LATEST NEWS: HER+ ABC
NEW TARGETS, NEW DRUGS

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Disclosures

Consulting/Advisor: Roche, Celgene, Cellestia, AstraZeneca, Biothera Pharmaceutical, Merus, Seattle Genetics, Daiichi Sankyo, Erytech, Athenex.

Honoraria: Roche, Novartis, Celgene, Eisai, Pfizer, Samsung.

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Stock, patents and intellectual property: MedSIR
Current Therapy HER2+ MBC

First-line MBC

- Gold standard: taxane/trastuzumab/pertuzumab (THP)
- Alternative: Trastuzumab or lapatinib plus endocrine therapy if HR+

Second-line MBC

- Gold standard: T-DM1

Third-line and beyond MBC

- Multiple options:
  - Trastuzumab/lapatinib
  - Lapatinib/capecitabine
  - Trastuzumab/capecitabine
  - Trastuzumab plus:
    - Vinorelbine
    - Gemcitabine
    - Taxane
    - Eribulin
    - CMF
    - Platinum
  - Lapatinib or Trastuzumab plus endocrine therapy
  - ??? Neratinib, margetuximab, DS8201, tucatinib???
New AntiHER2 opportunities

1. HER3 as a mechanism of resistance
2. New TKIs
3. Optimized molecular antibodies targeting HER2
4. PI3K signaling pathway
5. CDK 4/6 inhibitors
6. Immunotherapy-based approach
7. New ADCs
8. Other antiHER2 opportunities
New AntiHER2 opportunities

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HER2 inhibition with lapatinib is followed by upregulation of HER3 in HER2+ tumors

HER3 IHC

Pre-therapy

Post-therapy (2 wks)

P-HER3 was also upregulated upon tx

Biomarkers of combined HER2 and HER3 inhibition

HER3

ctrl  lap  lap+AMG-888

P-Akt

ctrl  lap  lap+AMG-888

FoxO3a

ctrl  lap  lap+AMG-888


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### MCLA-128

<table>
<thead>
<tr>
<th>Merus N.V.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
</tr>
<tr>
<td>120</td>
</tr>
<tr>
<td>HER2 / HER3 Mab</td>
</tr>
</tbody>
</table>

MCLA-128 + trast vs. MCLA-128 + trast + vinorelbine vs. MCLA-128 + endocrine therapy

<table>
<thead>
<tr>
<th>CBR</th>
</tr>
</thead>
<tbody>
<tr>
<td>(PFS, ORR, OS, DoR)</td>
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</table>

“Women with histologically or cytologically confirmed breast cancer with evidence of metastatic or locally advanced disease not amenable to any local therapy with curative intent”

<table>
<thead>
<tr>
<th>Q3 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03321981</td>
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New AntiHER2 opportunities

