ESMO Preceptoship in Immuno-Oncology

Clinical Development: Breast Cancer

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Outline

• Rational for immunotherapy in breast cancer
• Molecular characterization of BC immune-phenotypes
• Evidences from clinical trials
• Future perspectives
Somatic Mutations in Breast Cancer Subtypes

Mutation rate higher in TNBC compared to other subtypes

ER, estrogen receptor
## TILs in TNBC

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Trial</th>
<th>Endpoint</th>
<th>Subtype Analyzed</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denkert et al. 2010</td>
<td>840</td>
<td>GBG G-3</td>
<td>pCR</td>
<td>All</td>
<td>pCR: 41% in TIL+ BC Validated in G-5</td>
</tr>
<tr>
<td>Loi et al. 2013</td>
<td>2009</td>
<td>BIG 2-98</td>
<td>DFS</td>
<td>Preplanned analysis of molecular subtypes</td>
<td>Prognostic impact in TNBC (n = 256): HR: 0.31 (0.11-0.84)</td>
</tr>
<tr>
<td>Loi et al. 2014</td>
<td>935</td>
<td>FinHer</td>
<td>DFS</td>
<td>Preplanned analysis of molecular subtypes</td>
<td>Prognostic impact in TNBC (n = 134): HR: 0.31 (0.12-0.8)</td>
</tr>
<tr>
<td>Adams et al. 2014</td>
<td>506</td>
<td>ECOG 2197 ECOG 1199</td>
<td>DFS</td>
<td>TNBC</td>
<td>HR: 0.84 (0.74-0.95)</td>
</tr>
<tr>
<td>Dieci et al. 2014</td>
<td>278</td>
<td>MFS OS</td>
<td></td>
<td>TNBC</td>
<td>HR: 0.86 (0.77 -0.96)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: 0.86 (0.77 -0.97)</td>
</tr>
<tr>
<td>Denkert et al. 2015</td>
<td>580</td>
<td>Gepar-Sixto trial</td>
<td>pCR</td>
<td>TNBC and HER2</td>
<td>pCR rate was 59.9% in LPBC and 33.8% for non-LPBC (P&lt;.001)</td>
</tr>
</tbody>
</table>

## Immune-Signatures

<table>
<thead>
<tr>
<th>Reference</th>
<th># of Patients</th>
<th>Signatures</th>
<th>ER-</th>
<th>HER2+</th>
<th>ER+ Lum B</th>
<th>ER+ Lum A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teschendorff et al. 2007</td>
<td>1056</td>
<td>7-gene immune module</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexe et al. 2007</td>
<td>286</td>
<td>651 lymphocyte-associated genes</td>
<td>+</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt et al. 2008</td>
<td>788</td>
<td>B-cell metagene</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Desmedt et al. 2008</td>
<td>1605</td>
<td>Stat1 metagene</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rody et al. 2009</td>
<td>1781</td>
<td>Lymphocyte-specific kinase (LCK)</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bianchini et al. 2010</td>
<td>684</td>
<td>B-cell/plasma cell metagene</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Criscitiello et al 2018</td>
<td>99</td>
<td>4-gene signature</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Immunologic Constant of Rejection

Immune-Subtype and molecular subtype

TCGA (N=953) Validation (n=1660)

Overall Survival

Distant Metastases Free Survival

Determinants of Immune-Subtypes

- Mutational Load
- Mutations of Driver Genes
- Copy Number Alterations

CXCL9, CXCL10, CCL5, IFNG, TBX21, CD8A, IL12B, CD8B, STAT1, IFN, CD8, IL2, PRF1, GZMA, GZMB, CD8A, FOXP3, IDO1, IL12B, IFNG, CCL5, CXCL10, CXCL9, IRF1, STAT1

Copy number alterations

Mutational load vs Immune-Subtypes

Neoeptopes vs Immune-Subtypes

Immune-Subtype and molecular subtype

Adapted from Cell Immunity, May 3rd 2018
Chemotherapy and tumour-associated infiltrate

Metronomic cyclophosphamide and anti-HER2 therapy

80 patients evaluated and randomly allocated

39 patients randomly assigned to the trastuzumab plus pertuzumab group and started allocated treatment

41 patients randomly assigned to the trastuzumab and pertuzumab plus metronomic cyclophosphamide group and started allocated treatment

1 excluded: age <70 years with no fulfilled AEoL or IAIoL or CCI criteria per protocol

2 excluded: previous medical history including secondary cancer

38 eligible patients in per-protocol population

30 with measurable disease

2 without measurable disease

39 eligible patients in per-protocol population

36 with measurable disease

3 without measurable disease

14 patients started trastuzumab emtansine treatment

39 patients included in intention-to-treat and safety analyses

41 patients included in intention-to-treat and safety analyses

15 patients started trastuzumab emtansine treatment

The Lancet Oncology 2018 19, 323-336 DOI: (10.1016/S1470-2045(18)30083-4)
The median progression-free survival was 5.6 months (95% CI 3.6–16.8) with trastuzumab and pertuzumab versus 12.7 months (6.7–24.8) with the addition of metronomic oral cyclophosphamide.
How to Enhance Immunogenicity?

