Description of the I-SPY 2 TRIAL for investigators submitting concepts

This information is relevant for any investigators (non-profit/for profit) who wish to access data or obtain biospecimen from the I-SPY2 Trial

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Background Information

NCT01042379 https://clinicaltrials.gov/ct2/show/NCT01042379?term=I-SPy2&rank=1

Eligibility Criteria

- ≥2.5cM invasive tumor, stage II/III breast cancer
- Core biopsy for MammaPrint assessment, ER, PR, HER2 (IHC, TargetPrint)
- MammaPrint HIGH, any ER, any HER2
- MammaPrint LOW, ER-, any HER2
- MammaPrint LOW, ER+, HER2+
- **NOT** Eligible MammaPrint LOW, ER+, Her2-
    - Eligible patients are categorized into 8 subtypes based on HER2, hormone-receptor status, and MammaPrint Risk score.
    - Primary Endpoint is pathologic complete response.
    - Accrual to experimental arms stops for futility* or "graduation" (from phase 2) within a particular signature based on an 85% Bayesian predictive probability of success in a confirmatory phase 3 neoadjuvant trial.

*Regimens may leave the trial, if an experimental arm has a sufficiently low predictive probability of success for all signatures (<10%, futility), or maximum sample size is met (10%< probability of success <85%) .

Outcome Measures

- Pathologic Complete Response (pCR)
- Residual Cancer Burden
- RFS, OS

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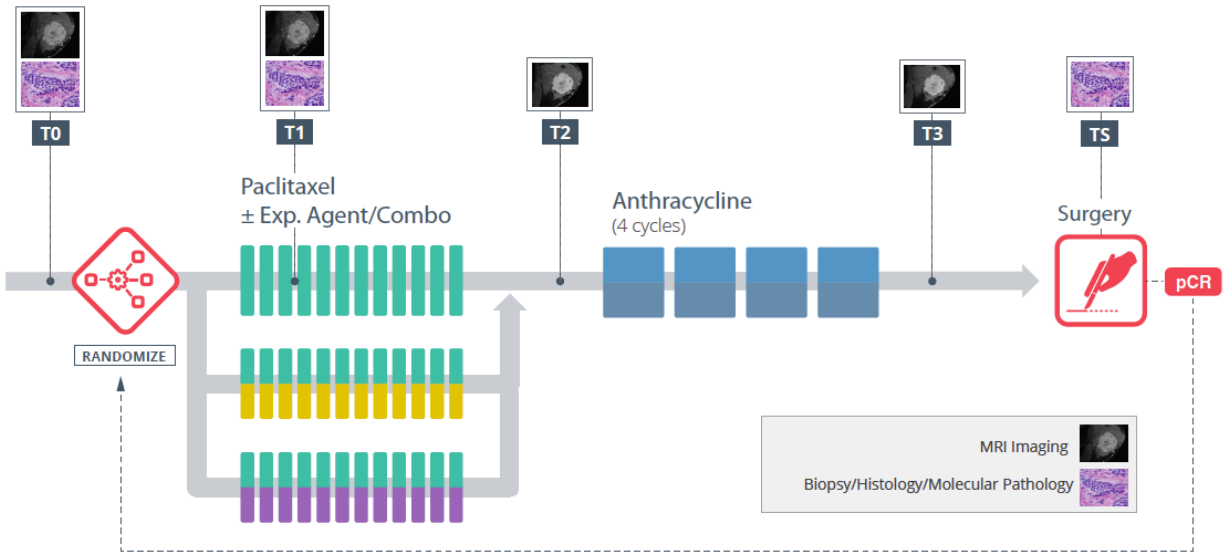
Trial Design



Agents

- **Drug: Standard Therapy**
  - Paclitaxel (HER2-negative patients)
  - Paclitaxel +/- trastuzumab (HER2+ patients) followed by 4 cycles AC

- **Investigational Arms (Novel Agent in schema)**
  - Experimental Agent + paclitaxel (+trastuzumab for HER2+) (12 weekly cycles) followed by 4 cycles AC

Evaluated Drugs

- Drug: Neratinib (in place of trastuzumab for HER2+) **GRADUATED in HR-/HER2+ signature**(Park et al., 2014)
- Drug: ABT-888 (veliparib) +carboplatin, HER2- patients only **GRADUATED in TN signature**(Rugo et al., 2014)
- Drug: MK-2206 **GRADUATED in 3 biomarker signatures: HR-, HER2+ and HR-/HER2+**(Tripathy, D. Chien, AJ., Hylton, NM., Buxton, MB. Ewing CA., Wallace, AM. Forero, A., Kaplan, H.G., Nanda, R., Albain, KS., Moulder, SL, Haley, B.B, DeMichele, A., Symmans, W.F., van 't Veer, L, Paoloni, 2015)
- Drug: AMG 386 **NO subtype reached threshold for graduation, possible benefit in a number of subtypes**(Albain et al., 2015)
- Drug: T-DM1 and Pertuzumab (instead of trastuzumab) HER2+ patients only: **GRADUATED from ISPY 2 in 3 signatures: all HER2+, HER2+/HR+, HER2+/HR** (DeMichele et al., 2016)

- Drug: Pertuzumab HER2+ patients only: **THP GRADUATED in 3 signatures: all HER2+, HER2+/HR+, and HER2+/HR** (Buxton et al., 2016)
- Drug: AMG 479 (Ganitumab) plus Metformin (HER2- patients only) **NO subtype reached threshold for graduation** (Yee et al., 2016)
- Drug: Ganetespib HER2- patients only – **NO subtype reached threshold for graduation**(Forero et al., 2016)
- Drug: Pembrolizumab 4 cycle- HER2- patients only- **Graduated in all 3 HER2- signatures**(Nanda et al., 2017)
- Drug: Talazoparib + Irinotecan-HER2- patients only- RESULTS TO BE REPORTED
- Drug: Patritumab + trastuzumab- HER2+ patients only-

Drugs Currently Being Evaluated

- Drug: Pembrolizumab - 8 cycle- HER2- patients only
- Drug: SGN-LIV1A- HER2- patients only

Data and Sample Collection in the trial

Biological samples in the trial consist of tumor material collected from patients and derivatives, as well as serum, buffy coat and plasma. Biospecimen is collected at multiple timepoints during neoadjuvant therapy, and stored in the I-SPY2 Central Lab at UCSF.

