Immunotherapy for Breast Cancer

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Lymphocytic infiltration assessed by HES and outcome in breast cancer

Loi S, ASCO, 2012
# Lymphocytic infiltration assessed by HES and outcome in breast cancer

<table>
<thead>
<tr>
<th>reference</th>
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<th>endpoint</th>
<th>Subclass analyzed</th>
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<tr>
<td>Denkert (J Clin Oncol, 2010)</td>
<td>840</td>
<td>GBG (G-3)</td>
<td>pCR</td>
<td>all</td>
<td>pCR: 41% in TIL+ BC Validated in G-5</td>
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<tr>
<td>Loi (J Clin Oncol, 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>
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<tr>
<td>Loi (ASCO 2012)</td>
<td>935</td>
<td>FinnHer</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></td>
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<td></td>
<td></td>
<td>Predictive value for trastuzumab efficacy: p=0.02</td>
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TIL as risk stratification for TNBC

FinnHer

BIG2-98
<table>
<thead>
<tr>
<th>Factor</th>
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<td>III</td>
<td>132 (47.48)</td>
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<tr>
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<td>Neg</td>
<td>135 (46.71)</td>
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<tr>
<td>Size_Tumor</td>
<td>&lt;=2cm</td>
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<td>Grade:3</td>
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<td>142 (48.80)</td>
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<td>15 (5.15)</td>
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<td>ADJ_anthra</td>
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<td>ADJ_tax</td>
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<td>212 (76.26)</td>
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<td></td>
<td>Tax:Yes</td>
<td>66 (23.74)</td>
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<tr>
<td>grp.SIT</td>
<td>&lt;=60</td>
<td>261 (90.31)</td>
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<tr>
<td></td>
<td>&gt;60</td>
<td>28 (9.69)</td>
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</table>

Anthra
Anthra+tax
Other
tax
DFS: IT and/or ST >60% vs >=60%
OS: IT and/or ST >60% vs >=60%
Extensively infiltrated tumors

Gu-Trantien et al, JCI 2013
Correlations between TILs and immune genes in HER2+ BC

Higher levels of TILs

- CXCL9 (\(\rho=0.46, p<0.01\))
- CD8A (\(\rho=0.41, p<0.01\))
- CXCL13 (\(\rho=0.3, p<0.01\))
- IFNG (\(\rho=0.23, p<0.1\))
- CD3D (\(\rho=0.13, p=0.017\))
- IGKC (\(\rho=0.13, p=0.02\))

Scaled expression

Anti-tumor effector immunity

Lower levels of TILs

- IDO1 (\(\rho=0.58, p<0.01\))
- FOXP3 (\(\rho=0.33, p<0.01\))
- PD-L1 (\(\rho=0.25, p<0.01\))
- CTLA-4 (\(\rho=0.22, p<0.01\))
- CD80 (\(\rho=0.15, p=0.005\))
- PD-1 (\(\rho=0.04, p=0.443\))
- VEGFA (\(\rho=-0.22, p<0.01\))

Pro-tumor/immunosuppressive
Correlations between TILs and immune genes

Tumor microenvironment is immunosuppressive, high levels of T effectors and T regs
High levels of lymphocytic infiltrate is associated with benefit from trastuzumab in HER2+ disease

Significant interaction test $p=0.02$
For every 10% increase in TILs, there was increasing benefit to trastuzumab

Loi et al, Annals Oncol 2014
Treatment with Trastuzumab relieves immunosuppression in some way

Loi et al, SABCS 2013
Augmenting T cell responses with trastuzumab

Days after H2N113 tumor inoculation

Background BALB/c MMTV/neu mice

SABCS 2013
A Phase Ib/II study of an anti-PD-1 monoclonal antibody in advanced, trastuzumab-resistant, *ERBB2*-overexpressing breast cancer: PANACEA

**Screening:** Locally advanced or metastatic breast cancer overexpressing HER2 at diagnosis → Submit an FFPE block from core biopsy for central testing

<table>
<thead>
<tr>
<th>Central Testing:</th>
<th>HER2 by IHC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2 neg:</strong></td>
<td>not eligible</td>
</tr>
<tr>
<td><strong>HER2 pos:</strong></td>
<td>Central PD-L1 testing</td>
</tr>
<tr>
<td><strong>PD-L1 neg:</strong></td>
<td>not eligible</td>
</tr>
<tr>
<td><strong>PD-L1 positive:</strong></td>
<td>enrol</td>
</tr>
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</table>

**Phase Ib:** dose finding for lambrolizumab in 3+3 design → **Phase II** at RP2D

<table>
<thead>
<tr>
<th>Treatment in 3 week cycles:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>PD</th>
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<tbody>
<tr>
<td><strong>T:</strong> trastuzumab 6mg/kg</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td>T</td>
<td></td>
</tr>
<tr>
<td><strong>L:</strong> lambrolizumab at RP2D</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td>L</td>
<td></td>
</tr>
</tbody>
</table>