Translocation of Calreticulin to the cell surface

Activation of HSP90

Release of High Mobility Group Box 1 protein
# How to Enhance Immunogenicity?

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT ON IMMUNE SYSTEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>- Induces immunogenic cell death&lt;br&gt;- Increases proliferation of CD8 T cells&lt;br&gt;- Stimulates antigen presentation by DCs&lt;br&gt;- Stimulates MCP1 and M6PR</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>- Induces immunogenic cell death&lt;br&gt;- Suppressed Treg inhibitory functions and restoration of the proliferative capacity of effector T cells and NK cell cytotoxicity</td>
</tr>
<tr>
<td>Taxanes</td>
<td>- Enhance T-cell and NK-cell function&lt;br&gt;- Increase recruitment of TIL&lt;br&gt;- Increase efficacy of immunostimulatory agents</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>- Reduce the number of myeloid suppressor cells&lt;br&gt;- Increase the antitumor activity of CD8(+) T cells and activated NK cells</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>- Induces immunogenic cell death&lt;br&gt;- Increases MHC I complex&lt;br&gt;- Inhibits PD-L2</td>
</tr>
</tbody>
</table>

DC, dendritic cells; MHC, major histocompatibility complex; NK, natural killer
• **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

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**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 ≥4 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.

CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PgR, progesterone receptor; PR, partial response; SD, stable disease
Pembrolizumab in TNBC

Efficacy (N = 27)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>18.5%</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>25.9%</td>
</tr>
<tr>
<td><strong>Median duration of response</strong></td>
<td>NR (15.0 to ≥47.3 weeks)</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>1.9 months</td>
</tr>
<tr>
<td><strong>6-month PFS</strong></td>
<td>24.4%</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>11.2 months</td>
</tr>
<tr>
<td><strong>12-month OS</strong></td>
<td>43.1%</td>
</tr>
</tbody>
</table>

**ORR**, overall response rate; **OS**, overall survival; **PFS**, progressive-free survival

# Pembrolizumab in TNBC

<table>
<thead>
<tr>
<th></th>
<th>Total Population</th>
<th>PD-L1 Positive</th>
<th>PD-L1 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 170</td>
<td>n = 105</td>
<td>n = 64</td>
</tr>
<tr>
<td><strong>ORR, n (%) [95% CI]</strong></td>
<td>8 (4.7) [2.3-9.2]</td>
<td>5 (4.8) [1.8-10.9]</td>
<td>3 (4.7) [1.1-13.4]</td>
</tr>
<tr>
<td><strong>DCR, n (%) [95% CI]</strong></td>
<td>13 (7.6) [4.4-12.7]</td>
<td>10 (9.5) [5.1-16.8]</td>
<td>3 (4.7) [1.1-13.4]</td>
</tr>
<tr>
<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>1 (0.6)</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>7 (4.1)</td>
<td>4 (3.8)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>SD</td>
<td>35 (20.6)</td>
<td>22 (21.0)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>PD</td>
<td>103 (60.6)</td>
<td>66 (62.9)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5 (2.9)</td>
<td>2 (1.9)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Not able to be assessed, n (%)</td>
<td>19 (11.2)</td>
<td>10 (9.5)</td>
<td>9 (14.1)</td>
</tr>
</tbody>
</table>

**DCR**, disease control rate
Pembrolizumab in TNBC

Events/Patients, n  Median (95% CI)
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Total$^a$  148/170  2.0 months (1.9 to 2.0)
PD-L1 positive  90/105  2.0 months (1.9 to 2.1)
PD-L1 negative  57/64  1.9 months (1.6 to 2.0)

ORR by sTIL Level $\geq$Median vs <Median

**Cohort A**
- sTIL level $\geq$5%: 6.4%, n=94, Responders=6, Ongoing responses=3
- sTIL level <5%: 1.9%, n=53, Responders=1, Ongoing responses=1

