L'immunoterapia: una realtà anche nel carcinoma della mammella

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Direttore Prof.ssa Rossana Berardi
✓ What’s immunotherapy?

✓ Breast cancer, mutational burden and TILs

✓ Data from clinical trials

✓ Looking at the Future: when, who and how?
The rationale for immunotherapy in urothelial cancer stems from the breakthrough made with BCG for NMIBC → efficiency in preventing recurrence.

Trastuzumab itself has intrinsic immune-modulating activity with the capacity to mediate antibody-dependent cellular cytotoxicity (ADCC) and promote Her2 specific T cell response.

The emtansine moiety of TDM1 may further augment immune priming by modulating DC activity.
PD-L1/PD1 interaction inhibits T cell activation, attenuates effector function, maintain immune homeostasis

Tumors & surrounding cells up-regulate PD-L1 in response to T cell activity

What's Immunotherapy?

Breast Cancer, mutational burden and TIL

Data From Clinical Trials

Looking at the Future: when, who and how?
What we have learned: immunosuppression is a rate limiting step to effective anti-tumor immunity... for some patients.

- Blocking PD-L1/PD1 restores or prevents loss of T effector function.
Targeting PD1-PDL1 pathway

What's Immunotherapy?

Breast Cancer, mutational burden and TIL

Data From Clinical Trials

Looking at the Future: when, who and how?
Response Rate correlates with mutation frequency

No or limited response to treatment
“non-inflamed cancer”

Active response to treatment
“inflamed cancer”

Breast cancer
Luminal A  Luminal B  HER2 positive breast cancer  TNBC

What’s Immunotherapy?  Breast Cancer, mutational burden and TIL  Data From Clinical Trials  Looking at the Future: when, who and how?
Behaviour of MBC according to subtype

<table>
<thead>
<tr>
<th>Subtype</th>
<th>n</th>
<th>Brain</th>
<th>Liver</th>
<th>Lung</th>
<th>Bone</th>
<th>Distant Nodal</th>
<th>Pleural/peritoneal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luminal A</td>
<td>458</td>
<td>7.6</td>
<td>28.6</td>
<td>23.8</td>
<td>66.6</td>
<td>15.9</td>
<td>28.2</td>
<td>13.5</td>
</tr>
<tr>
<td>Luminal B</td>
<td>378</td>
<td>10.8</td>
<td>32.4</td>
<td>30.4</td>
<td>71.4</td>
<td>23.3</td>
<td>35.2</td>
<td>19.3</td>
</tr>
<tr>
<td>Luminal/HER2</td>
<td>117</td>
<td>15.4</td>
<td>4.4</td>
<td>36.8</td>
<td>65</td>
<td>22.2</td>
<td>34.2</td>
<td>13.7</td>
</tr>
<tr>
<td>HER2 enriched</td>
<td>136</td>
<td>28.7</td>
<td>45.6</td>
<td>47.1</td>
<td>59.6</td>
<td>25</td>
<td>31.6</td>
<td>16.9</td>
</tr>
<tr>
<td>Basal Like</td>
<td>159</td>
<td>25.2</td>
<td>21.4</td>
<td>42.8</td>
<td>39</td>
<td>39.6</td>
<td>29.6</td>
<td>23.9</td>
</tr>
<tr>
<td>TN non basal</td>
<td>109</td>
<td>22</td>
<td>32.1</td>
<td>35.8</td>
<td>43.1</td>
<td>35.8</td>
<td>28.4</td>
<td>25.7</td>
</tr>
<tr>
<td>p</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.32</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Kennecke H, JCO 2010  
Gong Y, Sci Rep 2017
Lines of chemotherapy and duration according to BC subtype

What's Immunotherapy?  
Breast Cancer, mutational burden and TIL  
Data From Clinical Trials  
Looking at the Future: when, who and how?

Courtesy Maria Vittoria Dieci, Padua September 22° 2018
Clinical significance of mutation load

→ TIL can recognize somatic mutations and are correlated to the density of predicted mutant epitopes.

BC has a moderate mutational load

→ Higher mutation load in TNBC and HER2 BC

- Number of predicted immunogenic mutations and survival

*Total mutations and survival*

Ton N. Schumacher, and Robert D. Schreiber Science 2015
Scott D. Brown et al. Genome Res. 2014
Clinical Significance of TIL infiltration in BC

→ TIL have prognostic and predictive value in early stage BC, particularly in HER2+ and TNBC

<table>
<thead>
<tr>
<th>Trial analysed</th>
<th>Trial type</th>
<th>Treatment</th>
<th>TILs assessment</th>
<th>Population</th>
<th>n</th>
<th>Recurrence end points</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG-2-98 (REF. 18)</td>
<td>Adjuvant Prospective RCT</td>
<td>Doxorubicin, Cyclophosphamide, CMF, Docetaxel</td>
<td>Stromal on H&amp;E</td>
<td>ER+/HER2-</td>
<td>1,070</td>
<td>Not significant</td>
</tr>
<tr>
<td>FinHER2™</td>
<td>Adjuvant Prospective RCT</td>
<td>Doxorubicin, Docetaxel, Trastuzumab, Pertuzumab</td>
<td>Stromal on H&amp;E</td>
<td>TNBC</td>
<td>297</td>
<td>Not significant</td>
</tr>
<tr>
<td>E2197 and E1199 (REF. 52)</td>
<td>Adjuvant Prospective RCT</td>
<td>Doxorubicin, Cyclophosphamide, Docetaxel</td>
<td>Stromal on H&amp;E</td>
<td>TNBC</td>
<td>991</td>
<td>Not significant</td>
</tr>
<tr>
<td>SEARCH, BCRA, MBC, NEAT™</td>
<td>Prospective Observational RCT (NEAT)</td>
<td>Various, not standardised</td>
<td>Stromal on H&amp;E</td>
<td>TNBC</td>
<td>481</td>
<td>For each 10% increment of TILs: DFS, HR=0.84 (95% CI 0.74-0.95), P=0.0032</td>
</tr>
<tr>
<td>NeoALTITUDE™</td>
<td>Neoadjuvant Prospective RCT</td>
<td>Trastuzumab, Lapatinib, Paclitaxel, Pertuzumab, FEC</td>
<td>Stromal on H&amp;E</td>
<td>ER+/HER2-</td>
<td>187</td>
<td>3% decrease in rate of recurrence (event free survival) for every 1% increase in TILs</td>
</tr>
</tbody>
</table>

Trials overall include a total of 15,800 patients. BIC, Breast International Group; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; DFS, distant disease-free survival; DFI, disease-free interval; ER, oestrogen receptor; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; IHC, immunohistochemistry; IC, immunocompetent; P, randomized controlled trial; sTIL, stromal TIL; TIL, tumour infiltrating lymphocytes; TNBC, triple-negative breast cancer.
PD-L1 expression in metastatic BC

<table>
<thead>
<tr>
<th>PD-L1 IHC expression on</th>
<th>N = 111 (%)</th>
<th>Median (% cells-positive cases)</th>
<th>25th-75th percentile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor cells</td>
<td>3 (2.7)</td>
<td>1</td>
<td>1-5</td>
</tr>
<tr>
<td>Immune cells</td>
<td>12 (10.8)</td>
<td>5</td>
<td>5-10</td>
</tr>
<tr>
<td>Stromal cells</td>
<td>9 (8.1)</td>
<td>5</td>
<td>5-10</td>
</tr>
<tr>
<td>Any cells</td>
<td>17 (15.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

111 metastases from 11 sites including skin (40), ipsilateral breast relapse (23), liver (12), soft tissues (7), pleura (5), bone (6), brain (5), peritoneum (3), colon (1), lung (1), nodes (7)

PD-L1 positivity: 21% expression on tumor or immune or stromal cells

What’s Immunotherapy?
Breast Cancer, mutational burden and TIL
Data From Clinical Trials
Looking at the Future: when, who and how?
1- Major survival improvements in Her2 positive BC with the uso of mAbs targeting Her2 and their mechanism of action involve partially the immune system.

