PRESENT AND EMERGING TREATMENT OPTIONS IN HER2/NEU OVEREXPRESSING METASTATIC BREAST CANCER

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BREAST CANCER IS A HETEROGENEOUS GROUP OF DISEASES

INCIDENCE OF METASTASES IN DEPENDENCE FROM THE MOLECULAR SUBTYPE

Cumulative incidence curves of first distant metastasis by breast cancer subtype

OVERALL SURVIVAL FROM MBC IN DEPENDENCE ON MOLECULAR CHARACTERISTICS

- Analysis of outcome in 189 primary breast cancer cases
  - HER2 amplification in 30%
  - Significant correlation with DFS and OS
  - Stronger prognosticator of outcome than the most relevant “conventional” markers such as nodal status and hormone-receptor

- 3,726 patients
- Median observation: 14.8 years
- Median OS from diagnosis of MBC:
  - Luminal A: 2.2 years
  - HER2 positive: 0.7 years (remark: pre-Trastuzumab)
  - Basal: 0.5 years (p<0.001)

THE HER FAMILY OF RECEPTORS

*HER2 dimerizes with other members of the HER family.

HER2/NEU

Molecular pathways and clinical characteristics of breast cancer

- HER2 gene amplification is associated with increased tumour proliferation
- HER2 amplification is associated with high-grade disease, nodal metastases, tumour size, and inversely correlated with ER status
- HER2 activates ER in a low-oestrogen environment
- ER activates intracellular signalling potentiating HER2 activity and downregulates HER2 expression
  - This negative loop is neutralised by HER2 overexpression
- Tumour proliferation linked to RAS/MAPK cascade
- Increased cell migration and lymph node involvement linked to Akt/PI3 kinase activity

HER2-POSITIVE MBC

Evidence for targeted treatment

Current standards
- Chemotherapy plus trastuzumab
- Chemotherapy plus trastuzumab/pertuzumab
- T-DM1
- Trastuzumab/lapatinib
- Lapatinib/capecitabine

Specific treatment situations
- Trastuzumab or lapatinib plus aromatase-inhibitors
- Brain metastases

Novel approaches
- Second- and third-generation TKIs (neratinib, tucatinib)
- Immunotherapy with checkpoint inhibitors
- Optimised antibodies and ADCs
TRASTUZUMAB IN HER2-POSITIVE MBC
A unique story of success

Phase III trial, 469 patients, MBC, HER2-pos, first-line
- AC +/- trastuzumab or paclitaxel +/- trastuzumab
- PFS: 7.4 versus 4.6 months; p<0.001
- OS: 25.1 versus 20.3 months; p=0.046

Phase II trial, 186 patients, MBC, first-line
- Docetaxel +/- trastuzumab
- PFS: 11.7 versus 6.1 months; p=0.0001
- OS: 31.2 versus 22.7 months; p=0.0325

OS IN DEPENDENCE FROM TRASTUZUMAB-TREATMENT AND HER2-STATUS

Comparative pharmacokinetics of trastuzumab subcutaneous formulation administered using a proprietary single-use injection device, or manually using a syringe

- Bioequivalence for the co-primary PK endpoints, AUC0–21 days and $C_{\text{max}}$, between Herceptin SC administered using the SID and hand-held manual syringe was demonstrated
- Overall secondary PK parameters were also comparable between the two methods of administration
- SID: no failures, consistently high performance; tolerability did not differ from administration from the hand-held syringe
- Herceptin SID may have even greater potential to improve patient convenience

Randomised open-label Phase III non-inferiority study to compare the PK, efficacy and safety of trastuzumab SC and IV in HER2-positive EBC

**Primary endpoint**
Show non-inferiority of SC vs. IV based on co-primary endpoints
- PK: observed Trastuzumab $C_{\text{trough}}$ pre-dose Cycle 8 (pre-surgery)
- Efficacy: pathological complete response (pCR) in the breast

Pathological complete response to trastuzumab subcutaneous fixed-dose formulation in the HannaH study

- Subgroup analysis of patient demographics and tumour characteristics and influence of body weight (BW) and serum trough ($C_{\text{trough}}$) concentration of trastuzumab:
  - Numerically higher pCR rate point estimate in Herceptin SC vs. IV in the majority of subgroups
  - The 600 mg fixed dose of Herceptin SC is efficacious irrespective of body weight
  - Additional analyses and MLR showed neither body weight nor serum $C_{\text{trough}}$ of Herceptin affected efficacy in either treatment arm

