ESMO Preceptorship 2016
Zurich
Breast Cancer

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Breast Cancer Program
Division of Early Drug Development
Istituto Europeo di Oncologia
• Rational for immune-based therapy in BC
• How to enhance immunogenicity?
• Evidences from clinical data
• How to monitor and to predict response?
## TILs in EBC

<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>Loi (JCO, 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 (AnnOnc, 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 (JCO, 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 (AnnOnc, 2014)</td>
<td>278</td>
<td>MFS OS</td>
<td>TNBC</td>
<td></td>
<td>HR:0.86 (0.77 -0.96) HR:0.86 (0.77 -0.97)</td>
</tr>
<tr>
<td>Denkert (JCO 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>
Mutational load of breast cancer

Budczies J et al. The Journal of Pathology: Clinical Research, 2015, Volume 1, Issue 4, pages 225-238,
Classical pathology and mutational load of breast cancer – integration of two worlds

Budczies J et al. The Journal of Pathology: Clinical Research, 2015, Volume 1, Issue 4, pages 225-238,
We mined copy number variation, exome, and RNA-seq data from the The Cancer Genome Atlas (TCGA) breast cancer dataset. By using RNA-seq data from 1004 breast cancer samples, we defined 4 immune phenotypes (e.g., Immunologic Constant of Rejection (ICR) ICR1, ICR3, ICR3, and ICR4) characterized by progressive expression of immune-related genes previously associated with immune-mediated rejection.

G. Curigliano et al. 2016, submitted
Top 21 deferentially expressed pathways between ICR 1 and ICR 4

G. Curigliano et al. 2016, submitted
The Th-1 phenotype (ICR4), which also displays the upregulation of immune-regulatory transcripts such as PDL1, PD1, FOXP3, IDO1, and CTLA4, was associated with prolonged survival. We validated these findings in a large meta-cohort of two thousand breast cancer gene expression data.

G. Curigliano et al. 2016, submitted
Survival and immune phenotypes

A.

\[ p = 0.00142, \quad HR = 3.48 (1.54-7.87) \]

\[ p = 0.0222 \]

\[ p = 0.00457, \quad HR = 2.88 (1.34-6.19) \]

\[ p = 0.00668, \quad HR (95\%) = 1.62 (1.14-2.31) \]

\[ p = 0.000474, \quad HR (95\%) = 1.81 (1.32-2.49) \]

B.

\[ p = 0.00668, \quad HR (95\%) = 1.62 (1.14-2.31) \]

\[ p = 0.000474 \]

\[ p = 0.000204, \quad HR (95\%) = 1.81 (1.32-2.49) \]
The number of non-silent or total mutations progressively decreased from ICR4 to ICR1, with a strong interaction with intrinsic molecular subtypes. No differences were observed among ICRs regarding the proportion of somatic mutations yielding predicted neoantigens. TP53 mutations were enriched in the immune favorable phenotype (ICR4).

G. Curigliano et al. 2016, submitted
Specific somatic mutations and immunophenotypes according to intrinsic molecular subtypes
Mutational load, neoepitope load, and immune phenotypes.

G. Curigliano et al. 2016, submitted
Mutational load, neoepitope load, and immune phenotypes.

G. Curigliano et al. 2016, submitted
Phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer

G. Curigliano et al. 2016
Endpoints

- **Primary:**
  Safety

- **Secondary:**
  Humoral immunogenicity
  Cell-mediated immunogenicity
  Impact of escalating doses of HER2

G. Curigliano et al. 2016
<table>
<thead>
<tr>
<th>Cohorts</th>
<th>N</th>
<th>Dose</th>
<th>(Route: IM)</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>15</td>
<td>20 µg dHER2/AS15</td>
<td>D 0, 14, 28, 42</td>
<td>(70 &amp; 98)</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>15</td>
<td>100 µg dHER2/AS15</td>
<td>D 0, 14, 28, 42</td>
<td>(70 &amp; 98)</td>
</tr>
<tr>
<td>Cohort 3</td>
<td>15</td>
<td>500 µg dHER2/AS15</td>
<td>D 0, 14, 28, 42</td>
<td>(70 &amp; 98)</td>
</tr>
<tr>
<td>Cohort 4</td>
<td>16</td>
<td>500 µg</td>
<td>W 0, 4, 14, 34, 38</td>
<td></td>
</tr>
</tbody>
</table>
Study design: Treatment

<table>
<thead>
<tr>
<th>PBMC</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ab</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>MUGA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Immunogenicity

Cohort 3 (500 µg)

Cohort 2 (100 µg)

Cohort 1 (20 µg)

G. Curigliano et al. 2016
Responders anti ECD and anti ICD

G. Curigliano et al. 2016
d-HER2 induces antibodies that specifically bind the native HER2 receptor

- The ECD binding ratio seems to increase with the dose of HER2 protein when assessed after the administration of four dHER2 + AS15 doses.