1. HER3 as a mechanism of resistance
2. New TKIs
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### Neratinib Breast Cancer Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Indication / Population</th>
<th>n</th>
<th>Response Rate (%)</th>
<th>Clinical Benefit Rate (%)</th>
<th>PFS (months) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>Neratinib FIH</td>
<td>Advanced tumor (ErbB1+ or ErbB2+)</td>
<td>25</td>
<td>32 (15-54)</td>
<td>36 (18-58)</td>
<td>3.6 (1.7-5.6)</td>
</tr>
<tr>
<td>2205</td>
<td>Neratinib + Temsirolimus</td>
<td>Breast Cancer</td>
<td>12</td>
<td>17 (2-48)</td>
<td>25 (5-57)</td>
<td></td>
</tr>
<tr>
<td>201</td>
<td>Neratinib</td>
<td>HER2+ mBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior Trastuzumab</td>
<td></td>
<td>63</td>
<td>24 (14-36)</td>
<td>33 (22-46)</td>
<td>5.1 (3.7-7.3)</td>
</tr>
<tr>
<td></td>
<td>No Prior Trastuz.</td>
<td></td>
<td>64</td>
<td>56 (43-69)</td>
<td>69 (56-80)</td>
<td>9.1 (7.1-12.7)</td>
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<tr>
<td>202</td>
<td>Neratinib + Trastuzumab</td>
<td>HER2+ LABC or mBC</td>
<td>28</td>
<td>29 (13-49)</td>
<td>36 (19-56)</td>
<td>3.7 (3.5-7.2)</td>
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<tr>
<td>203</td>
<td>Neratinib + Paclitaxel</td>
<td>HER2+ mBC</td>
<td></td>
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<tr>
<td></td>
<td>≤ 1 cytotoxic reg.</td>
<td></td>
<td>68</td>
<td>71 (58-81)</td>
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<tr>
<td></td>
<td>≥2 cytotoxic regs</td>
<td></td>
<td>31</td>
<td>77 (59-90)</td>
<td></td>
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<tr>
<td>2204</td>
<td>Neratinib + Vinorelbine</td>
<td>HER2+ mBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior Lapatinib</td>
<td></td>
<td>12</td>
<td>8 (0-38)</td>
<td>42 (15-72)</td>
<td>5.2 (2.8-9.4)</td>
</tr>
<tr>
<td></td>
<td>No Prior Lapatinib</td>
<td></td>
<td>56</td>
<td>41 (28-55)</td>
<td>70 (56-81)</td>
<td>11.0 (7.1-15.0)</td>
</tr>
<tr>
<td>2206</td>
<td>Neratinib + Capecitabine</td>
<td>HER2+ mBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Prior Lapatinib</td>
<td></td>
<td>7</td>
<td>57 (18-90)</td>
<td>71 (29-96)</td>
<td>8.3 (4.4-13.8)</td>
</tr>
<tr>
<td></td>
<td>No Prior Lapatinib</td>
<td></td>
<td>61</td>
<td>64 (51-76)</td>
<td>72 (59-83)</td>
<td>9.3 (7.0-15.2)</td>
</tr>
<tr>
<td>3003</td>
<td>Neratinib</td>
<td>HER2+ LRBC / mBC</td>
<td>117</td>
<td>29 (21-38)</td>
<td>44 (35-54)</td>
<td>4.5 (3.1-5.7)</td>
</tr>
<tr>
<td></td>
<td>Lapatinib + Capecitabine</td>
<td></td>
<td>116</td>
<td>41 (32-50)</td>
<td>64 (54-73)</td>
<td>6.8 (5.9-8.2)</td>
</tr>
</tbody>
</table>
NALA Study Design (RP3)

- **HER2+ MBC (N=621)**
  - Prior treatment with at least two HER2-directed regimens for metastatic breast cancer

- **Treatment arms**
  - Capecitabine + Neratinib
  - Capecitabine + Lapatinib

- **Endpoints**
  - **Co-primary endpoints**: Independently-assessed PFS and OS
  - **Key secondary endpoints**: Investigator-assessed PFS ORR, duration of response, CBR, safety, QoL

Brufsky A, et al. ASCO 2019
Centrally confirmed PFS (co-primary endpoint)

Hazard ratio (95% CI) | Log-rank p-value
--- | ---
0.76 (0.63–0.93) | 0.0059

No. at risk:
N+C 307 183 113 69 54 35 20 13 9 7 3 2 2 2 2
L+C 314 183 82 39 24 9 8 3 2 2 2 2 2 2 1
OS (co-primary endpoint)

Mean OS (months) | Hazard ratio (95% CI) | Log-rank p-value
--- | --- | ---
Neratinib + Capecitabine | 24.0 | 22.2 |
Lapatinib + Capecitabine | 0.88 (0.72–1.07) | 0.2086 |

Restriction: 48 months

Adam Brufsky, et al. ASCO 2019

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ONT-380 (Tucatinib): an Oral HER2-Specific Inhibitor

- ONT-380 is a HER2 selective small molecule tyrosine kinase inhibitor with nanomolar potency
  - 500-fold more selective for HER2 compared to EGFR
  - HER2 IC$_{50}$: 8 nM; EGFR IC$_{50}$: 4000 nM
- HER2 selectivity leads to decreased potential for EGFR-related toxicities compared to dual inhibitors
- In a model of HER2+ CNS metastases, ONT-380 was associated with improved survival compared to either lapatinib or neratinib (Figure 1)
- ONT-380 is currently being evaluated in two ongoing Phase 1b combination studies [+ T-DM1 and ± capecitabine [C] ± trastuzumab [T]]

Figure 1: BT-474 CNS Metastases Model

Dinkel et al, AACR 2012
ONT-380 + C + T trial
Study ONT-380-005

- Phase 1 (N = 24 HER2-positive MBC)
- Patients with CNS M1 allowed
- 100% prior therapy with T and T-DM1
- 74% prior therapy with Pertuzumab
- Low rate of grade 3 diarrhea