TRASTUZUMAB: ESCAPE-MECHANISMS

- High EGFR expression (Smith I, et al. 1993)
- Somatic mutations of the HER2/neu gene (Shigematsu H, et al. 2006)
HALMARKS OF THE HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) -HER3 ACTIVATION AND SIGNALLING PATHWAY

PERTUZUMAB AND TRASTUZUMAB BIND TO DIFFERENT REGIONS ON HER2

Synergistic activity

TRASTUZUMAB PLUS PERTUZUMAB IN HER2-POSITIVE MBC

The CLEOPATRA trial

Phase III trial, 808 pat., MBC, HER2-pos., first-line Docetaxel (D) + trastuzumab (T) +/- pertuzumab (P)

Pertuzumab: Anti-HER2 antibody preventing HER2 / HER3 heterodimerization

PFS 18.5 vs. 12.4 months
HR=0.62; 95% CI 0.51–0.75; p<0.001

50 months median follow-up:
D+TP 56.5 vs. D+T 40.8 months
HR 0.68; 95% CI 0.56–0.84; p=0.0002


CLEOPATRA: PROGRESSION-FREE SURVIVAL IN PRESPECIFIED SUBGROUPS

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of patients</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>808</td>
<td>0.63 (0.52-0.76)</td>
</tr>
<tr>
<td>Previous neoadjuvant or adjuvant chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>432</td>
<td>0.63 (0.49-0.82)</td>
</tr>
<tr>
<td>Yes</td>
<td>376</td>
<td>0.61 (0.46-0.81)</td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>306</td>
<td>0.72 (0.53-0.97)</td>
</tr>
<tr>
<td>North America</td>
<td>135</td>
<td>0.51 (0.31-0.84)</td>
</tr>
<tr>
<td>South America</td>
<td>114</td>
<td>0.46 (0.27-0.78)</td>
</tr>
<tr>
<td>Asia</td>
<td>253</td>
<td>0.68 (0.48-0.95)</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 yr</td>
<td>681</td>
<td>0.65 (0.53-0.80)</td>
</tr>
<tr>
<td>≥65 yr</td>
<td>127</td>
<td>0.52 (0.31-0.86)</td>
</tr>
<tr>
<td>&lt;75 yr</td>
<td>789</td>
<td>0.64 (0.53-0.78)</td>
</tr>
<tr>
<td>≥75 yr</td>
<td>19</td>
<td>0.55 (0.12-2.54)</td>
</tr>
<tr>
<td>Race or ethnic group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>480</td>
<td>0.62 (0.49-0.80)</td>
</tr>
<tr>
<td>Black</td>
<td>30</td>
<td>0.64 (0.23-1.79)</td>
</tr>
<tr>
<td>Asian</td>
<td>261</td>
<td>0.68 (0.49-0.95)</td>
</tr>
<tr>
<td>Other</td>
<td>37</td>
<td>0.39 (0.13-1.18)</td>
</tr>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visceral disease</td>
<td>630</td>
<td>0.55 (0.45-0.68)</td>
</tr>
<tr>
<td>Nonvisceral disease</td>
<td>178</td>
<td>0.96 (0.61-1.52)</td>
</tr>
<tr>
<td>Hormone-receptor status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER-positive, PgR-positive, or both</td>
<td>388</td>
<td>0.72 (0.55-0.95)</td>
</tr>
<tr>
<td>ER-negative and PgR-negative</td>
<td>408</td>
<td>0.55 (0.42-0.72)</td>
</tr>
<tr>
<td>ER and PgR status unknown</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
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<tr>
<td>IHC 3+</td>
<td>721</td>
<td>0.60 (0.49-0.74)</td>
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<tr>
<td>FISH-positive</td>
<td>767</td>
<td>0.64 (0.53-0.78)</td>
</tr>
</tbody>
</table>

T-DM1: MECHANISM OF ACTION

Emtansine release
Inhibition of microtubule polymerisation

Internalisation
Lysosome

SCHEMATIC OF TRASTUZUMAB-DM1 (T-DM1) INCLUDING THE [N-MALEIMIDOMETHYL] CYCLOHEXANE-1-CARBOXYLATE (MCC) LINKER

1. **Pretreated** HER2-positive MBC: EMILIA phase III trial (T-DM1 vs. lapatinib/capecitabine)

