Systemic therapy for HER2+ Advanced Breast Cancer

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Consultant/Ad Board:

Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, Macrogenics, Merck-Sharp, Merus BV, Novartis, Pfizer, Pierre-Fabre, Roche, Sanofi, Teva
MANAGEMENT OF HER-2 + MBC:

• ABC: primary or metastatic HER-2 status?
  • Pivotal trials
  • Combinations with CT and ET: when & which agents?
• Continue HER-2 blockade beyond progression (change of paradigm)
  • Which anti-HER-2 agent? Dual blockade? Best sequence of therapies?
• Overall good safety profile of anti-HER-2 therapies but cardiac surveillance & management guidelines needed
  • Important problem of brain metastases
Anti-HER-2 therapy should be offered *early* to all HER-2+ MetaBC patients, except in the presence of contra-indications for use of such therapy (*LoE: 1 A*). (91%)
Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

Study design: H0648g Phase III registration trial

ErbB2+ metastatic breast cancer (n=469)

- Anthracycline pretreated
  - Paclitaxel (n=96)
    - Trastuzumab+ paclitaxel (n=92)
- Anthracycline naïve
  - Anthracycline (n=138)
  - Trastuzumab+ anthracycline (n=143)

Chemotherapy ± trastuzumab in the first-line treatment of ErbB2+ metastatic breast cancer

H0648g trial

- Longer OS: 25.1 vs. 20.3 ms (p=0.046)
- Longer TTP: 7.4 vs. 4.6 ms (p<0.001)
- Higher RR: 50 vs. 32% (p<0.001)
- Longer duration: 9.1 vs. 6.1 ms (p<0.001)
First-line treatment of ErbB2+ metastatic breast cancer with docetaxel ± trastuzumab

Study design: M77001 trial (Phase II trial)

N=188
ErbB2+ MBC (IHC3+ and/or FISH+)

Randomisation

Docetaxel* 100 mg/m² q3w×6
n=94

Docetaxel* 100 mg/m² q3w×6+
trastuzumab 4 mg/kg → 2 mg/kg → PD
n=92

2 patients did not receive study medication

*Patients progressing on docetaxel alone could cross over to receive trastuzumab
IHC, immunohistochemistry; FISH, fluorescence in-situ hybridisation; MBC, metastatic breast cancer; PD, progressive disease; q, every
First-line treatment of ErbB2+ metastatic breast cancer with docetaxel ± trastuzumab
Overall survival: M77001 trial

Overall result

Crossover analysis

IMPORTANCE OF STARTING ANTI-HER-2 AGENT EARLY ON

Median values are shown

For highly selected patients* with ER+/HER-2+ MBC, for whom ET is chosen over CT, **ET should be given in combination with anti-HER-2 therapy** (either trastuzumab or lapatinib) since the combination provides PFS benefit (i.e. “time without CT”) compared to ET alone. (LoE: 1 A) (72%)

The addition of anti-HER-2 therapy to ET in the 1st line setting has not led to a survival benefit but long-term follow was not collected in the available trials. In addition, this strategy is currently being directly compared with CT + anti-HER2 therapy.

* Will be defined in the manuscript
First-line anastrozole ± trastuzumab in HR+ and ErbB2+ metastatic breast cancer

TAnDEM study design

- Anastrozole 1 mg daily + trastuzumab 4 mg/kg loading dose → 2 mg/kg qwk until disease progression

ErbB2+, HR+ MBC (n=208)

- Crossover was actively offered to all patients who progressed on anastrozole alone

- Anastrozole 1 mg daily until disease progression

HR, hormone receptor; MBC, metastatic breast cancer; q, every; TAnDEM, TrAstuzumab in Dual HER2 ER-Positive Metastatic breast cancer

First-line anastrozole ± trastuzumab in HR+ and ErbB2+ metastatic breast cancer

TAnDEM trial: PFS

HR, hormone receptor; PFS, progression-free survival; TAnDEM, TrAstuzumab in Dual HER2 ER-Positive Metastatic breast cancer

For patients with ER+/HER-2+ MBC, for whom CT + anti-HER2 therapy was chosen as 1st line therapy and provided a benefit, it is reasonable to use ET + anti-HER2 therapy as maintenance therapy, after stopping CT, although this strategy has not been studied.