**ORR 54%**

C: Capecitabine; T: Trastuzumab

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Randomized Phase II trial with ONT-380

Prior therapy with Trastuzumab, Pertuzumab, and T-DM1 Patients with CNS M1 are allowed

- Primary endpoint: PFS
- Key secondary endpoints: ORR, OS, disease control rate, safety
Randomized Phase II trial with ONT-380

- Primary endpoint: PFS
- Key secondary endpoints: ORR, OS, disease control rate, safety

PFS HR=0.54 (p<0.00001).
OS HR=0.66 (p=0.0048)
For patients with brain PFS HR=0.48 (p<0.00001)

SABCS 2019

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Pyrotinib: An Irreversible Pan-HER TKI

Phase 1
DLT: grade 3 diarrhea
ORR 50% at MTD

Phase 2: capecitabine/pyrotinib vs. capecitabine/lapatinib
- PFS 18 vs 7mo
- Diarrhea 15% vs 5%
PHENIX Study Design

**Key eligibility criteria:**
- Pathologically confirmed HER2-positive* metastatic breast cancer
- Disease progression during or after treatment with trastuzumab#, and were not amenable or available for trastuzumab or lapatinib treatment
- Prior taxane-containing regimen
- No. of lines of prior chemotherapy in the metastatic setting ≤ 2
- At least one measurable lesion
- ECOG performance status of 0 or 1

*HER2-positive: immunohistochemistry 3+ and/or fluorescence in situ hybridization positive;
#Progression with trastuzumab: ≥2 cycles in the metastatic setting, or ≥3 months in adjuvant setting.

**Randomization 2:1**

- **Pyrotinib (400 mg, orally, qd) + Capecitabine (1000 mg/m², orally, bid on days 1–14 of each 21-day cycle)**
- **Placebo (400 mg, orally, qd) + Capecitabine (1000 mg/m², orally, bid on days 1–14 of each 21-day cycle)**

**Primary endpoint:**
- IRC-assessed PFS

**Secondary endpoints:**
- ORR
- DoR
- DCR
- CBR
- OS
- Safety profile

**Abbreviations:** IRC, independent review committee; DoR, duration of response; DCR, disease control rate; CBR, clinical benefit rate; OS, overall survival.

**Stratification:**
- Metastatic sites at screening (visceral versus non-visceral)
- Hormone receptor status (ER- and/or PR-positive versus ER- and PR-negative)

**At progression:**
- Patients in the placebo plus capecitabine arm were allowed to receive pyrotinib monotherapy at the investigator’s discretion
IRC-assessed PFS
FAS population, double-blind period

<table>
<thead>
<tr>
<th></th>
<th>Pyrotinib plus capecitabine</th>
<th>Placebo plus capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS events, n (%)</td>
<td>84 (45.4)</td>
<td>78 (83.0)</td>
</tr>
<tr>
<td>Median PFS (95% CI), months</td>
<td>11.1 (9.7–16.5)</td>
<td>4.1 (2.8–4.2)</td>
</tr>
<tr>
<td>Increase in median PFS, months</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.18 (0.13–0.26)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value*</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

* Stratified by metastatic sites and hormone receptor status

Jiang Z, et al. ASCO 2019
New AntiHER2 opportunities

1. HER3 as a mechanism of resistance

2. New TKIs

3. **Optimized molecular antibodies targeting HER2**

4. PI3K signaling pathway

5. CDK 4/6 inhibitors

6. Immunotherapy-based approach

7. New ADCs

8. Other antiHER2 opportunities
Margetuximab

To evaluate the safety of margetuximab using two dosing regimens.
FIH phase 1 Study with Margetuximab

All evaluable pts

- 39/60 prior antiHER2 therapy

- 22/23 prior antiHER2 therapy

Evaluable MBC

Pharmacokinetics

Burris HA, et al. ASCO 2015
HER2-positive locally advanced/metastatic BC (N=530)

Prior metastatic treatment with pertuzumab and T-DM1
Prior treatment with trastuzumab

