"Clearly, the results reported in this issue of the Journal are not evolutionary... but revolutionary."

G Hortobagyi
Trastuzumab biosimilars are currently undergoing regulatory review

<table>
<thead>
<tr>
<th>Company</th>
<th>Biosimilar</th>
<th>Submitted to EMA</th>
<th>Submitted to FDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amgen</td>
<td>ABP 980</td>
<td>March 2017</td>
<td>July 2017</td>
</tr>
<tr>
<td>Biocon/Mylan</td>
<td>MYL-1401O</td>
<td>August 2016</td>
<td>November 2016</td>
</tr>
<tr>
<td>Celltrion</td>
<td>CT-P6</td>
<td>October 2016</td>
<td>July 2017</td>
</tr>
<tr>
<td>Samsung Bioepis</td>
<td>SB3</td>
<td>August 2016*</td>
<td>Submitted</td>
</tr>
<tr>
<td>Pfizer</td>
<td>PF-05280014</td>
<td>July 2017</td>
<td>(date unknown)</td>
</tr>
</tbody>
</table>

*Positive CHMP opinion received September 15, 2017

ABP 980 is an investigational product
Phase 1 PK studies of trastuzumab biosimilars in healthy volunteers

Challenges in the implementation of trastuzumab biosimilars: an expert panel’s recommendations

1. Choosing a valid clinical endpoint is critical and challenging for the assessment of trastuzumab biosimilars
2. What should the comparison criterion be between trastuzumab biosimilars and their reference medicinal products?
3. Are safety events of particular importance during follow-up of trastuzumab biosimilars?
Choosing a valid clinical endpoint is critical and challenging for the assessment of trastuzumab biosimilars

Patient criteria\textsuperscript{1,2}
- Overall survival (OS)

Disease criteria\textsuperscript{1–3}
- Objective response rate (ORR)
- Disease-free survival (DFS)
- Disease-free progression (PFS)
- Pathological complete response (pCR)

Sensitive endpoints are recommended for biosimilar clinical trials\textsuperscript{4–6}
- Clinically relevant, objective measure, able to detect differences
- Continuous endpoints may be preferred over binary endpoints
- Length of study should be sufficient to allow for adequate safety and immunogenicity assessment

Relationship between pCR and EFS by breast cancer subtype
CTNeoBC pooled analysis
HannaH: Phase 3 trial to demonstrate non-inferiority of trastuzumab SC vs IV in terms of PK and efficacy

**Primary endpoints**
- **Non-inferiority of trastuzumab SC vs IV based on co-primary endpoints:**
  - PK: observed trastuzumab $C_{\text{trough}}$ pre-dose at Cycle 8 (presurgery)
  - Efficacy: pCR (breast only)

**Abbreviations**
- FEC: fluorouracil, epirubicin and cyclophosphamide
- IV: intravenous
- Q3W: once every 3 weeks
- R: randomisation
- SC: subcutaneous

**HER2+ EBC (N=596)**
- **Trastuzumab SC**
  - Fixed dose of 600 mg (5 mL over 5 minutes)
- **Trastuzumab IV**
  - 8 mg/kg loading dose; 6 mg/kg maintenance dose
- **Docetaxel 75 mg/m²**
- **FEC 500/75/500 mg/m² Q3W**

**Follow-up:** 2 years

**Results**
- Safety, tumour response, immunogenicity
- pCR
- Safety, EFS, OS, immunogenicity
- PK

**Statistical Analysis**
- n=299
- n=297
Neo-adjuvant setting has become the first choice for the assessment of new strategies.

“It allows for evaluation of innovative therapies an evaluation in a homogeneous population with rare confounding factors, and the relationship between pathological complete response (pCR) and survival outcomes is an early indicator of efficacy.”

X. Pivot, DG Cox. A new era for early development in HER2-positive breast cancer Lancet Oncology 2018
2. Equivalence margins: how similar is similar enough?

- ‘Minimally Clinically Important Difference’ (MCID)

Risk difference (RD)
Confidence interval for the **absolute difference** in primary endpoint between biosimilar and reference product

\[
\% \text{ biosimilar} - \% \text{ reference product}
\]

- If drugs have same efficacy, risk difference = 0

Risk ratio (RR)
Confidence interval for the **ratio** of primary endpoint for biosimilar versus reference product

\[
\frac{\% \text{ biosimilar}}{\% \text{ reference product}}
\]

- If drugs have same efficacy, risk ratio = 1


A Randomized Clinical Trial
With ERBB2 (HER2)-Positive Metastatic Breast Cancer
A clinically effective biosimilar may help increase access to this therapy.