2. **Pretreated** HER2-positive MBC: TH3RESA phase III trial (T-DM1 vs. treatment by physician’s choice)

3. **First-line treatment** for HER2-positive MBC: MARIANNE phase III trial (T-DM1 vs. trastuzumab + docetaxel vs. T-DM1 + pertuzumab)
T-DM1 IN PRETREATED HER2-POSITIVE MBC: EMILIA

- Phase III trial, 991 patients, HER2-positive MBC
- T-DM1 versus lapatinib plus capecitabine
- Second-line after progression on first-line therapy with taxanes plus trastuzumab
- Progression within 6 months after the end of trastuzumab-therapy for early-stage disease
- PFS 9.6 months versus 6.4 months (HR 0.65; 95% CI 0.55-0.77; p<0.001)

## EMILIA: PRIOR SYSTEMIC TREATMENT

<table>
<thead>
<tr>
<th>Prior Treatment Type, n (%)</th>
<th>Cap + Lap (n=496)</th>
<th>T-DM1 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Taxanes</td>
<td>494 (100)</td>
<td>493 (100)</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>302 (61)</td>
<td>303 (61)</td>
</tr>
<tr>
<td>Endocrine agents</td>
<td>204 (41)</td>
<td>205 (41)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Therapy for MBC, n (%)</th>
<th>Cap + Lap (n=496)</th>
<th>T-DM1 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>438 (88)</td>
<td>435 (88)</td>
</tr>
<tr>
<td>No</td>
<td>58 (12)</td>
<td>60 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior Trastuzumab Treatment, n (%)</th>
<th>Cap + Lap (n=496)</th>
<th>T-DM1 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EBC only</td>
<td>77 (16)</td>
<td>78 (16)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Duration of Trastuzumab Treatment, n (%)</th>
<th>Cap + Lap (n=496)</th>
<th>T-DM1 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 yr</td>
<td>212 (43)</td>
<td>210 (42)</td>
</tr>
<tr>
<td>≥1 yr</td>
<td>284 (57)</td>
<td>285 (58)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Median Time since last Trastuzumab, mos (range)</th>
<th>Cap + Lap (n=496)</th>
<th>T-DM1 (n=495)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 (0–98)</td>
<td>1.5 (0–63)</td>
<td></td>
</tr>
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</table>

EMILIA: OBJECTIVE RESPONSE RATE (ORR) AND DURATION OF RESPONSE (DOR) IN PATIENTS WITH MEASURABLE DISEASE

**ORR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ORR</th>
<th>Difference (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>30.8%</td>
<td>12.7% (6.0, 19.4)</td>
<td>0.0002</td>
</tr>
<tr>
<td>T-DM1</td>
<td>43.6%</td>
<td></td>
<td></td>
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</table>

**DOR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median, mos (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cap + Lap</td>
<td>6.5 (5.5, 7.2)</td>
</tr>
<tr>
<td>T-DM1</td>
<td>12.6 (8.4, 20.8)</td>
</tr>
</tbody>
</table>

EMILIA: 2ND INTERIM ANALYSIS OF OS

Stratified hazard ratio, 0.68 (95% CI, 0.55-0.85)  
p<0.001  
Efficacy stopping boundary, p=0.0037 or hazard ratio, 0.73

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Lapatinib-capecitabine</th>
<th>T-DM1</th>
</tr>
</thead>
<tbody>
<tr>
<td>496</td>
<td>404</td>
<td>310</td>
</tr>
<tr>
<td>176</td>
<td>129</td>
<td>73</td>
</tr>
<tr>
<td>73</td>
<td>53</td>
<td>35</td>
</tr>
<tr>
<td>35</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

T-DM1 IN PRETREATED HER2-POSITIVE MBC: TH3RESA

- Phase III trial, 603 patients, HER2-positive MBC
- T-DM1 versus treatment by physician’s choice (TPC)
- Prior treatment with ≥2 treatment line for MBC
- 2:1 randomisation, cross-over allowed
- >80% trastuzumab-base therapy as TPC

CURRENT STANDARDS AND CAVEATS

- **First-line: trastuzumab/pertuzumab/docetaxel (CLEOPATRA)**
  - PFS 18.5 vs. 12.4 months (HR 0.62)
  - ~10% of pts. prior exposure to adj. trastuzumab
  - PFS: 16.9 vs. 10.4 months (HR 0.62)
- **Second-line (and early relapse): T-DM1 (EMILIA)**
  - Caveat: None of the pts. in EMILIA treated with dual HER2-inhibition in the first-line setting
  - Activity of T-DM1 in pts. pretreated with trastuzumab/pertuzumab: Treatment duration ≥6 months 30.8% (95% CI 20.6-41.1)
  - Median treatment duration: 4 months (95% CI 2.7-5.1)
- **Further questions:**
  - T-DM1 first-line?
  - TP in the second-line setting?
  - Beyond second-line? The role of lapatinib?

