Evolving Strategies to Overcome Resistance to HER2 Targeted Agents

Sung-Bae Kim, MD, PhD
Professor, Dept of Oncology
Asan Medical Center
University of Ulsan College of Medicine
Seoul, Korea
Advanced HER2+ Breast Cancer: What have we accomplished?

Targeting HER-2 has led to the most impressive clinical advances in the medical treatment of breast cancer, in the last 15-20 years.
Trastuzumab altered the natural history

Dawood et al. JCO 2010

Important trials to consider in the HER2 positive metastatic setting

**CLEOPATRA**
- Trastuzumab + Docetaxel
- 1st line therapy
- Trastuzumab + Pertuzumab + Docetaxel

Swain et al. NEJM 2015
Phase III
No prior treatment for metastatic disease
PFS 12.4 m vs 18.7 m
HR 0.68 (p=<0.0001)
OS 40.8 m vs 56.5 m

**EMILIA**
- Lapatinib + XELODA
- 2nd line therapy
- TDM-1

Verma et al. NEJM 2012
Phase III
Prior taxane/trastuzumab
Progression on metastatic therapy
PFS 6.4 m vs 9.6 m
HR 0.65 (p=<0.0001)
OS 25.9 vs 29.9m
HR 0.75 p =0.0003

**TH3RESA**
- Physician Choice
- Beyond 2nd line therapy
- TDM-1

Krop et al. Lancet Oncol 2014, 2017
Phase III
>=2 prior anti HER2 lines of therapy
60% >= lines of therapy
PFS 3.3 m vs 6.2 m
HR 0.55 (p=<0.0001)
OS 15.8 m vs22.7 M
HR 0.677 (p=0.0007)
Anti HER2 therapies available today

Inhibition through direct antibody binding

- Dimerization domain
- Trastuzumab

Inhibition through dimerization inhibition

- Dimerization domain
- Pertuzumab

Targeting for intracellular drug delivery

- Internalization through endocytosis and intracellular release of DM1
- Trastuzumab

Inhibition of tyrosine kinase activity

- Tyrosine kinase
- Small-molecule tyrosine kinase inhibitor

TRASTUZUMAB
PERTUZUMAB
T-DM1
LAPATINIB

Baselga et al., Nat Rev Cancer 2009
For patients with ER+/HER2+ 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 in randomized trials.

LOE:1 C
Voters:39
Yes: 79% (31)
Abstain: 10% (4)

ABC3, Annals of Oncology 2016

The choice of the anti-HER2 agent will depend on country-specific availability, the specific anti-HER2 therapy previously administered, and the relapse free interval.
Do all women with HER2 positive MBC require chemotherapy? Can we de escalate therapy? “Triple Positive” Disease

The ER and HER2 signalling pathways are deeply interconnected

ER signalling plays a role in resistance to anti-HER2 Therapy

The unexciting nature of the results of early ET/anti-HER2 Trials have made CT-based combinations a more common standard

## HER2+HR+ MBC

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR, %</th>
<th>PFS, Mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole+trastuzumab (n=103)(^1)</td>
<td>20(^a)</td>
<td>4.8</td>
</tr>
<tr>
<td>Anastrozole (n=104)(^1)</td>
<td>7(^a)</td>
<td>2.4</td>
</tr>
<tr>
<td>Lapatinib+letrozole (n=111)(^2)</td>
<td>28</td>
<td>8.2</td>
</tr>
<tr>
<td>Letrozole (n=108)(^2)</td>
<td>15</td>
<td>3.0</td>
</tr>
</tbody>
</table>

• Adding trastuzumab to endocrine therapy improved outcomes, presumably by eliminating the synergy between endocrine and HER2 signaling pathways.

