BREAST CANCER REVIEW

Zahi Mitri, MD, MS
Knight Cancer Institute, OHSU
Portland, OR
April 16th, 2022
OUTLINE

• Triple Negative Breast Cancer
  – Chemo-Immunotherapy in Early Stage
  – Updates in Metastatic Disease

• BRCA-Associated Breast Cancer
  – Role in Metastatic Disease
  – Adjuvant Olaparib Approval
TRIPLE NEGATIVE BREAST CANCER
EARLY STAGE
Neo-adjuvant Chemo-Immunotherapy
Keynote-522
KEYNOTE-522 Study Design (NCT03036488)

Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Key Eligibility Criteria
- Age ≥18 years
- Newly diagnosed TNBC of either T1c N1-2 or T2-4 N0-2
- ECOG PS 0-1
- Tissue sample for PD-L1 assessment

Neoadjuvant Treatment 1 (cycles 1-4; 12 weeks)
- Carboplatinb + Paclitaxelc

Neoadjuvant Treatment 2 (cycles 5-8; 12 weeks)
- Doxorubicin/d+Epirubicin+ + Cyclophosphamidef

Adjuvant Treatment (cycles 1-9; 27 weeks)
- Pembrolizumab 200 mg Q3W
- Placebo

Primary Endpoints
- pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT
- Event-free survival (EFS) assessed by investigator in ITT

Notes:
- Must consist of at least 2 separate tumor cores from the primary tumor.
- Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
- Paclitaxel dose was 80 mg/m² Q1W.
- Doxorubicin dose was 60 mg/m² Q3W.
- Epirubicin dose was 90 mg/m² Q3W.
- Cyclophosphamide dose was 600 mg/m² Q3W.

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Definitive pCR Analysis

- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

\[ \Delta 13.6 (5.4–21.8)^a \]
\[ P = 0.00055 \]

64.8%  
51.2%

Placebo + Chemo  
Pembro + Chemo

\(^a\)Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.
Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

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EFS (ITT Population)

- Pembrolizumab–chemotherapy: 84.5%
- Placebo–chemotherapy: 76.8%

Hazard ratio for event or death: 0.63 (95% CI, 0.48–0.82)
P<0.001

No. at Risk
Pembrolizumab–chemotherapy: 784, 781, 769, 751, 728, 718, 702, 692, 681, 671, 652, 551, 433, 303, 165, 28, 0, 0
Placebo–chemotherapy: 390, 386, 382, 368, 358, 342, 328, 319, 310, 304, 297, 250, 195, 140, 83, 17, 0, 0
### Table 1. Summary of First Events in Analysis of Event-free Survival.

<table>
<thead>
<tr>
<th>First Event</th>
<th>Pembrolizumab–Chemotherapy (N = 784)</th>
<th>Placebo–Chemotherapy (N = 390)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>number (percent)</td>
<td>number (percent)</td>
</tr>
<tr>
<td>Any first event</td>
<td>123 (15.7)</td>
<td>93 (23.8)</td>
</tr>
<tr>
<td>Progression of disease that precluded definitive surgery</td>
<td>14 (1.8)</td>
<td>15 (3.8)</td>
</tr>
<tr>
<td>Local recurrence*</td>
<td>28 (3.6)</td>
<td>17 (4.4)</td>
</tr>
<tr>
<td><strong>Distant recurrence</strong></td>
<td><strong>60 (7.7)</strong></td>
<td><strong>51 (13.1)</strong></td>
</tr>
<tr>
<td>Second primary cancer†</td>
<td>6 (0.8)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>Death</td>
<td>15 (1.9)</td>
<td>6 (1.5)</td>
</tr>
<tr>
<td>Event</td>
<td>Pembrolizumab–Chemotherapy (N = 783)</td>
<td>Placebo–Chemotherapy (N = 389)</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Immune-mediated adverse event:</td>
<td>262 (33.5)</td>
<td>101 (12.9)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>118 (15.1)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Severe skin reaction</td>
<td>45 (5.7)</td>
<td>37 (4.7)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>41 (5.2)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>20 (2.6)</td>
<td>8 (1.0)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>17 (2.2)</td>
<td>7 (0.9)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>16 (2.0)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>15 (1.9)</td>
<td>10 (1.3)</td>
</tr>
</tbody>
</table>
KN-522: Conclusions

- Chemo + Pembrolizumab approved as neoadjuvant therapy
- No PD-L1 testing restriction / requirement
- Improves pCR, EFS
- OS analysis premature
KN-522: Questions?

