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

Metastatic Triple Negative Breast Cancer

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I. Background

- Approximately 15% to 20% of breast cancers are triple-negative; i.e., the tumors are negative for estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2) (Yadav et al, 2015).
- Patients with triple-negative breast cancer (TNBC) have a higher incidence of disease recurrence than those with other breast cancer subtypes (Hudis and Gianni, 2011).
- The median survival after recurrence is 12 to 18 months compared with >20 months for other types of breast cancer (Dent et al, 2007; Kennecke et al, 2010).
- Because TNBC is a heterogeneous disease and no single oncogenic driver has been identified, chemotherapy is the primary treatment (Gradishar et al, 2016).
- Current research is focused on defining appropriate targets for directed therapy.

II. Standard Regimens for the Treatment of mTNBC

A. Platinum-based therapy

- The aim of the phase II TBCRC009 trial was to identify patients with metastatic triple-negative breast cancer (mTNBC) who might benefit from platinum-based chemotherapy using biomarker assessment (Isakoff et al, 2015).
  - Patients (N = 86) received first- or second-line *cisplatin or carboplatin* and were divided into molecularly defined subgroups.
  - Response rate was over double in patients with germline BRCA1/2 mutations, whereas p63/p73 expression status, p53 and PIK3CA mutation status, or PAM50 gene expression subtype did not significantly predict outcome.
  - Of note, 6 long-term responding patients remained alive, progression free, and not receiving any therapy at a median of 4.5 years after platinum treatment; 5 of these patients lacked germline BRCA1/2 mutations, and two of them had increased tumor mean homologous recombination deficiency-loss of heterozygosity/homologous recombination deficiency-large-scale state transitions (HRD-LOH/HRD-LST) scores.
  - The authors concluded that a) platinum agents are active in mTNBC, especially in patients with germline BRCA1/2 mutations, and b) a measure of tumor DNA repair function may identify patients without mutations who could benefit from platinum therapy agents.
- The phase 3 TNT trial randomized 376 patients with TNBC or BRCA1/2 mutation-positive mBC to first-line treatment with docetaxel or *carboplatin* (Tutt et al, 2014).
  - In the unselected population, there was no difference between the two agents; however, patients with BRCA1/2 mutations who received carboplatin achieved a greater ORR (68.0% vs 33.3%) and longer PFS (6.8 vs 4.8 months).
  - Patients with homologous recombination deficiency (HRD) experienced similar outcomes between the docetaxel and carboplatin arm: in the HRD high arm, the ORR with carboplatin was 38.2% versus 42.6% with docetaxel.
- A phase III trial compared iniparib plus gemcitabine and carboplatin (GCI) vs. *gemcitabine and carboplatin* (GC) in 519 patients with stage IV/locally recurrent TNBC who had received no more than two prior chemotherapy regimens (O'Shaughnessy et al, 2014).
  - No statistically significant differences in efficacy were observed between the groups.
  - The GC arm demonstrated a median PFS of 4.1 months and a median OS of 11.1 months.
  - The most frequently reported grade 3 or 4 AEs in both arms were neutropenia (62% with GCI v 53% with GC) and thrombocytopenia (29% with GCI v 24% with GC).

B. Mitotic Inhibitors

- A pooled analysis of two phase III trials (EMBRACE and Study 301) assessed the efficacy of the anti-microtubule agent *eribulin* in 1,062 women with previously treated mBC (Twelves et al, 2014).
  - Median OS was 15.2 months with *eribulin* versus 12.8 months with control; significant improvements occurred in multiple subgroups, including patients with triple-negative disease.
- In the phase III Study 301 trial comparing eribulin with capecitabine in patients with locally advanced or metastatic breast cancer, eribulin did not significantly improve OS or PFS (Kaufman et al, 2015).
  - However, in the TNBC subgroup, there was a 5-month improvement in OS with eribulin (14.4 vs. 9.4 months).

- A randomized phase III trial evaluated *ixabepilone* plus capecitabine vs capecitabine in patients with mBC previously treated with an anthracycline and a taxane (Sparano et al, 2010).
  - In 1,221 patients, there was no significant difference in OS between the combination and capecitabine monotherapy arm; however, in 79% of patients with measurable disease, the combination significantly improved median PFS (6.2 vs 4.2 months) and response rate (43% v 29%).
  - Grade 3 to 4 neuropathy occurred in 24% treated with the combination, but was reversible.
- A pooled subgroup analysis of two large phase III trials assessed the benefit of adding ixabepilone to capecitabine in anthracycline-taxane pre-treated TNBC patients (Rugo et al, 2009): the study demonstrated a doubling in PFS (4.2 months vs. 1.7 months) and ORR (31% vs. 15%) with comparable OS (10.3 months vs. 9.0 months) in 400 TNBC patients receiving ixabepilone.