2- TILs have a positive prognostic impact on survival and predict a high probability of pathological response to neoadjuvant chemo.

3- PDL1 is expressed in BC and correlates with the presence of TILs, younger age, high grade, lack of ER, overexpression of Her2, TNBC subtype

Phase Ib of pembrolizumab in mTNBC
KEYNOTE 012

- Recurrent or metastatic ER-/PR-/HER2- breast cancer
- ECOG PS 0-1
- PD-L1+ tumor*
- No systemic steroid therapy
- No autoimmune disease (active or history of)
- No active brain metastases

PD-L1 positivity: 58% of all patients screened had PD-L1-positive tumors
Treatment: 10 mg/kg IV Q2W
Response assessment: Performed every 8 weeks per RECIST v1.1

*PD-L1 expression was assessed in archival tumor samples using a prototype IHC assay and the 22C3 antibody. Only patients with PD-L1 staining in the stroma or in ≥1% of tumor cells were eligible for enrollment.

**If clinically stable, patients are permitted to remain on pembrolizumab until progressive disease is confirmed on a second scan performed 24 weeks later. If progressive disease is confirmed, pembrolizumab is discontinued. An exception may be granted for patients with clinical stability or improvement after consultation with the sponsor.

Nanda R et al, San Antonio Breast Cancer Symposium 2014
32 patients with PDL1 + mTNBC
✓ ORR 18.5%
✓ 2 years survival rate 22%
✓ Heavily pre-treated pts and 78% with visceral involvement

Nanda R et al. JCO 2016
## Immuno check point inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Subtype</th>
<th>PD-L1</th>
<th>Nb pts</th>
<th>ORR</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td>Ia</td>
<td>TNBC PDL1+</td>
<td>≥ 1% TC Stroma+ (58% of screened pts)</td>
<td>32</td>
<td>27</td>
<td>18.5% KEYNOTE 012 Nanda et al. SABC 2014 JCO 2016</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Ia</td>
<td>TNBC</td>
<td>≥ 5% IC</td>
<td>115</td>
<td>112</td>
<td>10% Schmid et al. AACR2017</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Ia</td>
<td>ER+/HER2-PDL1+</td>
<td>≥ 1% TC Stroma+ (19% of screened pts)</td>
<td>25</td>
<td>12%</td>
<td>0 CR 3 PR KEYNOTE 028 Rugo et al. SABC 2015</td>
</tr>
<tr>
<td>Avelumab</td>
<td>Ia</td>
<td>All</td>
<td>TNBC</td>
<td>168</td>
<td>153</td>
<td>4.8% 1 CR 7 PR JAVELIN Dirix et al. SABC 2015</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ER+/HER2-</td>
<td></td>
<td>58</td>
<td>52</td>
<td>8.6% 2.8%</td>
</tr>
</tbody>
</table>

What's Immunotherapy?
Breast Cancer, mutational burden and TIL
Data From Clinical Trials
Looking at the Future: when, who and how?
What's Immunotherapy?

Breast Cancer, mutational burden and TIL

Data From Clinical Trials

Looking at the Future: when, who and how?

ORR according to PD-L1 expression

Phase Ia: Atezolizumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic TNBC

Phase Ib: Avelumab, an anti-PD-L1 antibody, in patients with locally advanced or metastatic BC

<table>
<thead>
<tr>
<th>PD-L1 expression</th>
<th>All patients (N=136)</th>
<th>TNBC (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1% TC</td>
<td>3/85 (3.5%)</td>
<td>2/33 (6.1%)</td>
</tr>
<tr>
<td>≥ 5% TC</td>
<td>1/23 (4.3%)</td>
<td>1/13 (7.7%)</td>
</tr>
<tr>
<td>≥ 25% TC</td>
<td>0/3 (0)</td>
<td>0/2 (0)</td>
</tr>
<tr>
<td>≥ 10% IC</td>
<td>4/12 (33.3%)</td>
<td>4/9 (44.4%)</td>
</tr>
</tbody>
</table>

Dirix L et al. SABC 2015

[Graph showing ORR + SD Rate for different PD-L1 expression levels]
170 pts with documented PD at the first line
61.8% PD-L1 positive

**ORR 5.3% in the overall population**
5.7% in the PD-L1 positive/ 4.7% in the negative

**Disease Control Rate 7.6%**
No difference in Survival between PD-L1 pos vs neg

**Primary Endpoint:**
- ORR (RECIST 1.1) in first line PD-L1+BC
- ORR (RECIST 1.1) in 2+ line BC
- Safety, tolerability

**Secondary Endpoints:**
- PFS, DOR, OS
Adams, ASCO 2017

No prior systemic tp and PDL1 positive tumor
Two pts reaching a SD for more than 24 weeks
Merck Provides Update on Phase 3 KEYNOTE-119 Study of KEYTRUDA® (pembrolizumab) Monotherapy in Previously-Treated Patients with Metastatic Triple-Negative Breast Cancer

MAY 20, 2019

KENILWORTH, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside the United States and Canada, today announced that the Phase 3 KEYNOTE-119 trial evaluating KEYTRUDA, Merck’s anti-PD-1 therapy, as monotherapy for the second- or third-line treatment of patients with metastatic triple-negative breast cancer (TNBC) did not meet its pre-specified primary endpoint of superior overall survival (OS) compared to chemotherapy (capecitabine, eribulin, gemcitabine or vinorelbine).

Other endpoints were not formally tested per the study protocol because the primary endpoint of OS was not met. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies involving patients treated with KEYTRUDA monotherapy; no new safety concerns were identified. Results will be presented at an upcoming medical meeting.
KEYNOTE-119 Study Design (NCT02555657)

Patients
- Recurrent mTNBC
- 1 or 2 prior systemic treatments for mTNBC
- Documented disease progression on/after most recent therapy
- Previous treatment with an anthracycline and/or a taxane in the neoadjuvant/adjuvant or metastatic setting
- ECOG PS 0-1

Randomize 1:1
N = 600

Pembrolizumab
200 mg Q3W up to 35 cycles

Follow-up for safety (≤90 days)
Follow-up for survival (every 3 months)

Investigator choice\(^a\) of:
- Capecitabine
- Eribulin
- Gemcitabine
- Vinorelbine

Stratification by:
- **PD-L1 tumor status** (CPS ≥1 vs CPS <1)
- Prior neoadjuvant/adjuvant therapy vs de novo metastatic disease at initial diagnosis

ECOG PS = Eastern Cooperative Oncology Group performance status; mTNBC = metastatic triple-negative breast cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.

\(^a\)Maximum enrollment cap of 80% of total enrollment for each chemotherapy drug.

