Can Anti-HER2 Treatment for Advanced Disease be Individualized in 2017?

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Breast International Group (BIG aisbl), Chair
Relevant disclosures for this talk

• **Consultant (honoraria)**: Roche-Genentech

• **Research grants to my Institute**: most companies, including Roche-Genentech

• **Speakers bureau/stock ownership**: none
A plethora of divinities...

Trastuzumab = Zeus
Pertuzumab, Lapatinib, T-DM1... : who marries whom?
Who is allowed to set the scene first?
Anti-HER2 therapies

**a** Inhibition through direct antibody binding
- Dimerization domain
- Trastuzumab

**b** Inhibition through dimerization inhibition
- Dimerization domain
- Pertuzumab

**c** Inhibition of tyrosine kinase activity
- Tyrosine kinase
- Small-molecule tyrosine kinase inhibitor

*J Baselga, S Swain, Nature Reviews Cancer, 2009*
HER2 signaling pathway

A revised mechanism of action of Trastuzumab

(1+2) Trastuzumab recruits Fc receptor expressing cells such as NK cells

(3) ADCC (or HER2 signaling blockade) causes cell death and the release of “death signals” such as HMGB-1, which triggers the activation of Antigen presenting cells (APC)

(4) As a result CD8-dependent adaptive anti-tumor immunity is generated

HMGB-1 = High Mobility Group Box 1 Protein

M. Smyth, Cancer Cell 2010
Trastuzumab-DM1 in HER2+ MBC

Trastuzumab-DM1

Antibody Drug Conjugate (ADC)

DM1

Maytansine (inhibitor of microtubule assembly)

- Potency > Vincristine or Vinblastine
- Maximal exposure of HER2+ tumors
- Minimal exposure of normal tissues
- Antitumor Properties of trastuzumab

Lewis-Phillips GD et al., Cancer Res 68:9280-9290, 2008
T-DM1 selectively delivers a highly toxic payload to HER2-positive tumour cells.

**Monoclonal antibody:** trastuzumab

**Target expression:** HER2

**Cytotoxic agent:** DM1

**Linker**

**Systemically stable**

**Breaks down in target cancer cell**

**Receptor-T-DM1 complex is internalised into HER2-positive cancer cell**

**Potent antimicrotubule agent is released once inside the HER2-positive tumour cell**

**T-DM1 binds to the HER2 protein on cancer cells**

**T-DM1:** 1st-in-class HER2 antibody-drug conjugate (ADC)
Systemic therapies for HER2+ advanced BC
Standards of care in 2017

First line
- Pertuzumab
- Trastuzumab
- Taxane

Second line
- Lapatinib
- Capecitabine

Later lines*
- TDM1
- Superior to trastuzumab + docetaxel (CLEOPATRA)
- Superior to capecitabine + lapatinib (EMILIA)
- Trastuzumab
- Trastuzumab
- Superior to lapatinib alone

*Best sequencing unknown...
First line setting
Dual anti-HER2 blockade: Trastuzumab and Pertuzumab

**a** Inhibition through direct antibody binding

**b** Inhibition through dimerization inhibition

J Baselga, S Swain, Nature Reviews Cancer, 2009
CLEOPATRA TRIAL

**HER2-positive (Centrally confirmed)**
ABC First-line (N=805)

- **Placebo + Trastuzumab**
  - Docetaxel (Recommended for a minimum of 6 cycles)
  - **PD**

- **Pertuzumab + Trastuzumab**
  - Docetaxel (Recommended for a minimum of 6 cycles)
  - **PD**

Primary endpoint: PFS (as determined by independent review facility)
Secondary endpoint: OS, PFS (investigator assessed), ORR, safety
Only 10-12% received prior adjuvant trastuzumab
# Trastuzumab + Pertuzumab: toxicities