C. VEGF Inhibitors

- The phase III MERiDiAN trial evaluated the efficacy and safety of first-line paclitaxel ± the VEGF inhibitor bevacizumab in mBC and investigated plasma VEGF-A as a potential predictive biomarker of bevacizumab efficacy in patients with HER2-negative mBC (Miles et al, 2015).
  - Overall, the addition of bevacizumab increased ORR from 33% to 54% and median PFS from 8.8 to 11 months; no predictive effect of pVEGF-A was observed.
  - Bevacizumab was associated with higher all-grade incidences of bleeding (45% vs. 27%), neutropenia (39% vs 29%), hypertension (31% vs. 13%), grade ≥3 incidences of neutropenia (20% vs. 9%), anemia (5% vs. 2%), pulmonary embolism (3% vs. 0.4%), and hypertension (11% vs. 4%).

II. Investigational Therapies for the Treatment of mTNBC

A. PARP inhibitors

- In the I-SPY2 trial, the poly (ADP-ribose) polymerase (PARP) inhibitor *veliparib* plus carboplatin and paclitaxel yielded a 52% response rate (vs. 26% for controls) overall and 70.9% for patients with no HER2 expression (Rugo et al, 2013).
  - The phase III neoadjuvant BRIGHTNESS trial of carboplatin ± veliparib in patients with early-stage TNBC has finished accrual and results are expected in 2017.
- Three other PARP inhibitors are currently in phase III trials of BRCA 1/2 mutated BC: talazoparib, niraparib, and olaparib.

B. Androgen Receptor Inhibitors

- The phase II MDV3100-11 trial evaluated first- or second-line enzalutamide, an androgen receptor (AR) inhibitor, in 118 patients with advanced AR+ TNBC (Traina et al, 2015).
  - Preliminary results indicated that in patients treated with *enzalutamide*, median PFS was 32 weeks in AR+ and 9 weeks in AR- patients; in addition, two CRs and 5 PRs were observed.
  - AEs in ≥10% of patients were fatigue (34%), nausea (25%), decreased appetite (13%), diarrhea, and hot flush (10%); fatigue (5%) was the only AE ≥ Grade 3 in ≥5%.
- A phase II study explored the AR antagonist bicalutamide in AR-positive, estrogen receptor (ER)-, and progesterone receptor (PR)-negative mBC (Gucalp et al, 2013).
  - Of 424 patients with ER/PR-negative BC, 12% tested AR-positive.
  - The 6-month clinical benefit rate was 19% for bicalutamide and the median PFS was 12 weeks.
  - Bicalutamide was well-tolerated with no grade 4/5 treatment-related adverse events observed.

C. Antibody-Drug Conjugates

- *Sacituzumab govitecan (IMMU-132)*, an anti-Trop-2 antibody-drug conjugate (ADC), was evaluated in a phase II trial of 58 patients with heavily pretreated mTNBC (Bardia et al, 2015).
  - Grade 3-4 toxicities included neutropenia (26%), febrile neutropenia (2%), diarrhea (2%), anemia (4%), and fatigue (4%); no patients discontinued therapy due to toxicity.
  - Preliminary ORR (CR+PR) was 31% of 49 evaluated patients (including 2 with CR), the clinical benefit ratio (CR+PR+SD>6 months) was 49%, and the median PFS was 7.3 months.
- *Glembatumumab vedotin*, a glycoprotein NMB-specific monoclonal antibody conjugated to the potent cytotoxin monomethyl auristatin E, was compared to investigator's choice chemotherapy in the phase II EMERGE trial of 124 patients with gpNMB+ refractory breast cancer (Yardley et al, 2015).
  - Glembatumumab vedotin was well tolerated as compared with chemotherapy (less hematologic toxicity; more rash, pruritus, neuropathy, and alopecia).
  - ORR was increased in patients with TNBC: 18% in patients treated with glembatumumab versus 0% in patients treated with chemotherapy.
  - A pivotal phase II trial (METRIC) is underway.

D. Checkpoint Inhibitors

- The programmed cell death protein 1 (PD-1) inhibitor *pembrolizumab* was evaluated in the phase 1b KEYNOTE-012 trial of 32 patients with heavily pretreated advanced PD-L1+ TNBC (Nanda et al, 2016).
  - Common toxicities were mild and similar to those observed in other tumor cohorts (e.g., arthralgia, fatigue, myalgia, and nausea), and included five (15.6%) patients with grade ≥ 3 toxicity and one treatment-related death.
  - The ORR was 18.5%, the median time to response was 17.9 weeks, and the median duration of response was not yet reached (range: 15.0 to ≥ 47.3 weeks).
- A phase Ib study evaluated the PD-L1 inhibitor *atezolizumab* plus nab-paclitaxel in 32 patients with mTNBC treated with ≤ 3 prior lines of therapy (Adams et al, 2016).
  - The most common treatment-related AE was decreased neutrophil count (53% all grade; 41% Gr 3-4) and no dose-limiting toxicities or related deaths occurred.
  - At a median follow-up of 5.2 months, ORR was 42%,

including 4% CR, 67% PR, and 21% SD, with responses occurring in patients whose tumors expressed PD-L1 and in those with little to no PD-L1 expression.

– An ongoing phase III trial (IMpassion130) is evaluating this regimen in previously untreated patients with mTNBC.

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