Lessons from Breast Cancer: The I-SPY2 Trial

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Disclosures

- Research funding: NIH, US Food and Drug Administration, GlaxoSmithKline, Bayer
- Medical advisory board/consulting: GlaxoSmithKline, Boehringer Ingelheim, Bayer, Roche/Genentech, Prometic, CSL Behring
- I am not a medical or surgical oncologist!
Overview

- What is the I-SPY2 trial
  - Adaptive randomization, platform trial
  - Stratified by biomarker subtypes
- Fundamental innovations that made the I-SPY2 trial possible
- Challenges in translating these concepts to sepsis/ARDS
- What might the path forward look like?
What is the I-SPY2 Trial?

- Enrolls high risk breast cancer patients
- Phase II clinical trial of novel agents for neo-adjuvant treatment
  - I.e. before surgery
- Platform trial: Can move new drugs in and out
- Adaptive randomization
  - Patients are randomized based on biomarker subtype
  - Randomization probabilities adjusted based on outcomes
- Bayesian statistics
  - Result is not effect size, but instead is probability of positive Phase III clinical trial
Prognostic Enrichment Informs I-SPY2 Eligibility

Assess Eligibility

Core Biopsy

Mammaprint High Risk or HR Negative

Tumor > 2.5 cm

HR Positive, HER2- and MammaPrint Low Risk

ELIGIBLE

I-SPY2 LOW RISK REGISTRY

NOT ELIGIBLE
Predictive Enrichment Via Adaptive Design

Subtype: Defined by HR/HER2/Mammaprint status

New patient accrues; assess subtype

Randomization
(Probabilities based on performance of each drug within each subtype)

Adaptive Randomization depends on treatment response

Outcomes (Short-term) Assessed

Update probabilities
Platform Trial: Designed to Test Multiple Agents

- The protocol and the Master IND* are structured to enable seamless addition and release of investigational agents over the course of the trial
  - Enrollment does NOT stop during agent transition
- When an investigational agent is added to or released from the trial only appendices require updating

*I The Master IND structure allows new investigational agents to be added to the protocol without the 30-day FDA review period.
I-SPY 2 Agent Timeline
Primary Endpoint: Pathologic Complete Response

- Defined as **no residual invasive cancer in the breast or lymph nodes at time of surgery**
  - Early surrogate endpoint that is highly predictive of long term outcomes

- Endpoint is assessed in 10 pre-specified “biomarker signatures”
  - By receptor subtype (HR, Her2) and Mammaprint Score
Example of Results: Pembrolizumab (PD-L1 Ab)

<table>
<thead>
<tr>
<th>Signature</th>
<th>Estimated pCR rate (95% probability interval)</th>
<th>Probability pembro is superior to control</th>
<th>Predictive probability of success in phase 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All HER2-</td>
<td>Pembro: 0.44 (0.33 – 0.55)</td>
<td>&gt;99.9%</td>
<td>98.5%</td>
</tr>
<tr>
<td></td>
<td>Control: 0.17 (0.11 – 0.23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TN</td>
<td>Pembro: 0.60 (0.44 – 0.75)</td>
<td>&gt;99.9%</td>
<td>&gt;99%</td>
</tr>
<tr>
<td></td>
<td>Control: 0.22 (0.13 – 0.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR+/HER2-</td>
<td>Pembro: 0.30 (0.17 – 0.43)</td>
<td>&gt;99.6%</td>
<td>83.4%</td>
</tr>
<tr>
<td></td>
<td>Control: 0.13 (0.07 – 0.19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Bayesian model estimated pCR rates appropriately adjust to characteristics of the I-SPY 2 population.

The raw pCR rates (not shown) are substantially higher than the model estimate of 0.604 in TNBC.

Nanda et al ASCO 2017
Example of Results: Pembro pCR Probability Distributions by Signature

**HER2−**
- **Control:** 17%
- **Pembrolizumab:** 44%
  - 95% PI: 11% - 23%
  - 95% PI: 33% - 55%

**HR−HER2−**
- **Control:** 22%
- **Pembrolizumab:** 60%
  - 95% PI: 13% - 30%
  - 95% PI: 44% - 75%

**HR+HER2−**
- **Control:** 13%
- **Pembrolizumab:** 30%
  - 95% PI: 7% - 19%
  - 95% PI: 17% - 43%

Prob(>Ctl)>99.9%
Prob(Ph3)=98.5%
Prob(>Ctl)=99.6%
Prob(Ph3)=83.4%

I-SPY2 PLATFORM TRIAL

Nanda et al ASCO 2017
# Categories of Biomarkers in I-SPY 2

<table>
<thead>
<tr>
<th>STANDARD</th>
<th>QUALIFYING</th>
<th>EXPLORATORY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ER/HER2</td>
<td>1. Signatures</td>
<td>1. RNA seq</td>
</tr>
<tr>
<td>2. Mammaprint</td>
<td>1. DNA Repair Deficiency</td>
<td>2. DNA seq</td>
</tr>
<tr>
<td>• FDA cleared 70 gene assay (used to determine randomization eligibility)</td>
<td>2. AKT pathway</td>
<td>3. Circulating DNA</td>
</tr>
<tr>
<td>• Used to determine response to treatment</td>
<td>4. Hi-2 (Mammaprint)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. Immune Signatures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Platforms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. 44k Agilent Array</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Reverse Phase Protein Arrays</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Vectra Multiplex Staining Environment</td>
<td></td>
</tr>
</tbody>
</table>
Qualifying Biomarkers Used in Exploratory Analyses