G. Curigliano et al. 2016
## How to enhance immunogenicity?

<table>
<thead>
<tr>
<th>DRUG</th>
<th>EFFECT ON IMMUNE SYSTEM</th>
</tr>
</thead>
</table>
| Doxorubicin     | Induces immunogenic cell death  
|                 | Increases proliferation of CD8 T cells  
|                 | Stimulates antigen presentation by DCs  
|                 | Stimulates MCP1 and M6PR                                                                  |
| Cyclophosphamide| Induces immunogenic cell death  
|                 | Suppressed Treg inhibitory functions and restoration of the proliferative capacity of effector T cells and NK cell cytotoxicity. |
| Taxanes         | Enhance T cell and NK cell function  
|                 | Increase recruitment of TIL  
|                 | Increase efficacy of immuno-stimulatory agents                                             |
| Gemcitabine     | Reduce the number of myeloid suppressor cells  
|                 | Increase the antitumor activity of CD8(+) T cells and activated NK cells                    |
| Oxaliplatin     | Induces immunogenic cell death  
|                 | Increases MHC I complex  
|                 | Inhibits PDL2                                                                             |
β-catenin signalling prevents anti-tumour immunity

Evidence from clinical trials

**Pembrolizumab** (Merck)
Humanized IgG4 anti-PD-1 antibody

**MPDL3280** (Genentech)
engineered human IgG1 anti-PD-L1 antibody
Pembrolizumab in TNBC

- **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 ≥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.*
Pembrolizumab in TNBC

n = 32

- Confirmed complete response (nodal disease)
- Confirmed partial response
- Stable disease
- Progressive disease

Objective response rate: 18.5%
Stable disease: 25.9%

Nanda, SABCS 2015
Pembrolizumab in TNBC

- Median follow-up duration: 9.9 months (range, 0.4-15.1)
- Median time to response: 18 weeks (range, 7-32)
- Median duration of response\(^a\): not reached (range, 15 to 40+ weeks)
- PFS 1.9 ms; 6 ms PFS - 23%

\(^a\)Kaplan-Meier estimate.
Analysis cut-off date: November 10, 2014.
Atezolizumab in ER+ BC

Patients Screened for Tumor PD-L1 Expression in the ER+/HER2- Breast Cancer Cohort

Nonevaluable
- Inadequate tissue sample (n = 13)

Samples Evaluable for PD-L1
n = 248

PD-L1–Positive Tumors
n = 48

Patients Treated as of July 1, 2015
N = 25

19.4% PD-L1+

Data cutoff date: July 1, 2015.

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### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 25</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>53.0 (36–79)</td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>16  (64)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>4   (16)</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>1   (4)</td>
<td></td>
</tr>
<tr>
<td>Not specified</td>
<td>4   (16)</td>
<td></td>
</tr>
<tr>
<td>ECOG performance status</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13  (52)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11  (44)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1   (4)</td>
<td></td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>10  (40)</td>
<td></td>
</tr>
<tr>
<td>Prior (neo)adjuvant therapy</td>
<td>17  (68)</td>
<td></td>
</tr>
</tbody>
</table>

- No. of lines of prior therapy for metastatic disease

<table>
<thead>
<tr>
<th>No.</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2 (8)</td>
</tr>
<tr>
<td>1</td>
<td>1 (4)</td>
</tr>
<tr>
<td>2</td>
<td>2 (8)</td>
</tr>
<tr>
<td>3</td>
<td>4 (16)</td>
</tr>
<tr>
<td>4</td>
<td>5 (20)</td>
</tr>
<tr>
<td>≥5</td>
<td>11 (44)</td>
</tr>
</tbody>
</table>

- Type of prior therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy</td>
<td>25 (100)</td>
</tr>
<tr>
<td>Hormonal therapy</td>
<td>22 (88)</td>
</tr>
<tr>
<td>Other investigational therapy</td>
<td>6 (24)</td>
</tr>
</tbody>
</table>

*Patients could have received ≥1 type of prior therapy. †Not all prior therapies are listed.

Data cutoff date: July 1, 2015.