What's Immunotherapy?
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Data From Clinical Trials
Looking at the Future: when, who and how?
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Pembro N = 312</th>
<th>Chemo N = 310</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, median (range), y</strong></td>
<td>50 (28 – 85)</td>
<td>50 (25 – 79)</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>264 (84.6)</td>
<td>260 (83.9)</td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>238 (76.3)</td>
<td>239 (77.1)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>169 (54.2)</td>
<td>158 (51.0)</td>
</tr>
<tr>
<td>1</td>
<td>141 (45.2)</td>
<td>151 (48.7)</td>
</tr>
<tr>
<td>No. prior lines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>187 (59.9)</td>
<td>187 (60.3)</td>
</tr>
<tr>
<td>2</td>
<td>124 (39.7)</td>
<td>123 (39.7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Pembro N = 312</th>
<th>Chemo N = 310</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior neoadjuvant/adjuvant</td>
<td>246 (78.8)</td>
<td>246 (79.4)</td>
</tr>
<tr>
<td>Time to progression on 1L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 mo</td>
<td>156 (50.0)</td>
<td>151 (48.7)</td>
</tr>
<tr>
<td>≥6 mo</td>
<td>156 (50.0)</td>
<td>159 (51.3)</td>
</tr>
<tr>
<td><strong>Chemotherapy received</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eribulin</td>
<td>-</td>
<td>167 (53.9)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>-</td>
<td>85 (27.4)</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>-</td>
<td>43 (13.9)</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>-</td>
<td>15 (4.8)</td>
</tr>
</tbody>
</table>
Study End Points

**Primary**
- OS in patients with PD-L1 positive tumors (CPS ≥10)\(^a\)
- OS in patients with PD-L1 positive tumors (CPS ≥1)\(^a\)
- OS in all patients

**Key Secondary**
- PFS in all patients
- ORR in all patients\(^b\)
- Safety and tolerability

**Exploratory**
- OS, PFS, ORR, and DOR in patients with PD-L1 positive tumors using additional CPS cutpoints

**Additional Secondary**
- DCR and DOR in all patients and patients with PD-L1 positive tumors (CPS ≥1 or CPS ≥10)\(^a\)

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\(^{a}\)Assessed at a central laboratory using the PD-L1 HC 22C3 pharmDx assay defined as the combined positive score (CPS), the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells x 100.

\(^{b}\)Assessed per RECIST v1.1 by blinded, independent central review.
PD-L1 Expression Analysis

• Measure of PD-L1 expression: combined positive score (CPS)

\[
\text{CPS} = \frac{\# \text{PD-L1-staining cells}}{\text{Total \# viable tumor cells}} \times 100
\]

(tumor cells, lymphocytes, macrophages)

• Assessed centrally in newly obtained core or excisional biopsy from metastatic, not previously irradiated, tumor lesion using PD-L1 IHC 22C3 pharmDx (Agilent Technologies)

• Positive PD-L1 expression: CPS ≥10 and CPS ≥1

Overall Survival: Primary Endpoints

CPS ≥10

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>77.1%</td>
<td>0.78</td>
<td>0.057</td>
</tr>
<tr>
<td>Chemo</td>
<td>88.8%</td>
<td>(0.57-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

12-mo OS

- Pembro: 52.1% (48.9%)
- Chemo: 60.0% (56.5%)

Median (95% CI)

- Pembro: 12.7 mo (9.9-16.3)
- Chemo: 11.6 mo (8.3-13.7)

CPS ≥1

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>84.2%</td>
<td>0.86</td>
<td>0.073</td>
</tr>
<tr>
<td>Chemo</td>
<td>90.6%</td>
<td>(0.69-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

12-mo OS

- Pembro: 45.6% (44.7%)
- Chemo: 60.0% (56.5%)

Median (95% CI)

- Pembro: 10.7 mo (9.3-12.5)
- Chemo: 10.2 mo (7.8-12.8)

*Data cutoff date: April 11, 2019.*
Prevalence of PD-L1 CPS Categories

CPS = combined positive score defined as the number of PD-L1-positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.

Data cutoff date: April 11, 2019.
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The application of incrementally restrictive cut-offs of CPS lends weight to the exploratory analysis showing better survival from pembrolizumab in tumors with CPS≥20.
Response Rate (RECIST v1.1, BICR)

<table>
<thead>
<tr>
<th>ITT</th>
<th>CPS ≥1</th>
<th>CPS ≥10</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 312</td>
<td>N = 302</td>
<td>N = 98</td>
</tr>
<tr>
<td>9.6%</td>
<td>12.3%</td>
<td>17.7%</td>
</tr>
<tr>
<td>10.6%</td>
<td>9.4%</td>
<td>9.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CPS ≥20</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 57</td>
<td>N = 52</td>
</tr>
<tr>
<td>26.3%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

PS in the ITT, CPS >1 and CPS >10 populations were secondary endpoints; ORR in the CPS >20 population was an exploratory endpoint. Data cut-off date: April 11, 2019.

Looking at the Future: when, who and how?

Data From Clinical Trials

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What's Immunotherapy? | Breast Cancer, mutational burden and TIL | Data From Clinical Trials | Looking at the Future: when, who and how?

**IMpassion130 study design**

**Key IMpassion130 eligibility criteria:**
- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

**Stratification factors:**
- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

Atezo + nab-P arm:
- Atezolizumab 840 mg IV
  - On days 1 and 15 of 28-day cycle
- nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle

**RECIST v1.1 PD or toxicity**

Double blind; no crossover permitted

Plac + nab-P arm:
- Placebo IV
  - On days 1 and 15 of 28-day cycle
- nab-paclitaxel 100 mg/m² IV
  - On days 1, 8 and 15 of 28-day cycle
## 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><strong>Median age (range), y</strong></td>
<td>55 (20-82)</td>
<td>56 (26-86)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>448 (99%)</td>
<td>450 (100%)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></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><strong>ECOG PS, n (%)</strong></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><strong>Prior (neo)adjuvant treatment, n (%)</strong></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>

**Site of metastatic disease, n (%)**

- Lung: 226 (50%) vs. 242 (54%)
- Bone: 145 (32%) vs. 141 (31%)
- Liver: 126 (28%) vs. 118 (26%)
- Brain: 30 (7%) vs. 31 (7%)
- Lymph node only: 33 (7%) vs. 23 (5%)
- PD-L1+ (IC), n (%): 185 (41%) vs. 184 (41%)

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. † Race was unknown in 12 patients in the Atezo + nab-P arm and 15 in the Plac + nab-P 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 = 448 in the Plac + nab-P arm.

Schmid P. et al. IMpassion130. ESMO 2018 (LBA1_PR).

---

**What’s Immunotherapy?**

**Breast Cancer, mutational burden and TIL**

**Data From Clinical Trials**

**Looking at the Future: when, who and how?**
What’s Immunotherapy?

Breast Cancer, mutational burden and TIL

Data From Clinical Trials

Looking at the Future: when, who and how?
However, as per protocol, the statistical significance could not be tested in this subgroup, since the OS improvement was not confirmed in the whole population at this time. Of note, in a recently reported update (second interim analysis after a median follow-up of 18 months), the median OS was still not significantly different between each arm (21 months versus 18.7 months, stratified HR = 0.86, p = 0.07) in the whole population, and the numerical difference in OS in the PD-L1-positive subset tended to decrease (median OS of 25 months versus 18 months, HR = 0.71, no formal p-value by protocol design).
Primary PFS analysis: PD-L1+ population

Stratified HR = 0.62
(95% CI: 0.49, 0.78)
P < 0.0001

<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 (95% CI), %</td>
<td>29% (22, 36)</td>
<td>16% (11, 22)</td>
</tr>
</tbody>
</table>

Data cutoff: 17 April 2018.