Margetuximab + Chemotherapy

Trastuzumab + Chemotherapy
PFS Analysis in ITT population

**24% Risk Reduction of Disease Progression**
Central Blinded Analysis (Primary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=266)</th>
<th>Trastuzumab + Chemotherapy (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events</td>
<td>130</td>
<td>135</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>5.8 months (5.52–6.97)</td>
<td>4.9 months (4.17–5.59)</td>
</tr>
<tr>
<td>HR by stratified Cox model, 0.76 (95% CI, 0.59–0.98)</td>
<td>Stratified log-rank $P=0.033$</td>
<td></td>
</tr>
</tbody>
</table>

**30% Risk Reduction of Disease Progression**
Investigator Assessed (Secondary Endpoint)

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=266)</th>
<th>Trastuzumab + Chemotherapy (n=270)</th>
</tr>
</thead>
<tbody>
<tr>
<td># of events</td>
<td>160</td>
<td>177</td>
</tr>
<tr>
<td>Median PFS (95% CI)</td>
<td>5.6 months (5.06–6.67)</td>
<td>4.2 months (3.98–5.39)</td>
</tr>
<tr>
<td>HR by stratified Cox model, 0.70 (95% CI, 0.56–0.87)</td>
<td>Stratified log-rank $P=0.001$</td>
<td></td>
</tr>
</tbody>
</table>

- PFS analysis was triggered by last randomization on October 10, 2018, after 265 PFS events occurred

ITT population: N=536. CI=confidence interval.

Rugo H, et al. ASCO 2019
Planned exploratory PFS analysis by CD16A Genotype

506 patients genotyped (94%)

**FF or FV, n=437 of 506 (86%)**

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=221)</th>
<th>Trastuzumab + Chemotherapy (n=216)</th>
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</thead>
<tbody>
<tr>
<td># of events</td>
<td>103</td>
<td>112</td>
</tr>
<tr>
<td>Median PFS</td>
<td>6.9 months (5.55–8.15)</td>
<td>5.1 months (4.14–5.59)</td>
</tr>
<tr>
<td>HR by unstratified Cox model</td>
<td>0.68 (95% CI, 0.52–0.90)</td>
<td>Unstratified log-rank ( P=0.005 )</td>
</tr>
</tbody>
</table>

**VV, n=69 of 506 (14%)**

<table>
<thead>
<tr>
<th></th>
<th>Margetuximab + Chemotherapy (n=37)</th>
<th>Trastuzumab + Chemotherapy (n=32)</th>
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</thead>
<tbody>
<tr>
<td># of events</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>Median PFS</td>
<td>4.8 months (2.46–5.65)</td>
<td>5.6 months (2.86–11.04)</td>
</tr>
<tr>
<td>HR by unstratified Cox model</td>
<td>1.78 (95% CI, 0.87–3.62)</td>
<td>Unstratified log-rank ( P=0.110 )</td>
</tr>
</tbody>
</table>

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Rugo H, et al. ASCO 2019

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ZW25: Azymetric™ Bispecific HER2-Targeted Antibody

- Designed using the Azymetric bispecific platform
- Biparatopic - simultaneously binds two HER2 epitopes
  - ECD4 (trastuzumab binding domain)
  - ECD2 (pertuzumab binding domain)
- Unique binding results in novel mechanisms of action
ZW25: Single-agent activity in HER2+ MBC after trastuzumab, pertuzumab and TDM1

Best Response: 0 CRs, 6/18 (33%) PRs, 3/18 (17% SD)

Meric-Bernstam F, et al. ASCO 2018
New AntiHER2 opportunities

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4. PI3K signaling pathway

5. CDK 4/6 inhibitors

6. Immunotherapy-based approach

7. New ADCs

8. Other antiHER2 opportunities
PI3K/AKT/mTOR inhibitors

PI3K signaling pathway alteration results in reduced response to trastuzumab
Everolimus
BOLERO 3 randomized phase III study: Primary endpoint

- Trastuzumab-resistant MBC
- Prior taxane
- ≤3 Lines chemotherapy
- HR status known

R

- Trastuzumab + Vinorelbine + Placebo
- Trastuzumab + Vinorelbine + Everolimus

Figure 2: Kaplan-Meier estimates of locally assessed progression-free survival in the full analysis set. Patients were stratified by previous lapatinib use. Symbols represent censoring events. PFS = progression-free survival.

