Disclosures

- **John M.S. Bartlett** has received honoraria for consultancy from Insight Genetics and BollMed (Non-CME) and currently has three pending patents: 1. "Method and Apparatus for Predicting Risk in Breast Cancer", 2. "Systems, Devices and Methods for Constructing and Using a Biomarker", 3. "Methods and Devices for Predicting Anthracycline Treatment".

- **Mitchell Dowsett** has received honoraria for consultancy from Genoptix, Radius, GIx, Roche, fees for Non-CME services from AstraZeneca, contracted research from AstraZeneca, Pfizer, Puma and has ownership interest in ICR Rewards for Investors Sciemi.

- **Beat J.K. Thürlimann** has the ownership interest in Novartis and Roche, and has received honoraria and travel support from Roche.

- **Marco A. Colleoni** has received honoraria from Novartis.

- **Jack Cuzick** has received research funding and honoraria from Speaker's Bureau - AstraZeneca.

- **Ihloaq Ahmed, Meredith M. Regan, Ivana Sestok, Elizabeth A. Mallon, Patrizia Dell'Orto, Caroline Seynaeve, Cornelis J.H. van de Velde Hein Putter, Cassandra L. Brookes, John F. Forbes, Jane Bayani, Giuseppe Viale, and Daniel W. Rea**

  All have no financial relationship(s) with commercial interests to disclose.
**Introduction**

- Evidence from the pivotal trials of aromatase inhibitors (AIs) versus Tamoxifen demonstrate the value of meta-analysis of key clinical questions.
  - Dowsett M. et al. Lancet 2015; 386; 1341-1352
- The “Trans-AIOG” group is tasked with delivery of key biomarker questions amenable to meta-analyses in AI trials.
- HER2 has long been proposed as a marker of endocrine “resistance”.
- A meta-analysis of the effects of HER2, specifically within the first 3 years of endocrine therapy, has potential to inform patient selection for upfront or switch strategies with AIs.

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**Meta-analysis TAM-AI “switch”**

- Dowsett M. et al. Lancet 2015; 386; 1341-1352
TRANS-AIOG HER2 meta-analysis:

Objective
- To determine by individual patient data (IPD) meta analysis the use of HER2 as a biomarker for selection of upfront aromatase inhibitors (AIs) compared to tamoxifen in the first 2-3 years of treatment in patients treated for early breast cancer.

Hypothesis
- HER2 is a predictive biomarker for greater AI benefit in HER2-ve patients during the first 2-3 years of endocrine therapy than in patients with HER2+ve disease.
- I.e. differential benefit from AIs vs tamoxifen is not seen in patients with HER2+ve disease during the first 2-3 years of treatment.

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HER2, TYPE 1 RTKS and endocrine therapy:

Multiple studies suggest HER2 is associated with early relapse during endocrine therapy. Other type 1 RTKs (EGFr/HER3) also contribute to this effect.

“We show that HER1-3 ......identify time-dependent de novo tamoxifen resistance with risk declining markedly after 3 years of tamoxifen treatment.”


HER2 effects time dependent in early breast cancer?

Methods

- Prospectively designed statistical analysis plan
- Survey of trials with available central HER2 status
  - ATAC, TEAM, BIG-1-98
- Centralization of patient level data
  - CRUK Clinical trials unit Birmingham UK
- Analysis and reporting of results

Statistical analysis plan

Outcome Measures

- Primary outcome: distant recurrence free interval (DRFI) up until the (pre-planned) 2-3 year treatment switch time (for trials with a switching element).

- Patients alive and in follow-up without evidence of disease were censored at the approximate date of treatment switch (around 2-3 years).
Statistical analysis plan

Sample Size
Using sample size calculations proposed by Schmoor, with two-sided a=0.05 and assuming an interaction hazard ratio (HR) of 2.44, 5.8% event rate within the 2-3 year treatment period, and 10% HER2-positive prevalence, 12448 patients gives 90% power to detect a treatment-biomarker interaction.

Analysis
An IPD meta-analysis of HER2 as a predictive biomarker for response to AI vs. tamoxifen treatment will be conducted. The statistical analysis will be done on an intent-to-treat basis within each of the three trials.

The interaction term between HER2 and the treatment will be calculated in each trial separately. This will then be pooled together across the three trials using a random-effects meta-analysis.


Biomarker data: ASCO-CAP guidelines.