Schmid P, et al. IMpassion130
ESMO 2018 (LBA1.PR)
Performance of PD-L1 immunohistochemistry assays in unresectable locally advanced or metastatic triple-negative breast cancer: post hoc analysis of IMpassion130

Methods

- Central testing of VENTANA PD-L1 SP142, DAKO 22C3 and VENTANA PD-L1 SP263 IHC assays were performed according to the respective package inserts\(^a\)
  - Each slide was read by a single pathologist out of a panel of 8 pathologists\(^b\)
  - Pathologists were trained and qualified to read IC 1% (SP142 and SP263) and CPS 1 (22C3) cutoffs\(^b\)

- The biomarker-evaluable population (BEP) in this retrospective exploratory analysis comprised 614 patients (68% of ITT) with samples tested with the 3 PD-L1 assays
  - Prevalence of PD-L1 IC+ status according to SP142 was higher in the BEP (46%) than the ITT (41%).
  - All other evaluated baseline characteristics were balanced between BEP and ITT
  - PFS outcome with A + nP in the BEP slightly outperformed compared with PFS outcome in the ITT
What's Immunotherapy?
Breast Cancer, mutational burden and TIL
Data From Clinical Trials
Looking at the Future: when, who and how?

PD-L1 IHC assays: prevalence and analytical concordance

PD-L1+ prevalence

<table>
<thead>
<tr>
<th>Assay</th>
<th>IC 1%</th>
<th>CPS 1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SP142</td>
<td>81%</td>
<td>46%</td>
</tr>
<tr>
<td>22C3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SP263</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

SP142 (IC 1%) and 22C3 (CPS 1%)

- SP142+ 22C3- (1%)
- SP142+ 22C3+ (45%)
- SP142- 22C3+ (36%)
- SP142- 22C3- (18%)

OPA 64%

<table>
<thead>
<tr>
<th></th>
<th>PPA</th>
<th>NPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>NPA</td>
<td>34%</td>
<td></td>
</tr>
</tbody>
</table>

SP142 (IC 1%) and SP263 (IC 1%)

- SP142+ SP263- (1%)
- SP142+ SP263+ (45%)
- SP142- SP263+ (30%)
- SP142- SP263- (24%)

OPA 69%

<table>
<thead>
<tr>
<th></th>
<th>PPA</th>
<th>NPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPA</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>NPA</td>
<td>45%</td>
<td></td>
</tr>
</tbody>
</table>

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.

* > 97% of SP142+ samples included in 22C3+ or SP263+ samples.
* ≥ 90% OPA, PPA and NPA required for analytical concordance.

Rugo et al. Abstract 6571
IMpassion130 PD-L1 IHC
https://bit.ly/300mOqz
PD-L1 assessment in either primary or metastatic?

These data do not inform whether PD-L1 assessment in primary and metastatic sites is equally informative!
(a comparison among PD-L1 assessment in different sites of the same patients needed)

Time and spatial heterogeneity of PD-L1 is known. Does site of PD-L1 assessment matter?
When multiple tumor sites are present, what should we prefer to biopsy for PD-L1 assessment?
What about inter tumor heterogeneity?

What’s Immunotherapy?  Breast Cancer, mutational burden and TIL  Data From Clinical Trials  Looking at the Future: when, who and how?
**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</th>
<th>Plac + nab-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 452)</td>
<td>(n = 438)</td>
</tr>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>All</td>
<td>103 (23%)</td>
<td>78 (17%)*</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>10 (2%)</td>
<td>8 (2%)f</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. *Six Grade 5 events occurred. fThree Grade 5 events occurred. bOne Grade 5 event occurred.

[Investigative Clinical Oncology](http://bit.ly/2DMhnyg)
**Immune checkpoint inhibitors seem to work better in earlier setting**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Anti-PD(L)-1</th>
<th>Single (S) or Combination</th>
<th>Study Title</th>
<th>Conditions or Disease</th>
<th>Treatment Line</th>
<th>Comparative Arm (for Phase II/III)</th>
<th>ORR (+/- 95% CI)</th>
<th>Duration of Response Median, Months (+/- 95% CI)</th>
<th>PFS Median, Months (+/- 95% CI)</th>
<th>OS Median, Months (+/- 95% CI)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>Atezolizumab</td>
<td>(Nab-paclitaxel + Cobimetinib)</td>
<td>COLET</td>
<td>LA or M+ TNBC</td>
<td>1 L /</td>
<td>34%</td>
<td>NA</td>
<td>6-mo PFS rate: 40.5%</td>
<td>6-mo OS rate: 84.1%</td>
<td>Brukski ASCO 2019 (#1013)</td>
<td></td>
</tr>
<tr>
<td>II-R</td>
<td>Pembrolizumab</td>
<td>Standard Chemo</td>
<td>I-SPY 2 trial</td>
<td>LA TNBC</td>
<td>Neo-adj</td>
<td>Placebo</td>
<td>Pembrol: 62% Placebo: 22%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Nanda ASCO 2017</td>
</tr>
<tr>
<td>II-R</td>
<td>Nivolumab</td>
<td>Doxo or Cyclo or RT (3*8 Gy)</td>
<td>TONIC</td>
<td>M+ TNBC</td>
<td>1 L to ≥3 L</td>
<td>Doxo or Cyclo or RT</td>
<td>Doxo = 35% Cyclo = 8% RT = 8%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Voorwer Nature Med 2019</td>
</tr>
<tr>
<td>II-R</td>
<td>Durvalumab</td>
<td>Nab-paclitaxel + standard BC</td>
<td>GeparNoveo</td>
<td>LA TNBC (cT2-cT4a-d)</td>
<td>Neo-adj</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Pembrolizumab</td>
<td>S</td>
<td>KEYNOTE-119</td>
<td>M+ TNBC</td>
<td>2 L or 3 L</td>
<td>single-agent CT (physician’s choice)</td>
<td>4.8%</td>
<td>NA</td>
<td>not superior to CT</td>
<td>Merck press release</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Atezolizumab</td>
<td>Nab-paclitaxel</td>
<td>IMPASSION-130</td>
<td>LA or M+ TNBC</td>
<td>1 L</td>
<td>Nab-paclitaxel</td>
<td>Atezol: 56% Placebo: 46%</td>
<td>HR 0.78 (0.63-0.98) Median DO: 7.4 mo Median DO Placebo: 5.6</td>
<td>HR 0.62 (0.49-0.78) Median PFS Atezol: 7.2 mo Median PFS Placebo: 5.8 mo</td>
<td>HR 0.86 (0.72-1.02) Median OS Atezol: 21.0 mo Median OS Placebo: 18.7 mo</td>
<td>Schmid NEJM 2018 Schmid ASCO 2019</td>
</tr>
</tbody>
</table>

Abbreviations: Ph = phase; IIIR = phase II Randomized; TNBC: Triple Negative Breast Cancer; LA = Locally Advanced; M+ = metastatic; ORR = Objective Response Rate; DOR = Duration of Response; PFS = Progression-Free-Survival; OS = Overall Survival; L = Line; mo = months; NR = Not Reached; gBRCA = germline BRCA-mutated;

The pCR was higher in durvalumab-arm (53.4% vs. 44.2% placebo), but not statistically significant
KEYNOTE-522: Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy as Neoadjuvant Treatment, Followed by Pembrolizumab versus Placebo as Adjuvant Treatment for Early Triple-Negative Breast Cancer (TNBC)

Peter Schmid1, Javier Cortes2, Rebecca Dent3, Lajos Pusztai4, Heather McArthur5, Sherko Kümmer6, Jonas Bergh7, Carsten Denkert8, Yeon Hee Park9, Rina Hui10, Nadia Harbeck11, Masato Takahashi12, Theodoros Foukakis17, Peter A. Fasching13, Fatima Cardoso14, Liyi Jia15, Vassiliki Karantza15, Jing Zhao15, Gursel Aktan16, Joyce O'Shaughnessy19