(LoE: 1 C) (80%)
HER-2 POSITIVE MBC

MAIN MESSAGES:

All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%)

CHANGE IN PARADIGM IN ONCOLOGY!
Capecitabine 2500 mg/m² bid d1-14 q21 days + continuation of trastuzumab 6 mg/kg q3 weeks (n = 78)

Capecitabine 2500 mg/m² bid d1-14 q21 days (n = 78)

R, randomization; TFI, treatment-free interval; MBD, metastatic breast cancer

Continuation of Trastuzumab Prolongs Time to Progression by Nearly 3 Months

HR = 0.69 (two-sided $P = .0338$; one-sided $P = .0169$)

In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.

(LoE: Expert Opinion) (93%)
In the 1st line setting, for HER-2+ MBC previously treated (in the adjuvant setting) or untreated with trastuzumab, combinations of CT + trastuzumab are superior to combinations of CT + lapatinib in terms of PFS and OS. (LoE: 1 A) (85%)
Progression Free Survival
Centrally-confirmed HER2+ Analysis

Median PFS TTAX/T = 13.7 months
Median PFS LTAX/L = 9.0 months
HR = 1.48 (95% CI = 1.15 - 1.92), P = 0.003

Overall Survival
Centrally-confirmed HER2 + Analysis

HR = 1.25 (95% CI = 0.81 - 1.93), P = 0.32

Gelmon, K. ASCO 2012

MA.31/ EGF108919
COMPLETE TRIAL
### Treatment Discontinuations

**OFF PROTOCOL TREATMENT**

(n = 382)

<table>
<thead>
<tr>
<th>Reason</th>
<th>LTAX/L=202</th>
<th>Number (%)</th>
<th>TTAX/T=180</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5 (2.5)</td>
<td>10 (5.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercurrent Illness</td>
<td>3 (1.5)</td>
<td>3 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>143 (70.8)</td>
<td>121 (67.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>36 (17.8)</td>
<td>19 (10.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Refused Treatment</td>
<td>2 (1.0)</td>
<td>4 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic Progression</td>
<td>4 (2.0)</td>
<td>3 (1.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>9 (4.5)</td>
<td>20 (11.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gelmon, K. ASCO 2012
NEW QUESTION:
The optimal timing to use lapatinib?

CEREBEL trial

HR: 1.70 (1.15-2.50)

ALTTO Trial

ADAPTED FROM JAVIER CORTES
EGF104900: Phase III Study Evaluated Dual HER2 Blockade

- HER2 (FISH+/IHC3+) metastatic breast cancer
- Progression on – Anthracycline – Taxane – Trastuzumab
- Progression on most recent trastuzumab regimen

Primary endpoint:
- Progression-free survival

Secondary endpoints:
- Overall survival
- Overall response rate
- Clinical benefit rate

Crossover allowed to lapatinib + trastuzumab if progression after at least 4 weeks on therapy

- Staging occurred at 4, 8, 12, 16 weeks, and then every 8 weeks
- Steady state of single-agent lapatinib occurs at approximately 7 days

EGF104900: Significant Overall Survival (OS) Benefit With Trastuzumab + Lapatinib Following Disease Progression

<table>
<thead>
<tr>
<th></th>
<th>L</th>
<th>L+T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died, N (%)</td>
<td>113 (78)</td>
<td>105 (72)</td>
</tr>
<tr>
<td>Median, months</td>
<td>9.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>.74 (.57-.97)</td>
<td></td>
</tr>
<tr>
<td>Log-rank P-value</td>
<td>.026</td>
<td></td>
</tr>
</tbody>
</table>

Patients at risk:
- L: 148
- L+T: 148

Survival, %
- 6 Month OS: 80%
- 12 Month OS: 41%

Time from Randomization, months

Trastuzumab and Pertuzumab Bind to Different Regions on HER2 and Have Synergistic Activity

- Trastuzumab suppresses HER2 activity
- Flags cells for destruction by the immune system
- Pertuzumab inhibits HER2 heterodimerization
- Suppresses multiple HER signaling pathways
- Flags cells for destruction by the immune system

THE CONCEPT OF DUAL BLOCKADE
Patients with HER2-positive MBC centrally confirmed (N = 808)

1:1

n=406

Placebo + trastuzumab

PD

n=402

Docetaxel*

≥6 cycles recommended

Pertuzumab + trastuzumab

PD

Docetaxel*

≥6 cycles recommended

• PRIMARY ENDPOINT: PFS
• Randomization was stratified by geographic region and prior treatment status (neo/adjuvant chemotherapy received or not)

*<6 cycles allowed for unacceptable toxicity or PD; >6 cycles allowed at investigator discretion

