Breast Cancer New Horizons in the Era of Immunotherapy

Javier Cortes,
Ramon y Cajal University Hospital, Madrid, Spain
Vall d’Hebron Institute of Oncology (VHIO),
Medica Scientia Innovation Research (MedSIR)
Barcelona, Spain
The Transformative Impact of Immunotherapy in Cancer Medicine

The interplay between immune system and cancer is complex. Cancer complexity Immune system complexity

The genetic... non-self signals which can be targeted by the immune system to control malignancies (necessary but not sufficient).
The Transformative Impact of Immunotherapy in Cancer Medicine

Why immunotherapy?

T cells:
1. Have exquisite specificity
2. Adapt to antigenic changes
3. Develop memory

Which leads to:
1. Durable clinical benefit
2. Improved overall survival

- Chemotherapy
- Genomically targeted therapy
- Immune checkpoint therapy
- Combination with genomically targeted agent and immune checkpoint therapy
Cancer and Immunity

Active Immune system (Host Immunity)
- TILs
- Activation Status
  - Activators
  - Inhibitors (Checkpoints)

Immune Targets (Neoantigens)
- Mutations

Somatic mutations in cancers

Breast Cancer and mutations: Lower median rate detected compared to the most immune-sensitive cancers but wide range of mutations detected

Alexandrov L,B. Nature 2013
Mutational rates in breast cancer

Classical pathology and mutational load of breast cancer – integration of two worlds
Tumor Mutational Burden & TIL correlation

A. Number of single nucleotide variants per exome by PAM50 subtype in TCGA breast cancers

- Luminal A
- Luminal B
- HER2E
- Basal-like

B. % stromal TILs by PAM50 subtype in TCGA breast cancers

- Luminal A
- Luminal B
- HER2E
- Basal-like

p < 0.001 **
Immune microenvironment in breast cancer
No tumor-infiltrating lymphocytes (TILs)

Tumor-infiltrating lymphocytes in the stroma (stromal TILS)

Low probability to respond to CIT

High probability to respond to CIT

Courtesy C Denkert
Predefined parameters for TILs evaluation

**Intratumoral TILs** = direct contact to tumor cells

**Stromal TILs** = between the tumor cells

**LPBC = Lymphocyte-predominant breast cancer**

"more lymphocytes than tumor cells"

(≥60% TILs /≥50% TILs)
TILs in breast cancer subtypes

Immune factors and pCR in breast cancer: GeparSixto Trial

Higher number of TILs associated better response to chemotherapy

TNBC or HER2+ (n=580)
Neoadjuvant treatment with paclitaxel q1wk NPLD q1wk +/- carboplatin q1wk

Lymphocyte predominant
24%

Non lymphocyte predominant
76%

TILs associated with higher pCR
OR 2.92 (1.98–4.31; p<0.001)

Benefit of carboplatin linked with TILs
LPBC, OR 3.71 non-LPBCs, OR 1.01

Test for interaction p=0.002

pCR rate (%)
0 20 40 60 80

N= 580 438 142

All patients
PM therapy
PMCb therapy

All tumours Non-LPBC LPBC

Neoadjuvant response is also continuously increased with TILs

STEPP Analyse in GeparSixto  
$p$CR Rate 70%  
$n=580$

![Histology Image](image)  
Courtesy C Denkert
Results (GeparSixto): mRNA analysis

Three different immune subtypes: correlation with response rate

Denkert, et al. JCO 2015
- Immunomodulatory TNBC subtype represents high TILs
Higher TILs = better survival in primary TNBC

Post-neoadjuvant setting in TNBC

Dieci et al, AoO 2014; Loi et al, JCO 2013; AoO 2014
Immune scenarios & Strategies for Breast Cancer

- Pre-existing tumours
  - “inflamed” or “hot” tumours
  - PD-L1/checkpoints
  - CD8 T cells/IFNγ
  - Mutational load
  - TILs

- Excluded infiltrate
  - Angiogenesis, MDSCs,
  - Reactive stroma,
  - Mutational load

- Immune ignorant
  - “cold tumours”
  - Low T cells,
  - Low MHC class I,
  - Proliferating tumours

- Single agent immune checkpoint inhibitors

- Priming & activation
  - (e.g. CTLA-4, OX40)

- Influence infiltration?
  - (e.g. VEGF, MEKi)

- Priming, activation & infiltration
  - Neoantigen expression?
  - (e.g. epigenetic modulation)

TILs – linked with CD8 T cells/IFNγ, PDL1/checkpoints
Promoting the immunogenicity of missed antigens

Radiotherapy & the Abscopal effect
Converting tumors from low TILs into high TILs
The Abscopal effect in breast cancer

- Proof-of-concept trial
- Included patients with stable or progressing metastatic solid tumors (≥3 measurable lesions) on single-agent chemotherapy or hormone therapy
- Simon two-stage design: ≥1 abscopal response in first 10 patients (stage 1)

Converting tumors from low TILs into high TILs
The Abscopal effect in breast cancer

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>No of pts</th>
<th>No of pts completing tx</th>
<th>Pts not assessable</th>
<th>Pts assessable for best abscopal response</th>
<th>Pts assessable for best abscopal response who completed tx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PD</td>
<td>SD</td>
</tr>
<tr>
<td>NSCLC</td>
<td>18 (44%)</td>
<td>13 (32%)</td>
<td>2 (5%)</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>14 (34%)</td>
<td>11 (27%)</td>
<td>1 (2%)</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Thymic cancer</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urothelial cancer</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>2 (5%)</td>
<td>0</td>
<td>1 (2%)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Eccrine cancer</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>SCLC</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>41 (100%)</td>
<td>30 (73%)</td>
<td>4 (10%)</td>
<td>5</td>
<td>21</td>
</tr>
</tbody>
</table>

Immunotherapy for breast cancer can target several steps in the cancer-immunity cycle:\(^1\)

1. Release of cancer cell antigens
2. Cancer antigen presentation (Vaccines:\(^2\))
3. Priming and activation
   - Anti-PDL1\(^{13}\)
   - Anti-PD1\(^{14}\)
   - Anti-CTLA4\(^{5,6}\)
   - Anti-OX40\(^7\)
   - Anti-41BB\(^8\)
4. Trafficking of T cells to tumours
5. Infiltration of T cells into tumours
6. Recognition of cancer cells by T cells
   - Adoptive T-cell therapy (e.g. CARs):\(^9-12\)
7. Killing of cancer cells
   - Anti-PDL1\(^{13}\)
   - Anti-PD1\(^{14}\)
   - Anti-LAG3\(^{13}\)
   - Anti-KIR\(^{14}\)
   - IDO inhibition\(^{15}\)
   - ADCC-inducing antibodies\(^{16}\)