“Triple positive” Breast Cancer
Recent Randomized trials of endocrine therapy combined with single or dual HER2 blockade

« FIRST LINE »
The « PERTAIN » trial (N=258)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS</th>
<th>HR</th>
<th>Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pertuzumab</td>
<td>15.8 m</td>
<td>0.65 (0.48 – 0.84)</td>
<td>55 vs 36 %</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>11.8 m</td>
<td>E.T.</td>
<td>Induction CTX in 57%</td>
</tr>
</tbody>
</table>

« SECOND+ LINE »
The « ALTERNATIVE » trial (N=355)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS</th>
<th>HR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lapatinib</td>
<td>5.7 m</td>
<td>0.7 (0.51 – 0.98)</td>
<td>+ 2.6m</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>5.7 m</td>
<td>E.T.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS</th>
<th>HR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab</td>
<td>8.3 m</td>
<td>0.62 (0.54 – 1.06)</td>
<td>+ 2.7m</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>8.3 m</td>
<td>E.T.</td>
<td></td>
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</table>

Gradishar et al ASCO 2017 abstract 1004
Arpino G et al SABCS 2016 abstract S3-04
Questions in the first line setting

CLEOPATRA

Swain et al NEJM 2015
Phase III
No prior treatment for metastatic disease
PFS 12.4 m vs 18.7 m
HR 0.68 (p<0.0001)
OS 40.8 m vs 56.5 m

YES : PFS prolongation, less toxicity
NO: No OS benefit, response rates higher with THP

Consider in patients with limited tumor burden or those not considered candidates for chemotherapy.

Should we use endocrine therapy+dual blockade for ER+/HER2+ disease?
**New Strategies**

**New Agents & New Combinations directed at the cancer cell**

### New Drugs

<table>
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<tr>
<th>New anti-HER TKIs (Neratinib, Tucatinib, Pyrotinib, Poziotinib)</th>
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<td>Antibody Drug Conjugates (ADCs) (SYD-985, DS 8201)</td>
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<td>New anti-HER Antibodies (Margetuximab, Panitumumab)</td>
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<td>Bi-specific Antibodies (ZW-25, MCLA-128, GBR1302)</td>
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### New Combinations

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<tr>
<td>Anti-HER2 + CDK 4/6 Inhibitors</td>
</tr>
<tr>
<td>Anti-HER2 + anti-PD(L)1</td>
</tr>
</tbody>
</table>
Second/third generation of HER inhibitors
Status of clinical development

<table>
<thead>
<tr>
<th>Type of HER inhibitor</th>
<th>Drug</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER1-2-4</td>
<td>Neratinib (N)</td>
<td><img src="image1" alt="Diagram" /></td>
</tr>
<tr>
<td>HER1-2-4</td>
<td>Afatinib (A)</td>
<td><img src="image2" alt="Diagram" /></td>
</tr>
<tr>
<td>HER2</td>
<td>Tucatinib (T)</td>
<td><img src="image3" alt="Diagram" /></td>
</tr>
<tr>
<td>HER1-2-4</td>
<td>Pyrotinib (Py)</td>
<td><img src="image4" alt="Diagram" /></td>
</tr>
<tr>
<td>HER1-2-4</td>
<td>Poziotinib (Po)</td>
<td><img src="image5" alt="Diagram" /></td>
</tr>
</tbody>
</table>

(12 mg poziotinib qd 14-day on/7-day off schedule)

**NALA** (NCT01808573) trial of Cape+N vs Cape+L in third line has completed accrual! (n=600)

(A) + vinorelbine not better than T + vinorelbine

Phase I Study and Biomarker Analysis of Pyrotinib, a Novel Irreversible Pan-ErbB Receptor Tyrosine Kinase Inhibitor, in HER2+ Metastatic Breast Cancer

- Dose limiting toxicity: diarrhea.
- MTD 400 mg/day
- ORR=50%; CBR24w=61.1%
- ORR=33.3% in trastuzumab-treated
- ORR=83.3% in trastuzumab-naive

Ma et al. J Clin Oncol 2017

N=38

Ma et al. J Clin Oncol 2017
A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer

This is an open label, multicenter, randomized phase II trial.