INTERVENTIONS
Treatment with the anti-ERBB2 humanized monoclonal antibody trastuzumab plus a taxane or trastuzumab plus a taxane in patients without prior treatment for ERBB2-positive metastatic breast cancer.

MAIN OUTCOMES AND MEASURES
Primary endpoints
• ORR (CR or PR) at Week 24; ITT population
• Pre-defined equivalence margins: 90% CI for RR 0.81–1.24; 95% CI for RD +/-15%*

Secondary endpoints
• TTP, PFS, OS at Week 48
• AEs, LVEF, and immunogenicity at Weeks 24 and 48; PK

CONCLUSIONS AND RELEVANCE
Among women with ERBB2-positive metastatic breast cancer; a clinically effective biosimilar may help increase access to this therapy.

*Additional analysis of RD requested by the EMA. AE, adverse event; CR, complete response; ITT, intention-to-treat; LD, loading dose; LVEF, left ventricular ejection fraction; MD, maintenance dose; ORR, overall response rate; PR, partial response; TTP, time to progression
Mylan/Biocon (MYL-1401O) vs trastuzumab RP in HER2+ MBC: primary efficacy results

Efficacy at Week 24 (ITT population) | MYL-1401O + taxane (n=230) | Trastuzumab RP + taxane (n=228) |
--- | --- | --- |
ORR, % (95% CI) | 69.6 (63.62, 75.51) | 64.0 (57.81, 70.26) |
Risk ratio (90% CI) | 1.09 (0.974, 1.211) |  |
Risk difference (95% CI) | 5.53 (-3.08, 14.04) |  |

Primary analysis: RR (90% CI) for ORR

0.974  1.09  1.211
0.81  1  1.24
Favours trastuzumab RP  Favor MYL-1401O
Pfizer (PF-05280014) vs trastuzumab RP in HER2+ MBC: Phase 3 equivalence study

**Primary endpoint**
- ORR (CR or PR by Week 25, confirmed at Week 33); ITT population
- Pre-defined equivalence margins: 95% CI for RR 0.8–1.25

**Secondary endpoints**
- DOR, PFS and OS rates at 1 year; PK; safety; immunogenicity

*80 mg/m² (with provision for dose reduction) D1, 8, 15 x ≥6 4-week cycles or until maximal benefit of response

† Following completion of the paclitaxel administration period and beginning no earlier than Week 33 of the study, the PF-05280014 or trastuzumab RP regimen may be changed at the discretion of the investigator to 6 mg/kg Q3W

‡ Until death or 1 year from randomisation ≥6 months following last dose of study drug, whichever was longer. QW, once every week
# Pfizer (PF-05280014) vs trastuzumab RP in HER2+ MBC: primary efficacy results

<table>
<thead>
<tr>
<th>Efficacy by Week 25 (confirmed at Week 33) (ITT population)</th>
<th>PF-05280014 (n=352)</th>
<th>Trastuzumab RP (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (ITT), % patients (95% CI)</td>
<td>62.5 (57.2, 67.6)</td>
<td>66.5 (61.3, 71.4)</td>
</tr>
<tr>
<td>Risk ratio* (95% CI)</td>
<td>0.940 (0.842, 1.049)</td>
<td>1.049 (1.049, 1.049)</td>
</tr>
<tr>
<td>CR, %</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>PR, %</td>
<td>59.7</td>
<td>62.8</td>
</tr>
</tbody>
</table>

**Primary analysis: RR (95% CI) for ORR**

![Risk Ratio Diagram]

- *RR and associated 95% CI based on the Miettinen and Nurminen method

Pegram M, et al. ESMO 2017; Poster 238PD
Biocad (BCD-022) vs trastuzumab RP in HER2+ MBC: Phase 3 non-inferiority study

Primary endpoints
• ORR at Day 127; pre-defined non-inferiority margin for RD of -20% (lower 95% CI)
• AUC after the first test drug administration (PK substudy)

Secondary endpoint
• Rates of CR, PR, SD and PD

Shustova M, et al. ESMO 2016; Abstract 224 (and corresponding poster presented by Burdaeva et al.);

*Or until progression or unbearable toxicity.