Nearly all of the specific sensitivity to veliparib/carboplatin is in the 40% of TN patients positive for BOTH sensitivity markers.
## Extensive Biospecimen Collection Allows Discovery

<table>
<thead>
<tr>
<th></th>
<th>Pre-Tx</th>
<th>Early-Tx</th>
<th>Inter-reg</th>
<th>Surgery</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen Cores</td>
<td>9,018</td>
<td>4,803</td>
<td>4</td>
<td>1008</td>
<td>14,833</td>
</tr>
<tr>
<td>FFPE</td>
<td>25</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>30</td>
</tr>
<tr>
<td>Plasma</td>
<td>4,323</td>
<td>3,044</td>
<td>2,688</td>
<td>2,559</td>
<td>12,614</td>
</tr>
<tr>
<td>Serum</td>
<td>4,333</td>
<td>3,032</td>
<td>2,680</td>
<td>2,543</td>
<td>12,588</td>
</tr>
<tr>
<td>Buffy Coat</td>
<td>2,875</td>
<td>2,023</td>
<td>1,787</td>
<td>1,698</td>
<td>8,383</td>
</tr>
</tbody>
</table>
Fundamental Innovations of I-SPY2 (Part 1)

- Combination of prognostic and predictive enrichment
  - Prognostic: High risk patients (large tumor, high risk Mammaprint)
  - Predictive: Randomization and treatment eligibility by biomarker subtype
- Adaptive randomization: Allows learning as the trial goes on
  - Requires early endpoint that is highly tied to treatment efficacy AND long term outcomes
  - Patient-centric: “Who wants to be in the control arm”
  - Acceptance of Bayesian approach to analysis
Fundamental Innovations of I-SPY2 (Part 2)

- Platform design: Can rapidly move new agents in and out
- Does not provide definitive answer: Requires prospective confirmation
- Extensive harmonization of care at sites: Took 3 years to develop
  - Complex analytic approach also required extensive planning
- Comprehensive biobank and biomarker working group that allows discovery to be integrated in trial
- Early involvement of key stakeholders:
  - FDA, IRBs, Pharma, Biotech, Academics, Community Cancer Ctrs, Advocates
Challenges in translating to sepsis/ARDS

- **Timeline**: Urgency of subtyping patients and randomizing within hours
  - No ability to rapidly subtype patients at present

- **Mechanistic understanding**:
  - Much deeper understanding of tumor biology in breast cancer
  - Decades of experience with biomarker defined subtypes prior to beginning trial

- **Uncertainty re: appropriate endpoint**:
  - pCR in breast cancer is entirely driven by chemo response and extremely predictive of long term outcomes
  - Mortality is early in ARDS: but how much is driven by treatment/ARDS
  - No good surrogate outcome
Challenges in translating to sepsis/ARDS

- Biomarker-defined subtypes:
  - Breast cancer: Established, FDA-cleared/approved tests for biomarkers that determine signatures (HR/HER2)
  - We have no analogous biomarkers in sepsis/ARDS for stratifying patients
  - Nor agreement on optimal approach to stratification
Adapting Innovations of I-SPY2 To Critical Care (Part 1)

- Combination of prognostic and predictive enrichment
  - Prognostic: High risk patients
    - ARDS: PF < 150? What about sepsis?
  - Predictive: Randomization and treatment eligibility by biomarker subtype
    - Which subtype?
    - No qualified biomarkers, no prospective validation, few rapid assays

- Adaptive randomization
  - Requires early endpoint that is highly tied to treatment efficacy AND long term outcomes
Adapting Innovations of I-SPY2 To Critical Care (Part 2)

- Platform design
  - Do we have an adequate pipeline of new therapies in sepsis and ARDS?
- Extensive harmonization of care at sites
  - Careful planning of complex analytic approach
- Comprehensive biobank that allows discovery to be integrated in trial
- Early involvement of key stakeholders:
  - FDA, IRBs, Pharma, Biotech, Academics, Community Cancer Ctrs, Advocates
Precision Medicine in ARDS/Sepsis: The Road Ahead

1970s: Differential response of breast cancer to hormone therapy by ER/PR status

1998: Trastuzumab (Herceptin) shown to benefit HER2+ patients

George Beatson, MD
Oophorectomy benefit for advanced breast cancer, 1896

Elwood Jensen, PhD
Described estrogen receptor, 1958

Laura Esserman, MD
I-SPY2 trial, NEJM 2016

Dennis Slamon, MD
HER2 receptor discovery, 1987

Traztuzumab (Herceptin) shown to benefit HER2+ patients

Adaptive Randomization of Veliparib-Carboplatin Treatment in Breast Cancer

2002: Mammaprint
70 gene array
Conclusions

- I-SPY2 trial has developed a new paradigm for adaptive, platform trial
  - Combination of prognostic/predictive enrichment
  - Stratification by established biomarkers, exploration within new biomarker subtypes
- Challenges in translating to critical care:
  - Compressed timeline, lack of mechanistic understanding, unclear endpoint, lack of well-established subtypes
- We can learn from the path our colleagues have taken
The only way to finding a new and better path forward is to imagine it and start with the first step, and learn as you go.

Laura Esserman, MD MBA
PI, ISPY-2 Trial
Thank you to the remarkable patients and families, our amazing advocates, all of the investigators, staff, and our DSMB for supporting the trial.
I-SPY2: Use of MRIs to Guide Adaptive Assignment