TREATMENT OF METASTATIC TRIPLE NEGATIVE BREAST CANCER

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SINGAPORE
ESMO wishes to thank the following companies for supporting this ESMO Preceptorship Programme

MSD

Roche
Disclosures

• Advisory Boards, Honorariums or Travel
  – Astra Zeneca, Eisai, Genentech, Merck, Novartis, Pfizer, Roche
Scope

• Chemotherapy
  – Special attention on platinum
• PARP inhibitors
• Further directions
  – Immune checkpoint inhibitors
  – Androgen receptor antagonists
  – AKT inhibitors
  – Antibody-drug conjugates
Current Treatment Options for Metastatic TNBC

• Sequential single-agent chemotherapy is the preferred approach for most pts with metastatic TNBC
  – Combination chemotherapy can be used for pts requiring more rapid response but does not improve OS
• Pts should generally remain on a regimen until best response, disease progression, or significant toxicity

<table>
<thead>
<tr>
<th>Taxanes</th>
<th>Anthracyclines</th>
<th>Antimetabolites</th>
<th>Microtubule Inhibitors</th>
<th>Platinum Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Doxorubicin</td>
<td>Capecitabine</td>
<td>Vinorelbine</td>
<td>Carboplatin</td>
</tr>
<tr>
<td>Nab-paclitaxel</td>
<td>Pegylated liposomal doxorubicin</td>
<td>Gemcitabine</td>
<td>Eribulin</td>
<td>Cisplatin</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Epirubicin</td>
<td>Ixabepilone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

[Diagram of treatment options]
Guidelines: ABC4

For non-BRCA-associated advanced TNBC, there are no data supporting different or specific ChT recommendations.

Therefore, all ChT recommendations for HER2-negative disease also apply for advanced TNBC.

In advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.

The AR is a potential target in advanced TNBC. There are, however, no standardised methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice. More definitive trials are needed, and research efforts must continue to optimise and standardise the determination of AR.

In patients with BRCA-associated advanced TNBC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option, if not previously administered and no suitable clinical trial is available. All other treatment recommendations are similar to sporadic ABC.

A PARPi (olaparib or talazaparib) is a reasonable treatment option for patients with BRCA-associated advanced TNBC or luminal (after progression on ET) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL, and a favourable toxicity profile. OS results are awaited. It is unknown how PARPi compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumours.

Cardoso F et al, Ann Oncol 2018
Study 301: Eribulin vs Capecitabine in Previously Treated LABC or MBC

- ≤3 prior chemo
- (≤2 for advanced disease)
- prior anthracycline & taxane
- N = 1102

Stratified by
- Geographical region
- HER2 status

Eribulin Mesylate 1.4 mg/m²
D1,8 q21d
(n = 554)

Capecitabine 1250 mg/m² BD
D1-14 q21d
(n = 548)

Kaufman PA et al, JCO 2015
Study 301: Eribulin vs Capecitabine

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Eribulin Median (months)</th>
<th>Capecitabine Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.879 (0.770, 1.003)</td>
<td>15.9</td>
<td>14.5</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.965 (0.688, 1.355)</td>
<td>14.3</td>
<td>17.1</td>
</tr>
<tr>
<td>Negative</td>
<td>0.838 (0.715, 0.983)</td>
<td>15.9</td>
<td>13.5</td>
</tr>
<tr>
<td>ER status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0.897 (0.737, 1.093)</td>
<td>18.2</td>
<td>16.8</td>
</tr>
<tr>
<td>Negative</td>
<td>0.779 (0.635, 0.955)</td>
<td>14.4</td>
<td>10.5</td>
</tr>
<tr>
<td>Triple negative</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.702 (0.545, 0.906)</td>
<td>14.4</td>
<td>9.4</td>
</tr>
<tr>
<td>No</td>
<td>0.927 (0.795, 1.081)</td>
<td>17.5</td>
<td>16.6</td>
</tr>
</tbody>
</table>

Twelves C et al, Breast Cancer (Auckl) 2016
Are There Any Clinically Relevant Subgroups of Triple-Negative Breast Cancer in 2018?

- TNBC
  - Germline BRCA1/2 and HR pathway gene mutation testing
    - (Somatic BRCA mutation testing)
    - (HRD score, HRD scar biomarkers)
  - Histologic examination for tumor-infiltrating lymphocytes (?)
    - (Immune signature by gene expression microarray)
  - IHC for androgen receptor (?)
    - (Androgen-related gene signature by genomic diagnostic assay)
  - (Sequencing for PIK3CA/AKT1/PTEN alterations)
  - IHC for targetable cancer epithelial antigens
  - Tested negative
    - Unclassified TNBCs:
      - chemotherapy and clinical trials
    - Unique antigen-expressing:
      - antibody-drug conjugates
    - PI3K/AKT/PTEN altered:
      - AKT inhibitors
    - Inflamed phenotype: androgen receptor-positive:
      - immunotherapy
    - Androgen receptor-positive:
      - blockade
    - Defective DNA repair:
      - platinum and PARP inhibitors

Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
*Journal of Oncology Practice*  May 11, 2018
Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial

Andrew Tutt, Holly Tovey, Maggie Chon U. Cheang, Sarah Kernaghan, Lucy Kilburn, Patrycja Gazinska, Julie Owen, Jacinta Abraham, Sophie Barrett, Peter Barrett-Lee, Robert Brown, Stephen Chan, Mitchell Dowsett, James M Flanagan, Lisa Fox, Anita Grigoriadis.