Combination generally well tolerated

No increase in cardiotoxicities

### Table 2. Adverse Events after the Discontinuation of Docetaxel in the Safety Population.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Control Group (N = 261)</th>
<th>Pertuzumab Group (N = 306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common events of any grade — no. of patients (%) †</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alopecia</td>
<td>6 (2.3)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Diarrhea‡</td>
<td>37 (14.2)</td>
<td>86 (28.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>13 (5.0)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>30 (11.5)</td>
<td>39 (12.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (9.6)</td>
<td>41 (13.4)</td>
</tr>
<tr>
<td>Rash‡</td>
<td>21 (8.0)</td>
<td>56 (18.3)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>23 (8.8)</td>
<td>41 (13.4)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>14 (5.4)</td>
<td>22 (7.2)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>32 (12.3)</td>
<td>28 (9.2)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (6.5)</td>
<td>30 (9.8)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>19 (7.3)</td>
<td>25 (8.2)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>4 (1.5)</td>
<td>11 (3.6)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (12.3)</td>
<td>52 (17.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>18 (6.9)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td>Upper respiratory tract infection‡</td>
<td>32 (12.3)</td>
<td>56 (18.3)</td>
</tr>
<tr>
<td>Pruritus‡</td>
<td>15 (5.7)</td>
<td>42 (13.7)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin</td>
<td>10 (3.8)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Muscle spasm‡</td>
<td>6 (2.3)</td>
<td>24 (7.8)</td>
</tr>
</tbody>
</table>

*Swain et al. NEJM 2015*
mOS 56.5 months in the pertuzumab group compared to 40.8 months in the control group.

Swain et al. NEJM 2015
Dual anti-HER2 blockade in first line setting: Can we improve the results?

a) Inhibition through direct antibody binding

b) Inhibition through dimerization inhibition

c) Targeting for intracellular drug delivery

J Baselga, S Swain, Nature Reviews Cancer, 2009
HER2-positive (Centrally confirmed)
ABC, First-line
- 6 months from prior (neo)adjuvant taxanes (N=1095)

**Trastuzumab + Taxane**

Primary endpoint: PFS (as determined by independent review facility) Non-inferiority and superiority assessed
Secondary endpoint: OS, PFS (investigator assessed), ORR, safety, patients-reported outcomes

Perez E. et al, JCO 35, 2016
Phase III MARIANNE Study

Perez E. et al, JCO 35, 2016
PERTAIN Study Design (Phase II Trial)

Postmenopausal patients with HER2-positive and hormone receptor-positive LA/MBC, not previously treated with systemic non-hormonal anticancer therapy in the advanced setting (N=258)*

Choice of chemotherapy must be specified before randomization

Stratification factors:
- Chemotherapy (yes/no)
- Time since adjuvant hormone therapy
  (<12 months/≥12 months/no prior therapy)

* 165 events to detect significant improvement in PFS from 7 months to 10.8 months (I.E. HR 0.645) with 80% power and a 2-sided log-rank test at an alpha level of 0.05.

** Choice of chemotherapy must be specified before randomization; administered per product labelling. LA, locally advanced; R, randomization)
### Previous Systemic Therapy for Breast Cancer (ITT Population)

<table>
<thead>
<tr>
<th>Previous systemic therapy for BC, n (%)*</th>
<th>Pertuzumab + Trastuzumab + AI (n=129)</th>
<th>Trastuzumab + AI (n=129)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67 (51.9)</td>
<td>67 (51.9)</td>
</tr>
<tr>
<td>Chemotherapy, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>20 (15.5)</td>
<td>18 (14.0)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>51 (39.5)</td>
<td>41 (31.8)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>53 (41.1)</td>
<td>36 (27.9)</td>
</tr>
<tr>
<td>Taxanes</td>
<td>33 (25.6)</td>
<td>36 (27.9)</td>
</tr>
<tr>
<td>Trastuzumab, n(%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>10 (7.8)</td>
<td>8 (6.2)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>30 (23.3)</td>
<td>24 (18.6)</td>
</tr>
<tr>
<td>Hormonal therapy, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neoadjuvant</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>54 (41.9)</td>
<td>51 (39.5)</td>
</tr>
<tr>
<td>Other**</td>
<td>2 (1.6)</td>
<td>4 (3.1)</td>
</tr>
</tbody>
</table>

Patients could be counted under ≥ 1 treatment setting, e.g. neoadjuvant/adjuvant if they received > 1 treatment with a different purpose.

* Includes previous lapatinib (n=1 in each arm) and bevacizumab (n=1 in Arm A)

** Metastatic disease (n=3), bone metastasis (n=1), first-line metastasis (n=1), cancer treatment (n=1)
Primary Progression-Free Survival Analysis (Stratified, ITT Population)

<table>
<thead>
<tr>
<th>Group</th>
<th>Events, n (%)</th>
<th>Median, months</th>
<th>(95% CI)</th>
<th>Δ, months</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab + Trastuzumab + AI</td>
<td>74 (57.4)</td>
<td>18.49</td>
<td>(14.09, 21.66)</td>
<td>3.09</td>
<td>0.65 (0.48, 0.89)</td>
<td>0.0070</td>
</tr>
<tr>
<td>Trastuzumab + Al</td>
<td>91 (71.3)</td>
<td>15.80</td>
<td>(11.64, 18.56)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Analysis based upon Kaplan-Meier approach including stratification factors from IXRS. HR from a stratified Cox proportional hazards model including stratification factors from IXRS. Median time of follow-up: 31 months. CI, confidence interval; HR, hazard ratio.