**Cohort B**
- sTIL level $\geq$17.5%: 39.1%, n=23, Responders=9, Ongoing responses=5
- sTIL level <17.5%: 8.7%, n=23, Responders=2, Ongoing responses=2

**Combined Cohorts**
- sTIL level $\geq$5%: 12.6%, n=135, Responders=17, Ongoing responses=10
- sTIL level <5%: 1.7%, n=58, Responders=1, Ongoing responses=1

Data cutoff date: Nov 10, 2016.
ORR by sTIL Level ≥Median vs <Median

Atezolizumab
(Cohort A: ≥2nd line)

Pembrolizumab
(Cohort B: 1st line)

Different levels by source of sample (archival vs new) and organ site sampled: LN>lung>liver

Metastatic breast cancer is a low TIL disease

**Eribulin and Pembrolizumab**

<table>
<thead>
<tr>
<th></th>
<th>ALL (n = 17)</th>
<th>1L (n = 17)</th>
<th>2L/3L (n = 18)</th>
<th>PD-L1+ (n = 17)</th>
<th>PD-L1− (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR</strong></td>
<td>34.4%</td>
<td>41.2%</td>
<td>27.3%</td>
<td>29.4%</td>
<td>33.3%</td>
</tr>
<tr>
<td><strong>CBR</strong></td>
<td>40.6%</td>
<td>47.1%</td>
<td>36.4%</td>
<td>35.8%</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

1L, first line; 2L/3L, second/third line; BOR, best overall response; CBR, clinical benefit rate; IC, tumor-infiltrating immune cell
TONIC Trial: Study Design

Radiation 3 x 8 Gy

Doxorubicin 15 mg x2

Cyclophosphamide 50 mg daily

Cisplatin 40 mg/m² x2

No treatment

Nivolumab

2 weeks

# Efficacy of Nivolumab After Induction

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best ORR (CR + PR) iRECIST</strong></td>
<td>24%</td>
</tr>
<tr>
<td><strong>CBR (CR + PR + SD)</strong></td>
<td>26%</td>
</tr>
<tr>
<td>CR</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>11 (22%)</td>
</tr>
<tr>
<td>SD ≥24 weeks</td>
<td>1 (2%)</td>
</tr>
<tr>
<td><strong>ORR RECIST1.1</strong></td>
<td>22%</td>
</tr>
<tr>
<td><strong>Median PFS [95% CI]</strong></td>
<td>3.4 months [2.5-3.7]</td>
</tr>
<tr>
<td><strong>Median time to response [range]</strong></td>
<td>2.1 months [0.5-3.5]</td>
</tr>
<tr>
<td><strong>Median duration of response [95% CI]</strong></td>
<td>9.0 months [5.5-NA]</td>
</tr>
</tbody>
</table>

NA, not available
Atezolizumab and *nab*-Paclitaxel in mTNBC

<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)&lt;sup&gt;a&lt;/sup&gt;</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)&lt;sup&gt;b&lt;/sup&gt;</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+.

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<sup>a</sup> Confirmed ORR defined as at least 2 consecutive assessments of complete or partial response.

<sup>b</sup> 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 ≥3 months.

Atezolizumab and \textit{nab}-Paclitaxel in mTNBC

- Including investigator-assessed unconfirmed responses.

- 11 of 17 responses (65\%) continued on treatment at time of data cut off

# Atezolizumab and nab-paclitaxel

<table>
<thead>
<tr>
<th></th>
<th>IC0 (n = 7)</th>
<th>IC1/2/3 (n = 9)</th>
<th>Unknown (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>57.1% (18.4, 90.1)</td>
<td>77.8% (40.0, 97.2)</td>
<td>75% (34.9, 96.8)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
<td>12.5%</td>
</tr>
<tr>
<td>PR</td>
<td>57.1%</td>
<td>77.8%</td>
<td>62.5%</td>
</tr>
<tr>
<td>SD</td>
<td>42.9%</td>
<td>22.2%</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>0</td>
<td>25%</td>
</tr>
</tbody>
</table>

Including investigator-assessed unconfirmed responses.