ER-, PgR-/unknown & HER2- or known BRCA1/2
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

A Priori subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

**Carboplatin (C)**
AUC 6 q3w, 6 cycles
On progression, crossover if appropriate

**Docetaxel (D)**
100mg/m² q3w, 6 cycles
n-376
BRCA1/2 = 9%/12%
On progression, crossover if appropriate

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

**Carboplatin (C)**
AUC 6 q3w, 6 cycles
Objective Response – *BRCA1/2* status

**Germline BRCA1/2 mutation**
- **Mutated BRCA**: 17 of 25 (68.0%)
  - Absolute difference: 34.7% (95% CI, 6.3 to 63.1)
  - Exact $P = 0.03$
- **Wild-type BRCA**: 36 of 128 (28.1%)
  - Absolute difference: −6.4% (95% CI, −17.4 to 4.6)
  - Exact $P = 0.30$

**Interaction test $P = 0.01$**

**Tumor BRCA1/2 mutation**
- **Mutated BRCA**: 12 of 18 (66.7%)
  - Absolute difference: 31.0% (95% CI, −2.2 to 64.2)
  - Exact $P = 0.15$
- **Wild-type BRCA**: 23 of 90 (25.6%)
  - Absolute difference: −10.0% (95% CI, −23.4 to 3.4)
  - Exact $P = 0.20$

**Interaction test $P = 0.03$**

**Key**
- **Carboplatin** (orange)
- **Docetaxel** (green)
- **95% CI**
TNT: Platinum Sensitivity Was Not Associated with Higher Myriad HRD Scores in mTNBC

High HRD score (n = 81)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage with OR at #3 or #6 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>13/34 (38.2%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>20/47 (42.6%)</td>
</tr>
</tbody>
</table>

Absolute difference (C-D)
-4.4% (95% CI -26.0 to 17.2)
Exact $P = 0.82$

Low HRD score (n = 114)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage with OR at #3 or #6 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>19/65 (29.2%)</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>17/49 (34.7%)</td>
</tr>
</tbody>
</table>

Absolute difference (C-D)
-5.4% (95% CI -22.7 to 11.9)
Exact $P = 0.55$

Interaction: randomised treatment & dichotomised HRD score: $P = 0.91$

Tutt A et al. SABCS 2014.
CBCSG006: PFS of 1\textsuperscript{st} Line Gem/Cis vs Gem/Pac in mTNBC

Zhang J et al, Ann Oncol 2018

median PFS and 95\% CI
GP: 7.73 months (6.46-9.00 months)
GT: 6.07 months (5.32-6.83 months)

\(P=0.005\)
CBCSG006: *No* Significant Interaction between gBRCA Status and Treatment for PFS

Germ-line BRCA1/2 mutation

- Objective response rate: 3/8 (37.5%) for GT, 5/6 (83.3%) for GP; Interaction test $P = 0.086$

No Germ-line BRCA1/2 mutation

- Objective response rate: 29/56 (51.8%) for GT, 38/62 (61.3%) for GP; Interaction test $P = 0.298$

Progression-free survival

- Median PFS: GP: 8.90 (3.94-13.86) months, GT: 3.20 (0.00-8.19) months; Interaction test $P = 0.459$

- Median PFS (95% CI): GP: 6.97 (5.12-8.82) months, GT: 5.97 (4.35-7.59) months; Interaction test $P = 0.347$

Interaction test $P = 0.485$
# Guidelines: ABC4

<table>
<thead>
<tr>
<th>Guideline statement</th>
<th>LoE/GoR</th>
<th>Consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>For non-BRCA-associated advanced TNBC, there are no data supporting different or specific ChT recommendations.</td>
<td>I/A</td>
<td>98%</td>
</tr>
<tr>
<td>Therefore, all ChT recommendations for HER2-negative disease also apply for advanced TNBC.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.</td>
<td>I/A</td>
<td>91%</td>
</tr>
<tr>
<td>The AR is a potential target in advanced TNBC. There are, however, no standardised methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice. More definitive trials are needed, and research efforts must continue to optimise and standardise the determination of AR.</td>
<td>II/D</td>
<td>85%</td>
</tr>
<tr>
<td>BRCA-associated ABC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>In patients with BRCA-associated advanced TNBC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option, if not previously administered and no suitable clinical trial is available. All other treatment recommendations are similar to sporadic ABC.</td>
<td>II/A</td>
<td>86%</td>
</tr>
<tr>
<td>A PARPi (olaparib or talazaparib) is a reasonable treatment option for patients with BRCA-associated advanced TNBC or luminal (after progression on ET) ABC, previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL, and a favourable toxicity profile. OS results are awaited. It is unknown how PARPis compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumours.</td>
<td>I/B</td>
<td>80%</td>
</tr>
</tbody>
</table>

Cardoso F et al, Ann Oncol 2018
PARP trapping > catalytic inhibition

Shen et al. CCR 2013.