Samples/Data Summary

T0	MRI, Core Biopsy, Blood	**Prior to randomization**
T1	MRI, Core Biopsy, Blood	**End of wk3**
T2	MRI*, Blood Draw**	**Prior to AC, 1 day* to 1 week **post paclitaxel**
T3	MRI, Surgical tissue if possible, Blood	**Prior to Surgery, > 2 weeks after AC**

Blood specimen collection is serum, plasma and buffy coat

Assay Platforms

There are currently two assay platforms, which are run on all patient pre-treatment (T0) tissue samples in the trial.

1) Agilent 44k gene expression microarray run by Agendia and utilized as part of screening for eligibility (MammaPrint risk score) in the trial.

2) Reverse Phase Microarray (RPMA) run by collaborators at George Mason University for assessment of total protein levels and phosphorylation status in a defined panel in the lysates of pre-treatment tissue samples for patients on treatment.(Wulfkuhle et al., 2016),(Wolf et al., 2014)

Additionally, two sequencing platforms covering RNA-seq and targeted exome sequencing have been run in specific investigational arms, which have graduated from the trial:

- Neratinib + concurrent controls – targeted exome sequencing (2000 cancer gene panel) (Collaborators Voest/Bernards,NKI)- T0 timepoint
- Veliparib (ABT-888) + concurrent controls – RNA-seq (Collaborators- Pourmand, UCSC), T0, T1 timepoints

Requests for Biological Samples and Data

Access for ANY data or biospecimen from the I-SPY 2 TRIAL is governed by a concept submission process. Requests should be made using the I-SPY 2 Concept Proposal Form as described below.

- The development of an I-SPY 2 concept should involve a number of discussions with the I-SPY 2 TRIAL Biomarker Chair (Laura van 't Veer), Scientific Program Manager (Gillian Hirst) and Statisticians (Denise Wolf/Christina Yau) to evaluate its feasibility in terms of data and sample availability, scientific merit balanced against other proposals and initiatives, and any contracting or budgetary requirements.
- Concept Development is discussed at the monthly I-SPY 2 TRIAL Biomarker Working Group and is an opportunity for the investigator to present preliminary data and refine concept proposals.
- Finalized concepts are evaluated by the I-SPY2 TRIAL DATA ACCESS and PUBLICATIONS COMMITTEE (DAPC) before any further action can be taken. (See below for details)
- When thinking about sample or data access, please remember that arm-specific data and biospecimen is not available until the investigational agent is no longer active in the trial and is also dependent on publication priorities of the trial.

Data Only Requests

Requests for data should be submitted using the standard I-SPY 2 Concept Proposal Form. There are I-SPY 2 statistical templates available, and I-SPY 2 statisticians available for consult. Data is only released once an arm has left the trial.

Please fill out the statistical plan in as much detail as possible and be clear and concise in your request for specific data variables and time points.

At this time, standard assay data is only available at the T0 time point, except for RNA-seq data which has been performed in the veliparib arm in 2 time points (see above).

Example of a Standard Data Request

Arm: eg Neratinib and concurrent controls
Timepoint: T0 (Pre-treatment timepoint)
Assay: Agilent Gene Expression 44k Array
Clinical Data: pCR, HR, HER2 status, MP status.

Concepts can include a request for specified data in future arms as when they are available.
Non-standard data requests MUST be discussed with the I-SPY Scientific Program Manager for feasibility. Before data release, all investigators and their institutional representative requesting data are required to sign the I-SPY 2 Data Use Agreement following approval of their concept.

Requests for Biospecimen and derivatives
Access to patient bio-specimen or derivatives in your concept requires approval from both the I-SPY 2 Biomarker Working Group and the I-SPY 2 DAPC group and must be weighed against the priorities for the trial. Please work closely with the I-SPY 2 Scientific Program Manager and BWG Chair to assess your proposal for feasibility, and development, before completing the concept request.

Description of I-SPY 2 TRIAL Review Committees

Biomarker Working Group
The working group is made up of pathway scientists and clinicians from I-SPY 2 sites across the country with representatives from different disciplines, i.e. pathology, imaging, different assay platforms, etc., as well as statisticians and representation from the trial sponsor. This group makes a determination to either approve or not approve the provision of patient samples and advises on data concept development. The group works to balance out the variety of biomarker analysis conducted on each arm. The group meets monthly.

Data Access and Publications Committee (DAPC)
The DAPC is chaired by the trial PIs (Esserman and Berry) and has representation from the sponsor, and the chairs of each trial area, pathology, imaging, agents, site operations, statistics, and advocates. The DAPC reviews ALL concepts and makes a determination to approve for execution or not. Investigators are informed of the outcome and may resubmit with revisions as necessary. The DAPC meets quarterly.

Post-Approval
Patient biospecimen or data are provided after completion of any related contracting, budgeting and at the minimum receipt of the signed I-SPY 2 Data Use Agreement.

Contact Information

I-SPY 2 TRIAL Scientific Program Manager

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