Baselga, J. SABCS 2011
CLEOPATRA TRIAL: Median PFS and OS

CAUTION!!!!
Only 21% -26% pts had previously received (neo)adjuvant trastuzumab

Ptz+T+D: 56.5 mo. Pla+T+D: 40.8 mo. \( \Delta = 15.7 \text{ mo.} \)

Ptz+T+D: 18.5 mo. Pla+T+D: 12.4 mo. \( \Delta = 6.1 \text{ mo.} \)

HR=0.62 \( p<0.0001 \)

HR 0.68 \( p = 0.0002 \)

Overall survival subgroup analyses

• An exploratory subgroup analysis was performed for patients who had received prior neoadjuvant and/or adjuvant trastuzumab therapy (88 patients). The observed hazard ratio of 0.68 (95% CI 0.30–1.55) indicates overall survival benefit in the pertuzuzumab arm for this subpopulation.
Adverse events (all grades) with ≥25% incidence or ≥5% difference between arms

<table>
<thead>
<tr>
<th>n (%)</th>
<th>Placebo + trastuzumab + docetaxel (n=396)</th>
<th>Pertuzumab + trastuzumab + docetaxel (n=408)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Diarrhea</strong></td>
<td>191 (48.2)</td>
</tr>
<tr>
<td></td>
<td><strong>Alopecia</strong></td>
<td>240 (60.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Neutropenia</strong></td>
<td>197 (49.7)</td>
</tr>
<tr>
<td></td>
<td><strong>Nausea</strong></td>
<td>168 (42.4)</td>
</tr>
<tr>
<td></td>
<td><strong>Fatigue</strong></td>
<td>148 (37.4)</td>
</tr>
<tr>
<td></td>
<td><strong>Rash</strong></td>
<td>95 (24.0)</td>
</tr>
<tr>
<td></td>
<td><strong>Decreased appetite</strong></td>
<td>105 (26.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Mucosal inflammation</strong></td>
<td>79 (19.9)</td>
</tr>
<tr>
<td></td>
<td><strong>Asthenia</strong></td>
<td>121 (30.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Vomiting</strong></td>
<td>97 (24.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Peripheral edema</strong></td>
<td>122 (30.8)</td>
</tr>
<tr>
<td></td>
<td><strong>Pruritus</strong></td>
<td>40 (10.1)</td>
</tr>
<tr>
<td></td>
<td><strong>Constipation</strong></td>
<td>101 (25.5)</td>
</tr>
<tr>
<td></td>
<td><strong>Febrile neutropenia</strong></td>
<td>30 (7.6)</td>
</tr>
<tr>
<td></td>
<td><strong>Dry skin</strong></td>
<td>23 (5.8)</td>
</tr>
</tbody>
</table>

Highlighted are adverse events with ≥5% higher incidence

No increase in cardiac toxicity!
Phase II Study of Pertuzumab, Trastuzumab, and Weekly Paclitaxel

- 36 evaluable pts with 1\(^{st}\) or 2\(^{nd}\) line HER2+ MBC
- ORR = 47%
- No cardiac events

Datko F et al, SABCS 2012. Abstract P5-18-20
Safety of pertuzumab plus trastuzumab plus vinorelbine for 1st line treatment of pts with HER2+ LABC or MBC

Edith A. Perez, José Manuel López-Vega, Lucia Del Mastro, Thierry Petit, Claudio Zamagni, Ulrich Freudensprung, Lydie Bastière-Truchot, Ru Walker, Michael Andersson. SABCS 2013, Poster 2-16-10

Discussion

A cross-study comparison of the incidence of selected AEs (Table 4) suggests that the safety profile of the combination of pertuzumab, trastuzumab, and vinorelbine observed to date in VELVET compares favorably with those seen previously in CLEOPATRA (pertuzumab, trastuzumab, and docetaxel) and HERNATA (trastuzumab and vinorelbine). However, it should be noted that it is difficult to compare results from different clinical trials.