<table>
<thead>
<tr>
<th>PARP inhibitor</th>
<th>PARP1 enzyme inhibition IC50, nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iniparib</td>
<td>No effect</td>
</tr>
<tr>
<td>Talazoparib</td>
<td>0.57</td>
</tr>
<tr>
<td>Olaparib</td>
<td>1.9</td>
</tr>
<tr>
<td>Rucaparib</td>
<td>2.0</td>
</tr>
<tr>
<td>Veliparib</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Olaparib/Talazoparib 50-100x more powerful at trapping than Veliparib

OLYMPIA-D & EMBRACA
Phase III PARPi Trials

Pts with HER2-negative MBC with deleterious or suspected deleterious gBRCA mutation; previous anthracycline and taxane, ≤ 2 previous lines of CT* for metastatic disease; if HR+, not suitable for ET or progressed on ≥ 1 ET (N = 302)

2:1

Olaparib 300 mg PO BID (n = 205)

CT† on 28-d cycles (n = 97)

Pts with HER2-negative LABC or MBC with deleterious or suspected deleterious gBRCA mutation; stratified by previous lines of CT* 0 or ≥1 if Hx CNS met or not

2:1

Talazoparib 1 mg PO OD (n = 287)

CT on 21/28-d cycles (n = 144)
Cross-trial comparison

**OS Results**

Mark Robson

Median OS **19.3** months with olaparib vs. **17.1** months with chemotherapy, HR = 0.90 (95% CI, 0.66-1.23; \( P = .513 \))

Still in search of biomarkers...
OLYMPIAD Overall Survival in prespecified subgroups

**No prior chemotherapy for mBC (1L)**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>30 (50.8)</td>
<td>21 (75.0)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>22.6</td>
<td>14.7</td>
</tr>
<tr>
<td>HR 0.51</td>
<td>[0.29-0.90]; P=0.02</td>
<td></td>
</tr>
<tr>
<td>Alive at 6 mo, %</td>
<td>93.2</td>
<td>88.5</td>
</tr>
<tr>
<td>Alive at 18 mo, %</td>
<td>62.1</td>
<td>46.2</td>
</tr>
<tr>
<td>Median follow-up, mo</td>
<td>25.5</td>
<td>26.9</td>
</tr>
</tbody>
</table>

**Prior chemotherapy for mBC (2/3L)**

<table>
<thead>
<tr>
<th></th>
<th>Olaparib</th>
<th>TPC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths, n (%)</td>
<td>100 (68.5)</td>
<td>41 (59.4)</td>
</tr>
<tr>
<td>Median OS, mo</td>
<td>18.8</td>
<td>17.2</td>
</tr>
<tr>
<td>HR 1.13</td>
<td>[0.79-1.64]; P=NS</td>
<td></td>
</tr>
<tr>
<td>Alive at 6 mo, %</td>
<td>93.1</td>
<td>84.9</td>
</tr>
<tr>
<td>Alive at 18 mo, %</td>
<td>50.8</td>
<td>48.8</td>
</tr>
<tr>
<td>Median follow-up, mo</td>
<td>25.2</td>
<td>26.0</td>
</tr>
</tbody>
</table>

Nominal P values calculated using a likelihood ratio test; OS stratification factors were prespecified but not alpha controlled. 1L, first line; 2/3L, second or third line; NS, not significant.
## Efficacy comparison – NB Caveats

<table>
<thead>
<tr>
<th></th>
<th>Olaparib OlympiaD (n=205)</th>
<th>Talazoparib EMBRACA (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% TNBC vs HR+</td>
<td>TNBC: 50%</td>
<td>TNBC: 46%</td>
</tr>
<tr>
<td></td>
<td>HR+: 50%</td>
<td>HR+: 54%</td>
</tr>
<tr>
<td>Median prior ctx lines for M+</td>
<td>na</td>
<td>TBD</td>
</tr>
<tr>
<td>% 1L mBC</td>
<td>29%</td>
<td>38%</td>
</tr>
<tr>
<td>Prior Platinum</td>
<td>29%</td>
<td>18%</td>
</tr>
<tr>
<td>ECOG PS 0</td>
<td>72%</td>
<td>55%</td>
</tr>
<tr>
<td>PFS (BICR)</td>
<td>7.0m vs. 4.2m</td>
<td>8.6m vs 5.6m</td>
</tr>
<tr>
<td></td>
<td>HR=0.58 (0.43-0.80)</td>
<td>HR: 0.54 (95% CI: 0.41, 0.71)</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>mDOR</td>
<td>6.4m vs. 7.1m (BICR)</td>
<td>5.4m vs. 3.1m (INV)</td>
</tr>
<tr>
<td>Median time on treatment</td>
<td>8.3m (7.6m with tx interruption)</td>
<td>6.1m vs. 3.9m</td>
</tr>
<tr>
<td>ORR (BICR)</td>
<td>59.9% vs. 28.8%</td>
<td>NA</td>
</tr>
<tr>
<td>ORR (INV)</td>
<td>57.6% vs. 22.2%</td>
<td>62.6% vs. 27.2%</td>
</tr>
<tr>
<td>OS</td>
<td>46% maturity</td>
<td>38% maturity</td>
</tr>
<tr>
<td></td>
<td>19.3m vs. 19.6m</td>
<td>22.3m vs. 19.5m</td>
</tr>
<tr>
<td></td>
<td>HR=0.90 (0.63-1.29)</td>
<td>HR=0.762 p=0.105</td>
</tr>
<tr>
<td></td>
<td>p=0.57</td>
<td></td>
</tr>
</tbody>
</table>
Safety comparison