PD, progressive disease; SD, stable disease
Biocad (BCD-022) vs trastuzumab RP in HER2+ MBC: primary efficacy results

<table>
<thead>
<tr>
<th>Efficacy (Day 127)</th>
<th>BCD-022 + paclitaxel (n=54)</th>
<th>Trastuzumab RP + paclitaxel (n=56)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % patients (95% CI)</td>
<td>53.6 (40.7, 66.0)</td>
<td>53.7 (40.6, 66.3)</td>
<td>0.862</td>
</tr>
<tr>
<td>Difference in ORR, % (95% CI)</td>
<td>-0.13 (-19.83, 18.35)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Primary analysis: RD (lower 95% CI) for ORR


*Yates-corrected Pearson’s test
CT-P6 compared with reference trastuzumab for
HER2-positive breast cancer: a randomised, double-blind,
active-controlled, phase 3 equivalence trial

Justin Stebbing, Yauheni Baranau, Valeriy Baryash, Alexey Manikhas, Vladimir Moiseyenko, Giorgi Dzagnidze, Edvard Zhavrid, Dmytro Boliukh,
Daniel Stroyakovski, Joanna Pikiel, Alexandru Eniu, Dmitry Komov, Gabriela Morar-Bolba, Rub K Li, Andry Rusyn, Sang Joan Lee, Sung Young Lee,
Francisco J Esteva

**Primary endpoint**
- tpCR** after neoadjuvant therapy and surgery (up to 30 weeks); per-protocol population
- Pre-defined equivalence margins: 95% CI for RR 0.74–1.35; 95% CI for RD +/-15%

**Secondary endpoints**
- Efficacy: pCR (breast only), tpCR (without DCIS), ORR, breast conservation rate, DFS, PFS, OS
- Other: PK, PD, biomarkers and safety

*Initial dose of 8 mg/kg IV, then 6 mg/kg for remaining cycles. **pCR in breast and axillary lymph nodes. †From the date of last patient enrolment. DCIS, ductal carcinoma in situ
Celltrion (CT-P6) vs trastuzumab RP in HER2+ EBC: primary efficacy results

Efficacy up to 30 weeks (Per-protocol population)

<table>
<thead>
<tr>
<th></th>
<th>CT-P6 (n=248)</th>
<th>Trastuzumab RP (n=256)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tpCR rate,* % (95% CI)</td>
<td>46.8 (40.4, 53.2)</td>
<td>50.4 (44.1, 56.7)</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>-4 (-12, 5)</td>
<td></td>
</tr>
<tr>
<td>Risk ratio (95% CI)</td>
<td>0.93 (0.78, 1.11)</td>
<td></td>
</tr>
</tbody>
</table>

Co-primary analysis: RD (95% CI) for tpCR

-12 -4 5
-15 Favours trastuzumab RP 0 Favours CT-P6 +15

Co-primary analysis: RR (95% CI) for tpCR

0.78 0.93 1.11
0.74 Favours trastuzumab RP 1 Favours CT-P6 1.35

*After neoadjuvant therapy and surgery (up to 30 weeks)
Amgen (ABP 980) vs trastuzumab RP in HER2+ EBC: Phase 3 equivalence study (LILAC)

Study population
- HER2+ invasive breast cancer
- Histologically confirmed, measurable disease (≥2.0 cm)
- No prior treatment
- Planning for surgical resection of breast tumour and sentinel node or axillary lymph node resection
- Planning neoadjuvant chemotherapy
- No distant metastases

Epirubicin + cyclophosphamide
Q3W for 4 cycles

Trastuzumab RP
Q3W for 4 cycles‡
+ paclitaxel
(n=361)

ABP 980
Q3W for 4 cycles†
+ paclitaxel
(n=364)

ABP 980
Q3W for up to 1 year‡
(n=349)

Trastuzumab RP
Q3W for up to 1 year‡
(n=171)

ABP 980
Q3W for up to 1 year‡
(n=171)

tpCR assessment; primary analysis

End of study

†Initial dose of 8 mg/kg IV then 6 mg/kg for remaining cycles;
‡Total of up to 1 year from the first day of ABP 980/trastuzumab RP administered in the neoadjuvant phase.

tpCR, total pathological complete response absence of invasive tumour cells in the breast tissue and axillary lymph node[s] regardless of residual ductal carcinoma in situ.