---

Checkpoint inhibition: balance between inhibitory and stimulatory receptors dictates T cell priming

T cell targets for modulating activity

Activating Receptors
CD28
OX40
GITR
CD137
CD27
HVEM

Inhibitory Receptors
CTLA-4
PD-1
TIM-3
BTLA
VISTA
LAG-3

Agonistic Antibodies

Blocking Antibodies

T cell stimulation

Mellman et al. Nature 2011
TNBC is a potential target for immunotherapy based on immunogenicity and unmet clinical need

The immunogenic characteristics of TNBC make it a potential target for immunotherapy

- The high mutation rate of TNBC may produce tumour-specific antigens that can induce an immune response\(^1\)
- TNBC shows T cell infiltration, an essential precursor to an anti-tumour immune response\(^2-4\)
- PD-L1 expressed on TNBC can suppress the immune response, and is a potential therapeutic target\(^5,6\)

There is a significant unmet clinical need in metastatic TNBC

- Outcomes with metastatic TNBC are poor\(^7-9\)
- Bevacizumab, given in combination with taxane chemotherapy, is the only recognised 1L targeted therapy\(^10,11\)
- Treatment options beyond bevacizumab plus taxane are limited to cytotoxic chemotherapy alone\(^10,11\)

Targeting PD-L1 and PD-1

**Anti-PDL1**

Targeting PD-L1 can block co-inhibitory signalling between the tumour cell and both PD-1 and B7.1, preventing down-regulation of T-cell activity\(^1,2,3\).

Preserves PD-L2/PD-1 interaction, minimising effects on immune homeostasis. This interaction may contribute to the prevention of autoimmune responses, particularly in the lung\(^1\).

**Anti-PD1**

Targeting of PD-1 blocks co-inhibitory signalling between the tumour cell and PD-1, sparing the interaction between the tumour cell and B7.1\(^1,2,3\).

Blocks PD-L2/PD-1 interactions involved in immune homeostasis, potentially increasing autoimmunity\(^1,4\).

---

# Anti-PDL1/PD1 therapeutics currently in development in breast cancer

<table>
<thead>
<tr>
<th>Therapeutic</th>
<th>Lead company</th>
<th>Antibody type</th>
<th>Phase and condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-PDL1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Roche</td>
<td>Engineered IgG1 (no ADCC)¹</td>
<td>TNBC (phase III)</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>AstraZeneca</td>
<td>Modified IgG1 (no ADCC)²</td>
<td>TNBC and HER2-positive (phase I/II)</td>
</tr>
<tr>
<td>Anti-PD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Bristol-Myers Squibb</td>
<td>IgG4³</td>
<td>TNBC (phase II) and HER2-negative (phase I)</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>Merck &amp; Co</td>
<td>IgG4 (humanised)⁴</td>
<td>TNBC, inflammatory and ER-positive (phase II), and HER2-positive (phase I/II)</td>
</tr>
</tbody>
</table>

Atezolizumab in TNBC

Ongoing Phase Ia Study

- Target Population: TNBC in a Phase Ia study expansion cohort
  - Measurable disease per RECIST v1.1
  - The TNBC cohort initially enrolled PD-L1–selected patients and was later expanded to include all-comers
- Treatment: atezolizumab IV q3w at 15 or 20 mg/kg or 1200-mg flat dose
- Duration:
  - Initially, patients received up to 16 cycles (or ≤ 1 year)
  - Later, protocol amendments allowed for:
    - Newly enrolled patients to be treated past PD until loss of clinical benefit per investigator
- Objectives:
  - Primary endpoint: safety
  - Key secondary endpoints: ORR, DOR and PFS (per RECIST v1.1 and irRC)
  - Key exploratory endpoints: OS and biomarkers of clinical activity

Schmid P, et al. AACR 2017
# Atezolizumab in TNBC

## Baseline Characteristics

<table>
<thead>
<tr>
<th>Patients (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range)</strong></td>
</tr>
<tr>
<td>**ECOG PS, 0</td>
</tr>
<tr>
<td><strong>Visceral metastatic sites</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Bone metastatic sites</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>PD-L1 status on IC</strong>&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>IC0/1 (&lt; 5%)</td>
</tr>
<tr>
<td>IC2/3 (≥ 5%)</td>
</tr>
<tr>
<td><strong>Median prior systemic therapies (range)</strong>&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anthracycline</td>
</tr>
<tr>
<td>Platinum</td>
</tr>
<tr>
<td><strong>Current line of therapy</strong>&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

- Prior to receiving atezolizumab, most patients were heavily pretreated.

---

<sup>a</sup> Includes lung, liver, adrenal and pelvis metastatic sites.  
<sup>b</sup> Includes bone and other sites.  
<sup>c</sup> Four patients (4%) had unknown IC status.  
<sup>d</sup> Refers to all treatment settings.  
<sup>e</sup> Refers to treatment in metastatic setting only. Data cutoff: March 31, 2016.

---

## Safety-Evaluable Patients

Received ≥ 1 dose of atezolizumab (N = 115)

## Efficacy-Evaluable Patients

Had ≥ 12 weeks of follow-up (n = 113)

## Objective Response—Evaluable Patients (n = 112)

- At data cutoff, median treatment duration was 2.1 mo (range, 0.0 to 36.6)  
  - Median of 4 cycles (range, 1 to 45)
The majority of treatment-related AEs were Grade 1-2
- All individual Grade 3-4 AEs occurred at 1%, except anemia at 2%
- Two related Grade 4 AEs occurred: hyperglycemia and pneumonitis
- Two related Grade 5 AEs occurred: pulmonary hypertension and death NOS in a hospitalized patient

Grade 3-4 AEs of special interest included Grade 3 pruritic rash, lichen planus, increased blood bilirubin and adrenal insufficiency and Grade 4 pneumonitis (as specified above)

---

### Treatment-Related AE (N = 115)

<table>
<thead>
<tr>
<th>AE Category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>63%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>11%</td>
</tr>
<tr>
<td>Grade 5</td>
<td>2%</td>
</tr>
<tr>
<td>AE leading to treatment withdrawal</td>
<td>3%</td>
</tr>
<tr>
<td>AE leading to dose interruption</td>
<td>10%</td>
</tr>
</tbody>
</table>

AE, adverse event; NOS, not otherwise specified. Data cutoff: March 31, 2016.