Table 4. Cross-study comparison of the VELVET, CLEOPATRA, and HERNATA trials

<table>
<thead>
<tr>
<th></th>
<th>VELVET</th>
<th>CLEOPATRA</th>
<th>HERNATA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) number of chemotherapy cycles</td>
<td>9 (0-21)</td>
<td>8 (1-35)</td>
<td>10.5 (2-42)</td>
</tr>
<tr>
<td>Median chemotherapy dose intensity, mg/m²/week</td>
<td>14.68*</td>
<td>24.6</td>
<td>NR</td>
</tr>
<tr>
<td>Incidence of selected AEs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16.1</td>
<td>86.8</td>
<td>11.6</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23.6</td>
<td>60.9</td>
<td>NR</td>
</tr>
<tr>
<td>Grade ≥ 3 neutropenia</td>
<td>23.6</td>
<td>41.5</td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>8.5</td>
<td>12.3</td>
<td>21</td>
</tr>
</tbody>
</table>

Conclusions

- There was an acceptable safety profile with the combination of pertuzumab, trastuzumab, and vinorelbine, and no new safety signals were observed.
- The incidences of alopecia and of grade ≥3 hematologic AEs are currently lower than those observed previously with trastuzumab plus vinorelbine or with pertuzumab plus trastuzumab plus docetaxel.
- Based on encouraging interim safety data, enrollment into Cohort 2 began in April 2013 and completed in September 2013. Final efficacy data from both cohorts are expected in 2015.
1st Line Phase III MARIANNE Study

Patients with HER2 positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer

Primary endpoints: PFS as assessed by IRF; Safety
Secondary endpoints: OS; PFS by investigator; PRO analyses; Biomarkers
Superiority design with a Non-inferiority analysis between each of the experimental arms and the control arm
Interim futility analysis: Option to drop experimental arm

DID NOT SHOW SUPERIORITY OF DUAL BLOCKADE!
Great majority of pts previously pretreated with Trastuzumab in the (neo)adjuvant setting

Patients stratified by:
- World region
- Visceral disease (Y/N)
- Neo/Adjuvant therapy (Y/N)
- Trastuzumab and/or lapatinib based therapy (Y/N)
- Visceral disease (Y/N)

n=1092
Trastuzumab + taxane
T-DM1 + placebo

Great majority of pts previously pretreated with Trastuzumab in the (neo)adjuvant setting
# Progression-Free Survival by IRF

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo.)</td>
<td>13.7</td>
<td>14.1</td>
<td>15.2</td>
</tr>
<tr>
<td>Events (no.)</td>
<td>231</td>
<td>236</td>
<td>217</td>
</tr>
<tr>
<td>Stratified HR vs HT</td>
<td>—</td>
<td>0.91</td>
<td>0.87</td>
</tr>
<tr>
<td></td>
<td>(0.73–1.13)</td>
<td>(0.69–1.08)</td>
<td>(P=0.31)</td>
</tr>
<tr>
<td>Stratified HR vs T-DM1</td>
<td>—</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(0.73–1.13)</td>
<td></td>
<td>(P=0.14)</td>
</tr>
</tbody>
</table>

**Note**: The graph shows the progression-free survival over time for different treatment groups. The table provides a summary of the median progression-free survival times, event counts, and hazard ratios (HR) with corresponding confidence intervals and p-values.
Objective Response and Duration of Response

Objective Response Rate

<table>
<thead>
<tr>
<th></th>
<th>Patients, %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>HT</td>
<td>195/287</td>
<td>67.9%</td>
<td></td>
</tr>
<tr>
<td>T-DM1</td>
<td>181/303</td>
<td>59.7%</td>
<td></td>
</tr>
<tr>
<td>T-DM1 + P</td>
<td>192/299</td>
<td>64.2%</td>
<td></td>
</tr>
</tbody>
</table>

Duration of Response

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1 + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo. (95% CI)</td>
<td>12.5 (10.5−16.6)</td>
<td>20.7 (14.8−25.0)</td>
<td>21.2 (15.8−29.3)</td>
</tr>
</tbody>
</table>

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1 + P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>195</td>
<td>181</td>
<td>192</td>
</tr>
<tr>
<td>Follow-up (mo.)</td>
<td>24</td>
<td>14</td>
<td>11</td>
</tr>
</tbody>
</table>
• T-DM1 treatment resulted in **non-inferior but not superior PFS** compared with **trastuzumab plus a taxane** in pts with locally advanced or metastatic HER2+ BC.

• The **addition of pertuzumab to T-DM1 provided no efficacy benefit**
PHEREXA study design
NCT01026142

- HER2-positive MBC (centrally confirmed)
- Prior taxane and H
- Progression during or after H-based therapy for MBC

N = 452

Arm A:
H (8 mg/kg → 6 mg/kg) + X (1,250 mg/m²)
N = 224

Arm B:
H (8 mg/kg → 6 mg/kg) + X (1,000 mg/m²) + P (840 mg → 420 mg)
N = 228

First pt included: Jan 30, 2010
Last pt included: Aug 12, 2013
Clinical cut-off: May 29, 2015

Presented by Ander Urruticoechea
Primary analysis: PFS by independent review facility
ITT population