1. Bert Cancer Institute, Queen Mary University London, London, UK; 2. IDIB Institute of Oncology, Quiron Group, Vall d'Hebron Institute of Oncology (VHI), Madrid & Barcelona, Spain; 3. University of Toronto, Toronto, Ontario, Canada; 4. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 5. Cedars-Sinai Medical Center, Los Angeles, CA, USA; 6. Breast Unit, Klinikum Essen Mitte, Essen, Germany; 7. Department of Oncology-Pathology, Karolinska Institute and Breast Cancer Centre, Karolinska University Hospital, Stockholm, Sweden; 8. Institute of Pathology, Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 9. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 10. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 11. Breast Center, University of Munich (LMU), Munich, Germany; 12. Hokkaido Cancer Center, Sapporo, Japan; 13. University Hospital Erlangen, Comprehensive Cancer Center Erlangen E MV, Erlangen, Germany; 14. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 15. Merck & Co., Inc., Kenilworth, NJ, USA; 16. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA.
KEYNOTE-522 Study Design (NCT03036488)

**Neoadjuvant Phase**
- Neoadjuvant Treatment 1 (cycles 1-4; 12 weeks)
- Neoadjuvant Treatment 2 (cycles 5-8; 12 weeks)
- Adjuvant Treatment: (cycles 1-5; 27 weeks)

**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

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

**Neoadjuvant phase:** starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

**Adjuvant phase:** starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

---

*Must consist of at least 2 separate tumor cores from the primary tumor.

\(^{1}\)Carboplatin dose was 500 Q3W or 1,000 QW.

\(^{2}\)Paclitaxel dose was 80 mg/m² QW.

\(^{3}\)Doxorubicin dose was 60 mg/m² Q3W.

\(^{4}\)Epirubicin dose was 90 mg/m² Q3W.

\(^{5}\)Cyclophosphamide dose was 600 mg/m² Q3W.
Study Endpoints

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

• Secondary Endpoints
  – pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)
  – Overall survival (OS)
  – pCR, EFS and OS in the PD-L1–positive population
  – Safety in all treated patients

• Key Exploratory Endpoints
  – Residual cancer burden (RCB)
  – EFS by pCR
  – pCR and EFS by TILs

---

1Subjects without pCR data due to any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non-pCR. To be presented at a later date.

2PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (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.
**Statistical Considerations**

What's Immunotherapy? Breast Cancer, mutational burden and TIL Data From Clinical Trials Looking at the Future: when, who and how?

**Pembro Arm vs. Control Arm**

Overall alpha controlled at one-sided 2.5%

- **pCR**
  - **IA1:** Primary pCR Analysis
    - Definitive pCR analysis if positive
    - Multiple IAs
    - Final Analysis
  - **IA2:** Final pCR Analysis
- **EFS**
  - **IA2:** First EFS Interim
  - Multiple IAs
  - Final Analysis

Planned Interim Analyses/Final Analyses per Group Sequential Approach

**Interims Completed:**

- **First IA (IA1)** performed after last subject enrolled:
  - Data Cutoff: Sep 24, 2019
- **Second IA (IA2)** performed ~24 mo after first subject enrolled:
  - Data Cutoff: Apr 24, 2019

- **IA1:** Primary pCR analysis to test primary hypothesis of pCR based on prespecified first 602 subjects (pre-calculated P value boundary for significance of 0.003)
- **IA2:** If pCR hypothesis successful at IA1 (thus definitive), pCR will not be formally tested at IA2
- **EFS at IA2** (first interim of EFS): precalculated P value boundary for significance of 0.000051 (HR <0.4)
- Prespecified analysis plan allows alpha passing from successful endpoint(s) to other(s)
Summary of Study Treatment and Analysis Populations: IA2

1174 patients randomized 2:1 from Mar 2017 to Sep 2018

Pembrolizumab + Chemotherapy Arm
- 784 allocated
- 778 (99.2%) started Carboplatin/Paclitaxel
- 726 (92.6%) started AC or EC
- 758 (96.7%) had documented surgery
- 547 (69.8%) started adjuvant treatment

Placebo + Chemotherapy Arm
- 390 allocated
- 389 (99.7%) started Carboplatin/Paclitaxel
- 369 (94.6%) started AC or EC
- 380 (97.4%) had documented surgery
- 314 (80.5%) started adjuvant treatment

Analysis Populations
- ITT: N = 784
- Safety-evaluable: N = 781
  Median follow-up: 15.3 mo

Analysis Populations
- ITT: N = 390
- Safety-evaluable: N = 389
  Median follow-up: 15.8 mo

- Includes radiographic and clinical PD.
- Patients did not have to complete all neoadjuvant therapy to undergo surgery.
- Includes all patients who received at least one dose of study treatment or underwent surgery.
- Defined as the time from randomization to the date of death or database cut-off date of April 24, 2010, if the patient was alive.
Pathological Complete Response at IA1

**Primary Endpoint**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR (%)</th>
<th>(95% CI)</th>
<th>pCR Diff</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>64.8</td>
<td>51.2</td>
<td>13.6(5.4–21.8)*</td>
<td>0.00055</td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Endpoints: Other pCR Definitions**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>pCR (%)</th>
<th>(95% CI)</th>
<th>pCR Diff</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro + Chemo</td>
<td>59.9</td>
<td>45.3</td>
<td>14.5(6.2–22.7)*</td>
<td></td>
</tr>
<tr>
<td>Placebo + Chemo</td>
<td>68.6</td>
<td>53.7</td>
<td>14.8(6.8–23.0)*</td>
<td></td>
</tr>
</tbody>
</table>

*Estimated treatment difference based on Wittinen & Nummenen method stratified by randomization stratification factors.

Data cutoff date: September 24, 2019.
Pathological Complete Response at IA1

Primary Endpoint: ypT0/Tis ypN0

By PD-L1 Statusb: ypT0/Tis ypN0

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

64.8%  51.2%

260/401  103/201

Pembro + Chemo
Placebo + Chemo

\[
\Delta 14.2 (5.3–23.1)^a
\]

66.9%  54.9%

230/334  90/164

PD-L1–Positive

\[
\Delta 18.3 (−3.3–36.8)^a
\]

45.3%  30.3%

29/64  10/33

PD-L1–Negative

Data from clinical trials included data from randomized trials that stratified by randomization stratification factors. PD-L1 assessed at a central laboratory using the PD-L1 IHC pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells). PD-L1-positive = CPS ≥1. Data cutoff date: September 24, 2018.
Event-Free Survival at IA2

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>764</td>
<td>390</td>
<td></td>
<td></td>
<td></td>
<td>Pembro + Chemo/Pembro</td>
<td>7.4%</td>
</tr>
<tr>
<td>3</td>
<td>730</td>
<td>386</td>
<td></td>
<td></td>
<td></td>
<td>Placebo + Chemo/Placebo</td>
<td>11.8%</td>
</tr>
<tr>
<td>6</td>
<td>785</td>
<td>380</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>668</td>
<td>337</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>519</td>
<td>264</td>
<td>186</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>376</td>
<td>116</td>
<td>36</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>242</td>
<td>73</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>73</td>
<td>36</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Preliminary. P value boundary of 0.000001 not reached at this analysis (the first interim analysis of EFS).
²Hazard ratio (CI) estimated based on a Cox regression model with treatment as a covariate stratified by the randomization stratiﬁcation factors. Data cutoff April 24, 2019.