ABP 980 is an investigational product
Amgen (ABP 980) vs trastuzumab RP in HER2+ EBC: primary efficacy results

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Co-primary analysis (local pathology assessment)</th>
<th>Sensitivity analysis (central pathology assessment)</th>
</tr>
</thead>
<tbody>
<tr>
<td>tpCR* evaluable population</td>
<td>ABP 980 (n=358)</td>
<td>ABP 980 (n=339)</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab RP (n=338)</td>
<td>Trastuzumab RP (n=330)</td>
</tr>
<tr>
<td>tpCR rate, %</td>
<td>48.0</td>
<td>47.8</td>
</tr>
<tr>
<td></td>
<td>40.5</td>
<td>41.8</td>
</tr>
<tr>
<td>Risk ratio (90% CI)</td>
<td>1.19 (1.03, 1.37)</td>
<td>1.14 (0.99, 1.31)</td>
</tr>
<tr>
<td>Risk difference (90% CI)</td>
<td>7.3 (1.2, 13.4)</td>
<td>5.8 (-0.5, 12.0)</td>
</tr>
</tbody>
</table>

Co-primary analysis: RD (90% CI) for tpCR
-13 Favours trastuzumab RP 0 Favours ABP 980 +13
Risk difference
-0.5 Favours trastuzumab RP 0 Favours ABP 980 13
Risk difference

von Minckwitz G, et al. ESMO 2017; Poster 151PD

ABP 980 is an investigational product.
Phase III, Randomized, Double-Blind Study Comparing the Efficacy, Safety, and Immunogenicity of SB3 (Trastuzumab Biosimilar) and Reference Trastuzumab in Patients Treated With Neoadjuvant Therapy for Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer

**INTRODUCTION**

HER2-expressing human tumor cell proliferation with human epidermal growth factor receptor 2 (HER2)–positive early breast cancer in the neoadjuvant setting. To compare the efficacy, safety, and immunogenicity of SB3 (Trastuzumab Biosimilar) with reference trastuzumab (TRZ).

**METHODS**

Patients were randomly assigned to receive neoadjuvant SB3 or TRZ for eight cycles concurrently with chemotherapy (four cycles of docetaxel followed by surgery, and then 10 cycles of FEC)—defined equivalence margins: 90% CI for RR 0.785–1.546; 95% CI for RD +/-13%.

**RESULTS**

Overall response rates were 96.3% and 91.2% with SB3 and TRZ, respectively. Overall, 96.6% and 95.2% of patients experienced one or more adverse events, and 10.5% and 10.7% had a serious adverse event, with the lower limit contained within and the upper limit was declared if the 95% CI of the ratio was within 0–6.

**CONCLUSIONS**

Efficacy was demonstrated between SB3 and TRZ on the basis of the ratio of early breast cancer pathologic complete response rates, safety and immunogenicity were comparable. Eight hundred patients were included in the per-protocol set (SB3, n = 402; TRZ, n = 398). The bpCR rate was 10.70% (95% CI, 4.13% to 17.26%), with the lower limit contained within and the upper limit outside the equivalence margin. The total pathologic complete response rate, event-free survival, overall survival, safety, and immunogenicity were comparable.

**DATA SUPPLEMENT**

DOI: https://doi.org/10.1200/JCO.2017.74.0126
Samsung Bioepis (SB3) vs trastuzumab RP in HER2+ EBC: primary efficacy analysis

<table>
<thead>
<tr>
<th>Efficacy (Per-protocol population)</th>
<th>SB3 (n=402)</th>
<th>Trastuzumab RP (n=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast pCR rate, % patients</td>
<td>51.7</td>
<td>42.0</td>
</tr>
<tr>
<td>Risk difference (95% CI)</td>
<td>10.70 (4.13, 17.26)</td>
<td>1.259 (1.112, 1.426)</td>
</tr>
<tr>
<td>Risk ratio (90% CI)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Co-primary analysis: RD (95% CI) for breast pCR

Co-primary analysis: RR (90% CI) for breast pCR

Although equivalence of efficacy was demonstrated based on the RR of breast pCR rates, the upper limit of the 95% CI for the RD was outside the pre-defined equivalence margin.