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Duration of Response (Unstratified, ITT Responders)

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab + Trastuzumab + Al (n = 19)</th>
<th>Trastuzumab + Al (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months</td>
<td>27.10</td>
<td>15.11</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>[14.13, 41]</td>
<td>(12.05, 29.96)</td>
</tr>
<tr>
<td>Δ, months</td>
<td>11.99</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.57 [0.36, 0.91]</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.0181</td>
<td></td>
</tr>
</tbody>
</table>

Unstratified analysis based upon Kaplan-Meier approach. HR from a stratified Cox proportional hazards model including stratification factors from IKRS.

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Messages from the PERTAIN trial

• In a patient population with prior exposure to adjuvant CTX (45%) and adjuvant trastuzumab (30%), dual HER2 blockade (T+P) with a taxane (and endocrine therapy) is of added value, but its effect is less impressive than in CLEOPATRA.

• There is a subgroup of patients at first relapse with more « indolent » disease that can be treated very efficiently with endocrine therapy (ET) and dual HER2 blockade (12m gain in PFS compared to ET + trastuzumab).
After first-line with trastuzumab
EMILIA TRIAL DESIGN

HER2-positive (central) ABC

Prior treatment with trastuzumab and a taxane

Progression on metastatic tx or within 6 months of adjuvant tx (N=991)

Primary endpoints: PFS, OS and safety
Majority of patients received only 0 to 1 prior therapy in the metastatic setting.

100% received prior trastuzumab - 84% in the metastatic setting.

Verma et al. NEJM 2012
EMILIA RESULTS

**PFS**
- Median Progression-Free Survival (mPFS): 9.6 months (T-DM1) vs 6.4 months (p < 0.001)

**OS**
- Median Overall Survival (OS): 30.9 months (T-DM1) vs 25.1 months (p < 0.001)

*Verma et al. NEJM 2012*
T-DM1 vs Lapatinib + Capecitabine

Improved outcomes:

- ↑ DFS
- ↑ OS

Good safety profile:

- ↓ Diarrhea
- ↓ Palmar-plantar erythrodysesthesia
- ↓ Vomiting
- ↓ Mucosal Inflammation

Lapatinib + Capecitabine

↓ Thrombocytopenia
↓ Elevated AST/ALT

T-DM1 better
HER2-positive ABC
≥ 2 prior HER2-directed therapy for
advanced BC
Prior treatment with
trastuzumab, lapatinib and a
taxane
(N=602)

T-DM1
PD

Treatment per
physician choice (TPC)
PD

T-DM1
(optional cross-over)

Co-primary endpoints: PFS and OS
Very advanced disease: >60% of patients with more than 3 lines of therapy in the metastatic setting

100% received previous trastuzumab and lapatinib
With results from TH3RESA + EMILIA, Trastuzumab emtansine should be considered as a new standard for patients with HER2-positive advanced breast cancer who have previously received anti-her2 therapy.

Ian E Krop, Lancet Oncol 2014
Recent clinical trials in advanced HER2 positive B.C. that have shown a P.F.S. (primary endpoint) and O.S. gain

First line setting (Cleopatra n=808)
- Trastuzumab + pertuzumab + docetaxel
- Median O.S. not reached (vs 37.6 mos)
- Minimally increased
- Minimal (10%) and interval of ≥12 mos required
- Excluded

Second line setting (Emilia n=991)
- Trastuzumab + docetaxel
- Gain of 5.8 mos
- In favour of T-DM1
- 100% [if adjuvant, free int < 6m] (= 16% of pts)

Third / Fourth line setting (EGF 104900 n=291)
- Capecitabine + lapatinib
- Gain of 4.5 mos despite cross-over in 52%
- Minimally increased

- Trastuzumab + lapatinib
- Lapatinib

- 100% (≥ 3 regimens)
- Absent or « controlled » (≈12%)

CNS disease?
- Absent or « controlled » (11%)

O.S. results

Side effects?

