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

![Event-free survival graph]

**Number at risk**

<table>
<thead>
<tr>
<th></th>
<th>Pathological complete response</th>
<th>No pathological complete response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since randomisation (years)</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pathological complete response</td>
<td>2131</td>
<td>1513</td>
</tr>
<tr>
<td>No pathological complete response</td>
<td>9824</td>
<td>6169</td>
</tr>
</tbody>
</table>

**HR**

- HER2-negative: 0.48 (95% CI 0.43-0.54)
- HER2-positive: 0.39 (95% CI 0.31-0.50)
- Triple negative: 0.24 (95% CI 0.18-0.33)
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

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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

<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>
</tr>
</thead>
<tbody>
<tr>
<td>pCR</td>
<td>100 (41%)</td>
<td>49 (18%)</td>
<td>52 (68%)</td>
<td>58 (39%)</td>
</tr>
<tr>
<td>no pCR</td>
<td>145 (59%)</td>
<td>226 (82%)</td>
<td>25 (32%)</td>
<td>91 (61%)</td>
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</table>
Agent Timeline

11 Agents Included in this analysis
pCR is a highly significant predictor of EFS and DRFS

**EFS**

- 3yr EFS: 94%
- 3yr EFS: 76%

**Hazard Ratio: 0.20**

(95% CI: 0.11-0.36)

Log rank p: 1.17e-09

**OVERALL**

**DRFS**

- 3yr DRFS: 95%
- 3yr DRFS: 79%

**Hazard Ratio: 0.20**

(95% CI: 0.11-0.37)

Log rank p: 1.75e-08

Number at Risk
- non-pCR: 487, 418, 288, 186, 89, 40, 13, 0
- pCR: 259, 232, 166, 109, 59, 23, 4, 0

Number at Risk
- non-pCR: 487, 430, 295, 193, 95, 41, 14, 0
- pCR: 259, 233, 167, 110, 60, 24, 4, 0

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pCR is predictive of EFS and DRFS in TNBC

EFS

HR-HER2- (n=245)

3yr EFS: 92%

3yr EFS: 67%

Hazard Ratio: 0.17
(95% CI: 0.07-0.39)
Log rank p: 2.60e-06

non-pCR

pCR

DRFS

HR-HER2- (n=245)

3yr DRFS: 94%

3yr DRFS: 70%

Hazard Ratio: 0.16
(95% CI: 0.06-0.40)
Log rank p: 8.62e-06

non-pCR

pCR

Number at Risk
non-pCR 145 118 70 48 24 12 3 0
pCR 100 92 61 44 25 10 2 0

Number at Risk
non-pCR 145 123 73 50 25 12 3 0
pCR 100 92 61 45 26 11 2 0

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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+

### EFS

**HR−HER2+ (n=77)**

- **3yr EFS:** 93%
- **Hazard Ratio:** 0.10
  - (95% CI: 0.03-0.37)
  - Log rank p: 1.98e-5

**Years**

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>non-pCR</th>
<th>pCR</th>
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<tbody>
<tr>
<td>7</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>47</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>39</td>
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<tr>
<td>1</td>
<td>7</td>
<td>23</td>
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<tr>
<td>0</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>0</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

### DRFS

**HR−HER2+ (n=77)**

- **3yr DRFS:** 93%
- **Hazard Ratio:** 0.14
  - (95% CI: 0.04-0.51)
  - Log rank p: 5.09e-4

**Years**

<table>
<thead>
<tr>
<th>Number at Risk</th>
<th>non-pCR</th>
<th>pCR</th>
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</thead>
<tbody>
<tr>
<td>7</td>
<td>25</td>
<td>52</td>
</tr>
<tr>
<td>4</td>
<td>21</td>
<td>47</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>39</td>
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<tr>
<td>0</td>
<td>1</td>
<td>4</td>
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<tr>
<td>0</td>
<td>1</td>
<td>0</td>
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</table>
pCR is predictive of EFS and DRFS in HR+/HER2+

**EFS**

HR+HER2+ (n=149)

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

**DRFS**

HR+HER2+ (n=149)

- 3yr DRFS: 92%

**Hazard Ratio:**

- **EFS:** 0.26 (95% CI: 0.06-1.14) Log rank p: 0.054
- **DRFS:** 0.19 (95% CI: 0.02-1.51) Log rank p: 0.080

Number at Risk

- **non-pCR**
  - EFS: 91 78 62 42 22 10 4 0
  - DRFS: 91 81 63 44 24 11 4 0

- **pCR**
  - EFS: 58 49 37 20 10 6 2 0
  - DRFS: 58 50 38 20 10 6 2 0

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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)

Number at Risk
- HR-HER2-: 100 92 61 44 25 10 2 0
- HR-HER2+: 52 47 39 23 13 4 0 0
- HR+HER2-: 49 44 29 22 11 3 0 0
- HR+HER2+: 58 49 37 20 10 6 2 0

Years
- 0 1 2 3 4 5 6 7

EFS
- 1.0 0.8 0.6 0.4 0.2 0.0

non-pCR (n=487)

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

Number at Risk
- HR-HER2-: 145 118 70 48 24 12 3 0
- HR-HER2+: 25 18 12 7 4 1 1 0
- HR+HER2-: 226 204 144 89 39 17 5 0
- HR+HER2+: 91 78 62 42 22 10 4 0

Years
- 0 1 2 3 4 5 6 7

EFS
- 1.0 0.8 0.6 0.4 0.2 0.0
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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<tr>
<td>ALL</td>
<td>746</td>
<td>0.20 (0.11-0.36)</td>
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<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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**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>
<thead>
<tr>
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<th>Cortazar Meta-analysis</th>
<th>Cooperative Group CALGB 40603</th>
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<tr>
<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>
<tr>
<td>HER2+</td>
<td>0.21 (0.08-0.55)</td>
<td>0.39 (0.31-0.50)</td>
<td></td>
</tr>
<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*
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
Acknowledgements

WORKING GROUP CHAIRS

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SPONSOR

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# Participating Organizations

## FUNDING PARTNERS

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## STUDY SPONSOR

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## BIOMARKER PLATFORMS & DATA SUPPORT

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