T-DM1 AS FIRST-LINE TREATMENT IN HER2-POSITIVE MBC: MARIANNE

- Phase III trial, 1,095 patients, HER2-positive MBC
- First-line; >6 months from prior adjuvant/neoadjuvant taxane- or vinorelbine-containing chemo

- HER2-positive (central) LABCa or MBC
- No prior chemotherapy for LABC/MBC
- >6 months from prior neo-/adjuvant vinca alkaloid or taxane chemotherapy

N=1095

- **Stratification factors:** World region, prior neo-/adjuvant therapy (if yes: prior trastuzumab/lapatinib), visceral disease
- **Primary endpoint:** PFS by independent review facility (IRF), non-inferiority and superiority assessed
- **Key secondary endpoints:** OS, PFS by investigator, ORR, safety, patient-reported outcomes

**Treatment Arms:***

- **Trastuzumab + docetaxel**
  - (8 mg/kg then 6 mg/kg + 100 or 75 mg/m² q3w)
  - Trastuzumab + paclitaxel
  - (4 mg/kg LD then 2 mg/kg + 80 mg/m² qw)

- **T-DM1 + placebo**
  - (3.6 mg/kg + 840 mg LD then 420 mg q3w)

- **T-DM1 + pertuzumab**
  - (3.6 mg/kg + 840 mg LD then 420 mg q3w)

T-DM1 AS FIRST-LINE TREATMENT IN HER2-POSITIVE MBC: MARIANNE

- Median follow-up 35 months
- Prior adjuvant/neoadjuvant trastuzumab: ~30% (CLEOPATRA ~10%)

CLEOPATRA (trastuzumab/pertuzumab plus docetaxel) as standard-of-care in the first-line setting but T-DM1 as relevant option in patients not deemed as candidates for standard treatment

<table>
<thead>
<tr>
<th></th>
<th>HT</th>
<th>T-DM1</th>
<th>T-DM1+P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (mo.)</td>
<td>50.9</td>
<td>53.7</td>
<td>51.8</td>
</tr>
<tr>
<td>Events (no.)</td>
<td>169</td>
<td>175</td>
<td>168</td>
</tr>
<tr>
<td>Stratified HR (97.5% CI) vs HT</td>
<td>—</td>
<td>0.93</td>
<td>(0.73–1.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.67–1.11)</td>
</tr>
<tr>
<td>Stratified HR (97.5% CI) vs T-DM1</td>
<td>—</td>
<td>1.00</td>
<td>(0.78–1.28)</td>
</tr>
</tbody>
</table>

TRASTUZUMAB/PERTUZUMAB AS SECOND-LINE TREATMENT: PHEREXA

- Phase III trial, 452 patients, HER2-positive MBC
- Disease progression on or after first-line trastuzumab
- Prior taxane-treatment required

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

- PFS (independently assessed): 9 vs. 11.1 months (HR 0.82; 95% CI 0.65-1.02; p=0.0731)
- OS 28.1 vs. 36.1 months (HR 0.68; 95% CI 0.51-0.90)
- Formally negative trial – T-DM1 remains the second-line standard in pts. Without prior dual HER2-inhibition (EMILIA)

LAPATINIB: MECHANISMS OF ACTION

- Lapatinib: First-generation (reversible) inhibitor of the tyrosine-kinase domains of HER2 and EGFR
- Inhibits Akt and ERK1/2, resulting in upregulation of pro-apoptotic genes\(^1\)-\(^3\)
- Increased rate of apoptosis is associated with clinical response (n=33 biopsy samples)\(^4\)

MA.31 (NCT00667251)

First direct comparison of trastuzumab vs. lapatinib in MBC

- Prospective randomised Phase III study
- 636 patients, HER2-positive MBC (525 centrally confirmed), first-line treatment
- Trastuzumab plus taxane versus lapatinib plus taxane
- First direct comparison of trastuzumab vs. lapatinib in MBC
- Taxanes: Paclitaxel weekly or docetaxel every three weeks
- Combination therapy for 24 weeks followed by anti-HER2 maintenance