Andre F et al Lancet Oncology 2014
### Everolimus: BOLERO 3 Subgroup Analysis

#### Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>N</th>
<th>Hazard Ratio [95% CI]</th>
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</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td>569</td>
<td>0.78 [0.65-0.95]</td>
</tr>
<tr>
<td><strong>Age</strong></td>
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<tr>
<td>&lt; 65 years</td>
<td>472</td>
<td>0.77 [0.62-0.95]</td>
</tr>
<tr>
<td>≥ 65</td>
<td>97</td>
<td>0.93 [0.56-1.57]</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>223</td>
<td>0.72 [0.53-0.99]</td>
</tr>
<tr>
<td>North America</td>
<td>123</td>
<td>0.86 [0.55-1.32]</td>
</tr>
<tr>
<td>Asia</td>
<td>166</td>
<td>0.83 [0.59-1.18]</td>
</tr>
<tr>
<td>Latin America</td>
<td>36</td>
<td>0.61 [0.27-1.38]</td>
</tr>
<tr>
<td>Other</td>
<td>21</td>
<td>1.28 [0.48-3.45]</td>
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<tr>
<td><strong>Prior lapatinib</strong>*</td>
<td></td>
<td></td>
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<tr>
<td>Yes</td>
<td>161</td>
<td>0.79 [0.56-1.11]</td>
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<tr>
<td>No</td>
<td>408</td>
<td>0.78 [0.62-0.99]</td>
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<td><strong>Prior adj/neotrastruzumab</strong></td>
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<tr>
<td>Yes</td>
<td>251</td>
<td>0.65 [0.48-0.87]</td>
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<tr>
<td>No</td>
<td>318</td>
<td>0.92 [0.71-1.18]</td>
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<td><strong>Baseline ECOG PS</strong></td>
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<tr>
<td>0</td>
<td>382</td>
<td>0.79 [0.63-1.00]</td>
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<tr>
<td>1 or 2</td>
<td>186</td>
<td>0.75 [0.53-1.05]</td>
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<tr>
<td><strong>Hormonal status</strong></td>
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<tr>
<td>ER−/PgR−</td>
<td>250</td>
<td>0.65 [0.48-0.87]</td>
</tr>
<tr>
<td>ER+/PgR+</td>
<td>317</td>
<td>0.93 [0.72-1.20]</td>
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<tr>
<td><strong>Visceral involvement</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>439</td>
<td>0.89 [0.72-1.10]</td>
</tr>
<tr>
<td>No</td>
<td>130</td>
<td>0.48 [0.30-0.76]</td>
</tr>
</tbody>
</table>

Favors EVE
Rationale for combining taselisib and fulvestrant
PI3K inhibition augments ER function and dependence in ER+ BC

New AntiHER2 opportunities

1. HER3 as a mechanism of resistance
2. New TKIs
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CDK inhibitors

Selection of trastuzumab resistant BT474 (BT474R) cells

BT474R do not respond to the antiproliferative effects of trastuzumab \textit{in vitro}.

Characterization of BT474R cells

BT474R cells present cyclin E amplification and overexpression

<table>
<thead>
<tr>
<th>CNV1</th>
<th>CNV2</th>
</tr>
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<tbody>
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</tr>
</tbody>
</table>

- CNV1 (Chr. 19)
  - UQCRFS1
  - POP4
  - PLEKHF1
  - C19orf12
  - CCNE1
  - C19orf2
  - ZNF536

- CNV2 (Chr. 14)
  - GALC
  - GPR65

Tras (100nM)
- -
- +

- BT474
- BT474R
- BT474R2

- Cyclin E
- pRB (S780)
- RB
- p27
- actin

IHC: CYCLIN E

Palbociclib and Trastuzumab: Patricia Trial

**Figure 5.** PFS within arms B [HER2+/HR+] (A) Luminal Vs Others (B) Her2-Enriched vs Others.

(A) Luminal Vs Others
- Hazard ratio, 0.34
  - (95% CI: 0.13-0.92)
  - \( P = 0.033 \)
- Progression-free Survival:
  - Luminals: 10.37 months
  - Others: 3.53 months
- Log Rank \( P = 0.0266 \)

(B) HER2-enriched vs Others
- Hazard ratio, 0.35
  - (95% CI: 0.14-0.89)
  - \( P = 0.0277 \)
- Progression-free Survival:
  - HER2-enriched: 8.17 months
  - Others: 3.5 months
- Log Rank \( P = 0.022 \)