**Randomization**
- HER2 positive metastatic breast cancer
- Age 18 – 70 years
- Previously treated with taxanes and anthracyclines
- With/without prior trastuzumab
- ≤2 lines of chemotherapy for advanced disease
- Previous treatment with capecitabine within 6 months is not permitted
- Brain metastasis is not permitted
- Stratification: prior treatment with anti-HER2 monoclonal antibody (yes, no)
- Primary endpoint: overall response rate (ORR), as assessed by investigator

**PC:** Pyrotinib (P) + Capecitabine (C)
- pyrotinib 400mg, qd, d1-21, q3wks
- capecitabine 1000mg/m², bid, d1-14, q3wks
- until disease progression, intolerable toxicity or withdrawal of consent

**LC:** Lapatinib (L) + Capecitabine (C)
- Lapatinib 1250mg, qd, d1-21, q3wks
- capecitabine 1000mg/m², bid, d1-14, q3wks
- until disease progression, intolerable toxicity or withdrawal of consent

**Secondary endpoints:**
- Progression free survival (PFS)
- Time to progression (TTP)
- Duration of response (DoR)
- Overall survival (OS)
- Safety

Xu et al. SABCS 2017

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A randomized phase II trial of pyrotinib/capecitabine versus lapatinib/capecitabine in HER2+ metastatic breast cancer

- Increased mPFS 18 vs. 7.0 months (HR=0.36, P<0.0001); irrespective of prior trastuzumab.

- Grade 3-4 toxicities higher in PC arm vs LC arm:
  - Hand-foot syndrome (24.6% vs 20.6%),
  - Diarrhea (15.4% vs 4.8%)
  - Decreased neutrophil (9.2% vs 3.2%)
  - Vomiting (4.6% vs 1.6%)

- Serious adverse events (SAEs): 7.7% vs. 6.3%.

- A Phase III trial is ongoing (NCT02973737).

Xu et al. SABCS 2017

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A Phase 1b Study of Tucatinib (ONT-380) Combined With Capecitabine and/or Trastuzumab in HER2+ Metastatic Breast Cancer

N=23

- 300mg BID
- Encouraging anti-tumor activity seen in the triplet combination, in a heavily pre-treated population including those with brain mets
- ORR=61% ; Median PFS=7.8m
- Median DOR=10 months
- Orphan drug designation by FDA for the treatment of BC brain metastases

NCT02025192

Hamilton et al. SABCS 2016
Metronomic CT (chemotherapy): cyclophosphamide 50 mg/d po continuously
On progression: Option to have T-DM1 (3.6 mg/kg iv q3w) till progression

**HER2+ MBC**
- ≥ 70 Years (or ≥65/≥60y with co-morbidity)
- No prior chemo for MBC
- ≤1 line of antiHER2 + endocrine therapy
- Prior endocrine therapy allowed

**Primary endpoint:**
PFS rate at 6 months

**EORTC 75111 – 10114 Trial Design**

<table>
<thead>
<tr>
<th>N=80</th>
<th>Pertuzumab + Trastuzumab</th>
<th>Pertuzumab + Trastuzumab + Metronomic Cyclophosphamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>PD</td>
<td>T-DM1 (optional)</td>
</tr>
</tbody>
</table>

Stratification: ER and/or PR pos vs both negative, previous HER2 treatment (none vs adj only vs metastatic), G8< or equal 1 vs G8>14

SABCS 2017 Wildiers et al ; Lancet Oncol 2017

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### EORTC 75111 – 10114 Patient Characteristics