PFS 9 vs. 11.3 months (HR 1.37; 95% CI 1.20 -1.83)

Safety (647 patients included in the safety analysis):
- Grade 3/4 rash 8% (lapatinib) vs. 0% (trastuzumab)
- Grade 3/4 diarrhoea 19% vs. 1%
- Febrile neutropenia rate 17.3% vs. 2%
LAPATINIB: ALTERNATIVE MECHANISMS OF ACTION

- Receptor dimerization results in receptor internalisation and degradation in lysosomes
- Lapatinib blocks ubiquitination and inhibits degradation by receptor stabilisation within the membrane
- Potentially improves activity of anti-HER2-mABs
T PLUS L: DUAL HER2 INHIBITION IN MBC: PFS AND OS BENEFIT

- Phase III trial, 296 patients, HER2-positive MBC
- Lapatinib vs. lapatinib plus trastuzumab
- Median number of prior trastuzumab-based regimens for MBC: 3

**PFS**

![PFS Graph]

**OS**

![OS Graph]

HER2-POSITIVE MBC

Evidence for targeted treatment

Current standards
- Chemotherapy plus trastuzumab
- Chemotherapy plus trastuzumab/pertuzumab
- T-DM1
- Trastuzumab/lapatinib
- Lapatinib/capecitabine

Specific treatment situations
- Trastuzumab or lapatinib plus aromatase-inhibitors
- Brain metastases

Novel approaches
- Second- and third-generation TKIs (neratinib, tucatinib)
- Immunotherapy with checkpoint inhibitors
- Optimised antibodies and ADCs
Evidence from two randomised Phase III studies\(^1,2\)
- First-line therapy AI +/- HER2-directed therapy
- PFS on AI alone approximately 3 months in both trials indicating primary resistance to endocrine therapy alone
- Limited PFS improvement by the addition of lapatinib or trastuzumab
- No OS benefit
- RR trastuzumab 20.3% vs. 6.8%; RR lapatinib 28% vs. 15%

HER2-TARGETED TREATMENT PLUS ENDOCRINE THERAPY IN LUMINAL B/HER2-POSITIVE MBC

HER2-POSITIVE MBC

Evidence for targeted treatment

Current standards
- Chemotherapy plus trastuzumab
- Chemotherapy plus trastuzumab/pertuzumab
- T-DM1
- Trastuzumab/lapatinib
- Lapatinib/capecitabine

Specific treatment situations
- Trastuzumab or lapatinib plus aromatase-inhibitors
- Brain metastases

Novel approaches
- Second- and third-generation TKIs (neratinib, tucatinib)
- Immunotherapy with checkpoint inhibitors
- Optimised antibodies and ADCs
Breast cancer is the second most common cause for brain metastases among solid tumours

- Most common cause of leptomeningeal carcinosis
- Increasing incidence since 2000

- Retrospective analysis of >50,000 pts.
- OR for BM 2004-2006 compared to 1998-2000: 1.44, 95% CI 1.13-1.85

- Increased incidence in HER2-positive and TNBC
- HER2-positive: BM in up to 40%;
- Non-luminal/HER2-positive associated with earlier development of BM (shorter BMFS)
BREAST CANCER – BRAIN METASTASES

The patients’ perspective

- Brain metastases (BM) increase morbidity
- BM reduce quality of life
- BM shorten survival
- Greatest conceivable threat for pts. at risk
- Today, OS >24 months is possible in patients with BM
- Prolonged survival of patients with BM – issue of WBRT-associated late toxicity

Survival depends upon ongoing systemic therapy:

- No further treatment: 3 months (95% CI 2.37-3.63)
- Chemotherapy only: 9 months (95% CI 0-20.69)
- + Trastuzumab: 13 months (95% CI 8.85-17.15)
- + Lapatinib: Median OS not reached at 24 months median time of observation
BREAST CANCER – BRAIN METASTASES
Evidence for systemic therapy I

Prospective single-arm phase II trial

242 pts., HER2-positive MBC, progressing after local therapy (~95% WBRT); amendment: Lap+Cap upon PD on lapatinib (50 Pat.)

