Immunotherapy for Breast Cancer
Clinical Development

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Introduction

- Breast Cancer immunogenicity?
- → accumulating evidence that BC patients elicit an antitumor immune response
  - TIL infiltration
  - Mutation load
  - PD-L1 expression
  - Responses in early phases immunotherapy trials

Clinical significance of TIL infiltration in BC

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

Introduction

- Breast Cancer immunogenicity?
- → accumulating evidence that BC patients elicit an antitumor immune response

  - TIL infiltration in primary tumors
  - Mutation load
  - PD-L1 expression
  - Responses in early phases immunotherapy trials

Estimate of the neoantigen repertoire in human cancer.
TNBC: the candidate for immunotherapy

- Worse prognosis than other BC subtype
- Limited treatment options
- Cancer immunotherapy represents a promising treatment approach for TNBC
  - Higher TIL infiltration
  - Higher mutation rate $\rightarrow$ immunogenic neoantigens
  - Higher PD-L1 expression $\rightarrow$ inhibit T-cell antitumor responses

Strategies to modulate the immune system in breast cancer

**Active**: priming of the immune system

- **Antigen-specific**
  - Peptide vaccine
  - DC-vaccine
  - DNA-vaccine
  - Whole cell vaccine

- **Non antigen-specific**
  - Checkpoint inhibitors
  - Cytokines

**Passive**: delivery of compounds that may use immune system

- **Monoclonal antibodies**
  - Trastuzumab
  - Pertuzumab

- **Adoptive cell transfer**
  - CAR T cells

**Cancer vaccines**

**Immune modulators**

**Targeted antibodies**

**Cellular immunotherapy**
IMMUNE CHECKPOINT INHIBITORS
Immune checkpoint inhibition

Phase Ib of pembrolizumab in mTNBC

KEYNOTE 012

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

Pembro 10 mg/kg Q2W

Complete Response
Discontinuation Permitted

Partial Response or Stable Disease
Treat for 24 months or until progression or intolerable toxicity

Confirmed Progressive Disease
Discontinue

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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aPD-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.
bIf 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.

Nanda R et al. San Antonio Breast Cancer Symposium 2014
Patients Evaluable for Response

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Patients Evaluable for Response&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>5 (18.5%)</td>
</tr>
<tr>
<td>Best overall response</td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (3.7%)</td>
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<tr>
<td>Partial response</td>
<td>4 (14.8%)</td>
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<tr>
<td>Stable disease</td>
<td>7 (25.9%)</td>
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<tr>
<td>Progressive disease</td>
<td>12 (44.4%)</td>
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<tr>
<td>No assessment</td>
<td>3 (11.1%)</td>
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Nanda R et al. JCO 2016
## Immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Subtype</th>
<th>PD-L1</th>
<th>Nb pts</th>
<th>ORR</th>
<th>References</th>
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</thead>
<tbody>
<tr>
<td>Pembrolizumab (anti-PD-1)</td>
<td>Ib</td>
<td>TNBC</td>
<td>PDL1+ ≥ 1% Any (58%)</td>
<td>32</td>
<td>27</td>
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<td></td>
<td></td>
<td>PDL1+</td>
<td></td>
<td></td>
<td></td>
<td>1 CR 4 PR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Nanda et al. SABC 2014 JCO 2016</td>
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<td>Atezolizumab (anti-PD-L1)</td>
<td>Ia</td>
<td>TNBC</td>
<td>≥ 5% Immune (69%)</td>
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<td>21</td>
<td>19%</td>
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<td>2 CR 2 PR</td>
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<td>Emens et al. SABC 2014 AACR 2015</td>
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<tr>
<td>Pembrolizumab (anti-PD-1)</td>
<td>Ib</td>
<td>ER+/HER2-</td>
<td>PDL1+ ≥ 1% Any (19.4%)</td>
<td>25</td>
<td></td>
<td>12%</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>0 CR 3 PR</td>
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<td></td>
<td></td>
<td>Rugo et al. SABC 2015</td>
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<td>Avelumab (anti-PD-L1)</td>
<td>Ib</td>
<td>All</td>
<td>TNBC ER+/HER2- PDL1+ ≥ 1% Tu (58%) ≥ 10%Im (9%)</td>
<td>168</td>
<td>153</td>
<td>4.8%</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 CR 7 PR</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Dirix et al. SABC 2015</td>
</tr>
</tbody>
</table>