<table>
<thead>
<tr>
<th></th>
<th>Olaparib (n=205)</th>
<th>Talazoparib (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥3 AEs</td>
<td>36.6%</td>
<td>55% (heme) / 32% (non-heme)</td>
</tr>
<tr>
<td>Dose interruption</td>
<td>35%</td>
<td></td>
</tr>
<tr>
<td>Dose reduction</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>AE leading to discontinuation</td>
<td>4.9% (vs. 7.7%)</td>
<td>7.7% (vs. 9.5%)</td>
</tr>
<tr>
<td>SAEs</td>
<td>15.6% (vs. 16.6%)</td>
<td>31.8% (vs. 29.4%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>all Gr</th>
<th>Gr≥3</th>
<th>all Gr</th>
<th>Gr≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>40%</td>
<td>16%</td>
<td>52.8%</td>
<td>39.2%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27%</td>
<td>9%</td>
<td>34.6%</td>
<td>20.9%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6.8%</td>
<td>1.5%</td>
<td>26.9%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>58%</td>
<td>0%</td>
<td>48.8%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30%</td>
<td>0%</td>
<td>24.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>20.5%</td>
<td>0.5%</td>
<td>22%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Liver Enzymes (AST/ALT)</td>
<td>9% / 11%</td>
<td>0% / 2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.5%</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>-</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>2.9%</td>
<td>50.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2.9%</td>
<td>2.9%</td>
<td>50.3%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>20%</td>
<td></td>
<td>32.5%</td>
<td>1.7%</td>
</tr>
<tr>
<td>Constipation</td>
<td>12.2%</td>
<td></td>
<td>22%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>16.1%</td>
<td></td>
<td>21.3%</td>
<td>0.3%</td>
</tr>
<tr>
<td>Back pain</td>
<td>11.7%</td>
<td>1.5%</td>
<td>21%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>7.8%</td>
<td>1.0%</td>
<td>17%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>
A series of point mutations have been characterized by extensive CRISPR screens – with functional correlations Preventing PARPi binding/activity
Enzymatic abrogation of replication fork stalling:
Potential addition of other DDR Targeted agents
AstraZeneca oral ATR inhibitor
AZD6738 and PARPi combinations

Combination therapy – preclinical activity

+Olaparib (PARPi) – breast primary explant xenograft

<table>
<thead>
<tr>
<th>ATR enzyme (pCHK1)</th>
<th>ATR cell (pCHK1)</th>
<th>mTOR cell (pS6)</th>
<th>PI3Kα cell (pAKT)</th>
<th>ATM cell (pATM)</th>
<th>DNAPK cell (pATM)</th>
<th>LoVo G150 (µM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.074</td>
<td>&gt;23</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>&gt;30</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Olaparib (PARP Trapping)

BRCA1/2 deficient cells can use ATR to protect fork and enable HR repair


Yazinski et al Genes and Development
**Guidelines: ABC4**

<table>
<thead>
<tr>
<th>Guideline statement</th>
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<th>Consensus</th>
</tr>
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<tbody>
<tr>
<td>For non-BRCA-associated advanced TNBC, there are no data supporting different or</td>
<td>I/A</td>
<td>98%</td>
</tr>
<tr>
<td>specific ChT recommendations.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Therefore, all ChT recommendations for HER2-negative disease also apply for advanced TNBC.

In advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.

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**BRCA-associated ABC**

In patients with BRCA-associated advanced TNBC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option, if not previously administered and no suitable clinical trial is available. All other treatment recommendations are similar to sporadic ABC.

A PARPi (olaparib or talazapanib) is a reasonable treatment option for patients with BRCA-associated advanced TNBC or luminal (after progression on ET) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL, and a favourable toxicity profile. OS results are awaited. It is unknown how PARPis compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumours.

Cardoso F et al, Ann Oncol 2018
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Germline BRCA1/2 and HR pathway gene mutation testing
(Somatic BRCA mutation testing)
(HRD score, HRD scar biomarkers)

Histologic examination for tumor-infiltrating lymphocytes (?)
(Immune signature by gene expression microarray)

IHC for androgen receptor (?)
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(Sequencing for PIK3CA/AKT1/PTEN alterations)

IHC for targetable cancer epithelial antigens

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Inflamed phenotype:
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Androgen receptor-positive:
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Unique antigen-expressing:
antibody-drug conjugates

Unclassified TNBCs:
chemotherapy and clinical trials

Tested negative

Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice  May 11, 2018
Tumour-infiltrating lymphocytes and outcome


Strongest link of TILs and outcome in TNBC

### Immune Checkpoint Inhibitors in mTNBC

<table>
<thead>
<tr>
<th>Target</th>
<th>Pembrolizumab (n = 32)</th>
<th>Atezolizumab (n = 71)</th>
<th>Avelumab (n=58 /9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour PD-L1</td>
<td>≥1% (58%+)</td>
<td>≥5%</td>
<td>All / ≥1%</td>
</tr>
<tr>
<td>ORR</td>
<td>18.5%</td>
<td>13%</td>
<td>8.6% / 44.4%</td>
</tr>
<tr>
<td>SD</td>
<td>25.9%</td>
<td>18%</td>
<td>22.4%</td>
</tr>
</tbody>
</table>

- Durable responses in heavily pretreated pts

Nanda et al, JCO 2016; Schmid et al, AACR 2017; Dirix et al, SABCS 2015
Pembrolizumab Monotherapy in mTNBC