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Proportion progression-free</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 5 10 15 20 25 30 35 40 45 50 55 60 65</td>
<td>0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0</td>
</tr>
</tbody>
</table>

Arm A: H + X (n = 224)
Arm B: H + X + P (n = 228)

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>mPFS (months)</th>
<th>Δ (months)</th>
<th>HR (95% CI)</th>
<th>Log-rank p-value</th>
<th>mFU (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A</td>
<td>158 (71)</td>
<td>9.0</td>
<td>2.1</td>
<td>0.82 (0.65–1.02)</td>
<td>28.6</td>
</tr>
<tr>
<td>Arm B</td>
<td>168 (74)</td>
<td>11.1</td>
<td></td>
<td>0.07</td>
<td>25.3</td>
</tr>
</tbody>
</table>

a Stratified. CI, confidence interval; FU, follow-up.
Secondary analysis: OS
ITT population

Presented by Ander Urruticoechea

Statistical significance cannot be claimed due to the hierarchical testing of OS after the primary IRF PFS endpoint

<table>
<thead>
<tr>
<th>Events, n (%)</th>
<th>Arm A: H + X (n = 224)</th>
<th>Arm B: H + X + P (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (months)</td>
<td>115 (51)</td>
<td>98 (43)</td>
</tr>
<tr>
<td>∆ (months)</td>
<td>28.1</td>
<td>36.1</td>
</tr>
<tr>
<td>HR (95% CI)a</td>
<td>0.68 (0.51–0.90)</td>
<td></td>
</tr>
<tr>
<td>mFU (months)</td>
<td>29.5</td>
<td>29.3</td>
</tr>
</tbody>
</table>

Arm A: H + X (n = 224)
Arm B: H + X + P (n = 228)

Stratified.

0.0 0.1 0.2 0.3 0.4 0.5 0.6 0.7 0.8 0.9 1.0
0 10 20 30 40 50 60 70 80
Time (months)
Proportion surviving

Arm A 224 190 130 51 19 6 0 0 0
Arm B 228 205 162 66 31 12 1 0 0

a Stratified.
HER-2 POSITIVE MBC: 1\textsuperscript{st} line

The **standard** 1\textsuperscript{st} line therapy for patients **previously untreated** with anti-HER-2 therapy is the combination of CT + trastuzumab and pertuzumab, because it has proven to be superior to CT + trastuzumab in terms of OS in this population. (LoE: 1 A) (86%)

For patients **previously treated** (in the (neo)adjuvant setting) with anti-HER-2 therapy, the combination of CT + trastuzumab and pertuzumab is an **important option** for 1\textsuperscript{st} line therapy. (LoE: 1 A) (76%)

Few (88) of these pts were treated in the Cleopatra trial and all with trastuzumab-free interval > 12 months.
There are currently no data supporting the use of dual blockade with trastuzumab + pertuzumab and CT beyond progression (i.e. continuing dual blockade beyond progression) and therefore this 3 drug regimen should not be given beyond progression outside clinical trials.

There are no data on how to treat patients who have a relapse after receiving CT + trastuzumab + pertuzumab in the early setting.
In a HER-2+ MBC patient, previously untreated with the combination of CT + trastuzumab + pertuzumab, it is acceptable to use this treatment after 1\textsuperscript{st} line, although currently no data exists in this setting.

(LoE: Expert Opinion) (76%)
After 1\textsuperscript{st} line trastuzumab-based therapy, T-DM1 provides superior efficacy relative to other HER-2-based therapies in the 2\textsuperscript{nd} line (vs. lapatinib + capecitabine) and beyond (vs. treatment of physician’s choice).

T-DM1 should be preferred in patients who have progressed through at least 1 line of trastuzumab-based therapy, because it provides an OS benefit.

(LoE: 1 A) (88%)

However, there are no data on the use of T-DM1 after dual blockade with trastuzumab + pertuzumab.
**EMILILIA Study Design**

**HER2+ (central) LABC or MBC (N = 980)**
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 mos of adjuvant tx

**1:1**

**T-DM1**
- 3.6 mg/kg q3w IV

**Capecitabine**
- 1000 mg/m² orally bid, days 1–14, q3w
- + Lapatinib
- 1250 mg/day orally qd

**Stratification factors:** World region, number of prior chemo regimens for MBC or unresectable LABC, presence of visceral disease