Direct comparison is not appropriate as no head to head trial comparing all agents has been conducted.
Immune checkpoint inhibitors in BC

- Mostly evaluated in TNBC
- Response rate (monotherapy) : 8-20%
- Acceptable safety profile in early phases trials in metastatic setting
- Higher response rate in PD-L1-positive cases
- Long-lasting responses in a subset of responders
Long lasting responses

On treatment vs. Discontinued treatment

Change From Baseline, %

Time, weeks

3 “exceptional” responders

Nanda et al. SABC 2014
Future directions for immune checkpoint inhibitors in BC

- Phases II & III clinical trials are ongoing
- Combined strategies
- Neoadjuvant/Adjuvant setting
- Identification of biomarkers of response for a better selection of patients
- Development of next generation co-stimulatory inhibitors/activators
KEYNOTE-119: A Randomized Phase 3 Study of Single-Agent Chemotherapy per Investigator’s choice for mTNBC

**Patients**
- Recurrent mBC
- 1 or 2 prior systemic treatments for mBC
- Documented disease progression on/after most recent therapy
- Previous treatment with an anthracyline and/or a taxane in the (neo)adjuvant or metastatic setting
- ECOG PS 0-1

**Stratification by:**
- PD-L1 tumor status (positive vs negative)
- Prior (neo)adjuvant therapy vs de novo metastatic disease at initial diagnosis

**Randomize 1:1 N = 600**

**Investigator’s choice of one of the following:**
- Capecitabine
- Enbulin
- Gemcitabine
- Vinorelbine

**Pembrolizumab 200 mg Q3W**

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

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

†Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug.
Future directions for immune checkpoint inhibitors in BC

- Phases II & III clinical trials are ongoing
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Combined strategies with immune checkpoint inhibitors

- Preclinical and clinical models have demonstrated **synergistic activities**
  - between immuno-oncology agents
  - and with chemotherapy, targeted therapies, radiotherapy, anti-angiogenic agents

- Development of multiple rationale combinations with compatible mechanisms that act synergistically to:
  - Increase anti-tumor efficacy
  - Reduce on-target side effects
Combined strategies with immune checkpoint inhibitors in BC

- **Immunotherapies**
  - Anti-PD-L1 & cancer vaccine

- **Chemotherapy**
  - Paclitaxel & Nab-Paclitaxel
  - Eribuline
  - Doxorubicin

- **Targeted therapies**
  - Trastuzumab (PANACEA)

- **Radiotherapy**
Combination with Chemotherapy:

**Phase I trial:** Safety and clinical activity of atezolizumab (anti-PD-L1) in combination with nab-paclitaxel in patients with mTNBC

- Arm F of a multi-arm, multi-cohort study (NCT 01633970)
- Nab-paclitaxel and atezolizumab were given concurrently

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>All patients N=24</th>
<th>1 Line (n=9)</th>
<th>2nd Line (n=8)</th>
<th>3rd Line (n=7)</th>
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<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>70.8% (48.9-87.4)</td>
<td>88.9% (51.7-99.7)</td>
<td>75% (34.9-96.8)</td>
<td>42.9% (9.9-81)</td>
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<tr>
<td>CR</td>
<td>4.2%</td>
<td>11.1%</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>66.7%</td>
<td>77.8%</td>
<td>75%</td>
<td>42.9%</td>
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<tr>
<td>SD</td>
<td>20.8%</td>
<td>11.1%</td>
<td>25%</td>
<td>28.6%</td>
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<tr>
<td>PD</td>
<td>8.3%</td>
<td>0</td>
<td>0</td>
<td>28.6%</td>
</tr>
</tbody>
</table>
Combination with chemotherapy

- **Ongoing Phase III trials:**
  - **Anti-PD1:**
    - KEYNOTE 355:
      - Pembrolizumab + chemo vs placebo + chemo
      - Chemo: gemci/carbo or paclitaxel or nab-paclitaxel
      - Locally recurrent or metastatic TNBC
      - PD-L1 positive cases
      - First line treatment
      - NCT02819518
  - **Anti-PD-L1:**
    - IMpassion 130:
      - Atezolizumab + nabpaclitaxel vs placebo + nabpaclitaxel
      - Locally advanced or metastatic TNBC
      - First line treatment
      - NCT02425891
Combined strategies with immune checkpoint inhibitors in BC