Pivot X, et al. JCO 2018
**Drifts in ADCC-related quality attributes of Herceptin®: Impact on development of a trastuzumab biosimilar**

Seokkyun Kim*, Jinsu Song*, Seungkyu Park, Sunyoung Ham, Kyungyeol Paek, Minjung Kang, Yunjung Chae, Heewon Seo, Hyung-Chan Kim, and Michael Flores

- Downward drift in %afucose (G0±G1±G2) observed (EU + US reference product)

---

**Graph**

- % afucose (G0 + G1 + G2)
- Relative area (%)
- Expired date: 2015 to 2020
- 1st drift: ~ July 2018
- 2nd drift: 1st drift
- EU Herceptin
- US Herceptin
- *p≤0.05
Impact of drifts on anti-proliferative potency and HER2 binding activity

Kim S, et al. mAbs 2017
Impact of drifts on ADCC and FcγRIIIa binding

Levels of %afucose and %high mannose should be tightly monitored as critical quality attributes for biosimilar development of trastuzumab

Kim S, et al. mAbs 2017
Summary: results of equivalence analyses of biosimilar vs trastuzumab in studies of HER2+ EBC

<table>
<thead>
<tr>
<th></th>
<th>Co-primary analysis: RD (95% CI) for tpCR</th>
<th>Co-primary analysis: RR (95% CI) for tpCR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Celltrion (CT-P6)</strong>&lt;sup&gt;1&lt;/sup&gt; (N=504)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>-12 -4 5</td>
<td>0.78 0.93 1.11</td>
</tr>
<tr>
<td><strong>Amgen (ABP 980)</strong>&lt;sup&gt;2&lt;/sup&gt; (N=696)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>-13 0 13</td>
<td>0.74 1.03 1.37</td>
</tr>
<tr>
<td><strong>Samsung Bioepis (SB3)</strong>&lt;sup&gt;3&lt;/sup&gt; (N=800)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>-13 0 13</td>
<td>0.76 1.07 1.42</td>
</tr>
</tbody>
</table>

- Favours trastuzumab RP
- Favours biosimilar

NOTE: results cannot be directly compared due to differences in study design.


<sup>*</sup>In per-protocol population. <sup>†</sup>In tpCR evaluable population. ABP 980 is an investigational product.
3. Are safety events of particular importance during follow-up of trastuzumab biosimilars?

- Adverse events
- Serious adverse events
- Adverse events of special interest
- Anti-drug antibodies
- Safety following a switch from reference product
HERITAGE study: safety

Table 5. Descriptive Statistics for Cardiac Function (LVEF Values) by Visit in the Safety Population

<table>
<thead>
<tr>
<th>Visit and Statistic</th>
<th>LVEF, %</th>
<th>Proposed Biosimilar + Taxane (n = 247)</th>
<th>Trastuzumab + Taxane (n = 246)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline**</td>
<td></td>
<td>Proposed Biosimilar **</td>
<td>Trastuzumab **</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 246)</td>
<td>(n = 244)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td>64.0 (63.3 to 64.7)</td>
<td>64.1 (63.4 to 64.8)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td>64.0 (51 to 82)</td>
<td>63.0 (51 to 84)</td>
</tr>
<tr>
<td>Week 12**</td>
<td></td>
<td>(n = 212)</td>
<td>(n = 212)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td>63.6 (62.4 to 64.1)</td>
<td>63.4 (62.6 to 64.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td>63.0 (28 to 79)</td>
<td>63.0 (52 to 82)</td>
</tr>
<tr>
<td>Week 24**</td>
<td></td>
<td>(n = 148)</td>
<td>(n = 140)</td>
</tr>
<tr>
<td>Mean (95% CI)</td>
<td></td>
<td>63.6 (62.8 to 64.4)</td>
<td>63.2 (62.2 to 64.2)</td>
</tr>
<tr>
<td>Median (range)</td>
<td></td>
<td>63.5 (50 to 81)</td>
<td>63.0 (41 to 82)</td>
</tr>
</tbody>
</table>

Table 4. Treatment-Emergent Adverse Events and Serious Adverse Events by Week 24 in the Overall Safety Population