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Antitumor Activity (N = 25)  
(RECIST v1.1, Investigator Review)

<table>
<thead>
<tr>
<th></th>
<th>n (%)</th>
<th>95 % CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Complete response</td>
<td>0 (0.0)</td>
<td>0.0-13.7</td>
</tr>
<tr>
<td>Partial response&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
<tr>
<td>Stable disease</td>
<td>4 (16.0)</td>
<td>4.5-36.1</td>
</tr>
<tr>
<td>Clinical benefit rate&lt;sup&gt;b&lt;/sup&gt;</td>
<td>5 (20.0)</td>
<td>6.8-40.7</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>15 (60.0)</td>
<td>38.7-78.9</td>
</tr>
<tr>
<td>No assessment&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3 (12.0)</td>
<td>2.5-31.2</td>
</tr>
</tbody>
</table>

In the 22 patients with at least one scan after baseline, ORR was 14% and CBR was 23%

<sup>a</sup>All patients with a partial response received ≥3 lines of therapy in the metastatic setting.  
<sup>b</sup>Complete response + partial response + stable disease for ≥24 weeks.  
<sup>c</sup>No assessment signifies patients who discontinued therapy before the first post-baseline scan. Data cutoff date: July 1, 2015.
Atezolizumab in ER+ BC

Change From Baseline in Target Lesion Size
(RECIST v1.1, Investigator Review)

Only patients with ≥1 evaluable postbaseline tumor assessment are included (n = 12). Data are presented for 20 patients; 2 patients were excluded due to non-evaluable postbaseline lesions.

Data cutoff date: July 1, 2015.

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Atezolizumab in ER+ BC

Treatment Exposure and Response Duration
(RECIST v1.1, Investigator Review)

- All 3 responders remain on study treatment for ≥26 weeks at time of data cutoff
- Median time to response: 8.0 weeks (range, 7.6-8.7)
- Median duration of response: not reached (range, 8.7+ to 44.3+ weeks)
- Median duration of SD: 16.0 weeks (range, 13.1+ to 24.0)

Ear length is equivalent to the time to the last imaging assessment. Includes patients with ≥1 postbaseline tumor assessment (n = 22).
Data cutoff date: July 1, 2015.

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### Phase Ib Study of 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><strong>Confirmed ORR (95% CI)</strong>&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><strong>ORR (95% CI)</strong>&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+

---

<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.

Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

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

## Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

### Table: Treatment Response by IC Status

<table>
<thead>
<tr>
<th>IC Status</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
Phase Ib Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- Proliferating activated CD8+ T cells transiently peaked at the end of the first cycle of atezolizumab treatment

Phase III Study of Atezolizumab and Nab-Paclitaxel in mTNBC

- Randomized, double-blind, placebo-controlled Phase 3 trial of nab-paclitaxel ± atezolizumab as 1st 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 pts

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

Secondary endpoints:
- OS
- ORR
- Response duration
- Safety/tolerability
- PK
- HR QoL

Emens et al. SABCS 2015 (abstract OT1-01-06)
Immunotherapy in TNBC

**Nivolumab**
(BMS)
Human IgG4 anti-PD-1 antibody

**Pembrolizumab**
(Merck)
Humanized IgG4 anti-PD-1 antibody

**MPDL3280**
(Genentech)
Engineered human IgG1 anti-PD-L1 antibody

**Tremelimimab**
(AZ)
Human IgG2 Anti-CTLA-4 antibody

**MEDI4736**
(AZ)
Human IgG1 anti-PD-L1 antibody
**Immunotherapy in TNBC**

<table>
<thead>
<tr>
<th>Phase</th>
<th>Setting</th>
<th>Subtype</th>
<th>PD-L1 expression as inclusion criteria</th>
<th>Combination/comparator</th>
<th>Primary EP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>Il</td>
<td>Metastatic</td>
<td>TN</td>
<td>No</td>
<td>Monotherapy after induction with RT and CT</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Il</td>
<td>Metastatic</td>
<td>IBC</td>
<td>HER2-</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Ib/II</td>
<td>Metastatic</td>
<td>TN</td>
<td>No</td>
<td>+ eribulin</td>
</tr>
<tr>
<td></td>
<td>Il</td>
<td>Metastatic</td>
<td>TN</td>
<td>Cohort B (positive)</td>
<td>Cohort C (strong)</td>
</tr>
<tr>
<td></td>
<td>Il</td>
<td>Metastatic</td>
<td>LABC</td>
<td>HER2+</td>
<td>Presence of PD-L1 expression</td>
</tr>
<tr>
<td></td>
<td>Il/II</td>
<td>Metastatic</td>
<td>HR+</td>
<td>No</td>
<td>+ Tamoxifen + Vorinostat</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Il/II</td>
<td>Metastatic</td>
<td>TN</td>
<td>No</td>
<td>+ nabpaclitaxel vs nabpaclitaxel</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Il</td>
<td>Metastatic</td>
<td>HER2-</td>
<td>No</td>
<td>+ tremelimumab (AZ)</td>
</tr>
</tbody>
</table>
# Immunotherapy in TNBC: neoadjuvant setting