Looking at the Future: when, who and how?
**Summary**

- KEYNOTE-522 is the first prospective randomized placebo controlled phase 3 trial of pembrolizumab in early TNBC in the neoadjuvant/adjuvant setting.
- Addition of pembrolizumab to platinum-containing neoadjuvant chemotherapy resulted in a statistically significant and clinically meaningful increase in pCR (ypT0/Tis ypN0) of 13.6 percentage points (P=0.00055)
  - Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis
  - Benefit of pembrolizumab independent of PD-L1 status
- Safety was consistent with the known profiles of each regimen; long-term safety follow-up is ongoing.

**NCCN Guidelines Version 3.2019**

**Invasive Breast Cancer**

**PREOPERATIVE/ADJUVANT THERAPY REGIMENs**

**HER2-Negative**

<table>
<thead>
<tr>
<th>Preferred regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dense AC (doxorubicin/cyclophosphamide) followed by paclitaxel every 2 weeks ^h</td>
</tr>
<tr>
<td>Dose-dense AC (doxorubicin/cyclophosphamide) followed by weekly paclitaxel ^b</td>
</tr>
<tr>
<td>TC (docetaxel and cyclophosphamide)</td>
</tr>
<tr>
<td>If triple-negative breast cancer and residual disease after preoperative therapy with taxane-, alkylator-, and anthracycline-based chemotherapy: capcitabine ^i</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Useful in certain circumstances:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose-dense AC (doxorubicin/cyclophosphamide)</td>
</tr>
<tr>
<td>AC (doxorubicin/cyclophosphamide) every 3 weeks (category 2B)</td>
</tr>
<tr>
<td>CMF (cyclophosphamide/methotrexate/fluorouracil)</td>
</tr>
<tr>
<td>AC followed by weekly paclitaxel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other recommended regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC followed by docetaxel every 3 weeks</td>
</tr>
<tr>
<td>EC (epirubicin/cyclophosphamide)</td>
</tr>
<tr>
<td>TAC (docetaxel/doxorubicin/cyclophosphamide)</td>
</tr>
</tbody>
</table>
TNBC: the candidate for immunotherapy
Can we cure cancer with immunotherapy?

✓ Single agent response rate: 5-20%

✓ Higher Rationale in TNBC (most of all in PD-L1 positivity)

✓ Long-lasting responses and survival in a subset of pts

✓ Acceptable safety profile in early phases trials in metastatic setting

Graph showing PFS (Progression-Free Survival) over months for different therapies: Standard therapy A, Target therapy, Immunotherapy.
Identification of biomarkers of response for a better selection of patients (Different PDL1 IHC test for each IMP)

- Limitations in defining PD-L1 as the biomarker
- Expression is dynamic and focal
- Biopsies / full sections
- Location of the metastases
- Expression depend of the antibody used
- Responses in PD-L1-negative cases
- 5-20% objective response rate in PD-L1 negative tumors (melanoma & NSCLC)
- Studies have used different threshold of positivity / different cells type
- Stratification < PD-L1 status in clinical trials

$SP_{142}$ the most accurate in BC!

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Antibody</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEMBROLIZUMAB</td>
<td>22C3</td>
</tr>
<tr>
<td></td>
<td>SP263</td>
</tr>
<tr>
<td>NIVOLUMAB</td>
<td>28-8</td>
</tr>
<tr>
<td></td>
<td>SP263</td>
</tr>
<tr>
<td>ATEZOLIZUMAB</td>
<td>SP142</td>
</tr>
<tr>
<td>DURVALUMAB</td>
<td>SP263</td>
</tr>
</tbody>
</table>
PD-L1 continues to be the most common biomarker assessed across cancer types, but a standardized protocol needs to be developed to facilitate data interpretation across clinical trials. 


✓ Early stage! (challenges with EndPoint)

✓ Development of multiple intriguing rationale combinations (Difficulty in assessing the success of a given combination when one agent is significantly more active than the other) with compatible mechanisms that act synergistically to:

- Increase anti-tumor efficacy (Recist 1.1? imRecist? What about cross-over?)
- Reduce on-target side effects (Different AEs profile! Different Management!)

✓ Adjuvant/neoadjuvant and metastatic settings (133 trials, 92 recruiting)
What Have we Learned?

THANKS!

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+ 39 071 596 4982
r_berardi@univpm.it
www.oncologiamarche.it

The benefit of experience is not in treating everyone, but in treating wisely.
Nelle donne con carcinoma mammario TRIPLO NEGATIVO (recettori ormonali negativi ed HER2-negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, è raccomandabile l’aggiunta del platino ad uno schema standard con antracicline e taxani rispetto alla sola chemioterapia a base di antracicline e taxani?

<table>
<thead>
<tr>
<th>Qualità Globale delle evidenze GRADE</th>
<th>Raccomandazione clinica</th>
<th>Forza della raccomandazione clinica</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderata</td>
<td>Nelle donne con carcinoma mammario triplo negativo (recettori ormonali negativi ed HER2 negativo) candidate a ricevere chemioterapia primaria/neoadiuvante, l’aggiunta del platino ad uno schema standard con antracicline e taxani può essere presa in considerazione.</td>
<td>Positiva debole</td>
</tr>
</tbody>
</table>

Leggere capitolo 14- Raccomandazioni prodotte secondo metodologia GRADE

Una recente revisione sistematica e metaanalisi ha incluso 9 studi randomizzati (n=2109) che hanno confrontato regimi chemioterapici neoadiuvanti contenenti platino vs regimi privi di platino per pazienti con carcinoma mammario triplo negativo. Dei 9 studi inclusi, 7 confrontavano carboplatino + antracicline e taxani vs antracicline e taxani, di cui 5 (GEICAM/2006-3, GeparSixto GBG66, CALGB 40603 Alliance, UMIN000003355 and BrightTNess) presentavano lo stesso backbone chemioterapico con antracicline e taxani nei due bracci di randomizzazione. La metaanalisi di questi 5 studi ha mostrato come l’aggiunta di platino si associi ad un’aumentata probabilità di ottenere una risposta patologica completa (54.2% vs 37.1% OR 2,04; 95% CI 1,39-3,00). Tuttavia, l’utilizzo del platino non è risultato associato ad una significativamente migliore sopravvivenza in termini di event-free survival o overall survival. Nel CALGB 40603, l’aggiunta di carboplatino ogni tre settimane a paclitaxel settimanale seguita da AC “dose-dense” non ha dimostrato a distanza di 3 anni alcun beneficio in EFS; al contrario, nello studio GeparSixto l’aggiunta di carboplatino, a uno schema chemioterapico non convenzionale, ha permesso di osservare un miglioramento assoluto del 10% in termini di sopravvivenza (EFS). Infine, dall’analisi di tutti e 9 gli studi inclusi, il trattamento con platino è risultato associato ad un maggior rischio di tossicitàematologiche di grado 3-4.

La terapia biologica

Incorporazione dei farmaci antiHER2 - Nelle pazienti con carcinoma mammario HER2+ candidate a ricevere chemioterapia neoadiuvante, l’aggiunta dei farmaci antiHER2 è raccomandata.

Leggere capitolo 15- Raccomandazioni prodotte secondo metodologia GRADE
Current approaches largely address patients with pre-existing immunity.

Pre-existing Immunity (20-30%?)