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) – Median (Range)</td>
<td>76.7</td>
<td>(61.4 - 91.4)</td>
</tr>
<tr>
<td>WHO PS 2-3</td>
<td>19</td>
<td>(23.8)</td>
</tr>
<tr>
<td>ER and/or PgR positive</td>
<td>55</td>
<td>(68.8)</td>
</tr>
<tr>
<td>No prior anti-HER2 therapy for MBC</td>
<td>72</td>
<td>(91.1)</td>
</tr>
<tr>
<td>Prior adjuvant endocrine therapy</td>
<td>24</td>
<td>(30.4)</td>
</tr>
<tr>
<td>Visceral involvement</td>
<td>74</td>
<td>(93.3)</td>
</tr>
<tr>
<td>G8 score at baseline ≤ 14</td>
<td>56</td>
<td>(70.9)</td>
</tr>
<tr>
<td>Frail (SPPB ≤ 7)</td>
<td>37</td>
<td>(52.9)</td>
</tr>
</tbody>
</table>
Median PFS was 5.6 months (95% CI 3.6-16.8) versus 12.7 months (95% CI 6.7-24.8)

HR=0.65 (95% CI 0.37-1.12)  
p=0.12

HR=0.92 (95% CI 0.44-1.91)  
p=0.83

SABCS 2017 Wildiers et al; Lancet Oncol 2017 in Press

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**EORTC 75111 – 10114 vs. CLEOPATRA**

<table>
<thead>
<tr>
<th>Wilders et al. (N=80)</th>
<th>CLEOPATRA (N=808; NEJM 202)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trastuzumab + Pertuzumab (TP)</strong></td>
<td><strong>Docetaxel + Trastuzumab</strong></td>
</tr>
<tr>
<td><strong>Cyclophosphamide + Trastuzumab + Pertuzumab (CTP)</strong></td>
<td><strong>Docetaxel + Trastuzumab + Pertuzumab</strong></td>
</tr>
<tr>
<td>ORR %</td>
<td>44.0%</td>
</tr>
<tr>
<td>Median PFS (months)</td>
<td>5.6</td>
</tr>
<tr>
<td><strong>T-DM1 (following CTP)</strong></td>
<td>13.0%</td>
</tr>
</tbody>
</table>

**ORR Δ 11.0%**

**PFS Δ 7.1 months**

**ORR Δ 10.9%**

**PFS Δ 6.1 months**

- Lower median PFS with CTP than in taxane + TP (12.7 vs. 18.5 months)
- **Adding cyclophosphamide achieves a similar magnitude of clinical benefit as pertuzumab on top of taxane + trastuzumab.**
- T-DM1 might help prolong progression in second-line in this elderly population.
- **More clinical trials are needed in elderly and/or frail patients!**

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**New Strategies: New Antibody Drug Conjugates**

The success of T-DM1 has created a lot of excitement around ADCs

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Antibody</th>
<th>Chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM - 302²</td>
<td>Humanized anti-HER2 antibody</td>
<td>Liposomal doxorubicin</td>
</tr>
<tr>
<td>DS – 8201a³</td>
<td>Humanized anti-HER2 antibody</td>
<td>Exatecan</td>
</tr>
<tr>
<td>SYD- 0985⁴</td>
<td>Trastuzumab</td>
<td>Duocarmycin</td>
</tr>
<tr>
<td>XMT - 1522⁵</td>
<td>HT-19 (Humanized anti-HER2 antibody)</td>
<td>Auristatin</td>
</tr>
<tr>
<td>MEDI 4276⁶</td>
<td>Bispecific anti-HER2/HER2 antibody</td>
<td>Tubulysin</td>
</tr>
</tbody>
</table>


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ADC Efficacy – Phase 1-2 Data

Responses seen in heavily pretreated patients!