**Tissue Samples:**
- at enrolment: FFPE block
- Fresh frozen block
- **re-biopsy at PD:** FFPE Block
- Fresh frozen block

**Blood samples:**
- whole blood
- plasma & serum prior to cycles 1, 2, 3, 4, 5 and then every 3 cycles and 6 months post end of tx
Challenges for Therapeutic vaccination

- Endogenous immunity: Features leading to disease eradication versus tolerance
- Stromal elements influencing local immunity
- Therapeutic vaccination: Challenges to achieving sterile immunity versus resetting equilibrium and rescuing a failed host response
Therapeutic vaccination in BC

- Drive setting of clinical trial according to the expression of the antigens in cancer subtype
- Select patients with no or minimal tumor burden
- Perform correlation studies of immunological/clinical response
- Evaluate genetic/immunological profile of responders
Phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer

- Breast cancer (stage II > 1 N+ or stage III)
- Adjuvant setting after standard treatment
- Herceptest 3+ or FISH positive
- No recurrence
- Adequate LVEF (MUGA scan)
Phase I open-label dose-escalation vaccine trial of dHER2 protein with AS15 adjuvant in HER2-overexpressing patients with high-risk breast cancer

Protein dHER2
1255 AA (185 kDa)

Recombinant truncated protein dHER2
919 AA

dHER2 + AS 15 ASCI

- Antibody target
- T-Cell target

AS 15 Adjuvant system (GSK proprietary)

- CpG
- MPL
- QS21
- Liposome formulation

ECD: Extracellular domain
TM: Transmembrane domain
ICD: Intracellular domain
PD: Phosphorylation domain
TK: Tyrosine kinase domain
Endpoints

• Primary:
  Safety

• Secondary:
  Humoral immunogenicity
  Cell-mediated immunogenicity
  Impact of escalating doses of HER2
<table>
<thead>
<tr>
<th>Cohorts</th>
<th>N</th>
<th>Dose</th>
<th>(Route: IM)</th>
<th>Timing</th>
</tr>
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<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>
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<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>
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<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>
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<tr>
<td>Cohort 4</td>
<td>16</td>
<td>500 µg</td>
<td>W 0, 4, 14, 34, 38</td>
<td></td>
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</tbody>
</table>
Study design: Treatment

- **Screening**: Week 0
- **Treatment**: 2 weeks, followed by 4 weeks
- **Analysis**: Week 14

<table>
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<tr>
<th>PBMC</th>
<th>X</th>
<th>X</th>
<th>X</th>
<th>X</th>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
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<td>MUGA</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>
Results

- 304 administrations in 61 patients

- The incidence and intensity of symptoms reported was similar across the study cohorts, which indicates that increasing doses of the dHER2 protein or a different schedule of treatment administration did not lead to a different safety profile
Safety

- No dose relationship toxicity
- 5 patients withdrawn from study for safety reason
- 1 Grade 2 cardiotoxicity (sinus tachycardia)
- 1 Grade 2 fatigue
- 1 patient with Grade 2 headache + myalgia + fatigue
- 2 Grade 1 / 2 asymptomatic decrease in LVEF (12-13%)
Immunogenicity

• For all the antigens investigated, the proportion of seropositive patients and of patients developing an antigen-specific Ab response increased with the dose of the recombinant dHER2 protein.

• At the higher dose level (500 µg), the majority of the patients developed a response to HER2, ECD and ICD after just a few doses of the dHER2 + AS15.
Immunogenicity

Cohort 1 (20 µg)

Cohort 2 (100 µg)

Cohort 3 (500 µg)
Responders anti ECD and anti ICD

% anti-ECD antibody responders

% anti-I CD antibody responders

<table>
<thead>
<tr>
<th>Cohort</th>
<th>% Responders</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
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<tr>
<td>3</td>
<td>88</td>
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<tr>
<td>4</td>
<td>61</td>
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</table>

<table>
<thead>
<tr>
<th>Cohort</th>
<th>% Responders</th>
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<tr>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
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</table>
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.
Immunogenicity

- No ADCC activity was detected.
- The HER2 specific CD4+ T-cell responses were assessed by an approach allowing detection of T-cells at frequencies as low as $10^{-5}$ (1 positive cell in $10^5$ T-cells). This method consists of a two-week repeated stimulation of blood lymphocytes with either a pool of overlapping ECD or ICD peptides. This is followed by intracytoplasmic staining for IFNγ and TNFα and analysis by flow cytometry.
## Immunogenicity