ER+HER2+ MBC patients 3-5L

ER: HER2+ MBC patients 3-5L

Randomization 1:1

**Stage I** \( N_1 = 15 \)

- **A**
  - **N_1 = 3+12**
  - Palbociclib 200 mg + Trastuzumab 3w

**Stage II** \( N_2 = 31 \)

- **B1**
  - **N_1 = 3+12**
  - Palbociclib 200 mg + Trastuzumab 3w

- **B2**
  - **N_1 = 6+9**
  - Palbociclib 200 mg + Trastuzumab 3w + Letrozole

Safety Run-in phase \( N_1 = 12 \)

INTERIM ANALYSIS Stage I
- Go on if > 8/16 PFS6

FINAL ANALYSIS Stage I+II
- Efficacy if > 18/46 PFS6

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monarcHER study: PFS and ORR

Eligibility Criteria:
- HR+, HER2+ ABC
- ≥2 prior HER2-directed therapies for ABC
- prior T-DM1 and taxane required
- ECOG PS ≤1
- CDK4 & 6 inhibitor naïve
- No untreated or symptomatic CNS metastases

Stratification Factors:
- number of previous systemic regimens (2–3 vs. >3)
- measurable vs nonmeasurable

Randomization
N = 237
1:1:1

Sample Size Calculations:
- 165 PFS events give 80% power at 2-sided alpha of 0.20, Assuming a HR of 0.667

Primary Endpoint
- PFS (A vs. C, then B vs. C)

Secondary Endpoint
- ORR, safety, OS, PRO, PK

Continue until PD

Arm A
abemaciclib 150 mg PO BID + trastuzumab IV q21d + fulvestrant IM q28d

Arm B
abemaciclib 150 mg PO BID + trastuzumab IV q21d

Arm C
trastuzumab IV q21d + investigator’s choice chemotherapy

Stratification Factors:
- Tumor ≥ 10 cm
- ≥3 prior HER2-directed regimens
- No prior T-DM1 or taxane
- ECOG PS ≤1

ITT Population
Total N = 237

Arm A N=79
Arm B N=79
Arm C N=79

95% CI (%)
(22.5-43.3)
(6.3-21.6)
(6.3-21.6)

Stratified 2-sided p-value (vs Arm C)
0.0042
1.0000
-

Duration of
12.5
9.5
not reached

Tolaney S et al. ESMO 2019

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A randomized, open-label, phase 3 trial to evaluate the efficacy and safety of Palbociclib (PD0332991) + anti-HER2 Therapy + endocrine therapy vs anti-HER2 therapy + endocrine therapy after induction treatment for HR+/HER2+ metastatic breast cancer (NCT02947685)

**HR+/HER2+ METASTATIC BREAST CANCER**
- No prior treatment in the advanced setting beyond induction treatment
- No evidence of disease progression after induction treatment

**Induction treatment**
Chemotherapy (taxane or vinorelbine) + anti-HER2 therapy (trastuzumab +/- pertuzumab)

1:1 randomization (N=496)

- Palbociclib + anti-HER2 therapy + endocrine therapy
- Anti-HER2 therapy + endocrine therapy

Disease progression or unmanageable toxicity
New AntiHER2 opportunities

1. HER3 as a mechanism of resistance

2. New TKIs

3. Optimized molecular antibodies targeting HER2

4. PI3K signaling pathway

5. CDK 4/6 inhibitors

6. Immunotherapy-based approach

7. New ADCs

8. Other antiHER2 opportunities
Immunotherapy in HER2+ MBC: PANACEA

- 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
### IMMUNOTHERAPY IN HER2+ MBC: KATE2

**Stratification factors:**
- Tumour PD-L1 IC status (IC0 [<1%] vs IC1/2/3 [≥1%])\(^{a}\)
- World region (Western Europe vs North America vs rest of world)
- Presence of liver metastases (yes or no)

\(^{a}\) Determined using VENTANA SP142.

**Primary endpoint:**
- Investigator-assessed PFS

**Secondary endpoints:**
- OS
- Objective response rate
- Duration of response

**Exploratory endpoints:**
- PFS in patients with PD-L1+ disease
- Exploratory biomarker subgroups (PD-L1, PIK3CA mutation status, HER2 expression, immune-related [TILs, CD8 IHC expression])

**Post hoc endpoint:**
- OS in PD-L1 subgroups

- Data cutoff for primary analysis: 11 December 2017
- Data cutoff for OS analysis: 11 December 2018

IC, tumour-infiltrating immune cell; IHC, immunohistochemistry; ITT, intention-to-treat; LABC, locally advanced breast cancer; MBC, metastatic breast cancer; OS, overall survival; PD, progressive disease; PFS, progression-free survival; TIL, tumour-infiltrating lymphocyte.
KATE2: PFS IN ITT AND PD-L1+ POPULATIONS

Emens LA, et al. San Antonio Breast Cancer Symposium; Dec 4-8, 2018; San Antonio, TX. Abstract PD3-01.