<table>
<thead>
<tr>
<th>Event</th>
<th>Participants, No. (%)</th>
<th>Proposed Biosimilar = Taxane (n = 247)</th>
<th>Trastuzumab = Taxane (n = 246)</th>
<th>Overall (n = 493)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment-Emergent Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE########################################</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>10 (3.8)</td>
<td>15 (5.8)</td>
<td>25 (5.2)</td>
<td>40 (2.1)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5 (2.0)</td>
<td>7 (2.9)</td>
<td>12 (2.4)</td>
<td>24 (1.3)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>14 (5.7)</td>
<td>13 (5.2)</td>
<td>27 (5.3)</td>
<td>46 (2.4)</td>
</tr>
<tr>
<td>Hypoalbumin</td>
<td>1 (0.4)</td>
<td>2 (0.8)</td>
<td>3 (0.6)</td>
<td>6 (0.3)</td>
</tr>
<tr>
<td>Hypothyroid</td>
<td>5 (2.1)</td>
<td>3 (1.2)</td>
<td>8 (1.6)</td>
<td>16 (0.9)</td>
</tr>
<tr>
<td>Immune-related reaction</td>
<td>14 (5.7)</td>
<td>10 (4.3)</td>
<td>24 (4.8)</td>
<td>38 (1.9)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10 (3.9)</td>
<td>21 (8.6)</td>
<td>31 (6.2)</td>
<td>52 (2.7)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>24 (9.9)</td>
<td>31 (12.6)</td>
<td>55 (11.0)</td>
<td>89 (4.5)</td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>4 (1.6)</td>
<td>7 (2.8)</td>
<td>11 (2.2)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td><strong>Serious Adverse Events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAE########################################</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>5 (2.2)</td>
<td>8 (3.3)</td>
<td>13 (2.6)</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>Sudden death</td>
<td>3 (1.3)</td>
<td>2 (0.8)</td>
<td>5 (1.0)</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Sudden death and cardiopulmonary resuscitation</td>
<td>4 (1.6)</td>
<td>3 (1.2)</td>
<td>7 (1.4)</td>
<td>12 (0.6)</td>
</tr>
</tbody>
</table>

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# Example safety findings: anti-drug antibodies (ADAs)

## ABP 980 vs trastuzumab RP: development of anti-drug antibodies – by phase

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant phase¹ (+ paclitaxel)</th>
<th>Adjuvant phase²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABP 980 (N=364) n (%)</td>
<td>Trastuzumab RP (N=361) n (%)</td>
</tr>
<tr>
<td>Development of binding ADAs during the study,* n (%)</td>
<td>2 (0.6)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Development of neutralizing ADAs, n (%)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*Patients with a negative or no result at baseline.


ABP 980 is an investigational product.
### Trastuzumab biosimilar clinical development: Summary of Phase 3 designs

<table>
<thead>
<tr>
<th>Neoadjuvant/adjuvant</th>
<th>Amgen ABP980&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Samsung Bioepis SB3&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Celltrion CT-P6&lt;sup&gt;3,4&lt;/sup&gt;</th>
<th>Pfizer PF-05280014&lt;sup&gt;5,6&lt;/sup&gt;</th>
<th>Biocon/Mylan MYL-14010&lt;sup&gt;7&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neoadjuvant regimen</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>(√)</td>
<td>-</td>
</tr>
<tr>
<td>N</td>
<td>725</td>
<td>875</td>
<td>549</td>
<td>226</td>
<td></td>
</tr>
<tr>
<td>Metastatic</td>
<td>-</td>
<td>-</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Regimen N</td>
<td>-</td>
<td>-</td>
<td>T + P 475</td>
<td>T + P 707</td>
<td>T + (D or P) 458</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>tpCR</td>
<td>pCR breast only</td>
<td>EBC: tpCR MBC: ORR</td>
<td>(EBC: PK endpoint) MBC: ORR</td>
<td>ORR</td>
</tr>
<tr>
<td>Equivalence margin for efficacy (risk difference)</td>
<td>90% CI ±13%</td>
<td>95% CI ±13%</td>
<td>EBC: 95% CI ±15% MBC: 95% CI ±15%</td>
<td>MBC: 95% CI 0.8–1.25 (risk ratio)</td>
<td>95% CI ±15%</td>
</tr>
<tr>
<td>Switch? Y/N</td>
<td>Y</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

E, epirubicin; C, cyclophosphamide; Ca, carboplatin; D, docetaxel; FEC, fluorouracil, epirubicin, cyclophosphamide; P, paclitaxel; T, trastuzumab (reference product or proposed biosimilar)