- Responses were observed in both IC0 and IC1/2/3 patients

Atezolizumab and \textit{nab}-Paclitaxel in mTNBC

Randomized, double-blind, placebo-controlled Phase 3 trial of \textit{nab}-paclitaxel ± atezolizumab as 1\textsuperscript{st} line therapy in mTNBC (NCT02425891)

**Study design**

- Histologically documented locally advanced or metastatic TNBC
- No prior therapy for advanced disease
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Patients with significant CV or CNS disease (except asymptomatic brain metastases), autoimmune disease or prior checkpoint inhibitor therapy are excluded
- Target accrual: ~350 patients

**Co-primary endpoints:**
- PFS in all patients
- PFS according to PD-L1 expression

**Secondary endpoints:**
- OS
- ORR
- Response duration
- Safety/tolerability
- Pharmacokinetics (PK)
- Health-related quality of life (HR QoL)

**Stratification factors:**
- Presence of liver metastases
- Prior taxane therapy
- PD-L1 expression status (centrally evaluated by IHC using the SP142 assay)

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PARP Inhibitors and Immuno-Oncology

The diagram illustrates the role of PARP inhibitors and DNA repair mechanisms in cancer therapy. PARP inhibitors can cause DNA strand breaks, leading to single-strand breaks, DNA adducts/base damage, and replication lesions, which are repaired by BRCA1/BRCA2 proteins.

Key points:
- DNA Strand Break
- Chemotherapy Radiotherapy
- DNA Repair
- PARP1
- BRCA1/BRCA2

The diagram shows how PARP inhibitors, by inducing DNA damage, can enhance the effects of chemotherapy and radiotherapy, thus targeting tumor cells more effectively.
TOPACIO Trial of Niraparib and Pembrolizumab

**Phase I**
- Patients with OC or TNBC
  - Dose level 1: Niraparib 200 mg + pembrolizumab 200 mg
  - Dose level 2: Niraparib 300 mg + pembrolizumab 200 mg
  - Endpoint assessment

**Phase II**
- Patients with OC (target n = 48) or TNBC (target n = 48)
  - RP2D
  - Endpoint assessment

Preliminary Best Percentage Change in Lesion Size in Patients Enrolled in Phase 2 with TNBC

Immunotherapy in HER2 positive

- Centrally confirmed HER2+
- ECOG 0-1
- Tumor biopsy sample <1yr
- Measurable disease RECIST 1.1
- No limit of prior systemic treatment
- Documented PD on trastuzumab or TDM-1

Phase Ib
Pembrolizumab
2mg/kg and 10mg/kg IV + trastuzumab Q3W

Phase II
- Pembrolizumab 200mg IV + trastuzumab Q3W

Protocol specified follow-up. Treatment until progression, toxicity, patient withdrawal or investigator decision of maximum 2 years

PD-L1 + N=46

PD-L1 - N=12

S. Loi et al San Antonio 2017
PANACEA Trial

Median follow-up: 13.6 months

Enrolled 58 (39.7% of screened)
- 6 phase Ib PD-L1 positive
- 40 phase II PD-L1 positive
  - 41% ER neg
  - 59% ER pos
- 12 PD-L1 negative
  - 50% ER neg
  - 50% ER pos

On treatment: 3 (5%)
Discontinued
- PD: 46 (79%)
- AE: 6 (10%)
- Death: 1 (2%)
- Withdrew consent: 1 (2%)
- Patient deterioration: 1 (2%)

146 patients screened
Feb. 2015 - April 2017
11 sites, 5 countries

Ineligible if HER2 negative

S. Loi et al San Antonio 2017
# Immunotherapy in HER2 positive

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase Ib PD-L1 positive</th>
<th>Phase II PD-L1 positive; N=40</th>
<th>Phase II PD-L1 negative; N=12</th>
<th>Overall n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs. median (range)</td>
<td>49 (38-57)</td>
<td>49 (28-72)</td>
<td>56.5 (43-61)</td>
<td>50.5 (28-72)</td>
</tr>
<tr>
<td>ER negative positive (≥1%)</td>
<td>4 (66%)</td>
<td>23 (57.5%)</td>
<td>6 (50%)</td>
<td>33 (56.9%)</td>
</tr>
<tr>
<td>Prior trastuzumab-containing therapy</td>
<td>6 (100%)</td>
<td>40 (100%)</td>
<td>12 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Additional anti-HER2 therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (16.7%)</td>
<td>6 (15%)</td>
<td>0 (0%)</td>
<td>7 (12.1%)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (83.3%)</td>
<td>34 (85%)</td>
<td>12 (100%)</td>
<td>51 (87.9%)</td>
</tr>
<tr>
<td>T-DM1</td>
<td>4</td>
<td>29</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>3</td>
<td>10</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>17</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Prior endocrine therapy</td>
<td>2 (33%)</td>
<td>13 (32.5%)</td>
<td>7 (58%)</td>
<td>22 (38%)</td>
</tr>
<tr>
<td>Prior chemotherapy (Anth/Taxane)</td>
<td>6 (100%)</td>
<td>40 (100%)</td>
<td>12 (100%)</td>
<td>58 (100%)</td>
</tr>
</tbody>
</table>