HR, hazard ratio; IC, tumour-infiltrating immune cell; ITT, intention-to-treat; NE, not estimable; PFS, progression-free survival.
KATE2: OS IN ITT

<table>
<thead>
<tr>
<th></th>
<th>T-DM1 + Atezolizumab (n=133)</th>
<th>T-DM1 + Placebo (n=69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up (mo)</td>
<td>19.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Patients with OS event, n (%)</td>
<td>32 (24.1)</td>
<td>20 (29.0)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>NE</td>
<td>NE</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.74 (0.42–1.30)</td>
<td></td>
</tr>
<tr>
<td>1-year survival rate (%)</td>
<td>89.1</td>
<td>89.0</td>
</tr>
</tbody>
</table>

Overall Survival (%)

Time (mo)

Emens LA, et al. ESMO 2019

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KATE2: OS IN ITT, IN PD-L1 IC+ AND PD-L1 IC− SUBGROUPS

OS in PD-L1 IC+ Subgroup (IC 1/2/3)

OS in PD-L1 IC− Subgroup (IC 0)
New AntiHER2 opportunities

1. HER3 as a mechanism of resistance
2. New TKIs
3. Optimized molecular antibodies targeting HER2
4. PI3K signaling pathway
5. CDK 4/6 inhibitors
6. Immunotherapy-based approach
7. New ADCs
8. Other antiHER2 opportunities
Advanced-unresectable or metastatic breast cancer or gastric or gastro-oesophageal adenocarcinoma* (n=24)

- Aged ≥20 years, with a life expectancy of ≥3 months
- ECOG PS 0-1
- Left ventricular ejection fraction of ≥50%
- Failed initial standard treatment/standard treatment unavailable

* tumour assessment by RECIST 1.1
HER2 status not relevant

**Primary Endpoints**
- Safety
- Tolerability
- Identification of maximum tolerated dose/recommended Phase 2 dose

**Secondary Endpoints**
- Pharmacokinetics
- Efficacy (tumour response)
- % change in target lesions
- Treatment duration
Efficacy

N = 115
82% ≥ 5 prior lines
100% prior T-DM1
86% prior HP

Is it necessary to have results from a phase 3 trial to use this drug?
Based on the results of the dose finding stage, the 5.4 mg/kg dose was selected for further breast cancer trials.
DESTINY-Breast02 and -Breast03: U301 & U302 Phase III HER2+ mBC Trials

**U301**

- **T-DM1 treated mBC**
- Archived sample
  - HER2 Positive (central)

Primary endpoints: PFS
- PFS: 90% power for HR of 0.70 in PFS with a 1-sided alpha of 0.025
- OS: 80% power for HR of 0.75 with a 1-sided alpha of 0.025
- PFS will be tested first, if positive, OS will be tested at the same alpha level. There is a planned OS interim analysis at the same time when PFS primary analysis is performed.

**U302**

- **Trastuzumab + taxane treated mBC**
- Archived sample
  - HER2 Positive (central)

Primary endpoint: PFS
- 90% power for HR of 0.70 with a 1-sided alpha of 0.025

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*Trastuzumab + capecitabine or lapatinib + capecitabine

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SYD-985

Best percentage change from baseline in target lesions

Percentage change from baseline in target lesions over time

HER2 IHC score 0/1+ 2+ 3+

New AntiHER2 opportunities

1. HER3 as a mechanism of resistance
2. New TKIs
3. Optimized molecular antibodies targeting HER2
4. PI3K signaling pathway
5. CDK 4/6 inhibitors
6. Immunotherapy-based approach
7. New ADCs
8. Other antiHER2 opportunities
Paradigm Shift?