<table>
<thead>
<tr>
<th>Patient</th>
<th>Anti-ECD CD4⁺</th>
<th>Anti-ECD CD8⁺</th>
<th>Anti-ICD CD4⁺</th>
<th>Anti-ICD CD8⁺</th>
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<tr>
<td><strong>Cohort 3</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>D</td>
<td>+</td>
<td>-</td>
<td>+</td>
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<tr>
<td>E</td>
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<tr>
<td>G</td>
<td>-</td>
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<td><strong>Cohort 4</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
<td>I</td>
<td>+</td>
<td>+</td>
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<tr>
<td>M</td>
<td>+</td>
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<td>+</td>
<td>-</td>
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<tr>
<td><strong>Responders</strong></td>
<td>7/13</td>
<td>3/13</td>
<td>6/13</td>
<td>3/13</td>
</tr>
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</table>
Five-year follow-up phase

- Forty-five (92%) of the 49 patients were still alive at the time of the database freeze (DBF, 6 October 2013).
- Four patients were dead.
- Three of the four deceased patients died of breast cancer, for one patient the cause of death was unknown.
Five-year follow-up phase

- Twenty-eight (62%) of the 45 patients with known breast cancer status at the end of the five-year follow-up period were disease-free at the time of DBF.

- 17 (32%) had relapsed and two patients had a new tumor of another histology than breast cancer.
Conclusions

• The dHER2 + AS15 was safe and well tolerated.
• The incidence and intensity of AEs was similar across the study cohorts.
• The dHER2 + AS15 administration schedule with the highest dose of dHER2 protein investigated gave the highest Ab concentrations and the highest rate of responding patients for all the antigens assessed.
Conclusions

- Three patients reported cardiac AEs during the follow-up period. One of these (mitral valve incompetence) was assessed to be possibly related to the study treatment.
- No other SAE was reported during the follow-up period.
- There was a trend for better DFS for patients receiving the highest dose of the dHER2 protein.
Open-label Phase I/II trial of the safety and efficacy of the dHER2 recombinant protein combined with immunological adjuvant AS15 in patients with HER2+ metastatic breast cancer

- Cohort 1: patients receiving the dHER2 + AS15 as first-line therapy of metastatic disease.

- Cohort 2: patients receiving the dHER2 + AS15 as second-line therapy after having received first-line therapy of metastatic disease with trastuzumab, either alone or combined with chemotherapy.
Inclusion Criteria

- A tumor lesion biopsied during or before screening showing either: overexpression of the HER2 protein as determined by IHC or amplification of the HER2 gene as determined by FISH test.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate organ function (bone marrow reserve, renal and hepatic function).
- Baseline left ventricular ejection fraction (LVEF) equal to or greater than the lower limit of normal.
Endpoints

- Safety
- Clinical activity: response according to modified RECIST criteria and TTP
- Immunological response:
  The proportion of patients being anti-dHER2, anti-HER2 ECD and anti-HER2 ICD Ab seropositive.
  Functional activity in vitro, assessed by growth inhibition of HER2-over-expressing breast tumor cells.
  Frequency of cellular immune response in vitro to dHER2, HER2 ECD and HER2 ICD.
Study treatment

Immunization schedule

q2w x 6
q2w x 6
q3w x 6

Cycle 1
Cycle 2
Cycle 3

Weeks
0 2 4 6 8 10
14 16 18 20 22 24
28 31 34 37 40 43

Injection of dHER2 ASCI

Unless progressive disease

→
Forty patients (17 in Cohort 1, 23 in Cohort 2) were enrolled and received at least Dose 1.
The patients’ mean age was 57 with a range from 34 to 76.
Thirty-five of the women were Caucasians and five had another ethnic background.
Fourteen study centers in five countries (Belgium, Colombia, France, Italy, and Peru) enrolled patients.
• The Grade 1 and 2 unsolicited AEs reported by most patients were: back pain, myalgia, arthralgia, pain in extremity, chest pain, injection site pain, asthenia, diarrhea, chills.

• Six Grade 3 AEs were reported and this was the most severe grade observed.

• No cardiac event was reported.
Activity

• One patient in Cohort 1 achieved a CR with a duration of 11 months and one patient in Cohort 2 achieved a PR which lasted for three months.
• Twelve patients had SD as their overall best response to the treatment.
• The duration of the SDs achieved ranged from 18 weeks to 47 weeks.
Activity

Patient with complete response.

