I SPY 2: The right drug, the right patient, the right time

Using Biology to Adaptively Guide Treatment for Early Breast Cancer and Predict Response

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I-SPY 2 TRIAL PI’s:
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Disclosure

• Co-founder & stockholder Agendia BV
• No other disclosures
Basic Principles of I-SPY

• Test new drugs where they matter most
  • Early stage rather than metastatic disease

• Change the order of therapy: learn about response early in the course of care
  • Neoadjuvant setting (systemic therapy before surgery)
  • Primary Endpoint is complete response to therapy (pCR)

• Build an efficient engine to evaluate drugs, accelerate knowledge turns
  • Master Protocol, Adaptive Design

• Use imaging and biomarker guidance
  • Focus on the population of patients who are at high risk for EARLY recurrence
  • Insights about who responds to what agents
  • “Graduation” for efficacy = threshold predictive probability of success in next phase III trial

• Collaborative by Design:
  • FDA, IRBs, Pharma, Biotech, Academics, Community Cancer Ctrs, Advocates
I-SPY 2 Participating Sites

16 Sites Open and Enrolling
+ 3 Opening in Q3/Q4 2018
Trial Patient Enrollment Overview

Registered (n = 2448)
- Actively Being Screened (n=36)
- Did Not Proceed to the Treatment Phase (n=991)

Randomized (n = 1420)

Completed Surgery (n = 1241)

Status as of October 31st, 2018
I-SPY 2 Investigational Agents

Anti-HER family signaling
- Neratinib
- trastuzumab/pertuzumab
- TDM1/pertuzumab
- trastuzumab/patritumab

Anti-IGF1R
- Ganitumab

AKT inhibition
- MK2206

Unfolded protein response inhibition
- ganetespib (HSP90i)

PARP inhibition + DNA damage
- Talazoparib/irinotecan
- veliparib/carboplatin

Immune checkpoint inhibition
- Pembrolizumab

TIE1/2 inhibition
- AMG386

Agents Developed Targeting Hallmarks of Cancer

**Diagnosis**
- MRI - tumor volume
- Biopsy - biological subtype

**5 Investigational Drug Arms + Control**
- Serial MRI (volume change) & pathology at surgery (residual cancer burden)
  - Informs adaptive randomization by subtype

**Surgery**

**Biomarkers:**
- Imaging
- Pathology
- Molecular Biology
  - 8 subtypes by:
    - Hormone Receptor +/-
    - HER2 +/-
    - MammaPrint High1/High2 (HR+/MammaPrint low excluded)

**Adaptive Randomization**

**Efficacy endpoint:** pCR (pathological Complete Response) on surgery specimen

**Survival endpoint:**
- EFS/DRFS at 3y & 5y (Event/Distant Recurrence Free survival)

* Patients who are HER2+ may also receive taseluzumab (Herceptin)

An investigational combination of one or more agents may be used to replace all or some of the standard therapy.
I-SPY 2 Adaptive Randomization

Adaptive randomization based on 8 subtypes
(hormone receptor (HR) +/-, HER2 +/-, MammaPrint-High 1 or High 2; $2^3=8$)
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(hormone receptor (HR) +/-, HER2 +/-, MammaPrint-High 1 or High 2; $2^3=8$)
I-SPY 2 Adaptive Randomization

Adaptive randomization based on 8 subtypes

- New patient accrues; assess subtype
- Randomize
  - Calculate adaptive randomization probs by subtype
  - Update probs arm > ctl by subtype
- Update all outcome data
- Update MRI→pCR model
- Update pred probs arm >> ctl in phase 3 for each signature
- Termination rule per arm
- Continue
- Add new arms accrual permitting
- Graduate

Graduation based on 10 signatures (combinations of subtypes)
Methods for Estimating Response Probability
(pathological Complete Response = pCR)

Distribution of pCR rates

Mean of distribution is the Point Estimate for pCR (estimated pCR)

Control (std)  
Agent + std

pCR rate

x%  y%  Estimated pCR rate
I-SPY 2 Framework:
Biomarkers Guide Enrichment of Drug Arm with Responding Subtype

Example: Veliparib (PARP-inhibitor)/Carboplatin
Biomarkers indicated while arm was ongoing:
- response in Triple-Negative (TN) Breast Cancer > ‘graduation’
- no response in Hormone receptor positive Breast cancer (HR+/HER2-)
and the adaptive randomization enriched the VC arm with TN Breast Cancer

VC response ~50%!
Timeline of Investigational Drugs and Graduating Subtypes
Biomarkers Guide Enrichment of Drug Arm with Responding Subtype

15 drugs of 10 Pharma entered the trial
2448 patients screened, 1420 pts randomized
10 completed evaluation
• 7 graduated w subtypes
• 2 dropped (no increase efficacy)
• 1 stopped (toxicity)
5 arms ongoing
1 control arm

- Efficacy endpoint:
Seven graduating drugs
Response rate at least doubled vs. control treatment
(20% > 40% pCR), some drug/subtype 65% pCR
pCR relates to survival regardless of treatment
10 treatment arms, 741 patients, minimal 2 yr and median 2.7 yr follow-up

pCR gives 94-95% 3 yr survival, regardless of drug vs.
no-pCR 76-79% 3 yr survival

Yee et all, SABCS 2017; DeMichele et all, ENA 2018 abstract 160
Qualifying Biomarkers to improve response prediction

• Important to get every patient to pCR (increased probability of survival)
• I-SPY 2 randomizes by 8 subtypes (HR +/-, HER2 +/-, MammaPrint High1/High 2)
• How can biology further identify responders?