- **Immunotherapies**
  - Anti-PD-L1 & cancer vaccine

- **Chemotherapy**
  - Paclitaxel & Nab-Paclitaxel
  - Eribuline
  - Doxorubicin

- **Targeted therapies**
  - Trastuzumab (PANACEA)

- **Radiotherapy**
Combination with targeted therapies

- **PANACEA**
  - Phase Ib/II trial (NCT02129556)
  - recruiting

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**Advanced HER2+ BC**
Trastuzumab resistant
Up to 3 lines previous anti-HER2 therapy

**Confirmed PD-L1 expression on a metastatic lesion**

**Trastuzumab + MK3475 until progression**
Biopsy on progression

*Savas P et al. Curr Opin Oncol 2014*
Future directions for immune checkpoint inhibitors in BC

- Phases II & III clinical trials are ongoing
- Combined strategies
- Neoadjuvant/ Adjuvant setting
- Identification of biomarkers of response for a better selection of patients
- Development of next generation co-stimulatory inhibitors/activators
<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial</th>
<th>Setting</th>
<th>BC</th>
<th>Immunotherapy</th>
<th>Control arm</th>
<th>Status</th>
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<tr>
<td>Ib</td>
<td>NCT02622074</td>
<td>Neoadjuvant</td>
<td>TNBC</td>
<td>Pembrolizumab (anti-PD1) and chemotherapy</td>
<td>NA</td>
<td>recruiting</td>
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<tr>
<td>I/II</td>
<td>NCT02489448</td>
<td>Neoadjuvant</td>
<td>TNBC</td>
<td>Durvalumab (anti-PD-L1) and weekly nab-paclitaxel &amp; dd AC</td>
<td>NA</td>
<td>recruiting</td>
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<tr>
<td>II</td>
<td>NCT02530489</td>
<td>Neoadjuvant &amp; Adjuvant</td>
<td>TNBC</td>
<td>Atezolizumab (anti-PD-L1) and nab-paclitaxel</td>
<td>NA</td>
<td>recruiting</td>
</tr>
<tr>
<td>III</td>
<td>NCT02620280</td>
<td>Neoadjuvant</td>
<td>TNBC</td>
<td>Atezolizumab (anti-PD-L1) and nab-paclitaxel + carboplatin</td>
<td>nab-paclitaxel + carboplatin</td>
<td>recruiting</td>
</tr>
<tr>
<td>Ib</td>
<td>NCT02826434</td>
<td>Adjuvant</td>
<td>TNBC</td>
<td>Durvalumab (anti-PD-L1) and peptide vaccine (PVX-410)</td>
<td>NA</td>
<td>Not yet recruiting</td>
</tr>
</tbody>
</table>
Future directions for immune checkpoint inhibitors in BC

- Phases II & III clinical trials are ongoing
- Combined strategies
- Neoadjuvant/ Adjuvant setting
- Identification of biomarkers of response for a better selection of patients
- Development of next generation co-stimulatory inhibitors/activators
Biomarkers of response

- **PD-L1 expression**
  - PD-L1 expression by *tumor cells* was associated to response in melanoma and NSCLC
    - But: 5-20% objective response rate in PDL-1 negative tumors
  - PD-L1 expression by *immune cells* was also associated to response in NSCLC, BC
    - Still controversial (< Multiple different IHC assays, different threshold of positivity on different cells type)
    - Stratification < PD-L1 status in clinical trials

- **TIL infiltration**
- **Mutational load**
TIL infiltration

Amplify:
existing anti-tumor immunity (immunogenic chemo, radiation and/or targeted therapy?)

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

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

CD45+/TIL/mg of tissue

Tumors (n=110)

Buisseret et al. Submitted data.
Possible trial design using TIL as a biomarker

TNBC or HER2-positive early-stage breast cancer

Neoadjuvant chemotherapy ± trastuzumab

High TILs

pCR

Excellent prognosis

Standard therapy

T-cell checkpoints (PD-1/PL-L1, CTLA-4, TIM-3, LAG-3)

Immuno-modulators (IDO, CD73, adenosine)

Angiogenesis (VEGF)

Oncogenic signalling pathways (MEK)