**Primary end points:** PFS by independent review, OS, and safety

**Key secondary end points:** PFS by investigator, ORR, duration of response, time to symptom progression

EMILIA Study
T-DM1 vs Cap+Lap

~5 MS BENEFIT IN OS
Probably a new standard of care!
**TH3RESA Study Schema**

- **Stratification factors:** World region, number of prior regimens for advanced BC, presence of visceral disease
- **Co-primary endpoints:** PFS by investigator and OS
- **Key secondary endpoints:** ORR by investigator and safety

---

**HER2-positive (central) advanced BC**
(N=600)

- ≥2 prior HER2-directed therapies for advanced BC
- Prior treatment with trastuzumab, lapatinib, and a taxane

**T-DM1**
3.6 mg/kg q3w IV
(n=400)

**Treatment of physician’s choice (TPC)**
(n=200)

**T-DM1**
( optional crossover)

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*Advanced BC includes MBC and unresectable locally advanced/recurrent BC.*

*TPC could have been single-agent chemotherapy, hormonal therapy, or HER2-directed therapy, or a combination of a HER2-directed therapy with a chemotherapy, hormonal therapy, or other HER2-directed therapy.*

*First patient in: Sep 2011. Study amended Sep 2012 (following EMILIA 2nd interim OS results) to allow patients in the TPC arm to receive T-DM1 after documented PD.*

*Excluding single-agent hormonal therapy.*

**BC,** breast cancer; **IV,** intravenous; **ORR,** objective response rate; **PD,** progressive disease; **q3w,** every 3 weeks.
**SUPERIOR PFS**

44.9% of TPC arm pts received T-DM1 crossover therapy

---

**Final OS Analysis**

3 ms OS BENEFIT
COMMON TOXICITIES OF T-DM1

• Thrombocytopenia
  – Grade ≥3 in approximately 10% of patients
  – Nadir on day 8; Nadir is typically lowest in cycle 1
  – Not typically cumulative
  – Usually manageable with dose reduction
  – Severe hemorrhage is rare, but small number of cases have been reported

• Transaminase elevation
  – Grade ≥3 in approximately 5% of patients
  – Not typically cumulative
  – Usually manageable with dose reduction
  – Severe hepatic dysfunction very rare

Diéras et al, SABCS 2012, Abstract P5-18-06
UNCOMMON TOXICITIES OF T-DM1

• Pneumonitis (≈1% of pts)
  – Typically grade 1/2
  – T-DM1 should be discontinued

• Nodular regenerative hyperplasia (<0.5%)
  – Can lead to noncirrhotic portal hypertension
  – Requires biopsy to diagnose
  – T-DM1 should be discontinued

Diéras et al, SABCS 2012, Abstract P5-18-06
In patients achieving a complete remission, the optimal duration of maintenance anti-HER2 therapy is unknown and needs to be balanced against treatment toxicity, logistical burden and cost.

Stopping anti-HER2 therapy, after several years of sustained complete remission, may be considered in some patients, particularly if treatment re-challenge is available in case of progression.

(LoE: Expert Opinion) (93%)
Regarding the CT component of HER-2 positive MBC treatment:

When pertuzumab is not given, 1\textsuperscript{st} line regimens for HER-2 MBC can include trastuzumab combined with a vinorelbine or a taxane. (LoE: 1 A) (88%)

Differences in toxicity between these regimens should be considered and discussed with the patient in making a final decision. Other CT agents can be administered with trastuzumab but are not as well studied and are not preferred.

In manuscript: Single agent vinorelbine in association with anti-HER-2 therapy has shown superior or equal efficacy compared to taxanes and has a better tolerability.
Extrapolating from HER-2+ disease: Vinorelbine seems at least as good as taxane and significantly less toxic

Vinorelbine & Capecitabine: Consistent efficacy results & NO ALOPECIA
For later lines of therapy, trastuzumab can be administered with several CT agents, including but not limited to, vinorelbine (if not given in 1st line), taxanes (if not given in 1st line), capecitabine, eribulin, liposomal anthracyclines, platinum, gemcitabine, or metronomic CM. (LoE: 2 A) 891%

The decision should be individualized and take into account different toxicity profiles, previous exposure, patient preferences, and country availability.
CT agents to combine with a dual blockade of trastuzumab + pertuzumab are docetaxel (LoE: 1 A) or paclitaxel (LoE: 1 B).

Also possible are vinorelbine (LoE: 2 A) and nab-paclitaxel (LoE: 2 B).