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Trastuzumab deruxtecan (DS-8201), a HER2-targeting antibody–drug conjugate

- Highly potent: Drug-to-antibody ratio = 7.8 vs 3.5 for T-DM1.
- Topoisomerase I inhibitor vs. tubulin inhibitor (T-DM1)
- Preclinically, DS-8201a has a potent bystander effect due to a highly membrane-permeable payload


http://dsi.com/adc-franchise
Safety, pharmacokinetics, and antitumor activity of DS-8201 in advanced breast/gastric cancer: a Phase 1 study

• No dose-limiting toxic effects or deaths.
• ORR=43% ; DCR=91%
• Responses observed at higher doses
• Antitumor activity observed in previously treated with T-DM1 or trastuzumab, and in patients with HER2-low tumors

Doi et al. Lancet Oncol 2017

N=24 (23 evaluable) in Japan

B=Breast
Safety and efficacy results from a phase 1 study of DS-8201a in patients with HER2+ breast cancers

N=130 (76 evaluable)

- The dose levels of 5.4 and 6.4 mg/kg IV every 3 weeks were chosen for Part 2.
- Grade 3 toxicities occurred in <10% of the patients.
- Most frequent grade 3 toxicity was nausea.

**TABLE 3. Efficacy – Confirmed ORR, DCR, and PFS**

<table>
<thead>
<tr>
<th>Population</th>
<th>ORR, n/N (%)</th>
<th>DCR, n/N (%)</th>
<th>PFS (months), median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2-positive</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>35/57 (61.4)</td>
<td>54/57 (94.7)</td>
<td>10.4 (1.2+, 16.8+)</td>
</tr>
<tr>
<td>HR-positive</td>
<td>22/39 (56.4)</td>
<td>36/39 (92.3)</td>
<td>NR (1.2+, 16.8+)</td>
</tr>
<tr>
<td>HR-negative</td>
<td>12/16 (75.0)</td>
<td>16/16 (100.0)</td>
<td>10.4 (1.2+, 14.1+)</td>
</tr>
<tr>
<td>Prior pertuzumab-treated</td>
<td>31/50 (62.0)</td>
<td>47/50 (94.0)</td>
<td>10.3 (1.2+, 16.8+)</td>
</tr>
<tr>
<td><strong>HER2-low</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>6/19 (31.6)</td>
<td>16/19 (84.2)</td>
<td>NR (0.5, 12.2+)</td>
</tr>
<tr>
<td>HR-positive</td>
<td>5/16 (31.3)</td>
<td>14/16 (87.5)</td>
<td>NR (1.2+, 12.2+)</td>
</tr>
<tr>
<td>HR-negative</td>
<td>0/2 (0.0)</td>
<td>1/2 (50.0)</td>
<td>7.6 (0.5, 7.6)</td>
</tr>
</tbody>
</table>

*Analysis set for ORR (CR+PR) and DCR (CR+PR+SD): efficacy evaluable for confirmed overall response, at least 2 postbaseline scans or progressive disease at the first scan.

Minimum and maximum of PFS include ‘+’ after value indicates censoring.

CR, complete response; DCR, disease control rate; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NR, not recorded; ORR, objective response rate; PFS, progression-free survival; SD, stable disease.

breakthrough therapy designation

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Modi et al. SABCS 2017
A Phase 2, Multicenter, Open-Label Study of DS-8201a in HER2+ Metastatic Breast Cancer Resistant/Refractory to T-DM1 (DESTINY-Breast01)

- N=230
- Primary objective: ORR
  - Men or women
  - Unresectable or metastatic
  - HER2 positive expression
  - ≥1 measurable lesion

PART 1 (N=120)
- High dose 7.4 mg/kg
- Intermediate dose 6.4 mg/kg
- Low dose 5.4 mg/kg

PART 2 (N=110)
- Final dose in T-DM1 Resistant/refractory (n=100)
- Final dose in T-DM1 intolerant (n=10)

NCT03248492
Trastuzumab Progression-Free Survival ~ CD16A (FcγRIIIA) genotype

Better Outcomes in Patients with Sticky Natural Killer Cells (CD16A V/V)

Musolino et al., J Clin Oncol 26: 1789-96 (2008)
New Strategies
New Anti-HER Antibodies - Margetuximab