Personalized vaccines

Adaptive T-cell therapy

Low TILs

No pCR

Good prognosis

Ineffective immunity

Absent immunity

No pCR

Poor prognosis

Aggressive therapy
Future directions for immune checkpoint inhibitors in BC

- Phases II & III clinical trials are ongoing
- Combined strategies
- Neoadjuvant/ Adjuvant setting
- Identification of biomarkers of response for a better selection of patients
- Development of next generation co-stimulatory inhibitors/activators
Next Generation of co-stimulatory inhibitors/activators
CANCER VACCINES
<table>
<thead>
<tr>
<th>Target</th>
<th>Description</th>
</tr>
</thead>
</table>
| HER2                        | Human epidermal growth factor  
Overexpressed in 20-30% of BC                                           |
| CEA                         | Glycoprotein involved in cell adhesion, normally expressed during fetal development |
| MUC-1                       | Membrane glycoprotein involved in immunologic and cell signaling functions  
Overexpressed in 70% of BC                                   |
| hTERT                       | Component of the telomerase complex, a ribonucleoprotein that maintain chromosome integrity during cell proliferation and division |
| Mammaglobin-A               | Glycoprotein overexpressed in 80% of mBC                                    |
| Cancer testis antigens      | Proteins expressed in normal germ cells of the testis and embryonic ovaries and in certain types of cancer |
## Therapeutic BC vaccines

<table>
<thead>
<tr>
<th>Metastatic setting</th>
<th>Vaccines</th>
<th>Phase</th>
<th>Targets</th>
<th>Nb patients</th>
<th>Clinical activity</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HER2 peptide + GM-CSF</td>
<td>I</td>
<td>HER2</td>
<td>64</td>
<td>NR</td>
<td>Disis 1999</td>
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<tr>
<td></td>
<td>HER2 peptide (E75) + GM-CSF</td>
<td>I</td>
<td>HER2</td>
<td>14</td>
<td>NR</td>
<td>Murray 2002</td>
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<tr>
<td></td>
<td>HER2 ICD protein + GM-CSF</td>
<td>I</td>
<td>HER2</td>
<td>29</td>
<td>NR</td>
<td>Disis 2004</td>
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<tr>
<td></td>
<td>hTERT peptide + montanide + GM-CSF</td>
<td>I</td>
<td>hTERT</td>
<td>19</td>
<td>NR</td>
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<td>Survivin-2B peptide</td>
<td>I</td>
<td>survivin</td>
<td>14</td>
<td>NR</td>
<td>Tsuruma 2008</td>
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<td></td>
<td>HER2 peptide + GM-CSF + trastuzumab</td>
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<td>HER2</td>
<td>22</td>
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<td><strong>Theratope (STn-KLH + Cy vs KLH+Cy)</strong></td>
<td>III</td>
<td>MUC-1</td>
<td>1028</td>
<td>Negative trial</td>
<td>Miles 2011</td>
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<tr>
<td></td>
<td>HER2 protein + AS15 + lapatinib</td>
<td>I</td>
<td>HER2</td>
<td>12</td>
<td>NR</td>
<td>Hamilton 2012</td>
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<td></td>
<td>MAM-A DNA vaccine</td>
<td>I</td>
<td>Mammaglobin-A</td>
<td>14</td>
<td>Possible benefit</td>
<td>Tiriveedhi 2014</td>
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<tr>
<td></td>
<td>PANVAC (poxviral-based) + docetaxel</td>
<td>II</td>
<td>MUC-1 + CEA</td>
<td>48</td>
<td>Possible benefit</td>
<td>Heery 2015</td>
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<tr>
<td></td>
<td><strong>dHER2 protein + AS15</strong></td>
<td>I/II</td>
<td>HER2</td>
<td>40</td>
<td>Possible benefit</td>
<td>Curigliano 2016</td>
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<td><strong>Cell-based vaccines</strong></td>
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<td></td>
<td>Lapuleucel-T</td>
<td>I</td>
<td>HER2</td>
<td>18</td>
<td>SD in 16.7%</td>
<td>Park 2007</td>
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<tr>
<td></td>
<td>p53-DC</td>
<td>I</td>
<td>p53</td>
<td>26</td>
<td>SD in 42%</td>
<td>Svane 2007</td>
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<td></td>
<td><strong>Allogenic GM-CSF-secreting breast tumor cells + low dose CY and DOX</strong></td>
<td>I</td>
<td>HER2</td>
<td>28</td>
<td>NR</td>
<td>Emens 2009</td>
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<tr>
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<td><strong>Allogenic GM-CSF-secreting breast tumor cells + low dose CY and trastuz</strong></td>
<td>II</td>
<td>HER2</td>
<td>20</td>
<td>NR</td>
<td>Chen 2014</td>
</tr>
</tbody>
</table>