RR lapatinib 6%; minor response 21%

RR lapatinib+capecitabine 20%; minor response 40%

PFS lapatinib: 2.40 months (95% CI 1.87-2.79)
PFS Lap+Cap: 3.65 months (95% CI 2.43-4.37)

BREAST CANCER – BRAIN METASTASES
Evidence for systemic therapy II

- LANDSCAPE: Primary treatment with lapatinib plus capecitabine in HER2-positive patients with brain metastases – aiming to delay WBRT
- Single-arm Phase II trial
- Primary endpoint RR (CNS): 66%
- Secondary endpoint time-to-WBRT: 8.3 months
- Caveat: non-randomised, 40% of pat. asymptomatic, 95% ECOG <2, no data regarding QoL
- Potential standard in this specific patient subset?

BREAST CANCER – BRAIN METASTASES
Prevention by systemic therapy?

Does modern systemic therapy offer a chance for BM prevention?

**CLEOPATRA:** Improved systemic disease control prolongs BMFS but does not reduce to overall incidence of BM

- (BMFS 11.9 versus 15.0 months; 95% CI, 0.39–0.85; p=0.0049)

**CEREBEL:** Prospective randomised Phase III trial, 540 patients, HER2-positive, Lap+Cap vs. Trast+Cap after progression

- BM incidence (early switch to lapatinib 3% versus 5% (ns)
- Superior PFS (A) and OS (B) with trastuzumab (ITT)

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THE BLOOD-BRAIN-BARRIER

- [11C]lapatinib as PET-Tracer in HER2-positive MBC patients with or without BM
  - Three patients with BM, three patients control
  - No significant uptake of [11C]lapatinib in healthy brain tissue, significant uptake in BM only (A)

- Clinical relevant concentration of lapatinib and capecitabine in resected BM without prior WBRT (n=12) – high variability (B)

1) Saleem A, et al. EJNMMI Research 2015;5:30. Reproduced under Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0);
THE BLOOD-BRAIN-BARRIER

- Decreased concentration of anti-cancer drugs in brain metastases as compared with extracranial lesions, even with small molecules
- Activity of conventional cytotoxics in brain metastases – response rate 50%
- Blood-brain-barrier impaired in the region of metastatic lesions enabling the penetration of anti-cancer drugs into brain metastases
- In principle, large molecules such as chemotherapeutics and even antibodies could provide activity in brain metastases – even trastuzmab can penetrate into brain metastases, but activity of trastuzumab in brain metastases is not proven

64Cu-DOTA-trastuzumab PET images of metastatic brain tumours in patients with HER2-positive primary breast tumours

T-DM1 IN BRAIN METASTASES

- Retrospective case series; T-DM1: Newly diagnosed or progressive brain metastases
  - n=10 patients; 80% prior local therapy; 60% prior lapatinib
  - Response: PR (RANO) 30%; SD 40%
  - PFS: median 5 months (95% CI 3.69-6.32)
  - OS: not reached at 8.5 months median FU

Preclinical models suggest increased EGFR-expression, increased EGFR-phosphorylation and increased heregulin-expression\(^1\)

Upregulation of HER2/EGFR-heterodimers\(^1\)

Increased HER2/HER3 signalling\(^2,3\)

Increased activity of the IGF-1 pathway\(^4,5\)

Neoadjuvant trial: IGF-1 receptor-expression correlates inversely with trastuzumab response\(^6\)

DIFFERENT MOLECULAR MECHANISMS DETERMINE RESPONSE AND RESISTANCE TO TRASTUZUMAB AND LAPATINIB

PI3K / AKT activation as resistance mechanism in HER2/neu overexpressing breast cancer resulted in clinical trials of PI3K inhibitors in trastuzumab-resistance

NEOALTTO\textsuperscript{1}: BENEFIT FOR COMBINATION

Adapted from The Lancet, 379(9816), Baselga J, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial, 633-640, Copyright 2012, with permission from Elsevier.
HER2/NEU SOMATIC MUTATIONS IN BREAST CANCER

Reprinted from Cancer Discovery, © 2013, 3(2): 145-147, Weigelt B and Reis-Filho JS, Activating Mutations in HER2: New Opportunities and New Challenges, with permission from AACR.
Single-arm phase II study of neratinib activity in HER2/neu mutated (HER2-negative) MBC

- Background: 2% of HER2-negative MBC cases have activating HER2/neu mutations
- Activity of neratinib may be retained
- 22/517 patients with activating HER2/neu mutations (4.3%)
- 95% ER-positive
- Higher mutation rate in lobular tumours (7.8%)
- CR 1, PR 1, SD ≥6 months 3 (CBR 36%)
- PFS 16 weeks (90% CI 8-31)
- ctDNA sequencing identified the same HER2/neu mutation in 11/14 tumour-positive samples