## Neoadjuvant setting

<table>
<thead>
<tr>
<th>Trial ID</th>
<th>Phase</th>
<th>Treatment Description</th>
<th>Status</th>
<th>Drugs</th>
<th>Sponsor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02622074</td>
<td>1</td>
<td>PD-1 blockade plus chemotherapy as neoadjuvant treatment for TNBC</td>
<td>Not yet opened</td>
<td>Pembrolizumab, Nab-paclitaxel, Anthracycline, Cyclophosphamide, Carboplatin</td>
<td>Merck Sharp &amp; Dohme Corp.</td>
</tr>
<tr>
<td>NCT02489448</td>
<td>1/2</td>
<td>Anti PD-L1 therapy plus Nab-Paclitaxel and dose-dense AC as neoadjuvant treatment for Stage I-III Triple Negative Breast Cancer</td>
<td>Recruiting</td>
<td>MEDI4736, Nab-Paclitaxel, Doxorubicin, Cyclophosphamide</td>
<td>Yale University</td>
</tr>
</tbody>
</table>
Immunotherapy in TNBC: neoadjuvant setting

N=272

Primary endpoint: EFS
Secondary endpoint: pCR (ypT0-ypTis ypN0)

Nab-Paclitaxel 125 mg/m²
+ CBDCA AUC2

+/- ATEZOLIZUMAB 1200 mg

surgery

Nab-Paclitaxel 125 mg/m²
+ CBDCA AUC2
Immunotherapy in TNBC: neoadjuvant setting

N=174

Primary endpoint: pCR (ypT0 ypN0)

- Nab-Paclitaxel
  - Nab-P 125 mg/m²
  - Epirubicin 90 mg/m² + Cyclophosphamide 600 mg/m²

- EC
  - MEDI 4736/Durvalumab 2g total q4w

Window of opportunity 2 weeks

surgery
## Adaptive Phase II Randomized Non-comparative Trial of Nivolumab After Induction Treatment in Triple-negative Breast Cancer (TNBC) Patients: TONIC-trial (The Netherlands Cancer Institute)

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Assigned intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active Comparator: Radiation therapy</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>Radiation therapy on metastatic lesion</td>
<td>Radiation: Radiation therapy 20 Gy to metastatic lesion</td>
</tr>
<tr>
<td>Active Comparator: Low dose doxorubicin 15 mg flat dose, once weekly for 2 weeks</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>Low dose doxorubicin</td>
<td>Low dose doxorubicin</td>
</tr>
<tr>
<td>Active Comparator: Cyclophosphamide metronomic schedule, 50 mg daily orally for 2 weeks</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>Metronomics CTX</td>
<td>Metronomics CTX</td>
</tr>
<tr>
<td>Active Comparator: Cisplatin 40 mg/m2, weekly for 2 weeks</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
<tr>
<td>Weekly cisplatin</td>
<td>Weekly cisplatin</td>
</tr>
<tr>
<td>Active Comparator: No induction treatment</td>
<td>Nivolumab 3 mg/kg, every 2 weeks after induction treatment</td>
</tr>
</tbody>
</table>
Targeting stroma and inflammation

- PD-L1 positivity: Stratification factor
- Treatment: metronomic CT plus pembrolizumab
- Response assessment: Performed every 8 weeks per RECIST v1.1

PI G. Curigliano et al.
Predicting immune-response

Predicting response

- Immune cells function in an interacting hierarchy that coordinates the activities of various cell types according to genetic and environmental contexts.
- Development of a graphical approaches to construct an extensible immune reference map from mass cytometry data of cells from different organs.
- The maps recapitulated canonical cellular phenotypes and revealed reproducible, tissue-specific deviations.
Democratizing systems immunology with modular transcriptional repertoire analyses

Conclusions

• Is there a rational for immune-based therapy in BC?  YES
• Evidences from clinical data?  LIMITED
• Can you enhance immunogenicity?  MAY BE
• Can we monitor and to predict response?  NO, BUT...
Challenges

• Predicting responsive patients by modular transcriptional repertoire analysis
• Tissue and blood biomarkers for combination immunotherapies
• Role of microbiome and modulation of microbiome
• Managing combination-associated toxicity
Thank you