Adapted from Cimino-Mathews et al. Oncology 2015
Theratope vaccine

**Phase III trial:**
- Largest double-blind, randomized vaccine study in mBC
- 1028 patients (525 vaccinated)
- MUC-1 peptide vaccine
  - carbohydrate epitope: Sialyl-Tn (STn) conjugated to a protein carrier (keyhole limpet hemocyanin (KLH))
- Low dose of cyclophosphamide to deplete Treg
- Concomitant hormone therapy allowed
- Median TTP: 3.4 months vs 3 months
- Median OS: 23.1 vs 22.1 months

Miles et al. The Oncologist. 2011
Theratope vaccine

Phase III, Randomized, prospective trial

Retrospective post-hoc analysis

→ No survival benefit!

→ Survival advantage for patients treated with endocrine therapy

Preventive BC vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Phase</th>
<th>target</th>
<th>Nb patients</th>
<th>Clinical activity</th>
<th>References</th>
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<tbody>
<tr>
<td>HER2 peptide (E75) + GM-CSF</td>
<td>I</td>
<td>HER2</td>
<td>53</td>
<td>possible benefit</td>
<td>Peoples 2005</td>
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<td>Oxidized mannan-MUC-1</td>
<td>Pilot</td>
<td>MUC-1</td>
<td>31</td>
<td>possible benefit</td>
<td>Vassilaros 2013</td>
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<td>HER2 peptide (E75) + GM-CSF</td>
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<td>HER2</td>
<td>187</td>
<td>5y DFS: 89.7% vs 80.2%</td>
<td>Mittendorf 2014</td>
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<td>HER2 peptide (GP2) + GM-CSF</td>
<td>II</td>
<td>HER2</td>
<td>180</td>
<td>5y DFS: 94% vs 85%</td>
<td>Mittendorf 2016</td>
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<td>HER2 peptide (AE37) + GM-CSF</td>
<td>II</td>
<td>HER2</td>
<td>298</td>
<td>5y DFS: 80.8% vs 79.5%</td>
<td>Mittendorf 2016</td>
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<tr>
<td>dHER2 + AS15</td>
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<td>HER2</td>
<td>61</td>
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<td>Triple peptide</td>
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<td>MUC-1+ HER2+CEA</td>
<td>14</td>
<td>possible benefit</td>
<td>Morena 2016</td>
</tr>
</tbody>
</table>

Adapted from Cimino-Mathews et al. Oncology 2015
NeuVax vaccine

- HER2-derived peptide, HLA-A2/A3+
- MHC class I epitope – CD8+ T cell response

⇒ **Phase III trial**: Prevention of Recurrence in Early-Stage, node-positive BC with low of Intermediate HER2 Expressions with NeuVax™ Treatment (PRESENT)
  - HER2 1+/2+ (IHC)
  - NeuVax + Sargramostim, GM-CSF
  - 758 patients included
SN-33 PHASE 2 HER2 IHC 1+/2+ (N=45)

REDEFINING THE STANDARD OF CARE

RECEIVES PRIMARY TREATMENT

- Surgery
- Chemotherapy
- Radiation

Disease free "survivor"

HER2 Status

<table>
<thead>
<tr>
<th>HER2 Status</th>
<th>Standard of Care</th>
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<tbody>
<tr>
<td>HER2, 3+ (20-25% of patients)</td>
<td>Multiple, including Herceptin®</td>
</tr>
<tr>
<td>HER2, 1+/2+ (50-60% of patients)</td>
<td>No FDA approved therapies</td>
</tr>
<tr>
<td>HER2, 3+ High Risk (20-25% of patients)</td>
<td>No FDA approved therapies</td>
</tr>
</tbody>
</table>