Reprinted from Clin Cancer Res, Copyright 2017;23:5687-5695, Ma CX, et al. Neratinib Efficacy and Circulating Tumor DNA Detection of HER2 Mutations in HER2 Nonamplified Metastatic Breast Cancer, with permission from AACR.
HER2-POSITIVE MBC

Evidence for targeted treatment

Current standards
- Chemotherapy plus trastuzumab
- Chemotherapy plus trastuzumab/pertuzumab
- T-DM1
- Trastuzumab/lapatinib
- Lapatinib/capecitabine

Specific treatment situations
- Trastuzumab or lapatinib plus aromatase-inhibitors
- Brain metastases

Novel approaches
- Second- and third-generation TKIs (neratinib, tucatinib)
- Immunotherapy with checkpoint inhibitors
- Optimised antibodies and ADCs
OUTLOOK: NERATINIB IN FIRST LINE, THE NEFERT-T^1 STUDY

- Second-generation (irreversible) TKI of EGFR and HER2
- NEfERT-T: Prospective randomised phase III study, trastuzumab plus paclitaxel vs. neratinib plus paclitaxel
- 479 pts., MBC, first-line, primary EP: PFS
- PFS neratinib 12.9 months (95% CI 11.1-14.9) vs. trastuzumab 12.9 months (95% CI 11.1-14.8) (HR 1.02; 95% CI 0.81-1.27; p=0.89)
- Lower rate of CNS recurrences and longer brain metastases-free survival (BMFS) with neratinib (RR CNS metastases 0.48; 95% CI 0.29-0.79; p=0.002; BMFS HR 0.45; 95% CI 0.26-0.78; p=0.004)
- Grade 3/4 diarrhoea 30.4% in the neratinib arm

OUTLOOK: TUCATINIB – 3RD-GENERATION HER2-TKI\textsuperscript{1,2}

- Third-generation (irreversible) TK: lower diarrhoea rate due to lower anti-EGFR activity
- Phase Ib study, 60 pts., MBC, prior treatment with trastuzumab, pertuzumab, T-DM1
- Tucatinib plus trastuzumab or capecitabine or both drugs
- Recommended phase II dose 300 mg BID
- Grade 3 diarrhoea 7%
- Response rate 83% (capecitabine), 40% (trastuzumab), 61% (trastuzumab plus capecitabine)
- Preliminary anti-tumour activity in a phase Ib study evaluating the combination of tucatinib and T-DM1

OUTLOOK

Immune checkpoint inhibition in HER2/neu overexpressing breast cancers: KEYNOTE-014 (PANACEA)¹

**Patients**
- Centrally confirmed HER2+
- ECOG 0-1
- Tumour biopsy sample <1 yr
- Measurable disease RECIST 1.1
- No limit of prior systemic treatment
- Documented PD on trastuzumab or TDM-1

**Primary endpoint Phase II:**
Safety and efficacy in PD-L1 expressing cancers

**Phase Ib**
- Pembrolizumab 2 mg/kg and 10 mg/kg IV+
- Trastuzumab Q3W

**Phase II**
- Pembrolizumab 200 mg IV+
- Trastuzumab Q3W

**Protocol-specified follow-up treatment until progression, toxicity, patient withdrawal, investigator decision, or maximum 2 years**

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HER2: PANACEA\(^1\)

- ORR (PD-L1 pos.) 15% (90% CI 7-29)
- DCR (CR+PR+SD ≥6 months) 25% (90% CI 14-49)
- No efficacy in the PD-L1 negative cohort

Margetuximab: HER2-directed antibody binding with higher affinity to CD16A (Fc-receptor important for antibody dependent cell-mediated cytotoxicity (ADCC) against tumour cells)

Phase 1 study, 66 pre-treated patients, different HER2-overexpressing tumours (27 BC), no standard treatment-option available

MTD not reached

Mainly grade 1/2 toxicity (pyrexia, nausea, anaemia, diarrhoea, fatigue)

PR 12%, SD 50%

Margetuximab treatment resulted in enhanced ADCC activity compared with trastuzumab

SOPHIA phase III trial ongoing (NCT02492711): margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy

