Event-free survival and gene expression signatures in CALGB (Alliance) 40601

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C40601: Phase 3 neoadjuvant study evaluating dual HER2 therapy in HER2+ BC

Clinical stage II-III HER2+

Research tissue

wT+H x 16wks

wT+L x 16wks

wT+H+L x 16wks

Recommended:
Dose-dense AC ➔ H x 34 wks

SURGERY

N=305

wT= weekly paclitaxel, H=trastuzumab, L=lapatinib
Outcomes Analyses

- Study powered for pCR endpoint. EFS and OS are secondary endpoints
  - correlative analyses are exploratory and are not corrected for multiple comparisons
- EFS and gene expression information is available for 265 of 305 participants
  - (THL, n=104; TH, n=103; TL, n=58)
  - No significant differences in clinical characteristics between this subset and the entire population
- Median follow-up = 5.4 years
  - 39 EFS events (THL n=7/103; TH n=19/104; TL n=13/58)
  - 23 OS events (THL n=3/103; TH n=13/104; TL n=7/58)
- Gene signatures categorized:
  - Intrinsic subset by centroid classification (Parker el al., JCO 2007, Prat el al., BCR 2010)
  - IgG signature (10 genes, rank ordered and defined as los (lowest quartile) vs high( quartiles 2-4))
EFS: Rx Effect by Intrinsic Subtype

**LUM A**
- Arm: TH, THL
- Events/total: 6/40, 0/30
- HR (95%CI): Reference 0.00 (0.00 - )
- Logrank P-value: 0.0241

**LUM B**
- Arm: TH, THL
- Events/total: 8/32, 4/31
- HR (95%CI): Reference 0.47 (0.14 - 1.57)
- Logrank P-value: 0.2121

**HER2 E**
- Arm: TH, THL
- Events/total: 3/24, 3/35
- HR (95%CI): Reference 0.69 (0.14 - 3.41)
- Logrank P-value: 0.6444
**EFS: Rx Effect by IgG Signature**

**IgG Low**

- Arm: TH, THL
- Events/total: 6/23, 5/28
- HR (95% CI): Reference 0.66 (0.20-2.18)
- Logrank P-value: 0.4858

**IgG High**

- Arm: TH, THL
- Events/total: 13/81, 2/75
- HR (95% CI): Reference 0.16 (0.04-0.69)
- Logrank P-value: 0.0050
## Multivariate Model for EFS

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P=value</th>
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</thead>
<tbody>
<tr>
<td><strong>Treatment arm</strong></td>
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<tr>
<td>THL</td>
<td>0.29</td>
<td>(0.12, 0.71)</td>
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<tr>
<td>TL</td>
<td>1.06</td>
<td>(0.51, 2.23)</td>
<td>0.87</td>
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<td>TH</td>
<td>Ref</td>
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<td><strong>Gene signatures</strong></td>
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<td>IgG immune active</td>
<td>0.70</td>
<td>(0.50, 0.98)</td>
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<td>HER2E Correlation</td>
<td>1.79</td>
<td>(1.24, 2.57)</td>
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<td><strong>PCR</strong></td>
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<tr>
<td>Yes</td>
<td>2.8</td>
<td>(0.12, 0.66)</td>
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<tr>
<td>No</td>
<td>Ref</td>
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<td><strong>Clinical stage</strong></td>
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<tr>
<td>II</td>
<td>Ref</td>
<td>Ref</td>
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<tr>
<td>III</td>
<td>2.19</td>
<td>(1.13, 4.24)</td>
<td>0.02</td>
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</tbody>
</table>
Conclusions

- The addition of lapatinib to trastuzumab/taxane regimen was associated with a significant improvement in EFS
  - OS was also increased, but the number of events was very small

- Consistent with other studies, pCR was associated with favorable long term outcome
  - Effect most pronounced in HR-negative cancers and HER2-Enriched subtype

- Immune activation by RNA was an independent predictor of favorable pCR and EFS

- EFS benefit of dual HER2-targeting primarily observed in Luminal A tumors
  - Contrasts with effect on pCR

- These data are hypothesis-generating and require validation
  - Combined analysis of the 40601 data with Neo-ALTTO and other trials is planned

- A better understanding of the clinical + molecular features in HER2+breast cancer are likely to be key in rationally escalating and de-escalating therapy