---

### Treatment-Related AEs in ≥ 10 patients (all grade) or ≥ 2 patients (G3-4)

![Graph showing frequency of treatment-related AEs](image)

Schmid P, et al. AACR 2017
Objective Response and Stable Disease Rate (by Subgroups)

- Numerically higher ORRs were observed in IC2/3 and 1L subgroups.
- irRC criteria captured non-classical responses to atezolizumab.
- Best response of SD were also observed:
  - DCR$^b$ per RECIST v1.1 was 23% in all patients.
    - 27% in IC2/3 patients.
    - 16% in IC0/1 patients.

DCR, disease control rate. $^a$ Objective response—evaluable patients. Four patients had unknown PD-L1 status. $^b$ Defined as CR + PR + SD = 3 months. Confirmed, investigator-assessed responses are plotted. Patients with missing or unreviewable responses are included (16 per RECIST v1.1 and 23 per irRC). Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Change in Tumor Burden On Study

All Response-Evaluable Patients

**RECIST v1.1 Response**

- PR/CR (n = 11)
- SD (n = 15)
- PD (n = 66)
- NE (n = 1)
- Discontinued
- New Lesion
- > 100%

Clinical benefit was observed in some patients with RECIST v1.1 SD or PD status.

**Overall TNBC cohort**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Median DOR (range)</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST v1.1</td>
<td>21.1 mo (2.8 to 26.5+)</td>
<td>1.4 mo (1.3, 1.6)</td>
</tr>
<tr>
<td>irRC</td>
<td>21.1 mo (2.8 to 33.9+)</td>
<td>1.9 mo (1.4, 2.6)</td>
</tr>
</tbody>
</table>

irPR, PR per irRC; SLD, sum of target lesion longest diameter. * Re-treatment period not plotted.

Confirmed, investigator-assessed RECIST responses are included for patients with post-baseline tumor measurements. Data cutoff: March 31, 2016.

Schmid P., et al. AACR-2017
Change in Tumor Burden On Study

Patients With RECIST v1.1 Response or Stable Disease or irRC Response

RECIST v1.1 Response

- Clinical benefit was observed in some patients with RECIST v1.1 SD or PD status

Overall TNBC cohort

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Median DOR (range)</th>
<th>Median PFS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RECIST v1.1</td>
<td>21.1 mo (2.8 to 26.5+)</td>
<td>1.4 mo (1.3, 1.6)</td>
</tr>
<tr>
<td>irRC</td>
<td>21.1 mo (2.8 to 33.9+)</td>
<td>1.9 mo (1.4, 2.6)</td>
</tr>
</tbody>
</table>

irPR, PR per irRC; SLD, sum of target lesion longest diameter. * Re-treatment period not plotted.
Confirmed, investigator-assessed RECIST responses are included for patients with post-baseline tumor measurements. Data cutoff: March 31, 2016.

Schmid P, et al. AACR 2017
Overall Survival by Response Status (RECIST v1.1 and irRC)

- Median OS was 9.3 mo (95% CI: 7.0, 12.6) in all patients (median follow-up, 15.2 mo)\(^a\)
  - Landmark OS rates (95% CI) were: 41% (31, 51) at 1 year, and 22% (12, 32) at both 2 and 3 years

### RECIST v1.1 Criteria

- 1-y OS: 100%
- 2-y OS: 100%
- 1-y OS: 69%
- 2-y OS: 11%
- 3-y OS: 11%

### irRC Criteria

- 1-y OS: 100%
- 2-y OS: 100%
- 3-y OS: 100%
- 1-y OS: 51%
- 2-y OS: 33%

#### Pseudo-progression was observed in patients with RECIST PD and long-term OS

\(^a\) Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients. \(^b\) Patients included in the Kaplan-Meier plots were alive for ≥ 6 weeks. Data cutoff: March 31, 2016.
Longer OS was observed in patients with higher PD-L1 IC status.

* Four patients had unknown PD-L1 status. Median survival follow-up (range) was 15.2 mo (0.4+ to 36.7) in all patients, 17.0 mo (0.43+ to 36.7) in IC2/3 patients and 12.8 mo (0.8+ to 16.9) in IC0/1 patients. Data cutoff: March 31, 2016.
Biomarker Analysis: Tumor-Infiltrating Lymphocytes

- Median TIL infiltration (% tumor area) in tumors from enrolled patients defined the cutoff used for analysis.

**Response and Stable Disease Based on TIL Levels**

- **ORR + SD Rate**
  - **RECIST v1.1**
    - SD: 7%, 19%, 21%
    - CR/PR: 13%, 9%, 13%
  - **irRC**
    - SD: 7%, 19%, 21%
    - CR/PR: 13%, 9%, 13%

- **No. At Risk:**
  - > 10% (n = 53)
  - ≤ 10% (n = 55)

**Overall Survival**

- OS Based on TIL Levels
  - **TIL Levels**
    - > 10% (n = 53)
    - ≤ 10% (n = 56)

- **P = 0.0028**

**Higher ORR and longer OS were seen with higher baseline TIL infiltration.**

**Similar results were observed with CD8 infiltration.**

*Samples unevaluable for TIL assessments (6 per RECIST v1.1 and 5 per irRC) are not included. Objective response–evaluable population includes patients with unevaluable response assessments (16 per RECIST v1.1 and 23 per irRC). Log-rank (Mantel-Cox) P value is exploratory. Data cutoff: March 31, 2016.*

Schmid P, et al. AACR 2017
Combining immunotherapy and conventional therapy

![Graph showing survival over time for chemotherapy, genomically targeted therapy, immune checkpoint therapy, and immunotherapy combination.]
Combination of Immunotherapy and Chemotherapy

Synergistic effect of chemotherapy and anti-PD-L1 treatment in vivo

Platinum or taxane therapy increased the number of tumor-infiltrating CD8+ T cells

- Increased tumor PD-L1 expression/infiltration of CD8+ T cells have been observed with serial biopsies in patients treated with atezolizumab + chemo

- High response rates and durable responses have been observed with atezolizumab plus chemotherapy in NSCLC

