I have no financial relationship(s) with commercial interests to disclose.
Pathological Complete Response Predicts Event-Free and Distant Disease Free Survival in the I-SPY 2 TRIAL

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Masonic Cancer Center, University of Minnesota

On behalf of I-SPY2 Investigators and authors:

pCR and EFS

- FDA Meta Analysis (Cortazar et al, Lancet 2014)
  - >11K patients from 12 neoadjuvant trials
  - Median follow-up for EFS: 5.4 years

BACKGROUND
San Antonio Breast Cancer Symposium, Dec 5-9, 2017

- FDA Meta Analysis
  - >11K patients from 12 neoadjuvant trials
  - Median follow-up for EFS: 5.4 years
Study Design

HR+/HER2- patients with low-risk MammaPrint Scores are not enrolled in I-SPY2
Analysis

• **Primary Endpoint:**
  - Pathological complete response (pCR)
  - Defined as no residual invasive cancer in breast or lymph nodes
  - Assessed using the Residual Cancer Burden (RCB) method*
  - Highly reproducible between local and central pathologist review

• **Intent-to-treat:**
  - Patients who did not complete assigned therapy are considered non-pCR (withdrew, left the institution, received non-protocol therapy, or progressed).

• **Secondary endpoints:**
  - RCB
  - EFS

• **I-SPY 2 To Date**
  - >1000 patients completed surgery
  - 11 investigational agents/combinations

EFS Dataset

- Evaluable population: 746
  - 259 (35%) pCR, 487 (65%) non-pCR
- Median follow-up: 2.7 yrs (0.02-7.2)
- 126 EFS events, 109 DRFS events

- 12 patients did not go to surgery
  - considered non-pCR per protocol

pCR distribution by subtype

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<table>
<thead>
<tr>
<th>pCR</th>
<th>HR-HER2- (n=245)</th>
<th>HR+HER2- (n=275)</th>
<th>HR-HER2+ (n=77)</th>
<th>HR+HER2+ (n=149)</th>
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<tbody>
<tr>
<td>no pCR</td>
<td>145 (59%)</td>
<td>226 (82%)</td>
<td>25 (32%)</td>
<td>91 (61%)</td>
</tr>
<tr>
<td>pCR</td>
<td>100 (41%)</td>
<td>49 (18%)</td>
<td>52 (68%)</td>
<td>58 (39%)</td>
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San Antonio Breast Cancer Symposium, Dec 5-9, 2017
Agent Timeline

11 Agent Combinations Included in this analysis, including control
pCR is a highly significant predictor of EFS and DRFS

**EFS**
- 3yr EFS: 76%
- 3yr EFS: 94%
- Hazard Ratio: 0.20 (95% CI: 0.11-0.36)
- Log rank p: 1.17e-09

**DRFS**
- 3yr DRFS: 79%
- 3yr DRFS: 95%
- Hazard Ratio: 0.20 (95% CI: 0.11-0.37)
- Log rank p: 1.75e-08

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pCR is predictive of EFS and DRFS in TNBC

**EFS**

- Hazard Ratio: 0.17
- (95% CI: 0.07-0.39)
- Log rank p: 2.60e-06
- 3yr EFS: 92%
- 3yr EFS: 67%

**DRFS**

- Hazard Ratio: 0.16
- (95% CI: 0.06-0.40)
- Log rank p: 8.62e-06
- 3yr DRFS: 94%
- 3yr DRFS: 70%
pCR is predictive of EFS and DRFS in HR+/HER2−

**EFS**

HR+HER2− (n=275)

- 3yr EFS: 94%
- 3yr EFS: 79%

Hazard Ratio: 0.21
(95% CI: 0.05-0.85)
Log rank p: 0.016

**DRFS**

HR+HER2− (n=275)

- 3yr DRFS: 94%
- 3yr DRFS: 80%

Hazard Ratio: 0.22
(95% CI: 0.05-0.93)
Log rank p: 0.024

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**pCR is predictive of EFS and DRFS in HR-/HER2+**

### HR-HER2+ (n=77)

**EFS**
- 3yr EFS: 93%

**DRFS**
- 3yr DRFS: 93%

### Hazard Ratio

- **EFS**: 0.10 (95% CI: 0.03-0.37)
- **DRFS**: 0.14 (95% CI: 0.04-0.51)

Log rank p: 1.98e-5 for EFS, 5.09e-4 for DRFS

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pCR is predictive of EFS and DRFS in HR+/HER2+