KN-086

Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

Cohort A (N = 170):
Previously Treated, Regardless of PD-L1 Expression

- Complete response
- Partial response
- Stable disease ≥24 wk

Cohort B (N = 52)¹:
Previously Untreated, PD-L1 Positive

- ORR: 23.1%
Combination of Immune- & Chemotherapy in mTNBC

Nab-Paclitaxel + anti-PD-L1 (Atezolizumab)

1\textsuperscript{st} line Patients

2\textsuperscript{nd}/≥3\textsuperscript{rd} line Patients

Independent of PD-L1 status

Eribulin + anti-PD-1 (Pembrolizumab)

<table>
<thead>
<tr>
<th>ORR</th>
<th>All</th>
<th>1\textsuperscript{st} line (n=17)</th>
<th>2\textsuperscript{nd}/3\textsuperscript{rd} line (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>34.4%</td>
<td>41.2%</td>
<td>27.3%</td>
</tr>
<tr>
<td>CBR</td>
<td>40.6%</td>
<td>47.1%</td>
<td>36.4%</td>
</tr>
</tbody>
</table>

Adapted from Adams S et al, SABCS 2015; Tolaney et al, SABCS 2016
**IMpassion130: Atezolizumab in 1\textsuperscript{st} line mTNBC**

Central testing for PD-L1 status

Patients with incurable advanced/metastatic TNBC (N=900)

Stratification:
- Tumour tissue PD-L1 expression (IHC 0 vs IHC 1, 2, 3)
- Liver metastases (Yes vs No)
- Prior taxane treatment (Yes vs No)

Study treatment phase

- Atezolizumab (840mg q2w) + nab-paclitaxel (100mg/m\textsuperscript{2} qw)
- Placebo + nab-paclitaxel (100mg/m\textsuperscript{2} qw)

Until loss of Clinical Benefit

Until PD

Survival Follow-Up

**Ongoing Phase III 1\textsuperscript{st} line Clinical Trials**

**KN-355: Randomized Phase III of Pembrolizumab + Chemo vs Placebo + Chemo in 1\textsuperscript{st} line mTNBC**

N=828

- Previously untreated locally recurrent inoperable or metastatic TNBC
- Central determination of TNBC and PD-L1
- No active CNS metastases

2:1

- Pembrolizumab + Chemotherapy*
- Placebo + Chemotherapy*

Progressive Disease*/Cessation of Study Therapy

Protocol-Specified Follow-Up

- Treatment may be continued until confirmation of PD

Primary Endpoints:
- PFS in all subjects and PD-L1-positive
- OS in all subjects and PD-L1-positive

2nd Endpoints:
- ORR, DCR, DOR in all subjects and PD-L1-positive
- Safety
# IMpassion130 baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atezo + nab-P (N = 451)</th>
<th>Plac + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), y</td>
<td>55 (20-82)</td>
<td>56 (26-86)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>448 (99%)</td>
<td>450 (100%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>308 (68%)</td>
<td>301 (67%)</td>
</tr>
<tr>
<td>Asian</td>
<td>85 (19%)</td>
<td>76 (17%)</td>
</tr>
<tr>
<td>Black/African American</td>
<td>26 (6%)</td>
<td>33 (7%)</td>
</tr>
<tr>
<td>Other/multiple</td>
<td>20 (4%)</td>
<td>26 (6%)</td>
</tr>
<tr>
<td>ECOG PS, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>256 (57%)</td>
<td>270 (60%)</td>
</tr>
<tr>
<td>1</td>
<td>193 (43%)</td>
<td>179 (40%)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant treatment, n (%)</td>
<td>284 (63%)</td>
<td>286 (63%)</td>
</tr>
<tr>
<td>Prior taxane</td>
<td>231 (51%)</td>
<td>230 (51%)</td>
</tr>
<tr>
<td>Prior anthracycline</td>
<td>243 (54%)</td>
<td>242 (54%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Atezo + nab-P (N = 451)</th>
<th>Plac + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic disease, n (%)</td>
<td>404 (90%)</td>
<td>408 (91%)</td>
</tr>
<tr>
<td>No. of sites, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>332 (74%)</td>
<td>341 (76%)</td>
</tr>
<tr>
<td>≥ 4</td>
<td>118 (26%)</td>
<td>108 (24%)</td>
</tr>
<tr>
<td>Site of metastatic disease, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>226 (50%)</td>
<td>242 (54%)</td>
</tr>
<tr>
<td>Bone</td>
<td>145 (32%)</td>
<td>141 (31%)</td>
</tr>
<tr>
<td>Liver</td>
<td>126 (28%)</td>
<td>118 (26%)</td>
</tr>
<tr>
<td>Brain</td>
<td>30 (7%)</td>
<td>31 (7%)</td>
</tr>
<tr>
<td>Lymph node only</td>
<td>33 (7%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>PD-L1+ (IC), n (%)</td>
<td>185 (41%)</td>
<td>184 (41%)</td>
</tr>
</tbody>
</table>

Data cutoff: 17 April 2018. * Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P arm. ** Of n = 450 in each arm. *** ECOG PS before start of treatment was 2 in 1 patient per arm. **** Of n = 450 in the Atezo + nab-P arm and n = 449 in the Plac + nab-P arm arm.
Primary PFS analysis: ITT population

Stratified HR = 0.80
(95% CI: 0.69, 0.92)

\[ P = 0.0025 \]

Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (N = 451)</th>
<th>Plac + nab-P (N = 451)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n</td>
<td>358</td>
<td>378</td>
</tr>
<tr>
<td>1-year PFS</td>
<td>24% (20, 28)</td>
<td>18% (14, 21)</td>
</tr>
</tbody>
</table>

Primary PFS analysis: PD-L1+ population

Stratified HR = 0.62
(95% CI: 0.49, 0.78)

\[ P < 0.0001 \]

Progression-free survival

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (n = 185)</th>
<th>Plac + nab-P (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n</td>
<td>138</td>
<td>157</td>
</tr>
<tr>
<td>1-year PFS</td>
<td>29% (22, 36)</td>
<td>16% (11, 22)</td>
</tr>
</tbody>
</table>
Interim OS analysis: ITT population

Stratified HR = 0.84 (95% CI: 0.69, 1.02)  
\[ P = 0.0840 \]

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. Median follow-up (ITT): 12.9 months.

For the interim OS analysis, 59% of death events had occurred. Significance boundary was not crossed.
Interim OS analysis: PD-L1+ population

Stratified HR = 0.62
(95% CI: 0.45, 0.86)\(^a\)

<table>
<thead>
<tr>
<th></th>
<th>Atezo + nab-P (n = 185)</th>
<th>Plac + nab-P (n = 184)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS events, n</td>
<td>64</td>
<td>88</td>
</tr>
<tr>
<td>2-year OS (95% CI), %</td>
<td>54% (42, 65)</td>
<td>37% (26, 47)</td>
</tr>
</tbody>
</table>

No. at risk:

<table>
<thead>
<tr>
<th>Atezo + nab-P</th>
<th>Plac + nab-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>185</td>
<td>184</td>
</tr>
<tr>
<td>177</td>
<td>170</td>
</tr>
<tr>
<td>160</td>
<td>147</td>
</tr>
<tr>
<td>142</td>
<td>129</td>
</tr>
<tr>
<td>113</td>
<td>89</td>
</tr>
<tr>
<td>61</td>
<td>44</td>
</tr>
<tr>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>NE</td>
</tr>
<tr>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>NE</td>
<td>NE</td>
</tr>
</tbody>
</table>

15.5 mo (13.1, 19.4)  25.0 mo (22.6, NE)

Data cutoff: 17 April 2018. Median OS durations (and 95% CI) are indicated on the plot. \(^a\) Not formally tested.

Schmid P. et al. IMpassion130. ESMO 2018 (abstract 2056).
Most common serious AEs

SAEs occurring in ≥ 1% of patients in either arm (regardless of attribution)

<table>
<thead>
<tr>
<th>SAE, n (%)</th>
<th>Atezo + nab-P (n = 452)</th>
<th>Plac + nab-P (n = 438)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>All</td>
<td>103 (23%)</td>
<td>78 (17%)^a</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (2%)</td>
<td>8 (2%)^c</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (1%)</td>
<td>2 (&lt; 1%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (1%)</td>
<td>3 (1%)</td>
</tr>
</tbody>
</table>

- A higher proportion of patients in the Atezo + nab-P arm than in the Plac + nab-P arm reported SAEs (23% vs 18%)
- No SAE was reported with a ≥ 2% difference between treatment arms

SAE, serious adverse event. Data cutoff: 17 April 2018. ^a Six Grade 5 events occurred. ^b Three Grade 5 events occurred. ^c One Grade 5 event occurred.

IMpassion130: PD-L1 expression on IC with SP142

Rationale for using SP142 in IC

TNBC is an IC-driven tumour
- PD-L1 on TC is less prevalent; 97% overlap with IC

PD-L1 expression in IC with SP142 reflects pre-existing immunity
- Patients with pre-existing immunity are more likely to benefit from PD-L1/PD-1 inhibition

SP142 is designed to enhance the visual contrast of IC
- It is easily trainable and reproducible on a global scale

### SP142 TNBC scoring algorithm

<table>
<thead>
<tr>
<th>PD-L1 IC staining criteria</th>
<th>Scoring algorithm in IMpassion130</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC score</td>
<td>% of tumour area occupied by PDL1–expressing IC of any intensity</td>
</tr>
<tr>
<td>IC3</td>
<td>≥10%</td>
</tr>
<tr>
<td>IC2</td>
<td>≥5% and &lt;10%</td>
</tr>
<tr>
<td>IC1</td>
<td>≥1% and &lt;5%</td>
</tr>
<tr>
<td>IC0</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

IC, immune cell; TC, tumour cell
**PD-L1 SP142 expression: prevalence across tumour types**

<table>
<thead>
<tr>
<th>Study (N)</th>
<th>RCC(^1)</th>
<th>mUC(^2)</th>
<th>NSCLC(^3)</th>
<th>TNBC(^4,5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IMmotion150 (253) phase II</td>
<td>IMvigor210 (592) phase II</td>
<td>POPLAR (287) phase II</td>
<td>PCD4989g (112) phase I</td>
</tr>
</tbody>
</table>

- TC ≥1%
- IC ≥1%

Only TC ≥1%:
- RCC: 59% (15% TC, 44% IC)
- mUC: 68% (22% TC, 46% IC)
- NSCLC: 30% (26% TC, 4% IC)
- TNBC: 56% (14% TC, 42% IC)