Prior Trastuzumab exposure?

Excluded
EGF104900: significant OS benefit with Herceptin + lapatinib following disease progression

- Median OS (months)
  - Herceptin + lapatinib (n=146):
    - 148
    - 121
    - 88
    - 64
    - 43
    - 25
    - 1
  - Lapatinib (n=145):
    - 148
    - 102
    - 65
    - 47
    - 28
    - 13

- Probability of survival (%)
  - Hazard ratio = 0.74
  - p = 0.026

* Median OS (months)

Not within EMEA-approved indication for Herceptin

Blackwell et al 2010
Most likely trastuzumab needs to be kept “on board” while using an anti-HER2 TKI!
Trials showing «loss of survival» with trastuzumab interruption in advanced disease

LUX BREAST 1

EGF104900 trial

Harbeck N, Presented at SABCS 2014, poster P5-19-01


PFS identical

OS worse for the non trastuzumab-containing arm
Beyond Guidelines

How can we improve treatment tailoring in advanced HER2+ BC?
Selection of the « optimal » use of approved anti-HER2 therapies in advanced disease
Selection of the « optimal » use of approved anti-HER2 therapies
Optimizing the use of new HER2 targeted agents in advanced disease:

No known brain metastases

- **Trastuzumab (T) naive or T-« sensitive » population** (adj. T- free interval ≥ 1y)
  - 1st line: Taxane + T + Pertuzumab
  - 2nd line: T-DM1
  - 3rd line: Lapatinib + Capecitabline
  - 4th line: Lapatinib + Trastuzumab

- **Trastuzumab (T) pretreated and doubt about T-« sensitivity »** (adj. T- free interval < 1y)
  - 1st line: T-DM1
  - 2nd line: Lapatinib + Capecitabline
  - 3rd line: Lapatinib + Trastuzumab
  - 4th line: Trastuzumab + Chemo

*With input from L. Dirix, M.D.*
Optimizing the use of new HER2 targeted agents in advanced disease:

No known brain metastases

“Indolent” disease
Patient “chemotherapy adverse”
and trastuzumab pre-treated
HER2+ HR+ disease

Endocrine therapy
+
Trastuzumab and Pertuzumab
Optimizing the use of new HER2 targeted agents in advanced disease: What if there are known brain metastases as well as distant metastases?

Symptomatic brain mets
- Brain SX (+ RT)
- Stereotactic RT
- Whole brain RT

Asymptomatic brain mets
- Capecitabine + Lapatinib (Landscape trial)*
- Experimental therapy
  - Everolimus-based?
  - Anti-PD1-based?
  - T-DM1-based?

Same sequencing of regimens as before

Then brain RT (± SX)

* 66% RR, most progressions (78%) in CNS after a median time of 5.5m, significant toxicities

Ramakrishna et al, ASCO Guidelines 2014
Patient 202:
response of brain metastases to T-DM1

Before: 1-AUG-2012

3 Cycles of T-DM1

After 3 cycles: 28-SEP-2012

Courtesy E. de Vries
Selection of the « optimal » use of approved anti-HER2 therapies
Individualization of T-DM1 therapy in advanced HER2+ BC

ZEPHIR trial (NCT01565200)
Belgium and Holland
Coordination : Nuclear Medicine Department
(P. Flamen, G. Gebhart - J. Bordet Institute)
Zirconium\textsuperscript{89} - positron emitting isotope $\rightarrow$ PET - compatible physical characteristic (Half-life 78.4 h)
The ZEPHIR Trial: Optimizing T-DM1 Administration in Advanced HER2+ BC

Rationale

1. For TDM1 to be active, the presence of an intact HER2 receptor is "key".
   The zirconium 89 labelled trastuzumab PET/CT is a non invasive test which shows promise in evaluating HER2 expression (extracellular domain) for the entire disease burden

2. It is desirable to identify early on, which patients are unlikely to benefit.
The ZEPHIR Trial: Optimizing T-DM1 Administration in Advanced HER2+ BC

<table>
<thead>
<tr>
<th>The ZEPHIR Trial</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Objective</td>
<td>To show that pre-treatment 89Zr-trastuzumab PET/CT is able to select lesions not responding from treatment with T-DM1</td>
</tr>
<tr>
<td>Primary Endpoint</td>
<td>NPV of the 89Zr-trastuzumab PET/CT</td>
</tr>
<tr>
<td>Secondary Objective</td>
<td>To show that early FDG PET/CT (performed after one cycle of T-DM1) is able to select lesions not responding from treatment with T-DM1</td>
</tr>
<tr>
<td>Secondary Endpoint</td>
<td>NPV of the early FDG PET/CT</td>
</tr>
</tbody>
</table>
ZEPHIR trial design