- HER2 status was determined centrally and recorded as either positive or negative for each study.
  - HER2 status for each trial complied with the ASCO-CAP guidelines updated in 2013.
  - Patients were excluded from the analysis if tumors were not ER positive on central testing (<1% immuno-reactive cells or ER not determined) or if HER2 status was not centrally determined.
  - ER status according to ASCO-CAP 2010 guidelines

Results

<table>
<thead>
<tr>
<th>Trial</th>
<th>TEAM</th>
<th>ATAC</th>
<th>BIG 1-98</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited</td>
<td>9779</td>
<td>5880</td>
<td>8010</td>
<td>23,669</td>
</tr>
<tr>
<td>Samples collected</td>
<td>4781</td>
<td>2006</td>
<td>6549</td>
<td>13,336</td>
</tr>
<tr>
<td>Stained</td>
<td>4598</td>
<td>1782</td>
<td>6291</td>
<td>12,671</td>
</tr>
<tr>
<td>Available for analysis</td>
<td>4263</td>
<td>1684</td>
<td>6182</td>
<td>12,129</td>
</tr>
<tr>
<td>HER2+ve</td>
<td>525</td>
<td>178</td>
<td>389</td>
<td>1092</td>
</tr>
<tr>
<td>Distant recurrence in the first 2-3 years</td>
<td>243</td>
<td>65</td>
<td>165</td>
<td>473</td>
</tr>
</tbody>
</table>

- 12129/12448 (97.4%) of required cases (centrally ER positive with HER2 data)

Patient characteristics:

<table>
<thead>
<tr>
<th></th>
<th>TEAM</th>
<th>ATAC</th>
<th>BIG 1-98</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Randomized</td>
<td>49.6%</td>
<td>48.9%</td>
<td>49.9%</td>
<td>49.9%</td>
</tr>
<tr>
<td></td>
<td>(N=4263)</td>
<td>(N=1684)</td>
<td>(N=6182)</td>
<td>(N=12129)</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>50.2%</td>
<td>51.1%</td>
<td>50.1%</td>
<td>50.2%</td>
</tr>
<tr>
<td>Aromatase Inhibitor</td>
<td>48.3%</td>
<td>66.9%</td>
<td>62.3%</td>
<td>58.0%</td>
</tr>
<tr>
<td>Tumour Size</td>
<td>&lt;20mm</td>
<td>&gt;20mm</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48.9%</td>
<td>32.7%</td>
<td>0.7%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Nodal Status</td>
<td>Negative</td>
<td>25.7%</td>
<td>30.2%</td>
<td>47.3%</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>57.6%</td>
<td>41.6%</td>
<td>45.7%</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>16.7%</td>
<td>4.2%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Grade</td>
<td>Well</td>
<td>11.3%</td>
<td>20.8%</td>
<td>18.3%</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
<td>51.2%</td>
<td>54.0%</td>
<td>54.0%</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>31.4%</td>
<td>22.3%</td>
<td>24.0%</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>6.2%</td>
<td>0.3%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Central Her2 status</td>
<td>HER2 Negative</td>
<td>87.7%</td>
<td>89.4%</td>
<td>91.0%</td>
</tr>
<tr>
<td></td>
<td>HER2 Positive</td>
<td>12.3%</td>
<td>10.6%</td>
<td>9.0%</td>
</tr>
</tbody>
</table>

Primary endpoint Distant recurrence free interval: Treatment by marker interaction (adjusted):

<table>
<thead>
<tr>
<th>Variable</th>
<th>Event/Patients</th>
<th>Event/Patients</th>
<th>Patients</th>
<th>HER2 (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aromatase</td>
<td>Inhibitor</td>
<td>Tamoxifen</td>
<td>Total</td>
<td>Adjusted %</td>
<td></td>
</tr>
<tr>
<td>HER2 and treatment interaction term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAM</td>
<td>106/2138</td>
<td>135/2123</td>
<td>4263</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>34/960</td>
<td>31/824</td>
<td>1664</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIG198</td>
<td>63/3096</td>
<td>102/3086</td>
<td>6182</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between groups: p =

Overall (I-squared = 58.5%, p = 0.000)

Significant treatment by marker effect (p<0.05)

Heterogeneity - not statistically significant
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**Distant recurrence free interval:**
Sub-group analysis by HER2 status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Aromatase Inhibitor</th>
<th>Tamoxifen</th>
<th>Total Patients</th>
<th>%</th>
<th>HR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2 positive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAM</td>
<td>34/139</td>
<td>25/386</td>
<td>525</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>11/85</td>
<td>7/93</td>
<td>178</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIG198</td>
<td>14/220</td>
<td>20/169</td>
<td>389</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 70.8%, p = 0.013)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HER2 negative</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEAM</td>
<td>74/1899</td>
<td>110/1839</td>
<td>3738</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>23/775</td>
<td>24/731</td>
<td>1506</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIG198</td>
<td>49/3876</td>
<td>82/2917</td>
<td>5793</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.887)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity between groups p = 0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 58.7%, p = 0.033)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

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**Distant recurrence free interval**

- **HER2-ve AI vs T HR = 0.70 (0.64-0.94)**
- **HER2+ve AI vs T HR= 1.13 (0.75-1.71)**