(86% Consensus)
New anti-HER agents
Margetuximab-Fc-optimized anti-HER2 Monoclonal Ab

- Derived from 4D5, parent antibody of trastuzumab
  - Margetuximab and trastuzumab bind same epitope on HER2 with high affinity
- Fc domain modifications enhance NK cell and macrophage activation
  - Enhanced binding to low affinity variants of activating Fcγ receptor, CD16A
  - Diminished binding to inhibitory Fcγ receptor, CD32B
- Enhanced antibody dependent cell-mediated cytotoxicity \textit{in vitro}
- Patients with high affinity Fc receptors had prolonged PFS with trastuzumab \textit{(Musolino et al., J Clin Oncol 26: 1789-96 (2008))}
- SOPHIA will test if enhanced ADCC leads to superior outcomes in HER+ MBC

SOPHIA Study to Establish Superiority to Trastuzumab

**Arm 1**
Margetuximab + chemotherapy

**Arm 2**
Trastuzumab + chemotherapy

**PI Choice of Chemotherapy**
(Capecitabine, eribulin, gemcitabine or vinorelbine)

**1:1 Randomization**
(n = 530)

**Sequential Primary Endpoints: Progression-Free Survival & Overall Survival:**
- **PFS** (N=257, HR=0.67, \(\alpha=0.05\), power=90%)
- **OS** (N=358, HR=0.75, \(\alpha=0.05\), power=80%)
Brain Metastases
## Incidence of CNS Metastases in Trastuzumab-Treated Patients

<table>
<thead>
<tr>
<th>Case Series</th>
<th>Patient Population</th>
<th>#</th>
<th>Overall</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bendell et al, 2003</td>
<td>Trastuzumab-treated</td>
<td>42</td>
<td>123</td>
<td>34</td>
</tr>
<tr>
<td>Clayton et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>23</td>
<td>93</td>
<td>25</td>
</tr>
<tr>
<td>Lai et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>38</td>
<td>79</td>
<td>48.1</td>
</tr>
<tr>
<td>Lower et al, 2003</td>
<td>Trastuzumab-treated Non-trastuzumab-treated</td>
<td>22</td>
<td>87</td>
<td>26</td>
</tr>
<tr>
<td>Pinder et al, 2007</td>
<td>Trastuzumab-treated first-line Non-trastuzumab-treated</td>
<td>95</td>
<td>231</td>
<td>41</td>
</tr>
<tr>
<td>Shmueli et al, 2004</td>
<td>Trastuzumab-treated</td>
<td>10</td>
<td>41</td>
<td>21</td>
</tr>
<tr>
<td>Stemmler et al, 2006</td>
<td>Trastuzumab-treated</td>
<td>42</td>
<td>136</td>
<td>30.9</td>
</tr>
<tr>
<td>Yardley et al, 2007</td>
<td>HER2-positive MBC</td>
<td>236</td>
<td>768</td>
<td>30.7</td>
</tr>
<tr>
<td>Yau et al, 2006</td>
<td>Trastuzumab-treated</td>
<td>23</td>
<td>87</td>
<td>26.4</td>
</tr>
</tbody>
</table>
Patients with a single or a small number of potentially resectable brain metastasis should be treated with surgery or radiosurgery. Radiosurgery is also an option for some unresectable brain metastases. (LoE: 1 B) (92%)

If surgery/radiosurgery is performed it may be followed by whole brain radiotherapy but this should be discussed in detail with the patient, balancing the longer duration of intracranial disease control and the risk of neurocognitive effects (LoE: 1 B) (72%)

✓ A multi-disciplinary discussion including neurosurgeons, radiation oncologists and medical oncologists is indispensable in determining the optimal treatment for each patient.
✓ The treatment plan can also be a combination of these three available therapeutic approaches
Because patients with HER2+ve MBC and brain metastases can live for several years, consideration of long term toxicity is important and less toxic local therapy options (e.g. stereotactic RT) should be preferred to whole brain RT, when available and appropriate (e.g. in the setting of a limited number of brain metastases).

(LoE: 1C) (89%)
HER-2 POSITIVE MBC & BRAIN METASTASES

in patients with HER2 positive ABC who develop brain metastases with stable extracranial disease, systemic therapy should not be changed. (LoE: 1 C) (95%)

For patients with HER2 positive cancers where brain metastases are the only site of recurrence, the addition of CT to local therapy is not known to alter the course of the disease. It is recommended to re-start the anti-HER2 therapy (trastuzumab) if this had been stopped. (LoE: 1 C) (83%)
Trastuzumab Improves Survival in Patients With mCNS Disease: U S Retrospective Analysis