S. Loi et al San Antonio 2017
## Best Overall Response (RECIST 1.1)

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 Positive Phase Ib, n=6</th>
<th>PD-L1 Positive Phase II, n=40</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR n (%) [90%CI]</strong></td>
<td>1 (17%) [1-58]</td>
<td>6 (15%) [7-29]</td>
</tr>
<tr>
<td><strong>DCR¹ n (%) [90%CI]</strong></td>
<td>1 (17%) [1-58]</td>
<td>10 (25%) [14-49]</td>
</tr>
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<td><strong>Best overall response, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response</td>
<td>1 (17%)</td>
<td>1 (2.5%)</td>
</tr>
<tr>
<td>Partial Response</td>
<td>-</td>
<td>5 (12.5%)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>-</td>
<td>7 (17.5%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5 (83%)</td>
<td>25 (62.5%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>-</td>
<td>2 (5.0%)</td>
</tr>
</tbody>
</table>

**Overall PD-L1 +**
- **ORR 15.2% [7-27]**
- **DCR 24% [14-36]**

¹DCR: CR, PR, or SD ≥ 6 months

S. Loi et al San Antonio 2017
### Best Overall Response (RECIST 1.1)

<table>
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<tr>
<th>PD-L1 Positive</th>
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<th>PD-L1 Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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**Best overall response, n (%)**

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<tr>
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<th>PD-L1 Positive Phase Ib, n=6</th>
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<th>PD-L1 Negative Phase II, n=12</th>
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<td>Complete Response</td>
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<td>-</td>
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<tr>
<td>Partial Response</td>
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<td>5 (12.5%)</td>
<td>-</td>
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<tr>
<td>Stable Disease</td>
<td>-</td>
<td>7 (17.5%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>5 (83%)</td>
<td>25 (62.5%)</td>
<td>9 (75.0%)</td>
</tr>
<tr>
<td>Not Evaluable</td>
<td>-</td>
<td>2 (5.0%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

**Overall PD-L1 +**

- **ORR 15.2% [7-27]**
- **DCR 24% [14-36]**

\(^1\)Disease Control Rate: CR, PR, or SD ≥ 6 months

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Maximum Change from Baseline in Target Lesions PD-L1 Positive Cohorts

Excludes 2 patients not evaluable for response

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Disease Control: PD-L1 Positive Cohorts

- Median DoR: 3.5 months (90% CI: 2.7 - ∞)
- Mean DoR: 10 months (90% CI: 2.7-23.1)
- Median duration of disease control: 11.1 months (90% CI: 6.2 - ∞)
- Median PFS: 2.7 months (90% CI: 2.6-4.0)
- 6-month PFS: 24% (14%-35%)
- 12-month PFS: 13% (6%-22%)
- Five patients (10.8%) continue with no progression (2 in CR, 1 PR)

\(^1\)DCR: CR, PR, or SD ≥ 6 months
S. Loi et al San Antonio 2017
PFS and OS

Median, months (90% CI):
PD-L1 Pos: 2.7 (2.6 to 4.0)
PD-L1 Neg: 2.5 (1.4 to 2.7)

\[ P = 0.07 \]

Median, months (90% CI):
PD-L1 Pos: 16.1 (13.1 to ∞)
PD-L1 Neg: 7.0 (4.9 to 9.8)

\[ P = 0.0006 \]

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sTIL $\geq$5% as Potential Predictive Marker, PD-L1 Positive

- 44% of PD-L1 positive had sTIL $\geq$5%
- For sTIL$\geq$5% v. sTIL<5%

**ORR**
- 39% vs. 5%
  - Sensitivity: 85.7%
  - Specificity: 61.8%
  - NPV: 95.5%
  - PPV: 31.6%

**DCR**
- 47% vs. 5%
  - Sensitivity: 90.0%
  - Specificity: 67.7%
  - NPV: 95.5%
  - PPV: 47.4%

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Summary and Conclusions

• PANACEA study of pembrolizumab added to trastuzumab in trastuzumab-resistant mHER2+ patients met its primary objective in the PD-L1 positive cohort (n=46: ORR 15%, DCR 25%)
  – No responses observed in PD-L1 negative patients
  – Stromal TIL levels associated with response: high TIL ≥5% patients (ORR 39%, DCR 47%)
  – For responders: pembrolizumab monotherapy with trastuzumab offers excellent QoL and durable control without chemotherapy