**EFS**

**HR+HER2+ (n=149)**

- 3yr EFS: 96%
- 3yr EFS: 87%

Hazard Ratio: 0.26  
(95% CI: 0.06-1.14)  
Log rank p: 0.054

**DRFS**

**HR+HER2+ (n=149)**

- 3yr DRFS: 97%
- 3yr DRFS: 92%

Hazard Ratio: 0.19  
(95% CI: 0.02-1.51)  
Log rank p: 0.080

**Number at Risk**

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<tr>
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<th>Years 0</th>
<th>Years 1</th>
<th>Years 2</th>
<th>Years 3</th>
<th>Years 4</th>
<th>Years 5</th>
<th>Years 6</th>
<th>Years 7</th>
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<tr>
<td>non-pCR</td>
<td>91</td>
<td>78</td>
<td>62</td>
<td>42</td>
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<td>pCR</td>
<td>58</td>
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EFS by pCR & non-pCR by Subtype

3yr EFS:
- HR-HER2-: 92%
- HR-HER2+: 93%
- HR+HER2-: 94%
- HR+HER2+: 96%

pCR (n=259)

non-pCR (n=487)

3yr EFS:
- HR-HER2-: 67%
- HR-HER2+: 53%
- HR+HER2-: 79%
- HR+HER2+: 87%

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EFS and DRFS Hazard Ratio for pCR vs non-pCR

<table>
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<tr>
<th>Subtype</th>
<th>N</th>
<th>Hazard Ratio (95% CI)</th>
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<tbody>
<tr>
<td>ALL</td>
<td>746</td>
<td>0.20 (0.11-0.36)</td>
</tr>
<tr>
<td>HR+HER2-</td>
<td>275</td>
<td>0.21 (0.05-0.85)</td>
</tr>
<tr>
<td>HR+HER2+</td>
<td>149</td>
<td>0.26 (0.06-1.14)</td>
</tr>
<tr>
<td>HR-HER2+</td>
<td>77</td>
<td>0.10 (0.03-0.37)</td>
</tr>
<tr>
<td>HR-HER2-</td>
<td>245</td>
<td>0.17 (0.07-0.39)</td>
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</table>

EFS

DRFS

Hazard Ratio (95% CI)

0.20 (0.11-0.37)
0.22 (0.05-0.93)
0.19 (0.02-1.51)
0.14 (0.04-0.51)
0.16 (0.06-0.40)
I-SPY2 EFS Hazard Ratio for pCR/non-pCR compared to FDA meta-analysis and cooperative group results

<table>
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<tr>
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<th>I-SPY 2</th>
<th>Cortazar Meta-analysis</th>
<th>Cooperative Group CALGB 40603</th>
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<td>Overall</td>
<td>0.20 (0.11-0.36)</td>
<td>0.48 (0.43-0.54)</td>
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<tr>
<td>*HR+HER2-</td>
<td>0.21 (0.05-0.85)</td>
<td>0.49 (0.33-0.71)</td>
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<tr>
<td>HER2+</td>
<td>0.21 (0.08-0.55)</td>
<td>0.39 (0.31-0.50)</td>
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<tr>
<td>HR-HER2-</td>
<td>0.17 (0.07-0.39)</td>
<td>0.24 (0.18-0.33)</td>
<td>0.30 (0.19-0.45)</td>
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*Mammaprint low patients excluded

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Summary

- pCR is a strong predictor of EFS and DRFS in the setting of a multiple agent platform trial that includes:
  - Standards for eligibility
    - *high risk for early recurrence (MP low risk, HR+Her2- excluded)*
    - *exclusion of metastatic disease*
  - All chemotherapy given before pCR determination
  - Standards for pathology assessment and multidisciplinary identification (surgeons, radiologists, pathologists)
  - Long term follow-up of patients over time (correlation of early, intermediate, and late endpoints)

- pCR is equally predictive across all tumor subsets

- pCR as an endpoint enables rapid evaluation of novel therapy combinations and can accelerate the identification of effective and potentially less toxic regimens
The Future of I-SPY 2

• Achieving pCR through any therapy for any subtype is a sufficient endpoint

• Develop minimally invasive techniques (MRI and biopsy) to identify pCR prior to definitive surgery
  • Validate robust MRI and tissue predictors of pCR
  • Deescalate toxic therapy (AC) if pCR obtained early

• Re-assign patients to new therapies if pCR is not predicted
  • Validate robust MRI and tissue predictors of non-PCR
  • Assign new therapies based on molecular profiling of tumor and link to investigational agents

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