• I-SPY 2 tests ‘Qualifying Biomarkers’, which have existing evidence for response prediction
  • Biology of Targeted agent, eg DNA repair deficiency, HER2 signaling, immune signatures, biology subtyping
• Presented here: 70-gene signature (MammaPrint) High1 versus High2 (high risk and very high risk for recurrence, and 80-gene molecular subtyping signature (BluePrint) which identifies luminal-, basal- and HER2-type
70-gene High1 and High2 risk as biomarker of response prediction

MammaPrint 70-gene expression signature identifies patients at low risk and high risk for recurrence. Here we use a High-risk1 and High-risk2 (ultra-high) sub-classification.

986 patients I-SPY 2 patients with MPHigh1/High2 class assessments (49% MP1, 51% MP2)

Control arm: paclitaxel (with trastuzumab (H) in HER2+), followed by doxorubicin/cytoxan (AC) (ctr treatment)

9 Experimental arms: veliparib/carboplatin (VC); neratinib (N); MK2206; Ganitumab; Ganetespib; AMG386; TDM1/pertuzumab(P); H/P; and Pembrolizumab; + ctr treatment

Assessment of association of MP1/2 class and pCR:

Univariate: Logistic model and Multivariate: Logistic model adjusting for HR and HER2 status, and treatment arm as covariates. Significance threshold: p value < 0.05

Denise Wolf, PhD
Computational Scientist
**MPHigh1/High2 predicts ‘chemo-sensitivity’**

- 986 I-SPY 2 patients across and within 10 treatment arms
- Association of MP High1/High2 with pCR across all, and within 5 arms

### MP1/2 class

<table>
<thead>
<tr>
<th></th>
<th>MP1</th>
<th>MP2</th>
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<tbody>
<tr>
<td>no pCR</td>
<td>392</td>
<td>277</td>
</tr>
<tr>
<td>pCR</td>
<td>111</td>
<td>206</td>
</tr>
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Across all arms combined, **MP High2 associates with pCR** (OR=2.43; p=1.31E-06) in a model adjusting for treatment arm, HR, and HER2 status

**MP High2 improves prediction**

<table>
<thead>
<tr>
<th>Arm</th>
<th>OR</th>
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</thead>
<tbody>
<tr>
<td>Ctrl</td>
<td>2.237</td>
</tr>
<tr>
<td>VC</td>
<td>5.365</td>
</tr>
<tr>
<td>N</td>
<td>3.777</td>
</tr>
<tr>
<td>MK2206</td>
<td>1.113</td>
</tr>
<tr>
<td>Ganitumab</td>
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<td>Ganetespib</td>
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<tr>
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<tr>
<td>TDM1/P</td>
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<tr>
<td>Pertuzumab</td>
<td>21.83</td>
</tr>
<tr>
<td>Pembrol</td>
<td>6.233</td>
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</table>

**Summary** 2.43

**MP High2 associated with pCR in half the arms** *(Veliparib-carbo, Neratinib, Ganitumab, Trastuzumab/Pertuzumab and Pembrolizumab)* in a model adjusting for HR and HER2 status (OR 2.43)
- most strongly in HR+/HER2- (OR 3.62; p=1.18E-0.5) (data not displayed)
80-gene Molecular subtype ‘basal’ as biomarker of response prediction

- BluePrint molecular subtype identifies functional luminal-, basal- and HER2-type

986 patients HR/HER2 Subtype Distribution

While the majority of **HR+HER2- patients** are Luminal (71%), **29% are Basal-type**
HR+/HER2- with Basal subtype predicts ‘chemo-sensitivity’

- 375 I-SPY 2 HR+/HER2- patients across 8 treatment arms
- Association of molecular BluePrint basal subtype with pCR

Within treatment arms, the estimated pCR rates among HR+HER2- Basal patients ranged from 29%-41%, compared to 7%-17% in HR+HER2- Luminal patients.
I SPY 2: Learning, Innovating, and Evolving

- Patient Centered
  - Adaptive randomization, they get the best agent for their subtype
- Maximizes chance of pCR and cure for each patient
  - pCR results in 95% 3 yr disease-free survival (no-pCR 76-79%)
- Qualifies predictive biomarkers to identify responders (ENA 2018)
  - MammaPrint High1/High2, BluePrint molecular subtypes
  - Can prioritize treatment in subsequent trials (I-SPY 2.2 trial design)
- Increases chance of pCR and cure for the high risk population
  - Learn, approve drugs and combinations that are effective and less toxic
- A design that patients like, that investigators like, where industry will participates- speeds the chance that patients will survive
- Advances regulatory science
I-SPY 2 TRIAL Study Team

Working Group Chairs

PI: Laura Esserman
PI: Don Berry
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Operations: Angie DeMichele
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PRO/QOL: Michelle Melisko

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Grants: Jeff Matthews

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