- Baseline FDG PET/CT
- Diagnostic CT
- T-DM1
  - D1
  - D15
  - D22
- Early FDG PET/CT
- Late FDG PET/CT
- Diagnostic CT
- FU until PD

G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015
Patterns of $^{89}$Zr-trastuzumab PET/CT confronted with FDG-PET/CT

All (A) or most (B) of the metastatic lesions are seen on the HER2 PET.

None (D) or very few (C) metastatic lesions are seen on the HER2 PET.

G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015
Baseline FDG PET

$^{89}\text{Zr-Trastuzumab}$ PET

Post 3 cycles TDM1 FDG PET
Heterogeneity in HER2 « mapping » and early FDG-PET predict time to treatment failure (TTF) under T-DM1 Therapy

Short TTF with HER2 PET patterns C+D

Short TTF if no early FDG-PET response

G. Gebhart et al., Annals of Oncology, published online Nov 23, 2015
Selection of the « optimal » use of approved anti-HER2 therapies
Translational Research efforts in HER2+ BC

- Microenvironment
  - Downstream signaling pathways
  - HER2 itself
  - Other membrane receptors & their ligands
Translational Research efforts in HER2+ BC

I. Advanced disease

- HER2 itself
- PIK3CA mutations
- Other membrane receptors & their ligands
- Downstream signaling pathways
High tumor HER2 mRNA means a better prognosis

Cleopatra:
docetaxel + trastuzumab + pertuzumab
> docetaxel + trastuzumab

Emilia:
T-DM1 > lapatinib + capecitabine

High HER2 mRNA : better prognosis independently from treatment arm
PiK3CA mutations (32% incidence): worse prognosis but still a benefit from treatment

**Cleopatra trial**

<table>
<thead>
<tr>
<th></th>
<th>Single blockade med PFS</th>
<th>Dual blockade med PFS</th>
<th>H.R.</th>
<th>Lap + Cap med PFS</th>
<th>T-DM1</th>
<th>H.R.</th>
</tr>
</thead>
<tbody>
<tr>
<td>piK3CA stats mutant</td>
<td>8.6 m</td>
<td>12.5 m</td>
<td>0.64</td>
<td>4.3 m</td>
<td>10.9 m</td>
<td>0.45</td>
</tr>
<tr>
<td>Wild type</td>
<td>13.8 m</td>
<td>21.8 m</td>
<td>0.67</td>
<td>6.4 m</td>
<td>9.8 m</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Dual blockade works in both cohorts... but larger magnitude of benefit in wild type cohort

**Emilia trial**

T-DM1 works in both cohorts... but larger magnitude of benefit in mutated cohort
Translational Research efforts in advanced HER2+ BC
Translational Research efforts in HER2+ BC
Are TILs prognostic or predictive in the context of advanced disease treated with anti-HER2 therapies?
TIL’s are prognostic in the context of advanced HER2 positive Breast Cancer treated with anti-HER2 MAbs

- Clinical trial = CLEOPATRA (adding pertuzumab to trastuzumab + docetaxel improves PFS by 6.3m and OS by 15.7m in the first line setting)

- Tissue collected from 678 out of 808 patients (N=155 fresh samples, 519 archival samples, only 20 “paired” samples)

- Stromal TILs: median = 10%, range 1-95% (significantly higher in ER negative tumors)

Each 10% increase in TILs is associated with an 11% decrease in the risk of death

TIL’s are prognostic in CLEOPATRA

CCTTG MA.31: Predictive effect of cytotoxic tumor infiltrating lymphocytes for PFS in HER2+ M.B.C.

Liu S et al., P1-09-08

- No demonstration of a prognostic effect

- A lack of cytotoxic CD8+ TILs predicts greatest benefit from trastuzumab over lapatinib

Independent validation needed... but in any case improved toxicity profile of Trastuzumab
When should we use TKI inhibitors?

• Unfortunately p95-HER2 not validated as a biomarker of preferential activity of lapatinib

• Lapatinib (or other TKI) to be explored in Zirconium PET “negative” patients?
Winning the battle against HER2 positive BC!