Adapted from Adams S, et al. SABCS 2015
Combination of Immune-and Chemotherapy in TNBC

Results

**BOR per RECIST v1.1 by line of therapy**

- 32 pts were evaluable for response
  - Median age (range): 55.5 y (32-84)
  - ECOG PS 1: 81%
  - Median no. (range) of prior systemic cancer therapies: 5 (1-10)
  - Prior taxane use: 88%

<table>
<thead>
<tr>
<th>BOR</th>
<th>1L n = 13</th>
<th>2L n = 9(^b)</th>
<th>3L+ n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed ORR (95% CI)(^a)</td>
<td>46% (19, 75)</td>
<td>22% (3, 60)</td>
<td>40% (12, 74)</td>
</tr>
<tr>
<td>CR</td>
<td>8%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>38%</td>
<td>22%</td>
<td>40%</td>
</tr>
<tr>
<td>SD</td>
<td>38%</td>
<td>67%</td>
<td>30%</td>
</tr>
<tr>
<td>PD</td>
<td>15%</td>
<td>0</td>
<td>30%</td>
</tr>
</tbody>
</table>

\(^a\) Confirmed ORR defined as ≥ 2 consecutive assessments of CR or PR.

\(^b\) One patient discontinued with clinical progression before first on-treatment tumor assessment.

Minimum efficacy follow up was ≥ 5 months

- Responses were seen in both patients with PD-L1-positive (IC1/2/3) and PD-L1-negative (IC0) tumors
- Baseline levels of tumor-infiltrating lymphocytes (TILs) showed a trend with increased ORR

Presented at: ASCO Annual Meeting '16

Slides are the property of the author. Permission required for reuse.

Adams, et al. ASCO 2016
Combination of Immune-and Chemotherapy in TNBC

Results

DOR\(^a\)

- Of 12 responders (38%), 6 remain on atezolizumab, 1 of whom has been on treatment for > 17 months
- PFS is not mature and median duration of response has not been reached
- 2 patients experienced decrease in tumor burden after an initial increase or the appearance of new lesions

\(^a\) Investigator-assessed confirmed objective response. Data cutoff date, Jan 14, 2016.

Presented at: ASCO ANNUAL MEETING ‘16

Adams, et al. ASCO 2016
Patient With Response to Atezolizumab/Nab-Paclitaxel

- Patient with TNBC that recurred in the liver within 5 months of completing neoadjuvant AC-T chemotherapy

- This patient experienced a complete metabolic response to atezolizumab/nab-paclitaxel after cycle 2 and an anatomic PR after cycle 4

Baseline  Post-cycle 2  Post-cycle 4

Atezolizumab: WO29522 phase III study TNBC

- **Atezolizumab**: 840mg flat dose given IV on Day 1 and Day 8 q4w
- **Placebo**: given IV on Day 1 and Day 8 q4w
- **Nab-paclitaxel**: 100mg/m² given IV on Days 1, 8 and 15 q4w

**Primary endpoint**: PFS

**Secondary endpoints**: OS (ITT and PD-L1-positive populations)
- ORR (ITT and PD-L1-positive populations)
- Duration of response (RECIST v1.1)
- Time to deterioration
- Safety and tolerability
Atezolizumab: NeoTrip – phase III study* neoadjuvant TNBC

- **Carboplatin**: AUC 2 given IV on day 1 and day 8 q3w
- **Nab-paclitaxel**: 125mg/m² given IV on day 1 and day 8 q3w
- **Atezolizumab**: 1,200mg IV infusion on day 1 q3w

**Primary endpoint**: 3 and 5 year EFS

- 5-year EFS in control arm is assumed to be 57%. Clinically meaningful improvement to increase the 5-year EFS to 72% (HR=0.584)

*Sponsored by Fondazione Michelangelo
**Phase III: randomised study of atezolizumab in 1L mTNBC in fast progressing patients (MO39193)**

**Key inclusion criteria:**
- Previously untreated inoperable locally advanced or metastatic TNBC
- Relapse during, or <12 months treatment
- Previous (neo)-adjuvant treatment and anthracycline
- Measurable disease

**Primary endpoint:**
- PFS

**Secondary endpoints:**
- ORR
- DoR
- CBR
- CBR
- PFS2
- 12m survival rate
- 18m survival rate
- QoL / PROs
- Safety

**1L metastatic TNBC**
N=392

R 1:1

Carboplatin/gemcitabine or capecitabine*

Carboplatin/gemcitabine or capecitabine* + atezolizumab

* 50%/50% split between chemotherapies

Physician’s choice of chemotherapy + atezolizumab

18 months minimum survival follow-up after enrolment
Combination of Immune-and Chemotherapy in TNBC

Eribulin + anti-PD-1 (pembrolizumab)

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

Tolaney, et al. SABCS 2016
Pembrolizumab single agent in TNBC

Study Design – KEYNOTE-086 Cohort A

**Patients**
- Age ≥18 y
- Centrally confirmed mTNBC
- ≥1 prior systemic treatment for mTNBC with documented PD on/after most recent therapy
- ECOG PS 0-1
- LDH <2.5 x ULN
- Tumor biopsy sample for TNBC status and PD-L1 evaluation
- No radiographic evidence of CNS metastases
- Measurable disease per RECIST v1.1 by central review

**Pembrolizumab**
- 200 mg IV Q3W for 2 years or until PD, intolerable toxicity, patient withdrawal, or investigator decision

**N = 170**

**Protocol-specified follow-up**

- Primary end points: ORR\(^b\) and safety
- Secondary end points\(^b\): DOR, DCR,\(^c\) PFS, OS