- Optimized IgG1 Fc domains: 5 amino acid substitutions
  - ↑ binding to activating CD16A (FcγRIIIA); ↓ binding to inhibitory CD32B (FcγRIIB)

Enhanced ADCC of the Fc optimized chimeric Mab Margetuximab, irrespective of the FcγR isoform

Burris H et al ASCO 2015
SOPHIA Study to Establish Superiority Over Trastuzumab

Phase 3 – Randomized Trial of Margetuximab in Third-Line Metastatic Breast Cancer

**Stratification:**
- Type of chemotherapy
- No. lines of prior chemotherapy (≤ 2 vs > 2)
- No. of metastatic sites (≤ 2 vs > 2)

**Sequential Primary Endpoints:**

*Progression-Free Survival* (PFS, N=257, HR=0.67, α=0.05, power=90%)

*then Overall Survival* (OS, N=385, HR=0.75, α=0.05, power=80%)
**New Strategies**

**New Agents & New Combinations directed at the cancer cell**

<table>
<thead>
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<th><strong>New Drugs</strong></th>
<th><strong>New Combinations</strong></th>
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*ClinicalTrials.gov*

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Strategies antagonizing the Pi3K-mTOR pathway
The first generation of trials

First line

- Taxane + Trastuzumab
- ? + Everolimus

*Bolero-1 trial* (1)
Negative trial
(Signal in HR subgroup)

Second line

- Vinorelbine + Trastuzumab
- ? + Everolimus

*Bolero-3 trial* (2)
Marginal ↑ PFS

(1) Hurvitz S et al Lancet Oncol 2015 16 (7) 816-29
(2) Andre F Lancet Oncol 2014 15 (6) p-580-591
Strategies antigenizing the Pi3K-mTOR pathway
The second generation of trials

First line
Taxane + Trastuzumab + Pertuzumab

Second line
T-DM1

Later lines...
Trastuzumab
Trastuzumab

LJM716*

? + Taselisib (3)

? + Alpelisib (2)

+ Buparlisib + Pilaralisib (1)

Very modest activity and significant toxicity

(1) Tolaney S et al. Breast Cancer Res Treat 2015 149 (1) 151-161; (2) NCT02167854 (3) Metzger O et al ASCO 2017

*anti-HER3 antibody
New Strategies
CDK 4/6 and anti-HER2 Resistance

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Advanced HER2+ Breast Cancer:
New strategies incorporating CDK4-6 inhibitors

**First line**
- Taxane
- +
- Trastuzumab
- +
- Pertuzumab

**Second line**
- T-DM1

**Later lines...**
- Trastuzumab (or Lapatinib)-based therapies

- +
  - Palbociclib
  - or Ribociclib (3)

- +
  - Abemacliclib (1)

- +
  - Abemacliclib
  - + Fulvestrant (2)

(1) Beeram M et al ESMO 2016 LBA18
(2) NCT02675231
(3) NCT02657343
New Strategies

Palbociclib - Phase 2 PATRICIA Design

**Patient Population**
- HER2+ locally advanced/MBC
- 2-4 previous lines of treatment
- At least 2 forms of anti-HER2 therapy
- At least one taxane or capecitabine containing regimen
- Tumour samples for biomarker research (preferably from metastasis)

**Endpoints**

**Primary**
- PFS at 6 months

**Secondary**
- CBR
- ORR
- PFS
- Safety
- OS
- Biomarker of response based on 110 genes expression panel

**ARM A (ER-) Palbo/Trastuzumab**

**ARM B1 (ER+) Palbo/Trastuzumab**

**ARM B2 (ER+) Palbo/Trastuzumab/Letrozole**

**Palbociclib regimen: 200mg 14 days/7 days rest**

**Clinical Trials.gov NCT02448420**

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What’s New in 2017 (immunotherapy)

