 2013 for use as a single agent for the treatment of patients with HER2-positive mBC who previously received treatment with trastuzumab and a taxane, separately or in combination.
  - In the pivotal trial of 991 patients treated with T-DM1 or lapatinib plus capecitabine, the median PFS was 9.6 months and 6.4 months, respectively; the median OS (30.9 vs. 25.1 months) and ORR (43.6%, vs. 30.8%) were also improved with T-DM1 (Verma et al, 2012).
  - Rates of grade 3-4 AEs were higher with lapatinib plus capecitabine than with T-DM1 (57% vs. 41%); the incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1, whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.
- *MM-302*, an antibody-drug conjugated HER2-targeted liposomal doxorubicin, was evaluated in a phase I trial of 69 heavily pre-treated patients administered MM-302 as monotherapy or in combination with trastuzumab or trastuzumab and cyclophosphamide (LoRusso et al, 2015).
  - Patients who received MM-302 plus trastuzumab had a median PFS of 7.6 months; those treated with the addition of cyclophosphamide had a median PFS of 10.6 months
  - Adverse events occurring in more than 20% of patients included constipation, cough, decreased appetite, diarrhea, dyspnea, fatigue, nausea, neutropenia, stomatitis, and vomiting.
  - The ongoing randomized phase 2 HERMIONE trial is comparing MM-302 plus trastuzumab with chemotherapy of physician's choice plus trastuzumab, in anthracycline-naive HER2-positive, locally advanced/metastatic BC patients previously treated with pertuzumab and T-DM1.

II. NCCN Guidelines

Key NCCN guidelines for the treatment of HER2+ mBC are as follows (Gradishar et al, 2016):

- The identification of HER2 status in patients with mBC should be determined using fluorescence in situ hybridization and/or immunohistochemistry.
- Pertuzumab plus trastuzumab in combination with a taxane (docetaxel or paclitaxel) is the preferred option for first-line treatment of patients with HER2+ mBC; T-DM1 should be considered in patients not suitable for the preferred treatment, although published experience on the efficacy of T-DM1 after progression on trastuzumab/pertuzumab is limited.
- For patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (such as vinorelbine or taxane or an aromatase inhibitor for hormone receptor-positive tumors) may be considered; the regimen of capecitabine plus lapatinib is also an option.

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