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Years since randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>5487</td>
<td>0</td>
</tr>
<tr>
<td>547</td>
<td>0</td>
</tr>
<tr>
<td>549</td>
<td>0</td>
</tr>
<tr>
<td>544</td>
<td>0</td>
</tr>
</tbody>
</table>

- 1 = Tamoxifen & HER2 Negative
- 2 = Tamoxifen & HER2 Positive
- 3 = AI & HER2 Negative
- 4 = AI & HER2 Positive
Conclusions

Conclusion

- A patient level meta-analysis demonstrated a significant interaction between HER2 status and treatment with AIs versus Tamoxifen
  - Prior to “switching” between tamoxifen and AIs.
  - Satisfies the required criteria for level 1B evidence according to Simon et al
  - Heterogeneity observed in the HER2 positive subgroup,
    - Heterogeneity did not reach statistical significance within the primary endpoint population.
CAVEATS

- Most HER2+ve cancers not treated with Trastuzumab™
  - The potential impact of HER2 directed therapies is unknown.
    - precludes recommendations to change practice for patients eligible for Trastuzumab™
- Small number of HER2+ve cancers and events
  - Rates of HER2+ve varied (6.3%-12.3%)
  - Results contrast with the EBCTCG meta-analysis
    - >70% of cases had “unknown” HER2 status
- Additional research is required using a broader approach to type I RTK signaling.

TEAM: HER1-3 expression predicts for early benefit from AIs

HER123 negative (n = 2,872: 64%)

\[ HR_{net} = 0.67 \ (95\%\ CI: 0.51, 0.86) \]

HER123 positive (n = 1,620; 36%)

\[ HR_{net} = 1.11 \ (95\%\ CI: 0.83, 1.48) \]
Summary:

- A patient level meta-analysis demonstrated a significant interaction between HER2 status and treatment with AIs versus Tamoxifen.
- The observed heterogeneity between trials, coupled with minimal treatment using HER2 directed therapies in this group precludes recommendations to change patient management at this time.
- The observed effect, coupled with other data (combining EGFr/HER2/HER3) provides strong support for further research in this field.

Acknowledgements

- Co-authors in particular statistical partners
- Co-investigators for trials included ATAC, BIG-1-98 and TEAM.
- Patients for donating tissues for research
- Investigators – particularly pathologists at multiple sites who have release material for research.
Funding for the Ontario Institute for Cancer Research is provided by the Government of Ontario.

**HER2 status in the EBCTCG overview:**

A: 5 years of AI (any) versus 5 years of Tamoxifen
B: 5 years of AI (any) versus 2-3 years Tamoxifen then AI (any) to year 5.
C: 2-3 years of tamoxifen then AI (any) to year 5 versus 5 years of tamoxifen
D: 5 years of AI versus 2 years of AI then tamoxifen to year 5
E: 2 years of AI then tamoxifen to year 5 versus 5 years of tamoxifen.

NB: comparison only during periods when treatment differed.
A = years 1-5, B = years 1-3, C = years 4-5, D = years 3-5, E = years 1-2.
HER2-ve cases benefit from AI: Trans-ATAC

HER2 patients:
- Anastrazole HER2-
- Tamoxifen HER2-

HER2+ patients:
- Anastrazole HER2+
- Tamoxifen HER2+

Patients % with relapse

Analysis time (years)

Adapted from Dowsett et al., JCO 26(10):2008

HER2 alone is a predictive marker for upfront AI benefit in TEAM

HER2 negative (8.7%)
- HR=0.71
- 95% CI, 0.57 - 0.89

HER2 positive (13.0%)
- HR=1.88
- 95% CI, 1.10 - 2.57

Test for interaction p=0.0004 (p=0.0007 adjusted)

Primary Endpoint DFI: Unadjusted Treatment by marker interaction

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Events/Patients</th>
<th>Events/Patients</th>
<th>Patients</th>
<th>HR [95% CI]</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAM</td>
<td>108/2138</td>
<td>105/2125</td>
<td>4160</td>
<td>2.96 [1.41, 4.62]</td>
<td>33.02</td>
</tr>
<tr>
<td>ATAC</td>
<td>184/3356</td>
<td>180/3348</td>
<td>6168</td>
<td>2.20 [1.34, 3.61]</td>
<td>16.80</td>
</tr>
<tr>
<td>BIG1-98</td>
<td>638/8892</td>
<td>622/8866</td>
<td>6162</td>
<td>0.96 [0.64, 1.46]</td>
<td>18.09</td>
</tr>
</tbody>
</table>

Heterogeneity between groups p = 0.95
Overall I^2 = 11%, p = 0.95

Significant treatment by marker effect (p<0.05)
Heterogeneity – not statistically significant