2016 2017 2018

**KEYNOTE-12** (Nanda et al, JCO 2016)

**JAVELIN** (Dirix et al, Breast Ca Res Treat 2017)

Multiple phase 1/2 IO + chemo reported/ongoing

**KEYNOTE-110 accrual completed**

**IMpassion-130 accrual completed**

**I-SPY2** (preop ER+/TNBC; Nanda et al ASCO 2017)

**PANACEA** (Loi et al, SABCS 2017)

IO combinations

IO + targeted tx

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Background: Anti-tumor immunity & HER2-positive breast cancer

- HER2-positive breast cancer has high levels of T cell infiltration

- TILs are associated with improved prognosis and response to trastuzumab and chemotherapy\(^1,2\)

- Trastuzumab has been shown to have immune mediated mechanisms of action\(^3,4\)

- Preclinical studies suggest immune-mediated mechanisms of trastuzumab resistance that can be overcome with checkpoint inhibition combinations\(^5\)

\(^1\) Loi et al, J Clin Oncol 2013; \(^2\) Loi et al, Ann Oncol 2014 \(^3\) Clynes et al Nat Med 2002 \\
\(^4\) Park et al, Cancer Cell 2011; \(^5\) Stagg, Loi et al, PNAS 2011
Anti-PD(L) 1 Strategies explored in advanced HER2+ BC

First line
- Taxane + Trastuzumab + Pertuzumab
  - ? + anti PD(L) 1
  - Pembrolizumab (5)
  - Atezolizumab (6)

Second line
- T-DM1
  - ? + anti PD(L) 1
  - Atezolizumab (3)
Pembrolizumab (4)

Later line
- Trastuzumab
  - ? + anti PD(L) 1
  - Pembrolizumab (1)
  - Atezolizumab (3)
  - Pembrolizumab (4)
  - Durvalumab (2)

(1) NCT02129556  (2) NCT02649686  (3) NCT02924883  (4) NCT03032107  (5) NCT03199885  (6) NCT03125928

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**New Strategies**

**PANACEA TRIAL**

ABC
Prior progression while on trastuzumab based

Central testing HER2 by IHC

- HER2 -
- HER2 +

Central PD-L1 testing

- PD-L1 -
- PD-L1 +

Enroll

Phase Ib (dose finding Pembrolizumab in 3+3 design) /Phase II at RP2D
Treatment in 3 weeks cycles

Trastuzumab 6 mg/kg q 3 w

Pembrolizumab

* PDL1 negative cohort added later
# Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Phase Ib PD-L1 positive; n=6</th>
<th>Phase II PD-L1 positive; n=40</th>
<th>Phase II PD-L1 negative; n=12</th>
<th>Overall n=58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age yrs. median (range)</td>
<td>49 (38-57)</td>
<td>49 (28-72)</td>
<td>56.5 (43-61)</td>
<td>50.5 (28-72)</td>
</tr>
<tr>
<td>ER negative positive (≥ 1%)</td>
<td>4 (66%)</td>
<td>23 (57.5%)</td>
<td>6 (50%)</td>
<td>33 (56.9%)</td>
</tr>
<tr>
<td>Prior trastuzumab-containing therapy</td>
<td>6 (100%)</td>
<td>40 (100%)</td>
<td>12 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Additional anti-HER2 therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1 (16.7%)</td>
<td>6 (15%)</td>
<td>0 (0%)</td>
<td>7 (12.1%)</td>
</tr>
<tr>
<td>Yes</td>
<td>5 (83.3%)</td>
<td>34 (85%)</td>
<td>12 (100%)</td>
<td>51 (87.9%)</td>
</tr>
<tr>
<td>T-DM1</td>
<td>4</td>
<td>29</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>3</td>
<td>10</td>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>17</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>Prior chemotherapy (Anth/Taxane)</td>
<td>6 (100%)</td>
<td>40 (100%)</td>
<td>12 (100%)</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Median time from Dx met disease to enrolment; months (range)</td>
<td>15.5 (6-83.6)</td>
<td>40.8 (1.1-111)</td>
<td>71.5 (9.9-179.1)</td>
<td>40 (1.1-179.1)</td>
</tr>
</tbody>
</table>
## Best Overall Response (RECIST 1.1)