*IC, immune cell; TC, tumour cell*

---

**In TNBC, the majority of PD-L1 expression is on IC, which SP142 is optimised to detect**

Response Biomarkers

**PD-L1 IHC:**
Associated with response to ICB in multiple solid tumors

**MSI/DNA mismatch repair deficiency**
Colorectal, endometrial, gastric, prostate, duodenal, bile duct

**Immune (IFN-γ) gene signature**
Correlates with response to pembrolizumab in Melanoma, gastric and HNSCC

**DNA damage response–deficient (DDRD) signature**
- Identify BC with inherent DNA repair deficiency who benefit from DNA-damaging anthracycline based chemotherapy.
- Correlates with TILs and PD-L1 expression
- Provides a link between DNA repair deficiency and activation of the immune checkpoint
- May identify patients likely to respond to ICB

**Mutational burden**
- Correlates with response to ICB in multiple cancers
- Most BC have low Mutational burden


Courtesy Priyanka Sharma, MD
Are There Any Clinically Relevant Subgroups of Triple-Negative Breast Cancer in 2018?

Germline BRCA1/2 and HR pathway gene mutation testing
(Somatic BRCA mutation testing)
(HRD score, HRD scar biomarkers)

Histologic examination for tumor-infiltrating lymphocytes (?)
(Immune signature by gene expression microarray)

IHC for androgen receptor (?)
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AKT inhibitors

Unique antigen-expressing:
antibody-drug conjugates

Unclassified TNBCs:
chemotherapy and clinical trials

Tested negative
## Targeting the Androgen Receptor (AR) in TNBC

### AR-Driven Biology in TNBC using Gene Expression Profiling Assay

<table>
<thead>
<tr>
<th></th>
<th>Bicalutamide</th>
<th>Enzalutamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR (%)</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>CBR 6m (%)</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

MDV3100-11. Traina T et al, JCO 2018  
TBCRC011. Gulpa A et al, CCR 2013
ENDEAR: Phase 3 Randomised, Placebo-Controlled 3-Armed Study

This trial was cancelled in May 2017
Numerous other ongoing Enzalutamide and other AR antagonist trials NEED better biomarker definition (prognostic vs predictive, IHC vs other)
## Guidelines: ABC4

<table>
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<th>LoE/GoR</th>
<th>Consensus</th>
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</thead>
<tbody>
<tr>
<td>For non-BRCA-associated advanced TNBC, there are no data supporting different or specific ChT recommendations.</td>
<td>I/A</td>
<td>98%</td>
</tr>
<tr>
<td>Therefore, all ChT recommendations for HER2-negative disease also apply for advanced TNBC.</td>
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<td>91%</td>
</tr>
<tr>
<td>In advanced TNBC patients (regardless of BRCA status) previously treated with anthracyclines with or without taxanes in the (neo)adjuvant setting, carboplatin demonstrated comparable efficacy and a more favourable toxicity profile, compared with docetaxel, and is, therefore, an important treatment option.</td>
<td>I/A</td>
<td></td>
</tr>
<tr>
<td>The AR is a potential target in advanced TNBC. There are, however, no standardised methods to assay AR. Limited data suggest a low level of efficacy for AR antagonist agents such as bicalutamide and enzalutamide. At this time, these agents should not be used in routine clinical practice. More definitive trials are needed, and research efforts must continue to optimise and standardise the determination of AR.</td>
<td>II/D</td>
<td>85%</td>
</tr>
</tbody>
</table>

### BRCA-associated ABC

In patients with BRCA-associated advanced TNBC or endocrine-resistant ABC previously treated with an anthracycline with or without a taxane (in the adjuvant and/or metastatic setting), a platinum regimen is the preferred option, if not previously administered and no suitable clinical trial is available. All other treatment recommendations are similar to sporadic ABC.

**A PARPi (olaparib or talazaparib)** is a reasonable treatment option for patients with BRCA-associated advanced TNBC or luminal (after progression on ET) ABC, previously treated with an anthracycline with/without a taxane (in the adjuvant and/or metastatic setting), since its use is associated with a PFS benefit, improvement in QoL, and a favourable toxicity profile. OS results are awaited. It is unknown how PARPis compare with platinum compounds in this setting and their efficacy in truly platinum-resistant tumours.

Cardoso F et al, Ann Oncol 2018
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TNBC

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antibody-drug conjugates

Unclassified TNBCs:
chemotherapy and clinical trials

Tested negative

Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice  May 11, 2018
Mutations in the PI3K/AKT signalling pathway can lead to the survival of tumour cells

There are multiple types of mutations that may result in overactive PI3K/AKT signalling, including:\textsuperscript{1,2}

\begin{itemize}
  \item Gain of function mutations of \textit{PIK3CA}
  \item Gain of function mutations of \textit{AKT}
  \item Loss of function or deletion of \textit{PTEN}
\end{itemize}

These mutations result in aberrant PI3K/AKT pathway signalling, which can lead to increased tumour cell survival\textsuperscript{1–3}

What can AKT inhibitors offer patients with \textit{PIK3CA/AKT1/PTEN}-altered metastatic TNBC?