ZW25: Bispecific HER2-directed antibody targeting HER2 extracellular domains ECD4 and ECD2 (binding sites of trastuzumab and pertuzumab)

Phase Ib study, 42 pts., different HER2-overexpressing tumours
20 pts. MBC, heavily pre-treated (100% trastuzumab, 95% T-DM1, 85% pertuzumab, 50% lapatinib, 35% other study drugs)

OUTLOOK

Optimising HER2-directed antibodies – trastuzumab-deruxtecan

DS-8201a: ADC with deruxtecan (toposiomerase-I inhibitor) linked to trastuzumab

Phase I study including patients with HER2-overexpressing MBC (prior T-DM1 treatment), gastric cancer (prior trastuzumab treatment), HER2-low MBC (IHC 1+, 2+; ISH negative), and other solid cancers with HER2 expression ≥1+

2 patients grade 5 pneumonitis; nausea 73.5% (≥ grade 3 3.5%), vomiting 39.5% (≥ grade 3 1.5%)

<table>
<thead>
<tr>
<th>Efficacy Outcomes by Cancer Type (5.4) or 6.4 mg/kg</th>
<th>Overall Safety Profile (5.4 or 6.4 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-Positive BC N=111</strong></td>
<td><strong>Overall N=241</strong>*</td>
</tr>
<tr>
<td>Confirmed ORR*, % (n/N)</td>
<td>Any TEAEs</td>
</tr>
<tr>
<td>54.5% (54/99)</td>
<td>238 (98.8%)</td>
</tr>
<tr>
<td>DCR, % (n/N)</td>
<td>Grade ≥3 TEAEs</td>
</tr>
<tr>
<td>93.9% (93/99)</td>
<td>121 (50.2%)</td>
</tr>
<tr>
<td>ORR in modified ITT**, % (n/N)</td>
<td>Drug-related TEAEs</td>
</tr>
<tr>
<td>48.6% (54/111)</td>
<td>235 (97.5%)</td>
</tr>
<tr>
<td>DOR</td>
<td>Grade ≥3 drug-related TEAEs</td>
</tr>
<tr>
<td>Median, (95% CI), months</td>
<td>101 (41.9%)</td>
</tr>
<tr>
<td>11.0 (NA)</td>
<td>Serious TEAEs</td>
</tr>
<tr>
<td>7.0 (NA)</td>
<td>50 (20.7%)</td>
</tr>
<tr>
<td>12.9 (2.8, 12.9)</td>
<td>Drug-related serious TEAEs</td>
</tr>
<tr>
<td>PFS</td>
<td>27 (11.2%)</td>
</tr>
<tr>
<td>Median, (95%, CI), months</td>
<td>TEAEs leading to treatment discontinuation</td>
</tr>
<tr>
<td>12.9 (NA)</td>
<td>23 (9.5%)</td>
</tr>
<tr>
<td>Min, max</td>
<td>TEAEs leading to death**</td>
</tr>
<tr>
<td>1.0, 22.2</td>
<td>10 (4.1%)</td>
</tr>
<tr>
<td>0.5, 19.6+</td>
<td></td>
</tr>
<tr>
<td>1.2, 19.6+</td>
<td></td>
</tr>
<tr>
<td>0.7, 14.1+</td>
<td></td>
</tr>
</tbody>
</table>

*Confirmed response includes subjects who had ≥2 postbaseline scans, had progressive disease, or discontinued treatment for any reason prior to second postbaseline scan.
**modified ITT population included all subjects who received ≥1 dose of DS-8201a at either 5.4 or 6.4 mg/kg, including those subjects who were too early to assess, but are ongoing on study.
+after value indicates censoring
DCR, disease control rate, DOR, duration of response, GC, gastric/gastroesophageal junction cancer, NR, not reached, ORR, overall response rate

Data cut-off for this analysis is April 18, 2018.
CONCLUSIONS

Evidence for ameliorated efficacy of HER2-targeting MBC

**Targeted monotherapy**
- Trastuzumab
- Lapatinib, reversible TKI
- T-DM1

**Targeted combinations**
- Trastuzumab + lapatinib
- Trastuzumab + pertuzumab

**Specific treatment situations**
- HER2-directed therapy in combination with ET
- Systemic therapy of brain metastases
OPTIMISING THE DEFINITION OF HER2 POSITIVITY

ASCO/CAP guidelines

Suggested algorithm for HER2-testing with dual-probe ISH-assay

THANK YOU!