- Four chemo backbone needed for everyone?
- Role of carboplatin?
- Adjuvant therapy for residual disease
  - Capecitabine + Pembrolizumab?
- Pembrolizumab maintenance in pCR?
BRIGHTNESS TRIAL
# pCR Analysis

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>pCR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel / Carboplatin / Veliparib</td>
<td>53% (168/316)</td>
</tr>
<tr>
<td>Paclitaxel / Carboplatin</td>
<td>58% (92/160)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>31% (49/158)</td>
</tr>
</tbody>
</table>
# EFS Analysis

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>4-Year EFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel / Carboplatin / Veliparib</td>
<td>78.2%</td>
</tr>
<tr>
<td>Paclitaxel / Carboplatin</td>
<td>79.3%</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>68.5%</td>
</tr>
</tbody>
</table>

Loibl et al, ESMO 2021
EFS Analysis

Loibl et al, ESMO 2021
OUTLINE

• Triple Negative Breast Cancer
  – Neoadjuvant Chemo-Immunotherapy (KN-522)
  – Carboplatin Impact (Brightness)
  – Sacituzumab for Metastatic
ADJUVANT THERAPY – RESIDUAL DISEASE
CREATE-X Trial

C Disease-free Survival among Patients with Triple-Negative Disease

- Probability of Disease-free Survival vs. Years since Randomization
- Hazard ratio for recurrence, second cancer, or death: 0.58 (95% CI, 0.39–0.87)

D Overall Survival among Patients with Triple-Negative Disease

- Probability of Overall Survival vs. Years since Randomization
- Hazard ratio for death: 0.52 (95% CI, 0.30–0.90)

No. at Risk

- Capecitabine: 139, 109, 96, 76, 42, 11
- Control: 147, 95, 84, 69, 47, 6

Masuda et al, NEJM 2017
Combine Cape & Pembro?

- Combination in stage IV disease
  - Safe, AEs similar to capecitabine monotherapy
  - Signal of efficacy in subgroup of patients
ADJUVANT THERAPY – pCR
**KN-522**

Event-Free Survival (%)

- **pCR Yes**
  - Hazard ratio for an event or death, 0.73
  - (95% CI, 0.39-1.36)

- **pCR No**
  - Hazard ratio for an event or death, 0.70
  - (95% CI, 0.52-0.95)

- Pembrolizumab–Chemotherapy Responder
- Placebo–Chemotherapy Responder
- Pembrolizumab–Chemotherapy Non-Responder
- Placebo–Chemotherapy Non-Responder

Months

0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51
Continue Pembro?

- KN-522 completed 1 year of pembrolizumab regardless of pathologic response
- Excellent outcomes for pCR in pembro / control arm
- Trials to address pembrolizumab maintenance question
TRIPLE NEGATIVE BREAST CANCER METASTATIC DISEASE
KEYNOTE – 355
CHEMO +/- PEMBRO
KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease

Pembrolizumab\(^a\) + Chemotherapy\(^b\)

R 2:1

Placebo\(^c\) + Chemotherapy\(^b\)

Progressive disease\(^d\)/cessation of study therapy

Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

\(^a\)Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
\(^b\)Chemotherapy dosing regimens are as follows:
- Nab-paclitaxel 100 mg/m\(^2\) IV on days 1, 8, and 15 every 28 days
- Paclitaxel 90 mg/m\(^2\) IV on days 1, 8, and 15 every 28 days
- Gemcitabine 1000 mg/m\(^2\)/carboplatin AUC 2 on days 1 and 8 every 21 days

\(^c\)Normal saline
\(^d\)Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group;
PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer

Presented By Javier Cortes at TBD
Progression-Free Survival: ITT

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Statistical significance was not tested due to the prespecified hierarchical testing strategy. Data cutoff December 11, 2019.
Progression-Free Survival: PD-L1 CPS ≥10

Presented By Javier Cortes at TBD

<table>
<thead>
<tr>
<th>PD-L1 CPS ≥10</th>
<th>n/N</th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P-value (one-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>136/220</td>
<td>61.8%</td>
<td>0.65 (0.49-0.86)</td>
<td>0.0012*</td>
</tr>
<tr>
<td>Placebo</td>
<td>79/103</td>
<td>76.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Prespecified P value boundary of 0.00411 not met.

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.
Progression-Free Survival: PD-L1 CPS ≥1

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Prespecified P value boundary of 0.00111 not met.

Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff December 11, 2019.