---

\(^a\)<1% tumor cells positive for ER and PR by IHC, irrespective of intensity, and HER2 IHC 0 or 1+ or FISH negative.\(^b\)Assessed in the total population and in the PD-L1-positive population.\(^c\)DCR = disease control rate = SD ≥24 wk + CR + PR.
## Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Total Population(^a) n = 170</th>
<th>PD-L1 Positive n = 105</th>
<th>PD-L1 Negative n = 64</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, median (range)</td>
<td>53.5 (28-85)</td>
<td>53.0 (30-85)</td>
<td>55.0 (28-80)</td>
</tr>
<tr>
<td>Female</td>
<td>170 (100)</td>
<td>105 (100)</td>
<td>64 (100)</td>
</tr>
<tr>
<td>Postmenopausal</td>
<td>140 (82.4)</td>
<td>85 (81.0)</td>
<td>54 (84.4)</td>
</tr>
<tr>
<td>ECOG PS 1</td>
<td>80 (47.1)</td>
<td>54 (51.4)</td>
<td>26 (40.6)</td>
</tr>
<tr>
<td>LDH &gt;1×ULN</td>
<td>87 (51.2)</td>
<td>51 (48.6)</td>
<td>36 (56.2)</td>
</tr>
<tr>
<td>Visceral ± nonvisceral disease</td>
<td>126 (74.1)</td>
<td>74 (70.4)</td>
<td>51 (79.7)</td>
</tr>
<tr>
<td>Prior taxanes and anthracycline</td>
<td>163 (95.9)</td>
<td>102 (97.1)</td>
<td>60 (93.8)</td>
</tr>
<tr>
<td>Prior (neo)adjuvant therapy</td>
<td>142 (83.5)</td>
<td>86 (81.9)</td>
<td>55 (85.9)</td>
</tr>
<tr>
<td>Prior lines of therapy for recurrent/metastatic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>53 (31.2)</td>
<td>36 (34.3)</td>
<td>17 (26.6)</td>
</tr>
<tr>
<td>2</td>
<td>43 (25.3)</td>
<td>27 (25.7)</td>
<td>15 (23.4)</td>
</tr>
<tr>
<td>≥3</td>
<td>74 (43.5)</td>
<td>42 (40.0)</td>
<td>32 (50.0)</td>
</tr>
</tbody>
</table>

\(^a\)Includes 1 patient with unknown PD-L1 status.

Data cutoff date: Nov 10, 2016.
# Best Overall Response
(RECIST v1.1, Central Review)

<table>
<thead>
<tr>
<th></th>
<th>Total Population a ( N = 170 )</th>
<th>PD-L1 Positive ( n = 105 )</th>
<th>PD-L1 Negative ( n = 64 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%) [95% CI]</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>DCR, b n (%) [95% CI]</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>Complete response</td>
<td>1 (0.6)</td>
<td>1 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (4.1)</td>
<td>4 (3.8)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>35 (20.6)</td>
<td>22 (21.0)</td>
<td>12 (18.8)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>103 (60.6)</td>
<td>66 (62.9)</td>
<td>37 (57.8)</td>
</tr>
<tr>
<td>Not evaluable, c</td>
<td>5 (2.9)</td>
<td>2 (1.9)</td>
<td>3 (4.7)</td>
</tr>
<tr>
<td>Not able to be assessed, d n (%)</td>
<td>19 (11.2)</td>
<td>10 (9.5)</td>
<td>9 (14.1)</td>
</tr>
</tbody>
</table>

---

a Includes the patient with unknown PD-L1 status. b DCR = disease control rate = SD ≥24 wk + CR + PR. c Patients who had ≥1 postbaseline tumor assessment, none of which were evaluable. d Patients who had no postbaseline tumor assessment because of death, withdrawal of consent, loss to follow-up, or start of new anticancer therapy. Data cutoff date: Nov 10, 2016.
Best Change From Baseline in Target Lesion Size, All Patients

Change From Baseline in Target Lesion Size, Patients With CR, PR, or SD at Any Time Point

-100 -80 -60 -40 -20 0 20 40 60 80 100
Change From Baseline, %

CR
PR
SD
PD
On therapy
Off therapy

Time, weeks
0 9 18 27 36 45 54 63

Left panel includes patients with ≥1 evaluable postbaseline assessment (n = 143). Right panel includes patients with CR, PR, and SD at any time point (n = 46). Response assessed per RECIST v1.1 by central review. Increases >100% truncated at 100%.

At the time of data cutoff (ie, Nov 20, 2016).
Kaplan-Meier Estimate of PFS
(RECIST v1.1, Central Review)

Events/Pts, n  Median (95% CI)
Total\textsuperscript{a} 148/170 2.0 mo (1.9-2.0)
PD-L1 positive 90/105 2.0 mo (1.9-2.1)
PD-L1 negative 57/64 1.9 mo (1.6-2.0)

\textsuperscript{a}Includes 1 patient with unknown PD-L1 status who experienced PD.
Data cutoff date: Nov 10, 2016.
Kaplan-Meier Estimate of OS

<table>
<thead>
<tr>
<th>Events/Pts, n</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>90/170</td>
</tr>
<tr>
<td>PD-L1 positive</td>
<td>58/105</td>
</tr>
<tr>
<td>PD-L1 negative</td>
<td>32/64</td>
</tr>
</tbody>
</table>

*Includes 1 patient with unknown PD-L1 status who was alive at data cutoff. Data cutoff date: Nov 10, 2016.
Overall Survival by Best Overall Response

Events/Pts, n | Median (95% CI)
--- | ---
CR or PR | 0/8 | Not reached (NR-NR)
SD | 6/35 | Not reached (12.7-NR)
PD | 66/103 | 7.1 mo (6.3-8.8)

Patients with response that was nonevaluable (n = 5) or not assessed (n = 19) per RECIST v1.1 by central review are not included. Data cutoff date: Nov 10, 2016.
Pembrolizumab Antitumor Activity in Previously Treated and Previously Untreated mTNBC

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

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

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

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

1. Adams S et al. ASCO Annual Meeting; Jun 2-6, 2017; Chicago, IL; abstr 1088; presented Sunday, Jun 4, from 8:00-11:30 am on poster board #80.
Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173

Schmid P, et al. ASCO 2017
Pembrolizumab (pembro) + chemotherapy (chemo) as neoadjuvant treatment for triple negative breast cancer (TNBC): Preliminary results from KEYNOTE-173

Figure 3. Pathologic Complete Response Rates in Cohorts A and B

<table>
<thead>
<tr>
<th>Cohort</th>
<th>pCR (ypT0 ypN0)</th>
<th>pCR (ypT0/Tis ypN0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>B</td>
<td>80%</td>
<td>80%</td>
</tr>
</tbody>
</table>

pCR, pathologic complete response.
Point estimates of pCR rates are shown with the corresponding exact 90% confidence intervals (CIs) based on the Clopper-Pearson method.