Non-functional immune response

Excluded infiltrate

Immune desert

CD8/IFNγ signature

Response to immunotherapy

Many or most patients may lack pre-existing immunity.
• Challenges with endpoints in combination trials
• Difficulty in assessing the success of a given combination when one agent is significantly more active than the other
• The utility of traditional radiographic response criteria for cancer immunotherapy (CIT) may be limited by the non-classical tumor kinetics (“pseudoprogression”) observed in some patients with clinical benefit
• ORR and PFS have underestimated the overall survival (OS) benefit in monotherapy studies with PD1/PDL-1 inhibitors: how do we keep later line cross-over from confounding and prolonging studies?
• Immune modified RECIST may capture of benefit of atypical responses otherwise missed with RECIST 1.1
• All atezolizumab trials include RECIST 1.1 and imRECIST
Table 2. Characteristics of adjuvant randomized trials evaluating tumor-infiltrating lymphocytes in stromal compartments as continuous variable per 10% increase according to disease subtype

<table>
<thead>
<tr>
<th>Author</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loi et al. 2014 [17]</td>
<td>0.990</td>
<td>0.736</td>
<td>1.332</td>
<td>.947</td>
</tr>
<tr>
<td>Dieci et al. 2015 [34]</td>
<td>1.010</td>
<td>0.889</td>
<td>1.148</td>
<td>.879</td>
</tr>
<tr>
<td>Loi et al. 2013 [18]</td>
<td>1.100</td>
<td>0.995</td>
<td>1.215</td>
<td>.061</td>
</tr>
<tr>
<td><strong>ER-Positive/HER2-Negative</strong></td>
<td><strong>1.060</strong></td>
<td><strong>0.962</strong></td>
<td><strong>1.144</strong></td>
<td><strong>.134</strong></td>
</tr>
<tr>
<td>Dieci et al. 2015 [34]</td>
<td>0.880</td>
<td>0.763</td>
<td>1.014</td>
<td>.078</td>
</tr>
<tr>
<td>Loi et al. 2013 [18]</td>
<td>0.890</td>
<td>0.775</td>
<td>1.022</td>
<td>.699</td>
</tr>
<tr>
<td>Loi et al. 2014 [17]</td>
<td>0.980</td>
<td>0.869</td>
<td>1.183</td>
<td>.837</td>
</tr>
<tr>
<td><strong>HER2-Positive</strong></td>
<td><strong>0.904</strong></td>
<td><strong>0.828</strong></td>
<td><strong>0.988</strong></td>
<td><strong>.025</strong></td>
</tr>
<tr>
<td>Loi et al. 2014 [17]</td>
<td>0.800</td>
<td>0.621</td>
<td>1.031</td>
<td>.085</td>
</tr>
<tr>
<td>Adams et al. 2014 [16]</td>
<td>0.810</td>
<td>0.680</td>
<td>0.950</td>
<td>.016</td>
</tr>
<tr>
<td>Loi et al. 2013 [18]</td>
<td>0.820</td>
<td>0.700</td>
<td>0.960</td>
<td>.014</td>
</tr>
<tr>
<td>Dieci et al. 2015 [34]</td>
<td>0.890</td>
<td>0.778</td>
<td>1.013</td>
<td>.069</td>
</tr>
<tr>
<td><strong>Triple-Negative</strong></td>
<td><strong>0.840</strong></td>
<td><strong>0.775</strong></td>
<td><strong>0.912</strong></td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Better OS  | Worse OS

Investigative Clinical Oncology

Carbognin et al, The Oncologist 2016
TILs in Early Breast Cancer

Table 1. Characteristics of neoadjuvant randomized trials evaluating tumor-infiltrating lymphocytes, including lymphocytes predominating breast cancer assay, according to disease subtype.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Reference</th>
<th>Study</th>
<th>Disease subtypes</th>
<th>Patients (n)</th>
<th>Treatment arms</th>
<th>TIL assay</th>
<th>pCR cutoff</th>
<th>pCR in LPBC (%)</th>
<th>pCR in new LPBC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denkert et al. 2010 [21]</td>
<td>GeparTino</td>
<td>HER2-eq</td>
<td>nTR, pCR &gt; 15% vs. TILs (TILs &gt; 10%)</td>
<td>254</td>
<td>TAC × 8 w.</td>
<td>TILs in HER2-positive</td>
<td>47.4</td>
<td>33.6</td>
<td></td>
</tr>
<tr>
<td>Denkert et al. 2015 [22]</td>
<td>GeparTino</td>
<td>HER2-eq</td>
<td>nTR, pCR &gt; 15% vs. TILs (TILs &gt; 10%)</td>
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<td>TILs in HER2-positive</td>
<td>47.4</td>
<td>33.6</td>
<td></td>
</tr>
<tr>
<td>Dieci et al. 2015 [23]</td>
<td>GeparTino</td>
<td>HER2-eq</td>
<td>nTR, pCR &gt; 15% vs. TILs (TILs &gt; 10%)</td>
<td>254</td>
<td>TAC × 8 w.</td>
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<td>47.4</td>
<td>33.6</td>
<td></td>
</tr>
</tbody>
</table>

Denkert et al. 2010 [21] GeparTino | HER2-eq | nTR, pCR > 15% vs. TILs (TILs > 10%) | 254 | TAC × 8 w. | TILs in HER2-positive | 47.4 | 33.6 |

Denkert et al. 2015 [22] GeparTino | HER2-eq | nTR, pCR > 15% vs. TILs (TILs > 10%) | 254 | TAC × 8 w. | TILs in HER2-positive | 47.4 | 33.6 |

Dieci et al. 2015 [23] GeparTino | HER2-eq | nTR, pCR > 15% vs. TILs (TILs > 10%) | 254 | TAC × 8 w. | TILs in HER2-positive | 47.4 | 33.6 |

Abbreviations: Basal, luminal A, luminal B, HER2-positive, TILs, intraductal papillomatosis, HER2, human epidermal growth factor receptor 2, pCR, pathological complete response, L, left; R, right; LH, lymphoepithelial breast cancer; S, small; pT, pathological T stage; pN, pathological N stage; OR, odds ratio; 95% CI, 95% confidence interval; pCR, pathological complete response.

Carbognin et al, The Oncologist 2016
Classifying Cancers Based on T-cell Infiltration and PD-L1

<table>
<thead>
<tr>
<th>Tumor Microenvironment</th>
<th>Early BC</th>
<th>Ovarian</th>
<th>Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I TIL+/PD-L1+</td>
<td>21%</td>
<td>57.4%</td>
<td>38%</td>
</tr>
<tr>
<td>Type II TIL-/PD-L1-</td>
<td>24%</td>
<td>5.1%</td>
<td>41%</td>
</tr>
<tr>
<td>Type III TIL-/PD-L1+</td>
<td>2%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Type IV TIL+/PD-L1-</td>
<td>53%</td>
<td>37.4%</td>
<td>20%</td>
</tr>
</tbody>
</table>


Type I: Adaptive immune resistance
Type II: Immunological ignorance
Type III: Intrinsic Induction
Type IV: Tolerance
### Cold and Hot Tumours

**Cold Tumour**
- Epigenetic silencing
- Active β-catenin signalling
- Mesenchymal-like cells
- Stem cell-like cells
- Less differentiated cells

**Cold Tumour Immunological Characteristics**
- Enriched in immunosuppressive cytokines
- High numbers of T\(_{\text{reg}}\) cells and MDSCs
- Few T\(_{\text{eff}}\) cells, NK cells, and CD8\(^+\) T cells
- Few functional APCs

**Hot Tumour**
- Epigenetic reprogramming
- Suppressed β-catenin signalling
- Endothelial cells
- Highly differentiated cells
- High PD-L1 expression

**Hot Tumour Immunological Characteristics**
- Enriched in T\(_{\text{1}}\)-type chemokines
- High numbers of effector immune cells (T\(_{\text{1}}\) cells, NK cells, and CD8\(^+\) T cells)
- High numbers of functional APCs

---

*Nogasheth et al, Nature Reviews Immunology 2017*
Immunogram; late stage disease
What we have learned: immunosuppression is a rate limiting step to effective anti-tumor immunity... for some patients.
Immunogram; earlier stage disease
Conclusion

• Immunotherapy represents an intriguing and potentially revolutionary approach in BC
• Immune Checkpoint Inhibitors are active and promising especially in TN subtype and in earlier lines of treatment
• Novel strategies and novel combinations to enhance activity and extend spectrum of efficacy of immunotherapy are needed and under investigation
The cancer immunogram

Blank et al, Science 2016
Rationale for combining PARP inhibitors + immune checkpoint inhibitors

Jiao et al, Clin Cancer Res 2017
MEDIOLA, phase II basket study of olaparib and durvalumab: gBRCAmut HER2- MBC (n=25)

Domchek et al. SABCS 2017
What is going to challenge the already unstable algorithm for mTNBC?