**LOTUS\textsuperscript{1}**

Phase II (n=124)

- Ipatasertib + paclitaxel
- Placebo + paclitaxel

**Primary endpoints:**
- PFS (ITT population) and PFS in predefined PTEN-low subgroup

**PIK3CA / AKT1 / PTEN-altered tumours (predefined analysis)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS events, n (%)</th>
<th>Median PFS, months (IQR)</th>
<th>Stratified HR (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipat + pac (n=26)</td>
<td>12 (46)</td>
<td>9.0 (3.7, NE)</td>
<td>0.44 (0.22, 0.87)</td>
</tr>
<tr>
<td>Pbo + pac (n=16)</td>
<td>13 (81)</td>
<td>4.9 (1.9, 6.3)</td>
<td></td>
</tr>
</tbody>
</table>

**PAKT\textsuperscript{2}**

Phase II (n=140)

- Paclitaxel + capivasertib
- Paclitaxel + placebo

**Primary endpoint:** PFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS, months (95% CI)</th>
<th>HR (95% CI)</th>
<th>P value two-sided p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pac + cap (n=17)</td>
<td>9.3 (3.7, 17.7)</td>
<td>0.30 (0.11, 0.79)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Pac + pbo (n=11)</td>
<td>3.7 (1.9, 5.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median DOR was prolonged with ipatasertib versus placebo in the \textit{PIK3CA/AKT1/PTEN}-altered subgroup (11.2 vs 6.1 months)

1. Kim, et al. Lancet Oncol 2017 (NCT02162719);
2. Dent, et al. ESMO 2017 (NCT02423603)
IPATunity130: phase III study of paclitaxel ± ipatasertib in first-line PIK3CA/AKT1/PTEN-altered HR+/HER2- BC or TNBC

Eligibility criteria
- Locally advanced or metastatic TNBC or HR+/HER2- metastatic breast cancer
- PIK3CA/AKT1/PTEN-altered tumour
- No prior chemo for locally advanced or metastatic breast cancer

N = 450

Stratification factors:
- Prior adjuvant/neoadjuvant treatment including chemotherapy
- Region
- Tumour PIK3CA/AKT1/PTEN-alteration status (Cohort A only)
- Prior therapy with a PI3K or mTOR inhibitor (Cohort B only)

Cohort A: metastatic TNBC (n = 249)
- Ipatasertib 400mg qd Days 1–21 q28d + paclitaxel 80mg/m² IV Days 1, 8, 15
- Placebo Days 1–21 q28d + paclitaxel 80mg/m² IV Days 1, 8, 15

Cohort B: HR-positive/HER2-negative metastatic breast cancer (n = 201)
- Ipatasertib 400mg qd Days 1–21 q28d + paclitaxel 80mg/m² IV Days 1, 8, 15
- Placebo Days 1–21 q28d + paclitaxel 80mg/m² IV Days 1, 8, 15

Primary endpoint: PFS
Key secondary endpoints: ORR*, DoR

*As determined locally by the investigator through the use of RECIST v1.1
FMI, Foundation Medicine, Inc.; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; q28d, every 28 days; qd, daily

IPAUnity130 will study patients with PIK3CA/AKT1/PTEN-altered tumours, assessed using the FMI genomic profiling test FoundationONE® on tumour tissue
Are There Any Clinically Relevant Subgroups of Triple-Negative Breast Cancer in 2018?

Germline BRCA1/2 and HR pathway gene mutation testing
(Somatic BRCA mutation testing) (HRD score, HRD scar biomarkers)

Histologic examination for tumor-infiltrating lymphocytes (?) (Immune signature by gene expression microarray)

IHC for androgen receptor (?) (Androgen-related gene signature by genomic diagnostic assay)

(Sequencing for PIK3CA/AKT1/PTEN alterations)

IHC for targetable cancer epithelial antigens

Defective DNA repair: platinums and PARP inhibitors

Inflamed phenotype: immunotherapy

Androgen receptor-positive: androgen blockade

PI3K/AKT/PTEN altered: AKT inhibitors

Unique antigen-expressing: antibody-drug conjugates

Unclassified TNBCs: chemotherapy and clinical trials

Tested negative

Jack J. Chan; Tira J.Y. Tan; Rebecca A. Dent
Journal of Oncology Practice  May 11, 2018
Sacituzumab Govitecan (IMMU-132)

- Humanised IgG Antibody against Trop-2
- Conjugated with a pH-sensitive linker to SN-38
- Heavily pretreated TNBC
- Median number of prior therapies = 4 (1-11)
Sacituzumab Govitecan: FDA Breakthrough Designation

Bardia A et al. JCO 2017.
What are the treatment options for metastatic TNBC in 1st line and beyond?

- Taxane (+/- Bevacizumab)
- Platinum single agent
- Platinum combination (e.g. Gemcitabine/platinum)
- Eribulin
- Capecitabine (+/- Ixabepilone)
- Vinorelbine (+/- Capecitabine)
- Anthracycline (including liposomal)
- Low dose Cyclophosphamide/MTX or CMF
- Nab-paclitaxel
- Oral etoposide
- Irinotecan

- TRIAL!!!!
In Practice: Management of Metastatic TNBC

• Chemotherapy remains the mainstay of treatment
  – Platinum preferred in gBRCA but as good as taxanes in unselected TNBC
• PARP inhibitors now approved in gBRCA mutation
• Immunotherapy
  – IMPASSION 130 + results for IO in 1st line PD-L1 +TNBC – await approval and updated OS data
  – Single agent vs combination therapy
  – Need for predictive signature
• PIK3CA/mTOR/AKT pathway is intriguing - > watch for phase III results
• Await Phase III data on Sacituzumab
ACKNOWLEDGEMENTS

Jack Chan
Shaheenah Dawood
Paul Mainwaring
Mark Robson
Shani Paluch-Shimon
Tira Tan
Andy Tutt