<table>
<thead>
<tr>
<th></th>
<th>PD-L1 Positive Phase Ib, n=6</th>
<th>PD-L1 Positive Phase II, n=40</th>
<th>PD-L1 Negative Phase II, n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR n (%) [90%CI]</strong></td>
<td>1 (17%) [1-58]</td>
<td>6 (15%) [7-29]</td>
<td>0 (0%) [0-18]</td>
</tr>
<tr>
<td><strong>DCR(^1) n (%) [90%CI]</strong></td>
<td>1 (17%) [1-58]</td>
<td>10 (25%) [14-49]</td>
<td>0 (0%) [0-18]</td>
</tr>
</tbody>
</table>

### Best overall response, n (%)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>PD-L1 Positive Phase Ib, n=6</th>
<th>PD-L1 Positive Phase II, n=40</th>
<th>PD-L1 Negative Phase II, n=12</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong></td>
<td>1 (17%)</td>
<td>1 (2.5%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>-</td>
<td>5 (12.5%)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>-</td>
<td>7 (17.5%)</td>
<td>2 (16.7%)</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong></td>
<td>5 (83%)</td>
<td>25 (62.5%)</td>
<td>9 (75.0%)</td>
</tr>
<tr>
<td><strong>Not Evaluable</strong></td>
<td>-</td>
<td>2 (5.0%)</td>
<td>1 (8.3%)</td>
</tr>
</tbody>
</table>

### Overall PD-L1 + cohort

<table>
<thead>
<tr>
<th></th>
<th><strong>ORR 15.2% [7-27]</strong></th>
<th><strong>DCR 25% [14-36]</strong></th>
</tr>
</thead>
</table>

PD-L1: assessed centrally by Merck

QualTek PD-L1 IHC Assay changed to 22C3 Q^2 Solutions

Positive was QualTek ≥1% tumor or stroma; Q^2: CPS ≥1%

\(^1\)DCR: CR, PR, or SD ≥ 6 months
PANACEA Trial: Summary and Conclusions

• PANACEA study of pembrolizumab with trastuzumab in trastuzumab-resistant mHER2+ patients met its primary endpoint in the PD-L1 positive cohort (ORR 15%, DCR 25%)
  – No responses observed in PD-L1 negative patients
  – Stromal TIL levels associated with responses: sTILs ≥ 5% patients (ORR 39%, DCR 47%)
  – For responders: combination offers durable control without chemotherapy

• Metastatic HER2+ disease in the heavily pretreated setting is poorly immunogenic (majority of patients had low TILs in their metastatic lesions)

• Future directions in IO in mHER2+ should focus on combinations with effective anti-HER2 therapy, especially in low TIL patients
KATE2 Study Overview

DESIGN: PHASE II | DOUBLE-BLIND | MULTICENTRE | RANDOMIZED | PLACEBO-CONTROLLED

Total study duration: 28 months – Recruitment: 9 months

Study Treatment Phase

Patients with HER2+ LABC or mBC
- Prior taxane and trastuzumab
- Progression on metastatic tx or within 6 months of adjuvant tx
- Measurable disease (n=200)

Stratification Factors:
- Tumour PD-L1 Status
- World Region
- Liver Metastases

1:2
n=67
T-DM1, 3.6 mg/kg q3w + Placebo, 1200 mg q3w

n=133
T-DM1, 3.6 mg/kg q3w + Atezolizumab, 1200 mg q3w

In the event of toxicity or loss of benefit per RECIST 1.1

Until PD

Survival Follow-Up

T-DM1: Trastuzumab-emtansine
Concluding Remarks

The next decade will see numerous drugs & combinations come to Phase III (and hopefully clinical practice).

Coming together is a beginning
Keeping together is progress
Working together is success

- Henry Ford-