*1 patient had no residual tumor in the breast but declined to undergo axillary lymph node dissection and was therefore not evaluable for ypN status and was counted as a non-pCR.
Pembrolizumab plus standard neoadjuvant therapy for high-risk breast cancer (BC): Results from I-SPY 2

<table>
<thead>
<tr>
<th>Signature</th>
<th>Current raw data: pCR/n [total assigned]</th>
<th>Estimated pCR rate (95% prob interval) [equivalent n]</th>
<th>Prob pembro superior</th>
<th>Pred prob of success in phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pembro</td>
<td>Control</td>
<td>Pembro</td>
<td>Control</td>
</tr>
<tr>
<td>HR+/HER2−</td>
<td>7/25</td>
<td>13/88</td>
<td>34.2%</td>
<td>13.6%</td>
</tr>
<tr>
<td></td>
<td>(28.0%)</td>
<td>(14.8%)</td>
<td>(17-51%)</td>
<td>(6-21%)</td>
</tr>
<tr>
<td></td>
<td>[40]</td>
<td>[99]</td>
<td>[29.4]</td>
<td>[72.4]</td>
</tr>
<tr>
<td>TNBC</td>
<td>15/21</td>
<td>16/83</td>
<td>62.4%</td>
<td>22.3%</td>
</tr>
<tr>
<td></td>
<td>(71.4%)</td>
<td>(19.3%)</td>
<td>(45-80%)</td>
<td>(12-33%)</td>
</tr>
<tr>
<td></td>
<td>[29]</td>
<td>[89]</td>
<td>[28.6]</td>
<td>[58.4]</td>
</tr>
</tbody>
</table>
KN-119: Randomized Phase III Study of pembrolizumab vs TPC as 2-3L for mTNBC

~600 patients
- mTNBC
- One or two prior lines of treatment for metastatic disease
- Previously treated with an anthracycline and/or taxane in the (neo)adjuvant or metastatic setting
- LDH < 2.5xULN
- ECOG PS 0-1
- No systemic steroids
- No autoimmune disease (active or history of)
- No active brain metastases

1:1

Pembrolizumab
200 mg IV Q3W

Progressive Disease*/Cessation of Study Therapy

Protocol-Specified Follow-Up

TPC from any one of the following (60% max cap for each drug option):
- Capecitabine
- Eribulin
- Gemcitabine
- Vinorelbine

Primary Endpoints
- PFS in subjects with PD-L1 positive tumors
- PFS in all subjects
- OS in subjects with PD-L1 positive tumors
- OS in all subjects

Stratification factors
1. PD-L1 tumor status (positive vs negative)
2. Prior (neo)adjuvant therapy vs de novo metastatic disease

*Treatment may be continued beyond verified 1st radiologic evidence of disease progression according to irRECIST
KN-355: Randomized Phase III of pembrolizumab + Chemo vs Placebo + Chemo in 1st line mTNBC (Safety Run-in part)

30 patients
- Recently or newly obtained tumor biopsy
- Central determination of TNBC and PD-L1
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of (neo)adjuvant treatment, if indicated, ≥6 months prior to randomization
- ECOG PS 0-1
- No systemic steroids >physiologic dose
- No active autoimmune disease that required systemic treatment in past 2 years
- No active central nervous system metastases

Primary Endpoint
- Safety and tolerability of pembrolizumab plus chemotherapy combinations

Protocol-Specified Follow-Up

Progressive Disease*/Cessation of Study Therapy

Pembrolizumab
+ Nab-paclitaxel

Pembrolizumab
+ Paclitaxel

Pembrolizumab
+ Gemcitabine/Carboplatin

*Treatment may be continued until confirmation of PD
KN-355: Randomized Phase III of pembrolizumab + Chemo vs Placebo + Chemo in 1st line mTNBC

828 patients
- Recently or newly obtained tumor biopsy
- Central determination of TNBC and PD-L1
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of surgery or adjuvant treatment, whichever occurred last, ≥6 months prior to randomization
- ECOG PS 0-1
- No systemic steroids >physiologic dose
- No active autoimmune disease that required systemic treatment in past 2 years
- No active CNS metastases

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

Secondary Endpoints
- ORR, DCR, DOR in all subjects and PD-L1-positive
- Safety

Exploratory Endpoints
- irORR, irPFS, irDCR, irDOR
- ePROs
- Correlative studies

Stratification factors
1. Chemotherapy treatment on study (taxane vs gemcitabine/carboplatin)
2. PD-L1 tumor status (positive vs negative)
3. Prior treatment with same class chemotherapy in the (neo)adjuvant setting (yes vs no)
### Immune checkpoint inhibitors in ER+ disease

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n = 25)</th>
<th>Avelumab (n=58 /9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target</td>
<td>PD-1</td>
<td>PD-L1</td>
</tr>
<tr>
<td>Tumour PD-L1</td>
<td>≥1%</td>
<td>All</td>
</tr>
<tr>
<td>ORR</td>
<td>12%</td>
<td>2.8%</td>
</tr>
<tr>
<td>SD</td>
<td>16%</td>
<td></td>
</tr>
</tbody>
</table>

Nanda et al. SABCS 2014, Dirix et al SABCS 2015
Ongoing clinical trials with immunotherapies that accrue breast cancer patients