Slight evidence of disease

Galena Biopharma
## Breast Cancer Programs

<table>
<thead>
<tr>
<th>Phase</th>
<th>Treatment</th>
<th>HER2 Status</th>
<th>Indication</th>
<th>Trial Status</th>
<th>Protocol Defined # of Patients</th>
<th>Collaborations</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Single agent PRESENT Study</td>
<td>1+, 2+</td>
<td>Node Positive HLA A2+, A3+</td>
<td>Enrolled 13 countries ~140 centers</td>
<td>700 (enrolled 758)</td>
<td>Teva, Leica</td>
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<tr>
<td>2b</td>
<td>Combination with trastuzumab</td>
<td>1+, 2+</td>
<td>Node Positive or High Risk Node Negative HLA A2+, A3+, A24+, A26+</td>
<td>Enrolling U.S. only 34 centers</td>
<td>300</td>
<td>Genentech, Roche, hjf</td>
</tr>
<tr>
<td>2</td>
<td>Combination with trastuzumab</td>
<td>3+ high risk</td>
<td>Node Positive HLA A2, A3+</td>
<td>Enrolling U.S. only 30 centers</td>
<td>100</td>
<td>CDMRP, Department of Defense</td>
</tr>
<tr>
<td>2</td>
<td>Single agent VADIS Study</td>
<td>1+, 2+, 3+</td>
<td>Ductal Carcinoma in Situ (DCIS) HLA A2+</td>
<td>Planned 4 U.S. sites</td>
<td>48</td>
<td>National Cancer Institute, MD Anderson Cancer Center</td>
</tr>
</tbody>
</table>
NeuVax vaccine

- HER2-derived peptide, HLA-A2/A3+
- MHC class I epitope – CD8+ T cell response
- **Phase III trial**: Prevention of Recurrence in Early-Stage, node-positive BC with low of Intermediate HER2 Expressions with NeuVax™ Treatment (PRESENT)
  - HER2 1+/2+ (IHC)
  - NeuVax + Sargramostim, GM-CSF
  - 758 patients included

June 2016: PRESENT trial is stopped due to futility
< interim analysis based on independent data monitoring committee recommendation
Cancer vaccines in BC

- HER2 is the most used antigen
- Disappointing results in the metastatic setting
- Higher potential for secondary prevention?
- Combining BC vaccines with other strategies
Future directions: personalized Immunotherapy

- Identification of tumor-specific neo-antigens
  - Sequencing (RNAseq & Whole exome sequencing)
  - In silico HLA binding prediction tools
  - Prioritization of potential unique tumor antigens

- Generation of highly personalized DNA-based vaccine or mature DC-based vaccine
Safety and Immunogenicity of a Personalized Synthetic Long Peptide Breast Cancer Vaccine Strategy in Patients With Persistent TNBC Following Neoadjuvant Chemotherapy

- Phase I trial (NCT02427581)
- Started in September 2015 at Siteman Cancer Center (Washington University School of Medicine)

Primary outcome:
- Safety of the vaccine regimen as measured by grade and frequency of adverse events

Secondary outcome:
- Immunogenicity of the vaccine regimen as measured by ELISPOT analyses
- Immunogenicity of the vaccine regimen as measured by multiparametric flow cytometry
ADOPTIVE T-CELL THERAPIES
Adoptive T-cell therapies

- Administration of autologous T cells with genetic material transferred into the cell to redirect them to target breast cancer cells rather than their usual target

→ T cells are activated by
  - Primary signal: CAR (Chimeric Antigen Receptor)
  - Second signal: costimulatory domains (CD28 or CD137)
Adoptive T-cell therapies

- Majority of early-phase trials are being performed to treat **B cell malignancies**
- Minority of trials targeting solid cancers
  - Ongoing studies (USA, Asia) including BC patients with CAR T cells targeting:
    - HER2 (NCT02547961)
    - CEA (NCT 02349724)
    - Mesothelin (NCT02792114)
    - MUC-1 (NCT02587689)
Perspectives for gene-engineered T-cell immunotherapy for solid cancers

IMMUNOMODULATORS
Immunomodulators

- **Cytokines**
  - Combination Therapy of F16IL2 and Paclitaxel in Solid Tumour Patients (NCT01134250)
  - A Study of Ad-RTS-hIL-12 With Veledimex in Subjects With Breast Cancer (NCT02423902)

- **IDO inhibitors**
  - Study of Chemotherapy in Combination With IDO Inhibitor in Metastatic Breast Cancer (NCT01792050)

- **TLR agonists**
  - Toll-like Receptor (TLR) 7 Agonist, Cyclophosphamide, and Radiotherapy for Breast Cancer With Skin Metastases (NCT 01421017)
Regulated intratumoral expression of IL-12 promotes activation of tumor-infiltrating lymphocytes to drive a cytotoxic immune response
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Conclusions

- Growing interest to identify immunotherapeutic approaches to treat BC
  - Numerous ongoing trials !!!

- Remaining challenges
  - Identification of the adequate strategy for the appropriate disease
  - Identification of biomarkers of response → selection of patients
Thank you for your attention