LANDSCAPE STUDY: a FNCLCC phase II study with lapatinib and capecitabine in pts with brain metastases from HER-2+ MBC before whole brain RT

Primary endpoint: CNS volumetric response

45 pts  

CNS-OR: 29/43 = 67.4% (95% CI: 52-81)

<table>
<thead>
<tr>
<th>CNS volumetric change</th>
<th>N = 43 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 80% reduction</td>
<td>9 (20.9)</td>
</tr>
<tr>
<td>50-&lt;80% reduction</td>
<td>20 (46.5)</td>
</tr>
<tr>
<td>20- &lt;50% reduction</td>
<td>6 (14)</td>
</tr>
<tr>
<td>&gt; 0- &lt;20% reduction</td>
<td>2 (4.7)</td>
</tr>
<tr>
<td>Progression*</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

* 2 patients had extra-CNS disease progression

NSS improvement: 14/24 = 58.3% (95% CI: 36.6-77.9)

IMP: pts previously untreated with WBRT; phase 2 study

Bachelot et al, ASCO 2011
CEREBEL Study: A Phase III Randomized Open-Label Study of Lapatinib plus Capecitabine vs Trastuzumab + Capecitabine in HER2-Positive Metastatic Breast Cancer

**Inclusion Criteria:**
- Stage IV HER2+ breast cancer
- Prior anthracycline and a taxane
- Prior treatment with CT, trastuzumab, HT, RT is permitted
- LVEF ≥ 50%, normal organ function

**Main Exclusion Criteria:**
- History and/or current evidence of CNS metastases
- Prior therapy with lapatinib or ErbB2 inhibitor other than trastuzumab

**Primary endpoint:** Incidence of CNS metastases at site of first relapse

**Secondary endpoints:** Incidence of CNS progression at any time, time to first CNS progression, PFS, OS, ORR, CBR, duration of response, toxicity, pharmacogenetics, and biomarker analysis

**Treatment Regimens:**
- Lapatinib 1250 mg PO qd continuously + capecitabine 2000 mg/m²/d PO days 1-14 q3 weeks
- Capecitabine 2500 mg/m² bid d1-14 q21 days

**EARLY CLOSURE!!**

475 pts enrolled
40% completed 12 months, had PD or died
Primary endpoint: CNS endpoints (modified ITT)

<table>
<thead>
<tr>
<th></th>
<th>Lapatinib + capecitabine (N=251)</th>
<th>Trastuzumab + capecitabine (N=250)</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS as first site of relapse, n (%)</td>
<td>8 (3)</td>
<td>12 (5)</td>
<td>0.65 (0.26, 1.63)</td>
<td>0.360</td>
</tr>
<tr>
<td>Incidence of CNS progression at any time, n (%)</td>
<td>17 (7)</td>
<td>15 (6)</td>
<td>1.14 (0.52, 2.51)</td>
<td>0.8646</td>
</tr>
<tr>
<td>Time to first CNS progression, median (range)</td>
<td>5.7 (2–17)</td>
<td>4.4 (2–27)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

OS (ITT population)

LOW NUMBER OF BRAIN METS

TRASTUZUMAB + CAPECITABINE BETTER
All patients with HER-2+ MBC who relapse after adjuvant anti-HER-2 therapy should be considered for further anti-HER-2 therapy, except in the presence of contraindications (LoE: 1 B) (97%).

The choice of the anti-HER-2 agent will depend on country-specific availability, the specific anti-HER-2 therapy previously administered, and the relapse free interval. (88%)

The optimal sequence of all available anti-HER-2 therapies is currently unknown. (88%)

The optimal duration of anti-HER-2 therapy for MBC (i.e. when to stop these agents) is currently unknown. (97%)
MANAGEMENT OF HER-2 + MBC:

MANY QUESTIONS SILL UNANSWERED

• Optimal duration of anti-HER-2 therapy for ABC (indefinitely?)
• At progression should only the cytotoxic drug be changed of both the cytotoxic and the anti-HER-2 agent
• Is treatment beyond PD also true for other anti-HER-2 agents?
• Dual blockade for everyone or some?
• The role of the dual blockade without CT
• Triple blockade?
• Best sequence of anti-HER-2 therapies
• Mechanisms of resistance & ways to overcome it; Predictive markers (role of PI3K mutations,...)
• NEW ANTI-HER-2 AGENTS in development
Advanced Breast Cancer

2-4 November 2017 • Lisbon, Portugal
Fourth International Consensus Conference

SAVE THE DATE

RECEIVE UPDATES AT: WWW.ABC-LISBON.ORG • #ABClisbon