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical Trial Gov</th>
<th>Disease setting</th>
<th>Type of disease</th>
<th>Breast cancer subtype</th>
<th>Immunotherapies</th>
<th>Combined treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NCT02303366</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>All</td>
<td>Pembrolizumab</td>
<td>Stereotactic Ablative Body Radiosurgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Metastatic and neoadjuvant</td>
<td>Only BC</td>
<td>HER2-pos</td>
<td>Alezolizumab</td>
<td>Trastuzumab/pertuzumab or T-DM1 or Trastuzumab/Pertuzumab/Carboplatin/Oxetaxel</td>
</tr>
<tr>
<td>I</td>
<td>NCT02649868</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>HER2-pos</td>
<td>Durvalumab</td>
<td>Trastuzumab</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02129536</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>HER2-pos</td>
<td>Pembrolizumab</td>
<td>Eribulin mesylate</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT0228132</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Durvalumab</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>I</td>
<td>NCT02411656</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC or ER+/HER2-</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02447003</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02499367</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Nivolumab</td>
<td>Doxorubicin low dose, Cyclophosphamide metronomic, Radiation therapy, Cisplatin</td>
</tr>
<tr>
<td>I</td>
<td>NCT02411656</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>HER2-neg</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02447003</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02395627</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>HR+ (endocrine resistant BC)</td>
<td>Pembrolizumab</td>
<td>Vorinostat and Tamoxifen</td>
</tr>
<tr>
<td>I</td>
<td>NCT02536794</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>Vemurafen and Cobimetinib</td>
</tr>
<tr>
<td>I</td>
<td>NCT02536794</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>Vemurafen and Cobimetinib</td>
</tr>
<tr>
<td>I</td>
<td>NCT02563925</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>All</td>
<td>Tremelimumab</td>
<td>Brain radiotherapy or Stereotactic</td>
</tr>
<tr>
<td>I</td>
<td>NCT00083278</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>All</td>
<td>Iplimumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02648477</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC and ER+/HER2-</td>
<td>Pembrolizumab</td>
<td>Doxorubicin or Letrozole or Anastrozole or Exemestane</td>
</tr>
<tr>
<td>I</td>
<td>NCT02555557</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02425891</td>
<td>Metastatic</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Atezolizumab</td>
<td>Nab-paclitaxel</td>
</tr>
<tr>
<td>I</td>
<td>NCT02622074</td>
<td>Neo-adjuvant</td>
<td>Only BC</td>
<td>TNBC (LABC)</td>
<td>Pembrolizumab</td>
<td>Nab-paclitaxel → AC or Nab-paclitaxel/Carboplatin → AC</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT0248448</td>
<td>Neo-adjuvant</td>
<td>Only BC</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT01042379</td>
<td>Neo-adjuvant</td>
<td>Only BC</td>
<td>All</td>
<td>Pembrolizumab</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>I</td>
<td>NCT02530489</td>
<td>Neo-adjuvant</td>
<td>Only BC</td>
<td>Atezolizumab</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02620289</td>
<td>Neo-adjuvant</td>
<td>Only BC</td>
<td>Atezolizumab</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT01502592</td>
<td>Pre-surgical</td>
<td>Only BC</td>
<td>All</td>
<td>Iplimumab</td>
<td>Cryoablation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase</th>
<th>Clinical Trial Gov</th>
<th>Disease setting</th>
<th>Type of disease</th>
<th>Breast cancer subtype</th>
<th>Immunotherapies</th>
<th>Combined treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NCT02453629</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Nivolumab +/-  Ipilimumab</td>
<td>Etinostat</td>
</tr>
<tr>
<td>I</td>
<td>NCT01375842</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Atezolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02390177</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT00936588</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Nivolumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02655822</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Atezolizumab</td>
<td>CPI-444</td>
</tr>
<tr>
<td>I</td>
<td>NCT01848834</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02054806</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>All</td>
<td>Pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT01772004</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>All</td>
<td>Avelumab</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT01975831</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>ER+/HER2- and HER2-</td>
<td>Pembrolizumab</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02656214</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Durvalumab</td>
<td>Gemcitabine/carboplatin or nab-paclitaxel/carboplatin</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02316901</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>HER2-pos</td>
<td>Pembrolizumab</td>
<td>Trastuzumab or TDM1</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02543645</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Atezolizumab</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02657889</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>Vemurafen (ER+/HER2-), Gemcitabine (TNBC)</td>
</tr>
<tr>
<td>I</td>
<td>NCT02178722</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Nab-paclitaxel</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02331251</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC and ER+/HER2-</td>
<td>Pembrolizumab</td>
<td>Vinorelbine (ER+/HER2-), Gemcitabine (TNBC)</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT01926394</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Nivolumab +/-  Ipilimumab</td>
<td></td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02452424</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>Plx3397 (anti-CSF1R)</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02331251</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>All</td>
<td>Pembrolizumab</td>
<td>Various CT</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02318901</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>HER2-pos</td>
<td>Pembrolizumab</td>
<td>Atezolizumab</td>
</tr>
<tr>
<td>I</td>
<td>NCT02543645</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>(CD27 agonist)</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02403271</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC and HER2-pos</td>
<td>Pembrolizumab</td>
<td>Durvalumab</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02404441</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td>PDR001</td>
</tr>
<tr>
<td>I/II</td>
<td>NCT02643303</td>
<td>Metastatic</td>
<td>Multiple</td>
<td>All</td>
<td>Pembrolizumab</td>
<td>Durvalumab and Poly-ICLC +/- Tremelimumab</td>
</tr>
<tr>
<td>I</td>
<td>NCT02661100</td>
<td>Metastatic</td>
<td>TNBC</td>
<td>Durvalumab and Poly-ICLC</td>
<td>Pembrolizumab</td>
<td>CDX.1401 and Poly-ICLC</td>
</tr>
<tr>
<td>I</td>
<td>NCT02644369</td>
<td>Metastatic</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02527434</td>
<td>Metastatic</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02478099</td>
<td>Metastatic</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>NCT02661100</td>
<td>Metastatic</td>
<td>TNBC</td>
<td>Pembrolizumab</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Clinical studies Targeting TAMs in Breast Cancer

<table>
<thead>
<tr>
<th>Target</th>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Clinical trial breast cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF1-CSF1R</td>
<td>IMC-CS4 (LY3022855)</td>
<td>Alters TAM activity by depletion or inhibiting recruitment/activation</td>
<td>NCT02265536-Phase I (recruiting)</td>
</tr>
<tr>
<td></td>
<td>AMG820</td>
<td></td>
<td>NCT01525502-Phase Ib/II (active, not recruiting)</td>
</tr>
<tr>
<td></td>
<td>PLX7486</td>
<td></td>
<td>NCT01804530-Phase I (recruiting)</td>
</tr>
<tr>
<td></td>
<td>PLX3397</td>
<td></td>
<td>NCT01596751-Phase Ib/II (recruiting)</td>
</tr>
<tr>
<td></td>
<td>RO5509554 (emactuzumab)</td>
<td></td>
<td>NCT01494688-Phase I (recruiting)</td>
</tr>
<tr>
<td>CCL2-CCR2</td>
<td>Carlumab (CNT0888)</td>
<td>Impairs monocyte recruitment</td>
<td>None</td>
</tr>
<tr>
<td>Macrophages (Phagocytes)</td>
<td>Clondonate</td>
<td>Induces apoptosis in macrophages</td>
<td>NCT01198457-Observational (completed)</td>
</tr>
<tr>
<td></td>
<td>Zeldronic Acid</td>
<td></td>
<td>NCT00873808-Observational (withdrawn due to lack of accrual)</td>
</tr>
<tr>
<td></td>
<td>Inbandronate</td>
<td></td>
<td>NCT0009945-Phase III (completed)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT00127205-Phase III active, not recruiting</td>
</tr>
<tr>
<td>TLR7 agonist</td>
<td>852A</td>
<td>Reprograms macrophages towards tumoricidal function</td>
<td>NCT00319748-Phase II (completed, has results)</td>
</tr>
<tr>
<td></td>
<td>Imiquimod</td>
<td></td>
<td>NCT00821964-Phase II (active, not recruiting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT00899574-Phase II (completed, has results)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT01421017-Phase I/II (recruiting)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NCT02276300-Phase I (recruiting)</td>
</tr>
</tbody>
</table>