Anti-ECD antibody response

CD4 anti-
ECD
ICD

Days

0 50 100 150 200 250 300

0 2000 4000 6000 8000 10000

Positive wells number / 12 wells

cycle 1  cycle 2  cycle 3

Stable Disease  CR
## Activity

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Categories</th>
<th>Cohort 1 (N = 17)</th>
<th>Cohort 2 (N = 23)</th>
<th>Total (N = 40)</th>
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<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Best response</td>
<td>CR</td>
<td>1</td>
<td>6.3</td>
<td>0</td>
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<tr>
<td></td>
<td>PR</td>
<td>0</td>
<td>-</td>
<td>1</td>
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<tr>
<td></td>
<td>SD</td>
<td>5</td>
<td>31.3</td>
<td>7</td>
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<tr>
<td></td>
<td>PD</td>
<td>10</td>
<td>62.5</td>
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</tr>
<tr>
<td></td>
<td>Missing</td>
<td>1</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>

Cohort 1 = dHER2 + AS15 (1st line)
Cohort 2 = dHER2 + AS15 (2nd line)
CR = Complete response
PR = Partial response
SD = Stable disease
PD = Progressive disease
n = number of patients in a given category
% = n / Number of patients with available results x 100
Thirty-four patients were withdrawn from the dHER2 + AS15 because of disease progression. The median time to progression was 2.8 months in Cohort 1 and 3.4 months in Cohort 2.

Four patients died during the study, three of breast cancer progression and one of an unrelated SAE (pulmonary embolism).
Figure 2  Kaplan-Meier curve for time to progression (TTC)

Median:
- Cohort 1: 2.8 [95%CI: 2.3 - 8.4]
- Cohort 2: 3.4 [95%CI: 1.4 - 5.2]

Number at risk:
- Cohort 1: 17 14 7 5 4 3 2 2 2 2 2 2 2 1 0
- Cohort 2: 23 18 11 9 5 5 3 2 2 2 2 1 0
• All the patients in Cohort 1 receiving the dHER2 + AS15 as first-line therapy mounted a humoral immune response against dHER2, HER2 ECD and HER2 ICD.

• The patients in Cohort 2 receiving the dHER2 + AS15 as second-line therapy all showed a humoral immune response against HER2 ICD, while the rate of responders against HER2 ECD was one out of seven, both after Dose 4.
Cohort 1 = dHER2 + AS15 (1st line)
Cohort 2 = dHER2 + AS15 (2nd line)
GMC = geometric mean concentration of Abs
95% CI = 95% confidence interval; LL = Lower limit, UL = Upper limit
Immunogenicity

• There are too few data available to make an assessment of the cell mediated immune response to the dHER2 + AS15 and the impact of the humoral response on tumor cell growth.
Conclusions

- The study met the protocol specified criterion for acceptable safety, namely < 10% of the patients in each cohort reporting a Grade 3 or higher AE, assessed by the investigator to be possibly treatment related.
- The study met the protocol specified criterion for acceptable clinical activity, namely to achieve at least one objective clinical response (CR or PR) in each cohort.
- The immunogenic character of the dHER2 + AS15 was demonstrated.
Antigens in BC subtypes

- **Lobular**: Highly endocrine-responsive
- **Highly endocrine-responsive**: WT1/NY-ESO-1, WT1/PRAME, NY-ESO-1/PRAME, WT1/NY-ESO-1/PRAME
- **HER2 positive**: WT1/NY-ESO-1, WT1/PRAME, NY-ESO-1/PRAME
- **Moderately endocrine-responsive**: WT1/NY-ESO-1, WT1/PRAME, NY-ESO-1/PRAME, WT1/NY-ESO-1/PRAME
- **Triple Negative**: WT1/NY-ESO-1, WT1/PRAME, NY-ESO-1/PRAME, WT1/NY-ESO-1/PRAME

![Bar chart showing the number of cases for different BC subtypes](chart.png)
Post neoadjuvant clinical setting
**IMPULSE trial**

- **Neoadj ChemoR/**: 35%  
- **TNBC**: 65%
- **Surgery**: 40% **pCR**  
  - **no pCR**: 60%
- **Chemotherapy & ASCI**: 3 w  
  - **ASCI alone**: 3 m
- **Placebo**: (5q3week – 8q3months)
- **R**: 1
  - **ChemoR/ * (max 6q3week)**
  - **Surgery**: 2
  - **N+**: X%
  - **N-**: Y%
  
*Chemotherapy*  
- SoC for “Adjuvant Cohort”  
- Authorized for no pCR cohort
  - Chemotherapy & ASCI
  - Chemotherapy alone
  - ASCI alone

PI’s Peter Dubsky and Giuseppe Curigliano
Summary

- Complexity of cancer, tumor heterogeneity and immune escape
- Lack of definitive biomarker(s) for assessment of clinical efficacy of cancer immunotherapies
- Conventional clinical response criteria do not take into consideration differences between response patterns to cytotoxic agents and immunotherapies
- Desperately need for clinical trials
Thank you

Labs
Luisa Lanfrancone
Saverio Minucci
Maria Rescigno
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