Dichotomous HER2 status (positive/negative)

- HER2-positive
- HER2-negative
- HER2-low
<table>
<thead>
<tr>
<th></th>
<th>HER2-Positive BC N = 111</th>
<th>HER2-Low BC N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed ORR</strong>, % (n/N)</td>
<td>54.5% (54/99)</td>
<td>50.0% (17/34)</td>
</tr>
<tr>
<td><strong>DCR</strong>, % (n/N)</td>
<td>93.9% (93/99)</td>
<td>85.3% (29/34)</td>
</tr>
<tr>
<td><strong>ORR in modified ITT</strong>, % (n/N)</td>
<td>48.6% (54/111)</td>
<td>50.0% (17/34)</td>
</tr>
<tr>
<td><strong>DOR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, (95% CI), months</td>
<td>NR</td>
<td>11.0 (NA)</td>
</tr>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, (95% CI), months</td>
<td>NR</td>
<td>12.9 (NA)</td>
</tr>
<tr>
<td>Min, max</td>
<td>1.0, 22.2+</td>
<td>0.5, 19.6+</td>
</tr>
</tbody>
</table>
Overall, 86.3% of subjects experienced tumor shrinkage.

Confirmed ORR* in the overall population is 49.3%.
HER2 mutation

- HER2 amplification is an increase in the number of copies of HER2 without an increase in other genes
- Activation ERBB2 mutations are somatic point mutations in ERBB2 that activate the pathway

HER2 mutation: SUMMIT trial

- Open-label, multinational, multihistology, phase 2, signal-seeking study of neratinib as monotherapy or in combination in patients with tumors harboring HER2 mutations
- Neratinib dosage: 240 mg oral daily as monotherapy or in combination until disease progression or toxicity
- Loperamide prophylaxis for cycle 1
- Fulvestrant 500 mg intramuscular on days 1 and 15 of first cycle and on day 1 of subsequent cycles
  - HER2-mutant breast cancer monotherapy: patients with HR-negative breast cancer, including TNBC
  - HER2-mutant breast cancer combination therapy: neratinib plus fulvestrant for patients with HR-positive breast cancer

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Neratinib Monotherapy (n = 24)</th>
<th>Neratinib + Fulvestrant (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response rate at 8 weeks, n</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>CR</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Objective response rate (95% CI)</td>
<td>33.3 (15.6, 35.3)</td>
<td>41.7 (15.2, 72.3)</td>
</tr>
<tr>
<td>Clinical benefit, n</td>
<td>10.0</td>
<td>7.0</td>
</tr>
<tr>
<td>CBR (95% CI)</td>
<td>41.7 (21.1, 63.4)</td>
<td>58.3 (27.7, 84.8)</td>
</tr>
<tr>
<td>Median PFS, months (95% CI)</td>
<td>3.5 (1.9, 4.3)</td>
<td>3.7 (2.1, 6.7)</td>
</tr>
</tbody>
</table>
Proposed Mechanisms of Resistance to HER2-targeted Therapy

- **Δ16HER2 splice isoform**  
  (Mitra et al. Mol Cancer Ther, 2009)

- **Activation of EPO receptor by rHuEPO**  
  (Liang et al. Cancer Cell 2010)

- **Upregulation of IGF-IR receptor**  
  (Gail Phillips, AACR, 2009)

- **Activation of AXL**  
  (Liu et al, Cancer Res, 2009)

- **Upregulation of MET receptor**  
  (Shattuck et al, Cancer Res, 2008)

- **Expression of ER**  
  (Xia et al, PNAS, 2006)

- **Shedding of ERBB2**  
  (Scaltriti et al, J Nat Cancer Inst, 2007)

- **Loss of PTEN and PIK3CA mutations**  
  (Eichhorn et al, Cancer Res, 2009)

- **MUC4/MUC1 steric hindrance of binding**  

- **Increase in p-ERBB3**  
  (Sergina et al, Nature, 2007)

- **Cyclin E amplification/overexpression**  
  (Scaltriti et al. PNAS 2011)

- **Upregulation of miR-21**  
  (Gong, et al, J Biol Chem, 2011)
Conclusion

1. Anti HER3 drugs..... ? New Clinical Trial designs
2. New TKIs...... Yes!!!
3. Optimized molecular antibodies targeting HER2...... Yes!!!
4. PI3K signaling pathway....... ? New Clinical Trial designs
5. CDK 4/6 inhibitors...... Probably
6. Immunotherapy-based approach....... Probably
7. New ADCs....... Yes!!!
8. Other antiHER2 opportunities....... Probably