Williams et al. *npjbcancer* 2016
## Dendritic cell-based Vaccines in Breast Cancer

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>N</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; outcome</th>
<th>Setting</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00197925</td>
<td>I/II</td>
<td>40</td>
<td>Tolerability/ safety</td>
<td>Metastatic</td>
<td>Oncopeptide loaded autologous DCs</td>
</tr>
<tr>
<td>NCT00107211</td>
<td>I</td>
<td>30</td>
<td>Feasibility/ safety/clinical response</td>
<td>DCIS neoadjuvant</td>
<td>HER-2/Neu-pulsed DC1 vaccine</td>
</tr>
<tr>
<td>NCT01431196</td>
<td>II</td>
<td>29</td>
<td>pCR</td>
<td>Stage II and III</td>
<td>Chemotherapy followed by DCs pulsed with tumor antigens</td>
</tr>
<tr>
<td>NCT00640861</td>
<td>II</td>
<td>45</td>
<td>Toxicity/ immune response</td>
<td>Stage II or III</td>
<td>MUC1/HER-2/Neu peptide DC vaccine</td>
</tr>
<tr>
<td>NCT00162929</td>
<td>I</td>
<td>5</td>
<td>Toxicity</td>
<td>Metastatic</td>
<td>DCs transduced by an adenovector expressing Her-2/neu</td>
</tr>
<tr>
<td>NCT01782274</td>
<td>II/III</td>
<td>60</td>
<td>All-cause mortality</td>
<td>Metastatic</td>
<td>Allogeneic/ autologous hematopoietic stem cells, DCs and cytotoxic lymphocytes</td>
</tr>
<tr>
<td>NCT00003432</td>
<td>I/II</td>
<td>26</td>
<td>Immune response/ clinical efficacy</td>
<td>Metastatic</td>
<td>CEA RNA-pulsed DC vaccine</td>
</tr>
<tr>
<td>NCT00879489</td>
<td>I/II</td>
<td>24</td>
<td>Toxicity</td>
<td>Metastatic</td>
<td>Autologous DCs pulsed with human recombinant oncofetal antigen (OFP/iLRP)</td>
</tr>
</tbody>
</table>

www.ClinicalTrials.gov
## Dendritic cell-based Vaccines in Breast Cancer

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Phase</th>
<th>N</th>
<th>Primary Outcome</th>
<th>Setting</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01730118</td>
<td>I</td>
<td>65</td>
<td>Safety/toxicity/immunogenicity</td>
<td>Metastatic</td>
<td>Autologous adenovirus HER2- transduced DC vaccine</td>
</tr>
<tr>
<td>NCT0088985</td>
<td>II</td>
<td>55</td>
<td>Response rate</td>
<td>Locally recurrent or metastatic</td>
<td>Autologous DCs pulsed with E75 and E90 peptides with trastuzumab and vinorelbine</td>
</tr>
<tr>
<td>NCT01042535 I/II</td>
<td>37</td>
<td></td>
<td>MTD/safety</td>
<td>Metastatic</td>
<td>Adenovirus p53- transduced DCs with 1-methyl-dtryptophan</td>
</tr>
<tr>
<td>NCT00266110</td>
<td>II</td>
<td>26</td>
<td>Efficacy</td>
<td>Locally recurrent or metastatic</td>
<td>Autologous DCs pulsed with E75 and E90 peptides with trastuzumab and vinorelbine</td>
</tr>
<tr>
<td>NCT00978913</td>
<td>I</td>
<td>14</td>
<td>Toxicity/immune response</td>
<td>Metastatic</td>
<td>DCs transfected with survivin, hTERT and p53 mRNA with cyclophosphamide</td>
</tr>
<tr>
<td>NCT00622401</td>
<td>I/II</td>
<td>41</td>
<td>Toxicity</td>
<td>Metastatic</td>
<td>DCs/tumor cell fusion vaccine ± IL-12</td>
</tr>
<tr>
<td>NCT00715832</td>
<td>I</td>
<td>25</td>
<td>Toxicity</td>
<td>Metastatic</td>
<td>DCs loaded with oncofetal antigen/ iLRP</td>
</tr>
<tr>
<td>NCT01522820</td>
<td>I</td>
<td>30</td>
<td>Safety</td>
<td>Adjuvant</td>
<td>DCs/NY-ESO-1 fusion protein vaccine ± sirolimus</td>
</tr>
<tr>
<td>NCT00923143</td>
<td>I/II</td>
<td>57</td>
<td>Safety/immune response</td>
<td>DCIS</td>
<td>HER-2/Neu-pulsed DC vaccine</td>
</tr>
<tr>
<td>NCT00197522</td>
<td>I</td>
<td>5</td>
<td>MTD/toxicity</td>
<td>Metastatic</td>
<td>DCs infected with an adenovirus expressing Her-2</td>
</tr>
<tr>
<td>NCT00082641</td>
<td>I/II</td>
<td>24</td>
<td>Safety/toxicity/immune response</td>
<td>Neoadjuvant or Adjuvant</td>
<td>Adenovirus p53- infected DC vaccine ± chemotherapy ± RT</td>
</tr>
<tr>
<td>NCT00128622</td>
<td>I</td>
<td>24</td>
<td>Safety</td>
<td>Metastatic</td>
<td>Autologous DCs infected with CEA-6D-expressing Fowlpox-Trico</td>
</tr>
<tr>
<td>NCT00004604</td>
<td>I</td>
<td>24</td>
<td>Safety</td>
<td>Metastatic</td>
<td>CEA RNA-pulsed DC vaccine</td>
</tr>
</tbody>
</table>
CONCLUSIONS

• Is there a rational for immune-based therapy in BC? **YES**

• Evidences from clinical data? **More and more, but limited**

• Can you enhance immunogenicity? **YES**