- Increasing use of platinum in early setting will challenge its role in MBC
  - «ovarian cancer-like» model based on platinum sensitivity for platinum rechallenge or PARPi for gBRCAmut? Need for data and biomarkers.

- Immunotherapy combinations in early lines (CT, PARPi)
  - In patients subgroups (which role of immune biomarkers in I/O combos?)
  - Opportunity for maintenance treatment
  - PARPi in BRCA non mut

- AKT inhibitors + taxane in 1st line
Rationale to develop immunotherapy in BC

- TIL infiltration
- PD-L1 expression
- Responses in early phase trials
- Mutation load

Features of BC
Goals of cancer immunotherapy
Broad activity for anti-PD-L1/PD-1 in human cancer

Broad activity, but only subset of patients benefit: ~10-30%
Modulation of tumor immune status by chemotherapy may be transient
Simultaneous combinations may help to maintain and extend tumor inflamed state
Immunosurveillance and immunoediting balance
Attempt to design a treatment algorithm for mTNBC: key considerations

• Metastatic TNBC pts
  • Most received A-T as adjuvant/neoadjuvant treatment
  • Visceral metastases
  • Poor survival from the onset of MBC
  • Limited options available with limited efficacy

→ Clinical trials!
→ A long-term treatment sequence is not possible (high attrition rate)
→ Best option first
Treatment options for metastatic TNBC

BRCAwt

(Poly)chemotherapy
Paclitaxel+Beva

Platinum + taxane

BRCAmut

(Poly)chemotherapy
Paclitaxel+Beva

PARPi | Platinum
Platinum for gBRCAmut metastatic TNBC

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Setting</th>
<th>ORR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCR009†</td>
<td>Cisplatin or Carboplatin</td>
<td>1-2 line</td>
<td>26%</td>
</tr>
<tr>
<td>BALI²</td>
<td>Cisplatin</td>
<td>1-2 line</td>
<td>10%</td>
</tr>
<tr>
<td>Byrski³</td>
<td>Cisplatin</td>
<td>1-2 line</td>
<td>--</td>
</tr>
</tbody>
</table>

What is going to challenge the already unstable algorithm for mTNBC?

- Increasing use of platinum in early setting will challenge its role in MBC
  - “ovarian cancer-like” model based on platinum sensitivity for platinum rechallenge or PARPi in gBRCAmut? Need for data and biomarkers.

- Immunotherapy combinations in early lines (CT, PARPi)
TIL infiltration

- Amplify: existing anti-tumor immunity (Immunogenic chemo, radiation and/or targeted therapy?)
- TIL_{hi}
- TIL_{int}
- TIL_{neg}

- Induce: nascent anti-tumor immunity; break tolerance (vaccines, adoptive cell therapy, cytokines?)

- Boost & Expand: developing anti-tumor immunity (immune checkpoint inhibitors; plus immunogenic or targeted therapies?)

Tumors (n=110)
Strategies to modulate the immune system in breast cancer

Active: priming of the immune system
- Antigen-specific
  - Peptide vaccine
  - DC-vaccine
  - DNA-vaccine
  - Whole cell vaccine
- Non antigen-specific
  - Checkpoint inhibitors
  - Cytokines

Passive: delivery of compounds that may use immune system
- Monoclonal antibodies
  - Trastuzumab
  - Pertuzumab
- Adoptive cell transfer
  - CAR T cells

Cancer vaccines

Immune modulators

Targeted antibodies

Cellular immunotherapy
Single Agent Activity of PD-1/PD-L1 Blockade in Relapsed/Refractory Cancer

- MPDL3280A/Atezolizumab
- Pembrolizumab
- Nivolumab

Overall response rate (%)

- HL
- B-NHL
- Melanoma
- NSCLC
- SCLC
- TNBC
- OVary
- RCC
- High PD-L1
- Low PD-L1
- MMR-deficient
- MMR proficient
- Gastric
- Esophageal
- Pancreas
- HCC

Immunotherapy in Cancer: Past, Present and Future

William Coley and the birth of cancer immunotherapy

Ever since the nineteenth-century observation by William Coley that postoperative infections were correlated with cancer regression and subsequently that injections for the treatment of erysipelas induced tumor regression, the immune system has been suspected to play a role in cancer.

Since then, a wealth of in vitro and in vivo data has led to an immunosurveillance model of cancer progression proposed by Schreiber and colleagues.

Elie Metchnikoff & Paul Ehrlich won the Nobel Prize 3 months later
Figure 1 | The prevalence of somatic mutations across human cancer types.

Every dot represents a sample whereas the red horizontal lines are the median numbers of mutations in the respective cancer types. The vertical axis (log scaled) shows the number of mutations per megabase whereas the different cancer types are indicated on the x-axis. The chart illustrates that breast cancer has the highest prevalence of somatic mutations. We thank G. Getz and colleagues for the design of this figure. ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia.

Alexandrov et al, Nature 2013
Immunotherapy in Cancer: Past, Present and Future

Background

Rationale in BC

First line DATA

Second line DATA

Look at the Future

Conclusion
Atezolizumab and Nab-Paclitaxel in metastatic TNBC

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>1L (n = 9)</th>
<th>2L (n = 8)</th>
<th>3L+ (n = 7)</th>
<th>All Patients N = 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)*</td>
<td>66.7% (29.9, 92.5)</td>
<td>25% (3.2, 65.1)</td>
<td>28.6% (3.7, 71.0)</td>
<td>41.7% (22.1, 63.4)</td>
</tr>
<tr>
<td>ORR (95% CI)*</td>
<td>88.9% (51.7, 99.7)</td>
<td>75.0% (34.9, 96.8)</td>
<td>42.9% (9.9, 81.6)</td>
<td>70.8% (48.9, 87.4)</td>
</tr>
<tr>
<td>CR</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
<td>4.2%</td>
</tr>
<tr>
<td>PR</td>
<td>77.8%</td>
<td>75.0%</td>
<td>42.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>SD</td>
<td>11.1%</td>
<td>25.0%</td>
<td>28.6%</td>
<td>20.8%</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>28.6%</td>
<td>8.3%</td>
</tr>
</tbody>
</table>

Response rates were higher for patients who received atezolizumab/nab-paclitaxel treatment as 1L therapy compared to 2L+.

* Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.
* Including investigator-assessed unconfirmed responses.
Efficacy-evaluable patients were dosed by June 1, 2015, and were evaluable for response by RECIST v1.1. Minimum efficacy follow-up was 2-3 months.