• Metastatic HER2+ disease in the heavily pretreated setting is a poorly immunogenic (majority of patients had low TILs in fresh biopsies from metastatic lesions)
  – Higher ORR observed than in metastatic TNBC (KN-086 Cohort A)

• Future directions in IO in mHER2+ low TIL patients should focus on combinations with effective anti-HER2 therapy
Immunotherapy in TNBC: Neoadjuvant Setting

N = 272
Primary endpoint: Event-free survival (EFS)
Secondary endpoint: pCR (ypT0-ypTis ypN0)

- Nab-Paclitaxel 125 mg/m²
- CBDCA AUC2
- +/- Atezolizumab 1200 mg

Surgery
Immunotherapy in TNBC: Neoadjuvant Setting

N = 174

Primary endpoint: pCR (ypT0 ypN0)

nab-Paclitaxel

EC

MEDI 4736/Durvalumab

Placebo

Window of opportunity 2 weeks

nab-P 125 mg/m²

Epirubicin 90 mg/m² + cyclophosphamide 600 mg/m²

MEDI 4736/durvalumab 2g total q4w

Surgery
Immunotherapy in TNBC: Neoadjuvant Setting

### KEYNOTE-173 Phase I/II Trial

<table>
<thead>
<tr>
<th>Cohort A (no platinum)</th>
<th>Cohort B (platinum)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy + anti-PD-1</strong></td>
<td><strong>60%</strong></td>
</tr>
<tr>
<td>Paclitaxel Q1W x 12 ± carboplatin Q1W x 12 + pembrolizumab Q3W x 4</td>
<td>AC Q3W x 4 + pembrolizumab Q3W x 4</td>
</tr>
<tr>
<td><strong>pCR = ypT0 ypN0</strong></td>
<td><strong>80%</strong></td>
</tr>
</tbody>
</table>

### I-SPY-2 Trial

<table>
<thead>
<tr>
<th>Control (no immunotherapy)</th>
<th>Immunotherapy (no platinum)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chemotherapy ± anti-PD-1</strong></td>
<td><strong>20%</strong></td>
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<td>Paclitaxel Q1W x 12 + pembrolizumab Q3W x 4</td>
<td>AC Q3W x 4</td>
</tr>
<tr>
<td><strong>pCR = ypT0/is ypN0</strong></td>
<td><strong>60%</strong></td>
</tr>
</tbody>
</table>

Immunotherapy in TNBC: Adjuvant Setting

Immunotherapy in TNBC: Adjuvant Setting

BRAVE Protocol

TNBC → Neoadj Chemo → Surgery → pCR
40%

No pCR
60%

R

1

Placebo

Radiotherapy

2

Avelumab

Principle Investigator: Pierfranco Conte
Tumor foreignness
*Mutational load*

Absence of inhibitory tumor metabolism
*LDH, glucose utilization*

Tumor sensitivity to immune effector
*MHC expression, IFN-γ sensitivity*

Absence of soluble inhibitors
*IL-6, CRP*

General immune status
*Lymphocyte count*

Immune cell infiltration
*Intratumoral T cells*

Absence of checkpoints
*PD-L1*

**Optimal Immunogenicity**

CRP, C-reactive protein; IFN, interferon; IL, interleukin; LDH, lactate dehydrogenase
Triple-negative BC
Mutational load

Tumor sensitivity to immune effector
MHC expression, IFN-γ sensitivity

Limited tumor burden
LDH, glucose utilization

Early Breast Cancer?

Immune cell infiltration
Intratumoral T cells

Absence of soluble inhibitors
Less inflammation
IL-6, CRP

Immune competent patient
Lymphocyte count

Absence of T cell checkpoints
PD-L1

Immunootherapy in BC

High risk breast cancer

High TILs/immune activation signature/ PDL1+/ High TMB
- I-O as monotherapy or combination of I-O
- Add CT to enhance immunogenicity or STING, TIGIT, RT

Low TILs/immune activation signature-/PDL1-
- High TMB
- Low TMB
- No I-O
Conclusions

• Is there a rationale for immune-based therapy in BC? YES
• Evidence from clinical data? LIMITED
• Can you enhance immunogenicity? YES
• Which the most promising setting? EBC or 1st-Line MBC
Thank You

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giuseppe.curigliano@ieo.it